平成２６年度
次世代医療機器・再生医療等製品
評価指標作成事業

生体吸収性ステント
審査ＷＧ報告書

平成２７年３月

審査ＷＧ座長　中村　正人
東邦大学医療センター 大橋病院
内科学講座 循環器内科

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Ⅰ　委員構成

委員（○：座長）

	岩﨑　清隆	早稲田大学理工学術院　先進理工学研究科　共同先端生命医科学専攻　教授
	新家　俊郎	神戸大学大学院医学研究科　内科学講座　循環器内科学分野　准教授
	中澤　学	東海大学医学部　内科学系　循環器内科学　講師
○	中村　正人	東邦大学医療センター　大橋病院　内科学講座　循環器内科　教授
	挽地　裕	佐賀大学医学部　循環器内科　准教授
	宮内　克己	順天堂大学医学部大学院医学研究科　循環器内科学講座　先任准教授
	山岡　哲二	国立循環器病研究センター研究所　生体医工学部　部長
	山本　玲子	物質・材料研究機構　MANA-ナノライフ分野　生体機能材料ユニット バイオメタルグループ　グループリーダー

厚生労働省

磯部　総一郎	大臣官房　参事官（医療機器・再生医療等製品審査管理担当）
近藤　英幸	医薬食品局　医療機器・再生医療等製品担当参事官室 医療機器規制国際調整官
金川　幸紀	医薬食品局　医療機器・再生医療等製品担当参事官室　医療機器指導官
間々田　圭祐	医薬食品局　医療機器・再生医療等製品担当参事官室　主査

独立行政法人　医薬品医療機器総合機構

木下　勝美	医療機器審査第一部　部長
方　眞美	医療機器審査第一部　審査役
相澤　浩一	医療機器審査第一部　審査役代理
桜井　淳	医療機器審査第一部　審査専門員
大内　貴司	医療機器審査第一部　審査専門員
竹下　康平	医療機器審査第一部　審査専門員
高橋　彩来	医療機器審査第一部　審査専門員
宮崎　生子	規格基準部　部長
松岡　厚子	規格基準部　医療機器基準課　テクニカルエキスパート

事務局

新見　伸吾	国立医薬品食品衛生研究所　医療機器部長
宮島　敦子	国立医薬品食品衛生研究所　医療機器部　室長
迫田　秀行	国立医薬品食品衛生研究所　医療機器部　主任研究官

Ⅱ　議事概要

平成２６年度　次世代医療機器・再生医療等製品評価指標作成事業
生体吸収性ステント審査ワーキンググループ　第１回会議　議事概要

開催日時：平成２６年８月２５日（月）１５：００－１７：１５
開催場所：ＴＫＰ品川カンファレンスセンター　カンファレンスルーム４Ｄ
（東京都港区高輪３－２６－３３　京急第１０ビル）

出席者（敬称略）
委員　　　：岩﨑清隆（早稲田大学）、新家俊郎（神戸大学）、中澤学（東海大学）
中村正人（東邦大学）、挽地裕（佐賀大学）、宮内克己（順天堂大学）
山岡哲二（国立循環器病研究センター研究所）、山本玲子（物質・材料研究機構）
欠席委員　：なし
オブザーバ：松崎邦男、岡崎義光（産業技術総合研究所）
厚生労働省：金川幸紀、間々田圭祐（医療機器・再生医療製品審査管理室）
ＰＭＤＡ　：方眞美、相澤浩一、竹下康平、高橋彩来（医療機器審査第一部）
松岡厚子（規格基準部）
事務局　　：新見伸吾、宮島敦子、迫田秀行（国立医薬品食品衛生研究所）

配布資料
資料１　第１回ＷＧ会議議事次第
資料２　次世代医療機器評価指標作成事業について
資料３　委員名簿
資料４　メーリングリストについて
資料５　生体吸収性ステントの開発状況
資料６　厚生労働省平成 15 年 9 月 4 日付通知「冠動脈ステントの承認申請に係る取扱いについて」
資料７　FDA ガイダンス「Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems」(2010/4/18)
資料８　FDA ガイダンス「Coronary Drug-Eluting Stents – Nonclinical and Clinical Studies DRAFT GUIDANCE」(2008/3/26)
資料９　評価項目対応表
資料１０　COI について

参考資料　平成 24 年度　次世代医療機器評価指標作成事業　重症下肢虚血分野審査 WG 報告書

概要
配布資料の確認に引き続き、厚生労働省より挨拶及び事業説明があり、当事業での成果は順次

通知という形になり実際の審査で活用されていることなどが紹介された。

座長挨拶及び各委員の自己紹介に引き続き、委員より情報提供があり、以下のような内容の報告があった。

中村座長「DES と比較して期待される BVS のメリットと懸念材料」

ステント治療は手技成功率が高いものの、再狭窄が問題であったため、薬剤溶出性ステント（DES）が開発された。しかし、DES では遅発性のステント血栓症のリスクが残ること、新規の動脈硬化が形成する可能性があり、しかも通常の Bare Metal Stent より早期に生じる可能性があることが指摘されている。また、永久に残存することから、破断の可能性や、血管の形態への影響、血流への影響等が永続的に残り、これらが有害事象につながる危険性がある。生体吸収性ステントでは、このような長期のリスクがなく、追加で処置が可能である等のメリットがある。一方で、強度不足、強度が維持される期間が不明なこと、厚さ、過拡張による破損の可能性、DES より長期の抗血栓剤投与の必要性、視認性の悪さ等が欠点として挙げられる。

中澤委員「報告されている pre clinical study の成績」

動物モデルは臨床の結果を予測するものであるが、モデルの選択と観察のタイミングにより、差がなくなってしまう場合があるので注意が必要である。DES では、豚を使用したモデルで 1 年後に炎症反応が見られ、晩期の評価に活用できる。ウサギを使用したモデルで、内皮化の良否が評価でき、遅発性血栓症の発生頻度とも関連性が見られる。吸収性ステントは、ウサギを使用した試験で、消失するまでにおよそ 4 年かかることがわかっている。動物モデルでは、吸収過程及び生体反応の評価ができるが、動物における生体反応は人間のおよそ 6 倍の速度であり、一方吸収速度は変わらないと考えられることから、注意が必要である。

新家委員「報告されている imaging の成績」

Imaging の手法としては、OCT（光干渉断層法）、IVUS（血管内超音波検査）、CAG（冠動脈造影）、MSCT（マルチスライス CT）、MRI（核磁気共鳴画像法）、Angioscopy（血管内視鏡）等がある。このうち OCT は、分解能が 10-20 um であり、吸収性ステントの観察に適している。吸収性ステントと DES の臨床成績を比較すると、吸収性ステントでは急性期合併症の発生率が高い可能性があり、その原因としては、デリバリーの困難さが考えられる。過拡張すると破損のリスクがあるため、圧着が不十分になる場合がある。オーバーラップができない、側枝の閉塞リスクが高いという問題が指摘されている。血管径にあったサイズを選択し、前拡張や後拡張を適切に行う必要がある。ポリマー製吸収性ステントでは造影で撮影しても写らないが、OCT では圧着不良等の確認が可能である。

山岡委員「ポリマー系吸収性材料について」

吸収性ステントの応用部位としては、血管、気管、食道、消化管、胆管等が考えられている。血管ステントへの適用としては、DES の薬剤溶出部分への適用、全吸収性ステント、ステントグラフト、カバードステントが考えられている。強度不足が最大の課題である。繊維状にすると配向化等により強度を出しやすいが、繊維を編んで機器を作製すると、オーバーラップした部分で内膜肥厚が起き、問題となる。ポリマーは溶けてなくなるイメージではなく、分子量が落ちて構造が壊れても、物質自体は長期間残存する。残存物は炎症反応の原因になる他、血中

への流出の危険性や、血栓症の原因になる可能性がある。その他のポリマー系吸収性ステントの問題点としては、分解産物による生体反応、クリープによるRadial forceの低下、強度不足を補うためのストラットの厚さが考えられる。

山本委員「メタル系吸収性材料について」

メタル系吸収性材料としては、マグネシウム合金、純鉄、鉄合金、純亜鉛が研究されている。マグネシウム合金は、血管ステントや骨接合材としての応用が検討されており、ステントの臨床試験も行われている。吸収速度が速いことが課題である。マグネシウムイオンは血中濃度が高く、排泄速度も速いため、毒性の問題はないと思われるが、他に添加されている金属の毒性については情報が乏しく注意が必要である。純鉄はステントの動物試験が行われたが、吸収速度が遅く、血中ではイオンとしてほとんど存在しないため、さびが沈着するなどの問題がある。純亜鉛はワイヤーの埋植試験が行われたところである。不純物により炎症反応が出たり、分解速度に影響が出たりする可能性がある。ガイドラインや規格で定められたin vitroにおける金属の溶解試験法では、生体内での金属の腐食反応の機構を再現していない場合があり、注意が必要である。

情報提供に関連して質疑応答があった後、座長より、本ワーキンググループでは冠動脈を中心とした血管ステントを対象とすること、ポリマー製及び金属製の吸収性ステントを対象とし、骨格が残るものは対象としないこと、薬剤を含む製品は対象とするが、薬剤部分の評価は対象外とすることが提案され、了承された。また、製品開発が企業を中心に行われていて情報が乏しく、情報収集が必要であることから、本年度は情報収集を行い、来年度末の評価指標案の作成を目指すことが提案され、了承された。

初めて臨床試験を行う際にはリスクを伴うため、小規模な臨床試験（Feasibility study）を行ってから大規模な臨床試験（Pivotal study）を行うことが一般的であるとの指摘があった。従って、検討すべき評価項目としては、非臨床試験、動物実験、小規模臨床試験、大規模臨床試験で構成されることになるとの意見があった。また厚生労働省より、薬事法改正に伴い市販後調査における評価項目についても検討をお願いする可能性があることのコメントがあった。

今年度の会議日程を、10月20日（月）及び12月15日（月）の15時30分から17時30分として、会議を終了した。

平成２６年度　次世代医療機器・再生医療等製品評価指標作成事業
生体吸収性ステント審査ワーキンググループ　第２回会議　議事概要

開催日時：平成２６年１０月２０日（月）１５：３０－１７：２０
開催場所：ＴＫＰ品川カンファレンスセンター　カンファレンスルーム４Ｆ
（東京都港区高輪３－２６－３３　京急第１０ビル）

出席者（敬称略）

委員　　　：岩﨑清隆（早稲田大学）、新家俊郎（神戸大学）、中澤学（東海大学）
中村正人（東邦大学）、挽地裕（佐賀大学）、宮内克己（順天堂大学）
山岡哲二（国立循環器病研究センター研究所）、山本玲子（物質・材料研究機構）

欠席委員　：なし

オブザーバ：花田幸太郎、岡崎義光（産業技術総合研究所）

厚生労働省：近藤英幸（医療機器・再生医療等製品審査管理室）

ＰＭＤＡ　：方眞美、相澤浩一、桜井淳、竹下康平、高橋彩来（医療機器審査第一部）
松岡厚子（規格基準部）

事務局　　：新見伸吾、宮島敦子、迫田秀行（国立医薬品食品衛生研究所）

配布資料

資料１　第２回ＷＧ会議議事次第

資料２　第１回議事概要（案）

資料３　厚生労働省 平成 20 年 4 月 4 日付通知「次世代医療機器評価指標の公表について」別添 1「次世代型高機能人工心臓の臨床評価のための評価指標」

資料４　ワークショップ資料（ASTM-FDA Workshop on Absorbable Medical Devices: Lessons Learned from Correlations of Bench Testing and Clinical Performance (2012/11/28)、Workshop Standardization of Absorbable Metals for Medical Devices (2013/11/4)）

資料５　評価指標案の項目のイメージ（たたき台）

資料６　報告書構成（案）

概要

配布資料の確認に引き続き、前回会議議事概要の確認を行った。1 か所の修正を行い、会議の終了をもって了承となった。

引き続き、委員より情報提供があり、以下のような内容の報告があった。

挽地委員「臨床的観点から考えられる構造的問題点」

慢性完全閉塞の場合には、吸収性ステントでは充分な Radial force が得られるか不安がある。急性心筋梗塞の場合には、再灌流させると血管径が次第に大きくなることから、不完全圧着が生じる可能性がある。これに対して過拡張をすると破損する可能性があるため、サイジングが

難しい。吸収性ステントを留置後数か月以内に、末梢側に対して追加治療を行うと、先に留置していた吸収性ステントが動く可能性があることが報告されている。CT により観察ができないため、慢性期の評価方法が課題である。

分岐部に吸収性ステントを設置した場合、ステントのストラットが何らかの組織に覆われる。ストラットの間隔が狭いと、膜状になり（Neointimal bridge）、側枝の入り口が狭くなる場合がある。そこで、ステント留置後、側枝に向かって拡張をすることが考えられるが、吸収性ステントでは破損を生じる可能性がある。

岩崎委員「in vitro 実験系について」

金属製ステントで使用される金属材料に比べると、吸収性ステントで使用されるポリマーでは、引張強度は数%程度、破断伸びは数%から十数%程度である。従って、吸収性ステントでは不完全圧着や破断のリスクが金属製ステントより高く、血栓症や、血管拡張保持力の低下が生じるリスクがあると考えられる。血管を模擬した透明のファントムを使用することにより、不完全圧着や、過拡張による破断、リコイルの評価などが可能である。テーパ血管に留置する場合の径の差の許容範囲や適切なステントサイズの選択の評価も必要と思われる。実臨床では側枝の拡張が必要になる可能性があることから、側枝の拡張の影響も評価しておくべきである。生体吸収性ステントに特有の評価試験法としては、狭窄血管モデルでの経時的な拡張保持力性能評価試験や、生理的拍動数や溶液、流れ環境を再現した耐久性評価試験が考えられる。

情報提供に関連して質疑応答及び討論を行った。Radial force の評価については、金属製ステントを対象とした現行の試験法では不十分で、検討が必要との意見があった。過拡張による破損を防ぐため、拡張限界についてしっかり評価すべきとの意見があった。Neointimal bridge については、最近になってようやく観察が可能になったものであり、まだ情報が不足している、また、動物実験による再現も容易ではないとの意見があった。側枝の拡張が臨床上必要になる可能性があることから、側枝の拡張限界について何らかの評価はしておくべきとの意見があった。

金属製ステントの疲労強度評価は加速して行っているが、吸収性ステントの場合は、実時間で行うことになるとの意見があった。また、吸収性ステントに加わる力により分解速度に影響があるとの指摘があった。ステントが破損した場合、その時期、破損する場所、破損した後の形状も重要との意見があった。

続いて、2012 年に FDA で開催された吸収性の医療機器に関するワークショップについて紹介があった。インターネットからプレゼンテーションの内容が見られることから、各自が関係すると思われるところを確認して頂き、FDA のワークショップで問題となっている点及び検討事項について次回会議で要約して頂くことになった。

報告書の構成案について確認し、各委員の執筆内容について、次回の会議で紹介して頂くことにした。報告書の原稿締め切りは、2 月 15 日とした。

今年度の会議日程を、12 月 15 日（月）の 15 時 30 分から 17 時 30 分と確認して、会議を終了した。

平成２６年度　次世代医療機器・再生医療等製品評価指標作成事業
生体吸収性ステント審査ワーキンググループ　第３回会議　議事概要

開催日時：平成２６年１２月１５日（月）１５：３０－１７：００
開催場所：ＴＫＰ品川カンファレンスセンター　カンファレンスルーム４Ｆ
（東京都港区高輪３－２６－３３　京急第１０ビル）

出席者（敬称略）
委員　　　：岩崎清隆（早稲田大学)、新家俊郎（神戸大学)、中澤学（東海大学）
中村正人（東邦大学)、挽地裕（佐賀大学)、宮内克己（順天堂大学）
山本玲子（物質・材料研究機構）
欠席委員　：山岡哲二（国立循環器病研究センター研究所）
オブザーバ：花田幸太郎、岡崎義光（産業技術総合研究所）
厚生労働省：金川幸紀（医療機器・再生医療等製品審査管理室）
ＰＭＤＡ　：相澤浩一、桜井淳、大内貴司、高橋彩来（医療機器審査第一部）
事務局　　：新見伸吾、宮島敦子、迫田秀行（国立医薬品食品衛生研究所）

配布資料
資料１　第３回ＷＧ会議議事次第
資料２　第２回議事概要（案）
資料３　ワークショップ資料（ASTM-FDA Workshop on Absorbable Medical Devices: Lessons Learned from Correlations of Bench Testing and Clinical Performance (2012/11/28)）
資料４　報告書構成（案）
資料５　生体吸収性材料関連規格リスト
資料６　ISO/TR 37137:2014 Cardiovascular biological evaluation of medical devices - Guidance for absorbable implants（抜粋）
資料７　ISO/TS 17137:2014 Cardiovascular implants and extracorporeal systems - Cardiovascular absorbable implants（抜粋）
資料８　ASTM ASTM F3036 - 13 Standard Guide for Testing Absorbable Stents（抜粋）
（当日配布）宮内委員プレゼンテーション資料

概要
配布資料の確認に引き続き、前回会議議事概要の確認を行った。特にコメントはなく、会議の終了をもって了承となった。
引き続き、PMDA 及び委員より情報提供があり、以下のような内容の報告があった。
PMDA 高橋様「生体吸収性ステントの審査について」
医療機器の審査は一般的に、製品のコンセプトの確認、製品の特性や性能設計の確認、製品

のコンセプトの実現の確認という流れで行われている。その中でまず確認するのが、その製品の臨床的位置づけである。具体的には、既存製品等と比較して、予想されるベネフィットとリスクとしてどのようなものがあるか確認を行う。例えば、生体吸収性ステントの場合は、薬剤溶出型ステントとの比較が考えられる。

次に、これらのベネフィットとリスクを正確に見積もる。ベネフィットは臨床的アウトカムが既存製品に対し非劣性であることを示す必要がある。また、製品特有のコンセプトがある場合は、期待される臨床的ベネフィットを確認する必要がある。安全性については、既存製品と比べ大きく劣らないことが大前提だが、既存製品に劣る場合は臨床的アウトカムの向上又は新たな臨床的ベネフィットの検証必要になる。

非臨床評価では、安定性や生体適合性の確認が必要と思われる。また、材料の特性や分解機構、吸収過程を考慮したベンチ試験や動物試験等が必要となると思われる。基本的性能は非臨床試験で評価し、臨床試験では手術の成功、吸収性ステントの物性及び生体反応による影響、再治療時の有害事象等について評価を行うことになると思われるが、非臨床評価と臨床評価の切り分けは難しい問題と思われる。また、材料により生体反応は異なるため、試験系の統一や規格値の設定は難しいと思われる。

宮内委員「BVS (Biodegradable Vascular Scaffolding) Clinical Trial」

生体吸収性ステントの臨床試験としては、ABSORB という一連の臨床試験が行われており、先行した一部の試験において結果が出ている。安全性の Clinical Endpoint としては、MACE（Major Adverse Cardiac Events）、TLF（Target Lesion Failure）、TVF（Target Vessel Failure）が用いられている。最初の臨床試験（Cohort A）における MACE は 5 年で 3.4 %で既存製品とほぼ同等であり、基本的な安全性は担保されたと言える。ただし、単群試験或は歴史的対照を使用していること、単純病変を対象としていることなどに注意が必要である。

一方、生体吸収性ステントでは、設置後 3 年から 5 年で血管が広がることが報告されており、生体吸収性ステント特有のベネフィットである可能性がある。

続く臨床試験（ABSORB EXTEND）では、より複雑な病変も対象とし、歴史的対照を使用して試験を行っている。3 年の観察により、安全性について非劣性が示されている。

続く臨床試験（ABSORB II）では、薬剤溶出型ステントを対照とした臨床試験で、試験治療患者と対照治療患者を 2：1 で割り付けている。1 年の結果で非劣性が示されている。また、狭心症の発生が有意に低下しており、吸収性ステント特有のベネフィットである可能性がある。狭心症の発生を主評価項目とした臨床試験も始まっている。

ヨーロッパでは認可されたため、レジストリーが稼働している。30 日以内の血栓症が多い等、従来の臨床試験の結果に比べ有害事象の発生率は高いようであるが、既存製品と比べ大きく上昇しているわけではないようである。

情報提供に関連して質疑応答及び討論を行った。30 日以内の血栓症については、ラーニングカーブがある可能性が指摘されているとの意見があった。また、症例選択により成績向上の可能性もあるのではないかとの意見があった。

次に、FDA で開催された吸収性の医療機器に関するワークショップについて、委員より以下の

ような内容の調査報告があった。
山岡委員（事務局代読）

吸収性ポリマーについては、縫合糸を対象とした規格等の文書があるがステントについての記載は無い。分解性についてはポリマー材料ごとに文書があるが、その試験方法に関するコンセンサスは特にない状況である。ポリマーの分解性には様々な因子が影響し、定量的な相関性もないため、材料ごとに評価する必要がある。形状や動き、応力等も分解性に大きな影響を与える。

山本委員

金属材料の製造工程によっても分解特性は影響を受ける。リン酸緩衝水溶液を使用した試験結果の報告があったが、生体内環境を十分模擬できているとは言えない。標準材料の作製の提案もあったが、分解特性には不純物の影響が大きく、品質管理が困難なため、議論は進んでいない。また、ドイツで 2013 年 11 月に開催された吸収性メタル医療機器に関するワークショップの内容について問い合わせをしたが、情報は得られなかった。

岩崎委員

吸収性ポリマーでは、応力負荷環境下の方が分解速度は速くなる。ステントの場合は、流れや拍動の影響を考慮する必要がある可能性がある。温度を上げると分解速度は上昇する。加速試験としての妥当性については、検証が必要と思われる。

続いて、報告書の構成案及び原稿締め切り（2 月 15 日）を確認した後、来年度の活動方針について議論を行った。ISO 及び ASTM 規格の紹介があった。報告書の作成作業終了後、今年度の議論及びこれらの資料を参考にしながら項目出しを行い、来年度一年をかけて評価指標案を作成することとし、会議を終了した。

Ⅲ　委員報告

Ⅲ－１　DES と比較して期待される BVS のメリットと懸念材料

東邦大学医療センター　大橋病院
中村　正人

１．はじめに

冠動脈インターベンション（percutaneous coronary intervention、PCI）の歴史は常に限界への挑戦であるが、この歴史の中の一里塚といえばステントの登場、薬剤溶出性ステント（drug eluting stent、DES）の登場であろう。そして、生体吸収性ステント（bioabsorbable stent）によって新たなページが書き加えられようとしている。

PCI の歴史は 1970 年代後半、バルーン拡張術によってはじまり、この時代を経ていわゆるニューデバイス時代へ至った。このニューデバイス時代には各種デバイスが開発され臨床応用がすすめられたが、この中で最終的に勝ち残ったのがステントであった。この 30 年間ステントを中心として開発がすすめられてきたといっても過言ではない。また、この時期には定量的な冠動脈造影が標準となり、デバイス間の優劣がサイエンティフィックに論じられることになった。ステントによって再狭窄のリスクは著しく軽減したものの、ステント留置後に生じるステント再狭窄は依然として 20-10%に見られ、PCI のアキレス腱と称された。この再狭窄の問題を解決するための開発がすすめられ DES が誕生した。最初に登場したのは sirolimus eluting stent（SES）であるが、2000 年より開始された最初の多施設比較検討試験 RAVEL[1)]では再狭窄率、late loss、ステント血栓症すべて“ZERO”であったことからゼロトライアルとも称され、その成績に世界は驚愕した。すべてが解決されたと思われた瞬間であった。しかし、適応が拡大されると様々な問題がクローズアップされることになり、DES 自体の改良が、重ねられた。また、金属が体内に遺残しないステントの開発も進められ実臨床での使用が始まっている。完全に生体吸収されるステントは理論的には非常に多くの利点を有すると考えられる。一方、吸収される過程で従来のステントとは異なった事象が生じることも懸念される。したがって、従来のステントとは異なった審査が必要となるであろう。このため、本邦における生体吸収性ステントの評価指標を作成することを目的として、本評価指標作成ワーキンググループ（WG）が立ち上がった。

２．DES 開発の軌跡と問題点

当初、DES 最大の関心事はベアメタルステント（bare metal stent、BMS）よりもステント血栓症のリスクが著しく高くなるのではないかという懸念であった。実際、そのリスクについての報告が相次いだ。剖検例による病理学的検討からは、内皮化の遅延および不均一な内皮化、ポリマーに対する過敏反応、mal-apposition、内皮機能障害などが報告された。これらの現象は、いずれも超遅発性ステント血栓症の誘因となりえるものであった。また、ステントの内側に生じる

新たな動脈硬化病変（neoatherosclerosis）は、DES では BMS よりも早期により高頻度に認められると報告された。このような内皮化障害を背景とした病態が DES の一つの懸念材料である。一方、DES によって高度屈曲病変、長区間のびまん性病変など複雑病変を積極的に治療するようになると、BMS 時代にはあまり問題とされなかったステントの破断、血管 geometry の変化が新たな問題として浮かびあがった。このため、これらの点を改善するための開発がすすめられ第 2 世代 DES が誕生した。その進化は、主としてポリマーの生体適合性ならびに抗血栓性の改良と、材質、プラットフォームの改良と言える（図１）。

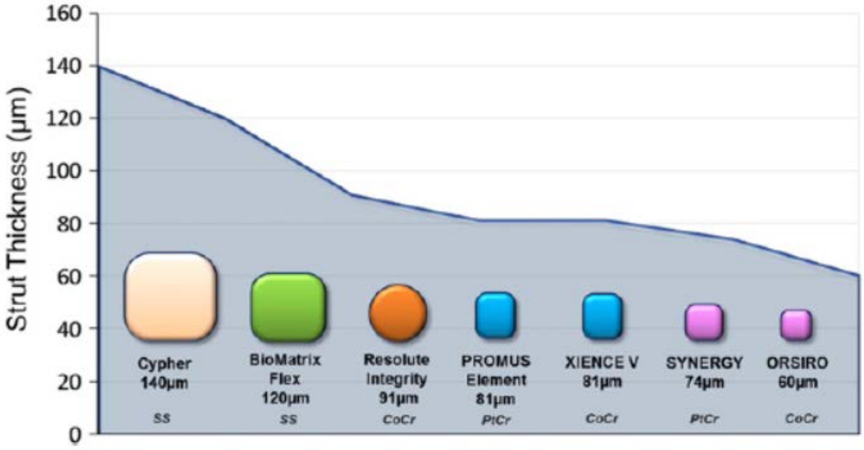


図１　ステントストラットの比較[2]。DES は材質の改良によってより金属量の少ない、薄いストラットのステントになってきている。結果、構造の改良と相まってステントの血管追従性は著しく改善された。

血管追従性の改良によって複雑病変へのアプローチがより簡便になり、ステント破断などのリスクも著しく軽減された。しかし、ステント破断の問題はステントが金属である以上完全に解決することは困難である（図２）

ポリマーの改良によってステント血栓症の懸念も払しょくされた。急性冠症候群のような血栓が関与する病態であっても DES のほうが BMS よりもステント血栓症のリスクが低いと報告されている（図３）。

次なる改良は、生体吸収性ポリマーの登場である。安定したポリマーであっても過敏反応を惹起するリスクは皆無でないということから、生体吸収されるポリマーによる DES の開発が進められ、今後はこの種の DES が主流になると予想されている。

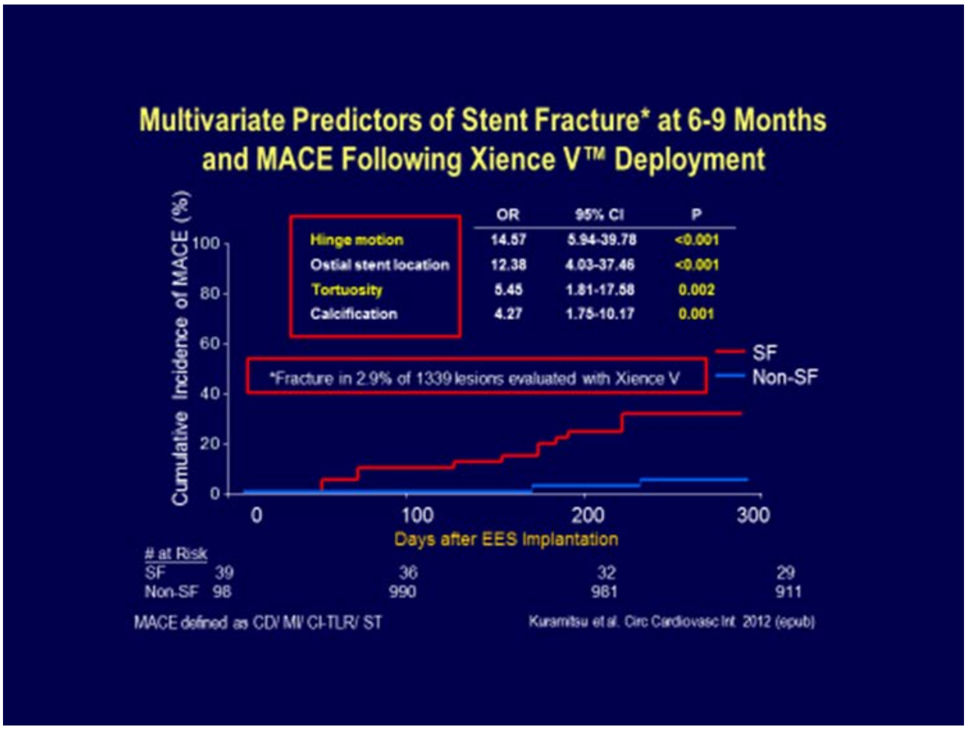


図２　第２世代の DES であっても、ステント破断はあり、その場合のイベントリスクは高くなる[3]。

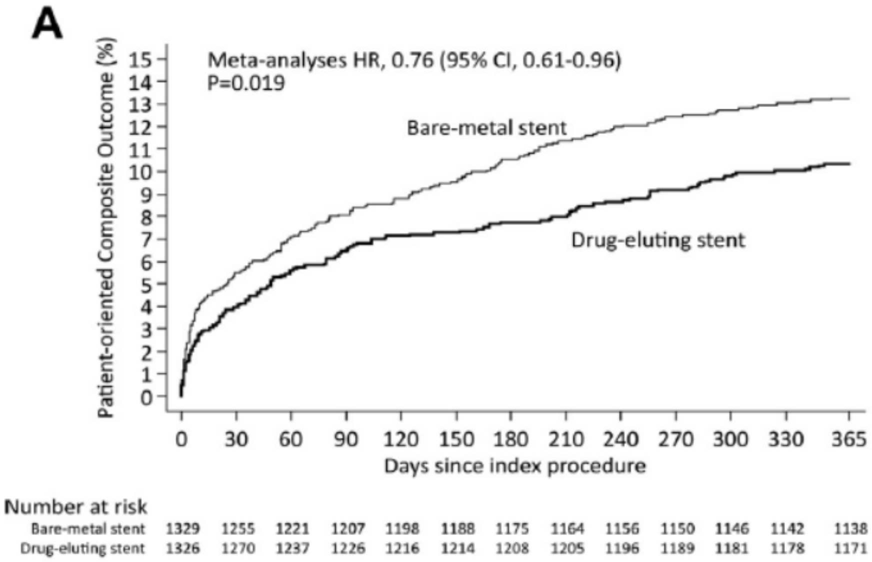


図３　心筋梗塞に対する BMS と DES; メタ解析の結果[4]。DES は BMS よりも安全性が優れている。

３．生体吸収性ステント開発の原動力

薄いステントストラット、生体吸収性ポリマー、薬剤量の減量と DES の開発は急速に進み、金属アレルギー、late catch up、ステントの破断、超遅発性ステント血栓症などのリスクは著しく低減した。しかし、金属が残存するため完全に解決されたわけではない。また、バイパス吻合の妨げになる、再治療の妨げになるなどの問題点も残存する。このため、完全に生体で吸収性されるステントの開発がすすめられた。コンセプト自体は決して最近のものではないが、臨床使用には限界があるとされ開発はストップしていた。しかし、薬剤溶出の技術と統合することによって一気に現実的なデバイスとして再度注目されることになった。異物が残らないことにより想定されるメリットとしては下記の項目が挙げられる。最大の差異は血管反応性を保持できるか否か、血管反応性保持による長期的なイベント回避の可能性であろう。動脈硬化は血管の shear stress と関係し、pulsatile で周期的な血流は血管の安定に関係するからである。

１）超遅発性ステント血栓症、遅発性ステント血栓症のリスク軽減
２）永続的な側枝閉塞のリスク軽減
３）Late catch up がない
４）ポリマーや金属に対する慢性炎症が少ない
５）mal-apposition、neoatherosclerosis の軽減
６）血管の geometry を維持して、新規病変の発現を減ずる
７）血管内皮機能の温存、vasomotion の温存
８）造影 CT など検査の妨げにならない
９）外科手術の妨げにならない
１０）次の PCI の妨げにならない
１１）内腔の拡大、血管の代償性リモデリング
１２）狭心症の軽減

４．生体吸収性ステントで懸念されること

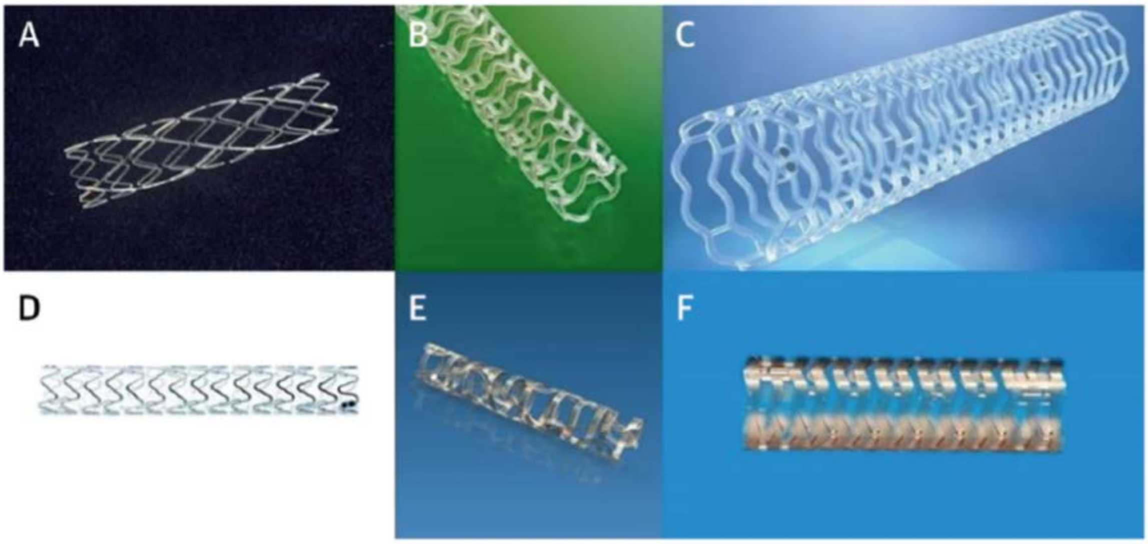
生体吸収性ステントは狭窄病変を拡張する医療機器であるため、血管の弾性収縮に抗してある一定期間血管を保持する能力が要求される。血管保持の必要性がなくなった後には吸収され、異物による副作用のリスクが消失する。これが理想の姿である。したがって、生体吸収性ステントであっても十分な radial force が必要であり、吸収の過程でステントの integrity が問われる。したがって、吸収のスピードが適切でないと早期の合併症が増加する。ステント破断は radial force を失うことになり、DES と同様に再狭窄の頻度、ステント血栓症の頻度が高くなるものと考えられる。ステント破断は様々な局面で想定される。ステントの拡張限界を超えて過拡張した場合、側枝を拡張してステントの構造が変形した場合、石灰化病変などでステントが不均等に拡張した

場合などである。吸収される過程でステントが破断した場合、末梢塞栓を生じないかといった懸念もある。Radial force を維持するためステントのストラットが厚くなるが、PCI 手技自体の難易度が高くなり、不十分拡張のリスクが高まる。ステントストラットが厚い場合には側枝閉塞、周術期心筋梗塞のリスクも高くなる。ポリマーによる生体吸収性ステントでは視認性が劣るため、over-lap させ複数のステントを留置することが困難であろうし、ステントのストラットが厚いとオーバーラップ部位ではさらに２重で厚くなる。現状、これら新規デバイスが不向きな病変は①静脈グラフト、②高度石灰化病変、③抗血小板薬２剤併用療法（dual antiplatelet therapy、DAPT）の継続服薬が不可能、④術前血流が TIMI＜3 などが指摘されている。

５．現在、臨床使用されている生体吸収性ステント

現在、20 社以上が臨床応用をめざし、開発を進めている。生体吸収性ステントは用いられる材料によって、①ポリ乳酸（poly lactic acid、PLLA）と co-polymer、②Thyrosine polycarbonate、③金属に大別される。最も応用が進んでいるのが PLLA であり、次いで応用されているのがマグネシウム合金による生体吸収性ステントである。その他に polylactic anhydride などが試みられている。なお、個々のデバイスによって光干渉断層法（optical coherence tomography、OCT）などのイメージング像も異なる。

現在、臨床が試みられている吸収性ステントの構造を図４に示す。



Different materials are currently used for bioresorbable scaffold (BRS). The Igaki-Tamai stent (Kyoto Medical Planning Co., Ltd., Kyoto, Japan) **(A)**, the ABSORB Bioresorbable Vascular Scaffold (Abbott Vascular, Santa Clara, California) **(B)**, and the DESolve bioresorbable scaffold (Elixir Medical Corporation, Sunnyvale, California) **(C)** are all manufactured from poly-L-lactic acid. The DREAMS magnesium alloy (Biotronik, Berlin, Germany) **(D)** is a metal bioresorbable vascular scaffold. The ReZolve 2 BRS (Reva Medical Inc., San Diego, California) **(E)** is produced on a desaminotyrosine polycarbonate basis, and the Ideal BioStent (Xenogenics Corp., Canton, Massachusetts) **(F)** is composed of a salicylate polymer and linker.

図４　現在臨床応用されている生体吸収性ステント[5)]。

６．本審査 WG における検討対象

生体吸収性ステントは、食道、肝胆膵などの管腔臓器と冠動脈、末梢動脈など血管ステントがありえるが、本審査 WG では冠動脈ならびに末梢動脈に対する血行再建治療のための医療機器を対象とした。また、構造物が完全に吸収され、消退する医療機器を対象とした。したがって、生体吸収性ポリマーを用いた DES は、ポリマー消退後に金属製のステントが残存するため対象に含まれない。また、一定期間血管を保持ずる能力を有するもの（ステント）が対象であり drug coated balloon（DCB）も対象しないこととした。

この新たなデバイスは、従来の金属ステントとまったく異なった効果が期待される。それは、主として長期的なメリットである。一方、主な欠点は構造や材質に伴うものであり、固有な合併症、手技に伴うものを含め比較的短期的に出現する。したがって、新たな視点にたった preclinical データが必要であり、基本的性能を臨床導入前に如何に評価するかが問われる。また、臨床試験におけるチェックすべき観察項目も従来の DES とは異なったものが必要であろう。

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Ⅲ－２　材料（ポリマー）

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山岡　哲二

１．生体吸収性医療機器

ポリ乳酸などのポリαヒドロキシ酸を基本構造とした生体吸収性縫合糸の国内市場は約 200 億円と大きい。非吸収性縫合糸の約２倍の市場を有しているにもかかわらず、その９割が輸入品であり、国内での規制整備は進んでいない。図１にポリαヒドロキシ酸の化学構造を示した。その分解特性は、何れも非酵素的加水分解であるが、化学構造などにより分解速度は大きく異なる。1990 年はじめに報告された組織工学的手法を用いた軟骨再生においても、生体内安全性が担保されていたこれらの高分子の中で、ポリグリコール酸（図１中上段、R＝H）不織布がスキャホールドとして使用された。

同様の理由から、吸収性ステントの材料としてポリαヒドロキシ酸が注目されたのは納得できるが、生分解性に加えて、柔軟性、結紮性、破断強度、などの特性が要求される縫合糸と、血管拡張性維持のための持続的ラジアルフォースが要求されるステントでは、その要求特性が大きく異なることは明白である。しかしながら、そのストラット基本部材に関する規格でさえも、具体的参考資料となる規格やガイドラインは国内に存在しない。海外でも、同様に吸収性ステントに対するガイドラインの重要性が認識されており、近年、その整備作業が進みつつある。

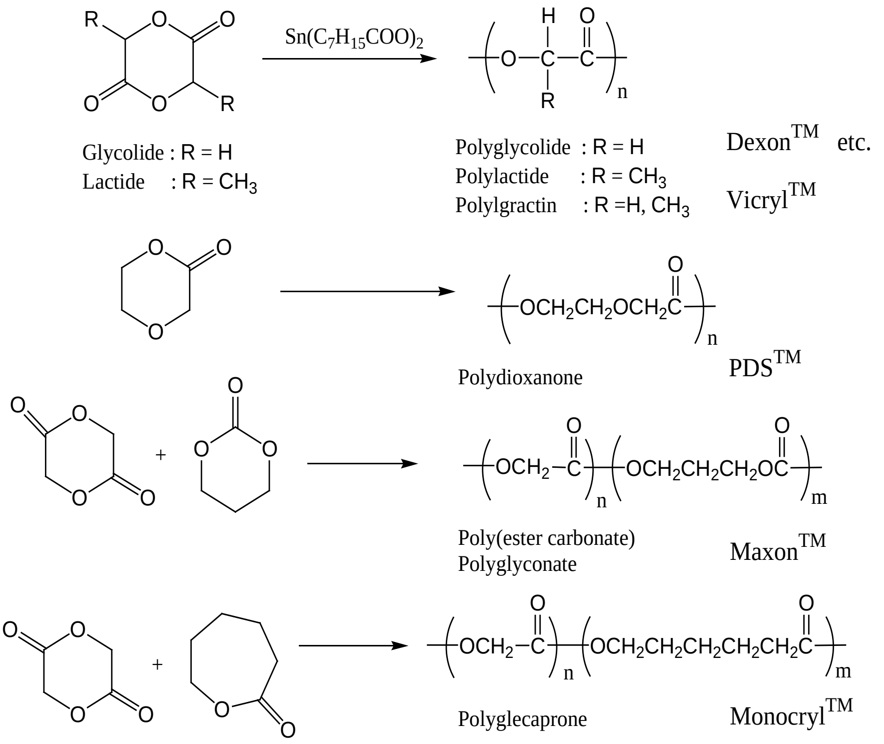

図１　生分解性縫合糸に利用されるポリ-α-ヒドロキシ酸

２．生体吸収性医療機器に関する規格

（１）JIS

吸収性医療機器に該当する JIS 規格は、腸線縫合糸（surgical sutures catgut）に関する JIS T4102 のみである。目標吸収期間を約 1 週間とした無加工 A 型から、特殊処理により吸収期間を 2、3、4 週間と制御した、B 型、C 型、D 型と、その素材と吸収速度に関する規格である。吸収期間とは、腸線が体内で吸収され、縫合目的を失うまでの期間であり、したがって、体内に物質が残存している状況である。その他、繊維径、引っ張り強さ、結び目の引っ張り強さ、包装などが記載されている。

（２）ISO

ISO では生体吸収性ステントの規制に関連すると考えられるものが幾つか存在する。ISO10993-6（Framework for identification and quantification of potential degradation products）では、吸収性か非吸収性にかかわらず、塊状体、多孔質体、液体、ペースト、微粒子などを埋入した際の局所反応の評価法に関して記載されている。また、分解性であるがゆえに局所反応だけでは不十分であることから、分解産物の体内への拡散を考慮して、分解性材料埋入時の全身反応試験法、あるいは、分解試験デザインが ISO10993-9 に記述されている。また ISO10993-13 では、生体模倣環境下での分解産物生成量の定量法などに関して言及されている。ISO/TS17137 では一般的な分解性材料に関する規制が記載されている。しかしながら、いずれの場合にもステントを対象としたものではなく、ステントが留置される生理的環境を十分に反映したテスト法を新たに策定する必要があり、ISO TC150/SC2/WG7（Cardiovascular absorbable implants）および、TC194 において同内容に関する検討が進んでいるので、継続的に情報を収集する必要がある。

（３）FDA-CFR[1)]

吸収性縫合糸に関しては、表 1 に示したようなレギュレーションが存在する。

表 1　吸収性縫合糸に関する FDA-Code of Federal Regulations

Absorbable Polydioxanone Surgical (PDS) Suture	21CFR§878.4840
Absorbable Poly(glycolide/L-lactide) Surgical Suture	21CFR§878.4493
Absorbable Gut Suture	21CFR§878.4830

（４）ASTM

ASTM F2902（Standard Guide for Assessment of Absorbable Polymeric Implant）においては、成形加工、デバイス物性、パッケージングや滅菌など基本的特性が、また、AFTM F1635 で

は、 in vitro 分解性テストに関して、さらに ASTM F1983 では、in vivo 生物学的安全性試験に関する標準化が進んでいるが、現状では吸収性ステントに特化されたものとはなっていない。

３．生体吸収性高分子の分解と国内での認可状況

（１）ポリ-α-ヒドロキシ酸の一般的分解特性

図１に示された生体吸収性高分子やその共重合体の分解挙動の研究は、古くから盛んに行われてきた。何れも、自然界では微生物分解や酵素的分解も報告されているが、生体内では非酵素的単純加水分解が中心である。分解に影響を与える材料側の要因として、図１に示したような化学特性（組成、分子量、表面特性）、物理特性（形状、結晶性、配向性、形状）、加工方法（吐出、遠心、アニーリング、溶媒キャスト、混合）、添加物（薬物、タンパク質、複合材料）などが知られている。ポリ乳酸（図１中、Ｒ＝CH_3）に比較してポリグリコール酸（図１中、Ｒ＝Ｈ）の分解速度は極めて大きく、その共重合組成により分解速度が調整可能であると同時に力学特定も大きく変化する。図２には、共重合体の一つである、乳酸-カプロラクトン共重合体の分解挙動を示した。分解速度の遅いポリ-ε-カプロラクトンとの共重合により、ポリ乳酸の分解は早くなる。これは、共重合による結晶性が低下するために、加水分解速度が上昇したためである。その他、分解試験に用いる環境の pH や温度など、分解条件が大きく影響する。

図２の縦軸は重量低下が示されているが、その分解による重量減少と強度低下は大きく異なる。一般的に、これらポリ-α-ヒドロキシ酸の分解挙動は、「溶解」のようなイメージではない。分子鎖の化学分解により、分解初期において材料にクラックが生じて力学強度が大きく低下する。続いて、図２に示すような重量低下が起こる。すなわち、生体吸収性ステントにおいては、ラジアルフォースが大きく低下した（あるいは消失した）後にも、血管内腔あるいは血管壁内に微細物質が残存して分解が継続するために、分子量低下、重量現象、力学強度低下、など多角的な指標から検討しなければ、ステントの機能性と、残存炎症性に与える影響を検討することは困難である。また、構造とこれらの分解挙動の一般的相関性は得られていないので、素材ごとにデータを取る必要がある。

（２）生体吸収性ステントの分解

Soares らは、図３のように、ステントの形状が分解に与える影響をシミュレートしている[2)]。特に応力集中部位や可動域での分解が加速され、ステント強度の支配要因となることから、上述の一般的分解試験とは異なる系の構築が必要である。

しかしながら、例えばステント形状に成形した後の in vitro、in vivo テストは煩雑かつ一般性に欠けることから、図４に示すような、加重下での in vitro テストの有効性を検証することが必要である[2)]。

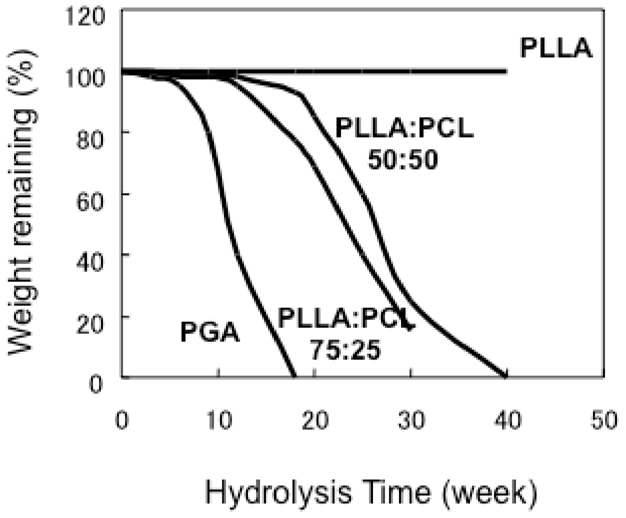

図２　ポリ乳酸、ポリグリコール酸、および、ポリ乳酸/ポリ－ε－カプロラクトン共重合体の共重合体の加水分解による重量低下

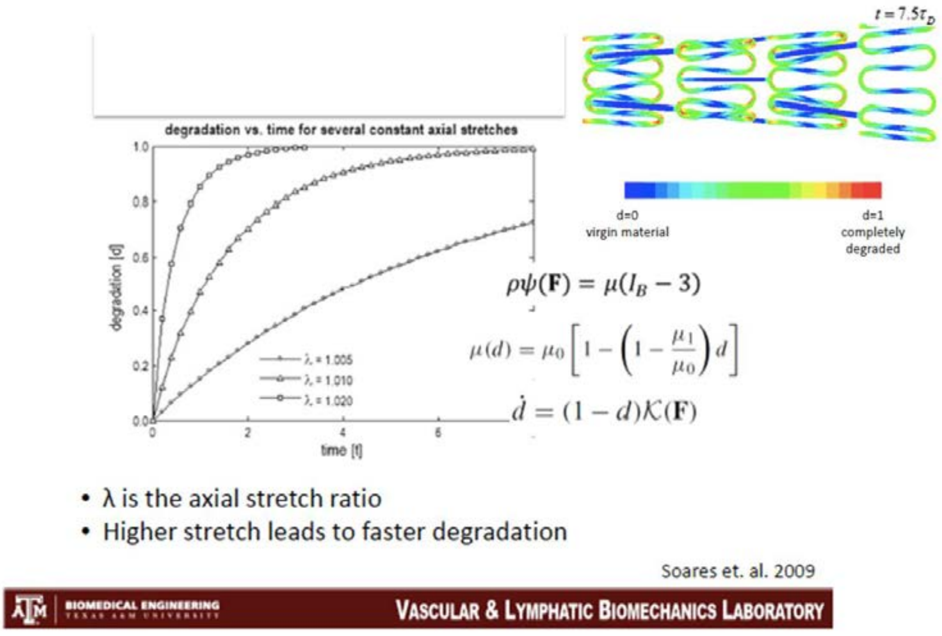

図３　ステントの形状が分解に与える影響の計算例[2)]

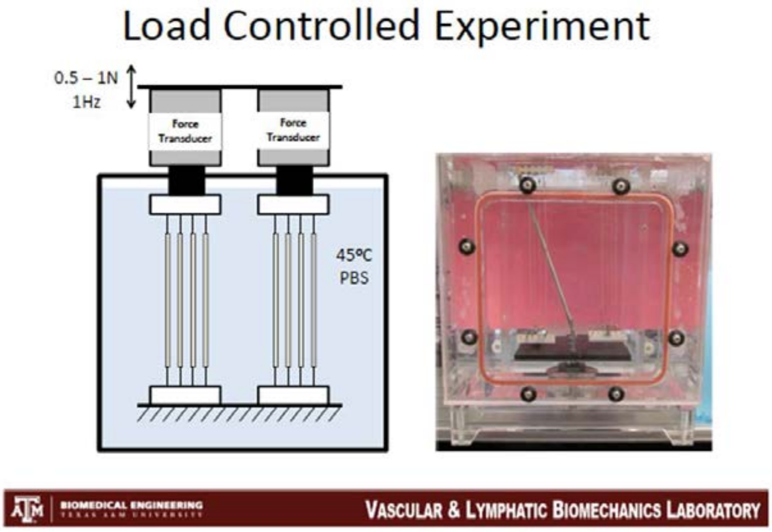

図４　加重下における分解試験の例[2)]

（３）国内で認可状況が公開されている分解性医療機器の例[3)]

以下の３例はPMDA開発前相談HPに審査報告書が公開されている例である。上述のごとく、国内では生体吸収性材料そのものに対する、規制などが整備されていないことから、これらの専攻する医療機器の許認可状況を集約する必要があろう。

A. ハイドロキシアパタイトとポリＬ乳酸との複合体からなる骨接合用スクリュー、ピン、ワイヤーがタキロン社から販売されているスーパーフィクソーブ™である。分解速度だけでなく分解により生じる粒状産物が周囲組織に与える影響についてもPMDAからの指摘も記されたようで、上述の局所生体応答として、ステントにも重要な項目であろう。

B. 最近、PGAを主体とする神経誘導管が東洋紡から販売された（ナーブリッジ™）。ISO10933-1に準拠した生物学的安全性試験を進めたようであるが、ポリαヒドロキシル酸重合時に用いられるスズ触媒の安全性も注目されている。

C. グンゼ株式会社は、ポリグリコール酸、あるいは、ポリ乳酸とポリカプロラクトンとの共重合体からなる埋入型医療機器を幾つか販売しているが、平成12年に人工硬膜を申請し、平成19年に承認されている（シームデュラ™）。先に欧州CEマークを取得していたが、かなりの一般的項目に関するデータが要求されたようである。

（４）リスク

ステントが分解性であるが故の大きなリスクファクターとしては、初期の急速な強度低下によるラジアルフォースの減弱あるいは消失が大きい。分解に伴う周囲組織のpH低下は、用いる物質量が小さいこと、分解が比較的遅いこと、血流に接していることから、その影響は極めて小さ

いと考えられるが定量的考察は必要であろう。さらに、分解産物が血管内腔皮に露出するか、血管壁内に埋没するかは、遠位での塞栓に繋がるリスクファクターとして考察する必要がある。

４．おわりに

分解性高分子の生体内利用においては、分解による医療機器としてのパフォーマンスの低下のみならず、分解中の分解産物顆粒などに対する生体反応も重要な検討要因である。複雑な形状に基づく、応力集中や継続的な動きによる分解加速現象も知られているが、全てを生体内で進める事は困難である。主に吸収性縫合糸に対して作成されてきた標準化仕様をベースにして、ステント独自の環境因子が分解等に与える影響を評価するための単純な in vitro 試験の標準化が必要と考えられる。

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Ⅲ－３　生体吸収性金属材料の現状と課題

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１．生体吸収性金属材料とその特徴

生体吸収性金属材料として純鉄やマグネシウム合金を適用する試みは、今世紀に入り冠動脈ステント応用を中心に本格化した。これまでに、生体吸収性金属材料としてマグネシウムおよびその合金、鉄およびその合金、亜鉛について検討が進められている。これらの金属材料には、１）生体必須元素であり、体内における存在量が比較的大きいため、溶出イオンが生体に及ぼす影響が小さいと期待されること、さらに２）純金属の標準電極電位は卑であり（表 1[1]参照)、水と反応して容易に腐食する、という特徴がある。２）の特性を生体内における分解性として利用するものである。

これらの金属（M）の水溶液中の腐食反応を以下に示す。

$$M + 2H_2O \rightarrow M^{2+} + 2OH^- + H_2\uparrow$$

鉄の場合、酸性溶液中では上記の反応が進むが、中性溶液では次のように溶存酸素がないと腐食しない[2]。

$$2Fe + 2H_2O + O_2 \rightarrow 2Fe^{2+} + 4OH^-$$

いずれの場合も腐食反応の進行に伴い OH^-が生じるため、溶液の pH が上昇する。それに伴い、腐食生成物[$M(OH)_2$：金属水酸化物]が金属表面を覆い拡散障壁層を形成するため、次第に腐食速度が低下する。すなわち、これらの金属の体内における分解速度は、埋入環境における腐食生成物の生成状況に依存する。

体液は種々の無機塩やアミノ酸・タンパク質等の有機物を含む溶液であり、その pH は部位により異なるがほぼ一定に保たれている。例えば血液の pH は主として炭酸緩衝系により、7.4 に維持されている[3]。大気中における炭酸ガス濃度は約 0.04％であるが、動脈血中の濃度は約 5%と 100 倍以上高い[3),4]。血中に溶け込んだ炭酸ガスは炭酸脱水素酵素の働きにより重炭酸イオンとの平衡状態にあり、血液の pH 恒常性維持に貢献している。一方、体組織中の酸素濃度は大気中の 1/4 以下である[4]。

体液中の無機塩・有機物は、これらの金属の腐食生成物形成に大きな影響を及ぼす。マグネシウムの腐食を例に説明すると、食塩水中では腐食の進行に伴い OH^-が生成し、溶液の pH が上昇する。すると、溶液中の溶解度が低下するため、水酸化マグネシウムが金属表面に析出（沈殿）する。このときの pH は 11 から 12 である。しかし、血漿と同等組成の疑似体液中では、より難溶性のリン酸塩、炭酸塩が pH8 前後で析出する。したがって、マグネシウムの疑似体液中の腐食速度は血漿と同濃度の食塩水中の約 1/50 である[5]。しかし、血流等によって溶出イオンが金属表

表１　各種金属の標準電極電位[1)]

元素名	電極反応	標準電極電位（V vs SHE）
金	$Au^{3+} + 3e^- \rightarrow Au$	1.50
白金	$Pd^{2+} + 2e^- \rightarrow Pd$	0.987
水銀	$Hg^{2+} + 2e^- \rightarrow Hg$	0.854
銀	$Ag^+ + e^- \rightarrow Ag$	0.800
銅	$Cu^{2+} + 2e^- \rightarrow Cu$	0.521
水素	$2H^+ + 2e^- \rightarrow H_2$	0.00（基準）
すず	$Sn^{2+} + 2e^- \rightarrow Sn$	-0.136
ニッケル	$Ni^{2+} + 2e^- \rightarrow Ni$	-0.250
コバルト	$Co^{2+} + 2e^- \rightarrow Co$	-0.277
インジウム	$In^{3+} + 3e^- \rightarrow In$	-0.342
鉄	$Fe^{2+} + 2e^- \rightarrow Fe$	-0.44
ガリウム	$Ga^{3+} + 3e^- \rightarrow Ga$	-0.53
クロム	$Cr^{3+} + 3e^- \rightarrow Cr$	-0.74
亜鉛	$Zn^{2+} + 2e^- \rightarrow Zn$	-0.763
マンガン	$Mn^{2+} + 2e^- \rightarrow Mn$	-1.18
ジルコニウム	$Zr^{4+} + 4e^- \rightarrow Zr$	-1.53
チタン	$Ti^{2+} + 2e^- \rightarrow Ti$	-1.63
アルミニウム	$Al^{3+} + 3e^- \rightarrow Al$	-1.66
マグネシウム	$Mg^{2+} + 2e^- \rightarrow Mg$	-2.37
ナトリウム	$Na^+ + e^- \rightarrow Na$	-2.71
カルシウム	$Ca^2 + 2e^- \rightarrow Ca$	-2.87
カリウム	$K^+ + e^- \rightarrow K$	-2.93
リチウム	$Li^+ + e^- \rightarrow Li$	-3.05

面近傍から除去される場合、あるいは疑似体液の緩衝作用により pH が上昇しない場合には、金属表面に析出する腐食生成物・難溶性塩の量が減少し、結果として腐食速度の低下度が変化する。すなわち、これらの金属の生体内における分解速度を推測するためには、生体内と同様の環境において、体液の組成や緩衝能、血流や総体液量などを考慮する必要がある。

生体吸収性材料の分解特性評価に限らず、生物学的安全性評価においても生体内と同様の環境を考慮することは重要である。なぜならば、生体吸収性金属材料の安全性は溶出物の濃度に依存し、その推定には材料の生体内における分解速度の推定が必須だからである。この点は従来の生体吸収性高分子・セラミックス材料と同じであるが、生体吸収性金属材料の体内における分解機序は、既存の生体吸収性材料とは異なる点に留意が必要である。例えば生体吸収性高分子材料であるポリ乳酸について、リン酸緩衝液浸漬に伴う強度低下が、ラット体内（軟組織中）埋植における強度低下と一致するという報告があり[6)]、そのため分解特性評価法として in vitro リン酸緩衝液浸漬試験が ISO にて推奨されている[7)]。ポリ乳酸の生体内における分解機序は加水分解であり、生体吸収性金属材料のように試料表面に腐食生成物層が形成され、分解反応が妨げられることがないため、生体内環境をリン酸緩衝液で模擬可能と推測される。

したがって、繰り返しになるが、生体吸収性金属材料については、生体内における分解機序が異なる生体吸収性高分子の分解特性評価法を適用してはいけない。同じく、従来の高耐食性金属材料（既に実用化されているチタン合金・ステンレス鋼・コバルトークロム合金等）に対する耐食性試験法の適用も不適切である。従来の高耐食金属材料については、耐食性が高ければ高いほど望ましいという観点から、体内よりも過酷な条件として生理食塩水中あるいは1%乳酸溶液中でのアノード分極試験等が実施されてきた。しかし、生体吸収性金属材料については、このような生体内とはかけ離れた環境における試験結果は生体内環境における重要な分解速度制御因子（例えば炭酸緩衝系、リン酸、有機物など）が含まれておらず、生体内における分解速度との相関性が得られないことは明白である。

２．生体吸収性金属材料ステントの開発状況

（１）マグネシウムおよびその合金

マグネシウム合金のステント応用については、ドイツのビオトロニーク社にてWE43系合金による開発が進められており、既に臨床例が報告されている[8)-11)]。WE43系合金製ステントの最初の臨床例は、安全性確認に主眼を置いた下肢の虚血症例への適用であった。20名の患者に23個のベアメタルステントが埋入されたが、ステント埋入にともなう急性毒性は認められず、ステントは6週間以内に分解したと報告されている[8)-10)]。ベアメタルステントの安全性が確認されたため、続いて冠動脈領域での埋植も実施された。63患者に71ステントが埋入されたが、術後12ヶ月でTarget Lesion Revascularization（TLR）が45%に至り、従来のステンレス製ベアメタルステント（28%）および薬剤溶出ステント（6%）よりも悪い結果となった[11)]。WE43系合金ステントは埋入後4か月以内に分解したと推測されている。これらの臨床例から、WE43系合金ステントが血管狭窄部位の拡張を維持する期間の不足が示唆される。そこで、ステントの分解期間を延長するために生体吸収性高分子被覆を施し、抗がん剤徐放と組み合わせた薬剤溶出ステントが開発された。既に、臨床例も報告されている[12)]。それによると、埋入12ヶ月後の時点でLate Lumen Loss (LLL)が0.52±0.39 mmであり、ベアメタル時の結果よりも改善されたが、先行する生体吸収性高分子製ステント（0.27±0.32 mm）には及ばない[13)]。そのため、図1に示すように、現在さらなる拡張維持期間の延長を目指し、ストラット形状の変更、生体吸収性高分子コーティング厚さの向上や抗がん剤の種類の変更などの改良が進められている[13)]。

動物埋入例については、WE43系合金のブタ・ミニブタ埋入例[14)-18)]に加え、生体吸収性高分子被覆AZ31合金のウサギ埋入例[19)]が報告されている。WE43系合金製ベアメタルステントのブタ埋入例では、埋入28日での内皮化および埋入3ヶ月でのストラット消失が報告されている。一方、AZ31合金製ステントのウサギ埋入例では、ポリマー被覆のない、表面リン酸処理のみのステントについて、105日でのストラット消失が報告されている[19)]。

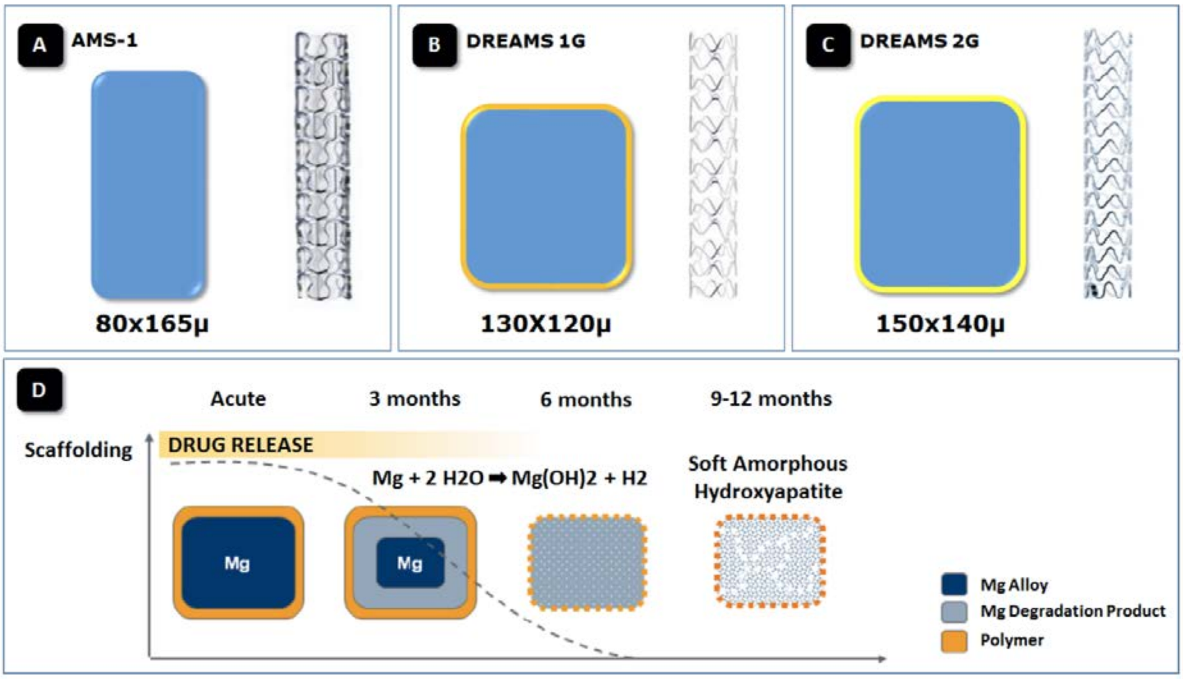

図１：WE43 系マグネシウム合金製ステントの変遷 [13)]
A: ベアメタルステント、B: 薬剤徐放ステント DREAMS 1G（1st generation）、C: DREAMS 2G（2nd generation）、D: WE43 系マグネシウム合金ステントの分解挙動を示す模式図。DREAMS 1G では、ポリ乳酸-ポリグリコール酸共重合体コーティング層にパクリタクセルを含浸。DREAMS 2G では、ポリ乳酸コーティング層にシロリムスを含浸。コーティングの厚さも 7 μm に増加させ、タンタル製マーカーも付与された。

（２）鉄およびその合金

前術したようにマグネシウム合金製ステントの臨床例では、体内における血管拡張維持期間の不足が示唆される。そこで、マグネシウムよりも強度が高く、また腐食速度も小さい鉄を生体吸収性ステントとして応用する試みが複数の研究グループにて検討されている。しかしながら、まだ臨床例は報告されていない。

純鉄製ステントのウサギ動脈への埋入実験では、ステントの分解量が小さく、18 ヶ月経過後でも分解速度の測定が不可能であったと報告されている [20)]。しかし、ストラット周辺には茶色の腐食生成物およびそれを貪食するマクロファージ像が観察され、軽い局所的な炎症反応が認められた [20)]。鉄は体液中の溶解度が低いため、ステント周辺部からイオンの状態で拡散するとは考えにくく、体外への排出が起こりにくいと予想される。ブタへの埋植実験においても、埋入 14 日後から茶色の腐食生成物が確認されている [21),22)]。埋入１ヶ月後から、網内系、すなわち細胞貪食によ

り処理される様子が観察された[22]。埋入3ヶ月後の時点では、脾臓内における腐食生成物の局所的に堆積が認められるが、重篤な鉄の過剰症は見られないと報告されている[22]。ステントとしての鉄埋入量は、動物個体全体に鉄過剰症を引き起こす量よりもはるかに小さいため、局所的な影響で留まるのであろう。埋入されたステントは、12-18ヶ月においても強度を保っており、内皮化され血栓形成もないことが報告されている[20),22]。

鉄ステントの分解期間の減少を目指し、窒化処理により強度を上げストラット厚さを70 µmまで低減したステントが開発されているが、これまでのところミニブタへの28日間埋入試験結果しか報告されておらず[23]、分解速度についてのデータは得られていない。

（3）亜鉛およびその合金

生体吸収性金属材料のステント応用において、これまでの臨床例、動物埋入例から、マグネシウム合金では強度維持期間が短く、鉄では分解期間が長過ぎることが推測される。そこで、両者の中間の分解速度であることを期待し、亜鉛の適用が検討されている。亜鉛は生体必須元素ではあるが生体内の存在量はマグネシウムよりも小さく、血漿中濃度は12-18 µMとマグネシウム（0.5-1 mM）の1/30程度である[24),25]。さらに、報告されている亜鉛の過剰症発症時の血漿中濃度は31.5-640 µMであり、通常の血漿中濃度の2倍程度である。すなわち、体内における亜鉛濃度の安全域が小さいことに留意が必要である[25]。

純亜鉛ワイヤのラット腹腔動脈への埋入例によると、顕著な毒性反応はなく、埋入1.5ヶ月後の分解速度は20 µm/year以下と報告されている[26]。しかしながら、純亜鉛の引張強度は純マグネシウム同様~120 MPaと低く、合金化が必須である。

3. 生体吸収性金属材料ステント開発における課題

生体吸収性金属材料ステントによる血行再建治療の成功には、埋入時および体内での分解に伴う機械的強度が重要であり、そのためには材料の分解特性制御が鍵となる。生体吸収性金属材料の分解特性制御には、不純物の削減、金属組織制御、合金化、表面処理（生体吸収性高分子との複合化を含む）等が有効である。現在開発が進められているマグネシウム合金についても、今後検討が進む可能性のある鉄および亜鉛についても、血管ステントとして実用化されるのは純金属ではなく合金と考えられる。合金開発およびその組織制御により、材料の機械的特性や分解特性を望ましいものに制御できる可能性があるが、従来の医療用金属材料以上に安全性への配慮が必要である。というのは、従来の非吸収・高耐食性金属材料とは異なり、生体吸収性金属材料は最終的には体内で全て分解する。したがって、マグネシウムや鉄などの主要元素だけでなく、合金化のために添加された元素も体内に排出されるため、これら添加元素の安全性も考慮しなければならない。例えば現在冠動脈ステント応用が進められているWE43系マグネシウム合金には、イ

ットリウムやミッシュメタルと呼ばれる希土類元素の混合物が合わせて 7 重量%（1 g 当たり 0.07 g）含まれている。マグネシウムは生体必須元素であり、一部のマグネシウム塩が薬として利用されていることもあり、体内存在量や排泄経路、過剰症を示す濃度など、ヒトについて色々なデータが得られている。一方、希土類元素については、ごく一部の元素は 19 世紀末から工業応用されていたが、その他多くの元素については第二次世界大戦後であり、個々の元素についての毒性データはほとんど得られていないのが現状である。一部の元素については有機錯体の形で造影剤として臨床応用されているが、他の元素についてはヒトに関するデータはほとんどない。

元素の利用の開始が近現代である場合、毒性報告例が少ないことが多いが、これは決して毒性がない、という意味ではない。むしろ、安全性未確認の部分が多い、と捉えるべきである。毒性報告例があれば、どの程度の量を摂取した際に問題が生じるかの予測が可能だが、データがなければリスクの推定はできない。ステント応用の場合、埋入量は他のデバイス（例えば骨折固定材など）よりも小さいとはいえ、口からではなく体内に直接埋入されるため、安全性未知の元素の使用は慎重に進めるべきである。

生体吸収性金属材料ステントの開発を進めるために現時点で予想される課題として、１）開発目標となる仕様が不明であること、２）in vitro および in vivo データの不足、ならびに３）評価法が未確立であること、があげられる。１）については、生体吸収性高分子材料ステントがごく最近海外にて上市されたばかりであり、その特性（強度保持期間約 6 ヶ月、分解・消失まで約 2 年）が冠動脈ステントにとって最適設計なのか否かは不明である。さらに、疾患タイプや患者の個人差等により最適な特性が変化する可能性がある。実際に、強度特性については生体吸収性高分子ステントと非吸収性金属ステントでは大きく異なっており、素材として、あるいは製品として目指す仕様が明らかになっているとは言い難い。

２）、３）に関しては１．でも述べたように、生体吸収性金属材料の分解特性およびその機序が従来の生体吸収性高分子材料や非吸収性金属材料と異なることに由来する。生体吸収性金属材料の生体内分解特性は環境に敏感であり、その評価には従来の単純な環境では不十分であり、より生体内に近い環境が求められる、というだけのことである。現時点ではまだ in vitro の評価条件の確立には至っていないが、それゆえ海外では in vitro の評価を不要とすべし、という意見もある。しかし、開発プロセスにおいて、候補材の絞り込みや素材・加工材の品質確認のための in vitro 評価は必須である。なんでもかんでも動物試験で確認すればよい、という考え方は、近年の動物愛護運動の高まりや細胞培養法を初めとするバイオ関連技術の進展に逆行している。実際に、医療材料の評価手法として動物を用いた試験は万能ではなく、その結果は必ず臨床結果と一致するとは限らない。要は開発プロセスにおいて in vitro 評価と in vivo 評価をいかに上手く組み合わせて利用するか、であり、分解特性評価環境の確立は必須である。

この点は分解特性の評価だけでなく、生物学的安全性評価についても同様である。既存の生物

学的安全性評価手法は、基本的に溶出物の Hazard Identification に主眼を置いているため、材料からの溶出物濃度が最大となるように抽出液を作製、それを用いて細胞・動物試験を行うという構造である。しかし、そのために既存ガイドラインが推奨する抽出液作製条件は、実際の生体内における使用条件とはかけ離れた過酷な環境となっている。繰り返しになるが、生体吸収性材料の安全性は溶出物濃度に依存するため、生体内に近い環境で試験をしないと、材料が生体内で使用可能かどうかの判断はできない。ガイドラインが推奨する抽出溶媒は水や生理食塩水であり、試験によっては培養液も使用可だが、抽出液を動物へ投与する場合には生理食塩水に限定される。しかし、先述したように、生体吸収性材料の生理食塩水中の分解速度は疑似体液中の数十倍であり、ガイドラインに従って生体吸収性金属材料の生物学的安全性を評価すると、使用可能な材料までも使用不可と判断されかねない。

このような評価法に関する課題を解決するためには、速やかな生体吸収性金属材料の生体内分解特性評価条件の確立と、生物学的安全性評価における抽出液作製条件の見直し（生体吸収性金属材料に適用可能な条件の明示）が求められる。両者に共通する点として、１）試験溶液・抽出溶媒は体液になるべく近い組成の溶液（炭酸緩衝液である必要がある）とすること、２）試験・抽出環境は体内同様の 5%炭酸ガス環境とすること、そして３）生体内で溶出物が体液中に速やかに拡散することを十分考慮して試料/抽出溶媒比を決定すること、があげられる。

１）に関しては、マグネシウムの腐食において、血清タンパク質に分解抑制効果が確認されており [5)]、動物血清あるいはヒト血漿をモデルに開発された Eagle's Minimum Essential Medium に血清を添加して用いるなどが望ましい。動物へ投与する場合は、タンパク質等の有機物が含まれると滅菌操作が難しくなるため、ISO10993-15:2000（Annex C）にあるように、人工血漿（無機塩のみ）を用いるのも一案である。２）については細胞培養等に広く用いられている 5%炭酸ガスインキュベータの利用で解決可能である。３）については、どのような部位に埋入することになっても、基本的に生体内の全組織には毛細血管網により血流があるため、総循環体液量を考慮して試験溶液・抽出溶媒量を決定することになる。しかし、例えば成人の血漿量は体重の約 5%、細胞外液量は約 15%であり、そのままのスケールで実施するとなると１L 以上の疑似体液が必要になる。生物学的安全性評価のための抽出液作製においては、例えば 1/100 にスケールダウンして実施した場合には安全率 100 を掛けている、との解釈も可能と考えられる。一方、生体吸収性材料の分解特性においては、成人の状況を念頭に十分量の試験溶液を用いること、および単位表面積当たりの試験溶液量が分解速度に及ぼす影響を検証することで対応可能と考えられる。

４．おわりに

生体吸収性金属材料およびその血管ステント応用について、開発の現状と課題について概説した。上述したように、いずれの材料についてもまだまだ研究開発の段階ではあるが、実用化まで

の開発プロセスにおいて、生体内分解性・生物学的安全性評価手法の確立は非常に重要である。今後、本事業を通してこれらの課題が解決され、我が国における生体吸収性材料製医療デバイスの早期実現に貢献できれば幸いである。

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Ⅲ－４　生体吸収性ステントの In vitro 評価

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１．はじめに

生体吸収性ステントは、永久留置型の金属製ステントと比較して体内で分解され血管内に最終的に異物が残らないというこれまでにない画期的な特徴を有する。永久留置型の薬剤溶出型金属ステントにおいて課題としてある、不完全な内膜被覆による長期に渡る血栓症のリスク[1),2)]、ステントの疲労破断に起因する再狭窄や血栓症のリスク[3)-5)]が低減される可能性が期待できる。その反面、ステントの材料、設計、厚さで決まる力学的特性が永久留置型金属製ステントと比較して小さく[6)-8)]、早期分解による血管拡張不全やステント断裂による再狭窄や血栓症のリスクがある。狭窄病変を拡張し、生体血管内で晒される負荷がステントに作用する環境での経時的な血管拡張力に関する性能、また、in vivo を想定した負荷環境での経時的な分解や破断の関係の特徴を示す耐久性は生体吸収性ステントの評価項目として重要であり、in vitro 試験法の開発は重要かつ急務である。本項では、永久留置型の金属製ステントで求められる評価に加え、生体吸収性ステントで新たに必要と考えられる in vitro 評価についてまとめる。

２．生体吸収性ステント材料の力学的特性

生体吸収性ステントは、主にポリ乳酸やマグネシウム合金を利用して開発されている。化学組成や製造方法等の違いにより、力学的特性や分解期間は表１のように異なる[6-8)]。

（１）引張破断強度

引張破断強度はステントの破断耐久性に影響を及ぼす力学的因子である。引張破断強度に関しては、バルーン拡張型の冠動脈ステントに現在最も使用されているコバルトクロム合金と比較して、ポリ乳酸では 3～12%程度、マグネシウム合金では 15～35%程度である。同様に、自己拡張型の大腿膝窩動脈ステントや頚動脈ステントに使用されているニッケルチタン合金と比較すると、破断強度は、ポリ乳酸では 3～16%程度、マグネシウム合金では 16～48%程度である。

（２）引張破断ひずみ

引張破断ひずみは、例えば冠動脈ステントではステントを過拡張する際にステント破断が生じるまでの伸びの限界を示す力学的因子である。コバルトクロム合金およびニッケルチタン合金と比較して、ポリ乳酸では 2～15%程度および 3～60%程度、マグネシウム合金では 4～44%程度および 5～200%程度である。したがって、ステント留置時の初期拡張成功を獲得するために、ステント材料の力学的特性を踏まえたステントの適正な拡張法と拡張限界に注意する必要がある。

表１　生体吸収性ステントと永久留置型金属製ステントに用いられる材料の力学的特性の比較

組成	引張弾性率 GPa	引張破断強度 MPa	引張破断 ひずみ %	分解期間 月
Poly(L-lactide)[6]	3.1-3.7	60-70	2-6	>24
Poly(D,L-lactide)[6]	3.1-3.7	45-55	2-6	6-12
Poly(glycolide)[6]	6.5-7.0	90-110	1-2	6-12
50/50 D,L-lactidde/glycolide[6]	3.4-3.8	40-50	1-4	1-2
82/18 L-lactide/glycolide[6]	3.3-3.5	60-70	2-6	12-18
Mg alloy[6]	40-45	220-330	2-20	1-3
Stainless steel 316L[6]	193	668	40+	生体内で安定
Stainless steel 316L[7]	193	595	60	生体内で安定
Cobalt chromium MP35N[7]	233	930	45	生体内で安定
Cobalt chromium L605[7]	243	1000	50	生体内で安定
Cobalt chromium[6]	210-235	1449	≈40	生体内で安定
Platinum chromium[7]	203	834	45	生体内で安定
Nitinol[6]	45	700-1100	10-20	生体内で安定
Nitinol[8]	120(austenite) 50(martensite)	690-1380	13-40	生体内で安定

３．生体吸収性ステントの拡張に関する検討項目

ステントの基本性能として拡張径がある。引張破断ひずみが本邦で臨床使用されて広く普及している永久留置型の金属製ステントと比較して小さいため、生体吸収性ステントでは、過拡張に対する制限があることに注意する必要がある。

（１）ステントが破断しない最大拡張径

血管は、一般に遠位部に行くにしたがって径が小さくなる。近位部と遠位部で血管径の差がある場合にはステントを血管壁へ圧着させるために、図１に示すようにバルーンによる後拡張が必要となる場合がある。また、病変の特徴に応じてバルーンを過拡張する場合もある。ポリ乳酸ステントの臨床報告で、後拡張した際にステントが破断して、血管内腔側に倒れてきたという報告がある[9]。したがって、ステント破断が起きない安全な拡張径の範囲を明示することが望ましい。

（２）分岐部血管にステント留置時にステントから側枝に向けてバルーンで後拡張した際のステント破断しない最大拡張径

冠動脈ステントを用いた血管治療の中で分岐部血管は15～20%を占めるといわれている[10]。

分岐部にステントを留置する際には、図２に示すように側枝に架かっているステントをそのままにして治療を終える場合と、側枝に架かっているステント部を拡張する場合がある[11)]。側枝を拡張する場合には、ステント破断を起こさない拡張径に関するデータを取得することが、安全な普及に向けて望まれる。

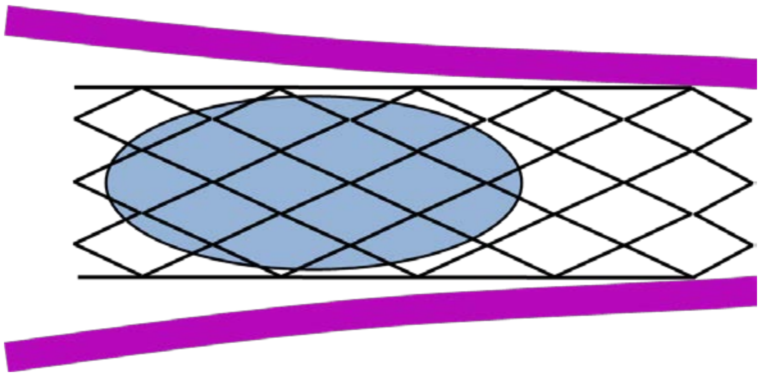


図１　テーパ血管でのステントの後拡張

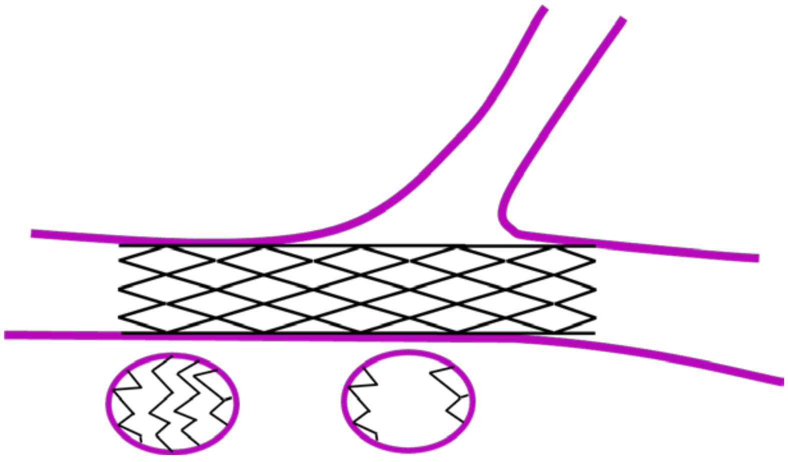


図２　血管分岐部にステント留置時の側枝流入部に架かっているステント部の拡張の有無

４．生体吸収性ステントの経時的拡張保持力の評価

狭窄病変を拡張した生体吸収性ステントは、留置初期が最も血管拡張保持力があり、分解とともに最終的に血管拡張保持力はなくなる特徴がある。図３は継時的なステントの分子量、質量損失、ステントの拡張保持力の関係の概念図を示したものである[6)]。内膜で覆われる一定期間まで必要な血管拡張力の経時的な特性を示す非臨床試験データの提示は、重要な評価項目である。以

下に、本試験における考慮すべき因子を示す。

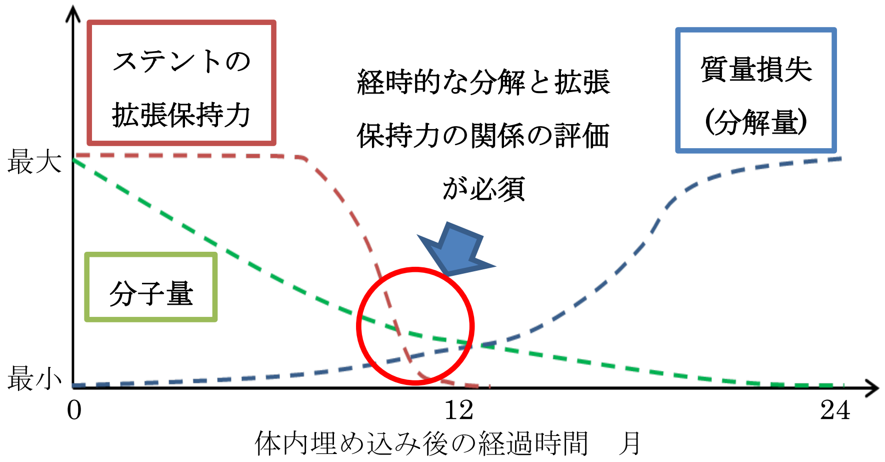


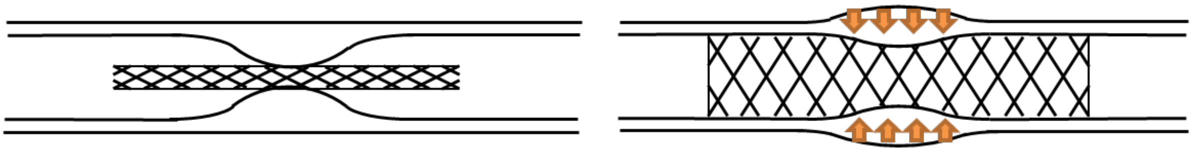
図３　生体吸収性ステントの分子量，質量損失とステントの拡張保持力の経時的変化の概略図（文献６を改変）

（１）溶液

分解性の評価では、溶液の pH、イオン構成・強度、温度を in vivo での生理的環境に合わせることが重要である[12), 13)]。溶液に関しては、ポリ乳酸を用いたステントに関して、リン酸緩衝生理食塩水を用いた in vitro 試験とブタでの in vivo 試験で数平均分子量の低下の遷移傾向が類似する結果が示されている[14)]。マグネシウム合金では、リン酸緩衝生理食塩水を溶液として用いた in vitro 試験では、ラットでの in vivo 試験と比較して分解速度が顕著に早いことが示されている[15)]。血清が分解を抑制する因子であることがわかっており[16)]、マグネシウム合金の試験では考慮すべき点である。

（２）狭窄血管モデル

狭窄部を拡張したステントは、図４に示すように血管壁から負荷を受けた状態で力が釣り合う。応力が高くひずみが生じている部分は分解速度が速くなるため[14), 17)]、in vivo を想定したステントへの負荷を組み込んだ試験が望まれる。



(a) ステント拡張前　　(b) ステント拡張後

図４　狭窄血管でステント拡張後の力の釣り合い

（３）流れ環境

In vivo では常に拍動血流・血圧に晒されている。In vivo を想定した生理的な拍動数かつ流れ環境での試験は、in vivo における分解過程を評価する上で重要な因子と考えられる。

５．生体吸収性ステントの耐久性評価

生体吸収性ステントに関しては、血管を拡張することが期待される一定期間、構造を保持することを示す耐久性試験が必要である。In vivo で想定される負荷環境での試験が重要である。拍動による血管の径方向の負荷は、冠動脈ステントの試験に関して『平成 15 年 9 月 4 日付薬食審査発第 0904001 号』[18]に記載されている最低限の基本的項目である。臨床では、図５に示すように、心臓の収縮・拡張にともない冠動脈が繰り返し屈曲変形する部位でステントに疲労破断が起こることが認知されている[4), 19), 20)]。In vitro の繰り返し屈曲負荷を作用する加速耐久試験において、各種ステントの臨床での破断傾向と合う結果が示されており[21), 22)]、繰り返し屈曲負荷は構造保持を示す耐久試験で検討すべき重要な因子である。

合わせて、溶液の pH、温度を生理的環境に合わせることが必要である。ポリ乳酸では、溶液の温度を上げることで分解速度が上昇することがわかっている[23)]。加速負荷試験を行う場合には、材料の化学的な分解速度を負荷の加速条件と合わせることが重要であり、加速試験の妥当性を示す必要がある。

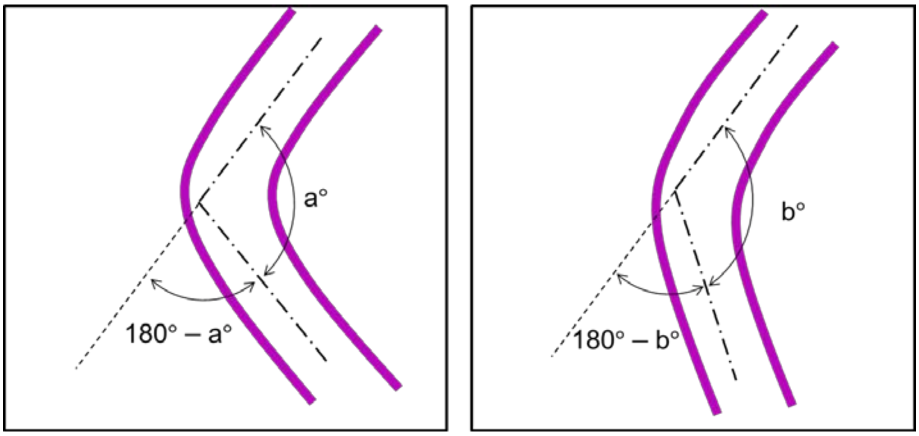


図５　心臓の収縮・拡張にともなう冠動脈の繰り返し屈曲変形

６．おわりに

生体吸収性ステントの材料特性を踏まえたステントの拡張に関する検討項目、そして、生体吸収性ステントの非臨床評価として新たに求められる経時的拡張保持力の評価試験、耐久性評価試験についてまとめた。これらの in vitro 試験が生体吸収性ステントの迅速評価の一助となれば幸いである。

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Ⅲ－５　In Vivo 評価について

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１．従来の冠動脈内デバイスの動物実験における評価

薬剤溶出ステントをはじめとする冠動脈内デバイスの動物実験を用いた評価には、豚の冠動脈モデルがゴールドスタンダードとして長らく使用されてきた。しかし、近年はうさぎ腸骨動脈モデルも一定の信頼を得て、多く使用されている。

一般的に動物モデルではステント留置後１ヶ月後の新生内膜増殖抑制効果をもとに有効性を判定する。しかし、長期的安全性の指標となる生体適合性に関しては、より長期（3 ヶ月～1 年）の留置期間で評価する。特に薬物溶出、生体分解などの過程が関与する場合は、その過程が終了し反応が沈静化するまでの期間を最低限評価する必要がある。また、ステントストラットの被覆化（再内皮化）に関しては、増殖の緩徐なうさぎ腸骨動脈モデルを選ぶか、もしくはブタ冠動脈モデルでより早いタイミングでの評価を行うことが好ましい（2 週間後など)。

モデルの特性として

ブタ冠動脈：

- 心臓の動きによる影響が判定できる（ステントの血管への追従性、フラクチャーなどの評価に適する）
- ステントを留置した周囲の組織への影響や（心筋の評価により）末梢塞栓などを評価できる

うさぎ腸骨動脈：

- 豚冠動脈モデルに比して個体差が比較的少ない
- 比較的反応が緩徐であるため再内皮化などの評価に適する
- 飼育や実験が簡便である

などが挙げられる。（図１）[1)]

２．実臨床での成績と動物実験での相関

適切なモデル、タイミング、評価方法を選択すれば、冠動脈内デバイスの実臨床における有効性、安全性に関して、かなり相関があると考えられる。

たとえば、第一世代薬剤溶出ステントについて例を上げると、動物実験において CYPHER ステント（シロリムス溶出ステント）は炎症反応が強く、また晩期に増加する傾向があるのに対して、TAXUS（パクリタキセル溶出ステント）はフィブリンの沈着が強く出る症例が多いことが報告されているが[2)]、剖検例を用いた実臨床での生体反応を見てみると、かなり類似した反応が得

られていることが分かる（図２）[3]。また、有効性の評価としても、うさぎ動脈硬化腸骨動脈モデルを用いた実験では実臨床での新生内膜増殖抑制効果を非常によく反映した結果が得られることが報告されている[4]。

一方で、古くはアクチノマイシン溶出ステントが豚冠動脈モデルにおいて留置後28日時点で有意な内膜増殖抑制を認めたため、臨床治験がスタートしたが、その後動物モデルで90日後には著しい炎症反応により Late catch-up（遅発性再狭窄）が見られ、同様に実臨床においてもステント両端を中心とする再狭窄が認められたため承認が得られなかった。また、開発当初のシロリムス溶出ステントを評価し有効性を示した豚冠動脈モデル実験において、留置後28日時点でのステントの内皮化を評価し、ベアメタルステントと違いはなかったと評価している[5]。しかし、後に実臨床では治癒過程障害による遅発性血栓症が問題になっており[6, 7]、この事象についてはこの動物実験では予知しきれなかったことになる。その後、うさぎ腸骨動脈を用いてこれらの薬剤溶出ステントの再内皮化が遅れることが示された[8]。

以上のように、適切なモデル、評価のタイミング、評価の方法が臨床成績を予知する上で非常に重要であると考えられる。

３．生体吸収性ステントの場合の特殊性

これまでに、臨床応用されているアボット社の Absorb（エベロリムス溶出生体吸収性スキャフォルド、bioresorbable scaffold、BRS）に関する動物実験が既にいくつか報告されている[9, 10]。これらの実験でも検討されているとおり、生体吸収性ステントの吸収過程を詳細に検討する必要が有り、その生体反応の変化などが主な評価対象となる。前述のとおり、デバイスの新生内膜抑制効果や長期の生体適合性などについては評価可能であるが、下記が生体吸収性ステント評価の際の特有の問題点として挙げられる（図３）。

① 一般的に生体反応は動物の方が早いことが知られているが、デバイスの吸収速度は動物内も人間内も概ね同じであると考えられる（ただし、下記Ｃも参照）。このため、反応と吸収過程にギャップが生じ、このため動物実験における吸収過程と生体反応のタイミングがどこまで人間の生体内の反応を反映するかが不明である。

② 一般的に用いられる動物モデルは病変モデルでないため、生体吸収性ステントで重要とされる Radial force の評価が困難である（線維性プラークや石灰化プラークに対する拡張能の評価が困難）。

③ 生体吸収性ステントの吸収速度に影響する炎症細胞、留置部の pH、病変部の脂質の含有などが人体内の冠動脈病変と違うため、吸収速度が動物実験では若干異なる可能性がある。

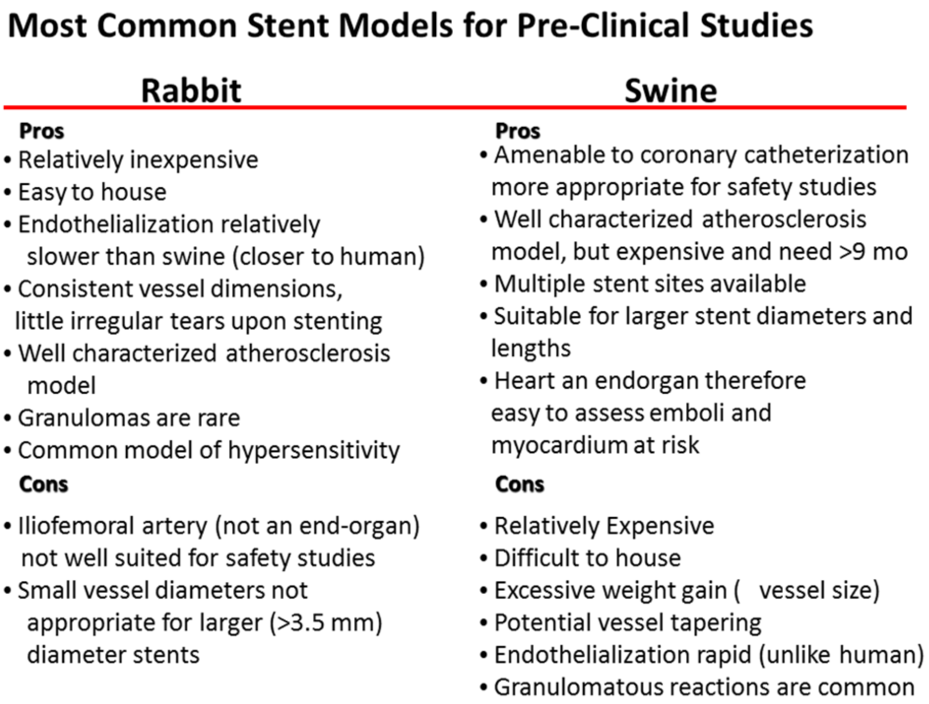

図１　豚冠動脈およびうさぎ腸骨モデルの利点と問題点

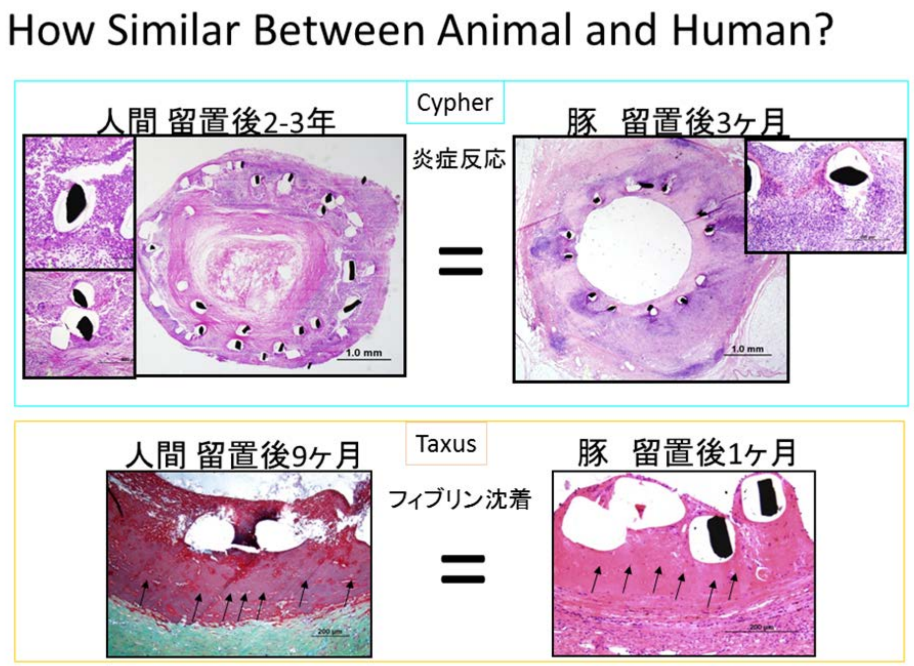

図２　動物モデルと人間での局所反応の類似性

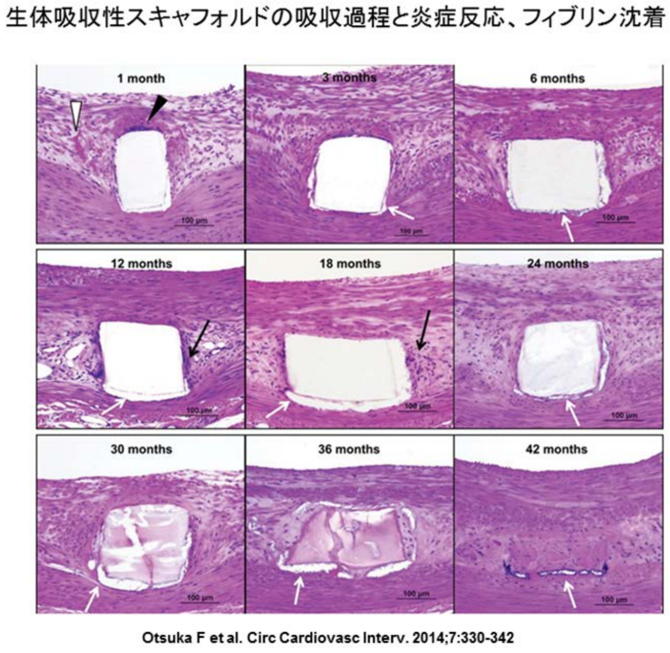

図３　生体吸収性スキャフォルドの吸収過程と炎症、フィブリン沈着[10)]

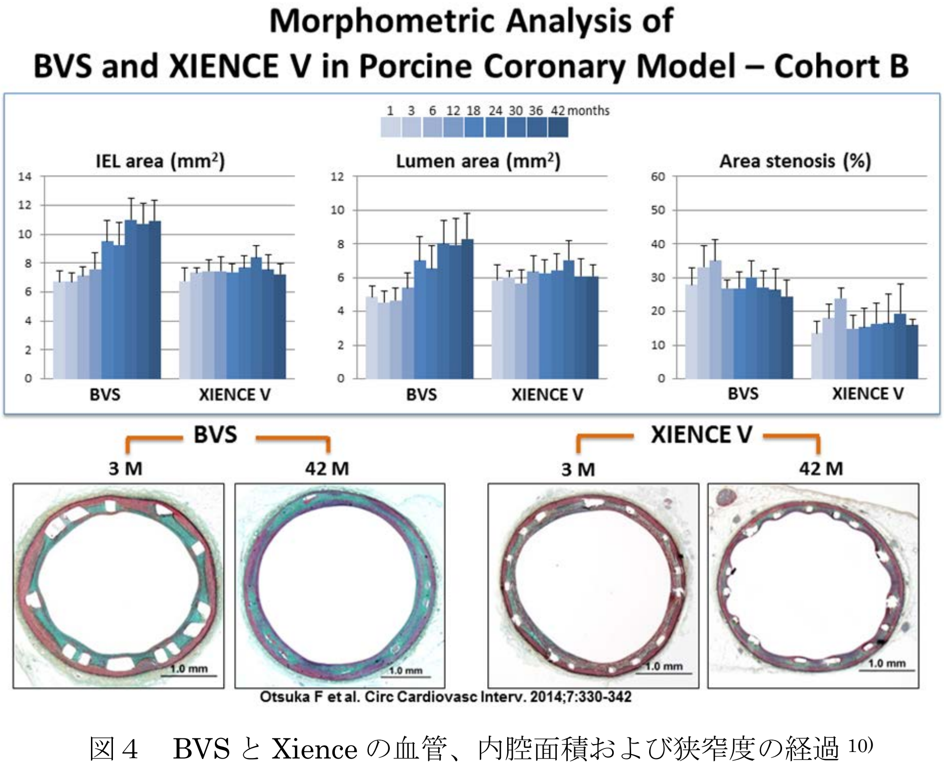

図４　BVS と Xience の血管、内腔面積および狭窄度の経過[10)]

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Ⅲ－６　イメージングによる評価

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１．はじめに

生体吸収性ステントは、新しい冠動脈疾患の治療デバイスである。狭窄や閉塞を解除し、一定期間冠動脈内腔を支持する（スキャホールド）役割を終えると、生体内に吸収されて血管は健常な機能を回復することが期待される。生体吸収性ステントを用いた冠動脈インターベンション（percutaneous coronary intervention、PCI）の潜在的利点としては以下の点が挙げられる。

- ✓ 不安定プラークのシーリング
- ✓ 金属ステント慢性期で見られるフラクチャーがない
- ✓ 血管形態が自然な形に戻り、生理的拡張能が回復する
- ✓ 慢性期に内腔が大きくなる
- ✓ CT / MRI での血管評価が可能
- ✓ 超慢性期に PCI / 冠動脈バイパス移植術（coronary artery bypass grafting、CABG）による再治療を妨げない
- ✓ 超遅発性血栓症、晩期再狭窄が少ない可能性
- ✓ 治療部位の新たな動脈硬化が少ない？

上記の長期的な利点が謳われる一方で、PCI 治療急性期の合併症が増加する可能性が指摘されており、冠動脈イメージングによる評価が重要である。

２．イメージングの種類

冠動脈イメージングとして、多数のデバイスの臨床的有用性が示されている（図１）。中でも、生体吸収性ステントの留置手技時と慢性期の血管反応性を評価するデバイスとしては、光干渉断層映像法（optical coherence tomography、OCT）の演じる役割は大きい。血管内超音波法（intravascular ultrasound、IVUS）に比し約 10 倍の解像度（20 µm）を有し、特に生体分解性ポリマーを用いたデバイスの可視化においては IVUS では描出困難なストラット断面像を明瞭に描出できる（図２）。

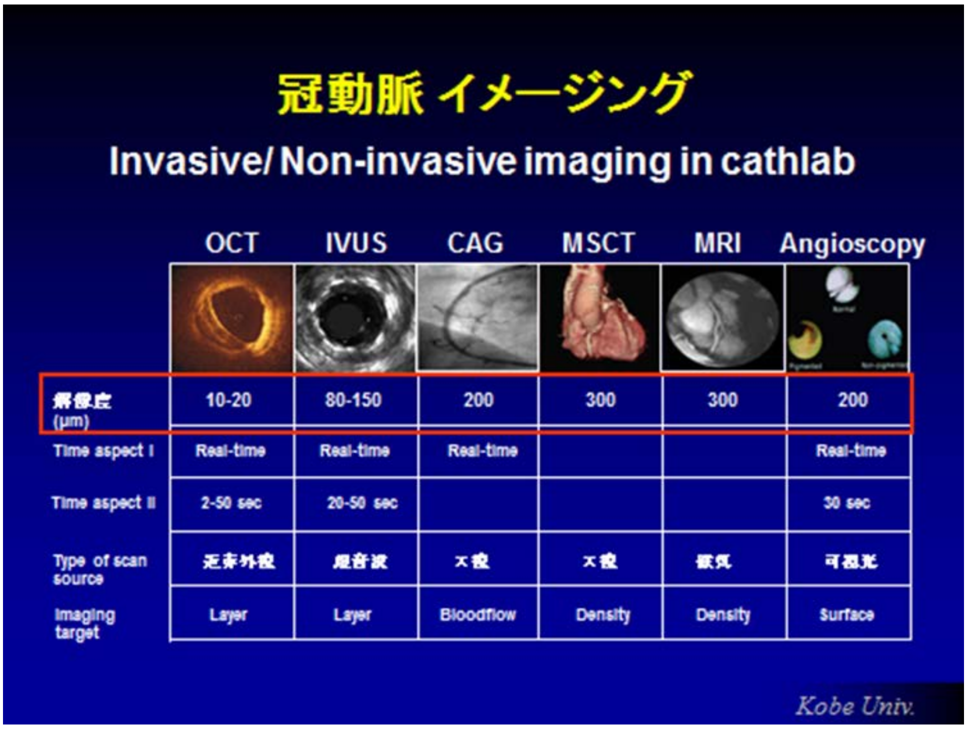


図１　冠動脈イメージングに使用されるデバイス

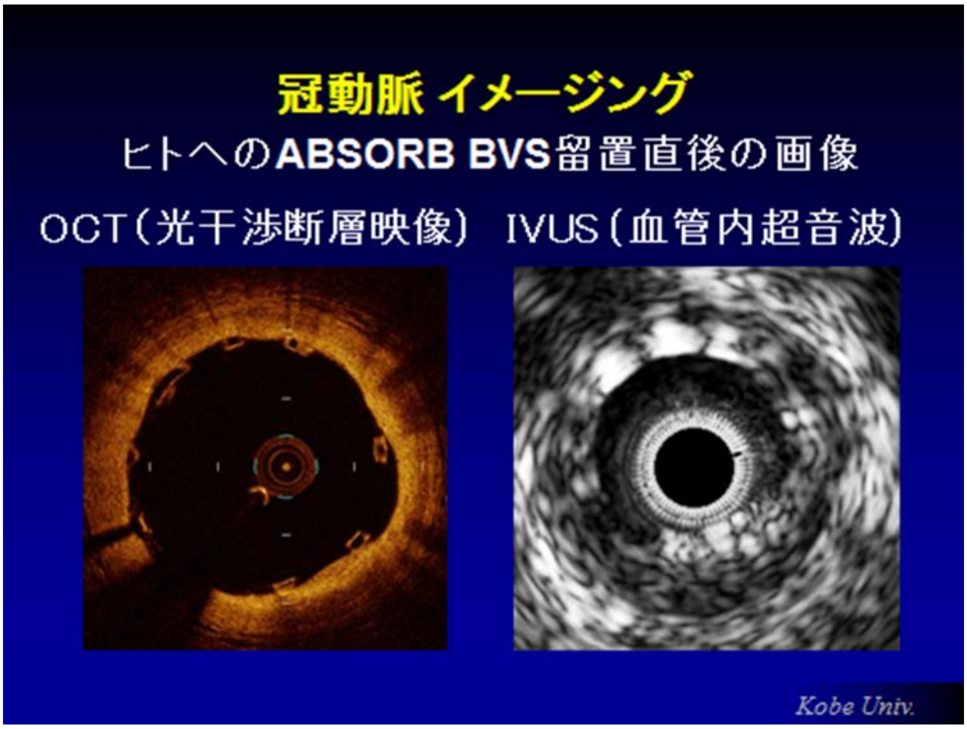


図２　冠動脈イメージング：生体吸収ステントをヒト冠動脈に留置直後のOCT 及び IVUS 像。OCT では、ステントの横断面が明瞭に描出される。

３．報告されている成績

（１）前臨床：慢性期、超慢性期における病理所見との対比

すべての冠動脈拡張用デバイスがそうであるように、前臨床試験によって、その効果と安全性が検証されてから臨床試験に移行する。生体吸収性ステントでは特に、慢性期の吸収過程を病理学的に評価して、冠動脈イメージングとの対応が検討される。OCT はストラットの吸収過程とステント内の新生内膜増殖を正確に評価することが可能であり、前臨床試験の中でも頻用されている。生体吸収性ステントはその分解吸収過程において、まず分子量の減少が起こり、ストラットの量的減少が続く。この際にストラット内に平滑筋細胞など新生組織が入り込んでいくが、前臨床試験で得た､病理所見と対応した OCT 画像は臨床試験に移行した際の重要な参照イメージとなる。

また、長期の血管反応性を評価することもイメージングの役割として重要である。Lane LP らは､豚冠動脈モデルを用いて最長 42 ヶ月までの血管反応性を評価したが､生体吸収性ステントは金属性薬剤溶出性ステント（drug eluting stent、DES）に比し、長期的な内腔面積の拡大を報告している（図３）[1)]。

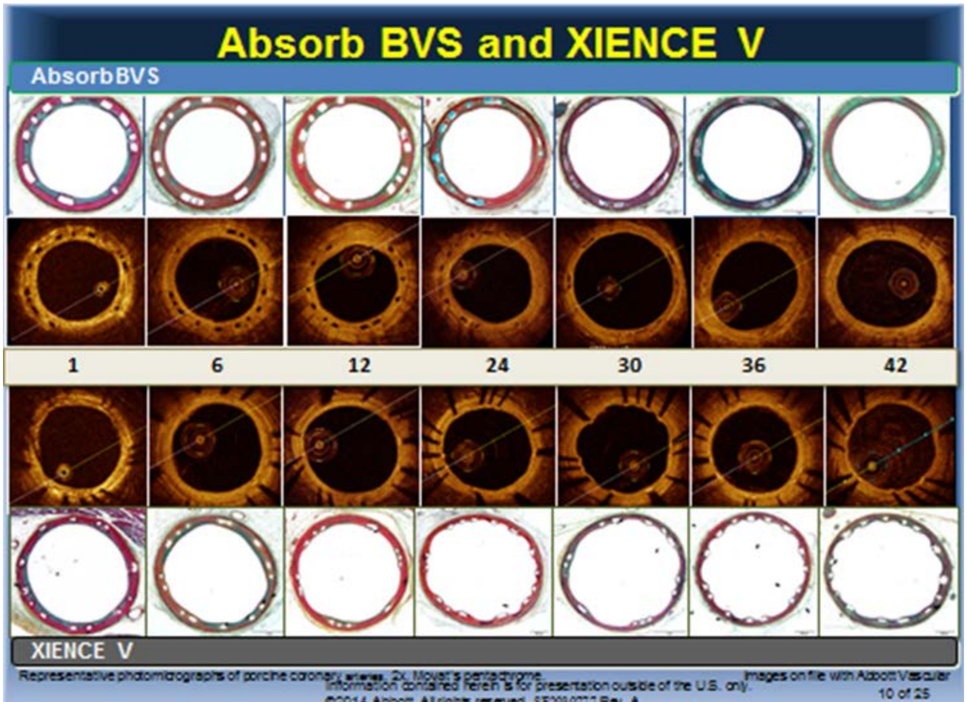
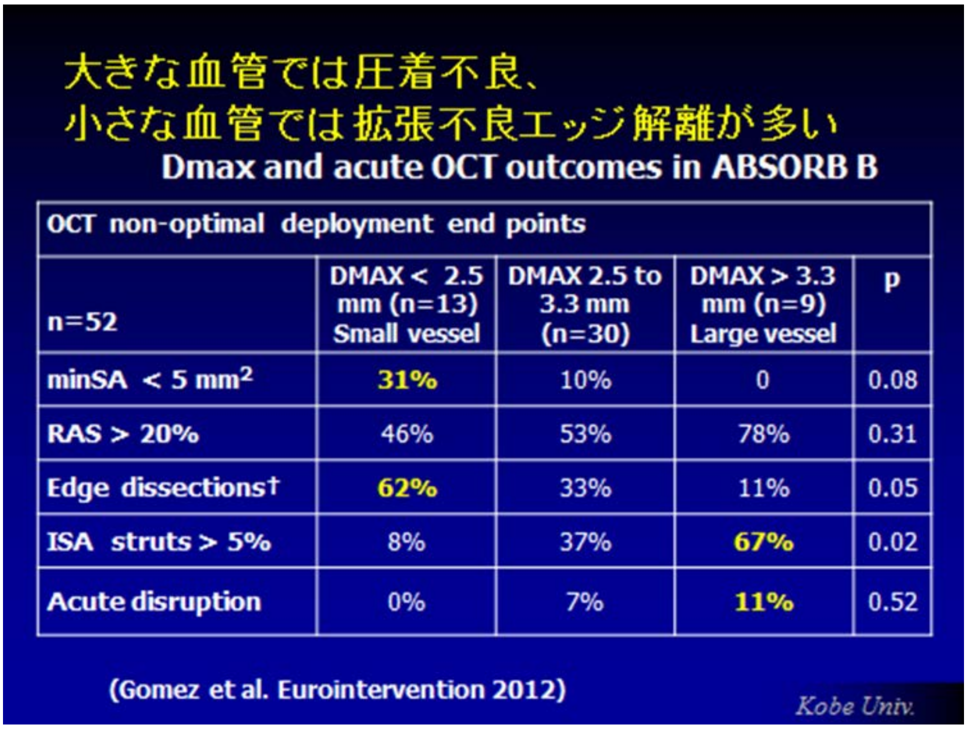


図３　薬剤溶出性生体吸収ステントおよび金属ステント留置後の経時的変化：豚冠動脈モデルにおける、留置 1, 6, 12, 24, 30, 36, 42 ヶ月後の病理像と対応する OCT 画像。OCT でも吸収過程を観し得る。

（２）臨床試験

１）急性期

現在一般臨床で使用されている生体吸収性ステントは、Abbott Vascular 社の BVS のみであるが、ステント留置時のいくつかの pit fall が報告されている。ストラットが金属製 DES に比して厚いため、狭窄部へのデリバリーが困難、圧着不良が起こりやすい、小さな側枝閉塞をきたしやすい、オーバーラップ留置時に内腔への突出が大きいなどが主な論点である。また、拡張力がやや弱いため、拡張不良が起こりやすく、それを回避するためには病変の前拡張を大きく行う必要がある。一方で、金属ほどの伸展能を有さない素材であるため、過拡張によるストラット破断の危険があること（拡張限界の存在）も指摘されている。OCT を用いた臨床研究では、径の大きな冠動脈では圧着不良の頻度が高く、径の小さい血管では拡張不良とエッジ解離が多く発生することが報告されている（図４）[2]。報告によって結果に差があるものの、金属製ステントに比して術後 30 日以内の早期ステント血栓症が多く発生する傾向にあり、留置手技の最適化が進められている現状と思われる。


大きな血管では圧着不良、
小さな血管では拡張不良エッジ解離が多い
Dmax and acute OCT outcomes in ABSORB B

OCT non-optimal deployment end points				
n=52	DMAX < 2.5 mm (n=13) Small vessel	DMAX 2.5 to 3.3 mm (n=30)	DMAX > 3.3 mm (n=9) Large vessel	p
minSA < 5 mm^2	31%	10%	0	0.08
RAS > 20%	46%	53%	78%	0.31
Edge dissections†	62%	33%	11%	0.05
ISA struts > 5%	8%	37%	67%	0.02
Acute disruption	0%	7%	11%	0.52

(Gomez et al. Eurointervention 2012)
Kobe Univ.

図４　生体吸収ステント留置直後の OCT 所見：定量的冠動脈造影による最大血管径（DMAX）ごとに差異が認められる。大きな血管に対して生体吸収ステントを留置すると圧着不良が高頻度に認められ、一方小さい血管では拡張不良とエッジ解離が多く認められる。

２）慢性期

Abbott Vascular 社の BVS においては、最長 5 年程度までフォローアップした報告が散見される。OCT を用いると、新生内膜によるストラット被覆、吸収過程を観察していると考えられるストラットイメージの変化を可視化できる。留置 3－5 年後には、ストラット構造が新生内膜と識別不能となり、均一な内膜肥厚として描出される。IVUS を用いた検討では、留置 6 ヶ月後と 2 年後を比較して、スキャホールド面積と内腔面積の拡大が認められた[3]。金属ステントで見られるようなストラットによるアーチファクトが少ないため CT で内腔の評価が可能とされる。また、アセチルコリン負荷試験後の血管径の変化を測定して、内皮依存性血管拡張反応が回復したとする報告や、パルポグラフィーを用いて、慢性期に生理的な血管捻弾性が回復したとする報告がある。側枝入口部を覆っていたストラットが留置慢性期には消失し、新しい側枝入口部が形成されるとするものもある。これまでのところ、いずれも長期的には生理的な血管機能の回復を観察するとしている報告が多く、それらが狭心症症状の再発抑制に寄与している[4]のか否か今後の検討が待たれる。

４．イメージングの評価指標として、追加考慮されるもの（今後の検討課題）

（１）前臨床

１）急性期：留置直後、早期のイメージングの報告は少ない

① 屈曲部に留置した場合の追従性

② 残存する拡張不良/ 圧着不良、エッジ解離の頻度

③ 急性リコイル

④ 前臨床試験での早期イベント例の病理学的検討、イメージングの収集

２）慢性期：実臨床を想定したモデルでの検討

① 障害血管モデル、動脈硬化モデルでの評価

② オーバーラップ留置例、分岐部への留置、先細り（tapered）血管

③ Radial force の経時的変化の評価

（２）臨床試験

１）急性期：

① 留置手技と術者教育の標準化策の提示

② 留置直後イメージ：急性期リコイル、圧着度、組織逸脱/血栓形成

③ オーバーラップ留置例

④ 分岐部留置例

⑤ ステント血栓症症例のイメージング

２）慢性期：

① オーバーラップ留置例

② 分岐部留置例

３）イベント例：

① イメージング評価

② 背景因子の検討

５．総括

生体吸収性ステントはその長期効果に期待が集まる一方で、急性期合併症が増加することが危惧される。評価指標の作成に際しては、急性期の効果と安全性、慢性期の治癒過程の評価、両面から検討する項目立てが必須と考えられる。OCT などのイメージングによる、留置手技のモニタリングと慢性期評価が必要である。

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Ⅲ－７　臨床的観点から考えられる構造的問題点

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１．はじめに

既に EU 圏内では Biodegradable Vascular Scaffolding（BVS）が臨床使用されており、その有効性が証明されるとともに今後解決すべき課題も示されてきた。この章では、メタルステントと比較して BVS で臨床使用時/留置後中長期に懸念される問題点として、

- サイズのミスマッチと過拡張による破損
- 留置後急性期・慢性期の評価方法
- 分岐部病変における BVS の経時的変化

の項目につき検討する。

２．サイズのミスマッチと過拡張による破損

（１）急性心筋梗塞

急性心筋梗塞の際には、閉塞した冠動脈の血管径が正常時より小さくなっていることが多々ある。再灌流を維持するために冠動脈ステントを留置するが、メタルステントであれば後拡張を追加する事で血管壁にステントを圧着させる事が可能である。

しかし、BVS を用いた場合には推奨拡張径より 0.5 mm を超える過拡張を行うと構造が破断することが確認されている。複数箇所で破断した際には、血管壁に対するラディアルフォースがなくなる。また血管壁に BVS の構造物が不完全圧着し、血管壁内で遺残することになるため、留置部位での血栓性が増す危険性が危惧される。

（２）労作性狭心症

冠動脈狭窄部位前後で血管径が 0.5 mm 以上異なる場合がある。さらに狭窄部を解除したことにより末梢血管径が大きくなる場合がある。対照血管径を測定するために血管内エコー検査・OCT/OFDI 等での計測を行う際にも狭窄解除前の計測では末梢側は小径に計測される。小さなステントを留置した際には、先に述べているような不完全圧着のままの BVS の遺残、過拡張にともなう BVS の破断が起こりうると危惧される。

３．留置後急性期・慢性期の評価方法

通常、冠動脈治療は連続透視撮影/記録を行える冠動脈造影装置による透視下で手技を行うのが基本である。しかし、BVS はその材料の特性上、デリバリーシステムマウント時、あるいは拡張後も透視下ではその本体を確認することは出来ない。確認できるのは両端の小さなゴールドマー

カーのみである。

ゴールドマーカーが着いていることにより冠動脈長軸方向におけるジオグラフィックミスは起こりにくい。しかし、拡張したあと BVS の不完全拡張の有無、血管壁への圧着の程度を冠動脈造影装置で確認することは出来ない。血管造影装置を使った様々な方法で留置した BVS を確認するためのソフトウェア開発が続けられているが、未だ確立されている方法はない。

血管内エコー検査では BVS は評価できないというのが定説である。実際には条件が良ければ留置直後の BVS を観察することは可能である。しかし、慢性期を含めると BVS を留置した部位が慢性的に観察できる方法には成っていない。

光干渉断層法（OCT/OFDI）は解像度が約 10-15 μm と IVUS の約 10 倍の高い分解能を有しており BVS を観察するために有用である。これを用いることで留置直後の BVS の不完全圧着や破損を確認することが可能である [1]。しかし、検査時には血液を遮断する/あるいは造影剤へに置換する必要があり、カテーテル検査と同じ侵襲を必要とする。従って慢性期の確認等で頻回に行うわけには行かない。

冠動脈造影 CT 検査（MDCT）を用いることで、メタルステントであれば留置位置を明瞭に把握することが出来る。しかし、MDCT を用いても BVS 本体を確認することは出来ない。両端のゴールドマーカーは確認できるため、再狭窄の有無を確認するためには造影剤を用いて撮影することによりその内腔を計測することが可能であるが、BVS の変形については確認することは困難である。また、両端マーカーのみしか認識されないため、複数の BVS を留置した際には、留置位置を把握することが困難になるものと危惧される。

４．分岐部病変における BVS の諸問題

冠動脈分岐部病変は冠動脈治療の対象病変のおよそ 20%を占めている。本管に BVS を留置した場合側枝入口部が Jail（本管にステントが留置された際に側枝入口部にストラットがかかっている状態）される場合も当然多くなる。この時点で側枝の血流低下を認めれば、側枝側に向けた拡張が必要になる。メタルステントであれば、この際に本管と側枝に向けて二本のバルーンで同時拡張を行う拡張方法（Kissing balloon dilatation technique、KBT）を通常実施する。しかし、BVS を本管に留置した際に側枝をいかに処理するかについては定かでない。懸念されるのは以下の二点である。

- KBT を行わない場合

  側枝入口部には血管壁に圧着しない BVS のストラットが遺残する。留置後数ヶ月以降に未圧着のストラットの表面には何らかの組織が付着し増生することが確認されている。さらに数年以内に BVS が完全に消失した際に neointimal bridge として残る場合がある [2]。これが臨床的に問題になりうるのかこれまで検討されておらず、対処の必要性も今後検討す

る必要がある。

- KBT を行う場合

  BVSのストラット越しにバルーンを拡張させるためストラットの破断を来す可能性が高い。ベンチ実験では本管に BVS の留置後に本管を径 3.5 mm のバルーン、側枝を径 3.0 mm のバルーンを用いて 5 気圧同時拡張することで、BVS のストラットが破断することなく側枝に向けて BVS を変形させることが出来ている[1)]。しかし、これ以上の拡張を行った場合には一部のストラットが破断する事が確認されている。一部分のみのストラット破断が臨床的になるのかは不明である。

以上、今後 BVS を臨床使用するにあたり解決すべき問題を挙げた。

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Ⅲ－８　Biodegradable Vascular Scaffolding (BVS) Clinical Trials

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１．緒言

冠動脈インターベンションは現在薬剤溶出ステント（Drug-Eluting Stent、DES）として Everolimus-Eluting Stent（EES）が最も臨床的に汎用されているが、ステントが異物として残存することやポリマーによる炎症反応惹起が長期的には問題となる可能性がある。超遅発性ステント血栓症や neoatherosclerosis という新たなプラークの進展などである。ステントが一定期間に消失、すなわち異物がなくなるという観点から開発されたデバイスが Biodegradable Vascular Scaffolding（BVS）である。理論的には異物やポリマーが消えれば、抗血小板薬の 2 剤併用は不要となるか、抗血小板薬自体が不要となる可能性もあり、出血リスクは減少すると考えられる。また、現在、DES は平均 4 本留置され、総ステント長は 100 mm に及ぶといわれているなかで、長期の観察期間で再血行再建が必要になることもあり、その時にステントが消えていればバイパスを含む治療選択肢は多く、かつ容易となる。以上のように BVS への期待は高まるが、支えとして血管リモデリングを抑制するのがステントであり、それが消失することは血管が収縮するリスクもはらんでいることになる。このような BVS の理論的な利点や欠点は臨床の場で検証する必要があるが、実践で使用するなかで思いがけてない欠点や利点を見出すこともある。そこで、実際の治験から欧州での実臨床での BVS の安全性から有益性までの治療成績を概説する。

２．臨床試験の目的とエンドポイント

現在、BVS の臨床試験は図１、２に示すような計画で進められている。検討事項は安全性と有効性であるが、前者はイベントとして心血管事故やステント血栓症、後者は画像診断で内膜肥厚や内腔面積であり、その結果を現在の標準治療である EES の成績と比較し、非劣勢を証明することが臨床試験の目的となっている。現在のステント臨床試験は 1 次評価項目として Target Lesion Failure（TLF）、Major Adverse Cardiac Events（MACE）、Target Vessel Failure（TVF）のいずれかを用いることが多い。最も多いエンドポイントである MACE は心血管死亡、心筋梗塞、臨床的虚血のある標的部位再血行再建（clinically-driven target lesion revascularization、CD-TLR）の 3 イベント、TLF は心血管死亡と標的血管を責任病変とする心筋梗塞、CD-TLR と定義し、TVF は CD-TLR の代わりに標的血管再血行再建（clinically-driven target vessel revascularization、CD-TVR）とする。心血管事故が重要であることはいうまでもないが、血管内の情報、すなわち留置部位の内腔や内膜肥厚の程度、血栓の有無、BVS の変化なども 2 次評価項目としている。これは最近の画像診断デバイスの発展におうところが大で、血管内超音波（intravascular

ultrasound、IVUS)、VH(virtual histology)-IVUS、光干渉断層法(optimal coherence tomography、OCT)、冠動脈 CT など様々な画像診断を駆使して経時的に観察している。

3.初期前向き臨床試験　ABSORB 試験

いわゆる FIM(First In Men)が ABSORB 試験であり、コホート A、B さらに B は画像診断時期により B1、B2 に分けられている。コホート A は BVS の安全性を担保する目的で 2006 年に 30 例の低リスク患者に施行され、単純病変の初回病変へステント長 12 mm あるいは 18 mm の BVS を単独で留置した [1)]。追跡は 6 ヶ月、1 年、2 年時に冠動脈造影(CAG)、IVUS、VH-IVUS などを施行した。MACE は 4 年の追跡で 3.4%、6 か月で 1 例のみ心筋梗塞を発症したが、6 か月から 5 年までのイベントやステント内血栓症は 1 例も認めなかった。少数例かつ単純病変に施行したとはいえ、BVS の安全性が担保できる妥当な臨床試験結果となった。また定量的冠動脈造影法(quantitative coronary angiography、QCA)の 6 ヶ月後の評価では損失血管径は 0.44 mm であり、これまで報告されている通常の金属ステント(BMS)の 0.8 mm に比べれば少なかったが、Xience ステントでの 0.11 mm と比べれば大であった。その原因は内腔面積が留置直後に比較して 11.8%減少していることによると考えられるが、内膜肥厚は少なく、血管がリモデリングしたためであった。この原因は早期に BVS の吸収が始まったことで、ステントの支えが減少したことによるリコイルに起因し、”scaffold shrinkage”と呼ばれている。この研究では BVS の内腔狭窄の評価などに多くの画像を用いている。冠動脈 CT は内腔面積や狭窄度を DES では金属反射で正確に評価できなかったが、BVS では QCA と比較し正確度に差異がないことが確認された。IVUS 画像からはステントストラットに一致する高エコー輝度領域は留置直後から 6 ヶ月(18.5% to 10.3%)、さらに 6 ヶ月から 2 年(10.3% to 7.7%)で減少したことから、BVS は 6 ヶ月という短期から 2 年までで確実に吸収されていることが判明した。また、最少内腔面積や平均内腔面積は留置直後から 6 ヶ月で減少するが、6 ヶ月から 2 年で増加したことから、”scaffold shrinkage”は時間の経過とともに改善することが明らかになった [2-4)]。

また、コホート B は BVS の形状や材質を一部変更して BVS の性能を向上させ、第 2 世代の BVS1.1 で施行された試験である [5)]。101 人の患者を 5 年間、QCA、IVUS、OCT 画像を用いて追跡し、BVS の溶解過程を追跡する有効性かつ安全性を検証する試験である。CAG での 6 か月の損失血管径(late lumen loss、LL)は 0.19 mm まで向上し、2 年、5 年での病変部位の狭窄度に変化はなく、これまで報告されている Xience ステントと同等であった。また IVUS や OCT での 6 か月後の BVS 内腔面積減少率はそれぞれ 2.9%、1.9%と第 1 世代で問題となった”scaffold shrinkage”も改善し、IVUS での 1 年時の新生内膜肥厚面積などの指標は図 3 に示すように、これまでの Xience ステント試験と比較して遜色のないものであった [6, 7)]。またコホート B の 101 例の心血管イベントは MACE 10 例、TVF 13 例、non-Q 心筋梗塞 3 例、再血行再建 3 例で、心血

管死亡は1例も認めなかった[8]。これはBVSだけの結果であり、DESと比較できないことに問題がある。そこで、これまで報告されたXience V試験を歴史的コントロールとして、背景因子を調整して予後を比較すると3年間で両群間のイベントに差は認めず、BVSの安全性が許容範囲であることが示された。また、BVSの消失は2年と5年の間で起こっていることも確認された。以上の点からABSORB A、B試験をまとめると、1）BVSの安全性が短期から長期で確認されたこと、2）単純病変に留置すれば心血管事故が少ないこと、3）BVSが冠動脈内から消えることなどが明らかになった。

患者数を増やし多施設で実施されているのがABSORB EXTEND試験[9]である。BVSの安全性を検証する目的で450人の患者を2年間追跡した前向き臨床試験である。いわゆるステント血栓症は1.1%、MACEは6.7%に認めた。3年まで追跡できた250人では心臓死0.8%、心筋梗塞4.0%、TLR 6.0%、MACE 9.3%、TVF 10.1%、TLF 8.9%、ステント血栓症は1.2%であった。この比率が高いか低いかの客観性を検証する目的で、現在のDESの標準治療であるXienceステントをコントロールにPropensity Score Matchingという統計学手法を用いて予後を比較した[10, 11]。このABSORB EXTEND 250例中の174例とXience、Spirit I-III試験の全患者862例中290例がPropensity Score Matchingの対象となり、両群の予後を比較した。結果は表1に示す通りステント血栓症を含めMACE、MI、ID-TLR再血行再建は観察期間3年で差は認めず、TVFは有意にBVS群で低率であった。この結果は後ろ向き解析であるという大きな限界はあるが、Propensity Score Matchingで背景因子を一致させたうえでBVSのDESに対する非劣勢を示しており、BVSがXienceステントと同等の予後であることを示した臨床的意義は極めて高い。

4．初期前向き臨床試験　ABSORB試験

次に必要な前向き臨床試験はBVS vs DESのhead to head試験であり、その意図に沿って企画されたのがABSORB II試験である。この試験ではBVS 335人、Xience（EES）166人に2:1で無作為化し、6か月から1－5年追跡される予定である。既に1年時の追跡結果が報告されている。表2に示すすべてのイベント（死亡、心筋梗塞、すべての再血行再建術率、ステント血栓症）は両群間で差を認めなかった。この解析で注目すべきは狭心症の出現頻度でEES 25.6% に対しBVS 16.4%と有意に低かったことである。ただ、その機序については不明である。

この試験結果をうけ、現在いくつかの大規模臨床試験が進行中である。一つはABSORB IIIで2000人を対象にBVS:EESを2:1で割り付け、観察期間5年でTLFを1次評価項目としたBVSの非劣勢を証明する試験である。ABSORB IVは5000人を対象にBVSとEESに割り付け、1年以内の狭心症と5年でのTLFを評価する。既に欧州ではBVSは認可されたデバイスであり、実臨床での登録研究も報告されている。1189名が登録され、実臨床さながら、複雑病変患者も登録され6ヶ月までの結果が報告されている。ただ気がかりな点は30日以内の血栓症が多く発生し

ていることである（図４）。BVS に適した病変選択を誤るあるいは手技上の注意を怠ると、ステント血栓症のリスクがあることに留意しなければならないが、血栓症のリスクは多くの症例数を積み上げていくことで明確になってくると考えられる。

５．臨床研究の総括

これまでの臨床試験結果からは BVS の心血管イベントやステント血栓症は第 2 世代 DES と同等であることが明らかになっている。さらに表３に示すような BMS をコントロールとして第 1 世代 DES、第 2 世代 DES、さらに BVS を血管傷害の程度から neoatherosclrosis まで比較すると興味深い。ステントによる血管傷害度や急性の血栓症は 4 群で差異はなく、炎症惹起や内皮細胞機能障害は第 2 世代 DES で改善し、BVS でも悪化させないことがわかる。注目すべきは血管リモデリングと血管拡張反応で、ステントを留置すれば DES の有無に関わらず血管の拡張性リモデリングは起こらないし、血管拡張反応も生じない。一方 BVS では血管リモデリングは長期で明らかに改善し、血管拡張反応も維持される。Neoatherosclrosis は第 2 世代 DES で問題となることもあるが、BVS ではこの点について長期追跡のデータがないため不明と言わざるを得ない。

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１１）Muramatsu T, Onuma Y, van Geuns RJ, et al. 1-year clinical outcomes of diabetic patients treated with everolimus-eluting bioresorbable vascular scaffolds: a pooled analysis of the ABSORB and the SPIRIT trials. JACC Cardiovasc Interv. 2014; 7: 482-93.

図1　Overview of ABSORB studies

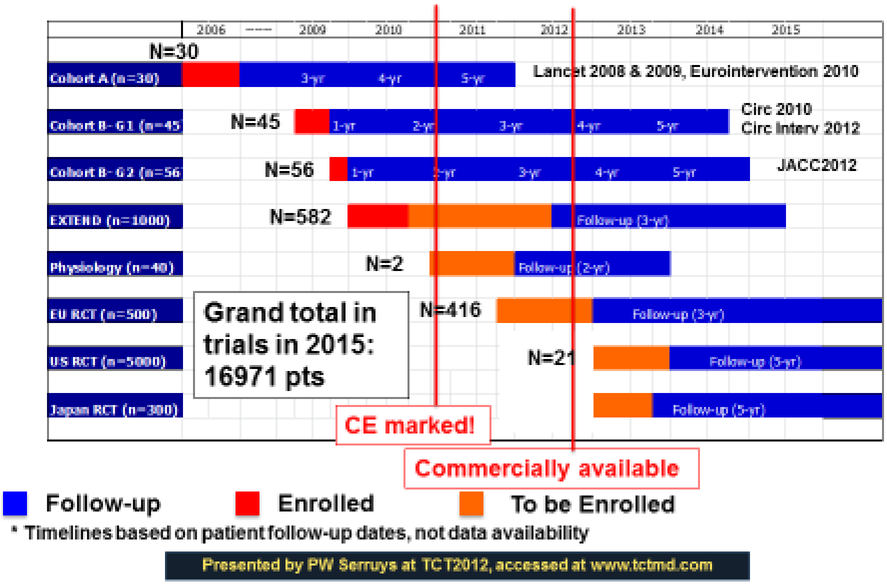
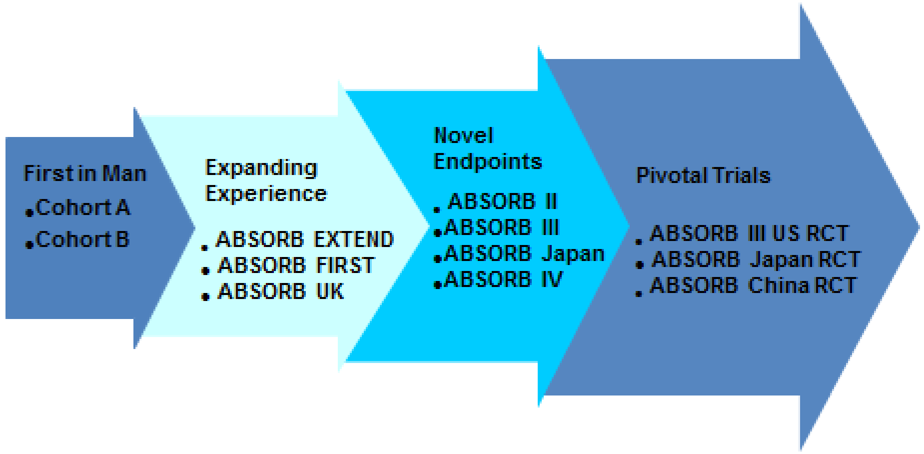
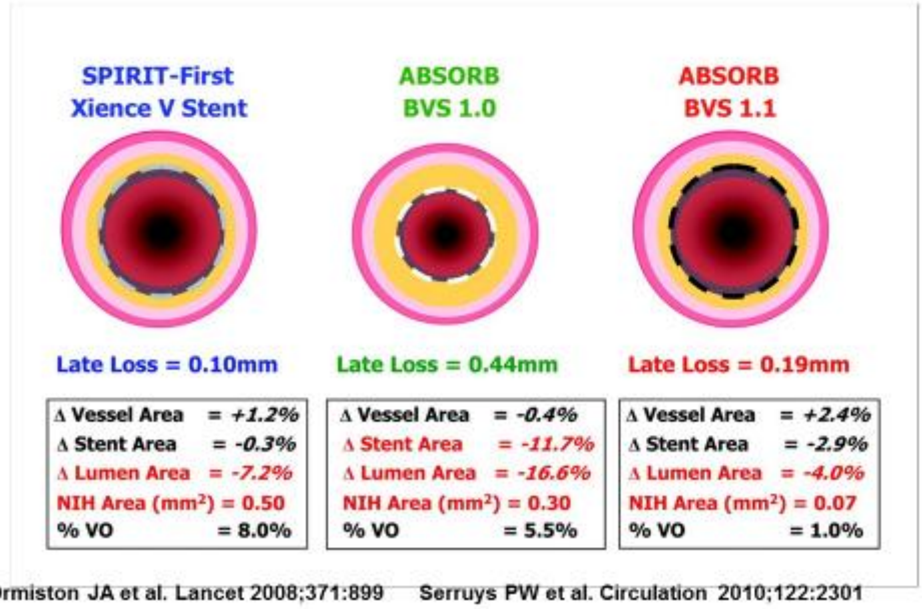


図2 Absorb: A Revolutionary Therapy Building Evidence



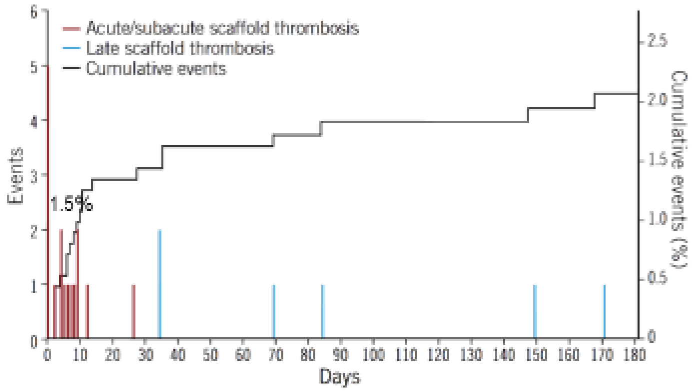
画像診断; Scaffolding, Neointima, Thrombus, Endothelization,
Safety; MI, Stent thrombosis, CV death, Revascularization
Non-Inferiority versus Everolimus-Eluting Stent

図3　BVS 1.1 scaffold: persistence pays off



Ormiston JA et al. Lancet 2008;371:899　　Serruys PW et al. Circulation 2010;122:2301

図4　Scaffold Thrombosisの頻度



- There were 20 cases of angiographically confirmed ST and three of probable ST.
- 70% occurred in the first month after PCI, **at a median of 5 days, suggesting the need for scrupulous lesion selection and PCI techniques when using BVS**
- Intravascular imaging was performed in only 9 of 23 patients who experienced ST
- 20 of 23 patients were on DAPT at the time of ST
- ST rates were numerically higher when more experience was accumulated and more complex patients were treated

表１

Propensity Score Matched Clinical Outcome 3-years

	Absorb EXTEND, 174 Pts	XIENCE V SP123, 290 Pts	P Value
NON-HIERARCHICAL COMPONENTS			
Cardiac Death %	0.6	1.4	0.65
Myocardial Infarction %	4.0	3.8	0.90
Ischemia Driven TLR %	4.6	5.9	0.56
MACE %	7.5	10.0	0.36
TVF %	8.0	14.1	0.05
TLF %	6.9	9.7	0.31
Scaffold Thrombosis (%)	0.6	0.7	1.00

MACE is the composite of cardiac death, MI and ID-TLR
TVF is the composite of cardiac death, MI and ID-TVR
TLF is the composite of cardiac death, TV-MI and ID-TLR

表2　Absorb 試験とXience 試験のイベント比較

Cumulative incidence in percentage	Absorb 335 pts	Xience 166 pts	*p* value
Composite of cardiac death, target vessel MI and clinically indicated target lesion revascularization (TLF, DoCE)	4.8 %	3.0 %	0.35
Cardiac death	0 %	0 %	1.00
Target vessel MI	4.2 %	1.2 %	0.07
Clinically indicated TLR	1.2 %	1.8 %	0.69
All TLR	1.2 %	1.8 %	0.69
Composite of all death, all MI and all revascularization (PoCE)	7.3 %	9.1 %	0.47
All death	0 %	0.6 %	0.33
All MI	4.5 %	1.2 %	0.06
All revascularization	3.6 %	7.3 %	0.08

表３　BMS と第１世代DES,第２世代DESとBVSの比較

Preclinical Parameters	BMS	First Generation DES	Second Generation DES	Bioresorbable Scaffold
Mechanical injury severity	standard	standard	standard	not worse
Acute thrombus	minimal	minimal	minimal	not worse
Inflammation	minimal	worse*	better**	not worse
Acute recoil	none	none	none	not worse
Neointimal hyperplasia	standard	better*	better**	not worse
Endothelialization	standard	worse*	better**	better**
Healing pattern	standard	worse*	better**	better**
Vessel remodeling	none	none	none	present
Vasoreactivity	impaired	impaired	impaired	better**
Calcification	none	present	present	not worse
Neoatherosclerosis	standard	worse*	present	unknown

*vs. BMS　　**vs. permanent polymer DES

Ⅳ　資料

生体吸収性材料関連規格リスト

ISO

1. ISO 10993-6:2007 Biological evaluation of medical devices -- Part 6: Tests for local effects after implantation
2. ISO 10993-9:2009 Biological evaluation of medical devices -- Part 9: Framework for identification and quantification of potential degradation products
3. ISO 10993-13:2010 Biological evaluation of medical devices -- Part 13: Identification and quantification of degradation products from polymeric medical devices
4. ISO 13781:1997 Poly(L-lactide) resins and fabricated forms for surgical implants -- In vitro degradation testing
5. ISO 15814:1999 Implants for surgery -- Copolymers and blends based on polylactide -- In vitro degradation testing
6. ISO 22794:2007 Dentistry -- Implantable materials for bone filling and augmentation in oral and maxillofacial surgery -- Contents of a technical file
7. ISO 22803:2004 Dentistry -- Membrane materials for guided tissue regeneration in oral and maxillofacial surgery -- Contents of a technical file
8. ISO 25539-3:2011 Cardiovascular implants -- Endovascular devices -- Part 3: Vena cava filters
9. ISO/TS 17137:2014 Cardiovascular implants and extracorporeal systems -- Cardiovascular absorbable implants
10. ISO/TR 37137:2014 Cardiovascular biological evaluation of medical devices -- Guidance for absorbable implants

JIS

1. JIS T4101 医療用絹製縫合糸
2. JIS T4102 腸線縫合糸

ASTM (standard)

1. ASTM F603-12 Standard Specification for High-Purity Dense Aluminum Oxide for Medical Application
2. ASTM F619-14 Standard Practice for Extraction of Medical Plastics
3. ASTM F748-06(2010) Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices
4. ASTM F1634-95(2008) Standard Practice for In-Vitro Environmental Conditioning of Polymer Matrix Composite Materials and Implant Devices
5. ASTM F1635-11 Standard Test Method for in vitro Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants
6. ASTM F1983-99(2008) Standard Practice for Assessment of Compatibility of Absorbable/Resorbable Biomaterials for Implant Applications
7. ASTM F2150-13 Standard Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue-Engineered Medical Products
8. ASTM F2212-11 Standard Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPs)
9. ASTM F2450-10 Standard Guide for Assessing Microstructure of Polymeric Scaffolds for Use in Tissue-Engineered Medical Products
10. ASTM F2451-05(2010) Standard Guide for in vivo Assessment of Implantable Devices Intended to Repair or Regenerate Articular Cartilage
11. ASTM F2502-11 Standard Specification and Test Methods for Absorbable Plates and Screws for Internal Fixation Implants
12. ASTM F2721-09 Standard Guide for Pre-clinical in vivo Evaluation in Critical Size Segmental Bone Defects
13. ASTM F2739-08 Standard Guide for Quantitating Cell Viability Within Biomaterial Scaffolds
14. ASTM F2789-10 Standard Guide for Mechanical and Functional Characterization of Nucleus Devices
15. ASTM F2883-11 Standard Guide for Characterization of Ceramic and Mineral Based Scaffolds used for Tissue-Engineered Medical Products (TEMPs) and as Device for Surgical Implant Applications
16. ASTM F2884-12 Standard Guide for Pre-clinical in vivo Evaluation of Spinal Fusion
17. ASTM F2902-12 Standard Guide for Assessment of Absorbable Polymeric Implants
18. ASTM F2942-13 Standard Guide for in vitro Axial, Bending, and Torsional Durability Testing of Vascular Stents
19. ASTM F3036-13 Standard Guide for Testing Absorbable Stents

20. ASTM F3089-14 Standard Guide for Characterization and Standardization of Polymerizable Collagen-Based Products and Associated Collagen-Cell Interactions

<u>ASTM (Work item)</u>

1. WK41613 Revision of F2902 - 12 Standard Guide for Assessment of Absorbable Polymeric Implants
2. WK43150 Revision of F1983 - 99(2008) Standard Practice for Assessment of Compatibility of Absorbable/Resorbable Biomaterials for Implant Applications

薬食審査発第0904001号
平成１５年９月４日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長

冠動脈ステントの承認申請に係る取扱いについて

医療用具の製造又は輸入の承認申請に際し添付すべき資料については、平成１１年７月９日付け医薬発第８２７号厚生省医薬安全局長通知「医療用具の承認申請について」及び平成１１年７月９日付け医薬審第１０４３号厚生省医薬安全局審査管理課長通知「医療用具の承認申請に際し留意すべき事項について」に規定されている。
今般、冠動脈ステントの承認申請にあたって、有効性、安全性を確保するために必要と考えられる添付すべき資料の範囲及び承認申請書の記載内容を下記のとおりとりまとめたので、申請にあたって留意するよう、貴管下関係業者に対し指導方御配慮願いたい。
なお、下記に挙げた事項はあくまで基本を示したものであり、品目の特性に応じて、資料や記載事項の追加が必要である場合、不要な項目がある場合があることを念のため申し添える。
おって、本通知の写しを財団法人医療機器センター理事長、日本医療機器関係団体協議会会長、在日米国商工会議所医療機器小委員会委員長及び欧州ビジネス協議会医療機器委員会委員長あて送付することとしている。

記

1．添付すべき資料について
有効性、安全性を確保するために必要と考えられる添付すべき資料の範囲は以下のとおりであること。原則として、滅菌済み最終製品で試験を行うこととし、ステントをデリバリーシステムにマウントした状態若しくはデリバリーシステムにて拡張されたステントに対して試験を行うこと。

（1）　物理的化学的性質並びに規格及び試験方法等に関する資料

1）　原材料について

原材料の組成、性状に関し、以下の項目について明らかにすること。

ア　化学的分析、不純物の限度、走査型電子顕微鏡検査（不正形状、表面汚染）等

イ　機械的特性（耐力、引張強さ、伸び等）

2）　ステント自体について

ア　外観、表面性状並びに寸法

イ　溶出物（参考：JIS T 0304 金属系生体材料の溶出試験方法）

ウ　耐食性

イ．溶出物及びウ．耐食性については、原材料のみならず、加工法によっても特性が異なる場合があるため、原則としてステント自体を用いて試験を実施すること。ただし、表面処理及びその他の特性についてステント自体と同一の条件を有する場合には、原材料検体を使用してもよいこと。

エ　拡張後のフリー（オープン）エリア

推奨拡張圧（Nominal Pressure）で拡張時、ステントストラット（支柱）が形成する格子構造（セル）単位あたりの血管がステント原材料によって覆われない面積。

オ　拡張前後のステント長変化率

展開前のデリバリーシステムに装着された状態のステントと、展開後のステントの長さを測定し、寸法の変化率を求める。

カ　展開均一性

展開したステントの両端と中央部の外径を測定し、ステントが全長を通して、意図する径まで均一に展開していることを確認する。

キ　ラディアルフォース

ステントの半径方向の強度を測定する。

ク　リコイル試験

推奨拡張圧（Nominal Pressure）でステントを展開し、バルーンを収縮させる前と後でのステント径を測定し、ステント径の弾性リコイル（収縮）率を求める。

ケ　最大拡張による亀裂検査

コ　MRI に対する影響

植え込まれたステントが及ぼす MRI 施行時の発熱、アーチファクト（磁場干渉）等の影響について評価すること。既承認類似品と同原材料（ステンレススチール等）を用いており、ステント植込み部位の内皮化

の特性などMRIに対する影響が既知の場合にあっては、文献等の考察により、申請品目を用いての試験実施に変えてもよい。

3） ステントとデリバリーシステムについて

ステントとデリバリーシステムに関し、以下の項目について明らかにすること。

ア 最大圧力

最大拡張圧（RBP、Rated Burst Pressure）以下でのバルーンの破裂、各部の漏れ・破断等が99.9%ないことを信頼度95%にて統計的に証明する。

イ ステント拡張後のステント内径（それぞれのバルーンとステントの組合わせについて、推奨拡張圧で拡張したときのステントの内径）

推奨拡張圧(Nominal Pressure)にて拡張したときのステント内径を測定する。

ウ 接合強度

接着その他の結合が施されている各接合部の強度を測定する。

エ バルーン収縮性

推奨された手順にてバルーンが確実に収縮されることを確認する。また、拡張したステントから収縮したバルーンが抜去できることを確認する。

オ バルーンの拡張、収縮時間

推奨された手順にて規定された時間内にバルーンが拡張、収縮することを確認する。

カ 先端の引張強さ

カテーテル先端部の接合部あるいは材料自身の強度を確認する。

キ ステントクリンプ（ステントがデリバリーカテーテルにマウントされていない場合）

クリンプの過程でステントやカテーテルに損傷を与えないことを確認する。

ク クロッシングプロファイル

ステントマウント部のプロファイルを測定する。

ケ ステント保持強度

ステントがデリバリーカテーテル上に保持されることを確認する。

コ キンク試験

規定された曲率半径においてデリバリーカテーテルがシャフトのキンクを生じないことを確認する。

サ ダイレクトステンティング

シ　エックス線不透過性

高分解能エックス線装置を用いてエックス線不透過度を確認する。既承認類似品と同原材料（ステンレススチール等）を用いており、エックス線不透過性が既知の場合にあっては、文献等の考察により、申請品目を用いての試験実施に変えてもよい。

ス　柔軟性の写真

規定された圧力にて拡張したステントを規定された曲率半径に曲げたときの写真を撮影する。

セ　デリバリー準備試験

パッケージ開封後、挿入前までの準備が問題なくできることを確認する。

ソ　バルーンの疲労試験

規定された圧力にてバルーンを拡張させたときのバルーンの耐久性を確認する。

（2）　安定性に関する資料

1）　安定性

既にその安定性が十分確認されているもの以外のものにあっては、実際に貯蔵される状態及び苛酷条件での保存における経時変化等安定性に関する試験を行い、その結果に基づき適切な貯蔵方法及び有効期間を設定すること。

（3）　生物学的安全性に関する資料

平成７年６月２７日付け薬機第９９号厚生省薬務局医療機器開発課長通知「医療用具の製造（輸入）承認申請に必要な生物学的試験のガイドラインについて」に準じて生物学的安全性に関し、明らかにすること。

（4）　性能に関する資料

1）　動物を用いた試験

動物を用いた埋め込み試験を行い、性能について明らかにすること。

①　一般的留意事項

ア　動物種の選択にあたっては、感受性等の評価が確立されており、人への外挿性の観点を考慮すること。(ブタは適切な動物の一種として推奨される。)

イ　臨床を想定した抗凝固療法を実施し、その詳細を記録すること。

ウ　有効性、安全性を検証する上で、術前、術後及び経過観察時の血管状態を詳細に確認し、内皮形成、内膜肥厚、血管径の変化や血管壁の損傷、埋め込み部位から遠位の塞栓の状況等についても明確に説明すること。

エ　少なくとも最大径と最小径でそれぞれの最長ステントについて、また、

最長のものがこれらと同一ではない場合は、最長のものの径について試験を実施すること。

② 観察項目

ア 血管の内径（留置前、留置後、フォローアップ時）

イ ステントの形状の実測値（長さ、拡張後直径、拡張圧等）

ウ ステントとデリバリーシステムの性能に関する評価

使用前の準備操作性の確認、併用する他の医療機器との適合性、プッシュアビリティー(デリバリーシステム近位部に加えた力が遠位部に均等且つ滑らかに伝わること)、トラッカビリティ（ステントをマウントしたデリバリーシステムが狭窄部を含む血管内に追従しガイドワイヤー上を前進すること）、柔軟性（ステントをマウントしたデリバリーシステムが挿入時に要求される屈曲や角度に応じて曲がり、またステントは血管走行に沿った状態で留置されること）、放射線不透過性、使用後のデリバリーシステムの損傷の有無について評価すること。

エ 留置後の血流、塞栓の有無、血圧や心電図の変化

オ 組織病理学的所見

2） ステント自体の耐久性

ア 最悪の生理的負荷を受けたときの最大ストレスを同定する有限要素解析又はその他のストレス解析。（残存ストレス量を求め、安全係数を算出する際に詳細を明らかにしなければならない。この解析は埋植寿命の間にステントの疲労破損が起こらないことを証明するものでなければならない。）

イ １０年分の拍動（約４億回）に相当する加速試験を示すこと。この際、統計学的に十分な数を用いて、直径を最大まで広げ、血管の状況を反映したものとすること。

（5） 臨床試験の試験成績に関する資料

1） 基本的な考え方

ア 冠動脈ステントの治験を実施する際には、原則として既承認品との無作為化比較試験を実施すること。

イ 新規材料を用いたもの、新規デザインのもの、薬剤や放射活性物質をコーティングしたものなどで新規性の高いものについては、その特徴に応じ有効性、安全性を担保するための評価項目を追加すること。また、その際には、より長期の試験が求められることがあること。

ウ 主要評価項目の設定とその有効性、安全性の判断基準や用いる症例数等については、治験計画届書及び承認申請資料で設定根拠を明らかにすること。また、評価項目の統計的な処理についても方法の妥当性を説明

すること。

エ　ステントの材料、基本デザイン、留置方法、径、長さ、性能指標等から既承認のステントとの類似性が高いと判断されるものにあっては、それぞれの対象患者における historical control を利用した一群のみの試験の実施も可能であること。この場合の試験の患者背景、評価項目、観察期間、症例数等については historical control と比較が可能なものとすること。なお、類似性が高いと判断した根拠、historical control 選定の妥当性については、治験計画届書の添付資料や申請資料の中で証明すること。

オ　治験にあたっては、申請上最も径が細く長いステントについても、十分な症例数を実施し、主たる評価項目（1の（5）の3）の①のオ及びキ、1の（5）の3）の②のカ等）毎にステントの各々の径と長さの組み合わせについて実施された症例数及び試験成績の一覧表を添付すること。

カ　小血管、病変長の長い病変へのステントの使用については、一般に再狭窄率が高いことが知られているので、使用目的を十分に考慮し、適切な臨床試験を設定する必要があること。

2）　観察項目

各背景と治験のスケジュール時期において観察が必要と考えられる項目を参考として示す。

①　患者背景

イニシャル（または識別番号）、年齢、性別

治療を必要とする高血圧の有無、治療を必要とする糖尿病の有無、高コレステロール血症（高脂血症）の有無、喫煙歴、家族の虚血性心疾患歴の有無

カナダ心臓病学会による狭心症の状態：CCS 4・CCS 3・CCS 2・CCS 1・狭心症の症状なし(CCS 0)

心筋梗塞歴、PTCA 歴、CABG 歴

心電図所見

②　病変背景

病変の種類（ネイティブ冠動脈、グラフト血管）

病変の部位

狭窄の履歴（*de novo*・再狭窄・ステント内再狭窄）

ACC/AHA 病変タイプ（タイプA・タイプB・タイプC）

③　手技記録

手技日

留置ステント数、ステント長・径
使用バルーンカテーテルのバルーン長・径・最大圧力
併用薬（抗凝固薬、抗血小板薬、心臓関連薬）
手技直前血管造影（最小血管径(mm)、対照血管径(mm)、径狭窄度(%)、病変長(mm)）
術後血管造影（最小血管径(mm)、対照血管径(mm)、径狭窄度(%)）
有害事象

④ 退院時
狭心症の状態
併用薬（抗凝固薬、抗血小板薬）
術後退院までの有害事象
心電図所見

⑤ 術後１ヶ月
併用薬（抗凝固薬、抗血小板薬）
退院後術後１ヶ月までの有害事象

⑥ 術後６ヶ月
併用薬（抗凝固薬、抗血小板薬）
術後１ヶ月以降に発現した有害事象
新規または再狭窄冠動脈病変の場合は、血管造影（最小血管径(mm)、対照血管径(mm)、径狭窄度(%)）

3） 評価項目

有効性及び安全性を評価するために、少なくとも以下の評価項目は必要であると考えられること。妥当である場合には各項目の定義の変更が可能であるが、試験実施前に治験実施計画書で定義しておくこと。

なお、再狭窄の測定については、施設間格差をなくすため、特定の施設において全ての症例の測定を行うことが望ましいこと。

① 有効性に関する評価項目

ア 技術的成功率：指定された機器のみを用いて、デリバリーに問題が発生することなく、指定されたステントを標的病変に留置でき、定量的冠動脈造影による残存狭窄度（病変の最小部径(mm)を対照血管径(mm)で除したもの（%））が50%未満を達成できた症例の割合

イ 手技的成功率（定量的冠動脈造影による手技終了時の径狭窄度が50％未満で、入院中に主要心事故（死亡（明らかに冠動脈虚血以外のものを除く）・心筋梗塞・TLR（Target Lesion Revascularization：標的病変の再血行再建術で、緊急冠動脈バイパス術によるものを含む）をいう。）の発生がなかった症例の割合（％）。

ウ　術直後の残存狭窄度

a) 平均値±標準偏差

b) 範囲（最小値、最大値）

エ　術後６ヶ月後のステント内狭窄度

a) 平均値±標準偏差

b) 範囲（最小値、最大値）

オ　術後６ヶ月間に発生した再狭窄症例（ステント内径狭窄度が 50%以上）の発生率(%)

カ　術後６ヶ月間の TLR のあった症例の割合

キ　術後６ヶ月間の TVF（Target Vessel Failure：標的血管不全、（死亡（明らかに冠動脈虚血以外のものを除く）・心筋梗塞・標的血管の再血行再建術（緊急冠動脈バイパス術によるものを含む）をいう。））のあった症例の割合。

②　安全性に関する評価項目

ア　入院中の有害事象発生率：入院中に、死亡、心筋梗塞、緊急冠動脈バイパス術、TLR、ステント血栓あるいは脳卒中が見られた症例の割合

イ　退院後の有害事象発生率：退院後に、死亡、心筋梗塞、緊急冠動脈バイパス術、TLR、ステント血栓あるいは脳卒中が見られた症例の割合

ウ　出血性有害事象発生率

エ　血管性有害事象発生率

オ　ステント血栓発生率：血管造影によって、ステント留置血管内に血栓あるいは亜急性閉塞が認められたもの、あるいは、血管造影によってステントの開存が確認されていない症例に認められた術後３０日以内の死亡で冠動脈虚血が否定できない症例の割合。

カ　術後６ヶ月間に見られた主要心事故のあった症例の割合。

キ　術後の入院日数

a) 平均値±標準偏差

b) 範囲（最小値、最大値）

ク　ステントデリバリーの不成功率（脱落を含む）

ケ　術後６ヶ月間に見られた非Ｑ波心筋梗塞のあった症例の割合（初期（入院中)、退院後）

コ　術後６ヶ月間に見られたＱ波心筋梗塞のあった症例の割合（初期（入院中)、退院後）

サ　術後６ヶ月間に見られた緊急冠動脈バイパス術のあった症例の割合（初期（入院中)、退院後）

シ　術後６ヶ月間に見られたステント血栓のあった症例の割合（初期（入

院中)、退院後)

ス　術後6ヶ月間に見られた死亡症例の割合（初期（入院中)、退院後)

セ　術後6ヶ月間に見られた出血性有害事象のあった症例の割合

ソ　術後6ヶ月間に見られた血管性有害事象のあった症例の割合

タ　術後6ヶ月間に見られた脳血管障害のあった症例の割合

2．承認申請書の作成上の留意事項について

承認申請書の各欄については、原則として以下の事項を記載するほか、ステントのデリバリーシステムのうち、バルーンカテーテルについては、平成１０年１０月２６日付け審査実務連絡Ｎｏ．９８‐２厚生省医薬安全局審査管理課事務連絡「カテーテル類の承認申請書の作成上の留意事項について」に沿ったものとすること。また、これ以外にも製品の特性に応じ必要な事項を記載すること。

（1）　「形状、構造及び寸法」欄

ア　形状、構造（パターン図、ステント拡張前後の形状図、溶接部の図示等)

イ　寸法（長さ、径：ステント拡張前のステント外径及び拡張後のステント内径または外径、厚み、幅等)

（2）　「原材料」欄

形状、構造及び寸法欄において記載した内容との対応関係が明確となるように、原材料、成分及び分量等を正確に記載し、その規格を明らかにすること。

（3）　「性能、使用目的、効能又は効果」欄

1）　性能

ア　デリバリーシステム引張強度

イ　デリバリーシステム接合部強度

ウ　デリバリーシステム推奨拡張圧（Nominal pressure）

エ　デリバリーシステム最大拡張圧(Rated Burst Pressure)

オ　拡張前後のステント長変化率

カ　ラディアルフォース

キ　リコイル率

ク　バルーンの拡張、収縮時間

ケ　ステント保持強度

コ　拡張後のフリー（オープン）エリア

2）　使用目的、効能又は効果

原則として実施された臨床試験成績に応じ、次の例に準じ記載するこ

ととする。

「対照血管径が○○mm から○○mm の範囲にあり、新規または再狭窄冠動脈病変（病変長○○mm 以下）を有する症候性虚血性疾患患者の治療（インターベンション治療の不成功に伴う急性若しくは切迫閉塞の治療を含む）。ただし、対照血管径が○○mm 若しくは病変長が○○mm 以上○○mm 以下のものについては、インターベンション治療の不成功に伴う急性若しくは切迫閉塞の治療に限定する。」

（４）　「規格及び試験方法」欄

ア　外観、寸法

イ　デリバリーシステム引張強度

ウ　デリバリーシステム接合部強度

エ　デリバリーシステム加圧強度及びもれ試験

オ　金属成分の溶出物試験（参考：JIS T 0304 金属系生体材料の溶出試験方法）

カ　無菌性に関する試験項目については、平成１０年３月３１日付け医薬審第３４７号厚生省医薬安全局審査管理課長通知「滅菌医療用具の製造（輸入）承認申請における滅菌に関する取扱いについて」及び、平成１２年７月１８日付け医薬審第８７７号厚生省医薬安全局審査管理課長通知「滅菌医療用具の製造(輸入)承認申請における滅菌に関する取り扱いについて（その２）」に準じること。

キ　エンドトキシン試験

ク　腐食試験（参考：JIS T 0305 擬似体液中での異種金属間接触腐食試験方法）

ケ　耐食試験（参考：JIS T 0302 金属系生体材料のアノード分極試験による耐食性の評価方法）

３．その他

申請資料の作成にあたっては、米国医薬品食品庁医療用具体外診断薬審査センターから出されている「guidance for the submission of research and marketing application for interventional cardiology devices」（１９９４年５月）も参考にすること。

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Medical Devices

Public Workshop - ASTM-FDA Workshop on Absorbable Medical Devices: Lessons Learned from Correlations of Bench Testing and Clinical Performance, November 28, 2012

The Food and Drug Administration (FDA) is announcing a public Workshop entitled "ASTM-FDA Workshop on Absorbable Medical Devices: Lessons Learned from Correlations of Bench Testing and Clinical Performance." FDA is co-sponsoring the workshop together with ASTM International, an organization responsible for the development and delivery of international voluntary consensus standards.

The purpose of the workshop is to provide a forum for industry, academia, FDA to discuss test methods for establishing correlations between in vitro and in vivo degradation of absorbable implant devices, and the interaction of mechanical loading and mechanical performance with degradation. While there will be an emphasis on cardiovascular indications as part of a panel session, characterization techniques and experiences from both cardiovascular as well as non-cardiovascular devices will be discussed and are encouraged.

- Date, Time and Location
- Federal Register Notice[1]
- Background and Discussion Topics
- Agenda
- Transcript
- Program and Booklet
- Contact Us

Date, Time and Location

This workshop was held November 28, 2012, beginning at 8:15AM at the following location:

FDA White Oak Campus
10903 New Hampshire Avenue
Building 31 Conference Center (Great Room, Room 1503)
Silver Spring, MD 20993

Background and Discussion Topics

Recent studies have identified promising results for the use of absorbable materials in implantable devices for endovascular therapies such as fully absorbable cardiovascular stents, where the stent platform degrades, as well as absorbable coatings. The use of these materials for cardiovascular indications poses new risks due to the critical fatigue and mechanical loading demands that the implant must withstand and perform. However, the optimal preclinical/bench testing paradigm to predict clinical performance of fully absorbable cardiovascular devices is not yet defined. This workshop will discuss the use of absorbable materials (including synthetic polymers as well as erodible metals) in medical devices across a broad range of indications with the aim of defining successful and unsuccessful methods to predict clinical performance, and will subsequently apply these methods to unique challenges for cardiovascular indications. Therefore, we invite presenters to share their experience from cardiovascular and non-cardiovascular medical devices, as

well as devices that are fully absorbable, and devices with only a component or coating that is absorbable. This workshop will bring together the expertise of academia and industry professionals to define test methods as well as to educate and inform their colleagues in industry, academia, and device regulation on the performance and predictability of absorbable medical device degradation. Workshop participants will seek to define the critical factors for preclinical/bench testing and clinical predictability. They will then apply lessons learned from marketed devices for non-cardiovascular indications to the emerging uses of absorbable devices to treat cardiovascular disease.

Topics to be discussed at the workshop include:

- Correlations of in vitro and in vivo absorption
- Quantitative characterization of absorption kinetics
- Test methods to identify interactions of absorption with mechanical loading and
- Test methods to assess mechanical performance of the absorbable product

The lessons learned from both early cardiovascular and well-established non-cardiovascular device experiences will be presented. These lessons will be discussed in the context of emerging cardiovascular uses of absorbable materials as part of a panel session at the end of the workshop.

Agenda

Time	Subject
7:30-8:15	**Registration**
8:15-8:30	**Opening Remarks**[2]
8:30-9:30	**Plenary Presentation** • John Middleton, *"Tailoring of Poly(lactide-co-glycolide) to Control Properties"*[3]
9:30-10:30	**Session I: Considerations for Modeling Degradation in Vitro** Moderator : Hany Demian • Karen Burg, *"Processing Considerations for Degradable Materials: The many profiles of 'polylactide'"*[4] • Elizabeth M. Perepezko, *"Establishing Accelerated In Vitro Aging Methods for Evaluating Resorbable Polymeric Implants"* • Jeremy Schaffer, *"Corrosion and fracture behavior of bioabsorbable wires in Bio-simulated fluid"*
10:30-10:45	**Break**
10:45-11:45	**Session II: *In Vitro-In Vivo* Correlation (IVIVC) & Predicting Corrosion in Degradable Metals** Moderator : Erica Takai • Frank Witte, *"Current Opinion of the Science Community on Guidelines and Testings of Biodegradable Metals"*[5] • Yeohung Yun, *"Testing Corrosion for Biodegradable Mg alloys: Science, Current Methods, and Limitation"* • John Disegi, *"In Vitro Mechanical Property Degradation of 2.0 mm Dynamic Compression Plates Fabricated from Absorbable Fe-28Mn Alloy"*
11:45-13:00	**Lunch on your own** Food for purchase will be available
13:00-14:45	**Session III: *In Vivo* Performance and *In Vitro-In Vivo* Correlation (IVIVC) of Polymer Systems** Moderator : Ji Guo • Kathryn Uhrich, *"Polymorphine: a biodegradable drug delivery system for extended analgesia"*[6] • Meng Deng, *"In Vitro and In Vivo Degradation of Absorbable Polymeric Biomaterials: Experiences and Learning"*[7] • Nathan Lockwood, *"Characterization of Novel Degradable Polymers for Drug Delivery Applications"* • Renu Virmani, *"Histopathologic results of bioabsorbable stent (BVS) in the*

porcine model"

- Yen-Lane Chen *et al.,"Characterization of the In Vivo and In Vitro Degradation of Poly(DL-lactic-co-glycolic acid) on a Drug-Eluting Stent"*

14:45-15:00**Break**

15:00-16:20**Session IV:Mechanical Interactions & Product Development Considerations** Moderator : Scott Anderson

- Lisa Ferrara, [8]*"Mechanical Evaluation of Biodegradable Magnesium and Magnesium Alloys: Identifying the Necessary Testing, Challenges, and Pitfalls for Biomaterial Characterization[9]"*
- Danika M. Hayman and James E. Moore Jr., *"Defining a Material Model for a Bioresorbable Stent Fiber"*[10]
- Julia Fox et al., *"Relationship between Mechanical Loading and Chemical Degradation in Polymeric Bioresorbable Vascular Scaffolds"*
- Byron Hayes, *"Standards Development in Absorbable Medical Devices"*[11]

16:20-16:30**Break**

16:30-17:30**Panel Discussion** Moderator : Maureen Dreher[12]

Transcript

- Transcript for November 28[13]

Program and Booklet

- Workshop Program and Booklet[14] (PDF)

Contact Us

For questions regarding workshop content please contact:

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Guidance for Industry and FDA Staff

Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems

Document issued on: April 18, 2010

On August 30, 2013 FDA issued a draft guidance ***Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*****.** When final, that guidance document will update and augment (but not replace) this guidance.

This document supersedes the guidance "Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems" dated January 13, 2005.

For questions regarding this document contact Hina Pinto or Elizabeth Hillebrenner at 240-276-4222 or hina.pinto@fda.hhs.gov or elizabeth.hillebrenner@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Interventional Cardiology Devices Branch
Peripheral Vascular Devices Branch
Division of Cardiovascular Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071863.htm. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 240-276-3151 to receive a hard copy. Please use the document number (**1545**) to identify the guidance you are requesting.

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Guidance for Industry and FDA Staff

Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

This guidance provides FDA's current thinking on non-clinical engineering tests that are submitted in investigational device exemption applications (IDEs) and premarket approval applications (PMAs) to support the safety and effectiveness of intravascular stents and their associated delivery systems. This guidance also provides recommendations for labeling for these devices.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Definition of Terms Used in this Guidance

Intravascular Stent

Intravascular stents are also known as endovascular stents or vascular stents. This document uses the term "intravascular stent" to refer to intravascular, endovascular, and vascular stents.

An intravascular stent is a synthetic tubular structure intended for permanent implant in native or graft vasculature. The stent is designed to provide mechanical radial support after deployment; this support is meant to enhance vessel patency over the life of the device. Once the stent reaches the intended location, it is expanded by a balloon or self-expanding mechanisms defined below.

Contains Nonbinding Recommendations

Balloon Expandable Stent

A balloon expandable stent is expanded by a balloon catheter. The diameter of the stent increases as the balloon diameter increases. The stent remains expanded after deflation of the balloon.

Self-expanding Stent

A self-expanding stent's diameter increases from its pre-deployed size to its post-deployed size in the absence of balloon inflation or other mechanical assistance. The self-expanding quality can result from material properties or geometry or both.

Stent Delivery System

A stent delivery system delivers a stent to a target site and then deploys the stent. A stent delivery system for a balloon expandable stent consists of a balloon catheter. Self-expanding stent delivery systems may or may not include a balloon.

II. Scope

This guidance document addresses self-expanding and balloon expandable extracranial intravascular stents and their associated delivery systems. The scope includes extracranial intravascular stents placed in coronary or peripheral arteries and saphenous vein grafts but is not limited to stents used in these locations; other vascular indications outside of the intracranial vasculature are also included.

Intravascular stents, including balloon expandable and self-expanding stents, are class III devices whose product codes are given in the table below.

Table 1: Product Codes for Stents Addressed in this Guidance

Product Code	Device
MAF	Stent, Coronary
NIM	Stent, Carotid
NIN	Stent, Renal
NIO	Stent, Iliac
NIP	Stent, Superficial Femoral Artery

These devices require a premarket approval (PMA) application before marketing. See sections 513(a) and 515 of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR Part 814.

Clinical studies conducted in the United States in support of a PMA approval must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. FDA believes that the intravascular stents addressed by this guidance document are significant risk devices as defined in 21 CFR 812.3(m),[1] and as such, are not exempt from the requirement to submit an

[1] Refer to http://www.fda.gov/oc/ohrt/irbs/devices.html#risk.

investigational device exemption (IDE) application (21 CFR 812.2(b), 812.20(a)(1). When an IDE application is required, a sponsor must not begin a clinical trial in humans in the United States until FDA has approved the application (21 CFR 812.20(a)(2), 812.42). Sponsors of such studies must comply with the following:

- IDE regulations (21 CFR 812)
- Regulations governing institutional review boards (IRB) (21 CFR 56)
- Informed consent (21 CFR 50). [2]

After FDA has approved a device, clinical studies conducted in accordance with the indications in the approved PMA, including clinical design validation studies conducted in accordance with the quality systems regulation, are exempt from the investigational device exemptions (IDE) requirements. However, such studies must be performed in conformance with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

Non-vascular stents meant for use outside the vasculature are not included in the scope of this document. This document also does not include stents used in the intracranial vasculature. You should contact the Division of Reproductive, Abdominal, and Radiological Devices for information about biliary stents, the Division of Anesthesiology, General Hospital, and Infection Control Devices for information about non-vascular stents, or the Division of Ophthalmic, Neurological, and Ear, Nose, and Throat Devices for information about stents used in the intracranial vasculature.

Some of the tests (and labeling recommendations) in this guidance are relevant to covered (NIV), drug-eluting (NIQ), and biodegradable stents, and stents used to treat aneurysms or dissections. However, FDA recommends additional testing to fully characterize these devices. For drug-eluting stents, please refer to the draft document **Coronary Drug-Eluting Stents— Nonclinical and Clinical Studies.**[3] For other coated stents, FDA recommends that you assess the need for additional testing to address coating characterization, coating integrity, and coating durability. The Interventional Cardiology Devices Branch and the Peripheral Vascular Devices Branch are available to discuss additional testing details for these stents and indications.

This guidance document supplements other FDA publications on PMA, PDP, and IDE applications and should not be construed as a replacement for those documents. For general information about these applications, see the CDRH Device Advice web site given below:

- PMAs (21 CFR Part 814):
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm

[2] You should review the statutory definition of applicable clinical trial to determine if your trial must be registered to comply with the law. *See* PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)). http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf Information can be submitted to ClinicalTrials.gov using the Protocol Registration System (PRS). For more information visit the PRS Information Page.

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072193.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072196.pdf

- PDPs (21 CFR Part 814.19):
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm048168.htm#pdp
- IDEs (21 CFR Part 812):
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm

This guidance also cites a number of voluntary standards, many of which are recognized by FDA. You may access a list of the FDA-recognized standards from the CDRH web site, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. See also the guidance, **Recognition and Use of Consensus Standards**, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077274.htm.

III. Content and Format of Test Data

A. Summary Reports

We recommend that you present test data in a summary that includes the elements described below.

Table of Contents

You should place a table of contents at the front of the document. Each line listing in the table of contents should refer to major section titles and the page numbers where each section can be found.

Test Summaries

You should briefly describe all tests performed.

Test Data Summaries

You should include test data summaries for all tests. The summaries should contain:

- minimum measured value (min)
- maximum measured value (max)
- mean
- standard deviation of the test data (std. dev.).

Summary of Conclusions

You should summarize your conclusions regarding whether the results support the safety and effectiveness of your device for each test.

B. Test Reports

You should include full test reports for all tests performed. Your test reports should include the sections described below.

Test Specimen Information

Your test specimen description should include:

- number of test specimens
- size (diameter, length, or other relevant dimensions) of all test specimens
- rationale for the number of test specimens and sizes tested
- whether the specimens represent the finished product
- sterilization parameters and number of sterilization cycles applied to the test specimens.

Test Protocol

You should submit your test method or protocol. It should contain enough detail that an individual familiar with intravascular stent testing will be able to interpret the test results.

Protocol Deviations

You should describe any protocol deviations and their effect on the ability of the test data to support the safety and effectiveness of the device.

Test Parameters and Acceptance Criteria

You should report the test parameters and acceptance criteria that you use, including:

- an explanation of and rationale for critical test parameters
- specifications or acceptance and rejection criteria
- a rationale for the specification or acceptance and rejection criteria based on the clinical requirements of the device.

Raw Data

We recommend that you include all raw data in appendices or on a CD-ROM, or make the raw data available for our review upon request.

Test Results

You should summarize your test results and include statistical analysis when it is appropriate.

Data Analysis

You should analyze the data, including any outlying points and anomalous results, and explain whether the data meet the given acceptance criteria.

Conclusions

We recommend that you describe the conclusions drawn from the test results, and the clinical significance of the conclusions.

C. Test Protocols

You should establish protocols for all experiments or computational analyses, including acceptance criteria when applicable, before you perform the tests. Established test protocols help to ensure consistent repetition of tests and allow comparison of data between test runs.

We are willing to informally review and provide comments on test protocols prior to conduct of a test, if there are aspects of a particular test that you feel might benefit from FDA input. While FDA does not approve test protocols, our input before testing may improve your ability to demonstrate the performance characteristics of your device.

Your test protocols should assess device performance when exposed to the most extreme clinical conditions that your device is likely to experience. Both device configuration and physiologic conditions affect the performance of devices in the human body. We recommend that you evaluate extreme device dimensions, tolerances, sizes, and any other important device parameters in your testing program. We also recommend that you examine the outer limits of physiologic variables such as blood pressure, vascular compliance, and anatomic types. You should clearly state all test conditions in the test protocol and support them with references to applicable literature, standards, or both.

Occasionally, the worst performing combination of device configuration and physiologic conditions occurs in the mid-range of the relevant variables. You should check for this situation when developing your protocols to ensure that you test the worst performing combination.

Several of the tests listed in this guidance do not apply to all intravascular stents and delivery systems. The designs or clinical indications to which these tests do apply are noted in their descriptions. We believe that each test helps to support the safety and effectiveness of intravascular stents for their stated indication. Each test's clinical or engineering significance is described in **Section V**.

If you believe a test recommended in this guidance does not apply to your device, you should include a heading for the test in your test summary, followed by an explanation of why the test is not applicable. We will then be aware that you did not inadvertently omit it from your application.

Your explanation should include a rationale for why you do not think the test should be performed in order to support the safety and effectiveness of your device. Your rationale should clearly demonstrate, by reference to a Failure Modes and Effects Analysis (FMEA) or other risk analysis method, that the particular test or data set is not necessary or appropriate to support the safety and effectiveness of your device. Alternatively, you may identify measures you have taken to mitigate the risks associated with the device in the failure mode that would usually be evaluated using the test that you have not performed.

Intravascular stents have been in clinical use for over a decade and some designs are in their fourth or fifth generation. Some attributes may not be modified when changes are made in the design of a next-generation device. For a particular attribute, rather than providing original data for a next-generation design, it may be appropriate to reference previously tested stents in the

same device family. However, a reference to previous generic device experience, for example, "alloy X has been used in stents," generally is not adequate. If you choose to reference testing previously performed on already marketed stents, you should explain why the previous testing is relevant. If a particular attribute of the next-generation device is re-evaluated, a comparison of the results to those of the previous generation may be helpful.

Sample Selection

You should use a statistically significant sample size whenever possible. When using a statistically significant number of samples is not possible, you should provide a scientific rationale to support the number of samples tested in your test summary and test protocols, and provide reasonable assurance that the test results support the safety and effectiveness of the device.

All test samples should represent the finished product. Your devices should be sterilized by the final production process, including repeat sterilization cycles. You should note any tests that use samples that are not finished, sterilized product in the test summary and test protocols, and explain why doing so does not affect the applicability of the test results to the evaluation of safety and effectiveness of the device.

You should test the full range of sizes that you intend to commercially distribute. The recommended default paradigm is a 2 x 2 factorial of the largest and smallest diameters and lengths, also known as the "four corners" paradigm for each different stent design. We recommend a different set of sizes for some of the tests in **Section V.** **Table 2** illustrates the four corners concept for a typical coronary stent. If you do not test a device using the four corners paradigm or the recommended sizes for a particular test, you should provide a scientific rationale to support the sizes that you do test in the test summary and test protocols. For some tests, we may recommend that you perform an analysis to identify the size or sizes that represent the worst case.

Table 2: Four Corners Test Paradigm Example

Stent Diameter (mm)	**Stent Length (mm)** 8	12	18	24
2.5	X			X
3.0				
3.5				
4.0	X			X

X = Recommended sizes for testing

IV. Non-Clinical Engineering Tests

A. Material Characterization

1. Material Composition

Significance

Material composition testing documents a baseline for evaluation of the effects of future changes in materials.

Recommendation

We recommend that you specify the device characteristics described below. If your stent material is identical to your previously marketed stents, we recommend that you identify the stent(s) and material(s) to which it is identical.

<u>Stent and Delivery System Materials</u>

We recommend that you list materials by trade or common name, for example, 316L stainless steel.

<u>Generic Chemical Formulation</u>

We recommend that you list formulations of all materials by generic name, for example, 18 Cr-14 Ni-2.5 Mo stainless steel. We recommend that you reference any applicable standard designations such as ASTM F138.[4]

<u>Chemical Composition and Formulation</u>

We recommend that you provide detailed specifications for the chemical composition or formulation of materials (or both) for any new materials, alloys, or formulations with no history of use in intravascular stents or PTCA catheters.

Surface finish is known to affect other material properties for nitinol (e.g. corrosion, nickel ion release). Therefore, for stents containing nitinol, we recommend that you characterize the material surface of your finished product in terms of passivation layer microstructure vs. depth. Special attention should be paid to surfaces which might include heat-affected zones (e.g., from laser cutting), or to geometric areas which may be affected differently by finishing (e.g., internal angles).

<u>Material Certification</u>

We recommend that you provide documentation to certify that incoming raw material conforms to specifications. We recommend that you submit supplier certification, incoming quality control test results, or equivalent documentation.

[4] ASTM F138 Standard Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants

2. **Shape Memory and Superelasticity of Intravascular Stents**

Significance

The transition temperature of nitinol or other shape memory and superelastic materials determines specific shape memory and superelastic properties.

Recommendation

We recommend that you document the following properties for any shape memory or superelastic materials present in your stent.

<u>Austenite Finish Transition Temperature (Af)</u>

We recommend using the methods described in ASTM F2004,[5] ASTM F2082,[6] or equivalent methods.

<u>Mode of Action</u>

We recommend that you describe the mode of action (e.g., thermal shape memory or superelasticity) by which the stent transitions to the specified size and shape.

3. **Stent Corrosion Resistance**

Significance

Stent corrosion can cause or contribute to premature stent failure. In addition, corrosion byproducts may be toxic or cause other adverse biological and tissue responses.

Recommendation

We recommend that you address the corrosion properties of your device described below. If some of these characteristics do not apply to your device, we recommend that you explain this in your application.

<u>Fretting Corrosion</u>

We recommend that you address the potential for fretting corrosion between two stents since there is a reasonable expectation of stent overlap during clinical use for most indications. We recommend that the examination of samples for fretting corrosion be incorporated as part of fatigue/durability testing (see **Section B.11. Accelerated Durability Testing**). You should ensure that overlapping stents are in contact with one another and that the setup does not preclude micromotion between strut elements. For coronary stents, because tortuosity of a target deployment site could result in increased micromotion between components or multiple stents, the mock deployment site should be bent to a worst-case clinically relevant radius of curvature, which should be smaller than most anatomical

[5] ASTM F2004 Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Alloys by Thermal Analysis
[6] ASTM F2082 Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Shape Memory Alloys by Bend and Free Recovery

situations encountered in clinical use. For example, for most coronary indications, FDA recommends a 15mm radius of curvature as this represents worst case for 90% of the population based on published angiographic measurements.[7] For other indications such as use in coronary bifurcations, please provide a similarly robust clinical rationale for the radius of curvature selected.

We recommend conducting a visual (e.g., SEM) inspection of samples after fatigue/durability testing for evidence of corrosion.

Results from testing through one year time equivalent should be provided in support of an IDE application. Results from testing through ten years time equivalent should be provided when they are available, but not later than at the time of PMA submission. A scientific rationale for the number of samples evaluated for fretting corrosion should be provided.

<u>Pitting and Crevice Corrosion Potential</u>

We recommend that you characterize the corrosion potential of your stent with any potential surface damage that may result from fatigue. We recommend testing the same samples used in the fretting corrosion evaluation described above according to the method in ASTM F2129.[8] Specifically, one stent from each overlapping pair subjected to fatigue cycling should be evaluated for pitting and crevice corrosion potential while the other stent from each pair is evaluated for fretting corrosion as described above. Test reports for pitting and crevice corrosion potential testing should include the recorded potentials as well as the polarization curves.

Results from testing through one year time equivalent should be provided in support of an IDE application. Results from testing through ten years time equivalent should be provided when they are available, but not later than at the time of PMA submission.

If results do not indicate an acceptable pitting and crevice corrosion potential, you should consider characterizing the corrosion potential of the finished, as manufactured stent to determine if the corrosion potential of your stent is affected by fatigue.

You may use literature citations or previous experience with stents to address this issue; however, the materials, design, and fabrication processes specific to your stent may reduce or eliminate the applicability of generic literature. For example, the pitting corrosion resistance of nitinol is sensitive to processing variables such as heat treatment and electropolishing; therefore, for a nitinol stent, you should characterize the corrosion potential of the finished stent.

[7] Liao R, Green NE, Chen SY, Messenger JC, Hansgen AR, Groves BM, Carroll JD. Three – dimensional analysis of in vivo coronary stent – coronary artery interactions. International Journal of Cardiovascular Imaging. 2004 Aug;20(4):305-13.
[8] ASTM F2129 Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices

Galvanic Corrosion

If your stent contains more than one type of metal, such as a base stent material with added marker bands, we recommend that you demonstrate the design's resistance to galvanic corrosion. If you expect that your stents will be overlapped during clinical procedures, and the contacting or overlapping stents may be made of different materials, we recommend that you address the potential for galvanic corrosion between stents. In this case, we recommend that you use the marketed stent with the highest galvanic coupling with your stent material in your evaluation. We recommend the methods described in ASTM G71[9] or their equivalents. These methods may be modified to provide for testing of finished stents, for example, by incorporating the experimental setup described in Appendix X3 of ASTM F2129.

Testing should be conducted even if an alloy conforms to a specific standard because manufacturing processes can affect the galvanic corrosion potential of the finished product.

B. Stent Dimensional and Functional Attributes

1. Dimensional Verification

Significance

Accurate stent dimensions help the physician to achieve proper stent sizing and accurate placement in the body. They also affect the functional behavior of the stent.

Recommendation

FDA recommends that you provide the information described below that applies to your stent. We recommend the methods used in ASTM F2081[10] or their equivalents. At a minimum, you should take measurements at each end and in the middle of the stent and at two circumferential points 90˚ apart (for a total of six measurements). You should take additional measurements as appropriate based on device design.

Un-expanded Stents

We recommend that you provide dimensional specifications and tolerances for un-expanded stents.

Balloon Expandable Stents

We recommend that you measure and report the expanded diameter of balloon expandable stents. You may do this as part of the process of creating a compliance chart. See **Section C. Delivery System Dimensional and Functional Attributes, 5. Balloon Compliance**.

[9] ASTM G71 Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes.
[10] ASTM F2081 Standard Guide for Characterization and Presentation of the Dimensional Attributes of Vascular Stents

Self-Expanding Stents

We recommend that you verify the unconstrained expanded diameter of self-expanding stents with measurement data.

2. Percent Surface Area

Significance

The area over which a stent contacts a vessel may affect the biologic response of the vessel. The amount of open, non-contact area may influence tissue prolapse or ingrowth.

Recommendation

We recommend that you report the percent surface area of the stent for both the smallest and largest nominal expanded diameters for each stent design. We recommend that you evaluate different lengths only if you expect that the percent surface area varies significantly with stent length. We recommend that you measure or calculate the contact area of the stent structure, and express the final value as a percentage of the reference area, as shown below:

Percent Surface Area = 100 x (Area in Contact with Vessel ÷ Full Cylindrical Surface Area)

(The reference area is defined as the full cylindrical surface area at the expanded stent diameter.) We recommend that you apply the methods described in ASTM F2081 or their equivalents.

3. Foreshortening

Significance

Foreshortening, i.e., dimensional changes that may occur when deploying a stent, influences final stent length. Knowledge of the foreshortening characteristics aids in proper stent length selection and proper placement in the body.

Recommendation

FDA recommends that you report the decrease in length of the stent between the catheter-loaded condition and the deployed diameters up to the maximum labeled diameter.

We recommend that the reported value reflect the maximum nominal diameter. We recommend that you report the results in terms of a percentage of the loaded length as shown below:

Percent Foreshortening = 100 x (Change in Length ÷ Loaded Length).

We recommend that you apply the methods described in ASTM F2081 or their equivalents.

See **Section VIII. Labeling** for recommendations on data presentation of the percent foreshortening of self-expanding stents.

4. Recoil for Balloon Expandable Stents

Significance

The recoil behavior of balloon expandable stents influences proper device selection, sizing, acute post-implant results, and long-term clinical outcomes. Recoil is a function of stent design and material selection; therefore, knowledge of stent recoil helps to characterize the behavior of a particular stent design.

Recommendation

We recommend that you report the measured change in diameter of your stent between post-balloon expansion and after balloon deflation.

We recommend that you measure and report values for each labeled stent diameter. If you expect that the percent recoil varies significantly with length, we recommend that you evaluate recoil for different stent lengths at various points along the length of the stent, including the ends. The number of locations along the length of the stent at which recoil is measured should be determined by initial assessment of the stent geometry.

We recommend that you present the results as a percentage of the expanded diameter.

We recommend the methods described in ASTM F2079[11] or their equivalents.

5. Stent Integrity

Significance

Stent defects, whether a result of manufacturing flaws or subsequent damage, can contribute to clinical complications. Laser cutting or other manufacturing processes may induce flaws that are not completely removed by polishing. Plastic deformation during loading or balloon expansion may cause cracks or other damage. Self-expanding stents that are stored loaded in a delivery system may exhibit permanent set or changes in expansion characteristics as a result of time or sterilization or both.

Recommendation

We recommend that you examine your deployed stent and report any evidence of stent defects such as, but not limited to:

- cracks
- scratches
- permanent set
- coating delamination.

[11] ASTM F2079 Standard Test Method for Measuring Intrinsic Elastic Recoil of Balloon expandable Stents

We recommend that you use optical or electron microscopy, or both to look for defects. We recommend that you support the level of magnification that you use on the basis of the size of the defect that your inspection attempts to detect.

When you are looking for post-deployment damage, we recommend that you examine or inspect:

- balloon expandable stents, after expansion to the largest diameter listed in your labeling
- self-expanding stents, after expansion to the unconstrained diameter.

6. Radial Stiffness and Radial Strength

Significance

Radial stiffness and stent recoil determine the diameter of balloon expandable stents deployed in compliant vessels. Radial stiffness and radial strength characterize the ability of the stent to resist collapse under short-term or long-term external loads.

Recommendation

We recommend that you report a value for the following:

- radial stiffness, i.e., the change in stent diameter as a function of uniformly applied external radial pressure; and
- radial strength, i.e., the pressure at which your stent experiences irrecoverable deformation.

FDA recommends that you measure and report values for each labeled stent diameter. If you expect that the radial stiffness varies significantly with length, we recommend that you also evaluate different stent lengths.

We recommend that you support the diameter or pressure range used in your tests for radial stiffness. The diameter and pressure range will probably vary depending on your stent's intended target site.

7. Radial Outward Force

Significance

It is important to characterize the radial outward force of self-expanding stents. Excessive radial force could injure the surrounding tissue, while a radial force that is too low can result in incomplete apposition of the stent to the vessel wall.

Recommendation

We recommend that you measure the radial force exerted by self-expanding stents against the vessel wall after deployment. If a particular stent size or model is indicated for use in a range of vessel sizes, your assessment should cover the range of possible vessel sizes, or should include a rationale for not assessing the entire size range to be marketed. We recommend that you evaluate different stent lengths if you expect that the radial force varies as a function of the total stent length. In addition, if

you expect that the radial force of your stent is not axially uniform (for example, if your stent has a tapered length), we recommend that you measure the radial force at multiple locations along the length of the stent. The specifications for radial outward force should include both minimum and maximum values.

8. Mechanical Properties

Significance

Raw material properties determine incoming material quality and uniformity, and predict subsequent thermomechanical effects. Thermomechanical properties of the implanted stent affect clinical performance, as well as stress and fatigue behavior.

Recommendation

We recommend that you specify the mechanical properties listed below for the stent raw material(s).

Mechanical Properties of the Raw Material(s)

- ultimate tensile strength (UTS)
- yield strength (YS)
- elongation
- plateau stresses, for nitinol
- elastic strain limits, for nitinol.

Post-Processing Mechanical Properties

FDA also recommends that you report the stress-strain response of the stent after deployment. We recommend that you present the stress-strain behavior in a plot or graph that shows both loading and unloading. We recommend that you report the following post-processing mechanical properties of your stent:

- UTS
- YS
- elongation
- elastic modulus
- Poisson ratio
- endurance limit
- plateau stresses, for nitinol
- elastic strain limits, for nitinol.

In addition, reporting other mechanical properties at previous stages of manufacture, may allow characterization of your material for use in your stress/strain analysis. See **Section 9. Stress/strain Analysis**. We recommend that you determine the stress-strain response, endurance limit, and post-processing mechanical properties through physical experiments or computational models that simulate stent material properties, manufacturing, and deployment processes. If you cite any quoted literature or

handbook values, we recommend that you explain how they are relevant to your device. Since the material properties of nitinol are widely variable depending on processing, we recommend for nitinol devices that you perform physical experiments on actual post-processing samples to determine the mechanical properties of your stent. We also recommend that you use and reference standard test methods whenever possible, and describe any nonstandard test methods in detail.

9. Stress /Strain Analysis

Significance

Failure of a loaded stent may result in loss of radial support of the stented vessel or in perforation of the vessel by the stent struts. Stress/strain analysis, combined with fatigue analysis and accelerated durability testing, provides an indication of device durability.

Recommendation

FDA recommends that you include the following elements in your stress/strain analysis and test report for each stent design.

Computational Model and Inputs

We recommend that you clearly identify and explain the sources and values of all inputs and assumptions used to create the stress/strain analysis model. You should identify any software used for analysis. We recommend that finite element analysis reports include the element types used to model the stent, loading surfaces, and boundary conditions. We also recommend that you indicate if mesh refinement analysis was performed and clearly describe how you model the surrounding vessel/tissue and the type of contact elements used. Specifically, we recommend that you consider the following:

- **Model Geometry**
  We recommend that you clearly describe the stent and vessel geometry used. If symmetry is used, we recommend that you explain why this is appropriate for your model.

  If you do not model all of your stent sizes, we recommend that you explain why the modeled stent size is the worst case with respect to critical stresses. We recommend that you address the effect of dimensional variation within allowable tolerances on the results of the stress/strain analysis (i.e., maximum critical stress).

  We recommend that you provide a justification for the physiological relevance of your vessel model parameters (e.g., vessel compliance).

- **Type of Element & Mesh Refinement Analysis**
  We recommend that you specify the number and type of elements used in your mesh, including any mesh refinement in transition regions or regions of complex geometry.

  We recommend that you perform a mesh refinement analysis to ensure that the solution is independent of element size. If you do not believe mesh refinement analysis is necessary for your model, we recommend that you provide a justification for not conducting such an analysis.

- **Contact Elements**
  We recommend that you specify the type of contact defined between any 2 contacting bodies modeled in your analysis; e.g., the vessel and outer surface of your stent.

- **Material Properties (Constitutive Model)**
  We recommend that you clearly describe the material stress/strain behavior of your stent in graphical and equation form. This discussion should include, but is not limited to the following considerations:
  - Linear vs. non-linear
  - Isotropic vs. anisotropic
  - Temperature-dependent behavior
  - Raw vs. processed material.

- **Finite Element Analysis (FEA) Validation**
  We recommend that you validate your FEA (material properties, geometry, and boundary conditions) with experimental bench testing. For example, you could perform radial loading of your device and compare the force-displacement results with FEA of a simulated radial loading experiment.

<u>Stress/Strain History</u>

FDA recommends that you include the entire stress history of the device in each loading step in order to incorporate the effects of residual stresses. The entire stress history may include, but is not limited to:

- manufacturing (fabrication, annealing, electropolishing, heat-setting, etc.)
- loading onto the delivery system and/or crimping
- expansion/deployment (including over- or underexpansion into an elastic vessel, if applicable)
- stent recoil
- physiologic loading conditions.

If you believe that you do not need to model the entire stress history, we recommend that you use material properties that are consistent with the starting point of your analysis. We recommend that the material properties accurately

reflect the processing history of the stent as described in **Section 8. Mechanical Properties**. We also recommend that you explain why the omitted loading steps either do not affect the stent fatigue life or are accounted for in your model.

<u>Physiologic Loading Conditions</u>

The modeled physiologic loading mode will depend on the implantation site and may include, but is not limited to the following:

- radial dilation
- torsion
- bending
- axial tension
- axial compression
- crushing, including focal, non-focal, or uniform radial compression.

We recommend that you address the list above as well as any other relevant loading conditions when you develop the model for your stent.

If you expect that your stents will be overlapped during clinical procedures, then we recommend that you address the possibility of the additional stress concentrations caused by overlapping stents.

We believe that most coronary stents indicated for use in non-bifurcated vessels should be modeled using radial dilation in a static bend to represent potential tortuosity of the target lesion. We recommend that you perform your stress/strain analysis such that the stent is in a mock deployment site bent to a clinically relevant radius of curvature as described in **Section IV. Non-Clinical Engineering Tests A. Material Characterization 3. Stent Corrosion Resistance – Fretting Corrosion**. You may also wish to consider dynamic bending to better evaluate the performance of your stent in clinical use conditions.

For non-coronary stents, long stents, and coronary stents used in other vessel configurations such as bifurcation lesions, we recommend that you determine the relevant loading conditions.

<u>Results: Stress or Strain Critical Locations and Magnitude</u>

We recommend that you identify the critical locations of stress or strain on the stent using finite element analysis and address the effect of dimensional variation within allowable tolerances on the results. We recommend that you report the location and magnitude of all maximum tensile and compressive stresses or strains as well as the stress-strain distribution using graphics. The stress or strain measure used should be clearly defined (e.g., principal stresses, Von Mises stresses, etc.). We recommend that you explain why the measure used is reasonable considering your constitutive model. Additionally, we recommend that you explain what safety issues may arise if the stent fails in the region of maximum stress or strain.

If you choose to perform a strain-based analysis instead of a stress-based analysis, we recommend that you explain why the strain-based analysis is more appropriate for your device.

10. Fatigue Analysis

Significance

Failure of a stent due to fatigue may result in loss of radial support of the stented vessel, thrombus formation or focal restenosis, or in perforation of the vessel by the stent struts. Fatigue analysis, combined with stress/strain analysis and accelerated durability testing, provides an indication of device durability.

Recommendation

FDA recommends that you determine the fatigue resistance of the stent to physiologic loading using a Goodman analysis or another fatigue life analysis method. We recommend that your test report include the following elements.

Modeled Stent Sizes

If you do not analyze all stent sizes, we recommend that you explain why the modeled stent size is the worst case for fatigue life.

Inputs and Assumptions

FDA recommends that you use the mean and alternating stresses/strains obtained from the stress/strain analysis as input for the fatigue life determination. We recommend that you clearly identify and support all inputs and assumptions used in your analysis. If you use literature values for any material properties, we recommend that you identify the source of the data and support that your values correspond to the as-implanted condition of the material.

If you expect that your stents will be overlapped during clinical procedures, we recommend that you address the possibility of the additional stress concentrations caused by overlapping stents.

We believe that most coronary stents indicated for use in non-bifurcated vessels should be modeled using radial dilation in a static bend to represent potential tortuosity of the target lesion. We recommend that you perform your stress/strain analysis such that the stent is in a mock deployment site bent to a clinically relevant radius of curvature as described in **Section IV. Non-Clinical Engineering Tests A. Material Characterization 3. Stent Corrosion Resistance – Fretting Corrosion**.

Since the material properties of nitinol are widely variable depending on processing, we recommend for nitinol devices that you perform physical experiments on actual post-processed samples to determine the mechanical properties of your stent, and use these values in your analysis.

Results

We recommend that you provide a Goodman diagram or other graphic that compares the stresses at critical locations in the stent to the mechanical properties of the stent material. We recommend that you report fatigue safety factors in a table and explain how the safety factors were calculated.

If you choose to perform a strain-based analysis instead of a stress-based analysis, we recommend that you explain why the strain-based analysis is more appropriate for your device.

11. Accelerated Durability Testing

Significance

Accelerated durability testing validates fatigue analysis. It evaluates failure modes such as fretting, abrasion, wear, and fracture. Durability testing can help in the identification of device conditions, such as manufacturing anomalies, that were not modeled using analytical or computational methods.

Recommendation

FDA recommends that accelerated durability testing of your stent address the following issues.

Sample Size

We recommend that you determine sample size based on your fatigue analysis, including boundary conditions, loading conditions, safety factors, and any other relevant factors.

We recommend that you consider a stent as one test specimen when you report reliability calculations and results. We recommend that you consider the stent as one test specimen regardless of the symmetries present in apices, repeat units, or struts of the stent.

Sizes Tested

We recommend that you select and support the stent size or sizes tested based on the stress and fatigue analyses or other factors. We recommend that the sizes tested represent the worst case fatigue life of your device.

Test Duration

We recommend that you test the durability of your stent to the equivalent of ten years of real-time use under pulsatile flow and physiologic loading that simulates blood pressure conditions in the human body. We believe that ten years of durability data provides sufficient proof of safety of the device for most patients. If you perform a rigorous and conservative fatigue analysis that indicates an acceptable analytical safety factor, you may propose to complete long-term durability testing concurrent with clinical trials and to submit the final results

when they are available, but not later than at the time of PMA submission. In this case, results from testing through a minimum of one year time equivalent should be provided in support of an IDE application.

<u>Loading and Boundary Conditions</u>

FDA recommends that you perform long-term durability testing that models the physiological loads and boundary conditions that your stent is likely to experience under its intended use.

We recommend that you address any other types of cyclic loading, such as bending, that you anticipate your stent will experience when used as intended, and incorporate these types of loading into your testing where possible. We recommend that you explain the clinical relevance of the loading conditions used for the accelerated durability testing. If the conditions you choose differ from the loading conditions that you modeled in the stress and fatigue analyses, we recommend that you report and explain the differences.

Stent systems should be tracked through a clinically relevant test fixture prior to deployment.

<u>Overlapping Stents</u>

If you expect that your stents will be overlapped during clinical procedures, we recommend that you address the possibility of the additional risk of stent failure caused by wear or other factors. Therefore, you should test overlapping stents as part of the durability experiment.

<u>Deployment Site</u>

The testing should be relevant for your intended clinical use and condition. For example, we believe that most coronary stents indicated for use in non-bifurcation vessels should be deployed in a mock vessel bent to a clinically relevant radius of curvature as described in **Section IV. Non-Clinical Engineering Tests A. Material Characterization 3. Stent Corrosion Resistance – Fretting Corrosion**.

<u>Results</u>

We recommend that you relate the outcome of your test to the stress and fatigue analysis results.

12. Particulate Evaluation

Significance

Particulate matter can be generated by the manufacturing process or from the breakdown of any coating (e.g., hydrophilic coating) or from the stent platform, stent delivery system, or product packaging. If particles are introduced in the bloodstream during stent delivery or deployment, they may present an embolic risk to the patient.

Measurement of the total quantity and size of particulates a device system may generate is an indication of embolic risk. Therefore, evaluation of particulate generation, size, and its potential impact on the end organ served by the stented vessels is critical.

Recommendation

We recommend that you measure the total number of particulates and size of the particulates generated during the simulated delivery and deployment of all coronary stents and any other stents that are determined to be high particulate risk based on a risk analysis that takes into account the clinical setting and susceptibility of the end organ to damage from emboli.

<u>Test Samples</u>

You should conduct all testing on the finished product subject to all manufacturing processes including sterilization. You should evaluate a robust number of stents from multiple stent lots (minimum of 3 batches) and specify the number of samples (we recommend that a sample equals one stent, not a strut or portion of a stent) used, the stent size(s), and the number of stent lots for each test. We recommend that you implement a sampling plan to examine multiple lots of product to assess both inter- and intra- lot variability. You should perform testing on sizes that represent four corners of the stent design (see **Table 2** above) as well as an intermediate size. You should provide a scientific or statistical justification for the selection of samples.

It may be possible to combine the Particulate Evaluation with Delivery, Deployment and Retraction testing (see **Section IV. Non-Clinical Engineering Tests C. Delivery System Dimensional and Functional Attributes 2. Delivery Deployment and Retraction**) and/or with Coating Integrity testing (see **Section IV. Non-Clinical Engineering Tests C. Delivery System Dimensional and Functional Attributes 11. Coating Integrity**) but you should take care to ensure that only minimal additional handling of the test samples is required for the coating integrity evaluation such that particulates are neither lost nor generated.

<u>Test Methods</u>

We recommend using an *in vitro* model intended to mimic *in vivo* physiologic and anatomic worst-case conditions (e.g., tortuous path, aqueous environment) to evaluate particulates. For coronary indications, FDA recommends the tortuous path described by Figure X2.4 of ASTM F2394[12]. If you expect your stents may be deployed in an overlapped configuration during clinical procedures, we recommend that you measure particulates generated during deployment of two overlapping stents in a mock vessel. For coronary stents, the mock vessel should be bent to a clinically relevant radius of curvature as described in **Section IV. Non-Clinical Engineering Tests A. Material Characterization 3. Stent**

[12] ASTM F2394 Standard Guide for Measuring Securement of Balloon Expandable Vascular Stent Mounted on Delivery System

Corrosion Resistance – Fretting Corrosion. The stent should be in direct contact with the simulated vessel without the use of other coatings, lubricants, sheaths, or protective wraps between the stent and the simulated vessel. To ensure measurement of the total number of particles that could be potentially introduced into the bloodstream, the stent delivery system should be inserted into the text fixture to the extent which it would be inserted in clinical use and expanded to rated burst pressure (for balloon-expandable stents) or the maximum labeled diameter (for self-expanding stents). Additionally, any accessory devices required for the placement of the product should be used in this evaluation. The total number of particulates including those from the stent, delivery system, and accessory devices should be reported in each of three size ranges: $\geq 10\mu m$, $\geq 25\mu m$, and at the largest size for which validation yields $\geq 75\%$ recovery. At a minimum, the largest size should be $\geq 50\mu m$. Appropriate precautions should be implemented to ensure that the particles are suspended during sampling for particle counting and sizing to minimize artifacts from the test system.

<u>**Validation**</u>

You should describe and validate particle counting and sizing methods. We recommend that a known amount of various particle sizes be introduced into the test setup and the amount of particles recovered quantified. The number of particles recovered should closely approximate the number artificially introduced into the system. For a system to be considered validated, $\geq 90\%$ recovery should be demonstrated for the $\geq 10\mu m$ and $\geq 25\mu m$ size ranges.

13. Magnetic Resonance Imaging (MRI) Safety and Compatibility

Significance

MRI of patients with stents poses the following potential hazards:

- movement of the implant, resulting in tissue damage or misplacement
- heating of the implant and subsequent tissue damage
- image artifacts that may render the MR images uninterpretable or misleading.

Recommendation

FDA recommends that you address the issues affecting safety and compatibility of your stent in the MRI environment as described in the **Guidance for Industry and FDA Staff: Establishing Safety and Compatibility of Passive Implants in the MR (Magnetic Resonance) Environment.**[13]

<u>**Test Environment**</u>

We recommend that you report details of the test environment, such as, but not limited to:

- magnetic field strength in Tesla (T)
- maximum spatial gradient

[13] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107705.htm

Contains Nonbinding Recommendations

- maximum time rate of change of magnetic field (dB/dt)
- local specific absorption rate (SAR) at the position of the stent in the phantom
- calorimetric assessed phantom averaged whole body specific absorption rate.
- heating data versus time
- close-up photos of temperature probe placement
- overview photos of the placement of the stent in the phantom
- details about the phantom gel
- details about the pulse sequence
- temperature increase at the location of the stent but without placing the stent in the gel
- close-up photo of the stent including the stent dimensions
- $B1_{rms}$ according to IEC 60601-2-33.

We recommend that the magnetically induced deflection force for a stent composed of ferromagnetic material be determined at the location where the spatial gradient of the magnetic field is a maximum. The magnetically induced deflection force for a stent composed of paramagnetic material should be determined at the location where the product of the magnitudes of the magnetic field and the spatial gradient of the magnetic field ($|\mathbf{B}|\ |\nabla\mathbf{B}|$) is a maximum. (It is possible that this location is off the central axis of the bore of the scanner.) The magnetically induced torque is a function of the field strength, and so should be measured where the static magnetic field is the greatest, within the bore of the magnet. Note that the physical locations of the maximum torque and displacement force will almost certainly be different. You should perform all testing on finished devices.

Please note that for radiofrequency (RF) heating testing using the phantom described in ASTM F2182 or equivalent, <u>anatomical</u> positioning of the stent in the phantom does not reliably predict the implant heating in the patient. Therefore, you should provide calorimetry data to demonstrate that your test conditions are applicable to reasonable worst-case clinical conditions for heating.

Because the potential for device heating is impacted by the relationship between the conductive length of the device and the wavelength of the RF, higher magnetic field strengths do not necessarily result in worst-case test conditions for a particular device. Therefore, we recommend that you test your device at all field strengths for which you are seeking MR Conditional labeling. Given the prevalence of 1.5 T and 3.0T MR systems, we recommend that, at a minimum, you test your device using both of these systems unless you are able to provide compelling evidence that a particular system represents a worst-case situation for your device. If you anticipate that your stents will be overlapped during clinical procedures, we recommend that you consider the total length of overlapping stents in your determination of worst case test conditions and test accordingly.

There is a large variability across available MR scanners of the actual specific absorption rate (SAR) delivered. In general, the actual SAR delivered is much lower than the value displayed on the scanner console. Therefore, we recommend that you determine the actual SAR delivered to your stent during testing by calorimetry and report this in the labeling.

We recommend that your labeling contain information for the patient and medical personnel about any potential hazards associated with MRI as a result of the presence of the implanted stent. See **Section VIII. Labeling** for examples of language describing the MRI compatibility of stents in labeling.

14. Radiopacity

Significance

Stent visibility using angiographic or radiographic imaging or both generally assures proper stent placement and allows follow-up and secondary treatment.

Recommendation

FDA recommends that you evaluate the radiopacity of your stent at the smallest diameter and the shortest length during the following stages in the life of the stent:

- delivery
- deployment, if separate from delivery
- after implantation.

We recommend that you provide a qualitative or quantitative indication of the visibility of the stent on real-time and plane film x-ray. It is acceptable to use data from images of animal implants, *in vitro* phantoms, or equivalent models.

15. Crush Resistance (Peripheral Indications Only)

Significance

Peripheral stents in some anatomic locations may experience external, non-cardiac, focal, or distributed loads. These loads could cause stent deformation and, possibly, adverse clinical consequences.

Recommendation

FDA recommends that you demonstrate the ability of your stent to recover its desired size and shape after application and removal of external loads, deformations, or both. We recommend that you support the nature, location, and extent of all external loads and deformations based on the intended implantation site, for example, the carotid or femoral arteries. Testing may include the application of focal loads, axially distributed loads, or both, depending on the target vasculature.

We recommend that you report the change in unloaded stent dimensions after the application and removal of all of the specified loads and displacements.

16. Kink Resistance (Peripheral Indications Only)

Significance

Peripheral stents used in some anatomic locations will bend during normal body motion, such as knee flexion. Such bends could cause stent deformation and possible adverse clinical consequences.

Recommendation

We recommend that you determine the smallest radius of curvature that your stent can withstand without kinking, and demonstrate that the stent recovers its original size and shape after testing. We recommend that you support the nature, location, and extent of all external loads and deformations based on the intended implantation site, for example, the carotid or femoral arteries.

17. Additional Tests for Stents Intended for In-Stent Restenosis

Significance

Deployment of stents within previously implanted stents to treat in-stent restenosis could result in increased corrosion potential, stress, fatigue, wear, coating damage, and particulate generation due to stent to stent interactions.

Recommendation

If you intend to label your stent for in-stent restenosis, we recommend you repeat the following tests within an expanded stent (i.e., with 100% overlapped stent pairs):

- Fretting Corrosion (refer to **Section A.3**)
- Stress/Strain Analysis (refer to **Section B.9**)
- Fatigue Analysis (refer to **Section B.10**)
- Accelerated Durability Testing (refer to **Section B.11**)
- Particulate Evaluation, if appropriate for the indications for use (refer to **Section B.12**).

18. Additional Tests for Stents Intended for Coronary Bifurcation Lesions

Significance

Stents designed for placement in coronary bifurcation lesions may be subjected to different loading conditions which could result in different corrosion potential, stress, fatigue, wear, coating damage, and particulate generation due to anatomical constraints and stent to stent interactions.

Recommendation

If you intend to label your stent for use in bifurcation lesions, we recommend that you simulate the target deployment site with a mock vessel which includes the following features:

- parent vessel bend at a clinically relevant radius of curvature (as described in **Section A. 3**),

- a bifurcation angle representative of the most challenging anatomical situation likely to be encountered in clinical use, and
- additional treatment of parent and/or side-branch vessels per expected clinical use, with simulated angioplasty and/or stenting if the bifurcation stent allows side-branch access.

The selection of the radius of curvature of the mock vessel and of the bifurcation angle should be supported by an analysis of clinical images from representative target vessels or referenced literature.

The following test methods should be updated to include the alternative target deployment site described above:

- Fretting Corrosion (refer to **Section A.3**)
- Stress/Strain Analysis (refer to **Section B.9**)
- Fatigue Analysis (refer to **Section B.10**)
- Accelerated Durability Testing (refer to **Section B.11**)
- Particulate Evaluation (refer to **Section B.12**)
- Delivery, Deployment, and Retraction (refer to **Section C.2**).

Additionally, if the bifurcation stent allows for side-branch access, compatibility testing should be performed to ensure the stent does not cause balloon rupture of a PTCA catheter. We recommend you evaluate the Balloon Rated Burst Pressure and Balloon Fatigue of PTCA catheters within your expanded stent. For more information, please refer to **Section IX.C. Additional Tests for Catheters Intended for In-Stent Restenosis or for Stent Expansion following Stent Deployment** from the Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters.[14]

C. Delivery System Dimensional and Functional Attributes

1. Dimensional Verification

Significance

Stent delivery system dimensions influence the ability of the device to track to and across lesions.

Recommendation

We recommend that you provide dimensional specifications and tolerances for your device as manufactured. At a minimum, we recommend that you report effective length, shaft inner and outer diameter, and crossing profile.
The crossing profile is defined as the maximum diameter found between the proximal end of the mounted stent and the distal tip of the delivery system. Testing should address potential differences in crossing profile that may exist in the circumferential

[14] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070984.htm

direction. For these situations, we recommend that you evaluate the crossing profile of your delivery system along different longitudinal paths (e.g., rotating test sample 90 degrees for measurements). We recommend that you report the crossing profile in the instructions for use, the outside package labeling, or both. We recommend the methods described in ASTM F2081 or their equivalents.

2. Delivery, Deployment, and Retraction

Significance

The delivery catheter should safely and reliably deliver the stent to the intended location according to the instructions for use, without damage to the stent.

Recommendation

FDA recommends that you conduct testing to demonstrate that the delivery catheter can safely and reliably deliver the stent to the intended location and that the stent is not adversely affected by the delivery catheter, both during deployment and withdrawal.

We recommend that this simulated use testing be performed by tracking the device through an *in vitro* fixture that mimics challenging *in vivo* physiologic and anatomic conditions (e.g., a tortuous path, aqueous environment), to the extent that the device would enter a patient in clinical use. For coronary indications, FDA recommends the tortuous path described by Figure X2.4 of ASTM F2394. For peripheral indications, please provide an appropriate justification for your final model, including schematics of the fixture and a clinically-based discussion of why it provides a sufficiently challenging model for device tracking. We recommend that you conduct all testing on complete sterilized assemblies with mounted stents and any accessory devices that would be used in a typical clinical procedure (e.g., introducer or guiding catheter), using worst-case sizes (e.g., smallest guiding catheter ID). We also recommend that you thermally equilibrate all test samples in a 37°C saline bath. You should report any abnormality or difficulty observed during the simulated procedure, as well as any damage observed on the stent, delivery system, or any of the accessory devices. We recommend that you measure and report the diameter and axial location of the largest deflated balloon profile (including the inner member or wire). This information can be used to determine the extreme dimensions of compatible accessory devices (i.e., minimum internal diameter), which should be identified in the labeling.

It may be possible to combine Delivery, Deployment and Retraction testing with Particulate Evaluation (see **Section IV. Non-Clinical Engineering Tests B. Stent Dimensional and Functional Attributes 12. Particulate Evaluation**) and/or with Coating Integrity (see **Section IV. Non-Clinical Engineering Tests C. Delivery System Dimensional and Functional Attributes 11. Coating Integrity**), but you should take care to ensure that only minimal additional handling of the test samples is required for the coating integrity evaluation such that particulates are neither lost nor generated.

3. Balloon Rated Burst Pressure (Balloon Expandable Stents Only)

Significance

The rated burst pressure (RBP) is the pressure at which 99.9% of balloons can survive with 95% confidence. Failure of a balloon to survive at the RBP could result in device failure or vessel damage.

Recommendation

We recommend that you test balloons with mounted stents that are not constrained by any test fixture, such as tubing. If the entire range of device sizes will have a single labeled RBP; we recommend that you conduct testing on the longest length of every balloon diameter, plus the smallest diameter at the shortest length and the largest diameter at the shortest length. **Table 3** illustrates the recommended test matrix for a stent design that ranges in diameter from 2.5 to 4.0 mm and ranges in length from 8 to 24 mm.

Table 3: Stent Delivery Sizes to Test for RBP

Stent Diameter (mm)	Stent Length (mm)			
	8	12	18	24
2.5	X			X
3.0				X
3.5				X
4.0	X			X

We recommend that you test according to the example in **Table 3** for each balloon size with a different labeled RBP. We recommend that you test balloons that are not constrained by any test fixture such as tubing, and that you inflate the balloons incrementally until failure.

We recommend that you record as test failures any loss of:

- integrity of the balloon, such as a rupture or leak
- pressure due to failure of the balloon, shaft, or seals.

We recommend that you record the pressure at which the device failed and the failure mode. We also recommend that you calculate RBP as the pressure at which 99.9% of the balloons will survive with 95% confidence based on statistical analysis of the test data. We recommend that you specify RBP in the device labeling.

4. Balloon Fatigue (Repeat Balloon Inflations; Balloon Expandable Stents Only)

Significance

Balloons on stent delivery systems are often inflated multiple times during clinical use. Failure of the balloon to withstand multiple inflations could lead to device failure or vessel damage.

Recommendation

FDA recommends that you determine the repeatability, to 10 inflations, of successful balloon inflation to the RBP. We recommend that your sample dimensions follow the four corners paradigm:

- largest diameter/longest length
- largest diameter/shortest length
- smallest diameter/longest length
- smallest diameter/shortest length.

We recommend that you test balloons with mounted stents that are not constrained by any test fixture such as tubing and that you inflate the balloons in increments until they reach the RBP. For each sample we recommend that you hold the RBP for 30 seconds (or the time specified in the instructions for use), deflate the balloon, and inflate it again to the RBP, for a total of 10 cycles. Note that the number of cycles recommended for this testing is different from our recommendations for balloon catheters indicated for angioplasty (PTCA catheters). This difference is intentional and reflects the likely number of inflations that would occur with use of a stent delivery system versus a stand-alone PTCA catheter. We recommend that you report any loss of pressure, whether due to failure of the balloon, shaft, or proximal or distal seals, as a test failure. We recommend that you record all failure modes, and that your results demonstrate that 90% of the balloons will survive the test with 95% confidence.

5. Balloon Compliance (Stent Diameter vs. Balloon Pressure; Balloon Expandable Stents Only)

Significance

The diameter of a deployed balloon expandable stent varies with the balloon inflation pressure. A compliance chart in the labeling that relates stent diameter to balloon pressure guides selection of stent size to fit the target lesion. Incorrect selection of stent size may lead to device failure or vessel damage.

Recommendation

FDA recommends that you test balloon sizes as illustrated in **Table 3**, and that you test multiple product lots. We recommend that you explain why you chose the test sample size. We recommend that you include data showing inflation pressure versus balloon diameter over the full range of recommended inflation diameters, and report the final results in the instructions for use, the outside package labeling, or both. A graphical or tabular presentation (i.e., a compliance chart) is desirable.
We recommend that you identify the nominal inflation pressure and RBP, as shown in the example below. The compliance chart may include pressures up to (but not exceeding) 25% above the RBP, if you provide data and statistics demonstrating that 99% of the balloons will not fail at the listed pressure with 95% confidence. We also recommend that you describe how you performed any data rounding and show all instances. **Table 4** below shows an example of a compliance chart for a stent with

3.0 mm, 3.5 mm, and 4.0 mm diameters, with a RBP of 16 atmospheres (atm). The nominal diameter occurs at 9.0 atm.

Table 4: Sample Compliance Chart for a Balloon Expandable Stent

Pressure (atm)	Stent Nominal Diameter where x = stent inner diameter at the given pressure		
	3.0 mm Stent Inner Diameter (mm)	**3.5 mm Stent Inner Diameter (mm)**	**4.00 mm Stent Inner Diameter (mm)**
9.0	x	x	x
10.0	x	x	x
11.0	x	x	x
12.0	x	x	x
13.0	x	x	x
14.0	x	x	x
15.0	x	x	x
16.0*	x	x	x

*RBP

6. Balloon Inflation and Deflation Time (Balloon Expandable Stents Only)

Significance

Balloons occlude the target vessel and obstruct blood flow while inflated. Inflation and deflation times affect occlusion time. Excessively slow inflation or deflation of a balloon could lead to prolonged ischemia and damage to the end organ.

Recommendation

FDA recommends that you demonstrate, using techniques recommended in your instruction manual (e.g., pre-dilation), that the balloon inflates and deflates within acceptable times, and provide the clinical basis for your acceptance criteria. We recommend that you test the largest diameter at the longest balloon length, and evaluate which other sizes to test. We also recommend you specify the balloon deflation times in your labeling. Please observe and describe any interference with balloon deflation or delivery system extraction from the deployed stent.

7. Catheter Bond Strength

Significance

Failure of bonds in the delivery catheter could lead to device failure or vessel damage.

Recommendation

We recommend that you test the bond strength at locations where adhesives, thermal fusion, or other joining methods are used for bonding components of the delivery system. Prior to evaluating tensile strength, we recommend you precondition catheters by tracking through a tortuous path fixture, as described above in **Section 2. Delivery, Deployment and Retraction)**. We recommend that testing demonstrate

that all bonds can withstand tensile forces greater than those that may be experienced during clinical use. We also recommend you provide the clinical basis for your acceptance criteria.

8. Tip Pull Test

Significance

Failure of bonds in the distal tip could lead to device failure or vessel damage.

Recommendation

For devices with one or more joints in the distal tip (e.g., spring or nose-cone tips), FDA recommends that you determine the tensile force that will separate the distal tip from the catheter. We recommend that you precondition catheters prior to tip pull testing by tracking through a tortuous path fixture, as described above in **Section 2. Delivery, Deployment and Retraction**.

9. Flexibility and Kink Test

Significance

Stent delivery systems may be subjected to tight angulations in tortuous vasculature during use. Inability to withstand flexural forces that are typical of clinical use could lead to device failure or vessel damage.

Recommendation

FDA recommends that you conduct testing which demonstrates that the stent delivery system will not kink at a bend radius that is appropriate for the intended anatomy. We recommend that you consider wrapping the catheter around a series of mandrels with successively smaller radii until the catheter kinks or the lumen collapses. We also recommend you provide the clinical basis for your acceptance criteria.

10. Torque Strength

Significance

Stent delivery systems may be subjected to torsional forces during use. Even non-fixed wire delivery systems could be subject to torsional forces if the tip is inadvertently caught on a previously deployed stent, calcified lesion, etc. Inability to withstand torsional forces that are typical of clinical use could lead to device failure or vessel damage.

Recommendation

FDA recommends that you measure the torque strength of the stent delivery system when the distal tip is not free to rotate, by rotating the proximal end of the catheter until failure. We recommend that you precondition delivery systems prior to evaluating torque strength by tracking through a tortuous path fixture, as described above in **Section 2. Delivery, Deployment and Retraction**. We recommend that you report the number of rotations to failure and the failure mode for each sample tested. Additionally, we recommend that you test the delivery system in a fixture that

simulates the anatomy of the aortic arch and coronary arteries. We also recommend you provide the clinical basis for your acceptance criteria.

11. Coating Integrity

Significance

Unintended delamination or degradation of a coating may lessen its benefit or otherwise negatively impact its clinical performance.

Recommendation

FDA recommends that you address the aspects described below for any coatings applied to the surfaces of your product.

Coating Description

We recommend that you describe the clinical purpose and intended function of the coating, such as enhanced radiopacity, thromboresistance, or lubricity.

We also recommend that you describe the physical structure of the coating, such as coating thickness, and indicate its chemical identity.

Test Samples

You should conduct all testing on the finished product subject to all manufacturing processes including sterilization. You should provide a scientific or statistical justification for the sample size for each test. We recommend that you implement a sampling plan to examine multiple lots of product (≥3) to assess both inter- and intra-lot variability. You should perform testing on sizes that represent four corners of the stent design (see **Table 2** above) as well as an intermediate size.

It may be possible to combine the Coating Integrity Evaluation with Delivery, Deployment and Retraction testing (see **Section IV. Non-Clinical Engineering Tests C. Delivery System Dimensional and Functional Attributes 2. Delivery Deployment and Retraction**) and/or with Particulate Evaluation (see **Section IV. Non-Clinical Engineering Tests B. Stent Dimensional and Functional Attributes 12. Particulate Evaluation**) but you should take care to ensure that only minimal additional handling of the test samples is required for the coating integrity evaluation such that particulates are neither lost nor generated.

Interpretation of Data

Coating integrity is considered a characterization test. Acceptance criteria are not required; however, you should provide an interpretation of the data.

In your coating integrity test reports you should include a detailed discussion of the surfaces using any practical methods to quantify defects. This may include counting the number of total defects per unit area, measuring representative defect areas, and measuring worst-case defect areas. You should support your

discussion with representative images (including worst-case) at a sufficient magnification to characterize the defects. Multiple magnifications may be needed to visualize and adequately characterize the product. The discussion of acceptable coating integrity should include a justification that the number and size of defects observed will not impact clinical performance.

We recommend that you address the aspects described below for any coatings applied to the surfaces of your product.

Baseline Coating Integrity

We recommend that you conduct a visual assessment of the coating integrity on all appropriate surfaces of the delivery system before stent deployment to establish a baseline for comparison to coating characteristics after testing performed under other conditions. We recommend that you appropriately quantify characteristics such as continuity and voids in the coating, as described above.

Simulated Use Coating Integrity

We also recommend that you evaluate the coating integrity after simulated use, via visual assessment. Devices should be tracked through a tortuous path fixture (as described above in **Section 2. Delivery, Deployment and Retraction**) and then expanded in air or an aqueous medium to the maximum labeled diameter described in the Instructions for Use prior to visual inspection. You should also assess the impact of simulated use on the functional aspects of the coating.

12. Stent Securement for Unsheathed Stents

Significance

Dislodgment of the stent prior to deployment can result in stent embolization. Stents without sheaths may dislodge if they catch on tortuous anatomy, guide catheters, or other devices.

Recommendation

FDA recommends that you measure the force that will dislodge the stent from the delivery system under clinically relevant conditions. We recommend that the test simulate the intended use, including insertion through a tortuous path that simulates the vasculature proximal to and including the lesion site. We recommend that the tortuous path be sized appropriately for the stent size being tested. We recommend that you submit a photo, diagram, or description of the tortuous path, including dimensions. For coronary indications, FDA recommends the tortuous path described by Figure X2.4 of ASTM F2394. For peripheral indications, please provide the clinical basis for your final model. We recommend that the stent sizes tested represent the worst case stent securement for your design. We recommend that you explain why your results are applicable to all sizes of your stent, including those not tested for stent securement.

FDA recommends that you address the modes of dislodgement as described below:

<u>Dislodgement by Forward Motion</u>

Advancing a stent delivery system across a tight lesion could result in stent dislodgement. We recommend testing the stent by passing it through a simulated tight lesion in the tortuous path.

<u>Dislodgement by Reverse Motion</u>

Withdrawing a stent delivery system into a guiding catheter, arterial sheath, or hemostasis valve could result in stent dislodgement. We recommend testing the stent by attempting to withdraw the un-deployed stent into a guide catheter or other opening of the smallest size for an accessory device recommended in the instructions for use.

D. Shelf Life

Significance

Aging can potentially affect the performance of the materials of construction for the stent and delivery system.

Recommendation

We recommend that shelf life testing address package integrity to ensure sterility, as well as stable device functionality over the expected life cycle.

To evaluate device functionality, we recommend that you repeat the following bench tests on aged devices:

- Stent Dimensional Verification (refer to **Section B.1**)
- Stent Foreshortening* (refer to **Section B.3**)
- Radial Outward Force* (refer to **Section B.7**)
- Particulate Evaluation (refer to **Section B.12**)
- Delivery System Dimensional Verification (refer to **Section C.1**)
- Delivery, Deployment, and Retraction (refer to **Section C.2**)
- Balloon Rated Burst Pressure (refer to **Section C.3**)
- Balloon Fatigue (refer to **Section C.4**)
- Balloon Compliance (refer to **Section C.5**)
- Balloon Inflation and Deflation Time (refer to **Section C.6**)
- Catheter Bond Strength (refer to **Section C.7**)
- Tip Pull Test (refer to **Section C.8**)
- Flexibility and Kink Test (refer to **Section C.9**)
- Torque Strength (refer to **Section C.10**)
- Coating Integrity (refer to **Section C.11**)

- Stent Securement for Unsheathed Stents (refer to **Section C.12**)

  *only repeat testing on aged stents if self-expanding

Additional tests may be recommended for certain devices, depending on their design, materials (alloys), or manufacturing processes.

We recommend that you provide the protocol used for your shelf life testing, the results of the testing, and the conclusions drawn from your results. If you use devices subjected to accelerated aging for shelf life testing, we recommend that you specify the way in which the device was aged. Since stent delivery systems contain polymeric materials, you should plan to conduct testing on real-time aged samples to confirm that accelerated aging is reflective of real-time aging. This testing should be conducted in parallel with PMA review and approval, with results submitted in a post-approval annual report.

E. Biocompatibility

Significance

Stents and delivery systems contain patient-contacting materials, which when used for their intended purpose, i.e., contact type and duration, may induce a harmful biological response.

Recommendation

We recommend that you determine the biocompatibility of all patient-contacting materials present in your device. If your materials are identical in composition and processing methods to materials with a history of successful use in cardiovascular product applications, you may reference the appropriate literature or previous testing experience. We recommend that you test novel materials, i.e., those with no history of successful prior use according to the methods in the FDA-recognized version of relevant ASTM, USP, and ISO standards. In addition, we recommend that you follow the guidance **Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing**[15] to identify the types of tests that should be considered.

Differences in formulation, processing or sterilization that could affect biocompatibility of the final product may warrant additional biocompatibility testing.

<u>Sample Preparation</u>

It is important to understand how the test samples compare to the final sterilized product. For biocompatibility testing conducted using extraction samples, we recommend that you:

- determine the appropriate amount of test material as outlined in **ISO 10993-12** or an equivalent method, using surface area to extractant volume ratios (mass

[15] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm

to extractant volume ratios should only be used if surface area cannot be calculated)

- use both polar and nonpolar extractants
- describe the condition of the extraction vehicle (e.g., color, presence of any particles)
- explain any changes in the post-extraction vehicle (compared to pre-extraction)
- describe the details of storage conditions, if applicable.

If extraction samples are not used immediately, we recommend that you follow the storage conditions described in **ISO 10993-12** or an equivalent method. We also recommend that you explain how storage does not affect your test results.

Stents

Because stents are implanted products in contact with cardiovascular tissue and circulating blood, with a permanent duration of contact (>30 days), we recommend the following tests be considered:

- cytotoxicity
- sensitization (guinea pig maximization with both polar and non-polar extracts)
- irritation (or intracutaneous reactivity)
- acute systemic toxicity
- material-mediated pyrogenicity
- hemocompatibility [hemolysis, in vivo thrombogenicity, and direct contact complement activation (C3a and SC5b-9)]
- sub-chronic toxicity
- genotoxicity (bacterial reverse mutation assay, mammalian cell in vitro assay, and in vivo cytogenetics assay in rodents)
- chronic toxicity
- implantation
- carcinogenicity.

Delivery Systems

Because delivery catheters are externally communicating products in contact with cardiovascular tissue and circulating blood, with a temporary duration of contact (<24 hrs), we recommend the following tests be considered:

- cytotoxicity
- sensitization (guinea pig maximization with both polar and non-polar extracts)
- irritation (or intracutaneous reactivity)
- acute systemic toxicity
- material-mediated pyrogenicity

- hemocompatibility [hemolysis, in vivo thrombogenicity, and direct contact complement activation (C3a and SC5b-9))
- genotoxicity (bacterial reverse mutation assay, mammalian cell in vitro assay, and in vivo cytogenetics assay in rodents).

Additional testing may be requested to fully characterize the toxicology profile, depending on the materials of use.

Additional Considerations

- Cytotoxicity

We recommend that extractions be conducted at 37°C for 24 hours using a vehicle with both mammalian cell culture media (MEM) and 5% serum, as these materials will allow for extraction of both polar and nonpolar constituents from the test sample.

- Sensitization (Guinea Pig Maximization Method)

We recommend that test reports confirm that all female animals used in the testing are not pregnant, as pregnancy can reduce the ability of a female animal to detect a sensitization response.

We recommend either that you run concurrent controls, or that the test laboratory run controls within 3 months of the test samples. We also recommend you provide protocols and results from positive control testing to confirm that you used the same methods for both the positive control testing and the test samples.

- Hemocompatibility

For blood-contacting devices (regardless of contact duration), we recommend that you consider hemolysis, immunology (complement activation), and *in vivo* thromboresistance.

Immunology testing should appropriately address the various complement activation pathways. We recommend that you assess *in vitro* C3a and SC5b-9 fragment activation using standard testing methods, such as those outlined in **ASTM F2065-00e1**[16] and **ASTM F1984-99 (2003)**[17]**,** or an equivalent method. Alternatively, you may provide a rationale for omitting this testing, if all the materials used in the formulation and processing of the device have a history of previous use in blood-contacting devices with similar contact duration.

In addition, you may assess *in vivo* thrombogenicity during preclinical animal testing in lieu of a separate canine *in vivo* thrombogenicity test. If a 4 hour canine *in vivo* thrombogenicity study is needed (e.g., due to the use of novel materials never before used in a medical devices or questionable findings from the vascular

[16] ASTM F2065-00e1 Alternative Pathway Complement Activation in Serum by Solid Materials.
[17] ASTM F1984-99 (2003) Whole Complement Activation in Serum by Solid Materials.

animal studies), we recommend the study be conducted in a venous, unheparinized model.

- Material-mediated Pyrogenicity

We recommend that you assess pyrogenic responses to chemical leachants over the duration of device contact with the patient. We recommend that you assess material-mediated pyrogenicity using traditional biocompatibility extraction methods, such as those outlined in the **USP 28 <151> Rabbit Pyrogen Test** (e.g., 50°C for 72 hours; 70°C for 24 hours; or 120°C for 2 hours) or an equivalent method. You should consider that temperatures above 37°C may result in toxicities not representative of the final product.

- Nickel ion release

For devices containing nitinol, we recommend that you consider the potential for nickel ion release from your device. Specifically, if you cannot demonstrate that your nitinol device exhibits sufficient corrosion resistance as well as an adequate passivation layer, we recommend that you quantify nickel ion release from your device over time. Testing can be performed by measuring concentrations of nickel leached from the device into a fluid with physiologic temperature and pH.

V. Labeling

General labeling requirements for medical devices are described in 21 CFR Part 801. Additional information may be obtained from **Device Advice.**[18] You must submit all proposed labeling in your PMA [21 CFR 814.20(b)(10)].

FDA recommends that labeling for extracranial intravascular stents include the sections described below. Some of these recommendations may also be relevant to covered, drug-eluting, and biodegradable stents; however, FDA recommends additional labeling, not described in this document, for those devices. The Interventional Cardiology Devices Branch and the Peripheral Vascular Devices Branch are available to discuss labeling for those stents and indications.

A. Device Description

We recommend that you describe the stent and delivery catheter, including the stent material, whether the stent is balloon expandable or self-expanding, etc. You should consider including a table with the following attributes, as appropriate:

- available stent diameters and lengths
- guiding catheter/sheath compatibility
- deployment and RBPs
- percent stent free area.

[18] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

Contains Nonbinding Recommendations

We recommend that you describe any ancillary or accessory devices that are packaged with your stent system when no separate labeling is available. An example would be a description of an embolic protection system that is packaged with your stent delivery system. You may add additional information where appropriate.

B. Indications for Use

We recommend that proposed labeling reflect the precise indications for use statement that is the subject of the application. The general statement of the "Indications for Use" identifies the target population in which sufficient valid scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device.

C. Contraindications

We recommend that you include contraindications to the use of the device. Contraindications describe situations in which the device should not be used because the risk of use clearly outweighs any possible benefit.

D. Warnings

We recommend that you include an appropriate warning if there is reasonable evidence of an association of a serious hazard with the use of the device. A causal relationship need not have been proved.

We believe a warning is also appropriate when the device is commonly used for a disease or condition for which there is a lack of valid scientific evidence of effectiveness for that disease or condition or use of the device is associated with a serious risk or hazard.

We also recommend that you include warnings to address the:

- need for appropriate anticoagulation or antiplatelet therapy or both
- recommendation that when multiple stents are used, they should be of similar composition
- fact that long-term outcomes following repeat dilatation of endothelialized stents are unknown.

E. Precautions

You should include as precautions information regarding any special care physicians or others should exercise for the safe and effective use of the device. Additionally, you should include any limitations on the use of a device for reasons including, but not limited to:

- lack of long-term safety and effectiveness data
- lack of safety and effectiveness data for special patient populations
- need for appropriate physician training
- anatomical or physiological limitations on the effectiveness of the device.

Stent handling, stent placement, stent system removal, and any post-implant precautions are appropriate for inclusion in this section. Additionally, you should address length of follow-up or use in special patient populations, for example:

> The safety and effectiveness of the ABC (coronary or peripheral) stent system has not been established in patients beyond x (months/years) of follow-up.
>
> or
>
> The safety and effectiveness of the XYZ coronary stent system has not been established in patients with recent acute myocardial infarction.

F. MR Environment

We recommend you follow the labeling guidelines given in **Guidance for Industry and FDA Staff: Establishing Safety and Compatibility of Passive Implants in the MR (Magnetic Resonance) Environment**[19]

Overlapping Stents or Stents with Fractured Struts

In addition to the labeling recommendations in the **Guidance for Industry and FDA Staff: Establishing Safety and Compatibility of Passive Implants in the MR (Magnetic Resonance) Environment,** FDA recommends that your labeling also describe whether you determined the effect of heating in the MRI environment for overlapping stents or stents with fractured struts. If you have not determined what those effects are, we recommend that your labeling reflect this, for example:

> The effect of heating in the MRI environment for overlapping stents or stents with fractured struts is not known.

G. Overview of Clinical Studies

You should provide a narrative description of the pivotal study or studies and any supporting or feasibility studies relevant to the stent. The narrative should be brief, and should include the following information for each study:

- whether the study was a pivotal, supporting, or feasibility study
- the design of the study, including any randomization, blinding, and the control or controls used
- the number of patients enrolled
- the number of investigational sites both inside the United States (US) and outside the United States (OUS)
- the primary study endpoint or endpoints
- the amount of available follow-up
- the total planned follow-up.

[19] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107705.htm

H. Adverse Events

Observed Adverse Events

You should provide a brief narrative statement about the source or sources of the adverse event experience followed by results in a tabular format. In the table, we recommend that you present adverse events using a "per protocol" (also known as an "evaluable") approach.

In this approach, the numerator consists of the number of patients presenting with the adverse event during or before the analysis window. For each adverse event, the denominator consists of:

The number of patients evaluated during the analysis window	+	Any patients not evaluated during the analysis window, but that had the specified adverse event between treatment and the analysis window

The numerator consists of the number of patients presenting with the adverse event during or before the analysis window.

You may also use an alternative approach known as "intent-to-treat" analysis, in which any patients not evaluated during the analysis window are assumed to have had an adverse event. If your trial involves substantial numbers of crossover patients, an intent-to-treat analysis may be more appropriate. In this analysis, adverse events would be assigned to the original treatment group regardless of actual treatment received or time at which the adverse event occurred.

You should include an adverse events table that captures data through the longest available follow-up for the study. You should also provide protocol definitions for adverse events as footnotes, or a reference to definitions included with the Principal Safety and Effectiveness Table.

We have provided a list of suggested elements for inclusion, below. Additional elements may be appropriate given the specific vessel or vessels to be stented.

Coronary Indications

You should separate in-hospital events from out-of-hospital events (through X days or months), for categories such as:

- major adverse cardiac events (MACE), which includes:
  - death
  - Q-wave myocardial infarction (MI)
  - non-Q-wave MI
  - emergent coronary artery bypass grafting (CABG)
  - target lesion revascularization (TLR)

- target lesion failure (TLF)
- target vessel failure (TVF)
- target vessel revascularization (TVR)
- TVR, non-TLR
- stent thrombosis (acute, subacute, late)
- cerebro-vascular accident (CVA)
- bleeding complications
- vascular complications

Peripheral Indications

You should separate events at specific time points (e.g. 30 days, 1 year) and cumulative events for categories such as:

- major adverse event (MAE) – may be study specific
    - death
    - stroke
    - Q-wave MI (in-hospital)
    - non-Q-wave MI
    - end organ injury or ischemia or both
    - TLR
    - target limb amputation
- TVF
- TVR
- TVR, non-TLR
- stent thrombosis (acute, subacute, late)
- bleeding complications
    - access site
    - non-access site
- vascular complications
    - perforation
    - aneurysm
    - pseudo-aneurysm
    - dissection

Potential Adverse Events

You should include potential adverse events associated with stenting of the intended coronary or peripheral vessel or vessels.

I. Clinical Studies

You should include additional specifics about the clinical studies described in the section titled "Overview of Clinical Studies," above. We suggest the following format:

Purpose/Objective

You should state the intent of the study, including the primary endpoint or endpoints.

Conclusions

You should briefly state the study outcome or outcomes.

Design

You should describe your study design. The following is a partial list of elements that may be appropriate to your design:

- whether the design is randomized or non-randomized
- whether the study is controlled
- which type of controls were used
- if the study results were compared to a performance goal
- how any performance goals were derived.

You should also describe the success criteria for the trial (i.e., superiority or non-inferiority when compared to the control).

You should include a brief description of patient entry criteria, such as:

- vessel location
- vessel size
- vessel type, (i.e., *de novo* or restenotic)
- type of evaluations (clinical, telephone, angiographic/intravascular ultrasound follow-up).

Demographics

You should describe characteristics of your patient populations that could affect the results of the study, including:

- age
- race
- gender
- percentage of smokers
- incidence of hyperlipidemia
- previous MI
- diabetes

- any other important covariates.

Methods

You should describe any use of a Clinical Events Committee, a Data and Safety Monitoring Board, and/or a core laboratory for adverse event adjudication, as appropriate.

Results

You should briefly describe the results of the study, including whether the primary endpoint or endpoints were met, for example:

The X stent demonstrated a lower rate of TVF as compared to the control group (X% vs. Y%, $P<0.001$).

You should refer to the Principal Safety and Effectiveness Table, which is described in the next section of this guidance.

J. Principal Safety and Effectiveness Table

We recommend that you present the clinical outcomes in a tabular format as "effectiveness measures" and "safety measures," separately or combined. Your data presentation should follow the same approach used for adverse event reporting (for example, per protocol or intent-to-treat). You should include protocol definitions for terms used in the table.

You should provide Kaplan-Meier estimates for relevant endpoints in your safety and effectiveness table, which may include, but are not limited to:

- MACE-free survival
- MAE-free survival
- TVF-free survival
- TVR-free survival
- TLR-free survival
- primary, primary assisted, and secondary patency survival.

In some instances, it may be appropriate to provide a graphical presentation of the most appropriate Kaplan-Meier survival endpoints (see examples of these endpoints below) and accompanying life tables. We believe that statistical comparisons between groups, as presented in a Kaplan-Meier presentation, are only appropriate for randomized trials. The review branches are available to advise you on this issue.

Examples of Kaplan-Meier survival endpoints

- "Freedom from MACE" for coronary and peripheral stenting studies
- "Patency survival" for peripheral stenting studies

If you provide a survival graph, it should include error bars representing a standard error (SE) of ± 1.5. The scale should either begin on the y-axis at a value greater than zero – we recommend using a value around 50 - 60% – or indicating a break in the scale to illustrate the differences in survival curves, if applicable.

Updates to Principal Safety and Effectiveness Table

For some devices, updates to the Principal Safety and Effectiveness Table to reflect additional clinical follow-up beyond the primary follow-up interval are identified as a condition of PMA approval. In this case, the updated labeling should be submitted as a PMA supplement.

If such an update is not listed as a condition of approval, you may provide the updated labeling in your annual report, as long as the updated information is based on the endpoints and follow-up schedule prospectively defined in your clinical study protocol. For updates that relate to new indications, see 21 CFR 814.39. The labeling should indicate which data were added or updated after the initial device approval.

If clinical results in the updates raise a safety or effectiveness concern when compared to the initial results of your study, we recommend that you update the labeling to reflect this new information.

K. Patient Selection and Treatment

We recommend that this section provide information related to individualization of treatment.

L. Directions for Use

You should include directions for proper preparation and use of the device in this section of the labeling. If multiple delivery systems are available, you should clearly indicate differences specific to the delivery system. An example would be to indicate the difference between an over-the-wire (OTW) and a rapid exchange (RX) delivery system.

Compliance Chart (Balloon Expandable Stents Only)

Pre-mounted Balloon Expandable Stents

You should include a compliance chart that provides the average stent inner diameter following deployment at various pressures derived from bench testing. You should display the data as determined from testing. However, if you round the data, you should footnote the chart to indicate that the data is rounded. We recommend the format presented in **Table 4** (see **Section IV. Non-Clinical Engineering Tests, B. Stent Dimensional And Functional Attributes, 4. Recoil For Balloon Expandable Stents**).

Percent Foreshortening (Self-Expanding Stents Only)

You should provide a table that shows:

- vessel lumen diameter
- unconstrained stent diameter
- percent foreshortening.

If you base your values on mathematical calculations, you should indicate this in a footnote to the table. See **Section IV. Non-Clinical Engineering Tests, B. Stent Dimensional And Functional Attributes**, **3. Foreshortening**, for information on testing stent percent foreshortening.

M. Patient Materials

You should provide all patient materials, such as the patient guide and implant card, that you will make available. See also **Guidance on Medical Device Patient Labeling,**[20]

For MR Conditional stents, we recommend you include the bulleted points from the Guidance for Industry and FDA Staff: Establishing Safety and Compatibility of Passive Implants in the MR (Magnetic Resonance) Environment. In addition, we recommend you include the following:

- the appropriate MR safety icon and term from ASTM F2503[21]
- if applicable, a statement similar to the following: Patients with the device may safely undergo MRI for (insert appropriate term: "Normal Operating Mode" or "First Level Controlled Operating Mode") of the MR System as defined in IEC 60601-2-33[22]
- a statement about the image artifact
- a recommendation that patients register the conditions under which the implant can be scanned safely with the MedicAlert Foundation (www.medicalert.org) or equivalent organization.

[20] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm
[21] ASTM F2503 Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment
[22] IEC 60601 Medical electrical equipment – Part 2-33: Particular requirements for the safety of magnetic resonance equipment for medical diagnosis

Appendix A: Test Summary Checklist

(continued on next page)

Test		Sizes Tested and Sample Sizes	Test Method or Standard Reference	Accept/Reject Criteria	Results
Material Characterization	Material Composition				
	Shape Memory and Superelasticity				
	Mechanical Properties				
	Corrosion Resistance				
Stent Dimensional and Functional Attributes	Dimensional Verification				
	Percent Surface Area of the Stent				
	Foreshortening				
	Recoil for Balloon Expandable Stents				
	Stent Integrity				
	Radial Stiffness and Radial Strength				
	Radial Outward Force				
	Stress/strain analysis				
	Fatigue Analysis				
	Accelerated Durability Testing				
	Particulate Evaluation				
	MRI Safety and Compatibility				
	Radiopacity				
	Coating Durability *(coated stents only)*				
	Crush Resistance (*peripheral indications only*)				
	Kink Resistance (*peripheral indications only*)				

Appendix A: Test Summary Checklist (*continued from previous page*)

Test		Sizes Tested and Sample Sizes	Test Method or Standard Reference	Accept/Reject Criteria	Results
Delivery System Dimensional and Functional Attributes	Dimensional Verification				
	Delivery, Deployment, and Retraction				
	Balloon Rated Burst Pressure (*balloon expandable stents only*)				
	Balloon Fatigue (*balloon expandable stents only*)				
	Balloon Compliance (Stent Diameter vs. Balloon Pressure) (*balloon expandable stents only*)				
	Balloon Inflation and Deflation Time (*balloon expandable stents only*)				
	Catheter Bond Strength				
	Tip Pull Test				
	Flexibility and Kink Test				
	Torque Strength				
	Coating Integrity				
	Stent Securement for Unsheathed Stents				
Shelf Life	Packaging				
	Stent Dimensional Verification				
	Stent Foreshortening				
	Stent Recoil				
	Particulate Evaluation				
	Delivery System Dimensional Verification				

	Delivery, Deployment, and Retraction				
	Balloon Rated Burst Pressure				
	Balloon Fatigue				
	Balloon Compliance				
	Balloon Inflation and Deflation Time				
	Catheter Bond Strength				
	Tip Pull Test				
	Flexibility and Kink Test				
	Torque Strength				
	Coating Integrity				
	Stent Securement for Unsheathed Stents				
Biocompatibility	Biocompatibility				

Appendix B: Applicable Standards

A list of FDA-recognized standards is available at
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

ISO Standard
10993 Biological Evaluation of Medical Devices

IEC Standard
IEC 60601 Medical electrical equipment – Part 2-33: Particular requirements for the safety of magnetic resonance equipment for medical diagnosis

ASTM Standards
F138 Standard Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants
F1984 Whole Complement Activation in Serum by Solid Materials
F2004 Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Alloys by Thermal Analysis
F2065 Alternative Pathway Complement Activation in Serum by Solid Materials
F2079 Standard Test Method for Measuring Intrinsic Elastic Recoil of Balloon expandable Stents
F2081 Standard Guide for Characterization and Presentation of the Dimensional Attributes of Vascular Stents
F2082 Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Shape Memory Alloys by Bend and Free Recovery
F2129 Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices
F2182 Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging
F2394 Standard Guide for Measuring Securement of Balloon Expandable Vascular Stent Mounted on Delivery System
F2503 Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment
G71 Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes

Guidance for Industry

Coronary Drug-Eluting Stents—Nonclinical and Clinical Studies

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDRH) Ashley Boam at 240-276-4222 or (CDER) Devi Kozeli at 301-796-2240.

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Food and Drug Administration
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)
March 2008
Combination Products

Guidance for Industry

Coronary Drug-Eluting Stents

Additional copies are available from:

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Rockville, MD 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

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Guidance for Industry[1]
Coronary Drug-Eluting Stents —Nonclinical and Clinical Studies

> This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide recommendations to sponsors or applicants[2] planning to develop, or to submit to FDA, a marketing application for a coronary drug eluting stent (DES). The guidance discusses the data and clinical studies needed to support such an application. This guidance does not discuss noncoronary DESs (e.g., peripheral drug-eluting, nonvascular biliary stents) or stents that contain biological product components such as cell or gene therapy or therapeutic biological products such as monoclonal antibodies. The guidance makes recommendations for stents made from metallic stent substrates, but does not provide complete information for degradable stents or stents made from other material substrates (e.g., polymer or ceramics).

The associated companion document provides additional information that may be useful, including suggested contents of investigational and premarket approval applications; various examples (e.g., example of a DES clinical study summary, a commitment table, test article certification); information on good animal husbandry, biocompatibility considerations, and issues related to U.S. and OUS (outside the U.S.) studies; and labeling recommendations. The companion document is intended to be used together with this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The

[1] This guidance has been prepared by a working group that included members of the Center for Devices and Radiological Health (CDRH), Center for Drug Evaluation and Research (CDER), and Office of Combination Products (OCP) in the Office of the Commissioner at the Food and Drug Administration.

[2] For purposes of this guidance, *sponsor* refers to any person who takes the responsibility for and initiates a clinical investigation; *applicant* refers to any person who submits an application, amendment, or supplement to obtain FDA approval of a new medical product or any other person who owns an approved application. *Sponsor* is used primarily in relation to investigational device exemption (IDE) applications and *applicant* is used primarily in relation to premarket approval (PMA) submissions.

use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Coronary stents are implantable devices that are placed percutaneously in one or more coronary arteries to maintain patency. DESs incorporate a pharmacologically active agent (drug) that is delivered at the site of stent deployment and is intended to reduce the incidence of restenosis due to neointimal hyperplasia associated with bare metal stenting. In many cases, the drug is incorporated into and released from a polymeric coating of sufficient capacity to accommodate the selected dose and to modulate its delivery at the intended site of action and for the intended duration. The chemical, physical, and mechanical attributes of the polymer coating system are important for stent deployment, biocompatibility, and stability. To perform a regulatory assessment of a DES, FDA would review data from a comprehensive evaluation of individual components (drug, polymer, and stent), as well as from a comprehensive evaluation of the finished drug-device combination product.

After briefly discussing some general FDA jurisdictional considerations related to this drug-device combination product, the guidance clarifies a number of issues related to the development of DESs including the following:

- How to characterize the drug substance, including chemistry, nonclinical systemic and local tissue pharmacology and toxicology, and how to evaluate the potential for and consequences of systemic clinical exposure
- How to characterize the drug-device combination product, including the chemical/physical/mechanical properties of the DES, the nonclinical local vascular and regional myocardial toxicology, and the clinical performance of the drug-stent combination
- Regulatory considerations that are unique to DES combination products

We encourage sponsors and applicants to consult closely with FDA during development of a DES.

A. Regulatory Basis

DESs are combination products subject to section 503(g) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 353(g)), because they are a combination of two different types of regulated components (a device and a drug) that are physically and/or chemically combined and produced as a single entity (21 CFR 3.2(e)(1)). A combination product is assigned to an Agency component, such as the Center for Devices and Radiological Health (CDRH) or the Center for Drug Evaluation and Research (CDER), for premarket review and regulation based on a determination of the product's *primary mode of action.*

In response to several *requests for designation* under 21 CFR 3.7, the Agency determined that for current DESs where the device component maintains coronary artery patency and the drug component augments the safety and/or effectiveness of the uncoated (bare) stent by preventing

restenosis, the device mode of action is the primary mode of action.[3] Therefore, the premarket review and regulatory responsibility for these coronary DESs has been assigned to CDRH with significant consultation from CDER.

B. Application Requirements

1. Product Classification

Coronary DESs, where the device component provides the primary mode of action, are regulated as Class III devices that require the submission and approval of a premarket approval (PMA) application prior to commercial marketing in the United States. To meet the standard for approval, the PMA application must contain (or include by reference) valid scientific evidence to provide a reasonable assurance of safety and effectiveness of the DES when used in accordance with its labeled indication (21 U.S.C. 360c(a)(1)(C), 360c(a)(2)-(3)). Such evidence will usually consist of nonclinical, animal, and human clinical testing.

2. IDE Application Requirements

FDA has determined that DESs pose a significant risk as defined in 21 CFR 812.3(m), and as such, are not exempt from the requirement to submit an investigational device exemption (IDE) application (21 CFR 812.2(b), 812.20(a)(1). When an IDE application is required, a sponsor must not begin a clinical trial in humans in the United States until FDA has approved the application (21 CFR 812.20(a)(2), 812.42). Sponsors of such studies must comply with the following:

- IDE regulations (21 CFR 812)
- Regulations governing institutional review boards (IRB) (21 CFR 56)
- Informed consent (21 CFR 50) [4]

The companion document contains a listing of the elements FDA recommends be included in an original IDE application.

FDA strongly encourages sponsors to use pre-submission interactions to obtain informal guidance regarding product development prior to submission of an original IDE application.[5] FDA comments provided to sponsors during the pre-submission process are informal input, intended to facilitate open communication between the sponsor and the Agency. Pre-submission interactions for a DES can be broad-based, or can focus on particular areas, such as engineering testing, CMC testing, or

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[3] See "Jurisdictional Update: Drug-Eluting Cardiovascular Stents," http://www.fda.gov/oc/combination/stents.html. This Jurisdictional Update discusses DESs for which the primary mode of action is the action of the device component in maintaining vessel patency. However, a DES for which the primary mode of action is attributable to the drug component would be assigned to CDER.

[4] You should review the statutory definition of applicable clinical trial to determine if your trial must be registered to comply with the law. *See* PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)). http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf Information can be submitted to ClinicalTrials.gov using the Protocol Registration System (PRS). For more information visit the PRS Information Page (http://prsinfo.clinicaltrials.gov).

[5] FDA intends to develop guidance on pre-submissions.

clinical protocols. Sponsors should clearly identify questions or particular items they would like to have addressed as part of the pre-submission interaction. It may be appropriate to meet or hold pre-submission discussions with Agency staff more than once, at different stages of the development process.

3. *IND Application Requirements*

Preclinical and clinical evaluation of the drug substance alone (e.g., not delivered via a stent) may be appropriate to fully characterize potential toxicities (see Section IV. below). Human studies of an investigational drug in the United States must be conducted under an IND application (21 CFR Part 312). The IND application should specify that the eventual intended use of the drug is to be in combination with a stent.[6]

4. *PMA Application Requirements*

To meet the standard for approval, a PMA application must provide reasonable assurance of the safety and effectiveness of the finished DES (21 USC 360c(a)(1)(C)). See the companion document for a list of the elements FDA recommends be included within an original PMA application.

Because of the extensive amount of nonclinical information that is typically needed (especially when the drug component is a new molecular entity, or NME, that has never been the subject of a new drug application) coupled with the relatively long primary endpoint timeline for a DES (e.g., 12 months or longer), applicants may wish to consider using the Modular PMA application program.[7] A modular PMA application is a compilation of discrete sections, or modules, submitted at different times, as each is completed. Together the modules make up a complete application. The potential advantage associated with the modular approach is that if any deficiencies in a particular section are noted by FDA, the applicant may be able to resolve them earlier in the review process than would occur with a traditional PMA application, where a complete application is submitted in a single submission.[8]

5. *Master Files*

Drug Master Files (DMFs) and Device Master Files (MAFs) permit the submission of proprietary information to FDA so that parties other than the owners of that information may rely on it. With the permission of the holder of that master file, a third party applicant may rely on the information in that master file to support the third party's application to FDA (e.g., IDE or PMA), even though the contents of the master file remain proprietary to the holder of the master file (See 21 CFR 314.420, 814.3(d), 814.9(a)). The Agency will not review a DMF or MAF in support of a third party's application unless the third party applicant submits in its application a letter of authorization (LOA)

[6] See the CDER guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drug*.
[7] See guidance for industry and FDA staff, *Premarket Approval Application Modular Review*.
[8] Ibid.

from the holder of the DMF or MAF, which authorizes FDA to refer to the master file in support of that application.[9]

As outlined in Section IV.C of the *Guideline for Drug Master Files*, each DMF should contain only one type of information and all supporting data. If the DMF is administratively incomplete or inadequate, it will be returned to the submitter with a letter of explanation from the Drug Master File Staff, and it will ***not*** be assigned a DMF number. If you intend to submit a DMF that does not conform to the *Guideline for Drug Master Files*, we recommend that you contact the appropriate review division or Drug Master File Staff before making the submission.

We recommend that a sponsor intending to reference (or file) a DMF allow for sufficient time for the Drug Master File Staff to administratively determine the adequacy of the DMF and assign a DMF number before an IDE is submitted, given the 30-day review timeframe for IDE applications. Additionally, sponsors who reference a DMF or MAF as a source of supportive data for an IDE or PMA should clearly identify the specific volume and page number of the referenced information for ease of review.

We have not issued guidance on the content of Device Master Files. In general, we will not accept a submission as a MAF if it is not substantive in nature and does not contain information that may reasonably be regarded as trade secret or confidential commercial information.

6. *Letters of Authorization (LOA)*

An LOA authorizes FDA, in its review of an application such as an IDE or PMA, to refer to information contained in another regulatory submission such as an NDA, IND, ANDA, DMF, MAF, IDE, or PMA. As part of its review of an IDE or PMA for a DES, FDA will review information from a referenced file only when the IDE or PMA applicant submits an LOA from the holder of that file, authorizing FDA to refer to the file in support of the IDE or PMA application. The extent of access granted to the IDE or PMA applicant is typically a business arrangement between the respective parties. An LOA may give the applicant the authority to rely on all of the information in a regulatory file, or, if the right to reference is not totally inclusive, on only specific portions of the file. A copy of the LOA should be included as part of the original IDE and subsequent PMA applications, with the original LOA submitted to the DMF. (Please refer to Section V.A of the *Guideline for Drug Master Files* for specific information to be included within an LOA.)

An LOA may grant FDA either the *right to reference* or the *right to reference **and** discuss* the information included within one regulatory submission (e.g., NDA, IND, ANDA, DMF, MAF, IDE, PMA) in support of another regulatory submission (e.g., IDE, PMA).

With a *right to reference* authorization letter, FDA will not discuss the contents of the referenced submission with the third party applicant. In the event there are outstanding or unresolved issues related to FDA's review of the referenced submission, the Agency will inform the third party applicant of the general nature of the outstanding issues that must be adequately addressed by the

[9] See FDA guidance on *Drug Master Files* and the *Introduction to Master Files for Devices* for more information on the submission of DMFs and MAFs

referenced application holder, but will not identify the specific issues. Alternately, if the holder of the referenced submission chooses not to address outstanding issues, the third party applicant could potentially generate the requested data independently.

A *right to reference and discuss* authorization letter allows FDA to review the reference submission as part of the third party's application, and permits FDA to discuss information within the referenced submission with the third party applicant. In the event that there are outstanding issues arising from FDA's review of the referenced submission that directly apply to the third party's IDE or PMA, this permission to discuss permits the Agency to discuss these issues directly with the IDE or PMA applicant instead of requiring FDA to discuss specific issues solely with the holder of the referenced submission.

C. Least Burdensome Principles

The issues identified in this guidance document are issues we believe should be addressed before a coronary DES can be marketed. In developing this guidance, we carefully considered the relevant statutory criteria for Agency decision making. We believe that we have identified the least burdensome approach to resolving the issues presented in the guidance. If, however, you believe that there is a less burdensome way to address an issue, we recommend you follow the procedures outlined in the guidance for industry *A Suggested Approach to Resolving Least Burdensome Issues.*

III. PRODUCT DEVELOPMENT PATHWAYS FOR DRUG ELUTING STENTS

The development of a new DES calls for a thorough exploration of the safety of all of the relevant components of the product intended for clinical use (e.g., stent, polymer/carrier, and drug), the composite finished DES, and the delivery system. DES development can present numerous challenges in that the action of the finished product (such as drug release profile) will affect the evaluations to be conducted on the individual components, especially the drug substance. However, testing of the finished product should be limited to in vitro and animal testing until sufficient safety information is generated to support the introduction of the DES into humans under IDE.

An overview of a potential development pathway is described directly below. The following sections discuss the factors that can affect the development pathway for a DES as well as how the amount of new information to be generated will be affected by both the extent of prior information on each of the components and the need to understand local and potentially systemic effects of the drug. Sponsors and applicants should carefully consider all of the information in this section in determining the appropriate development pathway for a particular DES.

A. The DES Development Pathway — Overview

The developmental process typically begins with selection of the drug, polymer or other carrier (if applicable), and stent platform. The stent platform may be chosen for its previously demonstrated performance, or it may be a new design developed specifically for use as a DES. In selection of the polymer or other carrier, considerations will include the following:

- The ability to control drug elution
- The compatibility of the polymer with the arterial tissue
- The ability of the polymer to conform to the stent platform without significant delamination upon stent delivery and deployment

Whether previously studied or newly developed, the drug substance is intended to limit the growth of excess neointimal hyperplasia after the injury caused by the stenting procedure without preventing ultimate re-endothelialization of the stented artery. Selection of the drug dose, both total dose and dose density, is critical. The amount of drug to be delivered should be carefully evaluated to ensure that the lowest effective dose is chosen to minimize potential toxicities. Sponsors are encouraged to consider dose-ranging studies of the DES in animals and possibly in humans to aid in identification of an optimal dose.

1. Drug Substance

The drug substance should be carefully characterized through evaluation of its chemistry, mechanism of action, and safety profile. In vitro and animal testing will reveal the types of toxicities that may result from the drug and the exposure levels at which those toxicities occur. Animal toxicology testing should establish the No Observed Adverse Effect Level (NOAEL), the highest exposure at which no adverse effects occur.

Developmental animal studies of the DES are encouraged to provide an understanding of the local and systemic exposure to the drug substance. Even if the amount of drug available systemically is below the limit of detection of the assay used, the potential for toxicity may still exist. Therefore, animal toxicology studies of the drug substance may be important to fully understand the potential for adverse effects following stent implantation. If implantation of the DES results in significant systemic exposure, data from human safety studies, specifically, single and multiple IV dose escalation studies, should be provided (previously conducted or new). If implantation of the DES in animals does not result in significant systemic exposure, data from human safety studies should not generally be needed (see Section IV.B. on how to determine when systemic exposure is considered to be significant).

When needed, these single and multiple IV dose escalation studies, conducted in healthy volunteers, will provide critical safety information about the drug and its potential toxicities in humans. The NOAEL determined in the animal studies described above should be used to select the starting dose. These studies, in addition to metabolic studies, which are intended to describe the distribution, metabolism, and excretion characteristics of the drug, should be performed ***prior*** to initiation of human clinical studies of the DES under an IDE.

Information regarding the drug substance may be available to the IDE or PMA applicant through the right to reference a third party's IND or NDA. However, if the referenced submission does not relate to intravenous or intra-arterial administration of the drug, as would be delivered by a coronary DES, FDA may require that additional information related to intravascular safety be included in the IDE and PMA applications. In some situations, particularly when the right of reference is not available and a sponsor is relying on information in the public domain, additional studies (e.g., drug interaction) may help the sponsor adequately support the safety of the drug, polymer, or stent

component of a DES. FDA should be consulted on the need for additional studies in this situation (See also Section IV. below).

2. Finished DES

The finished DES and its delivery system should be fully characterized. Characterization will include engineering studies, biocompatibility evaluation, animal studies, and development of complete chemistry, manufacturing and controls (CMC) information, including sterilization, packaging, and shelf life/stability testing.

Evaluation of the finished DES in humans should include meaningful clinical information related to stenting outcomes, as well as a systemic pharmacokinetic (PK) study. If significant systemic drug exposure occurs as a result of DES implantation (see Section IV.B. below), a careful evaluation of factors that may affect exposure, such as concomitant drugs and comorbidities (such as renal or hepatic failure), should be carried out.

The clinical study program should include the pivotal trial(s) to support marketing approval, extended follow-up of the patients in the pivotal trials following the primary endpoint evaluation, and appropriate postapproval studies.

More specific recommendations regarding each of these development steps can be found in the following sections of this document.

B. Factors Influencing Development: Prior Information on Components

1. Stent Platform

Stent platforms used in a DES may be chosen based on previously used bare metal stents or may be developed expressly for use in the DES. If nonclinical testing has been performed on the platform as a bare metal stent, much of this information may be incorporated by reference. Certain additional testing on the finished DES, such as coating integrity and particulate matter evaluation, should also be carried out. Additionally, the sponsor/applicant should consider whether the coating process or other manufacturing steps will affect the stent integrity or corrosion resistance and repeat appropriate bench testing (see Section VI.B.) as necessary.

2. Delivery System

Delivery system testing should be carried out as described in section VI.B. below. Evaluation of aspects such as delivery and handling characteristics, when previously studied in conjunction with a bare metal or other previously approved stent, can be incorporated by reference; however, delivery system testing that incorporates the drug-eluting stent (e.g., deployment, balloon burst) should be conducted using the intended DES and delivery system combination.

3. Polymer/Carrier

As described in section V below, a full physicochemical description of any polymers used as drug carriers should be provided either in the original application or by reference to DMFs, MAFs, or other sources. Any change in the properties of the polymer due to the incorporation of the drug substance within the polymer or the application of the polymer to the stent should be evaluated.

4. Drug Substance

An understanding of the systemic pharmacology and toxicology of the drug substance[10] and its metabolism in the body is essential to guide the design of the clinical studies of the DES with respect to monitoring for adverse events. Given this aim, testing should be performed ***prior*** to initiation of an IDE for the DES.

The amount of ***new*** evidence needed to support the safety and effectiveness of a DES will be determined by the amount of existing information about each of the components and, particularly, the drug substance. For a DES using a *studied* drug, that is, a molecular entity that has been previously approved or studied under IND (i.e., has an approved NDA or ANDA, or has undergone human clinical studies under an active IND), the information on systemic use described below may be available for the DES manufacturer to incorporate by reference. An *unstudied* drug that is a molecular entity that has not been approved for use in humans or that does not have study information available should undergo testing as described in Section IV below to develop this information before human testing of the DES.

C. Factors Influencing Development: Local and Systemic Exposure

For any DES, the primary exposure to the drug substance will occur at the coronary artery wall directly apposed to the stent and *downstream* in the stented vessel and myocardium. Exposure in the rest of the body will be much lower. At first glance, this could suggest that evaluation of the systemic toxicity of the drug substance alone should not be necessary and that the animal and clinical testing of the finished DES should be sufficient to demonstrate preliminary safety of the DES. However, several factors challenge this conclusion.

First, although the total dose of drug on a DES is almost always much lower than that given in a systemic administration (e.g., orally or by injection), the exposure at the artery wall may be many times higher than the blood levels achieved after an oral or injected dose. Therefore, the potential toxicity at the coronary wall at the DES implantation site and within the coronary vascular bed and myocardium distal to the DES implantation site should be studied. Animal studies of the finished DES will be critical to this understanding, but as is typical of animal toxicology studies, it is also important to assess the potential toxicity of exposure to higher doses than in the finished DES. Animal studies of local doses well above those expected from a DES to examine the safety margin over the doses that will be used in human DES implants should be completed.

Second, it has been our experience that in certain situations (i.e., multiple stents, major active metabolites), systemic drug exposure from a stent, or stents, can cause systemic toxicities.

[10] For the purpose of this guidance, *drug substance* is considered the active pharmacological agent.

Therefore, it is crucial to have information gathered under acute and chronic conditions on the systemic safety and toxicity profiles of the drug to be used in a DES system ***prior*** to initiating clinical studies.

Furthermore, there is a greater need for information about the safety of the drug component prior to beginning clinical studies of a DES because of the permanence of the DES. In addition, the planned DES clinical trials may not explore the full range of clinical use likely to occur after marketing approval, and there is a need to consider whether this more extensive use of permanent implants may place patients at risk. As a result, an appropriate understanding should be gained of the safety of the drug component prior to clinical studies with a DES.

In summary, a manufacturer of a new DES should establish preliminary evidence of the safety of the DES prior to beginning human clinical trials (under an IDE, or under an IND if intravenous clinical study of the drug substance alone is needed). A complete assessment of safety and effectiveness of the DES should be submitted in the PMA application. Recommended testing to address issues related to systemic pharmacology, toxicology, and safety of the drug substance follows. FDA remains open to alternative methods to obtain this information as well to other considerations, such as when the drug incorporated in the DES has known toxicities that may require modifications to the recommendations below.

IV. SYSTEMIC PHARMACOLOGY, TOXICOLOGY, AND SAFETY DATA FOR THE DRUG SUBSTANCE ALONE

FDA believes that systemic pharmacology, toxicology, and safety data on a drug substance to be incorporated in a stent are needed to fully understand the safety profile of the finished DES. Nonclinical, and often clinical, studies should be performed as part of the effort to demonstrate the safety of a DES.

A. General Considerations

A first step in characterizing a drug involves performing systemic nonclinical pharmacology and toxicology studies of the drug substance using in vitro (cell culture) or in vivo (animal) models. These nonclinical studies help provide an understanding of the metabolism of the drug, its distribution and accumulation (e.g., in the regional myocardium or other important organs), and whether the effects of the drug might be significantly affected by the presence of certain enzymes. Animal testing will also help assess potential toxicities that cannot be identified during clinical trials and will define the No Observed Adverse Event Level (NOAEL), which is used to determine the starting dose for human safety studies (see Section IV.B.). In some cases, animal testing may establish that an adequate factor of safety exists between the levels of drug exposure likely to be reached in humans and the levels of exposure at which toxicities are seen in animal studies. In some situations, when a sufficient safety margin exists, this testing may support the conclusion that human intravenous safety studies would not be necessary to ensure safety of clinical systemic exposure. In addition to determining the severity of the observed toxicities in animals and a careful definition of the local, regional, and systemic adverse effects in animals, it is important to define the *slope* of the

relationship between toxicity and exposure over a broad range of doses, extending to levels in excess of the dose anticipated for use in humans.

- Determining when human safety studies are needed – PK parameters and the NOAEL

When deciding whether human intravenous safety studies also will be needed, one should first consider what pharmacokinetic parameter—Cmax (maximum concentration) or AUC (area under the curve describing concentration versus time) over some specific time—should be the basis of the safety factor. If the parameter that best predicts toxicity is AUC (which is most likely the case), it is important to base any comparisons on AUCs integrated over the same or nearly the same time courses.

A second important consideration is identifying the preclinical toxicity that establishes the NOAEL. Usually, this is based on testing in the *most sensitive species* and on the adverse effect seen at the lowest dose.

When considering the relevance of a preclinical model for intravenous administration, the exposure should, ideally, resemble the exposure from a DES. Release of drug from a DES can generally be expected to follow two-phase kinetics—a first-order (or relatively fast) process with a time constant on the order of hours and a zero-order (or very long time constant) process. the preclinical intravenous exposure intended to match this would include infusion over several hours (first-order phase) followed by a lower prolonged or repeated infusion (if the half-life in plasma is much less than the release rate from a DES).[11] We recognize, however, that mimicking the time course of release from the stent can greatly complicate the animal study. Furthermore, matching the DES release should not be necessary when toxicity is likely to be mostly related to Cmax and the AUC over the first several hours, and the safety margin related to this period is of greatest concern. In such cases, preclinical assessment following a single bolus administration should be acceptable.
In such cases, preclinical assessment following a single bolus administration should be acceptable.

Another consideration for the relevance of a preclinical model is the possibility of species-specific metabolism. If a metabolite is prominent in humans, but not in the animal, the resulting NOAEL may not be pertinent to human exposure. If a sufficiently sensitive assay is available, it may be appropriate to do a microdose study in humans[12] to confirm similar metabolism.

If the parameter that best predicts toxicity is AUC, it is important to base any comparisons on AUCs integrated over the same or nearly the same time courses. Empirically, we recommend a comparison based on $AUC_{0\text{-}24h}$.

- Determining when human safety studies are needed – calculating the safety factor

Because multiple stents are commonly used in humans, the exposure parameter (generally,

[11] The DES should initially be studied in an animal model to inform the design of the animal IV toxicology study.

[12] See the CDER guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drug.*

$AUC_{0\text{-}24h}$) measured from implantation of the DES in the animal model should be adjusted to reflect the use of 120 mm of stented length as a likely maximum length to be encountered in common clinical use. In a vast majority of cases, if the safety factor (ratio of the NOAEL $AUC_{0\text{-}24h}$ level in the animal to the corresponding exposure $AUC_{0\text{-}24h}$ in humans) is a factor of 100 or more, DES clinical studies can be initiated without a prior intravenous administration human safety study. This conclusion is based on the observation that >100 fold increase in sensitivity to toxic effects in humans versus animals is extremely unusual for drugs. See the following example.

> The NOAEL for the most sensitive relevant toxicity (in the monkey) occurs at a dose that produces $AUC_{0\text{-}24h}$ = 4500 ng-h/mL. If a single 40 mm DES in the mini-pig produces $AUC_{0\text{-}24h}$ = 3 ng-h/mL; 120 mm of stent would be expected to yield an $AUC_{0\text{-}24h}$ of 9 ng-h/ml, still just 1/500 of the NOAEL. Absent other factors, it may be reasonable to conclude that no intravenous study in humans would be necessary before the first DES implantation in humans.

- Previously studied drugs

For a previously studied drug, much of the information discussed below may be available for incorporation in an IDE or PMA application through a right to reference or other means. However, in some cases, gaps in the preexisting safety data may be identified. For example, for a drug that has been developed for oral administration, additional nonclinical testing pertaining to the intravenous route (e.g., hypersensitivity, hemocompatibility) may not have been performed and should be conducted.

Where reference rights are unavailable, a sponsor may be able to use information in the public domain (e.g., published literature) in support of an application. When a DES relies for approval on data in a previously approved application for the drug substance to which the sponsor has an LOA, or on literature in the public domain, the sponsor or applicant should demonstrate that the active ingredient of the DES is the same as the active ingredient in the reference drug.

B. Nonclinical Pharmacology and Toxicology

For an unstudied drug that has never been studied in humans, preclinical safety testing and pharmacology studies should be conducted to fully characterize the drug-related effects, metabolites, and toxicities of the drug administered intravenously (IV). Studies should be designed to describe desired as well as off-target pharmacology and also potential drug toxicities; data from these studies should be used to select safe starting doses for clinical trials.[13]

The timing and types of studies that should be performed are described in International Conference on Harmonisation (ICH) M3, *Timing of Pre-clinical Studies in Relation to Clinical Trials*. Toxicology studies in two species, including one non-rodent species, should be designed to describe

[13] See also Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers at http://www.fda.gov/cder/guidance/5541fnl.htm.

a maximum tolerated dose (MTD) and determine the NOAEL. The duration of these studies should, at a minimum, span the length of time the DES is estimated to release drug in vivo. The minimum duration should be two weeks for a DES without a polymer or other drug carrier, which could be considered as a single IV dose drug study. The NOAEL from the IV studies should provide significant safety multiples over the clinical systemic exposure from multiple DES implants.

Other recommended toxicology studies are designed to assess potential toxicities that may not be monitorable in clinical studies. For example, tests for potential genetic toxicity (ICH S2A and S2B), tests for reproductive toxicity (ICH S5), and safety pharmacology studies (ICH S7A and S7B). Tests for the assessment of potential carcinogenicity are also described in the ICH guidances (S1A and S1B). However, if drug exposure to the local tissue is shown to last less than six months, carcinogenicity studies will generally not be required. Note that finished product biocompatibility testing does not obviate the need for safety and pharmacology testing of the drug substance alone.

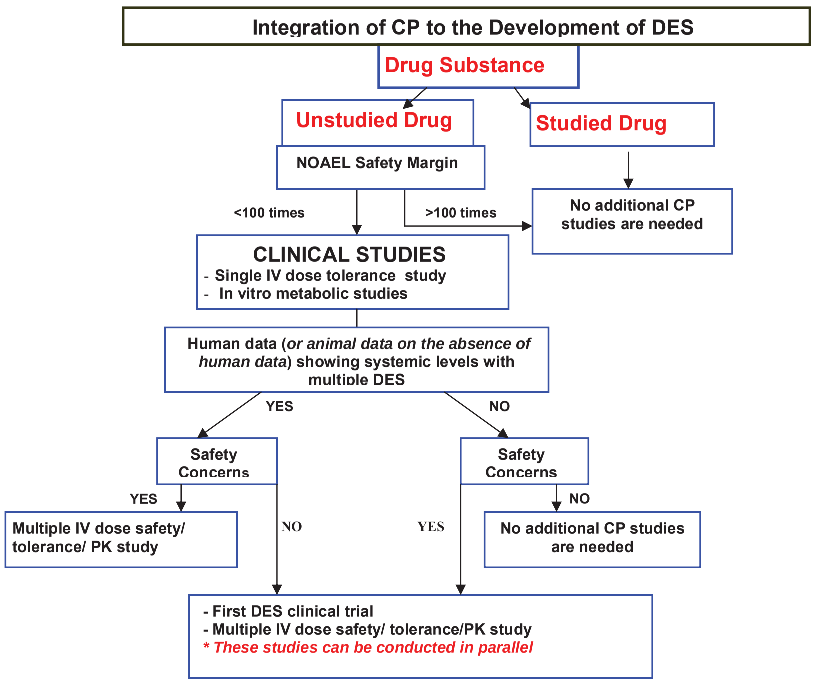
C. Clinical Pharmacology and Clinical Tolerance and Safety Information

The decision tree provided in this section describes the clinical pharmacology (CP) studies that should be considered for the assessment of the drug substance during the development of a DES. The key focus of the tree is the initial determination about whether the drug is an unstudied drug, about which little is known, or a previously studied drug, about which there already is a thorough understanding and adequate information with an appropriate safety profile is referenced in the application.

Human safety studies of the drug alone in healthy volunteers can provide critical information regarding the tolerability, safety, and pharmacokinetics of a drug substance. Whether such studies are needed will depend on the systemic exposure that will arise from the stent and how this compares with the exposure seen in animal studies, specifically the NOAEL, of the most sensitive species.

In general, for drugs that are well understood no additional clinical pharmacology studies are warranted since all the factors that affect a drug's safety and efficacy from a systemic point of view will already have been well characterized. If a drug has been previously studied and the resulting information is available, these studies need not be repeated. However, if the DES will incorporate a total amount of drug higher than that used in previous studies of the drug alone or result in higher sustained levels, additional information would be necessary to address the safety of the higher dose.

For an unstudied drug, the need for studies to elucidate the distribution, metabolism, and excretion of the drug, and any intrinsic or extrinsic factors that could affect exposure should be carefully assessed. Some of the metabolic information can be based on in vitro methods, notably the role of CYP450 enzymes in metabolism; some can be obtained from studies on the DES. As already mentioned, in some cases, human studies involving micro-doses may facilitate the assessment of the drug's pharmacokinetics.



Significant systemic exposure may not have been observed in animal studies of the DES, in part because the number of stents that can be implanted in an animal is limited. The potential for multiple stent use in routine clinical practice should be considered when determining whether a single IV dose escalation human study is needed to understand the systemic levels at which toxicities are first observed. Absent other factors that increase concern, a separation between the NOAEL established in the most sensitive animal species and the systemic exposure that could be reached of two orders of magnitude could mitigate the need for human studies of systemic drug safety.

If human PK data (using the DES) are available from previously conducted studies outside the United States, these data may provide a direct measure of systemic exposure (instead of the indirect measure based on animal data on the DES) and further determine whether such a substantial separation from toxicity causing concentrations exists. On the other hand, for DES where appreciable systemic drug concentrations can reasonably be expected and for drugs with animal or human toxicities that occur at only slightly above the anticipated human exposures, the full range of studies to evaluate the consequences of systemic exposure to the drug would be warranted. Animal

toxicology studies will then also serve to determine what is considered to constitute an initial safe dose for human systemic drug safety studies.

The usual next steps in developing a DES that incorporates an unstudied drug would involve single and multiple ascending dose studies. If the systemic exposure to the drug from a DES (or from multiple DESs) is sufficiently low (i.e., a reasonable safety factor exists between the NOAEL and the expected systemic exposure in man based on animal studies of the DES), such studies would probably not be informative.[14] However, it should be noted that an adequate assessment of systemic exposure from the DES in an animal model can only be made if the release characteristics of the drug are well-characterized and have been shown to have minimal variation from stent to stent.

For unstudied drugs, testing to elucidate the distribution, metabolism and excretion characteristics of the drug are essential in understanding the safety and efficacy profile of this new entity.

1. *Single IV Dose-Escalation Study*

If a single IV dose-escalation study is indicated, the selected initial dose should be based on the NOAEL information from the animal nonclinical studies. The drug should be given via intravenous administration (if feasible). This study should be designed to collect information on the drug substance's tolerance, safety, and pharmacokinetics following administration of single doses and escalating up to the maximum tolerated dose. The exposure should be engineered to resemble that produced by the DES.

2. *Multiple IV Dose-Escalation Study*

If the time course for release from a DES is long, data from a multiple IV dose- or from a continuous infusion dose-escalation study to mimic the stent exposure should be provided.

3. *Mass Balance Study*

We suggest that a mass-balance study be performed to define and assess the systemic exposure, the disposition and pathways of elimination (including metabolism and excretion), and pharmacokinetic measures or parameters of the drug substance administered intravenously.

The mass balance study should be based on the drug substance tagged with a radioactive label (i.e., ^{14}C, ^{3}H) to allow for sensitive monitoring of the distribution patterns of the tested drug after its intravenous administration. Blood (plasma or serum as appropriate), urine, and fecal samples should be collected and assayed for radioactive label. Other routes of elimination should be monitored as appropriate. Both the parent drug substance and any metabolites present should be identified.

4. *In Vitro and In Vivo Metabolic Studies*

[14] We note that single and multiple ascending dose studies are small and quite well monitored, and the insight into human toxicity can be quite valuable.

Since an integral part in understanding the safety of an unstudied drug is determining its metabolic pathway and whether there is formation of any active/toxic metabolites, the Agency recommends that a drug's metabolism and metabolic pathway, as well as the activity of major metabolites, be assessed relatively early in development of the DES.

In vitro metabolic studies designed to assess the P450 metabolizing enzymes of the drug as well as to characterize the P450 isoenzymes that are inhibited or induced by the drug should be conducted so that the clinical implications of interactions can be assessed later in the DES clinical studies.

In vitro metabolic studies can frequently serve as an adequate screening mechanism to assess the contribution of cytochrome P450 on the metabolism of the drug, so that subsequent in vivo testing will be unnecessary. In contrast, when positive findings of active or toxic metabolites arise in in vitro metabolic studies, we recommend that drug interaction information be obtained from the clinical trials using a drug interaction-population PK approach.

Information on the design and data analysis of the metabolic studies can be found in guidances *In Vivo Drug Metabolism/Drug Interaction Studies* and *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro.*

5. *Bioanalytical Methods*

Validated bioanalytical methods should be used when evaluating the concentrations of the drug and its metabolites in the clinical pharmacology and metabolic studies. Information on the validation of assays can be found in the guidance *Bioanalytical Method Validation.*

V. CMC INFORMATION

This section provides guidance on the information to be submitted regarding the chemistry, manufacturing, and controls (CMC) aspects of (1) the drug substance and (2) the finished product, followed by the information needed for (3) the engineering evaluation. The information can be provided in the submission, or incorporated by reference to another regulatory submission (e.g., DMF, NDA, ANDA, PMA, MAF) with copies of the LOA provided in the relevant section of the IDE or PMA application. All of the topics described for the drug substance and finished product should be included for both IDE and PMA submissions.

Because the product described in an initial IDE application will be permanently implanted into patients with potentially life-threatening coronary artery disease, the CMC section should address all of the items that would be provided in a PMA application. However, the level of detail and the degree of documentation will differ in that the information for the IDE will focus more on patient safety and product development and less on product and process controls.

In general, the information for the drug substance component is expected to be similar for both IDE and PMA submissions. However, it is recognized that the finished product is still under development at the time of the initial IDE submission. Consequently, clinical trials may be allowed to proceed even though manufacturing processes are not fully optimized, analytical methods

validation is incomplete, and the acceptance criteria for the finished product tests are still tentative, provided all parameters that relate to safety are well characterized. The sponsor/applicant is strongly encouraged to meet with the Agency before the initial IDE submission, during development and before submitting a PMA application to discuss critical drug-related issues and the information needed at various stages of development.

A. CMC for the Drug Substance Component[15]

The following items should be included for the drug substance in both the IDE and PMA submissions. When submitting an IND (e.g., when the drug substance is an unstudied drug and human safety studies will be conducted in the United States), guidance on Phase 1 (CMC section) should be carefully consulted.[16]

1. *Physical and Chemical Characterization*

The chemical structure of the drug substance (including stereochemistry), molecular formula, and molecular weight should be provided. All appropriate names or designations for the drug substance should be listed (e.g., USAN, Chemical Abstracts, IUPAC, code number). The physicochemical properties of the drug substance should be described and should include, but not be limited to, information on the following, as appropriate:

- General description (e.g., appearance, color, physical state)
- Melting or boiling points
- Optical rotation
- Solubility profile (aqueous and nonaqueous, as applicable)
- Solution pH
- Partition coefficients
- Dissociation constants
- Identification of the physical form (e.g., solid-state form, solvates, and hydrates) that will be used in the manufacture of the finished product

2. *Elucidation of Structure*

The chemical structure of the drug substance should be confirmed using physical and chemical techniques, such as elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, infrared (IR) spectroscopy, X-ray crystallography, and other tests (e.g., functional group analysis, derivatization, complex formation).

3. *Manufacturer*

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[15] See the CDER guidance *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*. Another drug substance guidance is forthcoming that, once finalized, will supersede this guidance.
[16] See the CDER guidance *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drug*.

The name, address, and manufacturing responsibility should be provided for each facility (including contract manufacturers and testing laboratories) that will be involved in the manufacturing or testing of the drug substance. The addresses should be those of the locations where the relevant manufacturing or testing operation will be performed. Registration numbers (i.e., CFN, FEI numbers) should be provided to facilitate CGMP inspections.

4. *Manufacture and Control*

The description of the manufacturing process should include a flow diagram and a narrative of the processes and process controls that will be used to manufacture the drug substance. The flow diagram should include each manufacturing step with chemical structure, solvents, reagents, auxiliary materials, critical operating parameters, and expected yield. A narrative description of the sequence of manufacturing steps and the scale of production should be provided in more detail than that given in the flow diagram.

Process controls used to monitor and adjust the manufacturing process should be provided and include in-process tests and acceptance criteria. These controls should ensure that intermediates and drug substance will conform to their established specifications.

Specifications, certificates of analysis, and quality or grade of the starting materials, reagents, solvents, and auxiliary materials that will be used to manufacture the drug substance (including deriving it from a biological source) should be provided. When appropriate, specific tests and acceptance criteria to control microbial contamination in materials derived from biological sources should be included in the specifications.

5. *Specifications*

Specifications are established to control the quality of the drug substance and should focus on those characteristics necessary to ensure the safety and efficacy of the finished product**.** The specifications should include all tests, analytical procedures, and associated acceptance criteria to which each batch of a drug substance will conform over its retest period/shelf-life.[17] Acceptance criteria are numerical limits, ranges, or other measures for the tests described. We recommend that the information be presented in tabular form.

Analytical procedures, including validation information, for each of the tests proposed in the specification should be described in detail. If the analytical procedure is in the current version of the United States Pharmacopeia (USP) or other FDA-recognized standard reference (e.g., AOAC International Book of Methods), details need not be provided. Analytical procedures should be validated to demonstrate that the methods are suitable for their intended use. Validation should include experimental data (e.g., representative chromatograms with peak identification).[18]

[17] See ICH Guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and Drug Products: Chemical Substances*.

[18] See ICH Guidances *Q2A Text on Validation of Analytical Procedures* and *Q2B Validation of Analytical Procedures: Methodology*.

Acceptance criteria should be primarily based on consideration of safety, efficacy, manufacturability, and stability. The justification for the acceptance criteria can be demonstrated by batch analysis data for all relevant batches, e.g., nonclinical, clinical, and primary stability batches. The batch analysis reports should include:

- Batch identity (i.e., batch number) and size
- Date of manufacture
- Site of manufacture
- Manufacturing process (e.g., synthetic route A)
- Intended use (e.g., clinical, nonclinical, stability)
- Results for each parameter tested; tabular format is recommended

6. *Reference Standards*

Information on the reference standards or reference materials used for testing the drug substance should be provided. A reference standard obtained from an official source should be identified. A reference standard not from an official source should be appropriately characterized. A list of any available reference standards for impurities should be included.

7. *Container/Closure System*

A description of the container closure system for the drug substance should be provided, including the identity of materials of construction for each primary packaging component and specifications.

8. *Stability*

Stability data should be generated in accordance with ICH guidances.[19] The studies conducted, protocols used, and the results of the studies should be summarized. The discussion should include (1) a summary of stability batches tested, storage conditions used, attributes tested, acceptance criteria, test schedule, and analysis of all available data (including a summary of the statistical analysis if performed) and (2) conclusions regarding the storage conditions and retest or expiration dating period, as appropriate. Data regarding stability under stressed (e.g., pH extremes, oxidation, heat, light) conditions should also be provided. We recommend that the results of stability studies be presented in tabular form.

B. CMC for the Finished Product

For the purpose of this section, the phrase *finished product* refers to a packaged and sterilized DES that contains all the materials (e.g., drug and polymer coating materials) applied to or incorporated within a bare metallic stent substrate and the stent delivery system. The following sections discuss the information on the finished product that should be submitted in support of an IDE or PMA

[19] See ICH guidance *Q1A(R2) Stability Testing of New Drug Substances and Products*.

application.[20] Section V.B. provides recommendations on the chemistry, manufacturing, and controls information on the finished product from a drug perspective. Section VI.B. (Engineering Evaluation) provides recommendations regarding assessment of coating integrity and Section VII.A. (Manufacturing -- Quality System (QS) Regulation and Current Good Manufacturing Practice (CGMP) Regulations) provides recommendations for additional manufacturing and quality control information needed for the finished product from a QS regulation/CGMP regulation perspective. You may wish to provide all of this information relating to the drug and device constituent parts of the combination product in one section of the PMA or separately with cross-reference to the other sections as appropriate.

1. *Description of the DES*

A detailed description of the finished DES should be provided and should include the proprietary name, model numbers, stent sizes, product code, and intended use. Detailed engineering drawings should also be provided. In addition to a detailed written description, a cross-sectional schematic of the stent platform, coating layers (e.g., primer layer, polymer/drug layer, drug-free polymer topcoat) and stent delivery system should also be included that pictorially depicts the coating and drug distribution across the stent geometry (e.g., length, circumference, strut sides, adluminal, abluminal). The schematic should also include a description of the drug release mechanism. The total drug content (µg/stent) and drug dose density (µg/mm^2) should also be provided for each stent size.

2. *Product Development*

This section should contain information on the development studies conducted to establish that the components of the finished DES, the formulation, manufacturing process and controls, and packaging system are appropriate for the purpose specified in the application. The studies included in this section can be distinguished from controls used for routine batch release. Additionally, this section should identify and describe the formulation and process attributes, including critical parameters that can influence batch reproducibility, product performance, and quality. Development reports allow the Agency to understand critical variables and focus attention on high-risk aspects of a product and process.

a. Components of the Finished DES Product

- Drug Substance

Key physicochemical characteristics (e.g., solubility, hydrophobicity, stability) of the drug substance should be discussed and those characteristics that can influence the performance and manufacturability of the finished product should be assessed. The compatibility of the drug substance with the excipients in the finished product should also be addressed, and if there is any evidence of physical or chemical incompatibility, justification for using the component should be provided.

[20] See the CDER guidance for industry *Submitting Documentation for the Manufacturing of and Controls for Drug Products* (1987). Another drug product guidance is forthcoming that will supersede the 1987 guidance.

- Excipients

The choice of excipients (e.g. polymer carriers), their concentrations, and the characteristics that can influence the finished product performance or manufacturability should be discussed. The applicant should demonstrate an understanding of the effects of excipient variability on the critical quality attributes of the finished product. Since organic solvents are usually employed to dissolve both the drug substance and polymer carrier to form a coating solution, the rationale for choice of solvent should be provided. The ability of functional excipients (e.g. antioxidants) to perform throughout the intended shelf life of the DES should also be discussed.

- Stent Substrate and Delivery System

The design of and the rationale for the selection of the key elements of the stent substrate[21] (e.g., materials, surface characteristics and area, cell structure, engineering performance), which can influence the performance and manufacturability of the finished DES, should be discussed. The applicant should also describe the components and design elements of the stent delivery systems used for stent deployment in the coronary vasculature.

b. Formulation Development

Since a DES is formulated to provide *extended release* of the drug substance, a description of the drug release mechanism (e.g. erodible polymer matrix, diffusion) should be provided. The development of target release rates of the drug from the polymer matrix should be discussed. The applicant should provide a scientific rationale for the selection of the final formulation by evaluating appropriate models for drug release. The applicant should show how the formulation and product construction were chosen, incorporating the principles of modern pharmaceutical development practices, Quality System regulations, and/or Design Control requirements as appropriate.[22,23,24]

c. Manufacturing Process Development

The selection of the manufacturing process with emphasis on understanding its critical aspects should be described. Manufacturing process development generally starts with the identification of critical quality attributes of the finished product, which are necessary for its desired performance. Manufacturing process options in conjunction with appropriate control

[21] See Guidance for Industry and FDA staff on *Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.*

[22] See also the CDER guidance for industry *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.*

[23] See ICH Guidance *Q8 Pharmaceutical Development.*

[24] See 21 CFR 820.30 for more detailed Design Control requirements.

strategies that can reliably result in finished product with critical quality attributes within acceptable ranges should be considered. Critical process parameters that should be controlled or monitored to ensure batch-to-batch reproducibility and to minimize intra-batch variability should also be discussed. This approach demonstrates knowledge and understanding of the product and associated processes, which in turn provides greater assurance of product quality. The benefits of having an efficient and reliable process, with reduced reliance on end-product testing, include enhanced manufacturing efficiency and a reduced risk of producing a poor quality product. These concepts, when implemented, would be a significant advantage to stent manufacturers who typically produce small batch sizes. Operations using process analytical technologies (PAT)[25] that measure an endpoint indicating the manufacturing process (e.g., coating) is under control are preferable to a measurement of a quality attribute on representative samples. Generally, this allows for adjustments to process parameters to mitigate anticipated variation in raw materials, equipment, environment, or other conditions.

d. Packaging System Development

The applicant should describe how the packaging system was selected and designed to provide protection and maintain sterility throughout the shelf life of the finished product. The suitability of the packaging system should be demonstrated with respect to protection from moisture, oxidation, and light, and compatibility of materials with all components of the finished product.

3. Physical and Chemical Characterization

The morphology of the solid drug-polymer carrier system in the finished product should be described (i.e., dispersed drug phase, continuous separate drug phase, reservoirs). Micrographs of the surface and full thickness cross-section of the coating should be provided. The micrographs will aid in gaining an understanding of the drug release process, which may have implications for coating durability and particulate matter formation.

A detailed description of the physical and chemical tests performed to characterize the finished product should be provided. The physical, chemical, and mechanical characteristics of a DES are critical to ensure finished product quality and performance. Physical and chemical characterization of a DES should include tests for surface coat composition, coating/carrier thickness and uniformity, and coating/carrier erodability as applicable. These tests are useful for characterization and may be provided as one-time tests—not to be confused with routine control and release testing.

Note: These tests are a subset of testing recommendations provided in Section VI.C of this guidance for the mechanical/engineering performance tests for the finished DES.

4. Components and Composition

[25] See 21 CFR 820.30 for more detailed Design Control requirements.

A qualitative and quantitative list of drug substance(s) and excipients making up the finished product should be provided. We recommend including a detailed components and composition table per unit and per batch for each stent configuration to be marketed. Ingredients used in the manufacture of the finished product, regardless of whether or not they appear in the finished product, such as solvents, should be identified. Ingredients of human or animal origin should also be identified and their use supported with appropriate safety information.

a. Component Function

The function (i.e., role) of each ingredient in the formulation should be described. Ingredients that are used in the manufacture but are not intended to be part of the finished product (e.g. solvents) should be identified as processing agents.

b. Component Controls

The applicant should identify all component tests that the finished product manufacturer will routinely perform as well as test results that will be accepted from the excipient and drug substance manufacturer (Certificate of Analysis, COA). At a minimum, the finished product manufacturer must perform an appropriate component identification test (21 CFR 211.84(d)(2)).

(i) Drug Substance

See Section V.A.

(ii) Excipients

Compendial excipients should comply at a minimum with the monograph standard in the official compendium and be identified as such. The monograph tests may not be sufficient or appropriate for use in a DES and additional testing may be needed, especially for the polymer/carrier (see below). When analytical procedures from an official compendium or other FDA recognized standard references (e.g., AOAC International Book of Methods, analytical procedures from EP or JP that are interchangeable with a USP *General Chapter*) are used, they should be verified as suitable under actual conditions of use. The following information should be provided for each compendial excipient:

- Name and address of the supplier
- COA from the supplier
- Results from any additional testing

For each noncompendial excipient, detailed information should be provided in the submission or in an MAF/DMF and should include the following:

- Name and address of the supplier

- Method of manufacture (e.g. flow chart, all components used in the manufacturing)
- Specifications and validation of analytical procedures
- COA from the supplier
- Additional information as appropriate (e.g. safety data for novel excipients)

Since most DESs use a polymer matrix as a carrier or barrier for the drug release, special attention should be paid to this component. In addition to the items listed above, the following information should also be included for the polymer:

- Description and function of polymer (including a rationale for each component, if a co-polymer)
- Polymer characterization and properties
- Chemical structure (monomer fractions, if co-polymer)
- Identity test (matches infrared or NMR reference spectrum) and any other acceptance tests with associated analytical methods
- Average MW, MW range, and MW distribution (including MW methodology validation)
- Glass transition temperature (Tg) (and melting temperature, Tm, if applicable)
- Density
- Residual levels of catalysts, solvents, impurities, and monomers
- Composition by weight percentage (if polymer carrier is a blend)
- Sampling and storage conditions
- Stability (e.g., measurement of polymer molecular weight, resistance to oxidation, light, heat, ionizing radiation)

Many of these items should be tested on a routine basis as part of the polymer specifications and adequate justification should be provided for any exclusions.

It is important to note that although an MAF/DMF may be referenced for the polymer, the MAF/DMF might not contain sufficient and/or appropriate information to support omission of testing on the finished product. For example, the MAF/DMF may only provide certificate of analysis (COA) information about the chemical properties of the unprocessed polymer, but additional data on the polymer following the intended processing/manufacturing (including sterilization) should be provided.

(iii) Stent Substrate and Delivery System

The following detailed information for each component used in the fabrication of the stent substrate and its delivery catheter system should be provided:

- Name and address of the supplier
- Method of manufacture (e.g., laser cutting for stent)
- Specifications and validation of analytical procedures
- COA from the supplier or incoming receiving specifications if no COA provided

5. *Manufacturer*

The name, address, and manufacturing responsibility should be provided for each facility (including contract manufacturers and testing laboratories) that will be involved in the manufacturing or testing of the finished product.[26] Addresses should be provided for the locations where the relevant manufacturing or testing operation will be performed. Registration numbers (i.e., CFN, FEI numbers) should be provided to facilitate GMP inspections. This information may be submitted in the Manufacturing -- Quality System (QS) Regulation and Current Good Manufacturing Practice (CGMP) Regulations section (see Section VII.A. below) and incorporated by reference or reproduced here for ease of review.

6. *Manufacturing Process and Controls*

A complete description of the manufacturing process and controls (or a reference to this information) should be provided within this section of an application to provide a thorough understanding of the critical attributes that should be assessed at final product release and to assess the potential impact of changes made in the manufacturing procedures used during the course of product development. A discussion of any differences between the manufacturing process to be used for the marketed product and any used to produce batches for clinical efficacy and/or primary stability studies should be addressed in the PMA application. This should include an evaluation of how the differences will not adversely affect the performance of the product. (See also Section VII.A below.)

a. Flow Diagram

A flow diagram (or series of flow diagrams) should be provided that includes all the steps in the manufacturing process for the finished DES. The diagram should include the following:

- Steps where materials enter the process (e.g., catheters, stents, polymers)
- Critical processing steps that may have an influence on the chemical or physical properties of the stent, polymer, or drug (e.g., application of coating, including any primers or coupling agents, use of oxygen scavengers or antioxidants, crimping of stent onto catheter, heat sets, use of sheath protectors)
- In-process testing (identify method) and the manufacturing step where it is performed
- Sterilization (identify method) and packaging steps
- Any end-process (reliability) testing conducted prior to product release
- Differentiation of manual versus automated processes
- Depiction of differences in manufacturing processes for the catheters (e.g., Over-The-Wire versus Rapid eXchange)

[26] A statement should be provided that ruminant-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are not used or manipulated in the same facility.

We recommend that the diagram be color-coded (and/or shape-coded) to differentiate materials, processes, and inspection steps.

b. Description of the Manufacturing Process

A description should be provided of the ***entire*** manufacturing process, including packaging, which should illustrate the sequence of steps undertaken and the scale of production. The description should include equipment identified by type (e.g., coating process chambers) and capacity. Any novel processes or technologies (e.g., coating methodology) should be described in detail.

c. Process Controls

Controls used to monitor the manufacturing process should be described, including operating parameters, environmental controls, and process/in-process tests. A description of critical process controls (as justified in section V.B.2.c. *Manufacturing Process Development*) should include tests, analytical procedures, limits (ranges), or other acceptance criteria.

In some cases, results from in-process controls can be used in lieu of finished product testing. This approach, however, should be supported with data that demonstrate a clear relationship between in-process testing and the critical quality attributes of the finished product.

d. Sterilization Process

The sponsor should clearly identify the method of sterilization (e.g., ethylene oxide, E-beam radiation, gamma) along with the specific parameters (e.g., concentrations, humidity, time, and temperatures) and an assessment of its effect on the finished product. The assessment should address the effects on such elements as coating integrity, drug substance, and polymer carrier stability.

See Section VI.C for engineering test methods to evaluate the effect of sterilization on the coating characteristics.

7. Packaging System

A description and the following information on each component of the primary packaging system for the finished product should be provided:

- Supplier/manufacturer
- Composition
- Quality/grade of materials
- Schematic drawing including dimensions, tolerances, etc.
- Specifications

The same type of information should be provided for functional secondary packaging components as well. For nonfunctional secondary packaging components (e.g., those that do not provide additional protection), only a brief description is necessary.

8. Finished Product Specifications

Regulatory specifications should be provided for the finished product; these specifications apply to every batch at release and throughout shelf-life. A specification consists of a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. An example of a regulatory specification table is provided in Appendix A. Finished product specifications should focus on those characteristics found to be useful in ensuring product quality as it relates to safety and efficacy. Testing should be performed on every batch of the finished product after packaging and sterilization. All testing should be performed on expanded stents, unless otherwise justified. To ensure that the regulatory specifications are met throughout the shelf life, tighter acceptance criteria may be established for product release.

When product knowledge and process understanding have been demonstrated in the application, and relevant in-process control strategies are being implemented routinely, it may be possible to use in-process tests in lieu of traditional off-line end-product testing. In addition, PAT, if applied, can serve as a basis for real-time release of the finished product to demonstrate that each batch conforms to established regulatory attributes. It should be emphasized that any alternate proposals to end-product testing should be discussed with the Agency during development and regulatory approval obtained before implementation.

The analytical procedures and their validation[27] should be described in detail for each test listed in the specifications. Acceptance criteria should be primarily based on consideration of safety, efficacy, manufacturability, and stability. The justification for the acceptance criteria can be based upon batch analysis data for all relevant batches (e.g., nonclinical, clinical, and primary stability batches). Ideally, the data should be representative of batches of finished product manufactured using different lots of drug substance, polymer, and coating solution. The sampling plan should be described. The batch analysis reports should include:

- Batch identity (i.e., batch number) and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Intended use (e.g., clinical, stability)
- Results for each parameter tested, in tabular format

A *batch* is defined as a quantity of DES produced according to a single manufacturing order during the same cycle of manufacture. A batch should be made with only one lot of coating solution. Combining stents having different expanded diameters into one batch would only be appropriate

[27] See ICH guidances *Q2A Text on Validation of Analytical Procedures* and *Q2B Validation of Analytical Procedures: Methodology*.

when the stents originated from the same diameter tubing, have the same design/platform, and only differ in the balloon diameter to be used. Combining stents of different lengths into one batch is discouraged.

Because DES batch sizes are typically small and end-product testing consumes a large quantity of test samples, the applicant may consider any of the following alternative approaches:

- Using in-process testing as a substitute for some release tests (e.g. residual solvents). In these cases, the tests should still be listed in the finished product specifications with appropriate notation.
- Using the same test samples for several release tests (e.g. identification, assay, and content uniformity).
- Using a smaller number of samples than recommended by USP for certain tests (e.g. content uniformity) with tighter acceptance criteria.
- Using *quality by design* principles, which rely less on end-product testing and more on building quality into the product and process design.

General tests that are expected to be included in the specifications for a finished DES are listed below. A tabular format similar to the example shown in the Appendix A is recommended for presentation of the specifications.

a. Appearance

A qualitative description of the finished DES should be provided. Any visualization or imaging methods adequate to ensure that the DES meets its specifications should be included.

b. Identification

Identification testing to establish the identity of the drug substance in the finished product should be specific (e.g., infrared spectroscopy or a chromatographic method in combination with an additional test such as UV diode array or MS) and able to discriminate between compounds of closely related structure that are likely to be present. Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles, or a combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally appropriate.

c. Assay

A specific, stability-indicating assay to determine content should be included for all drug substances in the finished product. In many cases, it is possible to employ the same procedure (e.g., HPLC) for assay of the drug substance and quantitation of impurities.

When use of a nonspecific assay can be justified, other supporting analytical procedures should be used to achieve overall specificity. When the assay is not stability indicating, a separate impurity assay can be employed. A specific procedure should be used when there is evidence of inactive ingredient interference with the nonspecific assay.

d. Impurities and Degradation Products

Any impurities, degradation products, and/or residual solvents are included in this category. We recommend sponsors refer to the ICH Q3B guidance covering finished product impurities. Appropriate stability-indicating analytical methodology should be used to monitor degradation products and acceptance limits should be defined for individual specified degradation products, both identified and unidentified, unspecified degradation products, as well as total degradation products.

e. Content Uniformity

This test assesses drug content variation from stent to stent within a batch and is to be distinguished from uniformity along an individual stent length. The latter is typically a one-time test to establish coating uniformity. The method and limits established in USP <905> Uniformity of Dosage Units are considered appropriate for determining content uniformity within DES batches.

f. Drug Release

The specification should include a test for in vitro drug release. The test should be performed over a sufficient period of time and include a sufficient number of time points to correlate to in vivo release. The test is generally used as a quality control tool and should be discriminatory. The results should ideally be reported as percent of label claim released per unit time. See section VI. E. for additional details regarding in vitro elution testing.

g. Package Integrity and Sterility

A test procedure and acceptance criterion for evaluation of sterility testing and package integrity should be included. When test methods differ significantly from compendial test methods, a demonstration of the equivalency to the compendial method should be provided. Parametric release can be proposed when appropriate data are generated during development and validation.

The tests and methods demonstrating the integrity of the microbiological barrier of the packaging system should be well defined and scientifically justified. Sufficiently sensitive packaging integrity testing may reduce the need for end product sterility testing.

h. Endotoxins

A test procedure and acceptance criteria for endotoxins, using a procedure such as the Limulus Amoebocyte Lysate (LAL) test, should be included in the specification.

Note: All blood-contacting cardiovascular devices and combination products should be non-pyrogenic regardless of whether any claims regarding their *non-pyrogenic* status are made in the labeling. Pyrogenicity testing is used to help define limits to protect patients from the risk of febrile reaction. Pyrogenic responses to gram-negative bacterial endotoxins can be tested using standard methods such as the USP Bacterial Endotoxins Test (<85>) using LAL. Pyrogenic responses to leachables over the implant life can be tested using a material-mediated pyrogenicity test. See the companion document (Section titled "General Biocompatibility Considerations") for additional specifics on materials-mediated pyrogenicity testing.

i. Particulate Matter—Batch Release

This test evaluates the presence of sub-visible particulate matter. Particulate matter may include particles shed from the formulation components as well as extraneous particles from the stent platform, stent delivery system, packaging, and environmental factors. Appropriate testing and acceptance criteria should be established for particulate matter. See section VI.B for analytical procedures for characterizing particulate matter.

j. Additional Testing

Additional testing of the finished DES may be necessary to address unique characteristics of an individual DES. Examples include tests for polymer molecular weight, residual monomers, catalysts, or other additives.

9. Stability

Stability testing is performed to support the establishment of a shelf life or expiration dating period for a DES (See also Section VII.C below). Stability studies should also be conducted during investigational phases to support product stability for the duration of clinical trials.

A stability protocol should be provided that includes storage conditions, time points, test parameters, analytical methods, and acceptance criteria. The formal stability protocol can include an appropriate matrixing and bracketing design. At a minimum, the protocol design should include the extremes (in terms of both stent dimensions and total drug load) as well as an intermediate size to provide assurance of consistent behavior across the entire proposed matrix of DES sizes to be commercialized.[28] If there are design differences (e.g., multiple stent platforms) within the proposed DES matrix, the sponsor should bracket each design or provide a scientific rationale to support the applicability of the sizes that are tested for the entire product matrix. We recommend that stability testing include samples from a minimum of three finished product batches for each size tested.

[28] See ICH guidance *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products.*

Stability testing should be conducted under ICH recommended conditions at room temperature (25°C/60% RH or 30°C/65% RH) and accelerated conditions (40°C/75% RH).[29] If long-term testing is conducted at 25°C/60% RH and a significant change as described in ICH Q1A(R2) is observed in the results obtained for a DES tested under accelerated conditions, additional testing using intermediate conditions (30°C/65% RH) should be conducted and evaluated against significant change criteria.

For each set of stability data provided, the sponsor should identify the packaging system, the batch number and scale, manufacturing date and site, the manufacturing process and formulation. For ease of review, the Agency recommends that all stability information be provided in tabular format. See Appendix A for an example of a stability table.

In general, the following tests should be performed at each of the preselected stability time points on a minimum of three finished product batches to generate the primary stability data used to support an expiration date:

- Appearance
- Assay/drug content
- Impurities/degradation products
- In vitro drug release
- Particulate matter[30]

In addition, some tests, such as sterility, and package integrity, should be performed at release, annually, and at expiry.

If different finished product manufacturing sites will be used, appropriate release/stability data to ensure the consistency and equivalency of the finished product should be generated. Generally real-time, room temperature data should be used to establish a DES shelf life. However, based on the quality of the data (e.g., accelerated, long-term testing) provided by the applicant, a reasonable extrapolation of data may be considered to assign the shelf life. It is recommended that simulated transportation/shipping studies also be conducted as a one-time test to support excursions that may occur during distribution of a DES.

10. Labeling

Detailed guidance on labeling and examples of text that can be used are included in the stand-alone companion document. CMC information should appear in the **Description** sections of the label.

11. Environmental Assessment

An Environmental Assessment or request for a waiver (with justification) should be submitted (21 CFR 814.20(b)(11)).

[29] See ICH guidance *Q1A(R2) Stability Testing of New Drug Substances and Products.*
[30] See section VI. B for test method considerations for particulate matter testing as part of the stability protocol.

VI. NONCLINICAL STUDIES OF THE FINISHED DES

A. Summary Tables

FDA recommends that a master table be compiled to summarize all mechanical performance, animal, and clinical testing that has been conducted in support of the DES to either be tested clinically (under the IDE) or commercialized (for the PMA application) in the United States. An example of the parameters to be captured in tabular format as part of the master table has been included in the Companion Document to this guidance. The master table should be provided and updated, as necessary, for both IDE and PMA applications. To enable the integration of the master table into the regulatory submission, the sponsor/applicant may decide to divide the table into more discrete units (e.g., separate tables for engineering, PK, pharmacology/toxicity studies for the drug substance, and animal studies in support of the DES). This table, or set of tables, will greatly aid in the sponsor's and the Agency's assessment of whether sufficient supportive acute and chronic safety and/or effectiveness data have been provided for the proposed DES as part of both the IDE and PMA reviews.

Also for ease of review, FDA recommends that a one-page summary of significant trial design parameters for each clinical study conducted in support of either the IDE and/or PMA applications be provided. The companion document includes more details regarding this recommendation.

In the event that the DES evaluated in nonclinical or clinical studies differs from the DES that is intended for commercialization, the sponsor/applicant should provide an appropriate justification for the applicability of testing provided. This justification, which can include additional limited testing, can be referred to as a *bridging* document. FDA will assess the significance of any such differences when determining whether sufficient information has been provided to support initiation of a clinical study (IDE) or whether valid scientific evidence has been submitted to provide reasonable assurance of safety and effectiveness for a PMA application.

B. Engineering Evaluation

The battery of tests and content and format of test data outlined in FDA's guidance document on bare metal intravascular stents and their associated delivery systems[31] are relevant for this guidance and for DES development. FDA recommends that sponsors complete ***all*** tests outlined in that guidance on the finished DES intended for commercialization. Additionally, for those tests that evaluate characteristics that could be affected by the addition of the drug and/or drug coating, sponsors should compare those results with the performance characteristics of the bare metal stent system in a side-by-side fashion. If a test article other than the finished, sterilized DES (e.g., bare metal stent, prototype, coupon) is used for a specific test, a scientific rationale should be provided for the applicability of the test article.

[31] See guidance for industry and FDA staff on *Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.*

FDA recommends that the final, finished DES be evaluated to determine the initial performance characteristics of the DES. However, if there are ***any*** differences between DES tested for initial characterization, clinical builds (DES used in the human studies) and the DES sought to be commercialized (due to scale up of the manufacturing process), the changes should be clearly documented and, as a part of the PMA submission, appropriate additional testing should be conducted or a scientific rationale provided to demonstrate that these modifications will not affect the safety and effectiveness of the DES.

A thorough description of the entire manufacturing process should be provided for review. This description should clearly indicate whether any modifications have been made to the native stent platform (e.g., texturizing of the stent surface, use of coupling agents, polishing) to facilitate coating deposition/adhesion onto the stent substrate. The potential effect of additional processing steps on the durability of the stent substrate as well as the coating should be evaluated.

Since unintended delamination or premature dissolution of a DES coating may influence its clinical performance and/or mechanical integrity, ***additional*** evaluations and suggested modifications to the battery of traditional engineering testing as outlined in the guidance document referenced above should be taken into consideration for a DES.

- Test protocols

In addition to the test data (summaries are not typically sufficient), detailed test protocols, which include the loading parameters, test conditions, samples tested, acceptance criteria, and conclusions drawn for each of the tests performed on finished, sterilized product, should be provided for FDA review. A brief description of the derivation or development of the test method, or identification of other applications in which the method has been previously used should be included.

Test protocols should assess the worst-case conditions that the DES is likely to experience in clinical practice. Both device configuration and physiologic conditions can affect the performance of a DES.

Extreme device dimensions, tolerances, sizes, and any other important device parameters should be evaluated. We also recommend that the outer limits of physiologic variables, such as blood pressure, vascular compliance, and anatomic types, be examined. All test conditions should be clearly stated in the test protocol and supported with references to applicable literature, standards, or both. Occasionally, the worst performing combination of device configuration and physiologic conditions occurs in the mid-range of the relevant variables. This should be considered when developing protocols to ensure that the worst performing combination has been evaluated.

The term *coating* may refer to the drug carrier (usually polymeric, but not limited to such), the drug itself if it is solely coated onto the stent platform, any other coating, or the drug carrier even if it is incorporated onto the stent in a geometry other than a coating.

1. Coating Characterization

As part of the overall coating characterization of a finished DES, the sponsor should conduct additional studies on a one-time basis as part of the product assessment to establish an understanding of their DES system as well as appropriate baseline data. FDA believes that adequate baseline characterization of a DES may help the sponsor identify potential coating integrity concerns earlier rather than later in the development process. It should be noted that the tests recommended to characterize the coating and to assess acute and chronic coating integrity are not typically considered quality control (QC) tests; however, tests for particulate matter recommended in Section VI.B.3.iii are suggested as part of the QC assessment as described.

Specifically, testing should be provided to address each of the following issues as part of characterization studies:

- Coating thickness and uniformity along the stent length (both abluminal and adluminal surfaces, if relevant), circumferentially, and along the sides of the struts.
- Adhesion of the coating to the stent substrate. We recommend a quantitative characterization of the adhesion strength. If the coating consists of multiple layers (e.g., primers), we recommend that a quantitative test be performed to determine the cohesive strength between the layers.
- Chemical identification of particles recovered as part of particulate matter testing (see Section VI.D.3 below)

2. *Coating Integrity*

The acute and chronic integrity of coating on the stent substrate should be assessed to provide reasonable assurance that the coating is able to sustain its integrity according to its design specifications. The Agency requests that the sponsor qualitatively and quantitatively determine whether subjecting a DES system to expansion, deployment, and repetitive cycling modalities as experienced in the clinical setting will influence the ability of the coating to interact appropriately with the stent substrate. Part of this evaluation will entail determining whether there are areas where the coating has not been adequately deposited onto the substrate (e.g., defects such as bare spots or webbing due to manufacturing) versus areas in which the coating may have physically dislodged (e.g., delaminated) from the substrate due to being subjected to mechanical forces.

As part of this testing, it is recommended that a sampling plan be implemented to examine multiple lots of DES as well as comparing regions of high stress/strain versus low stress/strain areas to assess both inter- and intra-lot variability. A sufficient number of images should be provided so that FDA can make an assessment of consistency.

Furthermore, FDA recommends that coating integrity be evaluated by testing under certain conditions ***before*** and ***after*** aging (at a minimum, the product should be aged to the requested shelf life). These samples do not need to be real-time aged, but can be subjected to accelerated aging conditions.

For this section of the guidance, *acute* refers to any time up through expansion and deployment of the DES, whereas *chronic* refers to any time after assessment of the initial stent deployment in a simulated vessel throughout the lifetime of the implant.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- Acute coating integrity

Acute coating integrity of a DES should be assessed via some visualization method (e.g., scanning electron microscope). The stents used for this characterization should be representative of the finished product, subjected to all manufacturing processes, including sterilization. A visual assessment of the coating integrity on all appropriate surfaces of the DES after expansion in air to nominal diameter with characteristics appropriately quantified (e.g., continuity, voids) is strongly recommended to establish a baseline for comparison to coating characteristics after testing performed under other conditions.

Further visual characterization of the coating should be performed after deployment of the DES to the maximum diameter as described in the Instructions for Use. If overexpansion of the DES (post-dilatation) is to be allowed, this should be taken into consideration as part of this testing. It is recommended that deployment be simulated in an in vitro model intended to mimic in vivo physiologic and anatomic conditions (e.g., tortuous path, aqueous environment). The stent should be in direct contact with the simulated vessel without the use of other coatings, lubricants, sheaths, or protective wraps between the stent and simulated vessel. The rationale for the final model selected should be provided.

Ideally, the coating should not significantly change in configuration or prematurely delaminate from the stent substrate upon expansion or deployment.

- Chronic coating integrity

Chronic coating integrity or, for a degradable polymer system, the loss of coating integrity over time, can be assessed by performing accelerated durability testing in a simulated in vivo environment. It is highly recommended that the visual integrity of a DES after 30 and 400 million cycles of fatigue testing (representing approximately 1 and 10 years of equivalent implant time) be compared to baseline data in a side-by-side fashion. For degradable polymer systems, timepoints for evaluation may be specific to the expected degradation profile. A detailed fatigue test protocol, clearly describing the test equipment, aqueous environment, frequency, loading parameters, and mounting of samples should be provided with the results from these tests.

The sponsor should consider the following when designing tests to appropriately demonstrate the chronic coating integrity of a DES:

1. The sponsor should clearly indicate whether the sample consists of single or multiple stents along with a justification supporting test methods testing multiple samples. Since there is a reasonable expectation that stents will be overlapped during some clinical procedures, accelerated durability testing should be performed on multiple stents in an overlapped configuration.
2. We recommend that testing be conducted with stents in a bent configuration, with a clinically relevant radius of curvature.

3. If a product's drug elution is completed in a short time relative to the intended lifetime of the product, coating integrity test samples should be pre-eluted for a worst-case evaluation. This is a particularly important consideration for those coatings that become porous over time because of drug elution.

4. At a minimum, we recommend that these additional tests be performed on the finished DES for the worst-case product sizes for each stent design to demonstrate that the acute and chronic integrity of the coating has not adversely affected the characteristics of the DES system.

5. This testing can be combined with fatigue testing intended to evaluate integrity of the stent platform, if the apparatus can accommodate both tests.

Refer to the section immediately below for additional issues related to characterization of the coating integrity of a DES.

3. Particulate Matter Characterization

FDA recommends measurement of particulate matter generated by breakdown of the coating or from the stent platform, stent delivery system, and product packaging both at release and after aging. Particulate matter testing serves multiple purposes: (1) it provides an indirect evaluation of the coating integrity of the finished product and (2) it establishes the number of particles that can potentially be introduced systemically using the stent system. FDA believes that the main purpose in particulate matter testing for DESs is to provide a level of assurance of patient safety in terms of total particulate matter introduced into the bloodstream. Therefore, since the concern applies to the total number of particles released into the bloodstream, the test should apply to the entire stent delivery system, not just the stent.

a. Testing Considerations

The sponsor should consider the following when designing tests to appropriately determine the number, size and/or type of particles for a DES system when subjected to the conditions described in b-d below.

1. Particle counting and sizing methods should be described and validated. It is recommended that as part of the method validation, a known amount of various particle sizes be introduced into the test setup and the amount of particles recovered quantified. The number of particles recovered should closely approximate the number artificially introduced into the system.

2. Appropriate precautions should be implemented to ensure that the particles are suspended during sampling for particle counting and sizing to minimize artifacts from the test system. In our experience, particles > 50 µm have the tendency to settle and/or stick to the reservoir between particle counting. We recommend running a *blank* in which no stent is present and any particles present in the system are captured and counted. These counts represent test artifact and should be subtracted from the results when a stent (or stents) is introduced into the system

3. The number of samples (a stent, not a strut or portion of a stent) used, the stent size, and the stent lot should be specified for each test. The selection of the samples should be scientifically justified.

4. We recommend that for baseline, overexpansion, and simulated use conditions described in sections b, c, and d immediately below, testing be performed on the extremes (*four corners* size matrix — see example table, below) and an appropriate intermediate stent size for the entire stent matrix proposed.

Example of *Four Corners* Size Matrix

	LENGTH (MM)							
Diameter (mm)		8	11	15	18	21	24	27
	2.5	X						X
	3.0				X			
	3.5							
	4.0	X						X

5. For evaluation of particulate matter generated on fatigue testing, the worst-case size(s) for each stent design should be tested. A justification for the sizes selected for testing should be provided; the rationale may include information gained from the finite element analysis.

6. For each test performed, a robust number of stents from multiple stent lots (minimum of 3 batches) should be evaluated.

7. Appropriate acceptance criteria should be proposed for particles ≥ 10 µm and ≥ 25 µm. The sponsor should provide valid scientific evidence, including chemical identification of the particles recovered to support the proposed specifications.

8. We recommend that particulate matter results be provided in a side-by-side fashion (e.g., comparing baseline and post-tracking deployment).

Note: In the event that an accessory device (e.g., embolic protection, atherectomy) is intended to be used in conjunction with a DES, the sponsor should provide appropriate supportive engineering performance test data to ensure that the integrity of the coating is maintained. We recommend that sponsors contact appropriate FDA staff to discuss engineering testing recommendations.

b. Characterization

For the purposes of *characterization* of the finished, sterilized DES, particulate matter testing should be performed and particles collected and appropriately measured for several different test cases:

- Baseline (expansion to nominal diameter)

Such testing should involve expansion of the stent to its nominal diameter in a beaker of solution. If the stent is not a balloon-deployed stent and is self-expanding, this condition and the over-expansion condition described below may be equivalent and combined into one test condition.

- Over-expansion (maximum deployed diameter, including post-dilatation limits, as specified in the IFU)

This testing should involve expansion of the stent to the maximum diameter allowed, as described in the post-dilatation limits in the IFU in a beaker of solution.

- Simulated use (e.g., during tracking and deployment)

This testing should be performed with use of an in vitro model as described in section B.2 (acute coating integrity) above. Note that physiologically relevant worst-case conditions should be applied. To ensure measurement of the total number of particles that could be potentially introduced into the bloodstream, the stent delivery system should be inserted into the text fixture to the point at which it would be inserted in clinical use.

- Fatigue/durability testing

This testing should be performed with use of a test fixture as described in section B.2 (chronic coating integrity) above. Note that physiologically relevant worst-case conditions should be applied. This should include multiple stents placed in an overlapped and bent configuration. It is recommended that particulate matter generation be measured at multiple time points, rather than at t=0 and 400 million cycles. One advantage of this approach is that a pattern/trend of particulate matter generation can be described (e.g., plateaus, monotonic increases). Depending on this trend, the sponsor may be able to determine the appropriate number of fatigue cycles (which may be significantly less than 400 million) necessary to demonstrate that the coating will not unintentionally break apart or, for a degradable polymer system, to quantify the particulate matter generation associated with the degradation of the polymer.

c. Quality Control

If the amount of particulate matter recovered from over-expansion testing and simulated use testing is substantially similar, either test may be used for quality control testing. However, if these two test conditions resulted in different amounts of particulate matter, the more challenging test, the simulated use condition, should be performed for quality control purposes. In either case, the test should be performed on every batch of product manufactured as part of batch release (see Section V.B.8 above for other parameters to be measured for batch release).

d. Stability

For stability testing, we recommend that aged samples be evaluated using the simulated use test condition. If the over-expansion condition is used for quality control purposes, additional testing using the simulated use condition should be performed on stability batches at t=0. It is highly recommended that particulate matter generation over time be evaluated at each time point in the stability protocol (instead of only at t=0 and t=proposed expiration date). In the event that the particle counts continually increase with aging or fail to meet the

acceptance criteria at the proposed expiration date, additional data will be available to support a shorter expiration date for the DES.

4. *Corrosion Potential of a DES*

If the underlying stent substrate of the DES is metallic, FDA recommends that the sponsor evaluate the effects of cracked or delaminated coatings on corrosion resistance. We recommend that corrosion testing be performed after intentionally creating a defect in the coating, which exposes the base stent substrate. We recommend testing according to the methods described in ASTM F746 [32] or an equivalent method. The sponsor can modify the method by incorporating the experimental setup described in ASTM F2129.[33]

Additionally, since there is a reasonable expectation of stent overlap during clinical procedures, the potential for fretting corrosion between two DESs should also be addressed. The sponsor should ensure that micromotion between strut elements is actually occurring. We recommend that the sponsor incorporate examination of samples for fretting corrosion as part of fatigue/durability testing. A scientific rationale for the number of samples evaluated for fretting corrosion should be provided.

If a stent contains more than one type of metal, such as a laminate, we recommend that the resistance of the stent to galvanic corrosion be demonstrated. If stents of different materials will be overlapped during clinical procedures and the contacting or overlapping stents may be made of different materials, we recommend that the potential for galvanic corrosion between stents be addressed. We recommend testing according to the methods described in ASTM G71,[34] or an equivalent method. Sponsors can modify the method by incorporating the experimental setup described in ASTM F2129.

5. *Degradable coatings*

If a DES has a degradable polymer carrier, the environments for the experimental tests described above should be carefully taken into consideration since they may affect the interpretation of the results. Therefore, we recommend that a full characterization be performed of the degradation profile (both in vitro and in vivo) of the biodegradable polymer carriers. The resulting information should be used to design the test environment for the evaluations described above, as well as to assess the appropriate timelines for additional nonclinical studies (e.g., supportive animal studies, elution characteristics).

The durability of the degradable coating becomes important near the end of the coating lifetime when degradation has weakened the coating. We therefore recommend that particulate matter testing be conducted in fatigue testing for the life of the coating. The trend or pattern of particulate matter generation as the coating degrades should be described. It may also be instructive to observe

[32] ASTM F746 Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials.
[33] ASTM F2129 Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices.
[34] ASTM G71 Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes.

the coating via visual/microscopic methods near the end of the coating lifetime to characterize the pattern of degradation to understand the potential for increased particulate matter generation (e.g., Does the degradation occur preferentially at the surface or stent interface once some interface has been exposed? Is the degradation patchy?).

Shelf life/stability characterization becomes very important for degradable/resorbable polymers. For example, exposure to humidity may begin the degradation process and therefore not only reduce the shelf life, but increase the elution at early stages of the product and decrease the effective lifetime of the coating.

It is also very important to characterize the effects of the sterilization processes on the coating, because many processes (e.g., irradiation) reduce the molecular weight of the polymers, which may allow an increase of elution at early stages of the product and reduce the effective lifetime of the coating.

C. **Biocompatibility**

Biocompatibility testing should be conducted in accordance with ISO 10993.[35] For certain tests, evaluation of the stent should be carried out separately from the delivery system. For additional considerations related to biocompatibility testing, refer to the companion document.

D. **Animal Safety Studies**

Prior to undertaking GLP animal safety studies, pilot DES animal studies should be conducted to evaluate the degree of systemic exposure, local vascular and regional myocardial levels of the drug component of the stent. This information can be discussed with FDA and will inform the need for, and extent of, separate studies or data on systemic clinical pharmacology.

DES nonclinical in vivo safety studies conducted in appropriate validated healthy animal models are intended to assess handling characteristics (delivery and deployment), the biological response to the DES, drug effects, and stent-related pathology. In addition, these studies are used to identify potential clinically relevant major adverse events that should be considered prior to beginning human clinical trials or that may influence clinical study design. The design of these studies should also evaluate stents that incorporate a safety margin over the highest drug dosage and greatest polymer concentration intended to be evaluated in the IDE clinical study as well as for all reasonably anticipated intended clinical uses of the DES.

Animal studies should compare combinations of the stent components (i.e., bare stent, and stent + polymer + drug) in both nonoverlapping and overlapping configurations. The sponsor should clearly identify any differences (e.g., stent design differences, polymer thickness, drug amounts) between the DES used for nonclinical studies and the proposed IDE study.

Studies of stent + polymer (without drug) should be performed if safety concerns are observed with the finished DES product so as to help identify whether pathologic changes are more likely due to

[35] ISO 10993-1 Biological evaluation of medical devices—Part 1: Evaluation and testing.

the drug or the coating. The *stent + polymer* sample should include both biodegradable and non-biodegradable polymer carriers as well as the primer layer.

If observed pathologic changes are believed to be secondary to species-specific arterial responses, an approved DES can be considered as an additional control treatment arm. Additionally, sponsors can consider using an approved DES as a control treatment arm to demonstrate superiority of the test DES with respect to sustained neointimal growth supression, more rapid stent endothelialization, reduced fibrin deposition, improved vasomobility, reduced inflammation, and reduced positive remodeling/stent strut mal-apposition.

Demonstration of probable product safety is currently considered to be the primary purpose of the nonclinical animal studies. Demonstrating potential product efficacy (i.e., inhibition of neointimal hyperplasia) is an important secondary endpoint. However, for any given drug-device combination, the potential efficacy observed during animal studies should be appropriate to ***balance*** any potential safety concerns that were observed during the same studies. Also, it is reasonable to presume that the demonstration of the potential efficacy of a new DES in an animal model may assume increasing importance over time if multiple DESs are approved for clinical use.

Refer to the companion document for general recommendations regarding good animal husbandry.

1. Appropriate Validated Models

Because of the similarities in the size, anatomic distribution, and time-dependent progression neointimal growth within stents in human coronary arteries, the swine model has historically been relied on for testing of intracoronary devices. However, because of inherent differences between animal and human vascular responses to stent implantation, animal testing is primarily focused on the evaluation of safety, rather than sustained long-term efficacy. Small animal models (e.g., rabbit iliac artery) can provide complimentary data on optimal dose finding and DES mechanism of action.

Currently, there is no animal model that can both (1) replicate the heterogeneity of human atherosclerotic coronary disease and (2) accommodate the sizes of catheters and stents used in humans. Due to potential experimental complexity and in the absence of studies demonstrating predictive capabilities, atherosclerotic animal models to test the safety and performance of these products have not been routinely requested. However, although advanced stenotic atherosclerotic lesions in animals may not be available, sponsors may consider DES implantation in modifications of normal vessels (e.g., intimal lipid/inflammatory cell-rich or fibrotic lesions) to test device performance in vascular environments that may be relevant to human use.

2. Standards for Evaluation

Unless there is a specific reason to do otherwise, the stent should be implanted in an artery that has no prior injury. Antiplatelet therapy should be administered based on the current clinical standard of care and that to be used during the clinical study.

The Agency recommends the use of, at minimum, general animal study guidelines, necropsy, and arterial histopathology methods, including those described below. The study findings from each stent

type (i.e., bare stent, stent + polymer + drug, and if indicated, stent + polymer) should be compared. We recommend the following.

- A complete general necropsy (gross and detailed histopathology) should be performed, as well as gross and radiographic evaluation of stented vessels and the heart, including an evaluation of vessel wall and stent structural integrity (e.g., strut fractures, polymer fragments), assessment of stent malapposition, and multiple anatomical regional sections from organs perfused by the stented artery.
- We recommend pressure perfusion fixation and plastic embedding for stented arteries.
- For stents $\leq$ 30 mm in length, we recommend evaluation of a minimum of three sections per stent (proximal, mid and distal), plus one section 5 mm beyond each end of the stent.
- For stents > 30 mm in length, see section VI.F.7 of this guidance.
- For arterial histopathologic sections, a descriptive histopathology report (including micrographs illustrating the findings) and histomorphometric analysis as well as interpretation of data are recommended. We also recommend a thorough evaluation of the arterial biological response to the DES describing the following points.
  - The morphologic features of the neointima and the extent of stent strut coverage by neointima
  - The extent of endothelialization (scanning electron microscopy should be considered)
  - Alterations of the media (e.g., necrosis, thinning of media or loss of cellularity) and adventitia
  - Locations and amounts of fibrin
  - Location and severity of dystrophic calcification
  - Evidence of the loss of vessel wall structural integrity
  - Characterization of the inflammatory response and fibrosis within the neointima, media, and adventitia
- We recommend that you specifically evaluate and report the presence of mural thrombus formation and evaluate the potential for thromboembolism and the significance of stent-related embolic material in selected regions of organs perfused by the stented vessel. Stent strut mal-apposition to the arterial wall should be reported. For the porcine coronary model, in particular, the presence of granulomas should be noted.
- We recommend that all pathology and histopathology reports be written by the examining pathologists or clinicians and attached as an appendix to the final GLP study report.
- We recommend inclusion of a broad selection of representative, thoroughly described gross photographs, radiographs (evaluating stent integrity, configuration, and extent of stent overlapping), and photomicrographs of arterial cross sections from stented arteries in the final pathology. We encourage the submission of representative photomicrographs describing the histopathology scoring system used to describe the severity of histopathology endpoints. In addition, thumbnail, low, and higher magnification photomicrographs of all

arterial sections should be included as an appendix in the final pathology report. To ease review, we recommend providing all gross photographs, radiographs, and photomicrographs in electronic format.

- Histomorphometric evaluation of sections is essential for the assessment of DES biological response and safety. These measurements should minimally include the following: neointimal area, neointima thickness at each strut site, medial area, internal and external lamina area, lumen area and percent area stenosis. Measurements should be performed on each stent section (proximal, middle, and distal), and a mean measurement for each parameter for the entire stent should be reported. From these data, the percentage of the stent narrowed by neointimal tissue (percent stent stenosis) can be calculated. A mean injury score for each stent should be determined.

  The non-stented adjacent arterial sections (5 mm proximally and distally) should undergo comprehensive histologic evaluation including an assessment of arterial injury, neointimal thickening, inflammation, and thrombus deposition.

Quantitative coronary angiography (QCA) is recommended for appropriate stent diameter implantation (stent to artery ratio) to avoid excessive vascular injury secondary to oversizing. The use of intravascular ultrasound (IVUS) evaluation is recommended in a subset of animal studies to demonstrate strut apposition to the arterial wall both post-procedure and at follow-up in a subset of animals.

Following DES implantation, any sudden or unscheduled animal deaths should be vigorously investigated for cause. In such cases, a thorough necropsy should be conducted, including evaluating all stented arteries and specifying the cause of death. Any clinical problems (e.g., fever, allergy, evidence of renal or hepatic dysfunction) should also be recorded. We recommend that complete data on thrombus, myocardial infarction, aneurysm, and perforation be collected and included with the pathology report within the IDE submission.

3. Study Duration

Animal studies designed to assess biological response and safety of the final clinical version of the DES should be conducted prior to first in human use. At a minimum, 1- and 6-month studies are suggested; 3-month animal data are optional, and depending on the results, may be sufficient to begin a clinical feasibility trial.

In view of the mechanism of action of most DESs, longer term follow-up studies (e.g., beyond 6 months) are likely to be necessary to assess (1) chronic inflammatory reactions, (2) delayed or incomplete endothelialization, (3) late stent thrombosis and restenosis, and (4) chronic biological responses to the surface polymer after complete drug elution and, in the case where a biodegradable polymer is used that takes longer than 6 months to fully degrade.

In nonclinical studies at all time points, histology should be carefully evaluated for polymer delamination from the stent.

Note: Given the differences in injury and healing responses between the animal models and humans, in addition to inherent variability between the designs of different DES systems, a definitive long-term follow-up time point for animal model studies to assess late effects cannot be explicitly recommended.

4. Biological Response

We recommend that a three-way comparison of the histopathological findings for the bare metal stent, polymer-only stent (if indicated), and the polymer-drug stent combination be conducted at appropriate time points, minimally to include 1 and 6 months. We recommend that at least six to eight samples of each of the stent types be evaluated with a minimum of three to four animals per time point. We recommend enrollment of extra animals in anticipation of possible early animal deaths.

a. Histopathology Endpoints Assessing Drug Effects

Study endpoints should focus on the characterization of localized drug effects within the vessel wall of the stented vessel as well as immediately proximal and distal to the stented vessel segment (i.e., to observe any potential edge effects). Evidence of DES-related drug effects and pathology includes factors such as mural thrombus formation, fibrin deposition, inflammation (strut associated; neointima, media, adventitia), granulomas, neointimal smooth muscle density, medial necrosis and thinning, dystrophic calcification, endothelialization, vessel wall hemorrhage, and neoangiogenesis. We recommend that a scoring system be used to record the incidence and severity reported by stent segment region (i.e., proximal, mid, distal).

b. Downstream and Edge Drug Effects

It is important to evaluate whether a drug produces pathology in the tissue ***downstream*** from the stent. Using the highest total drug dosage proposed for clinical use, a thorough gross and histopathology evaluation of multiple anatomic regional sections of myocardium perfused by the stented artery should be conducted to identify stent-related cardiac pathology (e.g., infarcts, thromboembolic material, myocardial necrosis and fibrosis).

In addition, the drug effects immediately proximal and distal to the stented segment of the vessel (referred to as an *edge effect*) should be assessed. Using similar histopathology and histomorphometric endpoints as described above (VI.C.2 and 4a), the findings should be compared to the stent segment of the vessel.

If long stents are evaluated separately (refer to section VI.F.7), this evaluation should be completed both for standard length stents and for long stents.

5. Drug Dosage Safety Margin

The objective of studies of stents with higher drug and polymer dosages than will be applied to the clinical or to-be-commercialized version of the stent is to establish a safety margin over and above the dose intended for clinical use. These studies can reveal whether adverse effects are observed at higher dosages, and at what dosage the effects are observed. The following drug formulation characteristics

should be used to describe a DES.

- Dose density
- Total dose loaded
- Coating thickness
- Amount of drug delivered to the tissues
- Residual amount of drug on the stent
- Release rate

In animal studies intended to establish a safety margin, the dose density, amount of drug or polymer loaded, and number of stents should be designed to justify a margin of safety over the proposed clinical trial dose. In addition, drug release characteristics should be analyzed in relation to local tissue drug concentration, vascular biological responses and local toxicity. The release rate is important because it directly correlates with the local vascular toxicity. Additional animal studies should be carried out to evaluate the safety of stents containing higher dosages of drug and polymer (i.e., a three- to ten-fold margin over the intended drug dosage density of the final product) to evaluate whether the DES has an appropriate local, regional, and (possibly) systemic safety margin with regard to drug dosage density. If loading high drug concentrations onto the stent is technically difficult or significantly alters the degradation profile for a degradable carrier, the Agency recommends evaluating regions of overlapped stents to theoretically support safety margins. Evaluation of over-dosage stents should include the longest, largest diameter stent, and if multiple stents are routinely used, the combined drug density of the highest number of, and the longest, stents allowed in the planned human study.

6. Overlapping Stents

Since overlapping stents are commonly implanted in current clinical practice, animal studies should be undertaken to evaluate the safety of overlapping DESs and provided as part of the IDE submission. Stents overlapping by a minimum of 4 mm should be evaluated at 1 and 6 months (optionally at 3 months), in a minimum of six stents per stent type. Histopathology sections should be obtained from both overlapped and non-overlapped regions. Histopathology and histomorphometric endpoints should be reported and compared by stent segment (i.e., proximal, overlapped, distal stent).

Due to the likely possibility that multiple overlapping stents will be used, FDA recommends that animal testing on overlapping stents be provided as part of the PMA submission whether or not testing is included within the clinical study to provide a preliminary assurance of safety.

7. Long Stents

A separate evaluation should be completed for the longest stent model if a long DES (i.e., >30 mm) is to be marketed. Evaluation of angiography and histopathology is particularly important to characterize the biological and drug response along the full length of the stent. Histopathology sections should cut at approximately 10 mm intervals, plus one section 5 mm proximally and distally beyond each end of the stent. The Agency will not routinely request comparisons to *long* stent

controls. Results of the long DES may be compared to those observed for standard-length control stents and DES.

E. Clinical Pharmacology and Drug Release Kinetics

This section provides suggestions on elements to consider in the assessment of the clinical pharmacokinetics of a DES and on the evaluation of both in vivo and in vitro release characteristics of the drug from a DES.

1. Clinical Pharmacology Information

a. Evaluation of the Systemic Pharmacokinetics of a DES

The evaluation of the pharmacokinetics (PK) of a DES can be accomplished in one of the trials of patients implanted with the DES. The sponsor should provide a detailed protocol describing the design of the PK study. The in vivo drug release kinetic information generated during the animal studies could be useful in designing the human PK study (i.e., appropriate PK sampling times, length of PK study).

To obtain PK information at the highest possible drug exposure, it is recommended that the PK evaluation occur in a trial including patients receiving multiple and overlapping stents. The measures or parameters for the drug should include area under the plasma concentration versus time curve (AUC), peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), elimination half-life ($T_{1/2}$), and total clearance (Cl_t). If there are major metabolites associated with the therapeutic or toxic effects of the drug, they should also be determined.

b. Population-PK

A population PK-sparse sampling approach can also be used for the collection of clinical PK data for the DES from patients enrolled in the clinical trials. See CDER’s guidance for industry *Population Pharmacokinetics.*

c. Bio-Analytical Methods

The evaluation of the samples collected during the PK study should be evaluated for drug content using properly validated analytical methods. Additional information on validation of methods can be found in CDER’s guidance for industry *Bioanalytical Method Validation.*

2. Drug Release Kinetic Information

a. Evaluation of In Vivo Drug Release

The in vivo drug release information generated in the animal studies can be very useful (1) in the design of the in vivo human PK assessment conducted as part of the clinical program (i.e.,

appropriate PK sampling times, length of PK study), (2) in the development of in vitro release methodology that mimics the in vivo drug release, and (3) in the development of an in vivo-in vitro correlation (IVIVC).

The in vivo release of a drug can be divided into two types. First, the release can be directly measured using the amount of drug remaining in explanted stents with respect to time until complete drug elution profile is obtained. The release can also be measured using the blood and/or tissue concentration data. The in vivo release profile generated using the first method represents drug release from the stent to the surrounding tissues and systemic circulation while that generated using the second method represents drug released from the stent and the surrounding tissue into the systemic circulation.

- Drug Tissue Levels and Systemic Distribution

The in vivo local and systemic drug kinetics of the DES to be used in the IDE clinical studies and submitted in the PMA application for marketing approval (if there are modifications) should be thoroughly characterized in an appropriate animal model. The release of drug from the stent should be evaluated at specified time intervals covering the complete drug elution profile (immediately after implantation until the drug is completely eluted from the stent). Drug concentrations should be assessed in the blood, in arterial tissue, and in myocardial tissue proximal and distal to the stent, as well as in remote tissue, such as the liver, lung, and kidney. In the tissue surrounding the stent, the drug should be evaluated until there are no longer detectable levels.

Assessments should include whether the drug's concentration is uniform along the stent length or preferentially distributed at either end. Evaluations should compare the terminal elimination $t_{1/2}$ of drug from stent to the true elimination $t_{1/2}$ obtained after IV administration. If drug release from the stent is slower than the elimination process (flip-flop phenomenon), the rate limiting step is the release of drug from the stent.

b. Evaluation of In Vitro Drug Release Kinetics

In vitro release testing is a powerful and useful tool for obtaining data related to a product's quality and, potentially, its clinical performance. The Agency considers the development of acceptable, discriminating in vitro elution methodology and specifications as critical for the adequate characterization of a DES product tested clinically as well as to validate consistency in the commercially manufactured product. Because this testing serves multiple important purposes, including use in DES characterization, batch release, and stability testing, the in vitro elution method for the testing of the release of drug from the DES should be developed and validated as early in the development process as possible and definitely prior to submission of the PMA application.

The in vitro drug release/elution kinetics should be evaluated under appropriate conditions based on the mechanism of drug release and to emulate hydrodynamic considerations of stent deployment. In vitro drug release kinetics characterization should provide valuable insight on the time course of drug release and on the drug remaining on the stent. The relative

solubility of the drug also determines the relative kinetics such that a more lipophilic drug exhibits a longer time of elution. We recommend that the in vitro release profile generated with the chosen method mimic the in vivo elution behavior of the drug from the DES. If this is not possible (e.g., the in vivo release is limited), the in vitro method should be optimized for its ability to detect manufacturing lots outside the boundaries established in the clinical trials.

A detailed description of the optimal in vitro elution methodology and the developmental parameters (i.e., equipment/apparatus, in vitro release media, agitation/speed, temperature, pH, assay) that were used to identify this method as most appropriate should be submitted to the Agency in the IDE. Also, the method validation information showing that the chosen method is able to detect manufacturing changes (under meaningful testing) that may have an effect on the release of the drug should be submitted. Validation studies are important for identifying critical formulation and manufacturing variables during development, establishing relevant controls for manufacturing, and developing a relevant stability indicating test method for final product testing. An in vitro test method based on mechanism of drug release can also be a valuable tool for ensuring unchanged performance of manufactured lots.

The elution profile should be complete and cover at least 80 percent of drug release of the label amount or whenever a plateau is reached. We recommend use of at least six samples per testing variable. The elution data (individual, mean, profiles) should be reported as the cumulative percentage of drug eluted with time (the percentage is based on the product's label claim).

In vitro drug release kinetics should be reproducible between stents within a lot and between manufacturing lots and should be stability-indicating. The chosen method should be discriminatory and sensitive enough to reject lots that would have less than acceptable clinical performance.

For the setting of the drug release/elution acceptance criteria, the following points should be considered:

- The in vitro elution specifications should encompass the timeframe over which at least 80 percent of the drug is eluted or where the plateau of drug elution is reached if incomplete elution is occurring.
- Data from lots used in the clinical trials and stability studies, and also on to-be-marketed batches, should be used.
- The establishment of at least three sampling times covering the initial, middle, and terminal phases of the complete elution profile data should be selected. The acceptance criteria ranges should be based on the overall elution data generated at these times.
- Acceptance criteria should be set in a way to ensure consistent performance from lot to lot.

- The chosen acceptance criteria should not allow the release of any lots with elution profiles outside those that were tested clinically.

The applicant should note that an agreed upon in vitro elution test (i.e., specifications and acceptance criteria) is critical as a quality control (QC) tool during the stability program and establishment of the DES shelf life and is part of the QC tests performed for the release of DES batches.

c. In Vitro-In Vivo Correlation

The ultimate goal of an in vitro-in vivo correlation (IVIVC) is to establish a meaningful relationship between in vitro behavior of a DES product and in vivo performance of the same product, which would allow in vitro release data to be used as a surrogate for in vivo behavior. Thus, the main objective of developing and evaluating IVIVC is to empower the in vitro release test to serve as a surrogate marker for in vivo bioavailability. One additional primary purpose of establishing an IVIVC is to minimize the number of human studies needed for the approval of scale-up and postapproval changes in manufacturing processes (e.g., those that do not change the mechanism of release). We recommend that the following factors be considered when establishing the IVIVC:

- Mechanism of drug release from the stent
- Formulation and manufacturing process factors that influence the release kinetics
- In vitro method conditions (e.g., hydrodynamics, media composition)
- In vivo stent deployment factors

To obtain an in vitro-in vivo relationship, two sets of data should be collected. The first set contains the in vitro data, usually drug release data from an elution test, and most often takes the form of percentage of drug released as a function of time. The second data set contains the in vivo data. For a DES, the in vivo release of a drug can be assessed by determining the blood-drug concentration data and also by measuring the amount of drug remaining to be released from the recovered stents. Although data from either or both methods can be used in the development of an IVIVC, for a DES, the systemic drug levels might be very low or below quantitation limit. Thus it becomes more feasible in constructing the IVIVC model to use the in vivo release data from the explanted stents. A model that integrates both (i.e., mechanism of drug release and systemic drug concentration) may provide a means for developing a physiologically based PK model for predicting drug disposition and for establishing relevant mechanism based IVIVC.

Once the in vitro and in vivo data sets are available, a mathematical model describing the relationship between the in vitro and in vivo data sets should be developed. One mechanism for determining whether a correlation exists between the in vitro release kinetics and the in vivo tissue uptake is to plot the amount of drug released in vitro versus the amount released in vivo at the same time points to see whether a point-to-point relationship exists (level A correlation). When trying to develop such a relationship, the in vivo data set is fixed. Once this information is generated, it establishes the relevant performance of the DES product. On

the other hand, the in vitro release profile may be modified through changes in the release test conditions to obtain a consistent relationship between the percentage of drug released in vitro and the fraction of drug released in vivo.

Additional information on the development and validation of an IVIVC can be found in CDER's guidance for industry *In vivo/In vitro Correlations.*

VII. FINISHED PRODUCT MANUFACTURING, STERILIZATION, PACKAGE INTEGRITY, AND SHELF LIFE

A. Manufacturing — Quality System (QS) Regulation and Current Good Manufacturing Practice (CGMP) Regulations

A PMA must include a complete description of the methods, facilities, and controls in sufficient detail that FDA can make a knowledgeable assessment of the quality control used in producing the finished DES (see 21 CFR 814.50). Although particular aspects of the manufacturing of the finished DES are addressed in Section V.B., Chemistry, Manufacturing, and Controls, a full description of the manufacturing methods, facilities, and controls must be provided at the time of the PMA submission (see 21 U.S.C. 515(c)(1)(C)).

A drug-device combination product must meet current good manufacturing practice requirements for both the drug and device constituent parts of the combination product (e.g., 21 CFR 210/211 for drugs, 21 CFR 820 for devices). For a discussion of the Agency's current thinking on how to apply these manufacturing requirements for a combination product, you may wish to refer to the draft guidance for industry *Current Good Manufacturing Practice for Combination Products*, issued by the agency in September 2004.[36] The draft guidance describes a quality management framework for combination products that, if properly implemented, would give manufacturers the flexibility to select either the CGMP regulations (21 CFR 210/211) or the Quality System regulation (21 CFR 820) as their umbrella manufacturing operating system, provided their current good manufacturing practice operating system incorporates key specific provisions pertaining to the other part of their combination product.[37] Under such an approach, if the Quality System (QS) regulation (21 CFR 820) is chosen as the umbrella set of regulations for the manufacturing operative system for a DES product, complete manufacturing and quality control information for the DES product would be provided pursuant to the QS regulation (see 21 CFR 814.20(4)),[38] incorporating key, specific provisions from the drug CGMP regulations (21 CFR 211). Likewise, if the CGMP regulation is chosen as the umbrella manufacturing operating system, complete manufacturing and quality control information should be provided for the DES product pursuant to the CGMP regulations (21 CFR

[36] See http://www.fda.gov/oc/combination/OCLove1dft.html.
[37] The Agency has since announced its intent to issue a Proposed Rule on Current Good Manufacturing Practice for Combination Products (72 Fed. Reg. No, 236 (2007), available at www.RegInfo.gov/public/do/eAgendaViewRule?ruleID=279375.
[38] See, e.g., guidance for industry *Quality System Information for Certain Premarket Application Reviews*, www.fda.gov/cdrh/comp/guidance/1140.pdf, for more information.

Parts 210 and 211), incorporating key, specific provisions from the device QS regulation (21 CFR 820).

B. Sterilization

The PMA application should identify the sterilization method and include the validation for the sterilization method and the sterility assurance level (SAL) achieved. In general, sterile devices would meet an SAL of 10^{-6}, unless there is a substantial scientific justification provided for not being able to achieve this level and for why patients would not be at increased risk. Sterilization validation should be carried out in accordance with a recognized standard or equivalent method.[39]

C. Package Integrity

Package integrity testing should be performed to demonstrate the ability of the package to maintain the sterility of the product contained within it. Package integrity testing generally consists of a whole package physical integrity test in conjunction with a seal integrity test. Some methods for package integrity testing may be found in ISO 11607.

Additionally, appropriate testing should be conducted to evaluate the ability of the packaging to withstand forces generated during shipping and distribution from the manufacturer to the end user. Test methods such as those described in ISO 2248 and ISO 8318[40] may be appropriate.

D. Shelf life testing

In addition to the tests recommended to demonstrate stability of the DES discussed above (see Section V.B.9), testing should also be performed to demonstrate that the functionality of the stent and delivery system (i.e., mechanical performance), the coating integrity, and the package integrity have not degraded over the requested shelf life. Testing should be performed on a finished, sterilized DES product that has been manufactured and packaged in the same manner as intended to be commercialized. Due to the presence of the polymer and drug components accelerated aging is not appropriate for stability testing as described in Section V.B.9 above; however, testing to establish the continued functionality of the stent and delivery system may be conducted using samples subjected to accelerated aging. For certain tests, such as coating integrity, accelerated aging conditions can have a significant detrimental impact on the DES such that real-time aging should be considered.

[39] FDA recognizes the following standards for steam, ethylene oxide, and radiation sterilization, respectively: ISO 11134, ISO 11135, and ISO 11137 (see guidance for industry *Recognition and Use of Consensus Standards,* http://www.fda.gov/cdrh/ost/guidance/321.html.

[40] ISO 2248 Packaging – Complete, filled transport packages – Vertical impact test by dropping; ISO 8318 Packaging — Complete, filled transport packages and unit loads — Sinusoidal vibration tests using a variable frequency

VIII. CLINICAL ASSESSMENT OF DRUG-STENT COMBINATIONS

A. General Considerations

Clinical trials of a new DES should not begin until the sponsor demonstrates that there is reason to believe that risks to subjects are outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained. Depending on the amount of available information, a feasibility study may be recommended to allow the collection of initial data in human subjects. If feasibility (sometimes referred to as "first in human") data are available from studies undertaken outside the United States (OUS), additional data collection in a feasibility study in the United States may not be necessary. However, the quality, applicability, and duration of such OUS feasibility studies will be critical to assess whether these data can be considered directly or indirectly applicable to the DES intended for clinical use in the United States. Such information should be reported in the Report of Prior Investigation section of an IDE. The companion document includes an example of a one-page summary that may be used for ease of review.

FDA encourages study sponsors to use the pre-submission process[41] to gain informal feedback on proposed clinical protocols for DES, including feasibility or pivotal studies. Additionally, although FDA generally does not regulate device clinical studies performed outside of the United States, we are willing to provide informal feedback on clinical protocols for OUS studies that are planned to support either an IDE or PMA application.

FDA believes that a clinical protocol for a coronary DES should include the following elements:

- Clear statement of the intended use
- Clinical development plan designed to develop the data needed to support the intended use
- Study hypothesis(es)
    - Primary and secondary study endpoints for both safety and effectiveness
    - Criterion for study success, (i.e., which hypotheses must be met for the study to be declared a success or *win*)
    - Allocation of Type I error (alpha) for primary and secondary hypotheses, as appropriate
- Plan for assessing safety in which all adverse events are identified and analyzed
- Plan for assessing safety and effectiveness on the basis of an intent-to-treat population as well as an evaluable population
- Study design with inclusion/exclusion criteria
- Case report forms
- Statistical analysis plan
- Risk/benefit analysis
- Informed consent[42]

[41] See guidance on *IDE Policies and Procedures,* http://www.fda.gov/cdrh/ode/idepolcy.pdf.

[42] You should review the statutory definition of applicable clinical trial to determine if your trial must be registered to comply with the law. *See* PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)). http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf

- Data and Safety Monitoring Board (DSMB) charter
- Balance of premarket and postapproval data development
- Labeling that accurately presents any previously collected study data

A number of the above elements are discussed in greater detail below.

B. Intended Use

The sponsor should identify, as clearly and precisely as possible, the intended use of the DES. The specific indications should include the following:

- Lesion types (e.g., de novo, in-stent restenosis)
- Target population (e.g., stable angina, acute coronary syndrome (ST elevation myocardial infarction, non-ST-segment elevation myocardial infarction, unstable angina)
- Conditions for use
- Anatomical sites of application of the DES (native coronary artery, saphenous vein or arterial grafts, left main coronary artery, ostial, chronic total occlusion, bifurcation) and range of lesion lengths and vessel diameters
- Expected outcomes

The intended use determines the objectives of the clinical trial, which are generally to demonstrate the safety (i.e., associated morbidity and mortality) and effectiveness (i.e., associated patient benefit) of the product for a defined clinical benefit in a target population under specific conditions of use.[43]

C. Objectives for DES Trials

Following the approval of the first two coronary DES, data were collected that suggested a small but significant increase in the rate of stent thrombosis associated with DES as compared to bare metal stents, occurring after the first year of implantation. FDA convened an Advisory Panel meeting on December 7 and 8, 2006, in an effort to fully characterize the risks, timing, and incidence of DES thrombosis. Three topics were discussed by the experts on the panel, DES manufacturers, and clinical investigators: (1) the rates of stent thrombosis and associated clinical sequelae (death and MI) when DES are used in accordance with their labeled indications; (2) the rates of stent thrombosis and associated clinical sequelae (death and MI) when DES are used in a broader, more complex population of patients and lesions; and (3) the optimal duration of dual antiplatelet therapy in patients who receive DES. More specific information about the meeting and the conclusions reached are available on FDA's Web site.[44]

Information can be submitted to ClinicalTrials.gov using the Protocol Registration System (PRS). For more information visit the PRS Information Page (http://prsinfo.clinicaltrials.gov).

[43] Although indications are commonly refined over time as clinical data from feasibility studies are analyzed, at the pivotal trial stage of product development, the intended use and indications should be in reasonably sharp focus.

[44] FDA statements available at http://www.fda.gov/cdrh/news/091406.html and http://www.fda.gov/cdrh/news/010407.html. Panel summary and transcript available at http://www.fda.gov/ohrms/dockets/ac/cdrh06.html#circulatory.

As an outcome of that panel meeting, FDA recommends that all DES clinical programs address the following questions as part of the information provided to demonstrate a reasonable assurance of safety and effectiveness:

1. The rates of critical clinical endpoints related to safety and effectiveness, such as death, myocardial infarction, and need for revascularization should be determined.

2. The rate of death and myocardial infarction (MI) should be determined. Not only are these critical safety endpoints, but adequate precision around the rates of death and MI is needed to understand the impact of stent thrombosis on the overall safety and effectiveness profile of a DES.

3. The rate of stent thrombosis over time should be addressed. For example, the rate of stent thrombosis up to and after 1 year should be determined, including whether the rate increases, decreases, or plateaus over time. Analyses should be presented for both patients receiving the DES within the labeled indication and patients representing broader use of the product.

4. The following aspects of adjunctive antiplatelet therapy (APT) should be addressed.
   - Describe the profile of patient compliance with recommended antiplatelet therapy
   - Determine how often dual APT is being extended beyond the recommended duration
   - Describe the frequency and duration of APT interruption
   - Identify what, if any, bridging strategies during interruption were used
   - Capture any and all invasive or surgical procedures that were deferred because of the need for continued APT
   - Define the rate of significant bleeding complications associated with APT

Clinical resistance to antiplatelet therapy (resistance to aspirin, clopidogrel, or both) may emerge as an important risk factor for stent thrombosis. Evaluation of responsiveness resistance to antiplatelet therapy may be a future recommended test. FDA is open to different approaches and trial designs to address these critical questions. Suggested approaches are discussed in the sections to follow.

D. Study Designs

Randomized controlled trials (RCTs) are the most appropriate trial design for a new DES, although for certain additional indications beyond initial approval (e.g., additional stent diameters, lengths or certain lesion types), other trial designs may be appropriate. Both superiority and noninferiority RCTs can be used to support the safety and effectiveness of a DES.

1. Superiority Study

For a DES, an RCT study design could compare a DES, as the investigational device, to a bare metal stent, as the control arm. However, the choice of control in a superiority design is not limited to a bare metal stent. A sponsor may choose to evaluate the superiority of an investigational DES to an *active* DES control (i.e., an FDA approved DES). The investigational DES should be shown to be superior to the preselected control by a margin agreed to be clinically significant by the clinical

community and FDA. In a bare metal control trial, it may also be useful to include a third arm, another DES; this enables assurance of comparability to other DESs.

2. *Noninferiority Study*

The noninferiority, or *equivalence*, approach to study design has been used increasingly in clinical trial settings where a placebo or previous standard of care as control is either unavailable or unacceptable for logistical or ethical reasons. In this design, patients are randomized to investigational DES or active DES control, as above, but the study hypothesis is noninferiority, not superiority.

A *noninferiority clinical trial* usually refers to a study designed to show that an investigational device is as effective, or almost as effective, as an approved device or a standard of care (active control), from which it is then inferred that the investigational device is effective. In fact, the study actually demonstrates that the investigational device is not inferior to the control by more than a prespecified noninferiority margin delta. The margin delta used would be the largest acceptable reduction in therapeutic response with the investigational device (i.e., the maximum tolerable treatment difference such that the new device would still be considered sufficiently effective). Before a noninferiority margin can be chosen, the treatment effect size for the active control device, compared to the previous standard of care (BSM, in the case of DES), should be established based on historical evidence of safety and effectiveness from controlled clinical trials. Subsequently, the noninferiority margin for a new trial can be chosen based on clinical judgment regarding the proportion of the initial effect size that should be maintained in the new comparison. It is also critical to consider whether there is reason to believe that past examples of safety and effectiveness would still be applicable to the current study (the *constancy assumption*). We recommend that sponsors discuss selection of an appropriate noninferiority margin with FDA as the clinical study is being designed.

To investigate whether the investigational device is noninferior to the control, the appropriate null hypothesis is that the control is better than the investigational device by at least the noninferiority margin. The alternative hypothesis is that the investigational device is not worse than the control by the noninferiority margin. These two hypotheses are the essence of how FDA views *noninferiority* trials.

Although the noninferiority trial design is a strategy that could be used when a placebo-controlled study cannot be conducted, there are some limitations to the noninferiority study design that should be considered prior to adopting this approach. When a noninferiority study includes as a control a DES that has not been directly compared to a BMS, the potential exists for a downward drift in the true difference in safety and effectiveness between the investigational DES and a BMS. After serial noninferiority studies, this so-called outcome drift could lead to a situation in which the investigational DES could be found noninferior to the latest *noninferior* DES, but no longer superior to a BMS, if such a direct comparison were made.

The quantification of delta should be clinically relevant and statistically feasible and should be established through cogent discussion and agreement between the sponsor and the Agency. The quantity needs to be sufficiently small so that, from a clinical point of view, the investigational

device can still be considered to be noninferior to the control as long as the advantage of the control over the investigational device is smaller than delta. Additionally, the delta should not be so large, that in a direct comparison with the previous standard of care (in this case, bare metal stents), the new treatment could be noninferior to the active control, but no longer superior to a bare metal stent (so-called *outcome drift*[45]). To investigate whether the investigational device is noninferior to the control, the appropriate null hypothesis is that the control is better than the investigational device by at least delta, against the alternative hypothesis that the investigational device is not worse than the control by delta. These two hypotheses are the essence of how FDA views *noninferiority* trials.

Although the non-inferiority trial design is a strategy that could be used when a placebo-controlled study cannot be conducted, there are some limitations to the noninferiority study design that should be considered prior to adopting this approach. For example, selection of an appropriate delta value, while ideally based on prior data and expectations of performance, should be determined by what is a clinically meaningful definition of a *delta*, agreed to by the clinical community and FDA. In addition, the trial design and analysis plan should take into consideration the potential for outcome drift.

3. *Endpoints for DES Trials*

Based on the definition of effectiveness (21 CFR 860.7), the most direct method of providing valid scientific evidence of effectiveness is to select an appropriate clinical outcome and design a study to evaluate a statistically significant and clinically meaningful treatment effect.

FDA recommends that definitions for outcomes of interest (death, MI, Target Lesion Revascularization (TLR), Target Vessel Revascularization (TVR), stent thrombosis) be standardized in the protocol. One potential set of definitions can be found in Cutlip et al.,[46] although alternate definitions may be proposed with a clinical justification.

a. Primary Endpoint – Clinical Endpoints

Historically, the conventional intracoronary device study endpoint has typically been a composite endpoint (e.g., target vessel failure (TVF), which is a composite of death, nonfatal myocardial infarction (MI), and target vessel revascularization (TVR) after an index stenting procedure). The paper by Cutlip et al. referenced above recommends the use of a patient-oriented composite including all death, MI, and TVR and a device-oriented composite including cardiac death, target vessel MI, and TLR. We recommend the use of the device-oriented composite as a primary clinical endpoint. Other endpoints may be appropriate for specific studies; a clinical justification should be provided for the endpoint selected.

Although a composite may not be the ideal primary endpoint, because the components have different weights, the use of such a composite allows for trials of reasonable sample size to be conducted. For example, a trial seeking to evaluate mortality would need tens of

[45] Outcome drift can occur when successive generations of inferior devices are found to be non-inferior to the previous generation as an active control, but might be inferior if tested against the original placebo treatment.

[46] Cutlip et al., on behalf of the Academic Research Consortium. Circulation 2007:115;2344-2351. Clinical endpoints in coronary stent trials: a case for standardized definitions.

thousands of patients to be enrolled to allow sufficiently powered hypothesis testing. Although trials will not be powered to enable assessment of the individual components, FDA will carefully consider the outcomes for each component of the composite when making our assessment of the risk-benefit profile for the new DES.

The initial DES approvals were based on a primary endpoint assessment at 9 months post-implant. FDA currently believes that a 12-month primary endpoint, with a substantial proportion of patients having 2-year data at the time of marketing application submission, is critical to assess the potential for important adverse events such as stent thrombosis (and related deaths and MIs) that may occur after 9 months. Patients in all trials to be used to support approval of a PMA application should be consented at the time of enrollment for follow-up to 5 years.

b. Primary Endpoint – Nonclinical Imaging Endpoints

Imaging-derived measures of restenosis, such as percent diameter stenosis and late lumen loss, are potentially powerful effectiveness endpoints. Such outcome measures have the advantage of providing quantitative data for the comparison of specific parameters of stent performance, such as suppression of neointimal hyperplasia. Furthermore, they can provide additional effectiveness data, even in patients who have not developed a major clinical adverse event, and consequently have the potential to increase the *sensitivity* of outcome measures between treatments. Imaging endpoints are commonly measured as continuous variables and this powerful discriminatory advantage can be apparent with sample sizes considerably smaller than typically needed for clinical endpoints. However, the use of these potential imaging measures as primary endpoints does not preclude the need for evidence of safety through evaluation of a clinical endpoint, such as death, MI, and/or TLR, either individually or as a composite.

FDA believes that use of an imaging endpoint as the sole primary effectiveness endpoint in pivotal DES trials is currently acceptable only for certain ***second-generation*** DESs, such as iterative modifications from currently approved DESs and/or indication expansion, in specific patient populations or in specific vessel or lesion types. For a novel DES, clinical studies performed to support regulatory approval should include at least one study of sufficient size that has as its primary endpoint a clinical endpoint and is appropriately powered for statistical demonstration of superiority or non-inferiority against an appropriate control. See Section VIII.D for more discussion of next-generation DESs.

It should be noted that there is a well-described impact of protocol-mandated angiography on clinical revascularization rates. For this reason, we recommend that angiography and IVUS be captured in a study separate from the pivotal trial or, if included in the pivotal trial, protocol-mandated angiography should be scheduled after the 12-month clinical visit.

c. Primary Endpoint – Use of Multiple Endpoints

An alternative strategy is the use of appropriate composite or co-primary clinical and imaging endpoints as outcome measures. For example, developing co-primary endpoints is

one potential method. If co-primary endpoints are proposed for the trial, the selection of the noninferiority margin for the clinical endpoint may be less conservative than when used as a stand-alone endpoint, reflecting the fact that additional information from another parameter (such as angiograph) is being evaluated. When using co-primary endpoints, FDA recommends that adequate adjustments for correlation between the endpoints and preservation of type I error be carefully considered. Study success using co-primary endpoints is typically defined as meeting both endpoints. Appropriate definitions for superiority and for selection of noninferiority margins should be discussed with the Agency when the use of multiple endpoints is contemplated.

d. Secondary Endpoints

Separate from the primary endpoint chosen for effectiveness, we recommend collecting additional vessel imaging information to evaluate healing and remodeling of the arterial wall, including parameters such as stent apposition, aneurysm formation, edge effects, and quantification of intimal proliferation, especially at the proximal and distal borders of an implanted DES. Quantitative coronary angiographic (QCA) analyses should report stent, lesion, and analysis segment parameters to assess the importance of any edge effects caused by the drug. The angiographic analysis should also include review and analysis for stent fracture; use of a grading system such as that described by Rocha-Singh et al.,[47] may be helpful for reporting the incidence and type of fracture, if observed. Side branch occlusion, when observed, should also be reported.

The secondary endpoints will, in most cases, not be descriptive and exploratory, not leading to additional claims. If a formal comparison of treatment arms for a secondary endpoint is desired, formal null and alternative hypotheses should be developed and pre-specified in the protocol. If no pre-specified hypotheses are included in the protocol, p-values for such comparisons will not be appropriate and should not be presented in labeling. If analyses beyond descriptive statistics are planned for secondary endpoints, appropriate steps should be taken to adjust for multiple comparisons and to preserve Type I error. Sponsors with studies ongoing prior to the issuance of this guidance should discuss with FDA an appropriate approach for presentation of such analyses in the labeling.

4. Considerations for DES incorporating an unstudied drug

When a DES incorporates an unstudied drug, the data from a sufficient number of patients exposed to the new DES should be collected for submission in the PMA. The number of patients should be large enough to enable the detection with adequate precision of low frequency adverse events (i.e., those occurring at a rate of 1 percent or less) that may be associated with the unstudied drug. A single study or multiple studies (both randomized trials and single-arm registry studies) can be used to complete this population.

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[47] Rocha-Singh, et al, Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheter Cardiovasc Interv 2007;69(6):910-919

Also, certain additional safety data beyond what are typically collected in a stent trial should be obtained and provided in the PMA to allow for analysis of potential drug-related adverse events. The specific safety data to be collected will generally be specific to the drug incorporated on the stent; however, the following are examples of typically requested information:

- Liver enzyme values pre- and post-procedure and at appropriate follow-up intervals
- Hypersensitivity reactions (definition should be pre-specified) including symptoms, signs, and relevant laboratory values, treatment, and clinical course
- White blood cell counts to document the incidence of leukopenia
- EKG parameters
- EKG changes, particularly QT intervals
- Concomitant medications

Sponsors with such DES are encouraged to meet with FDA prior to beginning clinical trials to ensure that case report forms capture appropriate cardiac and non-cardiac safety information.

5. Blinding Concerns in DES Clinical Studies

In a randomized controlled trial, the use of study blinding, or masking, further reinforces the integrity of the random allocation of patient assignment and assessment of treatment effect. In a superiority RCT study design using a DES and its corresponding bare metal stent, a triple-blinded (i.e., patient, physician and monitoring committee are all blinded) study design is logistically possible because of the physically similar appearance of the DES and bare metal stents. However, for some medical devices, designing a double-blinded (i.e., patient and physician are blinded to treatment assignment) or triple-blinded RCT can be impractical and logistically impossible because of the physical characteristics and/or the mode of action of the product (e.g., a DES versus coronary artery bypass grafting (CABG)). For noninferiority study designs that are evaluating a DES with different platforms, the DES might have different physical characteristics (e.g., radiologically and/or visually different in appearance), making such study blinding logistically difficult to implement. Because certain individuals involved in stent handling/implantation at the time of the index procedure will have knowledge of treatment assignment.

Nonetheless, because there is a potential for considerable investigator and/or patient bias introduced by knowledge of treatment assignment, possibly confounding study outcomes and diminishing the scientific validity of the study, the study design should incorporate blinding to the maximum extent possible, maintaining the blind for patients (single-blind), follow-up study investigators, and study staff to minimize the potential for bias and confounding. In addition, increasing the objectivity of study parameters as much as possible and including special analytical methods to evaluate for the potential influence of bias in study outcome are potential ways to maximize the scientific validity of study design.

Contains Nonbinding Recommendations

Draft — Not for Implementation

6. Independent Oversight of Drug-Eluting Stent Trials

Many of the novel technologies employed in a DES have never been used previously in the same combinations or anatomic locations in human beings. This fact raises new questions of safety for participants in investigational DES trials. Given that most DESs under development are intended to be permanent implants and that safe and reliable retrieval of deployed stents is generally not possible, a heightened and constant vigilance during the conduct of a DES trial is necessary. With this in mind, FDA strongly recommends the use of data monitoring committees (DMC, also called data safety monitoring boards, or DSMBs) for DES studies to keep track of and evaluate significant adverse events, including stent thrombosis, in real time (i.e., as the study enrollment progresses).[48] Sponsors are responsible for ensuring proper monitoring of the investigations (21 CFR 812.40), and must select monitors qualified by training and experience to monitor the investigational study (21 CFR 812.43(d)). Before the study begins, the DMC/DSMB charter should have an adequate monitoring plan (e.g., number of predetermined meetings, timing of reports, appropriate stopping rules, correspondence to FDA as appropriate) in place to adequately ensure that patients are not subjected to undue risk. For sponsors conducting multiple trials with the same investigational DES, FDA recommends that sponsors as part of their obligation to monitor the studies, use the same DMC/DSMB for both studies or have a *super-DMC/DSMB* that communicates with the DMC for each trial be considered. If this is not possible, the sponsor should ensure that the DMCs/DSMBs for each of the studies communicate frequently and regularly exchange safety information and ensure that all members of the committee are apprised of the global safety data for the investigational DES.

FDA strongly recommends that interpretation of data from tests such as angiograms, IVUS, and ECGs be performed by independent core labs and that blinded adjudication of clinical events be conducted by a clinical events committee (CEC Clinical adjudication committees should be independent of core lab analysis centers to avoid potential bias. .

E. Statistical Analysis Plan

The proposed protocol should include a comprehensive statistical analysis plan with prospectively defined methods to address the following:

- Study hypotheses
- Sample size calculation
- Blinding
- Number of proposed study centers
- Study success criteria
- Effectiveness patient populations (e.g., intent-to-treat, evaluable)
- Pooling of data
- Covariate adjustments

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[48] Guidance for clinical trial sponsors on *Establishment and Operation of Clinical Trial Data Monitoring Committees*, March 2006.

- Stratification
- Protocol deviations
- Handling drop-outs and methods to address missing data
- Analysis plan and statistical methods
- Data auditing

1. *Analysis Cohorts*

The *intention-to-treat* population, which is defined as the cohort of all patients randomly assigned to treatment in an RCT design, is usually the preferred population for superiority studies. Intention-to-treat analysis allows for the evaluation of all patients who enroll in the study, even though some may not complete the study (e.g., patients who are, for any reason, lost to follow-up, drop-outs, or terminated by investigator). In an RCT design, the intention-to-treat principle means that any comparison of the treatments is based on comparison of the outcome results of all patients in the treatment groups to which they were randomly assigned. Within the protocol, the sponsor should prospectively specify the analysis plans that will account for patients who do not complete the study. The sponsor should also present analysis of the per protocol patient cohort (i.e., patients who enter and complete the study according to protocol) and the as-treated patient cohort (recognizing such analyses are subject to bias).

Comparison of outcomes on the basis of intention-to-treat, per protocol, and as-treated patients allows assessment of outcome robustness. Analysis details should be prospectively agreed to by the sponsor and FDA.

2. *Poolability Considerations for DES Studies*

Pivotal studies of DES should be conducted at multiple investigational sites. Additionally, there can be advantages to conducting multiple clinical studies of the same DES. Potential advantages to combining data from different studies include having the ability to evaluate DES performance across a broader population than can be achieved by one study and could increase generalizability of study results because of wider demographic and geographic inclusion. Furthermore, demonstration of comparable DES performance across different investigational sites and studies can permit more robust conclusion of product safety and efficacy. However, when planning to conduct clinical studies at multiple investigational centers, or in centers OUS (outside the United States), an analysis of poolability of data should be included in the prospective analysis plan.

When FDA considers foreign data as supportive evidence for U.S. product approval, a key consideration in assessing the applicability of OUS studies in support of product safety and effectiveness is to evaluate the generalizability of the OUS studies to the patient population and to medical practice in the United States. Factors that FDA considers include, for example,

- Patient demographic and clinical characteristics
- Geographic differences in medical practice
- Differences in study protocol

These factors have the potential to affect DES performance in terms of both safety and effectiveness. Some examples of key factors that should be addressed when considering the poolability of results and extrapolating study results to those expected in the United States can be found in the stand alone companion document.[49]

Whether studies have been conducted solely in the United States or both in or out of the United States, statistical analysis should examine the homogeneity of demographic and procedural covariates across centers and geographical regions. Evaluation of interactions between treatment and region is recommended. Furthermore, outcome comparability should be examined after adjustment for covariate differences, using multivariate regression modeling and propensity scoring methodology. In addition, sensitivity analysis should be performed to verify the robustness of any statistical modeling using pooled data.

FDA is willing to comment informally on OUS study protocols through the pre-submission process. Such comments may increase the likelihood that these data can be used to support a PMA application.

F. Adjunctive Pharmaceutical Regimens

Optimal duration of antiplatelet therapy and use of glycoprotein IIb/IIIa inhibitors and direct thrombin inhibitor treatments in DES patients are currently unclear and may significantly affect clinical outcomes. Consequently, to minimize confounding variables in the interpretation of the study results, a uniform regimen of intra- and postprocedure concomitant medications should be used. Careful consideration should be given to the optimal dosage and duration of antiplatelet therapy for DES postimplantation, given the delay in endothelialization within DES compared to that of bare metal stents and subsequent concerns regarding stent thrombosis due to premature discontinuation of antiplatelet therapy.

At the December 2006 Circulatory System Devices Advisory Panel meeting on DES thrombosis , the Panel recommended that the labeling for the two approved DES include reference to the AHA/ACC/SCAI practice guidelines. FDA agreed with this recommendation and both approved DES Instructions for Use include this information. For this reason, for trials that use the CYPHER stent or TAXUS stent as the control DES, we currently recommend that the prescribed antiplatelet therapy follow the AHA/ACC/SCAI guidelines[50]; that is, patients should receive aspirin and a minimum of 3 (CYPHER) or 6 months (TAXUS) of clopidogrel with therapy extended to 12 months in patients at a low risk of bleeding. Despite the desire to have administration and use of dual antiplatelet therapy, circumstances will cause some patients to have different regimens, and FDA is particularly interested in how differences in duration affect patient outcome. Therefore, patients should be carefully monitored and case report forms should be designed to capture compliance with prescribed antiplatelet therapy and significant bleeding complications over the course of the trial.

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[49] See draft guidance for industry and FDA staff on *Coronary Drug-eluting Stents – Nonclinical and Clinical Studies: Companion Document*," published together with this document.

[50] Available at http://www.acc.org/qualityandscience/clinical/guidelines/percutaneous/update/index.pdf

Eventual product labeling should include both the prescribed antiplatelet therapy and patient compliance with that therapy as experienced in the clinical trials and should clearly specify the risks of premature antiplatelet medication discontinuation.

G. Follow-Up from Clinical Studies

Although nonclinical and clinical testing of DESs provide invaluable information on the short-term safety and effectiveness of these products in a select patient population, such as that typically found in the clinical trial setting, much information on the performance and safety profile of a DES can be obtained only when the product moves into the larger, more diverse patient population after marketing.

For purposes of regulatory approval, the current primary endpoint data for DES studies should be collected over a period of approximately 12 months after implantation of the DES. However, DES study length should be viewed in terms of the entire follow-up, which should extend through a 5-year clinical follow-up period. Although the 12-month postimplantation endpoint might be acceptable for a PMA submission, the study is not considered complete until study patients have completed their long-term clinical follow-up as described in the protocol. At a minimum, this would include annual follow-up telephone evaluations and, preferably, annual study visits, for five years in a significant cohort of patients enrolled in the pivotal, feasibility, and/or any additional clinical studies conducted to support product approval. During the long-term follow-up phase, the occurrence and sequelae of late phenomena, such as incomplete stent apposition, late stent thrombosis, and polymer compatibility issues, are important parameters that should be evaluated. The actual duration of dual antiplatelet therapy and any interruptions should be captured as well (see Section C above for objectives related to antiplatelet therapy).

At the time of PMA submission, all available long-term follow-up from the pivotal and supplementary clinical studies should be provided to demonstrate the ***chronic*** performance of the DES. Additionally, as part of the PMA review, the applicant is also required to submit a bibliography of all published reports and other information relevant to an evaluation of the safety and effectiveness of the device (see 21 CFR 814.20(b)(8)).

During the PMA review, a three-month update of any additional clinical data must be submitted (21 CFR 814.20(e)). The applicant must submit new information learned about the device from ongoing or completed studies that may reasonably impact an evaluation of the safety and effectiveness of the product or that may reasonably affect the draft labeling. Note that when reasonably limited in scope, this update would be considered a minor amendment to the PMA. Additional (i.e., later) endpoint evaluations, a significant increase in the number of evaluable patients, or new analyses may be considered a major amendment requiring significant review. In addition, as a condition of approval for a PMA application, applicants are required to submit updated clinical reports to the Agency (§ 814.82 and 814.84)

To minimize patient losses-to-follow-up, sponsors should request patient consent to five-year follow-up at the time of enrollment in clinical studies. Additionally, the case report forms should include the specific questions the sponsor or representative will ask the patient during telephone

follow-up to ensure that appropriate information is being collected and to minimize bias since treatment assignment may be known upon disclosure of the primary endpoint results.

VIII. POSTAPPROVAL CONSIDERATIONS

A. Postapproval Studies

Postapproval surveillance provides a framework for assessing unanticipated risks secondary to human factors, product manufacturing changes, or rare occurrences in real-world patient populations.

Therefore, in addition to postapproval follow-up of clinical outcomes from the patients enrolled in the preapproval clinical trials, the Agency will generally require the collection of additional postapproval data for a DES (§ 814.82(a)(2)). Serious but rare DES-related adverse events that might only be identified in a postapproval period include late stent thrombosis, drug interactions, unforeseen complications of multivessel or overlapping stent placement, and experience with a DES in different patient demographic subsets not adequately represented in preapproval studies (i.e., *real world* use). A proposed postapproval study protocol should be included in the PMA application.

The postapproval study should have two primary goals: assessment of the rate of stent thrombosis and assessment of the rate of cardiac death plus MI. As discussed above, the postapproval data collected on currently approved DESs have signaled a potential increase in late stent thrombosis after one year compared to bare metal stents. However, it is not known if this rate plateaus or continues to increase over time, nor is the impact of stent thrombosis on rates of cardiac death and MI completely understood. Therefore, one primary endpoint of the postapproval study should be the rate of stent thrombosis after one year. As stent thrombosis is closely associated with cardiac death and MI, a second primary endpoint of the postapproval study should be a comparison of the rate of cardiac death and MI between the new DES and the control stent used in the pivotal study. To gain a better understanding of these risks in the setting of actual clinical use of the product, FDA recommends that postapproval data be collected on a series of patients who are consecutively enrolled to avoid the introduction of selection bias.

A sufficient number of patients should be enrolled to confirm that the upper bound of the one-sided 95 percent confidence interval around the observed rate of stent thrombosis between 12 and 24 months, 24 and 36 months, 36 and 48 months, etc. is ≤ 1 percent with at least 80% probability for patients treated in accordance with the labeled indication. The total study sample size should be sufficient to ensure a sufficient number of patients treated in accordance with the labeled indication are available for analysis.

To evaluate the rate of cardiac death and MI, we suggest that the cohort of patients treated in accordance with the labeled indications be pooled with the preapproval pivotal trial to reach a sample size sufficiently large to provide adequate power to compare the rates of cardiac death and target vessel MI for the new DES and the control stent used in the pivotal study and to rule out an increased risk. This cohort of postapproval patients may be in a single-arm or randomized study, and data pooling may be approached from either a frequentist or Bayesian perspective.

Additionally, postapproval studies to date have demonstrated that routine clinical use of DESs typically includes the treatment of patients outside of the labeling indications, including higher risk patient and lesion subsets. Based on this previous experience, FDA recognizes that a postapproval study of consecutively enrolled patients is likely to include patients representing a broader use of the product and recommends that data from such patients be analyzed separately to better understand whether significant safety issues exist in the treatment of these patients.

All patients should be consented for five years of follow-up. If stent thrombosis rates are demonstrated to plateau or decrease in prior years, shorter follow-up may be sufficient. Alternatively, if stent thrombosis rates continue to increase, longer term follow-up or specific labeling changes may be appropriate.

A postapproval study protocol should include the following elements:

- Study hypothesis(es) - Primary and secondary endpoints
- Study design with inclusion and exclusion criteria
- Definitions for outcomes of interest
- Sample size calculation
- Statistical analysis plan
- Informed consent document
- DMC/DSMB information
- Case report forms
- Types of participating centers (e.g., teaching vs. non-teaching, location, size, primary vs. referral center and so on)
- Data monitoring procedures, including whether a CEC will be used
- Detailed study timeline, including enrollment goals (for sites, physicians and study subjects) and a plan in case enrollment goals are not met.
- Interim and final report schedule

The statistical plan should include planned descriptive statistics on certain subgroups of interest including:

Demographics

- Age (age < 65 years; age ≥ 65 years)
- Sex (male, female)
- Race and ethnicity

Patient characteristics

- Patients with diabetes, further characterized as insulin-requiring or noninsulin-requiring
- Patients with renal insufficiency, further characterized as creatinine clearance (rCl) using the Cockcroft-Gault equation (CrCl > 60 mL/min, CrCl ≥ 30 and ≤ 60 mL/min, CrCl < 30 mL/min)
- Degrees of left ventricular (LV) dysfunction (ejection fraction < 30%, 30-40%, > 40%)
- Patients with 3 vessel disease

- Patients with 2 vessel disease including proximal left anterior descending coronary artery disease

Lesion characteristics

- Lesions in the setting of acute ST elevation myocardial infarction (STEMI)
- Percutaneous coronary interventions within 36 hours of non-STEMI ACS
- Lesion length (≤ 20 mm, 21-30 mm, 31-40 mm, > 40 mm)
- Vessel diameter (2.0 - ≤ 2.5 mm; 2.6 – 2.9 mm; 3.0 - ≤ 3.5 mm, and > 3.5 mm)
- Ostial lesions
- Bifurcation lesions
- Trifurcation lesions (i.e., left main coronary artery, left circumflex coronary artery, left anterior descending artery, and ramus intermedius)
- Thrombus-containing lesions
- Lesions with residual dissection post stenting
- Left main coronary artery (LMCA) lesions
  - Include whether disease was ostial, mid, or terminal and whether or not it involved the ostial LAD +/- LCFX
- Chronic total occlusions (CTO)
- Saphenous vein grafts (SVGs)
- Arterial grafts (internal mammary artery, radial artery, gastroepiploic artery)
- Post-brachytherapy
- Instent restenosis (ISR) (BMS)
- Instent restenosis (ISR) (DES)
- Overlapping BMS
- Overlapping DES
- Overlapping BMS and DES
- Non-overlapped multiple stents (in the same vessel or in different vessels)
- Intravascular ultrasound guidance for initial stent deployment

Case report forms should capture patient compliance with prescribed antiplatelet therapy and significant bleeding complications.

For patients who experience stent thrombosis, in addition to the above characteristics, the following additional information should be reported:

- BMS or DES (name of stent, length, and diameter)
- Postdilatation (balloon diameter and lengths used as well as the postdilatation atmospheres achieved)
- Clarification of antithrombotic regimen received prior to initial stenting, including doses (aspirin, Plavix), including clarification of whether or not patient received a loading dose of Plavix and what the actual dose was.
- Antithrombotic regimen the patient was on at discharge (ASA, Plavix)
- Patient compliance with antiplatelet therapy and significant bleeding complications

- Any discontinuation of Plavix and/or aspirin and whether or not there was premature discontinuation of these medications

Effective postapproval identification of product risks relies on active collaboration of manufacturers, regulatory bodies, and healthcare facilities to detect and report product-related injuries and other adverse events. Although data collected as part of postapproval studies can and should be submitted to the FDA in postapproval reports to the PMA, sponsors should note that, to support an expansion in indications, they should conduct the study under an approved IDE. FDA is willing to consider the implementation of nested studies, with protocols approved under an IDE, within postapproval studies to support certain additional indications, such as long lesions and patients with two-vessel coronary artery disease. A prospective, hypothesis-driven analysis plan should be provided for FDA review in an IDE application or IDE supplement prior to initiation of the overall postapproval study. Alternatively, sponsors may choose to pursue additional indications in separate studies under an IDE to evaluate these uses in the intended patient population.

Sponsors should contact the CDRH review division for more information on the use of these studies to support additional indications. For more information on postapproval studies, see the CDRH guidance for industry and FDA staff on *Procedures for Handling Post-Approval Studies Imposed by PMA Order*.

B. Adverse Event Reporting

Because a DES is regulated under the device provisions of the Act, the adverse event and device defect reporting requirements for devices are applicable.[51] The medical device reporting (MDR) requirements mandate that manufacturers report to the Agency (1) all device-related deaths and serious injuries and (2) all malfunctions of the device or similar device that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur (21 CFR 803.3).

Serious injury/(*Serious illness*) (§803.3(aa)(1)) is an injury or illness that:

- Is life threatening, even if temporary in nature
- Results in permanent impairment of a body function or permanent damage to a body structure

or

[51] Each constituent part of a combination product is governed by a different set of postmarket reporting requirements (for drugs, 21 CFR Parts 310 and 314, and for devices 21 CFR Part 803). This is the case for a DES product. The Agency has announced its intention to issue a Proposed Rule, Postmarket Safety Reporting for Combination Products that would clarify the postmarketing safety reporting requirements for combination products (72 Fed. Reg. No. 82, 22515 (2007). The proposed rule would provide a framework for the reporting of adverse events for combination products and specify the circumstances in which following one set of postmarket safety reporting regulations (e.g., 21 CFR 803) generally would meet the requirements of another set and the circumstances in which these requirements would be supplemented with specific reporting provisions applicable to the constituent part of the combination product.

- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

A *malfunction* (§803.3(m)) means the failure of the device to meet its performance specifications or otherwise perform as intended.

Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed, as defined in 21 CFR 801.4.

An *MDR reportable event* (§ 803.3) means:

(1) An event that user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury

or

(2) An event that manufacturers or importers become aware of that reasonably suggests that one of their marketed devices:

(i) May have caused or contributed to a death or serious injury

or

(ii) Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Furthermore, as explained in the Preamble to the FR Notice of December 11, 1995, Vol. 60, No. 237, relating to 21 CFR Part 803 – in Comment 12:

A malfunction is reportable if any one of the following is true:

- The chance of a death or serious injury occurring as a result of a recurrence of the malfunction is **not** remote.
- The consequences of the malfunction affect the device in a catastrophic manner that may lead to a death or serious injury.
- ▪ A malfunction results in the failure of a device to perform its essential function and compromises the device's therapeutic, monitoring, or diagnostic effectiveness, which could cause or contribute to a death or serious injury, or other significant adverse device experiences required by regulation (the essential function of a device refers, not only to the device's labeled use, but for any use widely prescribed within the practice of medicine).
- ▪ The malfunction involves a long-term implant or a device that is considered to be life-supporting or life-sustaining and thus is essential to maintaining human life.

or

- The manufacturer takes or would be required to take action under section 518 or 519(f) of the Act as a result of the malfunction of the device or other similar devices.

For more information see the Medical Device Reporting (MDR) Web site at: http://www.fda.gov/cdrh/mdr/, and you may direct questions regarding MDRs to the Reporting Systems Monitoring Branch at 240-276-3464.

Instructions for completing MedWatch Form 3500A are available at http://www.fda.gov/medwatch/report/instruc_10-13-06.htm. MedWatch Form 3500A is available at http://www.fda.gov/medwatch/safety/3500a.pdf.

Adverse events reported through MDR are shared with CDER so that drug-related aspects of postapproval adverse events reported to CDRH can be evaluated.

C. Peri-Approval Studies

FDA has typically required postapproval studies for DESs. However, when the postapproval study protocol was approved only at the time of the PMA approval, FDA found that there were significant delays in beginning enrollment in the study due to delays in awaiting IRB review and approval. There was also confusion on the part of some IRBs regarding the rationale for an additional study of an approved product. The delays in enrollment and data collection in this scenario meant that an important source of postmarket data was unavailable to the manufacturer and to FDA for multiple months following PMA approval.

To minimize this delay, FDA has encouraged PMA applicants to submit the postapproval study protocol earlier in the PMA review process. If FDA has reached the conclusion that the PMA will be approved (e.g., only minor issues such as labeling are pending), the postapproval study protocol can be approved *in advance* of the PMA approval. A protocol for such a *peri-approval study* can be submitted as an IDE supplement. Upon IDE approval, the study can begin enrolling under the IDE with a prespecified patient limit, with the remainder of patients enrolled after PMA application approval. Consequently, the peri-approval study does not obviate the need for the collection of information after the initiation of marketing. The IDE approval does, however, enable a sponsor to ensure that IRB review/approvals are in place and selected sites are eligible for active enrollment of patients at the time of PMA application approval.

FDA strongly encourages sponsors to select a broad cross-sectional distribution of institutions (e.g., geographic location, private versus public versus academic hospitals, volume of procedures) to address generalizability of the study findings. The main impetus for the peri-approval approach has been to facilitate the enrollment of patients and streamline completion of the study so that both the FDA and the applicant can assess patient safety in a real-world scenario in a timely manner to support the total product life cycle of the DES.

D. Next Generation DES

DES candidates may employ a range of new and old technologies, making classification of a next-generation DES dependent on the specific components and/or modifications to the product. Unlike second-generation bare metal stents, in which modifications in a product line were limited to either the stent substrate (e.g., geometry, such as strut thickness, cell configuration, material), or delivery catheter, for DES, manufacturers should carefully consider that planned modifications to the stent substrate or polymer carrier may have unintended or unanticipated effects on other product performance parameters (e.g., changes in drug density, total drug load, elution kinetics) and on the overall safety and effectiveness of the finished product. Additionally, if a sponsor wants to make a manufacturing change in the coating process, depending on the change, it may be necessary to perform additional studies to ensure safety and/or effectiveness for the modified product if the rate and/or extent of drug elution is materially affected.

Some examples of questions for the sponsor or applicant to address regarding design modifications to a DES that may affect rate and/or extent of drug elution include, but are not limited to, the following:

- Is this a first generation DES, a combination of new and old technologies, or essentially a design iteration?

If the answer to "is this a first generation DES?" is no, some additional questions to address include:

- Which components of the DES system have stayed the same and/or which have been changed? Be sure to consider both intentional and unintentional changes that may have occurred.
- If the stent substrate has changed, what specifically has been altered (e.g., stent substrate material only (from 316L to CoCr); geometry elements, such as strut thickness, which can lead to differences in surface area; and/or a change in the drug density and/or drug content)?
- Has the delivery catheter been modified (e.g., distal tip or other elements)?
- Is the drug formulation the same or different (e.g., change in polymer/drug ratio, increased or decreased drug content)?
- Have any of these modifications resulted in alterations to the release kinetics (e.g., amount or significant modifications in profile)?
- Have there been any modifications in any critical manufacturing parameters (e.g., coating application, new sources of heat or humidity, sterilization method)?
- Does the new product still meet the original product specifications?
- How robust are the in vitro test methods and quality control specifications used to assess product variability to ensure product quality and consistency?

The significance of the changes in a DES system for a *second generation* DES will directly influence the amount of additional nonclinical and/or clinical testing needed to support the safety and efficacy

of a modified DES. FDA encourages sponsors and applicants to discuss with the Agency proposed changes to their DES and appropriate testing to validate those changes.

IX. COMPANION DOCUMENT

To facilitate the use of this guidance, a stand alone companion document is available to be used together with this guidance. It is posted with this guidance on the FDA Web site. The companion document contains the following:

- Suggested elements for an IDE application
- Suggested elements for a PMA application
- Example master table
- Example 1-pager describing DES clinical studies
- Example commitment table
- General biocompatibility considerations
- Example test article certification
- General guidelines regarding good animal husbandry
- Factors affecting poolability of US and OUS studies
- Guidance on labeling for a DES

APPENDIX A

Below is an example of a regulatory specification table for the finished DES product.

Tests	Acceptance Criteria[1]	Analytical Procedure
Appearance	Conforms to visual/microscopic description	Visual/Microscopic
Identification Tests	Retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation obtained as specified in the assay in combination with UV	HPLC with diode array detection
Assay (Drug content)	90% - 110% of label claim	HPLC
Content Uniformity	USP <905>	HPLC
Degradation Products/Impurities		HPLC
Degradant A	NMT 0.5%	
Impurity B	NMT 0.6%	
Degradant at RRT[2] 0.8	NMT 0.3%	
Any individual unspecified impurity	NMT Q3B identification threshold	
Total impurities	NMT 1.2%	
Residual Solvent A	NMT 200 ppm	GC
Particulate Matter[3]	Release : NMT 2500 particles ≥ 10 µm NMT 200 particles ≥ 25 µm Shelf Life : NMT 3500 particles ≥ 10 µm NMT 300 particles ≥ 25 µm	Light obscuration as per USP <788>
Endotoxins	NMT 0.5 EU/mL	LAL (USP <85>)
Sterility or package integrity	Pass	USP <71>
Drug Release	10% - 20% 2 hours 20% - 50% 4 hours 40% - 70% 8 hours > 80% 24 hours	USP <724>

[1]In the table above, all numerical limits and the time points in the drug release test are for illustrative purposes only.
[2]Relative retention time
[3]Example of an attribute for which tighter release limits are assigned in order to maintain a safety margin so that the product remains within the approved shelf life acceptance criteria for that attribute.

Below are examples of stability testing protocols.

Long Term (25°C/60%RH) Stability Testing Protocol

		Time Points (months)				
Tests	Acceptance Criteria*	0	3	6	9	12
Appearance		X	X	X	X	X
Assay (drug content)		X	X	X	X	X
Impurities Individual Total		 X X	 X X	 X X	 X X	 X X
Drug Release		X	X	X	X	X
Particulate matter**		X	X	X	X	X
Endotoxins		X				X
Sterility		X				X

*Same as regulatory specifications
X indicates testing is performed at this time point.
** FDA recommends testing for particulate matter at every time point, but if testing is conducted less frequently, the expiration date will be limited by the latest time point at which particulate matter testing was conducted with passing results.

Accelerated (40°C/75%RH) Stability Testing Protocol

		Time Points (months)			
Tests	Acceptance Criteria*	0	1	3	6
Appearance		X	X	X	X
Identity		X	X	X	X
Assay (drug content)		X	X	X	X
Impurities Individual Total		 X X	 X X	 X X	 X X
Drug Release		X	X	X	X
Particulate matter		X	X	X	X

*Same as regulatory specifications
X indicates testing is performed at this time point.

GLOSSARY OF TERMS

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of results of analytical procedures (see ICH guidance Q6A)

Acute: Refers to any time up through expansion and deployment of the DES

Chronic refers to any time after assessment of the initial stent deployment in a simulated vessel throughout the lifetime of the implant.

Adhesion: The degree of attachment between two different surfaces, such as a coating or film and the underlying material.

Area under curve (AUC): PK parameter, area under the blood concentration-time curve

(AOAC): Association of Official Analytical Chemists

Balloon expandable stent: A stent that is expanded by a balloon. The diameter of the stent increases as the balloon diameter increases. The stent remains expanded after deflation of the balloon.

Bare metal stent (BMS): An intravascular stent that is not coated with either a polymer or drug. Traditional materials for BMSs include 316L stainless steel and cobalt chromium alloy.

Batch: A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified acceptance criteria, and is produced according to a single manufacturing order during the same cycle of manufacture (21 CFR 210.3(b)(2)). See also "lot."

Bias (statistical and operational): The systematic tendency of any factors associated with the design, conduct, analysis, and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value. Bias introduced through deviations in conduct is referred to as *operational bias*. The other sources of bias listed above are referred to as *statistical bias*.[52]

Clinical batch: Batch used to support the efficacy, safety, bioavailability, or bioequivalence of a product

Cmax: PK parameter, maximum observed blood concentration

Coating: The drug carrier (usually polymeric, but not limited to such), the drug itself if it is solely coated onto the stent platform, any other coating, or the drug carrier even if it is incorporated onto the stent in a geometry other than a coating.

Cohesion: The sticking of a surface to itself

Combination product: A product (defined in further detail in 21 CFR 3.2(e)) comprised of two or more different types of regulated entities (i.e., drug-device, drug-biologic, device-biologic, or drug-device-biologic products).

Component: For a drug: Any ingredient intended for use in the manufacture of a product, including those that may not appear in such product (21 CFR 210.3(b)(3)).

Component: For a device: any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device (21 CFR 820.3(c)).

Chronic: See Acute.

Degradation product: A molecule resulting from a chemical change in a drug or polymer molecule brought about over time and/or by the action of light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure or packaging system. Also called decomposition product (see ICH guidance Q6A).

Device history record: (DHR) a compilation of records containing the production history of a finished device (21 CFR 820.3(i))

Double-blinded: A double-blind trial is one in which neither the subject nor any of the investigators or sponsor staff involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. This includes anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol; blinding is maintained throughout the conduct of the trial.[53]

Blinding, or masking, is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence that the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on.[54]

Drug-eluting stent (DES): A combination product consisting of both drug and device components. The device component consists of an intravascular stent platform that is used not only for radial support, but also as a vehicle for the delivery of an active pharmaceutical agent or drug. The drug component is commonly incorporated and released from a polymeric carrier, either a single polymer or a combination of polymers, which is physically or chemically adherent to the stent substrate. The purpose of the polymer carrier is to allow for adequate deposition of the drug onto the stent surface as well as to influence the release kinetics of the drug from the

[53] ICH Guidance E9 *Statistical Principles for Clinical Trials*
[54] ICH Guidance E9 *Statistical Principles for Clinical Trials*

stent surface. The DES is mounted onto a stent delivery system to deliver the stent to its final intended location in the vasculature.

Drug product: A finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)).

Drug substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

EP: European Pharmacopeia

Established name: The designated FDA official name, the compendial name, the USAN Council name, or the common or usual name (section 502(e)(3) of the Act and 21 CFR 299.4). Ordinarily, the established name of a drug will be the compendial name. However, FDA may designate an established name in cases where a monograph does not exist (see the CDER Data Standards Manual).

Excipient: Any component other than the drug substance(s) present in the finished product.

Extended release: Products that are formulated to make the drug available over an extended period after implantation.

Formulation: The qualitative and quantitative composition of the finished product. This is often called the composition statement.

Four corners: Refers to a 2 x 2 factorial of the largest and smallest diameters and lengths for *each* stent design.

Functional excipient: An excipient that performs a role in maintaining product quality or in achieving a desired in vivo performance.

Generalizability, generalization: The extent to which the findings of a clinical trial can be reliably extrapolated from the subjects who participated in the trial to a broader patient population and a broader range of clinical settings. [55]

Glass transition temperature (Tg): The temperature at which a polymer changes from glassy to elastomeric behavior.

Independent data monitoring committee (IDMC) (data and safety monitoring board, monitoring committee, data monitoring committee): An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical

[55] ICH Guidance E9 *Statistical Principles for Clinical Trials*

trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. [56]

In-process material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of a finished product.

Intention-to-treat principle: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e., the planned treatment regimen) rather than the actual treatment given (e.g., results from a patient who discontinues a treatment are counted in the treatment group). It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance with the planned course of treatment.[57]

Intravascular stent: For this guidance, an intravascular stent is a synthetic tubular structure intended for ***permanent*** implantation in the native coronary vasculature. The stent is designed to provide mechanical radial support after deployment; this support is meant to enhance vessel patency over the life of the stent. Once the stent reaches the intended location, it is expanded by a balloon or self-expanding mechanism.

JP: Japanese Pharmacopeia

Letter of authorization (LOA): A written statement by the holder or designated agent or representative (sponsor or applicant) permitting FDA the authority to access information included within one regulatory submission (e.g., IDE, PMA, MAF or DMF) to support a separate regulatory submission (e.g., IDE or PMA).

Lot: *Or batch* means one or more components or finished devices that consist of a single type, model, class, size, composition, or software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits (21 CFR 820.3(m)). (Note that a similar definition is provided within the CGMP regulations: A batch, or a specific identified portion of a batch, having uniform character and quality within specified acceptance criteria. In the case of a product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified acceptance criteria (21 CFR 210.3(b)(10)).)

Master file: A reference source submitted to FDA, which may include drug master files (DMF), device master files (MAF), etc. A master file may contain detailed information on a specific manufacturing facility, process, methodology, or component used in the manufacture, processing, or packaging of a drug (21 CFR 314.420) or a medical device (21 CFR 814).

[56] ICH Guidance E9 *Statistical Principles for Clinical Trials*

[57] ICH Guidance E9 *Statistical Principles for Clinical Trials*

Master production record: A record containing the method of manufacture of the product, including, in part, the master formula of defined size, complete manufacturing and control instructions, in-process tests and acceptance criteria, equipment and operating parameters, yield and yield reconciliation calculations, and provisions for packaging and labeling (see 21 CFR 211.186(b)) See also "Device history record."

Molecular weight (MW) (of a polymer): Weight of an average polymer molecule. The two most popular expressions of molecular weight of polymers are *number-average molecular weight* (Mn) and *weight-average molecular weight* (Mw). Mn is the total weight of all the polymer molecules in a sample, divided by the total number of polymer molecules in a sample. This number represents the average weight of a chain, *Mi*, weighted according to number fraction of each component i. Mw is the average molecular weight of a chain, Mi, weighted according to weight fractions of each component i.

No Observed Adverse Effect Level (NOAEL*NOAEL* means the highest dose level that does not produce a significant increase in adverse effects. The NOAEL can serve as the starting point for determining a reasonably safe starting dose of a new drug in healthy human volunteers. Studies to determine the NOAEL by examining at least two different species are needed to identify the starting dose for intravenous human studies (see guidance for industry *Estimating the Maximum Starting Dose in Initial Clinical Trials for Therapeutics in Adult Health Volunteers*). The duration of an animal study is determined by the duration of drug elution from the stent. The minimum duration should be 2 weeks for a nonpolymerized drug, which is considered a single dose. See the guidance for industry *Single Dose Acute Toxicity Testing for Pharmaceuticals* and *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*, for more information.[58]

Noninferiority trial: A trial with the primary objective of showing that the response to the investigational product is inferior to a comparative agent by more than a defined amount (the noninferiority margin).

Novel excipient: An ingredient used for the first time in a human drug or combination product in the United States or in a new route of administration.

OUS: Outside the United States

Packaging system: The sum of packaging components that together contain and protect the product. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to a DES.

Partition coefficient: The ratio of the concentration of a chemical species in one environment to its concentration in another environment.

[58] In December 2002, the Agency issued a draft guidance for industry and reviewers *Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers.* Once finalized, it will represent the Agency's current thinking on this topic.

Per protocol set (valid cases, efficacy sample, evaluable subjects sample): The set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations.[59]

Pharmacodynamics: The study of the biochemical and physiological effects of drugs (and/or metabolites) on the body and the mechanisms of drug action, including the characterization of the relationship between the drug exposure and pharmacologic effects (efficacious and toxic), and the factors influencing such relationships. Often, the time course of these effects is also described.

Primary stability data: Data on the finished product stored in the proposed package for marketing under storage conditions that support the proposed shelf life

Quality: The suitability of a DES for its intended use. This term includes such attributes as the identity, content, purity, and potency.

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an application to confirm the quality of drug substances, products, intermediates, raw materials, reagents and other components including packaging system, and in-process materials. A specification sheet includes the list of tests, references to analytical procedures, and acceptance criteria.

Specified degradation product: An identified or unidentified degradation product that is selected for inclusion in the product specification and is individually listed and limited to ensure the safety and quality of the product

Statistical analysis plan: A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. [60]

Stent platform: The component of the DES that provides mechanical structural support when deployed in a vessel and is usually metallic and either balloon expandable or self-expanding.

Stent delivery system: A stent delivery system delivers a stent through the vasculature to its intended target site and then deploys the stent. A stent delivery system for a balloon expandable stent consists of a balloon catheter. Self-expanding stent delivery systems may or may not include a balloon.

[59] ICH Guidance E9 *Statistical Principles for Clinical Trials*

[60] ICH Guidance E9 *Statistical Principles for Clinical Trials*

Studied drug: a molecular entity that has been previously approved or studied under IND (i.e., has an approved NDA or ANDA, or has undergone human clinical studies under IND)

Superiority trial: A trial with the primary objective of showing that the response to the investigational product is superior to a comparative agent (active or placebo control). [61]

Tmax: PK parameter, time to maximum concentration

United States Pharmacopeia (USP): The United States Pharmacopeia (USP) is the official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements, and other healthcare products manufactured and sold in the United States.

Unspecified degradation product: A degradation product that is not included in the list of specified degradation products

Unstudied drug: a molecular entity that has not been approved for use in humans, or that does not have human clinical study information available

[61] ICH Guidance E9 *Statistical Principles for Clinical Trials*

BIBLIOGRAPHY

The following documents have either been referenced in this guidance or will be of interest to DES applicants and sponsors. They are grouped by document type and listed in alphabetical order.

Food and Drug Administration Guidance Documents

Application User Fees for Combination Products

Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products

Combination Products: Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product (Dispute Resolution Guidance)

Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

Current Good Manufacturing Practice for Combination Products

Dissolution Testing of Immediate Release Solid Oral Dosage Forms

Drug Master Files

Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro

Environmental Assessment of Human Drug and Biologics Applications

Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application

Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application

Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

How to Write a Request for Designation

Immunotoxicology Evaluation of Investigational New Drugs

INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information

Master Files: Part III – Guidance on Scientific and Technical Information

Nonclinical Studies for Development of Pharmaceutical Excipients

Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems

PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Premarket Approval Application Modular Review

Single Dose Acute Toxicology Testing for Pharmaceuticals

Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances

Submitting Documentation for the Manufacturing of and Controls for Drug Products

International Conference on Harmonisation (ICH) Guidances

Q1A(R2) Stability Testing of New Drug Substances and Products

Q1B Photostability Testing of New Drug Substances and Products

Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

Q2B Validation of Analytical Procedures: Methodology

Q3A(R) Impurities in New Drug Substances

Q3B(R) Impurities in New Drug Products

Q3C Impurities: Residual Solvents, December

Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals

S7A Safety Pharmacology Studies for Human Pharmaceuticals

S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals

International Organization for Standardization (ISO)

2248 Packaging – Complete, filled transport packages – Vertical impact test by dropping

8318 Packaging — Complete, filled transport packages and unit loads — Sinusoidal vibration tests using a variable frequency

10993-1 Biological Evaluation of Medical Devices -- Part 1: Evaluation and Testing,

11607 Packaging for terminally sterilized medical devices —Part 1: Requirements for materials, sterile barrier systems and packaging systems

United States Pharmacopeia (USP)

<788> Particulate Matter in Injections (Small Volume)

<85> Bacterial Endotoxins

<71> Sterility

<724> Drug Release

<905> Content Uniformity

American Standards for Testing Materials (ASTM)

F746 Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials

F2129 Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion

G71 Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes

Susceptibility of Small Implant Devices