VI. 参考情報

１：平成 26 年 9 月 12 日付薬食機参発 0912 第 2 号厚生労働省大臣官房参事官（医療機器・再生医療等製品審査管理担当）通知「次世代医療機器・再生医療等製品評価指標の公表について」別紙３「三次元積層技術を活用した整形外科用インプラント」
２：講演資料１「骨腫瘍切除後の大骨欠損に対するカスタムメイド型デバイスの開発」
３：講演資料２「CT データ（DICOM）から骨モデル作成の実際と精度検証」
４：三次元積層技術に関する標準化動向について（事務局）
５：FDA Guidance “Custom device exemption – Guidance for Industry and Food and Drug Administration Staff”
６：EU council directive 93/42/EEC 及び EU directive 2007/43/EC（カスタムインプラント関連部分の抜粋）

参考情報１

薬食機参発０９１２第２号
平成２６年９月１２日

各都道府県衛生主管部（局）長　殿

厚生労働省大臣官房参事官
（医療機器・再生医療等製品審査管理担当）
（　公　　印　　省　　略　）

次世代医療機器・再生医療等製品評価指標の公表について

厚生労働省では、医療ニーズが高く実用可能性のある次世代医療機器・再生医療等製品について、審査時に用いる技術評価指標等をあらかじめ作成し、公表することにより、製品開発の効率化及び承認審査の迅速化を図る目的で、検討分野を選定して評価指標を検討してきたところです。

今般、同種iPS（様）細胞由来網膜色素上皮細胞（別紙１）、可動性及び安定性を維持する脊椎インプラント（別紙２）及び三次元積層技術を活用した整形外科用インプラント（別紙３）の評価を行うに当たって必要と考えられる資料、評価のポイント等を評価指標としてとりまとめましたので、下記に留意の上、製造販売承認申請に当たって参考とするよう、貴管内関係業者に対して周知いただきますよう御配慮願います。

なお、本通知の写しを独立行政法人医薬品医療機器総合機構理事長、一般社団法人日本医療機器産業連合会会長、米国医療機器・IVD工業会会長及び欧州ビジネス協会医療機器委員会委員長他の関連団体宛て送付することを申し添えます。

記

１．　評価指標とは、承認申請資料の収集やその審査の迅速化等の観点から、製品の評価において着目すべき事項（評価項目）を示すものである。評価指標は、法的な基準という位置付けではなく、技術開発の著しい次世代医療機器・再生医療等製品を対象として現時点で考えられる評価項目を示した

ものであり、製品の特性に応じて、評価指標に示すもの以外の評価が必要である場合や評価指標に示す評価項目のうち適用しなくてもよい項目があり得ることに留意すること。

２．　個々の製品の承認申請に当たって必要な資料・データを収集する際は、評価指標に示す事項についてあらかじめ検討するほか、可能な限り早期に独立行政法人医薬品医療機器総合機構の対面助言を活用することが望ましいこと。

（別紙３）

三次元積層技術を活用した整形外科用インプラントに関する評価指標

１．はじめに

今後の骨関節疾患治療は、高齢化社会と密接に関わっている。総務省統計局は、平成25年９月15日に我が国の高齢者動向を報告し、65歳以上(高齢者)の人口が、3186万人、総人口に対する割合が25.0%を初めて超えたことが明らかとなった（総務省統計局、統計トピックス No.72)。現在、我が国は、平均寿命、高齢化率及び高齢化のスピードという三点において、世界一の超高齢社会となっている。これに伴い、整形外科の日常診療においても、運動器障害を伴う変形性関節症や骨粗鬆症が増加しており、大腿骨頸部骨折や脊椎圧迫骨折も急増している。関節障害や骨折手術・変形矯正手術の治療に用いられる人工関節・骨接合用材料等の骨・関節インプラントの高機能化を図り、治療技術を向上させることは、今後高齢化社会を迎えるに当たり重要と考えられる。

従来の人工股関節、人工膝関節等、生体内埋め込み型の整形外科用インプラントは、その有効性及び安全性が認められ、術後10～20年間の耐久性が示され、整形外科医療及び国民の生活の質向上に貢献してきた。しかし、現在のインプラントの問題点の一つに、平均骨格形状に基づいた設計による画一的なサイズのみの提供となっているため、形状不一致による骨格形状への不適合が存在することが挙げられている。また、骨腫瘍症例における広範切除術後に生じる骨欠損や、インプラント再置換術の際の骨欠損に対する再建術が困難な症例も存在する。これらを解決する一つの手段として、形状のカスタムメイド化が考えられている。

従来の薬事法に基づく承認を取得している整形外科用インプラントの一般的な製造方法は、製品形状のデザイン・設計、鋳造・鍛造用の金型作製、精密鋳造・鍛造、表面加工等の過程を経ている。一方、インクジェットプリンター造形、電子ビーム積層造形、レーザー積層造形、光造形等の革新的な諸技術の開発により、少量（単品）かつ短期間にカスタムメイドインプラントを作成することが可能となってきた。したがって、これら革新的な三次元積層技術により製造された整形外科用インプラントの品質、有効性及び安全性を適切かつ迅速に評価を行うことが望まれている。そこで、今後開発されることが予想される三次元積層技術による新規整形外科用インプラント（骨関節インプラント及び手術支援ガイド）の迅速な上市に資するよう、当該技術に関する新たな評価指標を作成した。

２．本評価指標の対象

本評価指標は、整形外科用インプラントを製造する際の「三次元積層技術」全般を対象とするものであるが、他の医療機器を製造する際に同じ技術を用いた場合にも、その

技術に対して本評価指標を適用することを妨げるものではない。ただし、本評価指標は、既存品と類似のインプラントを三次元積層技術によって製造する場合を主な対象とする。

３．本評価指標の位置付け

本評価指標は、技術革新の著しい分野であり近年特にその医療機器製造技術への応用について着目されてきている「三次元積層技術（付加製造（AM : Additive Manufacturing）技術）」を対象とすることを踏まえ、問題点、留意すべき事項を網羅的に示したものではなく、現時点で考えられる点について示したものである。よって、今後の技術革新や知見の集積等を踏まえ改訂するものであり、申請内容等に関して拘束力を有するものではない。

実際に「三次元積層技術」を用いて製造された整形外科用インプラントの評価に関しては、個別の製造方法及び製品特性を十分に理解した上で、科学的な合理性を持って、柔軟に対応することが必要である。また、本評価指標以外に現存する国内外の関連ガイドライン等を参考にすることも必要である。なお、製品個別の特性が、現存するガイドライン等で評価できるか否か、十分に検討すべきであることに留意されたい。

４．三次元積層技術全般において評価・留意すべき点について

（１）品質管理上の留意点

①原材料

a）原材料の種類（材質、形状等。粉体であれば、その粒径と粒度分布等）

b）純度、化学成分、組成比等

特に、インプラント材料として頻繁に利用されるチタン及びチタン合金粉末については、酸素量の問題は材質に与える影響が大きく、ミルシート等で確認しておく必要がある。また、粉末を混合して合金化する場合にも、それぞれの粉末の純度、化学成分を確認することが必要である。

なお、チタン粉末の成分については、最終製品の品質が保証される粉末の化学成分や粒度等の具体的な値を製造販売承認申請書に記載する。

②原材料の再利用回数

未溶融の粉末や未反応の原材料は、再利用を繰り返すことで劣化するため、粉末品質に関してバリデーションを実施する必要がある。

③製造時に生じうる組成変動や内包欠陥

a）造形中に形成されうるポア、ピンホール等

X 線等で評価する等のバリデーションが必要となる。

b）造形ロット毎の化学的・物理的性質変化に関するバリデーション

サイズが大きく異なるものを混合して同時に製造した造形体は、その形状、

サイズ、数量等により、金属粉末を溶融・凝固する熱履歴が多少変動するため、造形ロット毎に化学成分、金属組織、機械的性質を評価する等のバリデーションが必要となる。

c）不純物の混合の有無

d）造形後に残留する原材料

特に、粉末を原材料とする場合には、造形後、その粉末を十分に除去することが求められる。

④造形パラメータ

造形パラメータは使用する機器、製造方法、造形体の形状やサイズに応じて、装置メーカー独自のアルゴリズム（ブラックボックス）により変化するため規定することはできないが、以下の項目のうち、製品性能に影響を及ぼすと考えられる条件については、製造販売承認申請時に規定すること。

a）製造方法（機器、型番）

b）出力又は電流／電圧

c）予備加熱温度域

d）スポット径

e）走査速度（造形速度）

f）積層間隔

g）走査間隔

h）造形雰囲気*

* 造形時の周囲雰囲気は、製品性能に影響を及ぼす場合がある。影響を及ぼすと考えられる場合には、酸素濃度や雰囲気（真空、アルゴンガス、ヘリウムガス、窒素ガス、混合ガス等）、さらに大気圧に比べて減圧又は加圧等について記載すること。

⑤製造装置の仕様（積層原理、ビームの種類及び出力、造形部のサイズ等）

使用する機器に応じて異なるため明確に規定することは困難であるが、製造販売承認申請時に仕様を示すこと。

⑥ 形状の再現性

- 製造後の製品形状が設計段階の形状と一定の誤差範囲以内で一致することが求められるため、精度を証明する必要がある。
- 基になるデータの精度、手術に求められる精度を勘案して、現実的な誤差の値を設定する。
- 造形後、マシニング等で追加工を行うことが多いため、最終製品を評価する必要がある。
- 特に、骨との接合部の精度は、最終製品の寿命に直結するため、高い精度が要求される。

（２）最終製品の非臨床評価における留意点

①物理的・化学的特性

最終製品の特性を考慮した上で、以下に示した項目に関して必要な評価を行うこと。

a）積層方向による異方性

サンプルによる強度試験を行い、強度異方性についてのデータを採取する。積層方向による強度異方性が存在することを考慮したデバイス設計や操作条件決定を行っていることを製造販売承認申請時に示す必要がある。

積層方向の異方性を特徴とするインプラントについては、臨床的に高機能性や耐久性等が必要とされる場合、基礎となる既存品より力学的に安全な方向への変更であることを説明し、審査ガイドライン（「人工股関節の審査ガイドラインについて」（平成 21 年 3 月 6 日付け薬食機発第 0306001 号厚生労働省医薬食品局審査管理課医療機器審査管理室長通知））等に従いワーストケースの力学試験を行う必要がある。

b）表面粗さ

骨と接触する部位については、表面粗さが骨親和性に与える影響は大きいため、表面粗さについての評価を行う必要がある。その際、造形後の加熱処理、化学処理等を行う場合にはそれらの処理によって表面粗さ、モホロジー等が異なることにも注意が必要である。

c）既存品との同等性評価（化学成分、機械的性質、疲労特性、耐食性、溶出特性）

粉末の積層造形法では酸素、窒素、水素等のガス成分が変化しやすいというプロセス特有の成分変化、物性変化があることに留意し、従来のインプラントと同様の規格で評価する。公的規格又は承認前例のない純度や化学組成比の原材料を使用する場合は、従来同様、物理的特性（化学組成、金属組織、機械的性質（降伏応力、引張強さ、破断伸び、強度及び延性）、疲労特性、耐食性、溶出特性等）について評価する。また、物理的特性に影響を与える製造工程（滅菌等）を含む場合は、その工程を経た後の材料について評価する。

d）物理的特性に影響を与える製造工程（滅菌等）を含む場合は、その工程を経た後の材料についての評価

e）形状精度

②生物学的安全性

- 基本的には、従来の医療機器と同様に、「医療機器の製造販売承認申請等に必要な生物学的安全性評価の基本的考え方について」（平成 24 年３月１日付け薬食機発 0301 第 20 号厚生労働省医薬食品局審査管理課医療機器審査管理室長通知）に基づき評価を行う。
- 既存品との製造工程の差分を踏まえた評価が必要である。（残存原材料（粉末等）、

不純物や化学変化の影響を考慮する。）

③ 機械的安全性

- 審査ガイドラインがあるインプラントについては、ガイドラインを参考に評価を行う。
- 積層方向を考慮し、最も強度的に弱いと考えられる検体、負荷方向で試験を行う。
- 造形後の残留応力、追加工に伴う形状及び力学的強度への影響を評価する。三次元積層技術により製造された造形物には残留応力が生じるため、留意が必要である。特に、造形後に機械加工を行う場合、造形時の残留応力が部分的に開放され、形状が変化する可能性がある。また、疲労強度への影響も想定されるため、形状及び強度評価は追加工後も行う必要がある。
- 最終製品の力学的強度評価を行う。適切に評価できる場合にあっては、有限要素解析（FEA : Finite Element Analysis）による力学強度評価を活用することができる。ただし、特殊内部構造又は特殊表面構造を有するものに関しては、原則、FEA 評価を行う必要がある。
- 汎用品については、既存品の力学的強度の評価指標に基づいて強度試験を行う。デバイス内部の多孔構造における変形や応力集中の評価には FEA の活用を考慮する。FEA に際しては、後述するような造形方法に応じた個別の配慮が必要となる。なお、500 ミクロン以下の微細な壁や柱等の造形を行うケースでは、造形用の STL（Standard Triangulated Language）データと実際に造形される壁や柱等のサイズが異なることがある（造形機の仕様による）。この寸法差異は設計三次元データを造形用 STL データへ変換する過程で調整されるため実用上の問題となることはない。しかし、デバイスデザインや FEA を行う際には、これらの点に配慮する必要がある。また、支柱サイズが小さくなると、表面の凹凸の影響が大きくなり、力学的強度も変化することにも留意する。以上の問題から、基本的な多孔構造についての FEA は実体の強度評価結果によるバリデーションは必要となる。

④安定性及び耐久性

最終製品の特性及び用途を考慮した上で、以下に示した項目に関して必要な評価を行うこと。

a）安定性

製品の有効期間（製造してから使用されるまで）において、性能が維持できること。また、経年劣化しないこと及び無菌状態が保たれること。

b）滅菌耐久性

放射線滅菌等により最終製品の物理的、化学的特性が変化しないこと。

⑤積層技術由来の内部構造／表面構造を付与した場合の評価

- インプラント本体に対して特殊内部／表面処理を施した場合には、本体－内部／表面処理間の境界面の機械的安全性を評価する。
- 特殊内部／表面処理の新規性により、既存品との内部／表面特性の同等性を示すことができない場合には、動物試験による評価を行う。

⑥動物試験

積層技術由来の特殊内部／表面処理について、既存品との内部／表面特性の同等性を示すことができない場合には、動物試験による評価を行う。評価項目としては、骨固定性能及び周囲の組織に異常が認められないことの確認、組織学的評価等が挙げられる。

（３）最終製品の臨床評価における留意点

非臨床試験（動物試験を含む）により、特殊内部／表面処理の有効性及び安全性を評価できない場合には、臨床試験が必要となる。

５．個別の三次元積層技術において評価・留意すべき点について

（１）インクジェットプリンターによる積層

形状付与の後の処理でセラミックスを焼結したものは、その焼結条件次第で、母骨との癒合・同化・置換が低下する。また、焼結時の収縮を考慮する必要がある。

（２）レーザー積層

- 造形物中の金属酸化度を評価する必要がある。
- 粉末の積層造形法では酸素、窒素、水素等のガス成分が変化しやすいというプロセス特有の成分変化、物性変化があるため、既存品の成分を基本に修正した規定となる。
- 電子ビーム積層と異なり、粉末は高温度で大気にさらされる場合があるので、再利用粉末の酸素量については、十分に管理しておく必要がある。なお、粉末の管理方法についても、保管状況、再利用状況等について規定する。

（３）電子ビーム積層

電子ビーム積層造形技術は、予備加熱（700℃～1000℃程度）を行ってから溶融するため、Z 軸方向（電子ビーム方向）に組織が異なる。そのため、造形後に組織均一化のための熱処理（材料により異なる）が必要となるため、力学的な評価等は、造形後に熱処理を施してから実施することが必要と考えられる。

（４）樹脂積層

樹脂積層造形法には、光硬化性樹脂を用いた造形方法（光造形法、インクジェット式等）、粉末樹脂材料を用いた方法（レーザー焼結方式等）、ワイヤー状樹脂を用いた熱溶解積層法等が存在し、それぞれの特性に応じて評価する必要

がある。

また、各造形方法に関する留意点としては以下の項目が挙げられる。

- 光造形に用いられる触媒には、発がん性等の細胞毒性を有するものが多く、これらの溶出を評価するため、発がん性、遺伝毒性に関する試験が必要である。
- 光硬化系樹脂の材料特性として耐衝撃性と耐光性が弱いことが挙げられるため、強度の担保と製品の保管方法に留意する。
- インクジェット式等サポート材を使用する方法では、サポート材が残留する可能性がある。サポート材の除去手順を決定し、十分除去できていることを確認する。

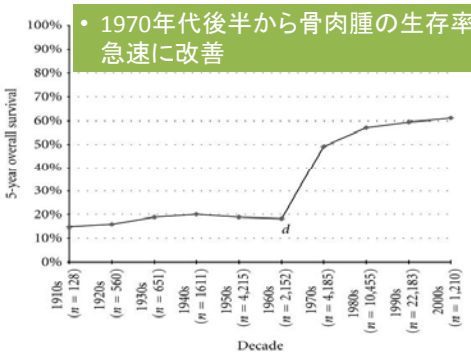
参考情報２

骨腫瘍切除後の大骨欠損に対するカスタムメイド型デバイス

三重大学医学部整形外科
松峯昭彦

Osteosarcoma 5-year overall survival

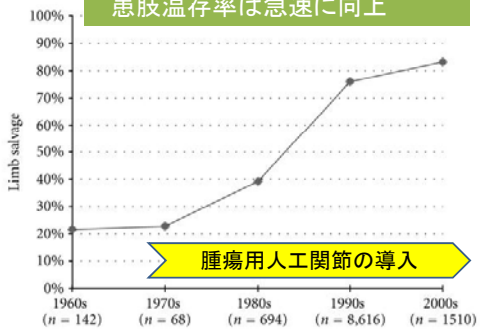
- 1970年代後半から骨肉腫の生存率は急速に改善



Allison DC et al: A meta-analysis of osteosarcoma outcomes in the modern medical era. Sarcoma. 2012

Osteosarcoma limb salvage rates

- 1970年代後半から骨肉腫患者の患肢温存率は急速に向上



Allison DC et al: A meta-analysis of osteosarcoma outcomes in the modern medical era. Sarcoma. 2012

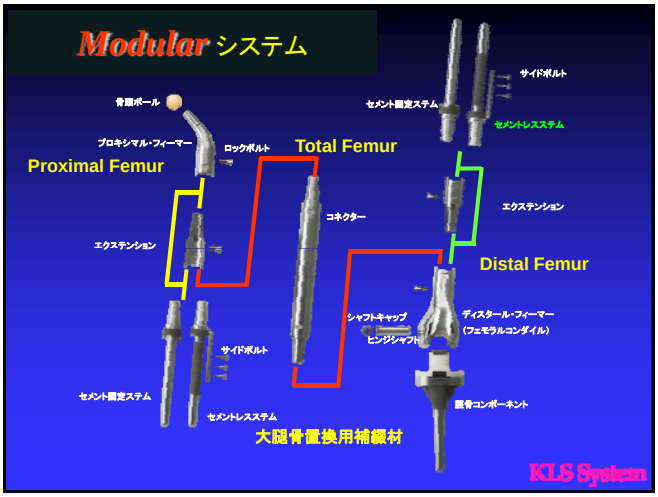
腫瘍用人工関節は、元々はカスタムメイドだった！！

4

カスタムメイドが廃れた理由

- 製作が難しい
- 迅速に対応できない
- ぴったり合わない
- 品質がバラバラで一定しない
- 術前のプランニングが面倒
- 手術中に変更ができない
- 作製する企業にしたら、modular system の方が制作費が安上がり

5

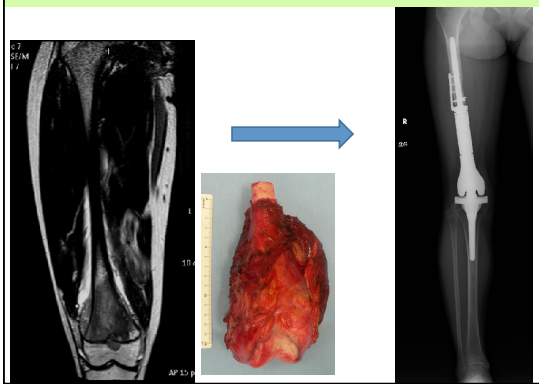


現在の腫瘍用人工関節の問題点

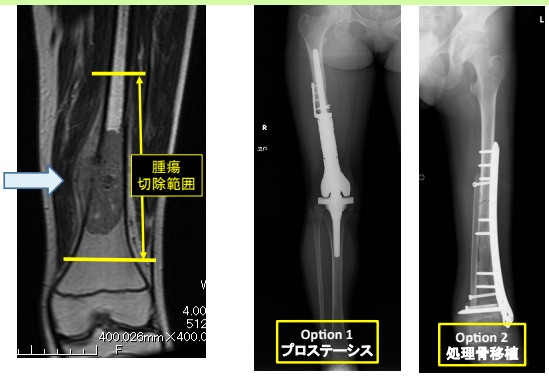
1. 骨幹端から骨幹の病変に対しても関節置換が強いられること
2. 設置できない症例あり（小さな人など）
3. 脛骨遠位などまれな部位に使用できる人工関節が無い
4. 骨盤腫瘍切除後の良い再建法がない

→ カスタムメイドの人工関節でこれらの問題が解決できないだろうか？

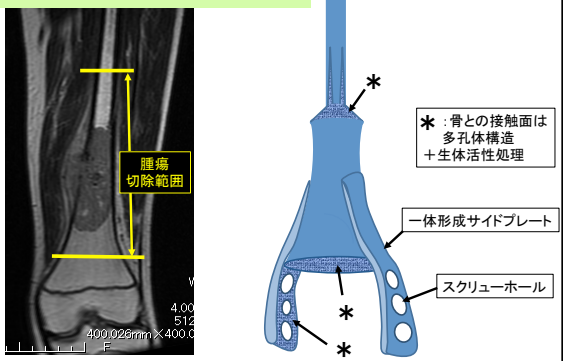
大腿骨骨幹端に発生した骨肉腫の手術



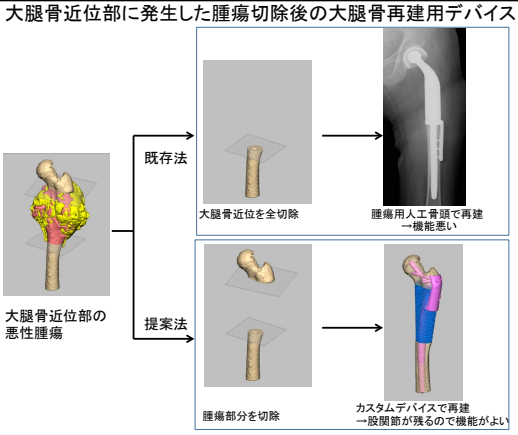
大腿骨骨幹端に発生した骨肉腫の手術



Option 3を作りたい！



大腿骨近位部に発生した腫瘍切除後の大腿骨再建用デバイス



骨腫瘍切除後のカスタムメイド型デバイスでの再建を成功させるためのポイント

- デバイスそのものが高性能
  - 高い強度
  - 良いデザイン
  - 複雑な形状にも対応できること
- 骨との親和性（生体活性）
- 正確な骨切り
  - 手術支援システム
    - 手術ナビ（MRI+CT）
    - カッティングガイド
    - 手術ナビ＋カッティングガイド

技術革新1
3D積層造形法

・ 電子ビーム積層技術
（ARCAM社 スエーデン）

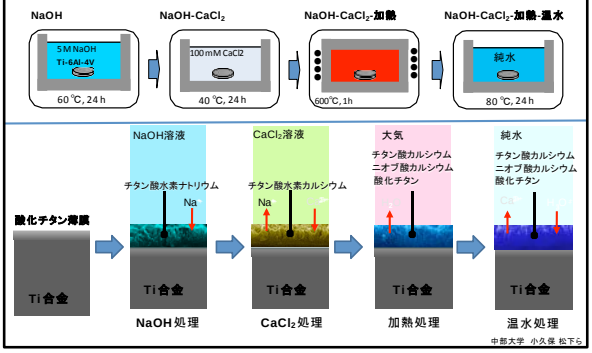
・ レーザー積層技術
（EOS社 ドイツ）

- Rapid prototyping (RP)
- Solid freeform fabrication (SFF)
- Layer manufacturing (LM)
- 3D printing (3DP)
- Additive manufacturing (AM)

"… the 3D printing that has the potential to revolutionize the way we make almost everything . . … "
President Obama in the State of the Union Address, Feb. 12, 2013

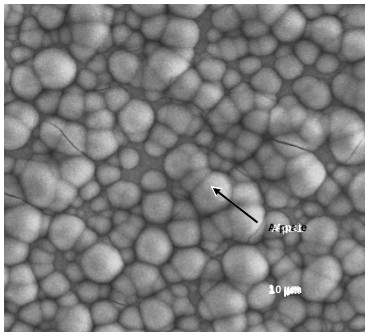
オバマ大統領は、アメリカが、製造業で優位性を生み出すためにNAMII (NaFonal AddiFve Manufacturing InnovaFon InsFtute)と呼ばれる3Dプリンターの研究所を設立

技術革新2　金属の生体活性化処理技術
アルカリ・塩化カルシウム・温水による生体活性化処理



中部大学 小久保 松下ら

擬似体液中で金属表面にアパタイトが析出する



16

硬組織切片標本

埋植

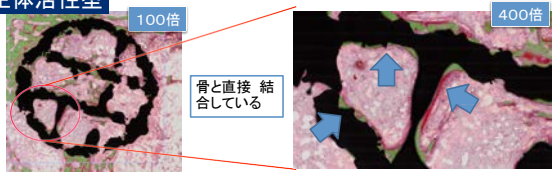
各サンプルの矢状断での

v.goldner染色

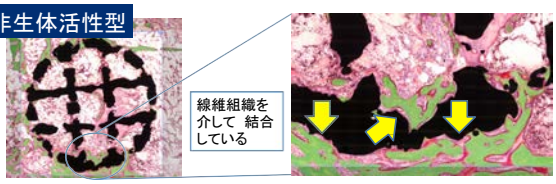
v.goldner染色

硬組織切片による骨との結合の評価

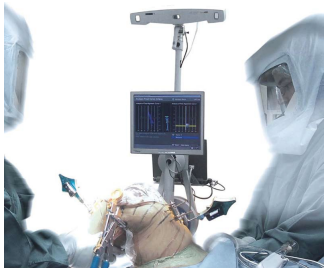
生体活性型

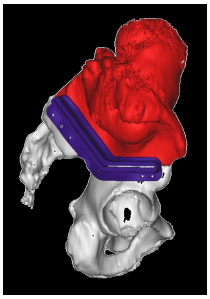


非生体活性型



技術革新3　手術支援システム



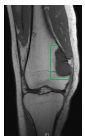


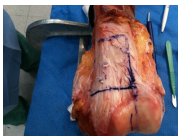
ナビゲーションシステム　カッティングガイド

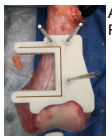
19

Khan FA et al: Computer-generated Custom Jigs Improve Accuracy of Wide Resection of Bone Tumors, Clin Orthop Relat Res (2013) 471:2007–2016

- Custom jigs
- hemiepiphyseal resection
- Cadaveric femurs (6 matched pairs)
- Standard manual tech. vs custom jig-assisted tech.







ABS plastic
Rapid prototyping machine

RESULTS: Absolute deviation of resections from the preoperative plan

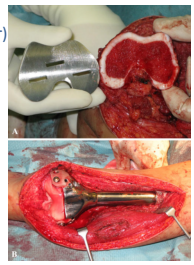
Outcome measure*	Manual	Custom jig	p value
Maximum deviation (mm)	9	2	0.002
Average deviation (mm)	3.1	0.8	< 0.001
Error in front angle (degrees)	4.7	0.9	< 0.001
Error in depth angle (degrees)	3.5	1.4	0.02
Error in reduced angle (degrees)	6.6	1.8	< 0.001

20

Wong KC, Kumta SM., Joint-preserving Tumor Resection and Reconstruction Using Image-guided Computer Navigation. Clin Orthop Relat Res (2013) 471:762–773

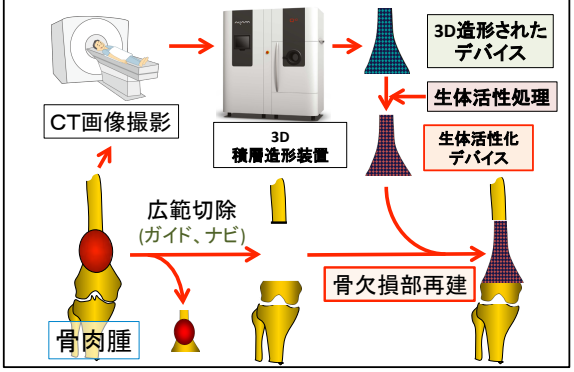
8 pts.
Navigation (with fused CT-MR images、Striker)
Age: 6-46 yrs(mean: 17 yrs)
FU: 25-60 mos(mean: 41 mos)
Location: femur: 6, tibia: 1, humerus: 1
Prosthesis: 6 pts

RESULS
accurate resection, difference<2mm
no recurrences
MSTS score: 29
no Complication,
no failure of fixation



21

カスタムメイドデバイスでの骨欠損部の再建

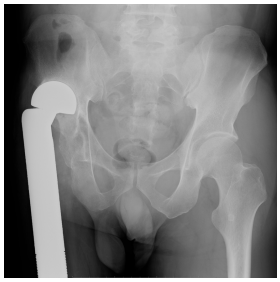


臨床応用の手順

徐々に難易度アップ！！

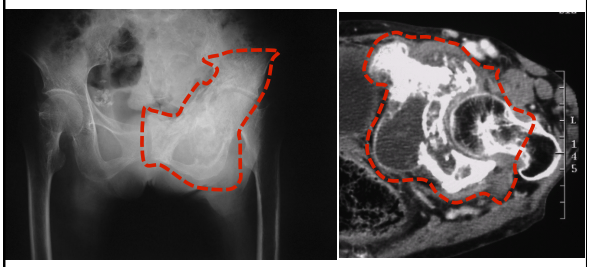
- ステップ1：　非加重部への使用
  →腸骨採骨部など
- ステップ2：　加重部の比較的単純なデバイス
- ステップ3：　切除端設置型骨盤デバイス
- （ステップ4：　骨盤輪再建型骨盤デバイス）

Step 2の再建



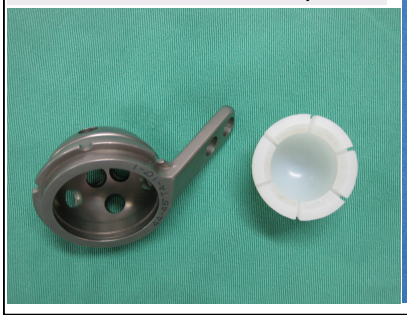
上方移動した腫瘍用人工骨頭

Chondrosarcoma

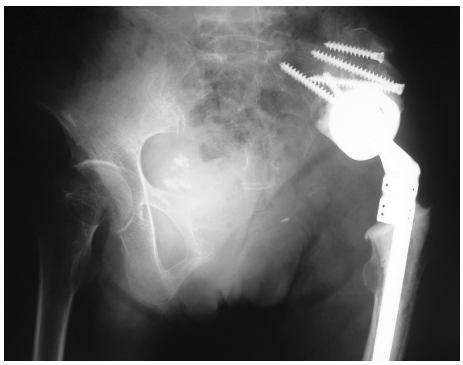


日本では・・・・

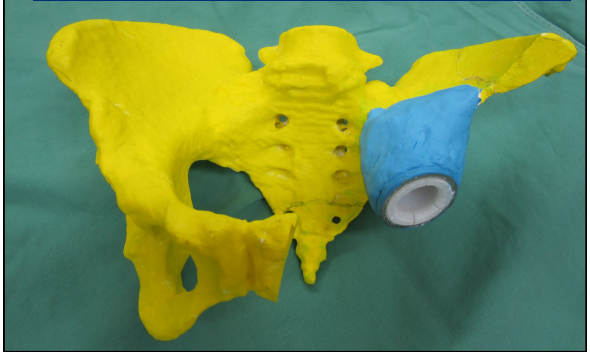
Constrained type reconstruction cup



Postoperative radiograph



Step3の再建
（切除端設置型骨盤デバイス）



海外では？？

Stanmore Implants
（in Royal National Orthopsaedic Hospital）

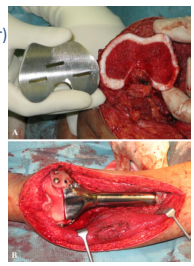
Titanium alloy implants via Additive Manufacturing

Electron Beam Melting

Direct Metal Laser Sintering

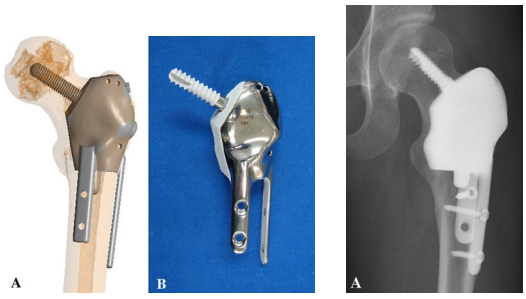
Wong KC, Kumta SM., Joint-preserving Tumor Resection and Reconstruction Using Image-guided Computer Navigation. Clin. Orthop Relat Res (2013) 471:762–773

8 pts.
Navigation (with fused CT-MR images、Striker)
Age: 6-46 yrs(mean: 17 yrs)
FU: 25-60 mos(mean: 41 mos)
Location: femur: 6, tibia: 1, humerus: 1
Prosthesis: 6 pts



RESULS
accurate resection, difference<2mm
no recurrences
MSTS score: 29
no Complication,
no failure of fixation

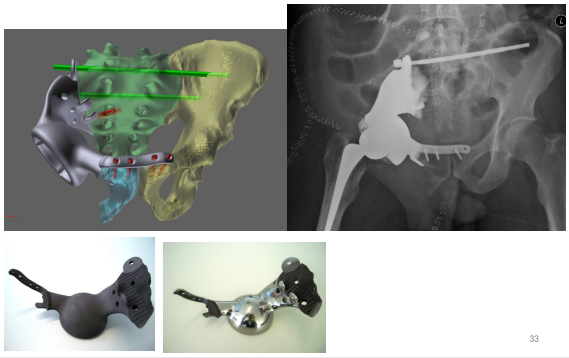
31



Wong KC, Kumta SM et al: Clin. Orthop Relat Res (2013) 471:762–773

32

62 yr male patient“ Chondrosarcoma “
(malignant bone cancer of the pelvic wing)



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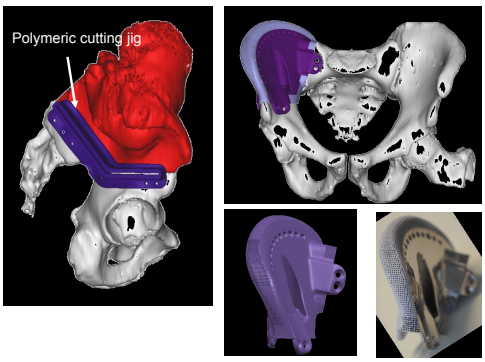
Type 1-S, Osteosarcoma

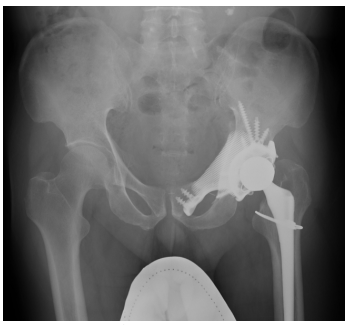


カスタムデバイスの利点と欠点

利点
- 多孔体にできる
- 複雑な形可能
- 表面構造
- 正確な造形が可
- 材料の節約
- 金属材料は既存のもの（Ti, CoCr）

欠点
- 不明な点が多い
  表面仕上げ
- 金属粉の除去
- 表面コーティング（HA）
- 感染対策（silver caoated）
- 金属の劣化

Mobelife

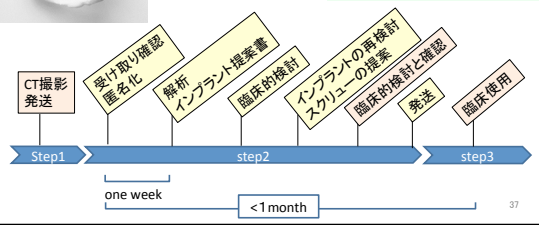


1-Stage Pelvic Tumor Reconstruction
（Mobelife）

- Selective Laser Melting (SLM)
- Ti6Al4V

The aMace Technology

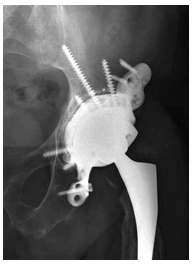
- Unique fit
  not require any structural bone reaming
- Personally fixation
  drill jig
- Individually evaluated
  finite element analysis

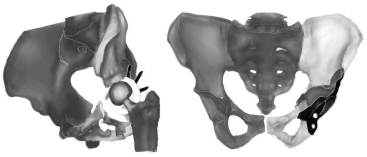


Colen S et al: A modified custom-made triflanged acetabular reconstruction ring (MCTARR) for revision hip arthroplasty with severe acetabular defectsActa Orthop. Belg., 2012, 78, 71-75

6 cases, FU:10-58 mos. Type3(3)/4(3)

- no component removed, dislocation, and infection,
- no sign of loosening, migration and breakage
- all pts: satisfied with the clinical result





AAOS Classification of pelvic bone defects

Type	Subtype	Description
1 – Segmental peripheral	Superior	Acetabular rim lysis
	Anterior	
	Posterior	
1 – Segmental central		Medial wall lysis
2 – Cavitary peripheral	Superior	Acetabular rim intact
	Anterior	
	Posterior	
2 – Cavitary central		Medial wall intact
3 – Combined deficiency		Rim + acetabular cavity lysis
4 – Pelvic discontinuity		Transverse acetabular fracture
5 - Arthrodesis		Hip joint fusion

Colen S et al: A modified custom-made triflanged acetabular reconstruction ring (MCTARR) for revision hip arthroplasty with severe acetabular defectsActa Orthop. Belg., 2012, 78, 71-75

6 cases, FU:10-58 mos. Type3(3)/4(3)

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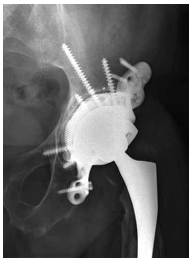
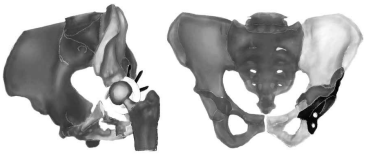




Implantcast

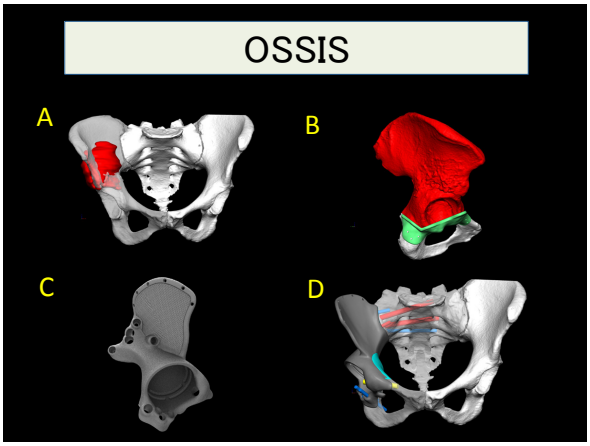
MUTARS® Partial Pelvis Replacement

indication
tumors in the pelvic area
acetabular cup revision surgery

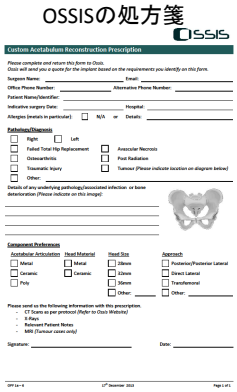
fixation method
stem fixation in the os ilium, large implant surface with colar additional initial fixation with cancellous bone screws

advantages
easy soft tissue reconstruction due to small prosthetic design
the model based on 3D CT leads to a high precision implant
no screw or stem fixation to the os ischii and os pubis facilitates the implantation
the use of the MUTARS® attachment tube prevents hip joint subluxation

OSSIS



OSSISの処方箋



Custom Acetabulum Reconstruction Prescription

Please complete and return this form to Ossis.
Ossis will send you a quote for the implant based on the requirements you identify on this form.

Surgeon Name: _____ Email: _____
Office Phone Number: _____ Alternative Phone Number: _____
Patient Name/Identifier: _____
Indicative surgery Date: _____ Hospital: _____
Allergies (metals in particular): ☐ N/A or Details: _____

Pathology/Diagnosis

☐ Right ☐ Left
☐ Failed Total Hip Replacement ☐ Avascular Necrosis
☐ Osteoarthritis ☐ Post Radiation
☐ Traumatic Injury ☐ Tumour (Please indicate location on diagram below)
☐ Other: _____

Details of any underlying pathology/associated infection or bone deterioration (Please indicate on this image):

Component Preferences

Acetabular Articulation	Head Material	Head Size	Approach
☐ Metal	☐ Metal	☐ 28mm	☐ Posterior/Posterior Lateral
☐ Ceramic	☐ Ceramic	☐ 32mm	☐ Direct Lateral
☐ Poly		☐ 36mm	☐ Transfemoral
		☐ Other: _____	☐ Other: _____

Please send us the following information with this prescription.
- CT Scans as per protocol *(Refer to Ossis Website)*
- X-Rays
- Relevant Patient Notes
- MRI *(Tumour cases only)*

Signature: _____ Date: _____

OPP Lv – 6 17th December 2013 Page 1 of 1

CT撮影時の注意点

- 骨盤全体が入るように
- スライス幅は0.75-1.25
- detector はmulti-, single どちらでもOK
- 標準 または軟部条件で再構成
- DICOMデーターで
- DVD or CD-ROMでOssis に郵送

カスタムメイド型デバイスは、技術革新の集合体！

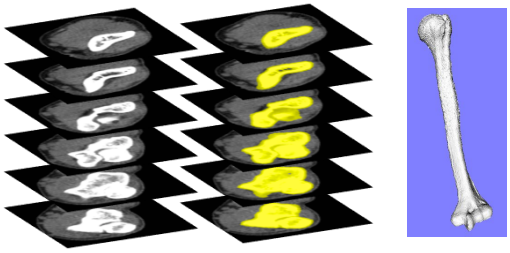
- 3D積層技術
- 金属の生体活性化処理技術
- 病変部の抽出とデバイス設計
- 応力/ひずみ解析（FEM)による解析
- 手術支援システムの開発
  （手術ナビ、カッティングガイド、カッティングドリル）
- 作製デバイスの強度評価

参考情報３

CTデータ(DICOM)から
骨モデル作成の実際と精度検証

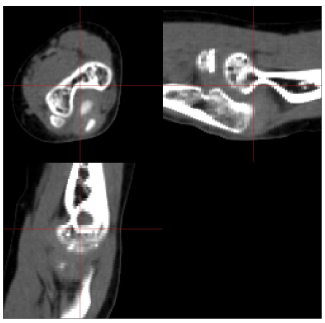
大坂大学整形外科
村瀬 剛

２次元断層画像から骨抽出領域を指定し、選択部分を３次元化。

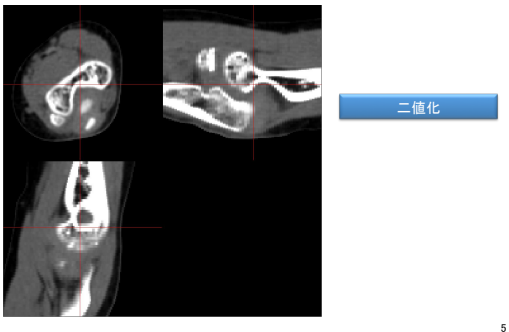


抽出方法 １
（自動抽出が可能な場合）

１．ＣＴ画像の読み込み



２．２値化
CT画像を白・黒表示に変換。
変換の閾値は、HU150～200で設定する。



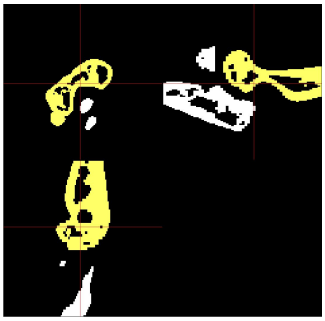
２．２値化
CT画像を白・黒表示に変換。
変換の閾値は、HU150～200で設定する。

３.任意の骨を選択
　オートの選択機能（＝リージョングローイングという）で
　任意の骨を選択（＝マスクという）する。

リージョングローイング

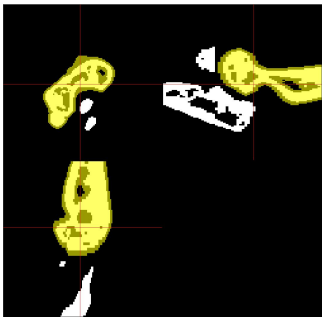
３.任意の骨を選択
　オートの選択機能（＝リージョングローイングという）で
　任意の骨を選択（＝マスクという）する。

４.マスク領域を拡張する。
　マスク領域内のデータを抽出するために、選択領域を１ピクセル単位
　で拡張する。

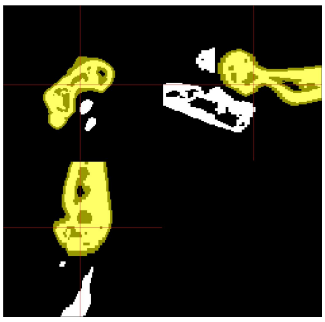


マスク領域拡張

４.マスク領域を拡張する。
　マスク領域内のデータを抽出するために、選択領域を１ピクセル単位
　で拡張する。

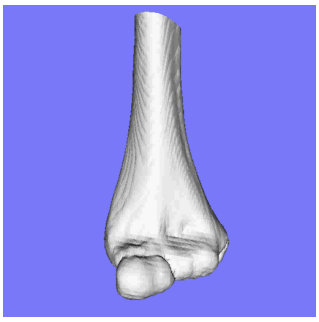


５.マスクで指定された領域内の骨表面モデル（サーフェスモデル）
　を作成する（Marching cubes:マーチングキューブ法）。

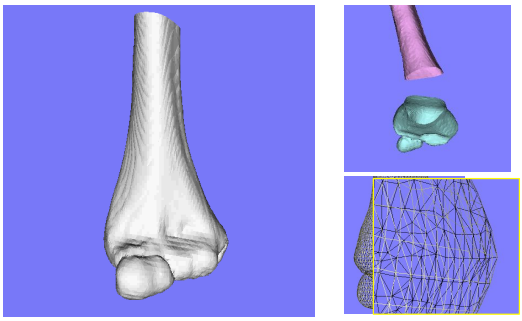


サーフェスモデル作成

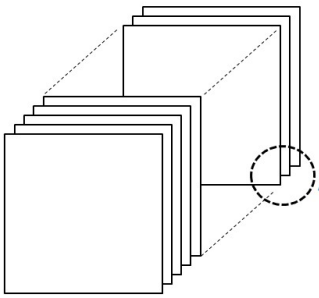
５.マスクで指定された領域内の骨表面モデル（サーフェスモデル）
　を作成する（Marching cubes:マーチングキューブ法）。



５．マスクで指定された領域内の骨表面モデル（サーフェスモデル）を作成する（Marching cubes：マーチングキューブ法）。



Marching cubes＊：マーチングキューブ法について

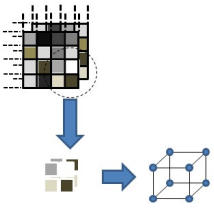


3Dデータは複数の画像データを積み重ねたものです。
また、画像データは、細かい点の集まりであり、その点（画素）１つは1色しか表せません。
CT画像の場合は、色ではなくCT値を表し、白黒の濃淡で表します。

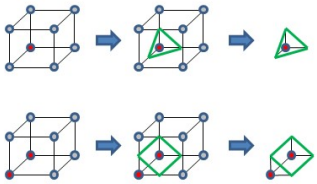
*William E. Lorensen, Harvey E. Cline: *Marching Cubes: A high resolution 3D surface construction algorithm.* In: *Computer Graphics*, Vol. 21, Nr. 4, July 1987

直方体の頂点となるように隣接する8つのピクセルについて着目し、画素値が閾値以上のピクセルと閾値未満のピクセルとの間に面を作成していきます。

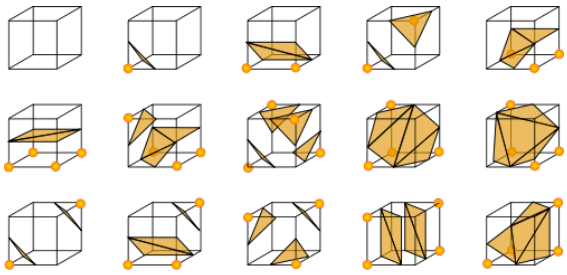
8つのピクセルに着目します。
これを分かり易く立方体の頂点として考えます。



例えば● を閾値以上のピクセルとすると、
緑線で囲まれた部分に面を作成します。

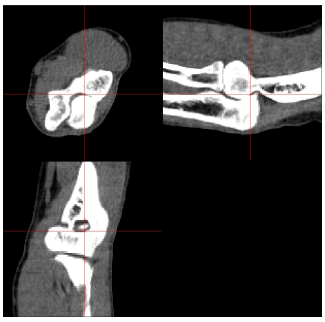


マーチングキューブ法で生成される サーフェスの様々なパターン

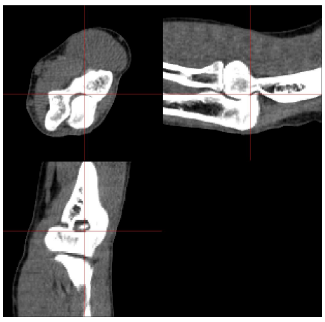


抽出方法 ２
（手動修正が必要な場合）

１． CT画像の読み込み



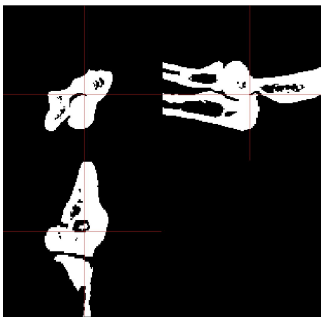
２．２値化
CT画像を白・黒表示に変換。
変換の閾値は、HU150～200で設定する。



二値化

19

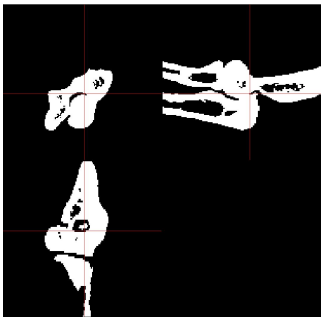
２．２値化
CT画像を白・黒表示に変換。
変換の閾値は、HU150～200で設定する。



二値化

20

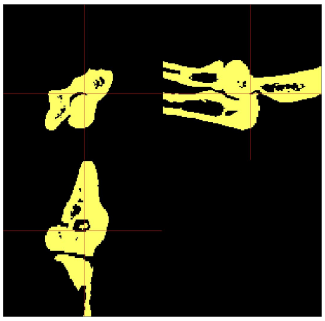
３．任意の骨を選択
オートの選択機能（＝リージョングローイングという）で
任意の骨を選択（＝マスクという）する。



リージョングローイング

21

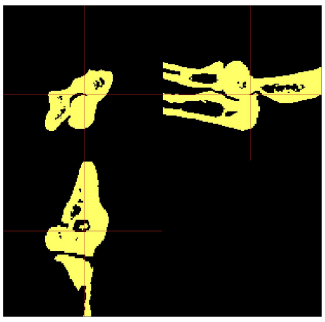
３．任意の骨を選択
オートの選択機能（＝リージョングローイングという）で
任意の骨を選択（＝マスクという）する。



リージョングローイング

22

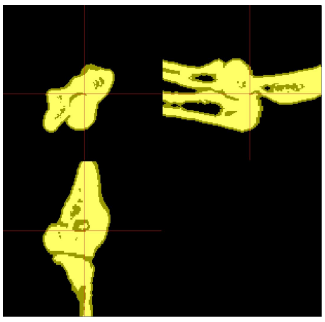
４．マスク領域を拡張する。
マスク領域内のデータを抽出するために、選択領域を１ピクセル単位
で拡張する。



マスク領域拡張

23

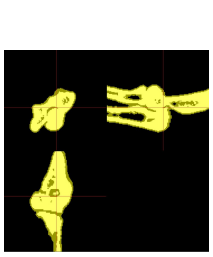
５．マスクで指定された領域内の骨表面モデル（サーフェスモデル）
を作成する（Marching cubes:マーチングキューブ法）。

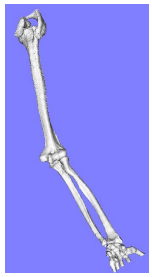


サーフェスモデル作成

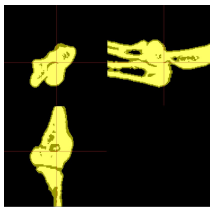
24

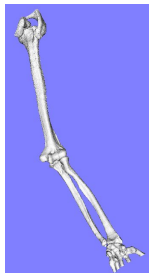
５．マスクで指定された領域内の骨表面モデル（サーフェスモデル）を作成する（Marching cubes:マーチングキューブ法）。





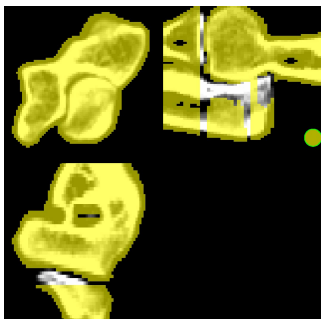
しかし、マスク領域が複数の骨を含んでいるために、複数の骨が連続したモデルとして作成される。

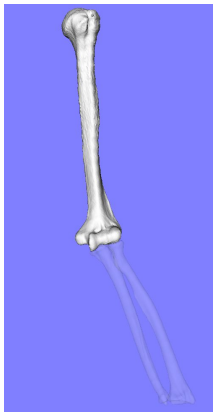




対象とする骨を分離するために、マスク領域の修正を行う。

６．選択領域の修正（マニュアルセグメンテーション）
複数の骨に連続したマスクの対象外の骨にかかる領域をマニュアル操作で削除する。

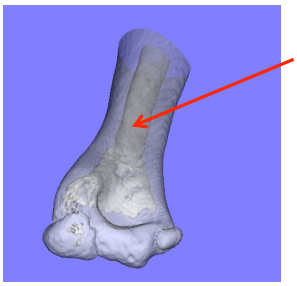




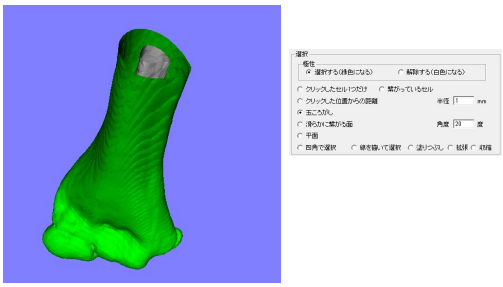
骨モデルの修正１

（髄腔除去）

１．３次元骨モデルの修正（STL編集）
表面骨以外のデータが残っている場合や、表面に穴が空いている場合は別ソフトを用い、修正する。

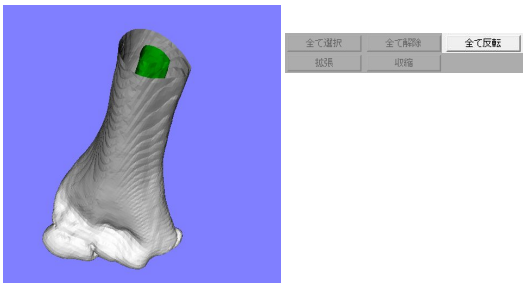


1．３次元骨モデルの修正（STL編集）
表面骨を選択。



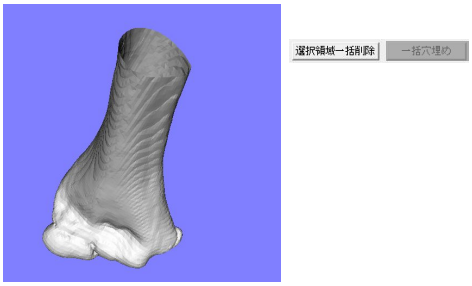
31

1．３次元骨モデルの修正（STL編集）
選択反転。



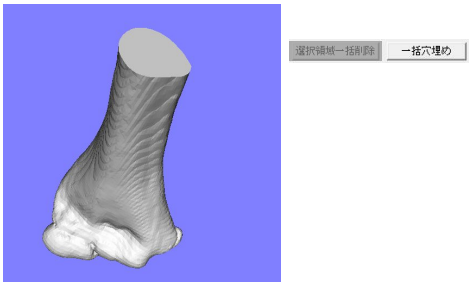
32

1．３次元骨モデルの修正（STL編集）
選択部分、削除。



33

1．３次元骨モデルの修正（STL編集）
自動穴埋め

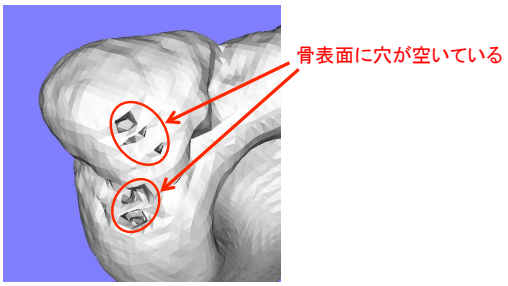


34

骨モデルの修正１
（表面の穴を修正）

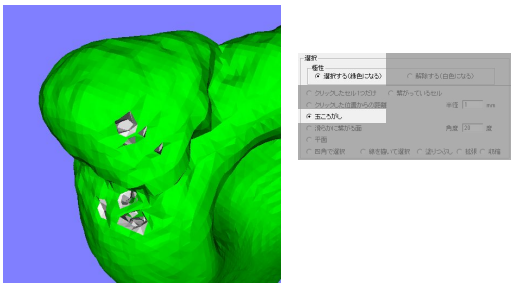
35

1．３次元骨モデルの修正（STL編集）



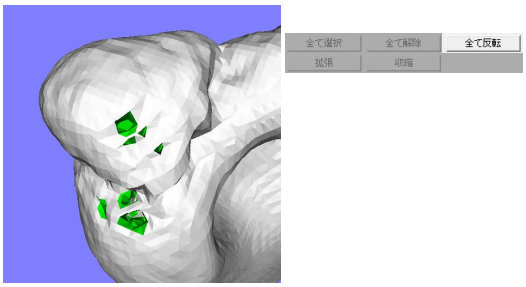
36

6．3次元骨モデルの修正（STL編集）



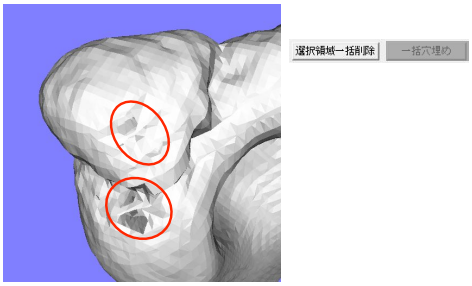
37

6．3次元骨モデルの修正（STL編集）



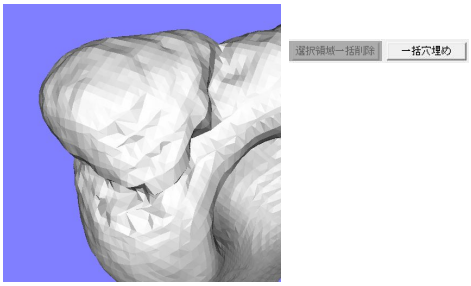
38

6．3次元骨モデルの修正（STL編集）



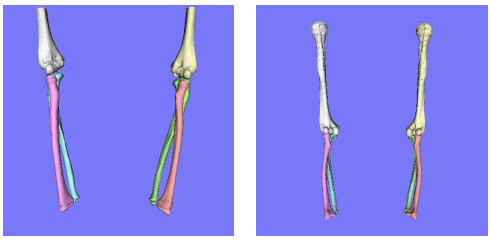
39

6．3次元骨モデルの修正（STL編集）



40

以上のような操作で、３次元骨モデル作成を行なっている。



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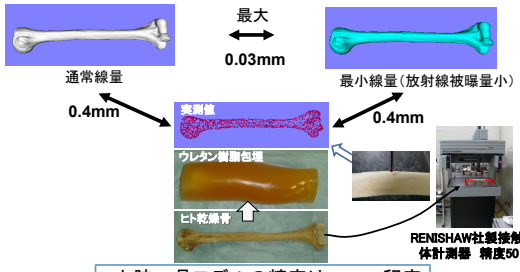
CT撮影条件による3D骨モデルの誤差　－放射線被曝量低減に向けて－

Oka K, et al. Int J Med Robot 2009

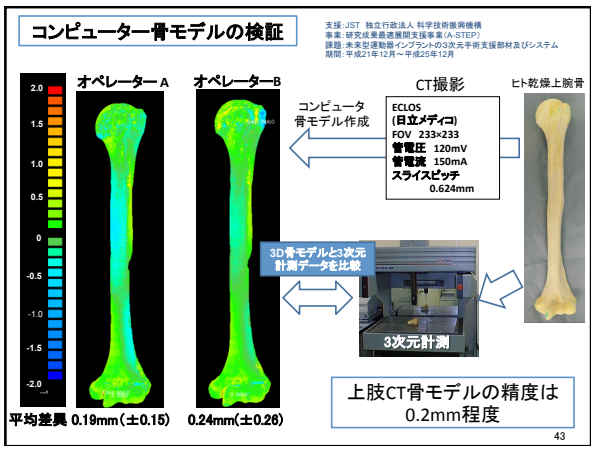
撮影条件	管電圧 (kV)	管電流 (mA)	scan time (s)	スライス厚/pitch/speed	FOV (cm)
通常線量	120	50	1	0.625/0.562:1/5.62	10
最小線量	120	10	0.5	0.625/1.75:1/5.63	10

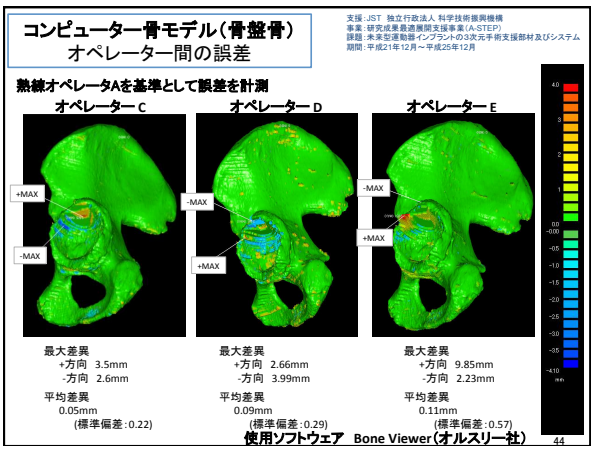


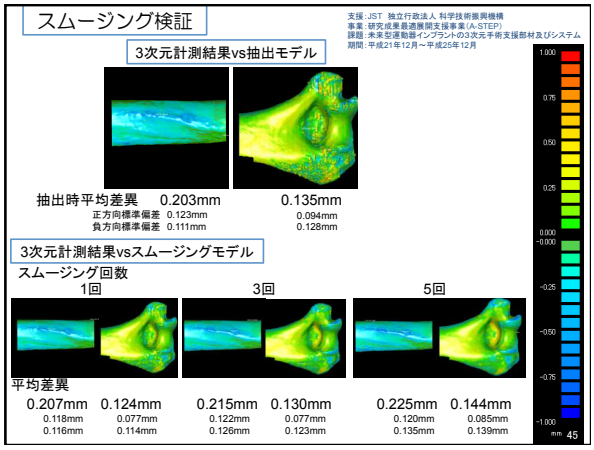
・上肢CT骨モデルの精度は0.4mm程度

・放射線被曝量1/30以下に低減可能

42







まとめ

- CTデータからコンピューター骨モデル作成する方法を概説した。
- 骨形状の3次元実測値とコンピュータ骨モデルの差異は0.2-0.4mm程度であった。
- オペレーター間での骨モデル形状差異は0.1mm以下であったが、関節近傍では局所的に数mmになることがあった。
- コンピューター骨モデルのスムージング操作が実測値との形状差異に与える影響は比較的少なかった。

参考情報４

三次元積層造形技術に関する国際動向に関して

＜標準化＞

１）ISO/TC 261 “Additive manufacturing”（2011 年設立、2014 年より日本も参加）

（http://www.iso.org/iso/home/standards_development/list_of_iso_technical_committees/iso_technical_committee.htm?commid=629086）

事務局：ドイツ（DIN）

議長：Lutz Wrede 氏（ドイツ：DIN 所属）。

参加国：P-member 19 ヶ国、O-member ４ヶ国

国内審議団体：技術研究組合次世代３D 積層造形技術総合開発機構（TRAFAM）この組合にはナカシマメディカルも参加（他の医療機器専門メーカーは見当たらないが、東芝等も参加している）。

構成：WG ４つ、ASTM との Joint advisory group（JAG） １つ

発行規格：４つ

うち２つが ISO/ASTM の共同文書という形で発行

- ISO/ASTM 52915:2013 “Standard specification for additive manufacturing file format (AMF) Version 1.1”（今後、改訂予定）
- ISO/ASTM 52921:2013 “Standard terminology for additive manufacturing -- Coordinate systems and test methodologies”

２）ASTM F42 “Additive manufacturing technologies”（2009 年設立）

（http://www.astm.org/COMMIT/SUBCOMMIT/F42.htm）

議長：Met-L-Flo Inc.（http://www.met-l-flo.com）代表の Carl Dekker 氏。

215 名以上のメンバーで構成されている

発行規格：７つ発行

うち２つが ISO と identical で、現在 ISO で審議されている文書のうち２つも ASTM と identical なものになると思われる。

本来、各々が独立して活動している ISO、ASTM 両団体であるが、現在、この２つの委員会は連携しており、ISO/TC 内に JAG がある。ISO 内の JAG は、他に１つ存在するだけで、そのカウンターパートは CEN である。ASTM と ISO とが連携して規格を発行している TC は TC 85 (Nuclear energy, nuclear technologies, and radiological protection)のみであったことから、TC 261 は珍しい形態で活動している ISO/TC である。なお、この JAG をどちらが主導

しているか、現時点では不明である。2015 年 1 月、ASTM F42 会議が Pennsylvania 州で開催され、TC 261 との合同会議も開催された（同様の会議は、既に 2014 年 7 月に英国 Nottingham で開催されている）。

現在作成中の文書も含めた ISO 及び ASTM 規格リストを、参考までに別資料として添付する。

＜規制関係＞

１）FDA

カスタムインプラント関係のガイダンスは既に 9/24 に発行済。

（ http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM415799.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery）

FDA のカスタムインプラントの定義は、個々の患者に適合する形状をもつフルカスタムインプラントのことである。このインプラントに対して、FDA は PMA も 510(k)も要求していない。

なお、FDA は三次元積層造形関連で規制ガイダンスを 2016 年迄に策定したいと公表しており、2014 年にはワークショップを開催している。

（http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm397324.htm）

２）欧州

医療機器規制のための文書に、カスタムメイド医療機器に関する記述が存在する（EU Council Directive 93/42/EEC 及び Directive 2007/43/EC）。それによると、カスタムメイド品は規制における従来の要求事項を満たす必要がないことが記載されている。

現在、複数の会社から三次元積層造形技術によるカスタムメイド整形外科用インプラントが販売されているが、この記載から鑑みるに、特別な規制は設けられていない様子である。

開発 WG より提供

積層造形法の特性評価・欠陥等の評価方法に関する規格・基準の調査

2014 年 10 月 7 日

JFE テクノリサーチ株式会社

●予備調査結果（規格一覧表）

1) Additive manufacturing に特化した規格および制定準備中規格（ASTM Committee F42 on additive manufacturing technologies や ISO/TC261 Additive manufacturing 所管規格等）

規格番号	題名	分野	Abstract/Scope/Significance and use	Note
ASTM F2792-12a	Standard Terminology for Additive Manufacturing Technologies	用語 全般	This terminology includes terms, definitions of terms, descriptions of terms, nomenclature, and acronyms associated with additive-manufacturing (AM) technologies in an effort to standardize terminology used by AM users, producers, researchers, educators, press/media and others.	Vol. 10.04 2014
ASTM F2924-14	Standard Specification for Additive Manufacturing Titanium-6 Aluminum-4 Vanadium with Powder Bed Fusion	評価 金属 成形品	This specification covers additively manufactured titanium-6aluminum-4vanadium (Ti-6Al-4V) components using full-melt powder bed fusion such as electron beam melting and laser melting. It indicates the classifications of the components, the feedstock used to manufacture Class 1, 2, and 3 components, as well as the microstructure of the components. This specification also identifies the mechanical properties, chemical composition, and minimum tensile properties of the components.	Vol. 10.04 On-line ($43), or 2015
ASTM F2971-13	Standard Practice for Reporting Data for Test Specimens Prepared by Additive Manufacturing	報告 様式	This practice describes a standard procedure for reporting results by testing or evaluation of specimens produced by additive manufacturing (AM). This practice provides a common format for presenting data for AM specimens, for two purposes: (1) to establish further data reporting requirements and (2) to provide information for the design of material property databases.	Vol. 10.04 On-line ($38), or 2015
ASTM F3001-14	Standard Specification for Additive Manufacturing Titanium-6 Aluminum-4 Vanadium ELI (Extra Low Interstitial) with Powder Bed Fusion	評価 金属 成形品	This specification establishes the requirements for additively manufactured titanium-6aluminum-4vanadium with extra low interstitials (Ti-6Al-4V ELI) components using full-melt powder bed fusion such as electron beam melting and laser melting. The standard covers the classification of materials, ordering information, manufacturing plan, feedstock, process, chemical composition, microstructure, mechanical properties, thermal processing, hot isostatic pressing, dimensions and mass, permissible variations, retests, inspection, rejection, certification, product marking and packaging, and quality program requirements.	Vol. 10.04 On-line ($43), or 2015
ASTM F3049-14	Standard Guide for Characterizing Properties of Metal Powders Used for Additive Manufacturing Processes	評価 粉末	This guide introduces the reader to techniques for metal powder characterization that may be useful for powder-based additive manufacturing processes including binder jetting, directed energy deposition, and powder bed fusion. It refers the reader to other, existing standards that may be applicable for the characterization of virgin and used metal powders processed in additive manufacturing systems.	Vol. 10.04 On-line ($38), or 2015
ASTM F3055-14	Standard Specification for Additive Manufacturing Nickel Alloy (UNS N07718) with Powder Bed Fusion	評価 金属 成形品	This specification defines the requirements for additive manufacturing of nickel alloy (UNS N07718) using full-melt powder bed fusion such as electron beam melting and laser melting. The standard may be used by purchasers and producers of additively manufactured UNS N07718 components to specify the requirements and ensure component properties, and by users to obtain components that will satisfy the minimum acceptance requirements. The standard covers terminology and classification as well as the requirements with respect to ordering information, manufacturing plan, feedstock, thermal processing, chemical composition, microstructure, mechanical properties, hot isostatic pressing, dimensions and permissible variations, retests, inspection, rejection, certification, product marking and packaging, maintenance of a quality program, and the significance of numerical limits.	Vol. 10.04 On-line ($43), or 2015
ASTM F3056-14	Standard Specification for Additive Manufacturing Nickel Alloy (UNS N06625) with Powder Bed Fusion	評価 金属 成形品	This specification defines the requirements for additive manufacturing of nickel alloy (UNS N06625) using full-melt powder bed fusion such as electron beam melting and laser melting. The standard may be used by purchasers and producers of additively manufactured UNS N06625 components to specify the requirements and ensure component properties, and by users to obtain components that will satisfy the minimum acceptance requirements. The standard covers terminology and classification as well as the requirements with respect to ordering information, manufacturing plan, feedstock, thermal processing, chemical composition, microstructure, mechanical properties, hot isostatic pressing, dimensions and permissible variations, retests, inspection, rejection, certification, product marking and packaging, maintenance of a quality program, and the significance of numerical limits.	Vol. 10.04 On-line ($43), or 2015

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規格番号	題名	分野	Abstract/Scope/Significance and use	Note
ASTM F3091 ASTM F3091M-14	Standard Specification for Powder Bed Fusion of Plastic Materials	評価 樹脂 成形品	This specification applies to plastic parts that are created using powder bed fusion processes, including unfilled formulations and formulations containing fillers, functional additives (for example, flame retardant), and reinforcements or combinations thereof. The requirements are intended for use by manufacturers of plastic parts using powder bed fusion and for customers procuring such parts. The specification covers process classification, ordering information, materials (material specification and virgin powder), fabrication of test specimens, and material processing. Dimensional tolerances, source inspection, retest and rejection of parts, material and process certification, certification for parts, and identification marking of product are also specified, together with part packaging and package marking. A figure presents the specifications for mechanical testing of powder bed fusion polymer parts.	Vol. 10.04 On-line ($43), or 2015
ISO/ASTM 52915-13	Standard specification for additive manufacturing file format (AMF) Version 1.1	成形用 データ 形式	ISO/ASTM 52915:2013 describes a framework for an interchange format to address the current and future needs of additive manufacturing technology. For the last three decades, the STL file format has been the industry standard for transferring information between design programs and additive manufacturing equipment. An STL file contains information only about a surface mesh and has no provisions for representing color, texture, material, substructure, and other properties of the fabricated target object. As additive manufacturing technology is quickly evolving from producing primarily single-material, homogenous shapes to producing multimaterial geometries in full color with functionally graded materials and microstructures, there is a growing need for a standard interchange file format that can support these features.	Vol. 10.04 2014
ISO/ASTM 52921-13	Standard Terminology for Additive Manufacturing- Coordinate Systems and Test Methodologies	用語 座標系 試験法	This terminology includes terms, definitions of terms, descriptions of terms, nomenclature, and acronyms associated with coordinate systems and testing methodologies for additive manufacturing (AM) technologies in an effort to standardize terminology used by AM users, producers, researchers, educators, press/media, and others, particularly when reporting results from testing of parts made on AM systems. Terms included cover definitions for machines/systems and their coordinate systems plus the location and orientation of parts. It is intended, where possible, to be compliant with ISO 841 and to clarify the specific adaptation of those principles to additive manufacturing.	Vol. 10.04 2014
ISO 17296-3:2014	Additive manufacturing -- General principles -- Part 3: Main characteristics and corresponding test methods	試験法	ISO 17296-3:2014 covers the principal requirements applied to testing of parts manufactured by additive manufacturing processes. It specifies main quality characteristics of parts, specifies appropriate test procedures, and recommends the scope and content of test and supply agreements. ISO 17296-3:2014 is aimed at machine manufacturers, feedstock suppliers, machine users, part providers, and customers to facilitate the communication on main quality characteristics. It applies wherever additive manufacturing processes are used.	On-line (CHF88)
ASTM Work Items				
ASTM WK26433	New Terminology for Directed Energy Deposition Additive Manufacturing Technologies	用語	This terminology includes terms, definitions of terms, descriptions of terms, nomenclature, and acronyms associated with directed energy deposition additive manufacturing (AM) technologies in an effort to standardize terminology used by AM users, producers, researchers, educators, press/media and others.	Draft
ASTM WK33833	New Specification for Additive Manufacturing Cobalt-28 Chromium-6 Molybdenum with Powder Bed Fusion	評価 金属 成形品	1.1 This specification covers additively manufactured CoCrMo alloy UNS R30075 components using full melt powder bed fusion such as electron beam melting and laser melting. The components produced by these processes are used typically in applications that require mechanical properties similar to machined forgings and wrought products. Components manufactured to this specification are often, but not necessarily, post processed via machining, grinding, EDM, polishing, etc. to achieve desired surface finish and critical dimensions. 1.2 This specification is intended for use of purchasers and /or producers of additively manufactured CoCrMo alloy UNS R30075 components for defining the requirements and assuring component properties. 1.3 Users are advised to use the specification as a basis for obtaining components which will meet the minimum acceptance requirements established and revised by consensus of the members of the committee. 1.4 User requirements considered more stringent may be met by the addition to the purchase order of one or more supplementary requirements, which may include, but are not limited to, those listed in supplementary section S1 through S10. 1.5 Units - The values stated in SI units are to be regarded as standard. The values given in parentheses are mathematical conversions to inch-lb units that are provided for information only and are not considered standard. Temperatures are in Celsius.	Draft

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規格番号	題名	分野	Abstract/Scope/Significance and use	Note
			This alloy is used in aerospace applications as well as for medical implants. A specification is needed in order for component manufacturers and purchasers to agree on component properties, material composition and process.	
ASTM WK37892	New Guide for General Design using Additive Manufacturing	ガイド（成形）	This guide is applicable during the design of all types of products, devices, systems, components, or parts that are to be fabricated by any type of additive manufacturing (AM) system. Note that this document is meant to serve primarily as guidance and best practices when using AM in product design. These guidelines help determine which design considerations can be utilized and are of importance.	Draft
ASTM WK38342	New Guide for Design for Additive Manufacturing	ガイド（デザイン）	This guide is applicable during the design of all types of products, devices, systems, components, or parts that are to be fabricated by any type of additive manufacturing (AM) system. This guide is meant to serve primarily as guidance and best practices when using AM in product design. These guidelines help determine which design considerations can be used in a design project or to take advantage of the capabilities of an AM process. General guidance and identification of issues are supported, but specific design solutions and process-specific or material-specific data are not supported. The intended audience comprises three populations of users: 1.1.1 Designers who are designing products to be fabricated in an AM system and their managers, 1.1.2 Students who are learning mechanical design and computer-aided design, and 1.1.3 Developers of AM design guidelines and design guidance systems.	Draft
ASTM WK40419	New Test Methods for Performance evaluation of additive manufacturing systems through measurement of a manufactured test piece.	評価法	This test method covers the general description of a benchmarking test piece along with quantitative and qualitative measurements to be taken on the benchmarking test piece to assess the performance of additive manufacturing (AM) systems. The benchmarking test piece is primarily used to quantitatively assess the geometric performance of an AM system. Additional performance characteristics that can be determined using the test piece are discussed in Annex A2 A5. Data from measurements described in this test method are used to assess the performance of an AM system, especially in comparison with similar data from other systems. Geometric performance of an AM system is the primary characterization obtained using this test method. The test piece described in this test method can act as an acceptance piece for a contract between a buyer and seller of an AM system. The test piece can also be used for periodic performance assessment of an AM system. Data from measurements described in this test method can be used to determine quantities used for machine compensation (see Annex A2 for further discussion). Non-destructive evaluation (NDE) can be performed on the benchmarking test piece to help ascertain physical properties of parts manufactured using the chosen process parameters on the AM system under investigation (see Annex A3 for further discussion). Mechanical testing specimens can be extracted from the benchmarking test piece described in this test method to help determine mechanical properties of parts manufactured using the AM system under investigation.	Draft
ASTM WK40606	New Guide for Characterizing Properties of Metal Powders Used for Additive Manufacturing	ガイド（粉末特性評価法）	This standard guide covers the metal powder that is used for powder-based additive manufacturing processes including binder jetting, directed energy deposition, and powder bed fusion. Determining the properties of the powder used in these processes is a necessary condition for developing industries confidence in powder selection and ability to produce consistent parts with known and predictable properties. The intention for this standard guide is to provide purchasers, vendors, or producers of metal powder to be used in additive manufacturing processes with a reference for existing standards or variations of existing standards that may be used to characterize properties of metal powders used for additive manufacturing processes. It will serve as a starting point for the future development of a suite of specific standard test methods that will address each individual property or property type that is important to the performance of metal-based additive manufacturing systems and the parts produced by them. While the focus of this standard is on metal powder, some of the referenced methods may also be appropriate for non-metal powders. The intention for this standard guide is to provide purchasers, vendors, or producers of metal powder to be used in additive manufacturing processes with a reference for existing standards or variations of existing standards that may be used to characterize properties of metal powders used for additive manufacturing processes.	Draft

開発 WG より提供

規格番号	題名	分野	Abstract/Scope/Significance and use	Note
ASTM WK40638	New Guide for The Roadmap of F42.05 Materials and Process Subcommittee on Additive Manufacturing	ガイド（ロードマップ）	This guide is to be updated annually and shows the status of standards that have been or are being written for additive manufacturing in the area of materials and process. Finished standards are noted by the corresponding designation. Standards in progress are noted by the work item number. Standards without either a designation or work item number do not have task group assembles and there is no current activity in F42.05 on that standard. A roadmap describing the standards that are planned and underway for additive manufacturing is essential. This standard will allow anyone interested in materials and process standards for additive manufacturing direct access to all standards that are under developments as well as a guide to those standards that are approved.	Draft
ASTM WK43112	New Guide for Evaluating Mechanical Properties of Materials Made via Additive Manufacturing Processes	ガイド（機械的性質の評価法）	This standard serves as a guide for existing standards or variations of existing standards that may be applicable to determine specific mechanical properties of materials made with an additive manufacturing process. This standard serves as a guide to existing standards that may be applicable for measuring the mechanical properties of parts made via additive manufacturing. Currently there are no AM-specific ASTM standards that provide measurement methods for the mechanical properties of AM parts. Until such AM-specific standards are developed this document will reference existing standard methods that may be applicable, and as such is useful to those who need to measure the mechanical properties of AM parts.	Draft
ASTM WK46201	New Specification for Extrusion Based Additive Manufacturing of Plastic Materials	樹脂材料規格（AM 品の押出）	This standard describes a method for defining requirements and assuring component integrity for plastic parts created using extrusion based additive manufacturing processes. Materials include unfilled, filled, special additives (e.g. flame retardants, stabilizers, etc.) and reinforced plastic materials suitable for processing into parts. Processes include all extrusion based additive manufacturing processes. 1.2 This specification is intended for use by manufacturers of plastic parts using extrusion based additive manufacturing and for customers procuring such parts. 1.3 Units - The values stated in either SI units or inch-pound units are to be regarded separately as standard. The value stated in each system may or may not be exact equivalents; therefore, each system shall be used independently of the other. Combining values from the two systems may result in non-conformance with the standard. A standard is necessary to define requirements and assure component integrity for plastic parts created using extrusion based additive manufacturing processes. This standard is intended for use by manufacturers of plastic parts using extrusion based additive manufacturing and for customers procuring such parts.	Draft
ISO drafts		分野		
ISO/DIS 17296-1	Additive manufacturing -- General principles -- Part 1: Terminology	用語	Stage 40.00 (DIS registered) DIS: Draft International Standard	Draft
ISO/DIS 17296-2	Additive manufacturing -- General principles -- Part 2: Overview of process categories and feedstock	原料とプロセス	Stage 40.00 (DIS registered) DIS: Draft International Standard	Draft

2）その他医療関係規格で、積層造形法により成形した部材に適用可能性がある規格（粉末焼結、溶接等により成形された部材やその評価法）

規格番号	題名	分野	Abstract/Scope/Significance and use	Note
ASTM F648-14	Standard Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants	材料 樹脂 粉末	This specification covers ultra-high-molecular-weight polyethylene (UHMWPE) powder and fabricated forms for use in surgical implants. UHMWPE powder shall be of virgin polymer manufactured from a homopolymer of ethylene, while the fabricated forms shall be manufactured from the same UHMWPE powder without any stabilizers or processing aids. Tests for viscosity number, elongation stress, ash content, extraneous matter, and trace elements shall be performed for UHMWPE powders, while tests for density, ash content, tensile strength, yield strength, elongation, and impact strength shall be performed for fabricated forms. All tests shall conform to the requirements specified.	Vol. 13.01 2014
ASTM F1377-13	Standard Specification for Cobalt-28Chromium-6Molybdenum Powder for Coating of Orthopedic Implants (UNS R30075)	材料 粉末	This specification covers the requirements for cobalt-28chromium-6molybdenum alloy powders for coating of orthopedic implants. This specification covers powder requirements only and does not address coating properties. Materials may be manufactured by rotating electrode process, inert gas atomization, or other methods that meet the powder requirements of this specification. The powder shall conform to chemical composition, sieve analysis, and cleanliness requirements of this specification.	Vol. 13.01 2014

開発 WG より提供

規格番号	題名	分野	Abstract/Scope/Significance and use	Note
ASTM F1580-12	Standard Specification for Titanium and Titanium-6 Aluminum-4 Vanadium Alloy Powders for Coatings of Surgical Implants	材料 粉末	This specification covers the chemical, particle size, and cleanliness requirements for unalloyed titanium and titanium-6aluminum-4vanadium alloy powders for use as coatings, formed by sintering or thermal spraying techniques, onto titanium alloy surgical implants. The powders may be manufactured by the plasma rotating electrode, inert gas atomization, or hydride-dehydride process, or other method capable of producing powder meeting the requirements of this specification. This specification addresses only the powder requirements, and not the properties of the coatings formed from them.	Vol. 13.01 2014
ASTM F1854-09	Standard Test Method for Stereological Evaluation of Porous Coatings on Medical Implants	評価 ﾎﾟｰﾗｽ	All of these test methods are recommended for elementary quantification of the morphological properties of porous coatings bonded to solid substrates. These test methods may be useful for comparative evaluations of different coatings or different lots of the same coating. With the exception of using the alternate mounting method, all the methods should be performed on the same working surfaces. The alternate mounting method can only be used for 9.2 and 9.3. A statistical estimate can be made of the distributions of the mean coating thickness and the volume percent void. No estimate can be made of the distribution of intercept lengths. There are limits to the accurate characterization of porosity, depending on spacing between the lines in the line grid (or points in the point grid) and the individual and cumulative fields used for the measurements. Increasing the size of the fields, increasing the number of fields, or decreasing the grid spacing will increase the accuracy of the measurements obtained. This method is not suitable for ceramic coatings for which accurate coating cross sections cannot be produced using metallographic techniques. This test method does not address characterization of coatings having a thickness of less than 300μm.	Vol. 13.01 2014
ASTM F2695-12	Standard Specification for Ultra-High Molecular Weight Polyethylene Powder Blended With Alpha-Tocopherol (Vitamin E) and Fabricated Forms for Surgical Implant Applications	材料 UHMW PE 樹脂	This specification covers ultra-high molecular weight polyethylene (UHMWPE) powder blended with alpha-tocopherol (vitamin E) intended for use in surgical implants. The requirements apply to alpha-tocopherol-containing UHMWPE in two forms. One is virgin polymer powder blended with alpha-tocopherol prior to consolidation. The second is any form fabricated from this blended, alpha-tocopherol-containing powder from which a finished product is subsequently produced. This specification does not apply to finished or semi-finished products that are doped with vitamin E after consolidation, or to the packaged and sterilized finished implant, or to UHMWPE materials extensively cross-linked by gamma and electron beam sources of ionizing radiation. Required material characteristics including composition, foreign matter, morphology, and mechanical characteristics are addressed by this specification.	Vol. 13.02 2013
ASTM F2885-11	Standard Specification for Metal Injection Molded Titanium-6Aluminum-4Vanadium Components for Surgical Implant Applications	材料 粉末 冶金 （MIM）	1.1 This specification covers the chemical, mechanical, and metallurgical requirements for two types of metal injection molded (MIM) titanium-6aluminum-4vanadium components to be used in the manufacture of surgical implants. 1.2 The Type 1 MIM components covered by this specification may have been densified beyond their as-sintered density by post sinter processing. 1.3 Values in either inch-pound or SI are to be regarded separately as standard. The values stated in each system may not be exact equivalents; therefore, each system shall be used independent of the other. Combining values from the two systems may result in non-conformance with the specification.	Vol. 13.02 2013
ASTM F2886-10	Standard Specification for Metal Injection Molded Cobalt-28Chromium-6Molybdenum Components for Surgical Implant Applications	材料 粉末 冶金 （MIM）	This specification covers chemical, mechanical, and metallurgical general requirements for metal injection molded (MIM) cobalt-28chromium-6molybddenum components to be used in manufacturing surgical implants. In this specification, the MIM components covered may have been densified beyond their as-sintered density by post-sinter processing. For the chemical requirements, the components supplied in this specification must conform in accordance to the chemical requirements specified herein in Table 1. The product analysis tolerances must also conform to the product tolerances presented in Table 2. The specification also enumerates the mechanical requirements for MIM components wherein the tensile properties of the MIM must conform to the mechanical properties in Table 3. The microstructural requirements and specimen preparation shall be in accordance with Guide E3 and Practice E407.	Vol. 13.02 2013
ASTM F2989-13	Standard Specification for Metal Injection Molded Unalloyed Titanium Components for Surgical Implant Applications	材料 粉末 冶金 （MIM）	1.1 This specification covers the chemical, mechanical, and metallurgical requirements for three grades of metal injection molded (MIM) unalloyed titanium components in two types to be used in the manufacture of surgical implants. 1.2 The Type 1 MIM components covered by this specification may have been densified beyond their as-sintered density by post-sinter processing. 1.3 Values in either inch-pound or SI are to be regarded separately as standard. The values stated in each system may not be exact equivalents; therefore each system shall be used independent of the other. Combining values from the two systems may result in non-conformance with the specification.	Vol. 13.02 2013

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3) 非医療向け一般材料規格で、積層造形法により成形した部材に適用可能性がある規格（残留応力の評価法等）

規格番号	題名	分野	Abstract/Scope/Significance and use	Note
ASTM E915-10	Standard Test Method for Verifying the Alignment of X-Ray Diffraction Instrumentation for Residual Stress Measurement	残留応力	This test method provides a means of verifying instrument alignment in order to quantify and minimize systematic experimental error in X-ray diffraction residual stress measurement. This method is suitable for application to conventional diffractometers or to X-ray diffraction instrumentation of either the diverging or parallel beam types. , Application of this test method requires the use of a flat specimen of stress-free material that produces diffraction in the angular region of the diffraction peak to be used for stress measurement. The specimen must be sufficiently fine-grained and isotropic so that large numbers of individual crystals contribute to the diffraction peak produced. The crystals must provide intense diffraction at all angles of tilt, ψ, which will be employed (see Note 1).	Vol. 03.01 2014

Note：

1) ASTM F2544～が掲載されている ASTM Annual Book Vol. 10.04 (2014)は発行済だが、最近制定された ASTM F2924-14 等は未収録で、On-line で購入する必要あり。

2) ASTM Annual Book Vol. 13.01 (2014)は発行済。

3) ASTM Annual Book Vol. 13.012(2014)は未発行だが、近日中に発行と思われる。

参考情報５

Custom Device Exemption

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 24, 2014

The draft of this document was issued on January 14, 2014.

See additional PRA statement in Section VIII of this guidance.

For questions regarding this document, contact the Division of Premarket and Labeling Compliance (DPLC) at the Center for Devices and Radiological Health (CDRH):

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

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to http://www.regulations.gov. Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Rm 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2013-D-1601. 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. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1820 to identify the guidance you are requesting.

Contains Nonbinding Recommendations

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Custom Device Exemption

Guidance for Industry and Food and Drug Administration Staff

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

The Food and Drug Administration (FDA) has developed this document to provide guidance to industry and FDA staff about implementation of the custom device exemption contained in Section 520(b) of the Food, Drug and Cosmetic Act (FD&C Act). The guidance provides definitions of terms used in the custom device exemption, explains how FDA interprets the "5 units per year of a particular device type" language contained in section 520(b)(2)(B) of the FD&C Act, describes what information should be submitted in a Custom Device Annual Report ("annual report"), and provides recommendations on how to submit an annual report for devices distributed under the custom device exemption.

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.

II. Background

Effective July 9, 2012, section 617 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144) required the implementation of changes to the custom device exemption contained in section 520(b) of the FD&C Act. The new provision amended an existing custom device exemption and introduced new concepts and procedures applicable to custom devices addressing, among other things:

- devices created or modified in order to comply with the order of an individual physician or dentist;[1]
- the potential for multiple units of a device type (not to exceed 5 units per year) qualifying for the custom device exemption; and
- annual reporting requirements by the manufacturer to FDA about devices manufactured and distributed under section 520(b) of the FD&C Act.

Although the revisions to the custom device exemption clarify the availability of the exemption in certain circumstances—for example, when more than one (but not greater than five) devices are manufactured per year and when modifications are made to a marketed device—the new statutory language does not create a broad, new exemption from sections 514 and 515 of the FD&C Act. Under the revised provision, as under the original custom device exemption, custom devices should represent a narrow category for which, due to the rarity of a patient's medical condition or physician's special need, compliance with premarket review requirements and performance standards under sections 514 and 515 of the FD&C Act is impractical.

Historically, practitioners and manufacturers have sought custom device exemptions for devices more properly considered under a compassionate use protocol. FDA notes that some devices deemed ineligible for custom devices status prior to FDASIA would remain ineligible under the new provision, but may qualify for compassionate use. Although a full discussion of compassionate use is outside the scope of this guidance, a short discussion of compassionate use is included in the Question and Answer section of this guidance.

III. Definitions

Device Type
A generic device type is defined as a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.[2]

Importer
"Importer" means any person who imports a device into the United States.[3]

Necessarily Deviates
"Necessarily deviates" means that a device should be sufficiently unique so that clinical investigations would be impractical and could not be performed to demonstrate conformance to applicable performance standards and/or support premarket review.[4]

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[1] For the readability of this document, the word "physician" is defined to represent "physician or dentist (or any other specially qualified person designated under regulations promulgated by the Secretary)." Section 520(b)(2)(A) of the FD&C Act.
[2] See 21 CFR 860.3(i).
[3] See, e.g., 21 CFR 806.2(f).
[4] 48 FR 248 Pages 56778, 56796, December 23, 1983.

Not Generally Available
A device that is "not generally available" is a device not generally available in finished form through labeling or advertising by the manufacturer, importer, or distributor for manufacture and/or commercial distribution in the United States and is of a type available for introduction into commercial distribution in quantities of no more than five units per year. This includes, but is not limited to, devices not addressed in electronic or hard copy literature, promotional material, or available testimonials. For example, a manufacturer could make a custom device in response to an unsolicited request by a physician who specifies unique design inputs when no similar product is commercially available in the United States and clinical investigations on such device would be impractical.

Order of a Physician
"Order of a physician" refers to the written request for a custom device made by a physician. In the case of a prescription device, this would include the written or electronic prescription.

Special Need
A "special need" is a need related to an individual physician's unique pathology or unique physiological condition.

Sufficiently Rare Condition
A "sufficiently rare condition" is a condition in a patient population in which the incidence or prevalence is so small that conducting clinical investigations on a device to treat it would be impractical.

Unique Pathology
"Unique pathology" is pathological anatomy that no other device is domestically available to treat.

Unique Physiologic Condition
A "unique physiologic condition" is a physiologic condition that no other device is domestically available to treat.

IV. No More Than Five Units Per Year of a Device Type

Under FDASIA, devices that qualify for the custom device exemption contained in section 520(b) of the FD&C Act are "limited to no more than 5 units per year of a particular device type" that otherwise meet all the requirements necessary to qualify for the custom device exemption.

FDA has applied the definition of device type to take into account multiple considerations such as anatomical location, disease state, material, technology, and indications. For example, knee replacement device systems comprise multiple device types; although used in the same anatomical location, knee systems with different technological characteristics (including materials) or used in different disease states can constitute different types of knee systems.

FDA interprets the five units in terms of five new custom device cases per year (i.e., five new ***patients*** for the patient-focused custom device or five new physicians for the physician-focused custom device, assuming all other required elements for the custom device exemption are satisfied). The five-unit limitation includes all devices of a type provided by a manufacturer to, and remaining in the possession of, the ordering physician and/or the patient.

FDA does not intend to include in the tally of five units per year any extra units produced for a unique case because of sizing concerns, so long as the ordering physician has either destroyed those devices not used for that case or they have been returned to the manufacturer and not redistributed without valid U.S. marketing authorization or for a subsequent valid custom device case. FDA expects the manufacturer to use appropriate quality system procedures to control returned product and ensure they are only redistributed under appropriate circumstance (i.e., another valid custom device case or U.S. marketing authorization). For example, if four sizes of a valid custom orthopedic implant are manufactured for a specific patient and one device is ultimately implanted into the patient, then the remaining three sizes should either be returned to the manufacturer or destroyed by the ordering physician. If these units are not returned to either the manufacturer or the ordering physician does not provide the manufacturer a statement of destruction, then FDA considers four of the five total units per year of that device type to have been used. On the other hand, if the three other units are returned to the manufacturer or the ordering physician provides the manufacturer a statement of destruction, only one of the five units per year will have been used to treat this patient, provided the returned devices are not redistributed without valid U.S. marketing authorization or for use in a subsequent valid custom device case.

The devices used in the case where a patient requires multiple devices of the same type (such as bilateral conditions) to treat multiple anatomical locations within a given reporting year will be considered one unit for purposes of tallying the five units of a device type per year, so long as those devices are ordered together and the ordering physician either destroys any unused devices or those devices are returned to the manufacturer and not redistributed without valid U.S. marketing authorization or used in a subsequent valid custom device case. For example, in the event that a patient requires valid custom bilateral joint replacement devices (such as might occur in bilateral knee replacement procedures), so long as those devices are ordered together in the same reporting year, and the ordering physician provides the manufacturer with either a statement of destruction or returns all unused product to the manufacturer, FDA will consider the multiple joint replacement devices needed to treat the bilateral patient as only one of the five allotted units per year of a device type. If the patient's multiple replacement devices are ordered during different reporting years, each treatment will contribute one unit to the tally for the reporting year in which the ordering occurs (so long as the ordering physician provides the manufacture a statement of destruction for the unused devices or returns them to the manufacturer, and the manufacturer does not redistribute without either a valid U.S. marketing authorization or for use in a subsequent valid custom device case).

V. Questions and Answers/Examples of Custom Devices

A. From which premarket and postmarket requirements is my custom device exempt ?

Under Section 520(b) of the FD&C Act, custom devices are exempt from Premarket Approval (PMA) requirements and conformance to mandatory performance standards. [5] Custom Devices are *not* exempt from any other requirements, including, but not limited to, the Quality System Regulation, including Design Controls (21 CFR Part 820); Medical Device Reporting (21 CFR Part 803); Labeling (21 CFR Part 801); Corrections and Removals (21 CFR Part 806); and Registration and Listing (21 CFR Part 807).

B. The custom device exemption describes two types of custom devices: one specific to the special needs of the physician's practice, and the other specific to the patient's unique physiological/pathology needs. Can a single custom device be unique both to a physician's practice and the patient's unique needs?

No, the custom device provision allows for development of two different categories of custom devices. One is patient-centric, and the other physician-centric; a custom device cannot be both patient- and physician-centric. A custom device made to treat a patient's sufficiently rare condition leaves a medical practice with the patient, while a custom device made to satisfy a physician's unique special need remains with that physician for use in his/her practice.

C. Can a device subject to an IDE be a custom device?

No, a device that is currently being studied or capable of study under an IDE does not meet the definition of a custom device. Additionally, the IDE is a broad exemption under which devices used in clinical investigations that meet IDE requirements are exempt from FD&C Act sections 514, 515, 502, 510, 516, 519, 510(e), 520(f) and 721. There is no reason to seek a custom device exemption for a device capable of study under an IDE, because custom devices represent a narrow category of devices used to treat sufficiently rare conditions or rare physician needs for which clinical investigations cannot be practicably conducted.

D. What is the relationship between compassionate use and a custom device?

Devices that do not meet all elements of the custom device definition described in section 520(b) of the FD&C Act may qualify, under appropriate circumstances, for compassionate use. An unapproved and uncleared medical device may be used on human subjects when its use is under clinical investigation and complies with all

[5] A device not covered by an existing marketing approval would require either a PMA or a valid exemption from the requirements to obtain PMA approval in order to be introduced into interstate commerce. Examples of potential valid exemptions or alternatives from the PMA requirement include: (1) establishing the substantial equivalence of the new device to a valid predicate device, (2) approval of an Investigational Device Exemption (IDE) or (3) meeting all custom device exemption requirements.

applicable requirements.[6] FDA recognizes there may be limited circumstances under which a health care provider may seek to use an unapproved and uncleared device to treat a patient suffering from a serious disease or condition for which no alternative therapy exists. FDA provides more information on how to request compassionate use of an unapproved device in the guidance document "Guidance on IDE Policies and Procedures" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm).

Compassionate use of an unapproved and uncleared device may occur when a device is the only option available to a patient with a serious condition. All compassionate uses require, among other things, prior FDA approval. See Section 561(b) of the FD&C Act and 21 CFR 812.35(a). Please refer to the guidance listed above for more information on compassionate use of unapproved devices.

E. Can modifications to an existing 510(k)-cleared device be made under the custom device exemption?

Modifications to a 510(k)-cleared device that maintain its original intended use and could be clinically studied do not appropriately qualify as a custom device and should be handled in accordance with 21 CFR 807.81 and the guidance document "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)" (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080235.htm) (i.e., submission of a new 510(k) application, or documentation to the design history file explaining why the change does not require a new 510(k), as appropriate). However, if an existing 510(k)-cleared device is modified to treat a unique pathology or unique physiological condition, which renders clinical study impractical, the device could potentially qualify as a custom device.

It is worth noting that FDA reviews, clears, and approves for marketing many patient-specific devices (also referred to as patient-matched devices). Patient-specific devices are, in general, ones in which ranges of different specifications have been approved or cleared to treat patient populations that can be studied clinically. Premarket submissions for such devices are sometimes referred to as "envelope" submissions because their approval or clearance covers the entire range of specifications data they contain to support. The final manufacturing of these devices can be delayed until physicians provide imaging data or other information to the manufacturer to finalize device specifications within cleared or approved ranges. As a result, such devices are specifically tailored to patients.[7] For example, a manufacturer of an ankle replacement device could submit a 510(k) to cover a range of specifications for

[6] See Section 520(g) of the FD&C Act and 21 CFR Parts 50, 56, and 812, *Investigational Device Exemptions* (IDE), includes requirements for the conduct of clinical studies on human subjects with medical devices, such as the content of the IDE application, responsibilities of sponsors and investigators, labeling, recordkeeping, and reporting to FDA.

[7] CDRH has received 510(k)s and PMA applications for patient-specific/patient-matched medical devices in a number of different product areas including but not limited to TMJ implants, dental abutments, orthopedic surgical cutting guides, orthopedic joint replacement implants, and trauma and dental bone plates.

different system components to accommodate multiple patients with different anatomical characteristics. While some in industry have sometimes colloquially referred to these devices as "customized," they *are not custom devices* meeting the FD&C Act custom device exemption requirements unless they comply with all of the criteria of section 520(b). Marketing applications are required for these device types because the devices and patient populations can be defined and studied.

F. How are revisions and servicing of existing valid custom devices included in the total of five units of a device type per year?

A device that meets all requirements of section 520(b) of the FD&C Act when initially distributed will not be counted against the five device units per year allotment if it has later been revised or serviced, *provided that* such revision or servicing is performed in furtherance of meeting the special needs of the person or physician for whom the custom device was intended before being revised and/or serviced. If you have any questions, you can contact CDRH's Office of Compliance to discuss the specifics of your situation prior to revising or servicing such device.

G. If a patient needs to undergo revision surgery to replace a component of her implant that is no longer being manufactured, is the component a custom device?

The component is only a custom device if it is designed to treat a unique pathology or physiological condition that no other device is domestically available to treat and meets all the other requirements of section 520(b). That the component is no longer being manufactured does not make the component a custom device. However, under these circumstances, a compassionate use request to allow the component to be manufactured and implanted could be submitted to FDA.

H. Are pediatric devices automatically custom devices, simply because they are for a pediatric population?

No. Pediatric patient populations may be studied just like adult populations, and, to the extent possible, they should be studied so that a device can be labeled properly. The proper labeling of a device can provide users a better understanding of the device's performance characteristics.

I. How should I label my custom device?

Custom devices remain subject to all device labeling requirements, among them requirements that the labeling bear adequate directions for use or may not be false or misleading, as well as many other labeling requirements, including those in 21 CFR 801.1. In addition, the labeling accompanying a custom device should include the following information: (1) a statement that the device is a custom device; (2) the name of the ordering physician, (3) identifying information for the patient (if applicable) whom the device is intended to treat; (4) indications for use; (5)

sterilization status; (6) relevant composition information (materials, components, etc.); and (7) storage conditions.[8]

J. Can I market my custom device to the general public?

No. A custom device is made at a physician's order on patients with a sufficiently rare condition or for a physician's special needs (e.g., unique pathology or unique physiologic condition). Section 520(b)(1)(C) specifies that, among other things, a custom device is not made generally available in finished form through labeling or advertising.

K. What are some examples of devices that are potential custom devices?[9]

A possible example of a custom device might be one manufactured for a patient with skeletal dysplasia requiring a total hip replacement procedure to treat her osteoarthritis. The patient's skeletal dysplasia could be characterized by abnormalities in the growth and/or remodeling of cartilage and bone, resulting in short stature and angular and torsional deformities of the patient's hip. In this particular case, it is possible that currently available total hip replacement devices marketed in the United States might not successfully treat the patient's unique pathological anatomy. Other elements of the custom device exemption—for example, too small a patient population to support a clinical study—would need to be met.

Another possible example of a custom device might be an artificial cervical disc replacement for reconstruction of the cervical disc following cervical discectomy to treat cervical radiculopathy in a 7'2" male patient. Under this hypothetical scenario, the osseous dimensions of this patient's cervical spine exceed those which an available artificial cervical disc available in the United States would accommodate, and the patient represents a population which, at this time, appears to be too small to support a clinical study.

An additional example of a possible custom device might be one manufactured for a toddler needing occipital condyle screws after surviving a severe car accident that left her paralyzed from the neck down and in need of instrumentation to help hold up her head. Her physician concludes that an occiput to C2 posterior cervical fusion would be best for her. In the United States, no cleared or approved screws for placement in the occipital condyle are available in the sizes needed for this pediatric patient. At this time the pediatric patient population requiring posterior occipital condyle fusion within the size range the toddler needed could be too small to support a clinical study. Because this scenario might satisfy the custom device exemption, her physician

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[8] For additional information on device labeling, refer to 21 CFR Part 801, 21 CFR 809.10, and "Guidance on Medical Device Patient Labeling" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm).

[9] This is not intended to exhaustively list devices that might satisfy the custom device exemption and represents only a subset of the information needed to meet the statutory requirements for a valid custom device. If you question whether your scenario might satisfy the custom device exemption, we encourage you to contact CDRH's Office of Compliance at customdevice@fda.hhs.gov to discuss.

should request custom occipitocervical implants for non-standard, pediatric sized screws for use in the occiput, cervical spine and upper thoracic spine of this specific patient. The multiple screws used in this procedure would be considered one unit if the physician provided the manufacturer with either a statement that the unused devices were destroyed or returned them to the manufacturer. FDA expects the manufacturer to use appropriate quality system procedures to control returned product and ensure they are only redistributed under appropriate circumstance (i.e., another valid custom device case or U.S. marketing authorization).

FDA issued a call for comments[10] on the use of custom devices in developing this guidance document. We received no examples describing a potential physician-centric custom device. Assuming all other aspects of the custom device exemption in the FD&C Act are met, a potential example of a physician-centric medical device could be one for a surgical instrument requiring premarket review that needs to be modified to accommodate a deformity of a surgeon's hand.

L. What are some examples of a device that is not a custom device?

A primary total knee replacement (TKR) patient received company X's TKR device. Later, the patient needs a revision of one side of the TKR joint replacement, which use of company X's currently legally marketed off-the-shelf component for revision surgeries could accomplish. However, the hospital where the patient's doctor practices only uses company Y's products. The doctor would like to request that a custom company Y component be made to replace the patient's failing company X component. This hypothetical situation would not satisfy the requirements for a custom device exemption because a legally marketed device is domestically available to treat the patient. [See Section 520(b)(1)(D) of the FD&C Act.] This situation may be more appropriately addressed through application of the compassionate use program in order to distribute the device in interstate commerce without a cleared or approved marketing application.

VI. Annual Report

The statutory amendments to the custom device exemption under FDASIA added a new reporting requirement; namely, that *"… the manufacturer of such [custom] device notifies the Secretary on an annual basis, in a manner to be prescribed by the Secretary, of the manufacture of such device."* See 520(b)(2)(C) of the FD&C Act. In short, the manufacturer must report to FDA annually on the custom devices it supplied. The annual report should include the number of patients who received a new device or revisions of a previous custom device. Additionally, multiple custom devices or components used in one patient should be accounted for in the annual report. As noted in Section IV of this guidance, typically only new custom devices will be counted toward the maximum allotment of five units per year of a particular device type. However, revisions to an existing custom device should be accounted for in the annual report. Furthermore, the annual report should account for the number of custom devices physicians are provided, return to the manufacturer, or destroy.

[10] See 77 FR 69488 (Monday, November 19, 2012).

The annual report should summarize the number of custom devices manufactured and distributed in the United States during a 1-year reporting period. Each annual report should cover an entire calendar year (i.e., January 1-December 31 of a given year). The first report should contain information on custom devices manufacturered e from the date of enactment of FDASIA (July 9, 2012) through the date of the first report. For all subsequent reporting periods, the report should be submitted to FDA within the first quarter of the following calendar year (i.e., no later than March 31). FDA will not enforce the annual reporting requirement until the end of the calendar year following publication of the final guidance.

A complete annual report should include all of the information set forth below. FDA can review complete annual reports more efficiently, and FDA may be less likely to request additional information if a company submits a complete annual report. The following sections provide guidance on how to submit an annual report to FDA and the content of that report for both patient-centric and physician-centric custom devices.

A. Annual Report – General Contents

The following general information should be included in both patient-centric and physician-centric annual reports.

1. Cover Letter

Your report should include a cover letter that clearly states that the reason for the submission is a "Custom Device Annual Report" in the reference line. The cover letter should contain your complete contact information (i.e., the company name, company address, company website, contact person, contact person's title, contact person's phone number, contact person's fax number, and contact person's email address). The cover letter should also clearly identify the custom devices manufactured and distributed during the reporting period, and include the signature of the contact person or other responsible party within the company. The cover letter should also specify the reporting period (i.e., the dates the reporting period begins and ends).

2. Truthful and Accurate Statement

Your report should include a signed Custom Device Annual Report Truthful and Accurate statement that indicates that the submitter is an authorized representative for the manufacturer and that all information provided in the paper and electronic copies of the Custom Device Annual Report is truthful and accurate to the best of your knowledge and that no material fact has been omitted. See Appendix II for a copy of the statement we recommend you use.

3. Other Logistical Information

Your Custom Device Annual Report should be written in English. Any material provided in a foreign language should be accompanied by an accurate and complete English translation. You should send two copies of your Custom Device Annual Report to the address below, including at least one hard copy:

Attn: Custom Device Annual Report Submission Coordinator
Division of Analysis and Program Operations
Office of Compliance
Center for Devices and Radiological Health
U.S. Food and Drug Administration
WO66, Room 2622
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Though not required for Custom Device Annual Reports, we strongly encourage you to submit one of the two required copies as an eCopy (i.e., a PDF file on a CD, DVD, or flash drive). See "eCopy Program for Medical Device Submissions: Guidance for Industry and Food and Drug Administration Staff" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf) for more information about submitting an eCopy.

B. Annual Report – Patient-Centric Custom Device Information

As described in Section V.B. of this guidance, a custom device is either patient-centric or physician-centric, but not both. In addition to the requested elements listed in Section VI.A. (above), the following elements should be provided to FDA in a Custom Device Annual Report for patient-centric devices to ensure the conditions listed in sections 520(b)(1) and 520(b)(2) are met.

1. Explanation of how the device satisfies the elements of Section 520(b) of the FD&C Act.

In your report, you should include a justification for how or why the device manufactured to treat an individual patient meets each of the following conditions contained in the FD&C Act:[11]

a) To explain how sections 520(b)(1)(B) and (b)(2)(A) are met, you should provide an explanation of why the device necessarily deviates from the premarket requirements, including treating a sufficiently rare condition, such that conducting clinical investigations on it are impractical. You may include information on the incidence or prevalence of the condition or disease the device is intended to diagnosis, treat, mitigate, prevent, or cure, or for which it is otherwise intended to affect the structure or any function of the body. References for the data provided should also be included. If the incidence or prevalence material referenced is not available in the published literature, you should include a copy of the reference in the annual report. If you believe that information on the incidence or prevalence of the condition or disease is not available, you

[11] See Section VII of this guidance document for the complete text contained in section 520(b) of the FD&C Act.

should provide an explanation why you believe the information is not available.

b) To explain how section 520(b)(1)(A) is met, you should indicate whether the device is a newly created device or modified from an existing legally marketed device in order to comply with the order of an individual physician.

c) To explain how section 520(b)(1)(C) is met, you should attest that the device is not generally available in the United States in finished form through labeling or advertising by the manufacturer, importer, or distributor for commercial distribution.

d) To explain how part of section 520(b)(1)(D) and section 520(b)(2)(B) are met, you should provide a complete description of the device, including device type (e.g., product code, as applicable), as well as the patient's unique pathology or physiological condition the device was designed to treat.

e) To show that section 520(b)(1)(D) is met, you should provide a statement that no other device is domestically available to treat the patient's unique pathology or physiological condition. You should maintain records of the evaluation that you used to determine that no other device is domestically available to treat the patient's unique pathology or physiological condition.

f) To explain how section 520(b)(1)(E)(ii) is met, you should provide a unique patient identifier for the individual patient in the physician's order.

g) To explain how section 520(b)(1)(F) is met, you should state whether the device is assembled from components or manufactured and finished on a case-by-case basis to accommodate the unique needs of individuals. Additionally, you should explain under section 520(b)(1)(G) whether the device or device components have common, standardized design characteristics, chemical and material compositions, and the same manufacturing processes as commercially distributed devices.

2. Summary of Custom Devices Shipped, Used, Returned, and Destroyed

You should provide a summary of all the custom devices the ordering physician supplied, used, returned, and destroyed during the reporting period. This includes the name or description of the device and product code (if available). This summary should also include information on the number of each type of device that was shipped, used/remaining with the patient (e.g., implanted) in new and revision patients, and the number of custom devices that were returned to the manufacturer/distributor or the ordering physician destroyed. To facilitate FDA's review of your summary report, we recommend using the format described in Table 1 of Appendix I for reporting this information.

3. Details on Custom Device Use

You should provide the following detailed information on custom devices manufactured during the reporting period.

a) Patient Information. You should indicate the total number of patients receiving custom devices. This should be broken down into patients receiving a new device and those undergoing revisions of previously existing custom devices. Additional information on the patients should also be provided, including unique patient identifiers and a description of the condition that necessitated use of a custom device.

b) Physician information. You should provide the name, address, and other contact information for the treating physician for each patient procedure.

c) Custom device or custom device components. For each custom device or device component remaining with the patient, you should provide details on each device or device component. These details should include the date of manufacture; the product name, brand name, product model number, product catalog number, or other product identifier information, and product code (if applicable).

To facilitate FDA's review of your detailed custom device report, FDA recommends the format described in Table 2 in Appendix I for presenting patient, physician, and device information.

C. Annual Report – Physician-Centric Custom Device Information

As described in Section V of this guidance, a custom device is considered to be patient-centric or physician centric, but not both. In addition to the requested elements listed in Section VI.A. (above), the following elements should be provided to FDA in a Custom Device Annual Report for a physician-centric device to ensure that the conditions listed in sections 520(b)(1) and 520(b)(2) are met.

1. Explanation of how the device satisfies the elements of Section 520(b) of the FD&C Act

In your report, you should include a justification for how or why the device manufactured meets the special needs of a physician in the course of his/her professional practice and satisfies each of the following conditions contained in the FD&C Act:[12]

a) To explain how sections 520(b)(1)(B) and (b)(2)(A) are met, you should provide an explanation of why the device necessarily deviates from the premarket requirements including addressing a sufficiently rare condition, such that conducting clinical investigations are impractical. You may include information on the incidence or prevalence of the condition

[12] See Section VII of this guidance document for the complete text contained in section 520(b) of the FD&C Act.

or disease the device is intended to diagnose, treat, mitigate, or prevent. References for the data provided should be included. If the incidence or prevalence material referenced is not available in the published literature, you should include a copy of the reference in the annual report. In addition, you should include an explanation of why conducting clinical investigations on such device would be impractical. If you believe that information on the incidence or prevalence of the condition or disease is not available, you should identify why you believe the information is not available.

b) To explain how section 520(b)(1)(A) is met, you should indicate if the device was a newly created device or modified from an existing legally marketed device in order to comply with the order of an individual physician, as well as the name of the individual doctor in the order.

c) To explain how section 520(b)(1)(C) is met, you should attest that the device is not generally available in the United States in finished form through labeling or advertising by the manufacturer, importer, or distributor for commercial distribution.

d) To explain how part of section 520(b)(1)(D) and section 520(b)(2)(B) are met, you should provide a complete description of the device,; including device type (e.g., product code, as applicable), as well as the doctor's special need that the device was designed to meet.

e) To show that sections 520(b)(1)(D) and 520(b)(1)(E)(i) are met, you should provide a statement that no other device is domestically available to address the doctor's special need in the course of conducting his/her practice. You should maintain records of the evaluation that you used to determine that no other device is domestically available to address the doctor's or dentist's special needs are met.

f) To explain how section 520(b)(1)(F) is met, you should explain whether the device was assembled from components or manufactured and finished on a case-by-case basis to accommodate the special needs of individuals described above. Additionally, per 520(b)(1)(G), you should explain whether the device or device components have common, standardized design characteristics, chemical and material compositions, and manufacturing processes as commercially distributed devices.

2. Accommodating a Physician's Special Need

You should provide an annual summary of all the custom devices a physician is supplied and/or returns or destroys to accommodate a special need. This information should include the name or description of the device and product code (if applicable). This summary should also include information on the number of each type of device that was shipped/used during the reporting period and the number of custom devices that were returned to the manufacturer/distributor or the ordering physician destroyed. To facilitate

FDA's review of your summary custom device report, we recommend you use the format described in Table 1 in Appendix I.

3. Details on Custom Device Use

You should provide the following detailed information on custom devices distributed during the reporting period:

a) Physician information. You should provide the name, address, and other contact information for the physician ordering the custom device.

b) Custom device or custom device components. You should provide information on the number of custom devices or custom device components that were shipped, sold, and returned or destroyed by the ordering physician during the reporting period. This includes the date of manufacture, the product name, brand name, product model number, product catalog number, or other product identifier information, and product code (if applicable).

To facilitate FDA's review of your detailed custom device report, FDA recommends the format described in Table 3 in Appendix I for presenting physician and device information.

D. FDA's Review of Your Annual Report

FDA's review of annual reports allows the agency to assess several important issues related to the manufacture and distribution of custom devices. These issues include the adequacy of report documentation and fulfillment of the requirements of section 520(b) of the FD&C Act. If we find that the information provided in your annual report is insufficient to allow a complete review, we may request additional information by letter, telephone, or e-mail.[13] If we only need clarification of an issue, we may communicate on such issues either via telephone or e-mail, whichever we believe will be the most efficient.

VII. Complete Text of Section 520(b) of the Food, Drug and Cosmetic Act

Section 520(b) (21 U.S.C. 360j(b)) is amended to read as follows:
(b) CUSTOM DEVICES.—
(1) IN GENERAL.—The requirements of sections 514 and 515 shall not apply to a device that—

(A) is created or modified in order to comply with the order of an individual physician or dentist (or any other specially qualified person designated under regulations promulgated by the Secretary after an opportunity for an oral hearing);

[13] Section 520(b)(2)(C) of the FD&C Act now requires that custom device manufacturers submit annual reports for all devices distributed under the custom device exemption. Without submission of the required annual report to FDA, devices distributed as "custom devices" would not be exempted from any applicable premarket requirements.

(B) in order to comply with an order described in subparagraph (A), necessarily deviates from an otherwise applicable performance standard under section 514 or requirement under section 515;
(C) is not generally available in the United States in finished form through labeling or advertising by the manufacturer, importer, or distributor for commercial distribution;
(D) is designed to treat a unique pathology or physiological condition that no other device is domestically available to treat;
(E)(i) is intended to meet the special needs of such physician or dentist (or other specially qualified person so designated) in the course of the professional practice of such physician or dentist (or other specially qualified person so designated); or (ii) is intended for use by an individual patient named in such order of such physician or dentist (or other specially qualified person so designated);
(F) is assembled from components or manufactured and finished on a case-by-case basis to accommodate the unique needs of individuals described in clause (i) or (ii) of subparagraph (E); and
(G) may have common, standardized design characteristics, chemical and material compositions, and manufacturing processes as commercially distributed devices.

(2) LIMITATIONS.—Paragraph (1) shall apply to a device only if—
(A) such device is for the purpose of treating a sufficiently rare condition, such that conducting clinical investigations on such device would be impractical;
(B) production of such device under paragraph (1) is limited to no more than 5 units per year of a particular device type, provided that such replication otherwise complies with this section; and
(C) the manufacturer of such device notifies the Secretary on an annual basis, in a manner prescribed by the Secretary, of the manufacture of such device.

(3) GUIDANCE.—Not later than 2 years after the date of enactment of this section, the Secretary shall issue final guidance on replication of multiple devices described in paragraph (2)(B).

Please see Appendix III for a flow diagram of the decision tree needed to implement the custom device provisions in the FD&C Act.

VIII. Paperwork Reduction Act of 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average one hour per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR 814, subparts B and E have been approved under OMB control number 0910-0231; the collections of information in 21 part 812 have been approved under OMB control number 0910-0078; and the collections of information in 21 part 807, subpart E have been approved under OMB control number 0910-0120.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for collection of annual reporting is 091-0767.

Appendix I
Format for Summary Data Tables

Table 1. Summary of Custom Devices Shipped, Used and Returned

Custom Device Identification	**Product Code**	**Number Shipped**	**Number of New Cases Patient-Centric or Physician-Centric (as applicable)**	**Number of Revision Cases (Patient-Centric or Physician-Centric)**	**Number Returned or Destroyed**

Table 2. Patient-Centric Devices - Summary of Patient, Physician and Device Information for Patient-Centric Devices

Patient Identifiers	**Date of manufacture**	**Description of the condition that necessitated use of a custom device and alternative treatments**	**Name and address of physician**	**Custom device or custom device components**	**Other relevant Information**
				Product name (if specified,) Brand name (if specified,) Product model number (if specified), Product catalog number (if specified,) Other product identifier information, Product code (if applicable), Material composition	

Table 3. Physician-Centric Devices - Summary of Physician and Device Information

Physician name, degree and address	**Date(s) of procedures**	**Description of special need necessitating custom device**	**Custom device name or custom device components**	**Other relevant information**
			Product name, Brand name, Product model number, Product catalog number, Other product identifier information, Product code, Product classification regulation, Material composition	

Appendix II

Custom Device Annual Report Truthful And Accurate Statement

I certify that, in my capacity as (*the position held in company*) of (company name), I believe to the best of my knowledge, that all data and information submitted in the custom device annual report are truthful and accurate and that no material fact has been omitted.

_____

(Signature)

_____

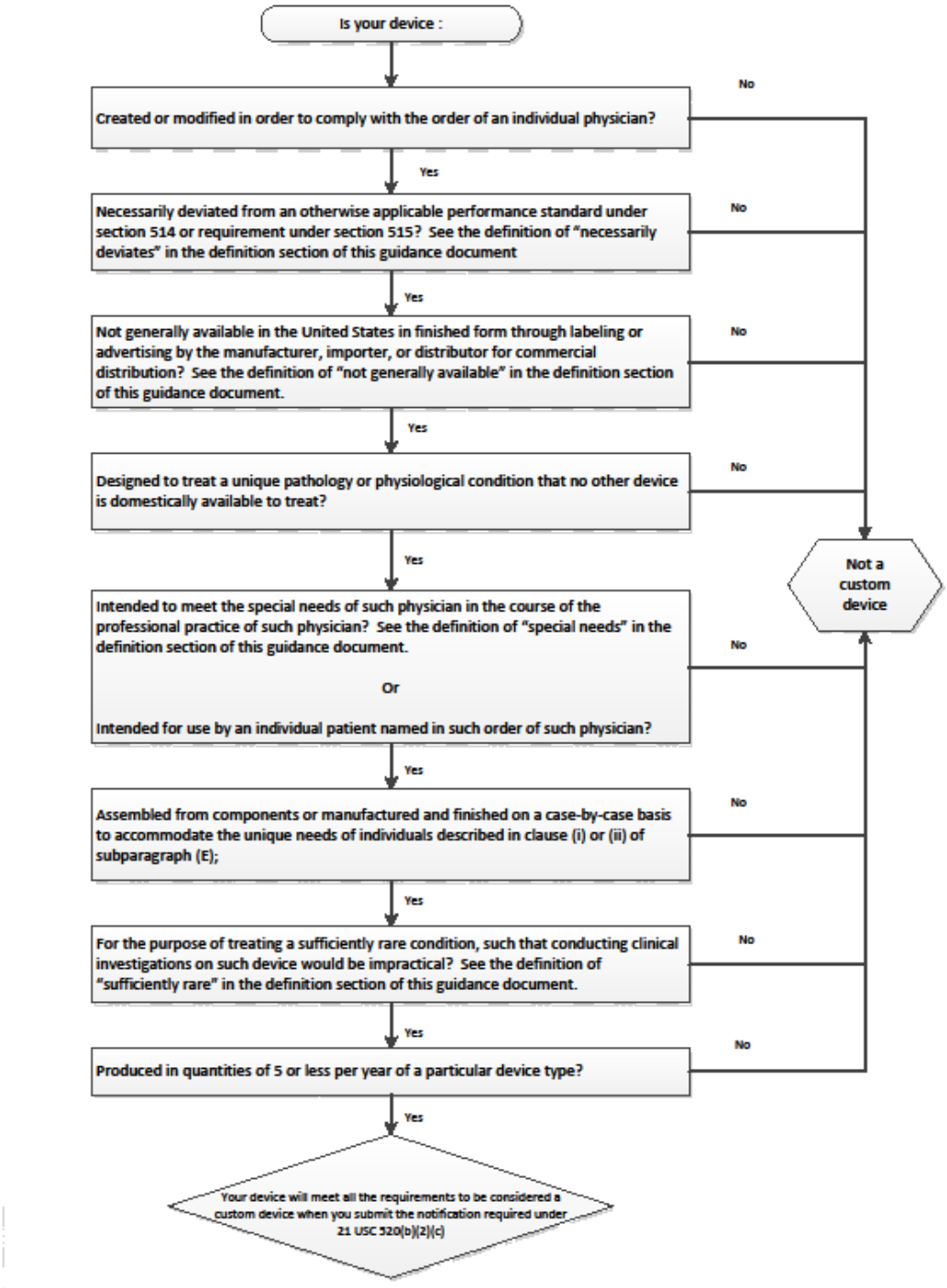
(Typed Name)

_____

(Date)

Appendix III
Custom Device Decision Tree

Note the term physician in the decision tree stands for physician, dentist or specially qualified person as noted in Section 520(b) of the FD&C Act.



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— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,

— investigation, replacement or modification of the anatomy or of a physiological process,

— control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;

(b) 'accessory' means an article which whilst not being a device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device;

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(c) '*in vitro* diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations,

derived from the human body, solely or principally for the purpose of providing information:

— concerning a physiological or pathological state, or

— concerning a congenital abnormality, or

— to determine the safety and compatibility with potential recipients, or

— to monitor therapeutic measures.

Specimen receptacles are considered to be *in vitro* diagnostic medical devices. 'Specimen receptacles' are those devices, whether vacuum-type or not, specifically intended by their manufacturers for the primary containment and preservation of specimens derived from the human body for the purpose of *in vitro* diagnostic examination.

Products for general laboratory use are not *in vitro* diagnostic medical devices unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for *in vitro* diagnostic examination;

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(d) 'custom-made device' means any device specifically made in accordance with a duly qualified medical practitioner's written prescription which gives, under his responsibility, specific design characteristics and is intended for the sole use of a particular patient.

The abovementioned prescription may also be made out by any other person authorized by virtue of his professional qualifications to do so.

Mass-produced devices which need to be adapted to meet the specific requirements of the medical practitioner or any other professional user ►M5 shall not be ◄ considered to be custom-made devices;

(e) 'device intended for clinical investigation' means any device intended for use by a duly qualified medical practitioner when conducting investigations as referred to in Section 2.1 of Annex X in an adequate human clinical environment.

For the purpose of conducting clinical investigation, any other person who, by virtue of his professional qualifications, is authorized to carry out such investigation shall be accepted as equivalent to a duly qualified medical practitioner;

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6. Where a device is intended by the manufacturer to be used in accordance with both the provisions on personal protective equipment in Council Directive 89/686/EEC [1] and this Directive, the relevant basic health and safety requirements of Directive 89/686/EEC shall also be fulfilled.

7. This Directive is a specific Directive within the meaning of Article 1(4) of Directive 2004/108/EC of the European Parliament and of the Council [2].

8. This Directive shall not affect the application of Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionising radiation [3], nor of Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionising radiation in relation to medical exposure [4].

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Article 2

Placing on the market and putting into service

Member States shall take all necessary steps to ensure that devices may be placed on the market and/or put into service only if they comply with the requirements laid down in this Directive when duly supplied and properly installed, maintained and used in accordance with their intended purpose.

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Article 3

Essential requirements

The devices must meet the essential requirements set out in Annex I which apply to them, taking account of the intended purpose of the devices concerned.

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Where a relevant hazard exists, devices which are also machinery within the meaning of Article 2(a) of Directive 2006/42/EC of the European Parliament and of the Council of 17 May 2006 on machinery [5] shall also meet the essential health and safety requirements set out in Annex I to that Directive to the extent to which those essential health and safety requirements are more specific than the essential requirements set out in Annex I to this Directive.

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Article 4

Free movement, devices intended for special purposes

1. Member States shall not create any obstacle to the placing on the market or the putting into service within their territory of devices bearing the CE marking provided for in Article 17 which indicate

(1) Council Directive 89/686/EEC of 21 December 1989 on the approximation of the laws of the Member States relating to personal protective equipment (OJ L 399, 30.12.1989, p. 18). Directive as last amended by Regulation (EC) No 1882/2003 of the European Parliament and of the Council (OJ L 284, 31.10.2003, p. 1).

(2) Directive 2004/108/EC of the European Parliament and of the Council of 15 December 2004 on the approximation of the laws of the Member States relating to electromagnetic compatibility (OJ L 390, 31.12.2004, p. 24).

(3) OJ L 159, 29.6.1996, p. 1.

(4) OJ L 180, 9.7.1997, p. 22.

(5) OJ L 157, 9.6.2006, p. 24.

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that they have been the subject of an assessment of their conformity in accordance with the provisions of Article 11.

2. Member States shall not create any obstacle to:

— devices intended for clinical investigation being made available to medical practitioners or authorized persons for that purpose if they meet the conditions laid down in Article 15 and in Annex VIII,

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— custom-made devices being placed on the market and put into service if they meet the conditions laid down in Article 11 in combination with Annex VIII; Class IIa, IIb and III devices shall be accompanied by the statement referred to in Annex VIII, which shall be available to the particular patient identified by name, an acronym or a numerical code.

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These devices shall not bear the CE marking.

3. At trade fairs, exhibitions, demonstrations, etc. Member States shall not create any obstacle to the showing of devices which do not conform to this Directive, provided that a visible sign clearly indicates that such devices cannot be marketed or put into service until they have been made to comply.

4. Member States may require the information, which must be made available to the user and the patient in accordance with Annex I, point 13, to be in their national language(s) or in another Community language, when a device reaches the final user, regardless of whether it is for professional or other use.

5. Where the devices are subject to other Directives concerning other aspects and which also provide for the affixing of the CE marking, the latter shall indicate that the devices also fulfil the provisions of the other Directives.

However, should one or more of these directives allow the manufacturer, during a transitional period, to choose which arrangements to apply, the CE marking shall indicate that the devices fulfil the provisions only of those directives applied by the manufacturer. In this case, the particulars of these directives, as published in the *Official Journal of the European Communities*, must be given in the documents, notices or instructions required by the directives and accompanying such devices.

Article 5

Reference to standards

1. Member States shall presume compliance with the essential requirements referred to in Article 3 in respect of devices which are in conformity with the relevant national standards adopted pursuant to the harmonized standards the references of which have been publishes in the *Official Journal of the European Communities*; Member States shall publish the references of such national standards.

2. For the purposes of this Directive, reference to harmonized standards also includes the monographs of the European *Pharmacopoeia* notably on surgical sutures and on interaction between medicinal products and materials used in devices containing such medicinal products, the references of which have been published in the *Official Journal of the European Communities*.

3. If a Member State or the Commission considers that the harmonized standards do not entirely meet the essential requirements referred to in Article 3, the measures to be taken by the Member States with regard to these standards and the publication referred to in

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(a) the procedure relating to the EC verification set out in Annex IV;

or

(b) the procedure relating to the EC declaration of conformity set out in Annex V (production quality assurance);

or

(c) the procedure relating to the EC declaration of conformity set out in Annex VI (product quality assurance).

Instead of applying these procedures, the manufacturer may also follow the procedure referred to in paragraph 3 (a).

3. In the case of devices falling within Class IIb, other than devices which are custom-made or intended for clinical investigations, the manufacturer shall, in order to affix the CE marking, either:

(a) follow the procedure relating to the EC declaration of conformity set out in Annex II (full quality assurance); in this case, point 4 of Annex II is not applicable; or

(b) follow the procedure relating to the EC type-examination set out in Annex III, coupled with:

(i) the procedure relating to the EC verification set out in Annex IV;

or

(ii) the procedure relating to the EC declaration of conformity set out in Annex V (production quality assurance);

or

(iii) the procedure relating to the EC declaration of conformity set out in Annex VI (product quality assurance).

4. The Commission shall, no later than five years from the date of implementation of this Directive, submit a report to the Council on the operation of the provisions referred to in Article 10 (1), Article 15 (1), in particular in respect of Class I and Class IIa devices, and on the operation of the provisions referred to in Annex II, Section 4.3 second and third subparagraphs and in Annex III, Section 5 second and third subparagraphs to this Directive, accompanied, if necessary, by appropriate proposals.

5. In the case of devices falling within Class I, other than devices which are custom-made or intended for clinical investigations, the manufacturer shall, in order to affix the CE marking, follow the procedure referred to in Annex VII and draw up the EC declaration of conformity required before placing the device on the market.

6. In the case of custom-made devices, the manufacturer shall follow the procedure referred to in Annex VIII and draw up the statement set out in that Annex before placing each device on the market.

Member States may require that the manufacturer shall submit to the competent authority a list of such devices which have been put into service in their territory.

7. During the conformity assessment procedure for a device, the manufacturer and/or the notified body shall take account of the results of any assessment and verification operations which, where appropriate, have been carried out in accordance with this Directive at an intermediate stage of manufacture.

8. The manufacturer may instruct his authorized representative ►M5 ———— ◄ to initiate the procedures provided for in Annexes III, IV, VII and VIII.

9. Where the conformity assessment procedure involves the intervention of a notified body, the manufacturer, or his authorized repre-

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ANNEX VIII

STATEMENT CONCERNING DEVICES FOR SPECIAL PURPOSES

1. For custom-made devices or for devices intended for clinical investigations the manufacturer or his authorized representative ►M5 ——————— ◄ must draw up the statement containing the information stipulated in Section 2.

2. The statement must contain the following information:

2.1. for custom-made devices:

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— the name and address of the manufacturer,

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— data allowing identification of the device in question,

— a statement that the device is intended for exclusive use by a particular patient, together with the name of the patient,

— the name of the medical practitioner or other authorized person who made out the prescription and, where applicable, the name of the clinic concerned,

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— the specific characteristics of the product as indicated by the prescription,

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— a statement that the device in question conforms to the essential requirements set out in Annex I and, where applicable, indicating which essential requirements have not been fully met, together with the grounds;

2.2. for devices intended for the clinical investigations covered by Annex X:

— data allowing identification of the device in question,

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— the clinical investigation plan,

— the investigator's brochure,

— the confirmation of insurance of subjects,

— the documents used to obtain informed consent,

— a statement indicating whether or not the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 7.4 of Annex I,

— a statement indicating whether or not the device is manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC,

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— the opinion of the ethics committee concerned and details of the aspects covered by its opinion,

— the name of the medical practitioner or other authorized person and of the institution responsible for the investigations,

— the place, starting date and scheduled duration for the investigations,

— a statement that the device in question conforms to the essential requirements apart from the aspects covered by the investigations and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

3. The manufacturer must also undertake to keep available for the competent national authorities:

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3.1. For custom-made devices, documentation, indicating manufacturing site(s) and allowing an understanding of the design, manufacture and performances of the product, including the expected performances, so as to allow assessment of conformity with the requirements of this Directive.

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The manufacturer must take all the measures necessary to ensure that the manufacturing process produces products which are manufactured in accordance with the documentation mentioned in the first paragraph;

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3.2. For devices intended for clinical investigations, the documentation must contain:

— a general description of the product and its intended use,

— design drawings, methods of manufacture envisaged, in particular as regards sterilisation, and diagrams of components, sub-assemblies, circuits, etc.,

— the descriptions and explanations necessary to understand the above-mentioned drawings and diagrams and the operation of the product,

— the results of the risk analysis and a list of the standards referred to in Article 5, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of this Directive if the standards referred to in Article 5 have not been applied,

— if the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 7.4 of Annex I, the data on the tests conducted in this connection which are required to assess the safety, quality and usefulness of that substance or human blood derivative, taking account of the intended purpose of the device,

— if the device is manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC, the risk management measures in this connection which have been applied to reduce the risk of infection,

— the results of the design calculations, and of the inspections and technical tests carried out, etc.

The manufacturer must take all the measures necessary to ensure that the manufacturing process produces products which are manufactured in accordance with the documentation referred to in the first paragraph of this Section.

The manufacturer must authorise the assessment, or audit where necessary, of the effectiveness of these measures.

4. The information contained in the declarations concerned by this Annex shall be kept for a period of time of at least five years. In the case of implantable devices the period shall be at least 15 years.

5. For custom-made devices, the manufacturer must undertake to review and document experience gained in the post-production phase, including the provisions referred to in Annex X, and to implement appropriate means to apply any necessary corrective action. This undertaking must include an obligation for the manufacturer to notify the competent authorities of the following incidents immediately on learning of them and the relevant corrective actions:

(i) any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health;

(ii) any technical or medical reason connected with the characteristics or performance of a device for the reasons referred to in subparagraph (i) leading to systematic recall of devices of the same type by the manufacturer.

instructions for use. Moreover, the Commission should engage in further analysis in order to see if additional measures are appropriate to ensure a high level of protection for patients.

(8) In the light of technical innovation and the development of initiatives at the international level it is necessary to enhance the provisions on clinical evaluation, including clarification that clinical data is generally required for all devices regardless of classification and the possibility to centralise data on clinical investigations in the European databank.

(9) In order to provide clearer evidence of the compliance of custom-made device manufacturers, an explicit requirement for a post market production review system involving incident reporting to authorities should be introduced, as is already in place for other devices, and to enhance patient information, a requirement should be introduced that the 'Statement' under Annex VIII to Directive 93/42/EEC should be available to the patient and that it should contain the name of the manufacturer.

(10) In the light of technical progress in information technology and medical devices, a process should be provided to allow information supplied by the manufacturer to be available by other means.

(11) Manufacturers of Class I sterile and/or measuring medical devices should be given the option of using the full quality assurance conformity assessment module in order to provide them with more flexibility in the choice of compliance modules.

(12) In order to support market surveillance activities by Member States it is necessary and appropriate, in the case of implantable devices, to increase the time period for the retention of documents for administrative purposes to at least 15 years.

(13) For the appropriate and efficient functioning of Directive 93/42/EEC as regards regulatory advice on classification issues arising at national level, in particular on whether or not a product falls under the definition of a medical device, it is in the interest of national market surveillance and the health and safety of humans to establish a procedure for decisions on whether or not a product falls under the medical device definition.

(14) To ensure that, where a manufacturer does not have a registered place of business in the Community, authorities have a single individual person authorised by the manufacturer whom they can address in matters relating to the compliance of the devices with the Directives it is necessary to introduce an obligation for such manufacturers to designate an authorised representative for a device. This designation should be effective at least for all devices of the same model.

(15) To further ensure public health and safety it is necessary to provide for a more consistent application of the provisions on health protection measures. Particular care should be taken to ensure that, when in use, the products do not endanger patients' health or safety.

(16) In support of transparency in Community legislation, certain information related to medical devices and their conformity with Directive 93/42/EEC, in particular information on registration, on vigilance reports and on certificates, should be available to any interested party and the general public.

(17) To better coordinate the application and efficiency of national resources when applied to issues related to Directive 93/42/EEC, the Member States should cooperate with each other and at international level.

(18) As design for patient safety initiatives play an increasing role in public health policy, it is necessary to expressly set out the need to consider ergonomic design in the essential requirements. In addition the level of training and knowledge of the user, such as in the case of a lay user, should be further emphasised within the essential requirements. The manufacturer should place particular emphasis on the consequences of misuse of the product and its adverse effects on the human body.

(19) In the light of experience gained regarding activities of both the notified bodies and the authorities in the assessment of devices which require intervention of the appropriate authorities for medicines and human blood derivatives their duties and tasks should be clarified.

(20) Taking account of the growing importance of software in the field of medical devices, be it as stand alone or as software incorporated in a device, validation of software in accordance with the state of the art should be an essential requirement.

(21) In the light of the increased use of third Parties to carry out the design and manufacture of devices on behalf of the manufacturer, it is important that the manufacturer demonstrates that he applies adequate controls to the third party to continue to ensure the efficient operating of the quality system.

(22) The classification rules are based on the vulnerability of the human body taking account of the potential risks associated with the technical design and manufacture of the devices. Explicit prior authorisation with regard to conformity, including an assessment of the design documentation, is required for Class III devices to be placed on the market. In performing its duties under the quality assurance and verification conformity assessment modules for all other classes of devices, it is essential and necessary for a notified body, in order to be assured of the

manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,

— investigation, replacement or modification of the anatomy or of a physiological process,

— control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;'

(ii) points (d), (e) and (f) shall be replaced by the following:

'(d) "custom-made device" means any device specifically made in accordance with a duly qualified medical practitioner's written prescription which gives, under his responsibility, specific design characteristics and is intended for the sole use of a particular patient. Mass-produced devices which need to be adapted to meet the specific requirements of the medical practitioner or any other professional user shall not be considered to be custom-made devices;

(e) "device intended for clinical investigation" means any device intended for use by a duly qualified medical practitioner when conducting clinical investigations as referred to in Section 2.1 of Annex 7 in an adequate human clinical environment.

For the purpose of conducting clinical investigation, any other person who, by virtue of his professional qualifications, is authorised to carry out such investigation shall be accepted as equivalent to a duly qualified medical practitioner;

(f) "intended purpose" means the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in promotional material;'

(iii) the following points shall be added:

'(j) "authorised representative" means any natural or legal person established in the Community who, explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the Community instead of the manufacturer with regard to the latter's obligations under this Directive;

(k) "clinical data" means the safety and/or performance information that is generated from the use of a device. Clinical data are sourced from:

— clinical investigation(s) of the device concerned, or

— clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated, or

— published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.';

(b) paragraph 3 shall be replaced by the following:

'3. Where an active implantable medical device is intended to administer a substance defined as a medicinal product within the meaning of Article 1 of Directive 2001/83/EC (*), that device shall be governed by this Directive, without prejudice to the provisions of Directive 2001/83/EC with regard to the medicinal product.

(*) OJ L 311, 28.11.2001, p. 67. Directive as last amended by Regulation (EC) No 1901/2006 (OJ L 378, 27.12.2006, p. 1)'

(c) paragraph 4 shall be replaced by the following:

'4. Where an active implantable medical device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the

human body with action that is ancillary to that of the device, that device shall be evaluated and authorised in accordance with this Directive.';

(d) the following paragraph shall be inserted:

'4a. Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product constituent or a medicinal product derived from human blood or human plasma within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the human body with action that is ancillary to that of the device, hereinafter referred to as a "human blood derivative", that device shall be assessed and authorised in accordance with this Directive.';

(e) paragraph 5 shall be replaced by the following:

'5. This Directive constitutes a specific Directive within the meaning of Article 1(4) of Directive 2004/108/EC (*).

(*) Directive 2004/108/EC of the European Parliament and of the Council of 15 December 2004 on the approximation of the laws of the Member States relating to electromagnetic compatibility (OJ L 390, 31.12.2004, p. 24).';

(f) the following paragraph shall be added:

'6. This Directive shall not apply to:

(a) medicinal products covered by Directive 2001/83/EC. In deciding whether a product falls under that Directive or this Directive, particular account shall be taken of the principal mode of action of the product;

(b) human blood, blood products, plasma or blood cells of human origin or to devices which incorporate at the time of placing on the market such blood products, plasma or cells with the exception of devices referred to in paragraph 4a;

(c) transplants or tissues or cells of human origin or to products incorporating or derived from tissues or cells of human origin, with the exception of devices referred to in paragraph 4a;

(d) transplants or tissues or cells of animal origin, unless a device is manufactured utilising animal tissue which is rendered non-viable or non-viable products derived from animal tissue.';

2. Article 2 shall be replaced by the following:

'Article 2

Member States shall take all necessary steps to ensure that the devices may be placed on the market and/or put into service only if they comply with the requirements laid down in this Directive when duly supplied, properly implanted and/or properly installed, maintained and used in accordance with their intended purposes.';

3. Article 3 shall be replaced by the following:

'Article 3

The active implantable medical devices referred to in Article 1(2)(c), (d) and (e), hereinafter referred to as "devices", shall satisfy the essential requirements set out in Annex 1 which apply to them, account being taken of the intended purpose of the devices concerned.

Where a relevant hazard exists, devices which are also machinery within the meaning of Article 2(a) of Directive 2006/42/EC of the European Parliament and of the Council of 17 May 2006 on machinery (*) shall also meet the essential health and safety requirements set out in Annex I to that Directive to the extent to which those essential health and safety requirements are more specific than the essential requirements set out in Annex 1 to this Directive.

(*) OJ L 157, 9.6.2006, p. 24.';

4. in Article 4, paragraphs 1, 2 and 3 shall be replaced by the following:

'1. Member States shall not create any obstacle to the placing on the market or the putting into service within their territory of devices complying with the provisions of this Directive and bearing the CE marking provided for in Article 12, which indicates that they have been the subject of an assessment of their conformity in accordance with Article 9.

2. Member States shall not create any obstacles to:

— devices intended for clinical investigations being made available to duly qualified medical practitioners or authorised persons for that purpose if they satisfy the conditions laid down in Article 10 and in Annex 6,

— custom-made devices being placed on the market and put into service if they satisfy the conditions laid down in Annex 6 and are accompanied by the statement, which shall be available to the particular identified patient, referred to in that Annex.

These devices shall not bear the CE marking.

89/686/EEC (*) and this Directive, the relevant basic health and safety requirements of Directive 89/686/EEC shall also be fulfilled.

(*) Council Directive 89/686/EEC of 21 December 1989 on the approximation of the laws of the Member States relating to personal protective equipment (OJ L 399, 30.12.1989, p. 18). Directive as last amended by Regulation (EC) No 1882/2003 of the European Parliament and of the Council (OJ L 284, 31.10.2003, p. 1).'

(g) paragraphs 7 and 8 shall be replaced by the following:

'7. This Directive is a specific Directive within the meaning of Article 1(4) of Directive 2004/108/EC of the European Parliament and of the Council (*).

8. This Directive shall not affect the application of Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionising radiation (**), nor of Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionising radiation in relation to medical exposure (***).

(*) Directive 2004/108/EC of the European Parliament and of the Council of 15 December 2004 on the approximation of the laws of the Member States relating to electromagnetic compatibility (OJ L 390, 31.12.2004, p. 24).
(**) OJ L 159, 29.6.1996, p. 1.
(***) OJ L 180, 9.7.1997, p. 22.'

2. in Article 3 the following paragraph shall be added:

'Where a relevant hazard exists, devices which are also machinery within the meaning of Article 2(a) of Directive 2006/42/EC of the European Parliament and of the Council of 17 May 2006 on machinery (*) shall also meet the essential health and safety requirements set out in Annex I to that Directive to the extent to which those essential health and safety requirements are more specific than the essential requirements set out in Annex I to this Directive.

(*) OJ L 157, 9.6.2006, p. 24.'

3. the second indent of Article 4(2) shall be replaced by the following:

'— custom-made devices being placed on the market and put into service if they meet the conditions laid down in Article 11 in combination with Annex VIII; Class IIa, IIb and III devices shall be accompanied by the statement referred to in Annex VIII, which shall be available to the particular patient identified by name, an acronym or a numerical code.';

4. in Article 6(1) the reference '83/189/EEC' shall be replaced by the reference '98/34/EC (*)

(*) Directive 98/34/EC of the European Parliament and of the Council of 22 June 1998 laying down a procedure for the provision of information in the field of technical standards and regulations and of rules on Information Society services (OJ L 204, 21.7.1998, p. 37). Directive as last amended by the 2003 Act of Accession.'

5. Article 7 shall be replaced by the following:

'Article 7

1. The Commission shall be assisted by the Committee set up by Article 6(2) of Directive 90/385/EEC, hereinafter referred to as "the Committee".

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. Where reference is made to this paragraph, Article 5a (1) to (4) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

4. Where reference is made to this paragraph, Article 5a (1), (2), (4) and (6) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.';

6. In Article 8 paragraph 2 shall be replaced by the following:

'2. The Commission shall enter into consultation with the Parties concerned as soon as possible. Where, after such consultation, the Commission finds that:

(a) the measures are justified:

(i) it shall immediately so inform the Member State which took the measures and the other Member States. Where the decision referred to in paragraph 1 is attributed to shortcomings in the standards, the Commission shall, after consulting the Parties concerned, bring the matter before the Committee referred to in Article 6(1) within two months if the Member State which has taken the decision intends to maintain it and shall initiate the advisory procedure referred to in Article 6(2);

(ii) when necessary in the interests of public health, appropriate measures designed to amend non-essential elements of this Directive relating to withdrawal from the market of devices referred to in paragraph 1 or to prohibition or restriction of their placement on the market or being put into service or to introduction of particular requirements in order for such products to be put on the market, shall be adopted in

12. Article 13 shall be replaced by the following:

'Article 13

Decisions with regard to classification and derogation clause

1. A Member State shall submit a duly substantiated request to the Commission and ask it to take the necessary measures in the following situations:

(a) that Member State considers that the application of the classification rules set out in Annex IX requires a decision with regard to the classification of a given device or category of devices;

(b) that Member State considers that a given device or family of devices should, by way of derogation from the provisions of Annex IX, be classified in another class;

(c) that Member State considers that the conformity of a device or family of devices should, by way of derogation from Article 11, be established by applying solely one of the given procedures chosen from among those referred to in Article 11;

(d) that Member State considers that a decision is required as to whether a particular product or product group falls within one of the definitions in Article 1(2)(a) to (e).

The measures referred to in the first subparagraph of this paragraph shall, as appropriate, be adopted in accordance with the procedure referred to in Article 7(2).

2. The Commission shall inform the Member States of the measures taken.';

13. Article 14 shall be amended as follows:

(a) in the second subparagraph of paragraph 1, the words 'Classes IIb and III' shall be replaced by the words 'Classes IIa, IIb and III';

(b) paragraph 2 shall be replaced by the following:

'2. Where a manufacturer who places a device on the market under his own name does not have a registered place of business in a Member State, he shall designate a single authorised representative in the European Union. For devices referred to in the first subparagraph of paragraph 1, the authorised representative shall inform the competent authority of the Member State in which he has his registered place of business of the details referred to in paragraph 1.';

(c) paragraph 3 shall be replaced by the following:

'3. The Member States shall on request inform the other Member States and the Commission of the details referred to in the first subparagraph of paragraph 1 given by the manufacturer or authorised representative.';

14. Article 14a shall be amended as follows:

(a) the second subparagraph of paragraph 1 shall be amended as follows:

(i) point (a) shall be replaced by the following:

'(a) data relating to registration of manufacturers and authorised representatives and devices in accordance with Article 14 excluding data related to custom-made devices;';

(ii) the following point shall be added:

'(d) data relating to clinical investigations referred to in Article 15;';

(b) paragraph 3 shall be replaced by the following:

'3. The measures necessary for the implementation of paragraphs 1 and 2 of this Article, in particular paragraph 1(d), shall be adopted in accordance with the regulatory procedure referred to in Article 7(2).'

(c) the following paragraph shall be added:

'4. The provisions of this Article shall be implemented no later than 5 September 2012. The Commission shall, no later than 11 October 2012, evaluate the operational functioning and the added value of the databank. On the basis of this evaluation, the Commission shall, if appropriate, present proposals to the European Parliament and the Council or present draft measures in accordance with paragraph 3.';

15. Article 14b shall be replaced by the following:

'Article 14b

Particular health monitoring measures

Where a Member State considers, in relation to a given product or group of products, that, in order to ensure protection of health and safety and/or to ensure that public health requirements are observed, such products should be withdrawn from the market, or their placing on the market and putting into service should be prohibited, restricted or subjected to particular requirements, it may take any necessary and justified transitional measures.

The Member State shall then inform the Commission and all other Member States, giving the reasons for its decision.

The Commission shall, whenever possible, consult the interested Parties and the Member States.

The Commission shall adopt its opinion, indicating whether the national measures are justified or not. The Commission shall inform all the Member States and the consulted interested Parties thereof.

— the investigator's brochure,

— the confirmation of insurance of subjects,

— the documents used to obtain informed consent,

— a statement indicating whether or not the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 10 of Annex 1,

— the opinion of the ethics committee concerned and details of the aspects covered by its opinion,

— the name of the duly qualified medical practitioner or other authorised person and of the institution responsible for the investigations,

— the place, date of commencement and duration scheduled for the investigations,

— a statement affirming that the device in question complies with the essential requirements apart from the aspects constituting the object of the investigations and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.';

(c) in Section 3.1, the first paragraph shall be replaced by the following:

'For custom-made devices, documentation, indicating manufacturing site(s) and enabling the design, manufacture and performances of the product, including the expected performances, to be understood, so as to allow conformity with the requirements of this Directive to be assessed.';

(d) in Section 3.2, the first paragraph shall be amended as follows:

(i) the first indent shall be replaced by the following:

'— a general description of the product and its intended use,';

(ii) in the fourth indent, the words 'a list of the standards' shall be replaced by the words 'the results of the risk analysis and a list of the standards';

(iii) the following indent shall be inserted after the fourth indent:

'— if the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 10 of Annex 1, the data on the tests conducted in this connection which are required to assess the safety, quality and usefulness of that substance, or human blood derivative, taking account of the intended purpose of the device,';

(e) the following two sections shall be added:

'4. The information included in the declarations covered by this Annex shall be kept for a period of at least 15 years from the date of manufacture of the last product.

5. For custom-made devices, the manufacturer must undertake to review and to document experience gained in the post-production phase, including the provisions referred to in Annex 7, and to implement appropriate means to apply any necessary corrective action. This undertaking must include an obligation for the manufacturer to notify the competent authorities of the following incidents immediately on learning of them and the relevant corrective actions:

(i) any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health;

(ii) any technical or medical reason connected with the characteristics or performance of a device for the reasons referred to in point (i) leading to systematic recall of devices of the same type by the manufacturer.';

(c) in Section 4, the introductory part shall be replaced by the following:

'4. The manufacturer shall institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase, including the provisions referred to in Annex X, and to implement appropriate means to apply any necessary corrective actions, taking account of the nature and risks in relation to the product. He shall notify the competent authorities of the following incidents immediately on learning of them:';

(d) in Section 5, the words 'Annex IV, V or VI' shall be replaced by the words 'Annex II, IV, V or VI';

8. Annex VIII shall be amended as follows:

(a) in Section 1, the words 'established in the Community' shall be deleted;

(b) Section 2.1 shall be amended as follows:

(i) the following indent shall be inserted after the introductory phrase:

'— the name and address of the manufacturer,';

(ii) the fourth indent shall be replaced by the following:

'— the specific characteristics of the product as indicated by the prescription,';

(c) Section 2.2 shall be amended as follows:

(i) the second indent shall be replaced by the following:

'— the clinical investigation plan,';

(ii) the following indents shall be inserted after the second indent:

'— the investigator's brochure,

— the confirmation of insurance of subjects,

— the documents used to obtain informed consent,

— a statement indicating whether or not the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 7.4 of Annex I,

— a statement indicating whether or not the device is manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC,';

(d) in Section 3.1, the first paragraph shall be replaced by the following:

'3.1. For custom-made devices, documentation, indicating manufacturing site(s) and allowing an understanding of the design, manufacture and performances of the product, including the expected performances, so as to allow assessment of conformity with the requirements of this Directive.';

(e) Section 3.2 shall be replaced by the following:

'3.2. For devices intended for clinical investigations, the documentation must contain:

— a general description of the product and its intended use,

— design drawings, methods of manufacture envisaged, in particular as regards sterilisation, and diagrams of components, sub-assemblies, circuits, etc.,

— the descriptions and explanations necessary to understand the abovementioned drawings and diagrams and the operation of the product,

— the results of the risk analysis and a list of the standards referred to in Article 5, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of this Directive if the standards referred to in Article 5 have not been applied,

— if the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 7.4 of Annex I, the data on the tests conducted in this connection which are required to assess the safety, quality and usefulness of that substance or human blood derivative, taking account of the intended purpose of the device,

— if the device is manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC, the risk management measures in this connection which have been applied to reduce the risk of infection,

— the results of the design calculations, and of the inspections and technical tests carried out, etc.

The manufacturer must take all the measures necessary to ensure that the manufacturing process produces products which are manufactured in accordance with the documentation referred to in the first paragraph of this Section.

The manufacturer must authorise the assessment, or audit where necessary, of the effectiveness of these measures.';

(f) Section 4 shall be replaced by the following:

'4. The information contained in the declarations concerned by this Annex shall be kept for a period of time of at least five years. In the case of implantable devices the period shall be at least 15 years.';

(g) the following section shall be added:

'5. For custom-made devices, the manufacturer must undertake to review and document experience gained in the post-production phase, including the provisions referred to in Annex X, and to implement appropriate means to apply any necessary corrective action. This undertaking must include an obligation for the manufacturer to notify the competent authorities of the following incidents immediately on learning of them and the relevant corrective actions:

(i) any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health;

(ii) any technical or medical reason connected with the characteristics or performance of a device for the reasons referred to in subparagraph (i) leading to systematic recall of devices of the same type by the manufacturer.';

9. Annex IX shall be amended as follows:

(a) Chapter I shall be amended as follows:

(i) in Section 1.4, the following sentence shall be added:

'Stand alone software is considered to be an active medical device.';

(ii) Section 1.7 shall be replaced by the following:

'1.7. **Central circulatory system**

For the purposes of this Directive, "central circulatory system" means the following vessels:

arteriae pulmonales, aorta ascendens, arcus aorta, aorta descendens to the bifurcatio aortae, arteriae coronariae, arteria carotis communis, arteria carotis externa, arteria carotis interna, arteriae cerebrales, truncus brachiocephalicus, venae cordis, venae pulmonales, vena cava superior, vena cava inferior.';