平成 22 年度経済産業省委託事業

平成２２年度戦略的技術開発委託費
医療機器開発ガイドライン策定事業
（医療機器に関する開発ガイドライン作成のための支援事業）

医療機器評価指標ガイドライン
画像診断分野（コンピュータ診断支援装置）
開発ＷＧ報告書

平成２３年３月

独立行政法人　産業技術総合研究所

平成２２年度　画像診断分野（コンピュータ診断支援装置）開発 WG 委員名簿

（敬称略、※座長）

※小畑　秀文	東京農工大学 学長
安藤　裕	放射線医学総合研究所 重粒子医科学センター病院 病院長
鴛田　栄二	㈳日本画像医療システム工業会 法規・安全部会ソフトウェア委員会 副委員長 富士フイルム㈱ メディカルシステム事業部 事業部長附
椎名　毅	京都大学大学院 医学研究科 人間健康科学系専攻 教授
軸丸　幸彦	㈳日本画像医療システム工業会 法規・安全部会副部会長 ソフトウェア委員会 委員長 コニカミノルタエムジー㈱ 品質保証センター シニア アドバイザー
清水　昭伸	東京農工大学大学院 工学部電気電子工学科 准教授
縄野　繁	国際医療福祉大学 三田病院 放射線医学センター 教授
仁木　登	徳島大学大学院 ソシオテクノサイエンス研究部 教授
藤田　広志	岐阜大学大学院 医学系研究科 知能イメージ情報分野 教授
古川　浩	㈳日本画像医療システム工業会 法規・安全部会部会長 法規委員会 委員長 東芝メディカルシステムズ㈱ 社長附
森山　紀之	国立がんセンター がん予防・検診センター センター長
諸岡　直樹	㈳日本画像医療システム工業会 法規・安全部会 副部会長（CAD-WG 主査） ㈱島津製作所 医用機器事業部 品質保証部 規格・製造品質管理グループ 課長
横井　英人	香川大学医学部附属病院 医療情報部 教授

タスクフォース（TF）委員名簿

性能評価項目選定小委員会	評価用代替データ小委員会	CAD ソフトウェア品質管理 評価項目選定小委員会
藤田　広志	安藤　裕	横井　英人
仁木　登	縄野　繁	軸丸　幸彦
椎名　毅	清水　昭伸	古川　浩
清水　昭伸	藤田　広志	鴛田　栄二
縄野　繁	椎名　毅	諸岡　直樹
鴛田　栄二		
軸丸　幸彦		
古川　浩		
諸岡　直樹		

開発WG事務局

本間　一弘　産業技術総合研究所 ヒューマンライフテクノロジー研究部門

坂無　英徳　産業技術総合研究所 情報技術研究部門
センサーコミュニケーション研究グループ

画像診断分野（コンピュータ診断支援装置）開発 WG　委員会開催日

第 1 回開発 WG 委員会
　開催日　平成 22 年 10 月　5 日　(火)
第 2 回開発 WG 委員会
　開催日　平成 22 年 11 月 10 日　(水)
第 3 回開発 WG 委員会
　開催日　平成 22 年 12 月 28 日　(火)
第 4 回開発 WG 委員会
　開催日　平成 23 年 1 月 25 日　(火)
第 5 回開発 WG 委員会
　開催日　平成 23 年 2 月 28 日　(月)

目　次

1. 当該技術分野の現状

コンピュータで画像診断を支援するという基礎研究は 1960 年代には始まっており、当時は“自動診断”と言うネーミングが使われていた。胸部単純 X 線写真や胃二重造影写真の分野を中心に、欧米に負けず本邦から世界をリードするすばらしい多くの学術的な研究成果が発信されてきた。

一方、実用化面では、世界最初のコンピュータ支援検出（computer-aided detection; CAD）装置として、マンモグラフィ CAD 装置が米国の FDA（Food and Drug Administration, アメリカ食品医薬品局）の認可を得て 1998 年に発売されており、すでに 10 年以上の年月が経過している。現在の米国では、乳がん検診において年間 3800 万人の対象患者の半数以上は CAD 装置を用いて診断されると推定されている（販売台数は 1 万台規模）。マンモグラフィ CAD 装置に続いて、胸部単純 X 線写真、肺 CT (Computed Tomography)、大腸 CT コロノスコピー、乳房 MR (Magnetic Resonance)、前立腺 MR、乳房超音波の領域で CAD もしくはそれに類する商品（後者の 3 例はどちらかというとコンピュータ支援診断の範疇になる）が商用化されている。

本邦では、残念ながら薬事承認された商品はいまだにマンモグラフィ CAD 装置のみという現状であり、販売総数はいまだに 100 台未満と推定される。そのため、商用の CAD 装置を使った臨床評価に関する論文も、皆無に近いと言っても過言ではない。世界をリードできる技術力を古くから有しているにも関わらず、産業面でも学術的な臨床評価の面でも世界に大きな遅れをとってしまったのは、誠に残念な限りである。その理由の一つとして、本邦には薬事承認のための定まったガイドラインがこれまでになく、承認までにはいたずらにかなりの時間を要していることが挙げられる。米国では 2009 年 10 月に、コンピュータ支援検出を行う CAD 装置の承認基準を、FDA の審査の基準の見直しにあわせて厳しく設定したために、それ以降 CAD 装置開発に対する企業の意欲を減退させ、その普及も大きく遅らせている悪因になっている。本邦ではそのようなことが起きないよう、CAD 装置の本質を見極めたガイドラインの策定が関連する工業界から渇望されており、本開発 WG 委員会で協議を重ねてきた次第である。

本ガイドラインにより多くの商用 CAD 装置が出現し、次の 10 年で CAD 装置の商用化が活況を呈するような状況になり、世界をリードするようになることを願ってやまない。

2. 当該技術分野におけるガイドライン策定の意義

1998 年、世界で最初に米国において医療機器として FDA に認可されたマンモグラフィ CAD（Computer-Aided Detection/Diagnosis）装置は、検診に保険適用が認められたことも加わって普及が目覚ましい。既に１万台を超える CAD 装置が臨床に使用され、医師の診断支援のツールとして高い評価が得られている。最近では乳房以外の部位に対応した CAD ソフトウェアの実用化が進むのに伴い、米国 FDA が CAD ソフトウェア用のガイドラインを策定し、CAD ソフトウェアを開発する大学や企業の研究機関へのサービスを提供している。

一方日本では、医療機器のイノベーションとしての代表的な技術の一環に位置づけられている CAD 装置は、診断医から高い評価を得ていながら、米国に対して約 10 年も市場導入が遅れているとみられている。2010 年 12 月の時点で国内でのマンモグラフィ CAD 装置の導入施設が 100 に達しない状況である。2000 年 1 月 31 日にフィルムマンモグラフィ CAD 装置が薬事承認されたが、画質・その他の要因であまり普及せず、2007 年 4 月 9 日にデジタルマンモグラフィ CAD 装置が、また 2007 年 12 月 4 日、2010 年 3 月 17 日及び、2010 年 5 月 21 日に国内企業がマンモグラフィ CAD 装置の薬事認可を取得したのみである。このように、CAD 装置に関する薬事承認事例がまだ 5 件（2011 年 3 月現在）と非常に少なく、日本国内ではソフトウェアに関する薬事法での取扱いが不明確な状況の中、CAD 装置の定義が定まっていない実情が存在する。その上、これまで CAD 装置の薬事承認申請期間が約 3 年と時間がかかっており、薬事認可を取得した段階ではソフトウェアが陳腐化してしまっているという問題と、ソフトウェアの開発費と薬事申請に多額の経費がかかる問題のために、中小企業はもちろんのこと大企業でも医療機器としての CAD 装置の商品化を躊躇している。

そのような厳しい状況下にあるにも関わらず、各大学の研究室や医療機器関連企業及びソフトウェアベンチャー企業等の研究開発部門では、将来性を見越して新たな CAD 装置の開発を試みている。装置も X 線撮影装置から X-CT、USI、MRI、PET/CT、眼底カメラ、及びカプセル内視鏡等と、また対象部位においても、これまでの乳房から肺、大腸、肝臓、膵臓、脳神経、前立腺、歯科パノラマ、及び病理等、多岐にわたった CAD 装置の研究・開発が進められている。

これらの実情を鑑み、日本の医療機器産業の活性化を考慮し、当開発ワーキンググループ(WG)委員会では医療機器としての価値を認められている CAD 装置としての効果・効能を謳える「CAD ソフトウェア＋ハードウェア」のシステム、並びに将来ソフトウェアの単独医療機器が設定された場合を想定し、「CAD ソフトウェア」も念頭において、各企業がそれらを医療機器市場に早急に導入できるよう製品開発と薬事申請を行ないやすくすることを目的として本ガイドラインを策定することとした。

3. ガイドラインの検討過程

CAD (Computer-Aided Detection/Diagnosis)装置を開発するために必要な項目に関するガイドラインの策定、CAD 装置などで用いるソフトウェアの在るべき姿を検討することを目的に、開発ワーキンググループ委員会を設置し、本年度は、5 回（10 月 5 日、11 月 10 日、12 月 28 日、1 月 25 日、2 月 28 日)開催した。開発 WG の下に、3 つの TF：タスクフォース（TF１：性能評価項目選定小委員会、TF2：評価用代替データ検討小委員会、TF3：CAD ソフトウェア品質管理評価項目選定小委員会）を設け、各 TF で必要な項目を詳細に検討し、開発ＷＧ委員会で総括審議を行った。

3.1 画像診断分野（コンピュータ診断支援装置）開発 WG 委員会概要

3.1.1 第 1 回開発 WG 委員会

⑴ 開催日時: 平成 22 年 10 月 5 日（火） 18:00～20:00

⑵ 配布資料

資料 1：開発 WG 委員名簿

資料 2：審査 WG 委員名簿

資料 3：Ｘ線による乳房の診断装置（既承品医療機器）

資料 4：基本要件適合性チェックリスト（据置型アナログ式乳房用Ｘ線診断装置等基準）

資料 5：医療機器の臨床試験の実施の基準の運用について（薬食機発 1224 第４号）

資料 6：COCIR（欧州放射線・医療電子機器産業連合会）のメモ

COCIR Internal Briefing　Status in Canada, EU and US on Medical Software

資料 7：資料 6 にある欧州のドラフトガイドライン

Guidelines for the qualification and classification of software used in healthcare environment within the regulatory framework of medical devices

資料 8：資料 6 にある米国のパブコメ募集文書

資料 9：資料 6 にあるカナダの NOTICE

Classification of Medical Devices Class I or Class II patient management software

資料 10：米国の CAD に関するパブコメ募集文書１

Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions

資料 11：米国の CAD に関するパブコメ募集文書 2

Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions

資料 12：GHTF 最終文書

『医療機器の安全性及び性能の基本要件』

資料 13：GHTF 最終文書

『医療機器のクラス分類の原則』

資料 14：GHTF 最終文書
『医療機器の安全性及び性能に関する基本要件への適合を立証するための
サマリーテクニカルドキュメンテーション(STED)』
資料 15：討議事項（開発ガイドラインにおける技術的評価項目）
参考資料 1：医療機器ガイドライン事業における従来の成果
参考資料 2：過去に策定した開発ガイドラインの例（高機能人工心臓システム）

(3) 出席者
委員： 小畑秀文、森山紀之、安藤裕、縄野繁、清水昭伸、藤田広志、仁木登、横井英人、
鴛田栄二、軸丸幸彦、古川浩
経済産業省：安達昌孝、吉野正人
国立医薬品食品衛生研究所：葩島由二、植松美幸
事務局：赤松幹之、本間一弘、山根隆志、鷲尾利克（産業技術総合研究所）

(4) 議事概要
①今年度の検討方針
CAD 装置の開発において必要な評価項目に検討し、ガイドラインの策定を推進する。このために、下記の TF（タスクフォース）を設置し、詳細を検討する。各 TF における検討状況は開発 WG 委員会にて報告し、同委員会にて審議する。
TF1：性能評価項目選定小委員会（取り纏め：藤田委員）
コンピュータ診断支援装置の性能、有効性などに関する技術的評価項目を選定する。
共通する評価項目、部位・モダリティ特有の評価項目
TF2：評価用代替データ検討小委員会（取り纏め：安藤委員）
標準 DB の構築や疾患モデル、シミュレーションの可能性など
TF3：CAD ソフトウェア品質管理評価項目選定小委員会（取り纏め：横井委員）
医療機器のソフトウェアに対する品質管理、技術的に規定すべき項目など

②対象とする医療機器の名称と定義
対象とする医療機器の名称と定義(使用目的・適用範囲)に関して審議した結果、以下を案とする。審査 WG 委員会の審議を踏まえ、今後、さらに審議するものとする。
1) CADe：コンピュータ検出支援ソフトウェア
2) CADx：コンピュータ診断支援ソフトウェア

3.1.2 第 2 回開発 WG 委員会
(1) 開催日時: 平成 22 年 11 月 10 日 (金) 18:00〜21:00

(2) 配布資料
資料 2-1：第 1 回開発 WG 議事録

資料 2-2：開発 WG 委員名簿（10 月 1 日現在）

資料 2-3：TF1（性能評価項目選定小委員会）

1. 小委員会 議事録（性能評価項目に関する検討結果）
2. 関連資料（医用画像処理表示装置:MV-SR657 添付資料）
3. 関連資料（Small Pulmonary Nodules:Effect of 2 CAD Systems on Radiologist Performance）

資料 2-4：TF2（評価用代替データ検討小委員会）

評価用代替データの検討結果

資料 2-5：TF3（CAD ソフトウェア品質管理評価項目選定小委員会）

1. 小委員会 議事録
2. 品質管理に関する検討結果（CAD ソフトウェアの品質管理の考え方）

資料 2-6：コンピュータ診断支援装置　審査 WG の活動状況

資料 2-7：開発ガイドライン（項目案）

(3)出席者

委員： 小畑秀文、森山紀之、縄野繁、清水昭伸、藤田広志、椎名毅、仁木登、横井英人、鴛田栄二、軸丸幸彦、古川浩、諸岡直樹

医薬品医療機器総合機構：池田潔

国立医薬品食品衛生研究所：葩島由二、植松美幸

事務局：本間一弘、鷲尾利克、坂無英徳、安佛尚志（産業技術総合研究所）

(4) 議事概要

①TF（タスクフォース）の検討状況の報告

1)TF1：性能評価項目選定小委員会報告（藤田委員）

過去のマンモグラフィ CAD システムの薬事申請時に係わる評価方法を踏まえて、CADe の評価項目の選定に対する検討を行った。その結果、CADe の目的（検出対象）、適用範囲、機能、使用方法などの明確な記述、及び、評価対象の画像データベースの詳細の記述が必要である。

また、評価項目は、画像データベースを用いて、必ず統計的な有効性を示す。CAD 装置の使用目的・用途を検討し、それに対応した機器の仕様を明確にする。あわせて、評価用臨床用臨床データの要否、その理由などを検討する。

2)TF2：評価用代替データ検討小委員会報告（縄野委員）

代替案として「データベース用画像収集」、「CAD 評価用のファントムによる評価」「電子ファントムによる評価」が考えられる。データベースの構築にかかる時間や、評価用ファントムを作成する費用等を考慮すると、「電子ファントムによる評価」がもっとも有望である。これらの使用に関して詳細を検討する。

3)TF3：CAD ソフトウェア品質管理評価項目選定小委員会報告（横井委員）

CAD ソフトウェアに関する品質管理についての検討方針を固め、IEC62304（JIST62304（仮称））を元に、その基準に必要な項目を CAD ソフトウェアに対応した形で表記した。関連する全ての基準などを洗い出し、あらたに加えるべき評価項目を検討する。

②コンピュータ診断支援装置　審査 WG の活動状況の報告（葩島審査 WG 事務局）

審査 WG より今年の指針及び作業内容についての報告があった。

③開発ガイドライン（骨子案）について

現在までの議論の内容を踏まえての骨子案の提示を行った。さらに各 TF 内での審議を進め、次回 WG にて結果を取り纏めていくものとする。

④その他

審査 WG との資料・情報の共有化が了承された。

3.1.3 第 3 回開発 WG 委員会

(1) 開催日時: 平成 22 年 12 月 28 日 (火) 10:00〜12:00

(2) 配布資料

資料 3-1：第 2 回開発 WG 議事録

資料 3-2：コンピュータ診断支援装置　審査 WG の活動状況　評価指標案

資料 3-3：CAD の定義

資料 3-4：TF1（性能評価項目選定小委員会）の活動状況報告

資料 3-5：TF2（評価用代替データ検討小委員会）の活動状況報告

資料 3-6：TF3（CAD ソフトウェア品質管理評価項目選定小委員会）の活動状況報告

資料 3-7：TF3　品質管理に関する検討結果（CAD の品質管理の考え方）2010.12.27 改訂

(3)出席者

委員： 小畑秀文、安藤裕、縄野繁、清水昭伸、藤田広志、椎名毅、仁木登、横井英人、鴛田栄二、軸丸幸彦、古川浩、諸岡直樹

経済産業省：加藤二子

医薬品医療機器総合機構：池田潔

国立医薬品食品衛生研究所：植松美幸

事務局：本間一弘、山根隆志、鷲尾利克、坂無英徳、安佛尚志（産業技術総合研究所）

(4) 議事概要

①コンピュータ診断支援装置　審査 WG の活動状況の報告（植松審査 WG 事務局）

審査 WG よりコンピュータ診断支援装置（画像情報処理の部分）に関する評価指針案についての報告があった。

②CAD の定義に関する討議

CAD の定義に関し、今までに出された案を討議した。審査 WG 委員会側の定義との整合を行い、事務局から次回の開発 WG にて提案し、再審議する。

③TF（タスクフォース）の検討状況の報告

1)TF1：性能評価項目選定小委員会報告（藤田委員）

CADe 及び CADx に対する評価項目に関して技術的側面から検討した。次回の開発 WG において、CADe の開発ガイドライン（案）を提案する。

2)TF2：評価用代替データ検討小委員会報告（安藤委員）

評価用の代替案のためのモダリティと部位の対応を検討した。評価用代替の画像 DB や電子ファントムの仕様に関して検討し、次回の開発 WG において、開発ガイドライン（案）を提案する。

3)TF3：CAD ソフトウェア品質管理評価項目選定小委員会報告（横井委員）

ソフトウェア品質管理に対する評価項目を選定し、関連する基準の選定、新しく検討すべき項目と内容を検討した。次回の開発 WG において、開発ガイドライン（案）を提案する。

④次回の WG にて、今年度において提案する開発ガイドラインの内容を審議する。

3.1.4 第 4 回開発 WG 委員会

(1) 開催日時: 平成 23 年 1 月 25 日 (火) 18:00～21:00

(2) 配布資料

資料 4-1：第 3 回開発 WG 議事録（案）
資料 4-2：CAD の定義
資料 4-3：TF1（性能評価項目選定小委員会）
資料 4-4：TF2（評価用代替データ検討小委員会）
資料 4-5：TF3（CAD ソフトウェア品質管理評価項目選定小委員会）
資料 4-6：関連規格のリスト（案）
資料 4-7：平成 22 年度 CAD 開発 WG 報告書（骨子案）

(3)出席者

委員： 小畑秀文、安藤裕、縄野繁、清水昭伸、藤田広志、椎名毅、仁木登、鴛田栄二、軸丸幸彦、古川浩、諸岡直樹
経済産業省：安達昌孝、吉野正人、加藤二子
医薬品医療機器総合機構：池田潔
国立医薬品食品衛生研究所：葩島由二、植松美幸
事務局：本間一弘、山根隆志、鷲尾利克、坂無英徳、大塚幸雄（産業技術総合研究所）

(4) 議事概要

①コンピュータ診断支援装置　審査 WG の活動状況の報告（葩島審査 WG 事務局）

審査 WG より検討状況に関して報告がなされた。審査 WG は 3 回開催し、コンピュータ診断支援装置に関する評価指標に関して検討した。今年度末には審査ガイドラインを提案する予定であ

る。

②CAD 装置の定義に関する審議

資料 4-2 をもとに、本開発 WG としては CAD（コンピュータ診断支援）装置を CADe と CADx に分類し、各々、以下の定義とすることを決定した。

1)コンピュータ検出支援ソフトウェア CADe (Computer-Aided Detection)

画像を解析し､内蔵する基準に基づいて異常と想定される位置をコンピュータが自動的に抽出するソフトウェアあるいはそれを具備する装置。

用途：医師の診断を支援する。

2)コンピュータ診断支援ソフトウェア CADx (Computer-Aided Diagnosis)

画像を解析し､内蔵する基準に基づいて病変の候補部位をコンピュータが自動的に分析し､疾患の候補やその進行度あるいはリスク評価に関する情報などを提供するソフトウェアあるいはそれを具備する装置。

用途：医師の診断を支援する。

③開発ガイドライン(案) に関する審議

性能評価項目選定小委員会（タスクフォース TF1)、評価用代替データ検討小委員会（TF2)、CAD ソフトウェア品質管理評価項目選定小委員会（TF3）から、検討した開発ガイドライン(案)に関して報告がなされた（資料 4-3～5)。審議において以下の指摘があり、これに基づいて再検討し、次回の開発 WG にて報告する。また、各々の開発ガイドライン(案)には、欄外あるいは末尾に記載内容の解説を付記する。

〇コンピュータ検出支援装置の性能評価(案)

・審査 WG で検討する内容との差別化が必要である。
・臨床データ収集不要の範囲あるいは代替案を科学的根拠をもって示すことを検討する。
・CADx に関する審議は未了と判断し、平成 22 年度に提案する開発ガイドラインは CADe の内容に限定する。これに起因して、資料 4-3 に記載される CADx に関する記載は削除する。
・開発 WG としては、CADx は来年度において検討することを希望することとする。

〇性能評価用データの代替法(案)

・利用者が必要な内容の全てを規定する。
・電子ファントムに対する要求仕様を詳細に記載する。
・臨床データに対する要求仕様を詳細に記載する。
・DB を構築する場合に必要となる条件を記載する。
（GCP への対応の要否、必要な場合はその内容）
・上記に関する評価項目は科学的根拠をもって示す。

〇医療機器におけるソフトウェア品質管理(案)

・ソフトウェアそのものを技術的に評価する際に必要な評価項目の全てを検討する。

④平成 22 年度の報告書

資料 4-7 に基づいて平成 22 年度報告書の目次案を審議し、執筆分担を定めた。

3.1.5 第 5 回開発 WG 委員会

(1) 開催日時: 平成 23 年 2 月 28 日（月) 18:00～20:10

(2) 配布資料

資料 5-1：第 4 回開発ＷＧ議事録（案）

資料 5-2：ガイドライン「コンピュータ検出支援装置の性能評価項目」（案）

資料 5-3：電子ファントムによる CAD の性能評価（案）Ver.1（案）

資料 5-4：ガイドライン「医療機器におけるソフトウェア品質管理」（案）

資料 5-5：平成 22 年度 CAD 開発 WG 報告書（骨子案）

資料 5-6：平成 22 年度開発ＷＧ報告書における「開発 WG からの提言」への記載案

参考資料 5-1：CAD の定義確定版

参考資料 5-2：第 10 回合同検討会 HP

参考資料 5-3：合同検討会資料（案）

(3) 出席者

委員： 小畑秀文、安藤裕、縄野繁、清水昭伸、藤田広志、椎名毅、仁木登、横井英人、
鴛田栄二、軸丸幸彦、古川浩、諸岡直樹

経済産業省：安達昌孝

国立医薬品食品衛生研究所：植松美幸

内閣官房:廣瀬大也

事務局：本間一弘、山根隆志、鷲尾利克、坂無英徳、大塚幸雄(産業技術総合研究所)

(4) 議事概要

・各タスクフォースにおける検討の結果として提示された 3 件の開発ガイドライン(案)「CADe（コンピュータ検出支援ソフトウェア)」、「医療機器におけるソフトウェアの品質管理」、「性能評価用データ収集の代替法」に関して審議を行った。

・CADe に関する開発ガイドライン(案)は、審査ガイドラインにおける記載内容との重複を避け、開発者の視点に立った評価項目を具体的かつ詳細に記載することとする。

・ソフトウェアの品質管理に関する開発ガイドライン(案)は、ソフトウェアを単独で評価するために必要不可欠な評価項目を選定し、加筆修正する。

・前 2 者に対して本日の審議内容を反映させ、開発ガイドライン案として提案する。また、性能評価用データ収集の代替法及び CADx（コンピュータ診断支援ソフトウェア）に関しては、詳細な検討と審議の継続が必要なことから、次年度において開発ガイドラインの策定を検討

する。
・平成 22 年度の報告書は委員及び事務局の分担執筆とする。

3.2　TF1（性能評価項目選定小委員会）の総括

本ガイドライン策定のために，主に以下の点を中心に議論が行われた。

3.2.1. 過去の薬事申請時の性能項目に関する調査

国内企業 2 社から過去のマンモグラフィ CAD の薬事承認過程に関わる情報を収集し議論を行った。

3.2.2 評価項目選定に関して

1)　CADe の目的（検出対象）、適用範囲、機能、使用方法などの記述について
2)　評価対象の画像データベースの詳細（症例数、病変の特徴など）の記述について
3)　1) の効能を実証する技術的な評価データを提示について
・評価項目は、画像データベースを用いて、CADe の検出率（真陽性率）と偽陽性数（あるいは偽陽性率）による定量的データ、あるいは ROC（Receiver Operative Characteristic）解析等の技術で評価を行い、必ず統計的な有効性を示す。
・過去に承認された事例がある場合には、システムの性能の呈示と承認事例の性能との差違を検討し､統計的に有効性を示す｡過去に認可された類似の CADe がない新規事例の場合には、医師の単独性能と医師が CADe を利用したときの性能との比較評価などで、CADe の有効性を示す。
4)　CAD 装置の真の評価（有効性の実証）の難しさ

CAD 装置は「うっかりミス」を防ぐ目的で設計されていることが多く、そのような状況を模擬した臨床的な環境下でプロスペクティブ（前向き）に実証実験をすることが望ましい。しかし、集団検診のような状況下ではがん発生率が極めて少ないので（0.3%程度のオーダー）容易ではない。ROC 実験は、実験室における極めて特殊な環境下（データ数や読影環境など）における一つの評価実験に過ぎない。また、最近の国際学会でも議論があるが、クリニックにおける CAD 装置の有効性の評価例は、まだどこからも出ていない。

3.2.3 性能評価用の画像データの問題

1)　臨床画像の収集の難しさ

CAD 装置開発の生命線である臨床画像データの収集は、非常に困難であるのが一般的である。その理由は、倫理委員会承認の問題もあるが（次項）、それが解決したとしても、特にがんなどの異常症例の収集作業については一般病院ではかなりの時間を要する｡CAD アルゴリズムの学習やテスト（学習には使わないデータで実行する必要がある）に使うために十分な枚数の病変（特にがん病変）の出現頻度が小さいことが多いためである。

そのため、研究開発段階で収集したものでも、訓練データとして使用していことが担保でき、薬事申請用にも十分な条件を満たしている場合には、問題なく利用できるような仕組みも採用す

べきと考える。

また、統計的な偏りのないことを示す十分な根拠があれば、一施設で収集されたデータの薬事申請用としての使用についても将来的に認められるべきと考える。

2) 倫理委員会

施設の倫理委員会承認のクリアも必ずしも容易ではない。同意書について個別同意が必要か、包括的同意でよいか、あるいは不要かなどは、各施設の倫理委員会によっても方針が大きく異なり、特に検診施設では個別同意書はとれない（むしろ、CAD 装置の研究では画像を完全に匿名化処理して使うため、同意書は不要で承認すると倫理委員会から言われることさえある）のが現状である。

なお、CAD は医師による読影の診断の支援であり、薬の臨床試験（治験）のように患者に直接危害を加える可能性はゼロであることを根拠として、臨床試験を行う施設の倫理審査委員会の承認を得ている画像データであれば､必ずしもすべて GCP 準拠である必要はないのではないかとの意見もあった。

3) 代替画像データ

学術団体（学会）など公開している公共の画像データベースが使えるケースも希にあり得る。例えば、肺癌 CT のケースを集めた LIDC (Lung Image Database Consortium)データベースや南フロリダ大学のマンモグラフィ用の画像データベースがある。ただし、一般的には小規模なものが多く､CAD 装置の評価用には十分ではない｡医師の教育用の画像データベースの利用もあり得るが、現状では、CAD 装置の評価に利用できるものは非常に少ないと考えられる。

4) 電子ファントム

電子ファントムを代替に利用するという手段があるが、現状では、国内外の学会を見る限りでは、CAD 装置の評価に使えるような電子ファントムはまだ開発されていない状況である。電子ファントムが開発されれば、本 CAD の性能評価には有効に活用できる可能性があると考える。

5) 開発と薬事審査における画像データの扱い

開発時の画像データと薬事申請時の画像データは全く異なるデータを使う必要性があり、両者が混合されないように特に注意が必要である。

3.3 TF2（評価用代替データ検討小委員会）の総括

ガイドラインの検討を以下の項目において行った。

3.3.1 使用目的

本ガイドラインは､臨床データを用いた性能評価の代替法を科学的根拠に基づいて明確にする。

3.2.2 適応範囲

検出支援装置（CADe）、診断支援装置（CADx）の性能評価に適用する。

3.2.3 代替法

CADe に対する性能評価に活用できる臨床データの仕様及び新たなデータ収集を代替できる方策に関して検討を行った。

CADe の性能を評価するために利用できる臨床データは GCP を遵守することが不可欠である。ただし、レトロスペクティブな評価が可能になると判断されることから、GCP を遵守した臨床データと同等の状態で確保されたデータであれば、評価に利用可能と判断する。現状の技術においては電子ファントムや評価用データベースがその候補となる。これらに関する詳細な仕様は今後において詳細を検討するものとする。

3.4　TF3（CAD ソフトウェア品質管理評価項目選定小委員会）の総括

本内容については、主として CAD ソフトウェアの開発に関連する業界団体の有識者を中心に検討を進めた。

CAD ソフトウェアに限らず、医療機器ソフトウェアの品質とは、通常の医療機器の品質とは大きく異なる性格を持つ。つまりソフトウェアは物質・物体として製造するものではないので、その生産から出荷に於ける品質管理の要素はごく僅かである。現実的な製造行為は、ソフトウェアを記入したメディアの製造であり、これらはコンピュータ上でおよそ内部処理的に行われるので、通常の医療機器のような品質管理を必要としない。

ソフトウェアの品質としてはむしろ、開発時からソフトウェア流通の全てのフェイズに於ける設計管理をはじめとしたプロセス管理が寄与する割合が大きい。現在、このプロセス管理のために IEC62304 (国内に於いては JIS T 2304) の適用が一般的になっている。欧米に於いては本規格に準拠した管理文書の提出が求められている。

CAD ソフトウェアの計算アルゴリズムにおける臨床的な性能の評価項目（性能評価項目）については、本 WG に於いては TF1 等で議論されているので、本 TF では、ソフトウェアの開発過程の技術的な部分に焦点を絞って、必要な項目を案出した。

IEC62304 に準拠する場合、ISO14971 にも準拠が必要になる。また、薬事上の QMS (Quality Management System)としては ISO13485 への準拠も必要となる。したがって「JIS Q 13485 医療機器－品質マネジメントシステム」「JIS T 14971 医療機器－リスクマネジメントの医療機器への適用」も視野に入れた上で、CAD 開発に関する具体的な各ステップについての必要条件を検討していった。

まず、CAD 装置の品質管理項目を、組み合わせるハードウェアとソフトウェアとして、その詳細の設計開発プロセスへの適用として、以下の各開発段階に於いての評価項目として挙げた。

①製品に関連する要求事項の明確化（意図する用途）
②設計開発のインプット
③ソフトウェア要求事項分析
④アーキテクチャ設計
⑤システム試験
⑥リスクマネジメント

⑦構成管理プロセス
⑧設計開発の検証
⑨設計開発の妥当性確認（臨床評価）

本案では、論理の明確化のために対象のソフトウェアを「画像を解析し、内蔵する基準に基づいて異常と想定される位置をコンピュータが自動的に抽出するソフトウェア、あるいはそれを具備する装置」としたが、今後、質的診断に寄与するソフトウェアに関する内容も含め議論が必要になる。

本案は以上のような意図を持って開発に於ける基準の明確化を図ることを目的に作成されたものである。

4. ガイドラインの検討結果

コンピュータ検出支援装置の性能評価項目開発ガイドライン 2010（案）

（確定作業中のため本文の掲載は省略）

コンピュータ検出支援装置におけるソフトウェア品質管理
開発ガイドライン 2010（案）

本ガイドラインは、平成 23 年度 医療機器開発ガイドライン策定事業（医療機器に関する開発ガイドライン作成のための支援事業）画像診断分野開発 WG において改訂され、経済産業省より「コンピュータ診断支援装置におけるソフトウェア設計・開発管理　開発ガイドライン 2012」として平成 25 年 3 月に公開された。

経済産業省　医療機器開発ガイドライン策定事業
http://www.meti.go.jp/policy/mono_info_service/service/iryou_fukushi/index.html

5. 開発 WG 委員会からの提言

5. 1 CAD の発展のために

産業界は、品質、有効性及び安全性が担保された医療機器としてのCADの普及と医療への貢献を切に願っている。しかしながら最近では、CADの使用目的や性能を持ちながらも、未承認のまま製造販売したり、単なる解析ソフトウェアとして認証取得し製造販売したりするケースが多々見られる。このままでは薬事規制を遵守した品質、有効性及び安全性が担保された医療機器としてのCADが日本の市場から消え去ってしまうことが強く懸念される。

以下にCADがこのような状況に陥っている理由や背景を考察し、この現状を改善するための提言を行う。

■CADの定義の周知とリスクに見合った審査基準の設定

この現状は、CADの定義や使用目的・使用方法の明確化及びその周知がなされていないということと、薬事承認取得のハードルがCADの使用時のリスクに比較してあまりに高いというところに起因しているものと考える。CADはあくまでも病変の見落とし防止の注意喚起など、医師等が読影や診断の際に補助的に利用するツールであって、最終的な読影や診断はオリジナル画像を見て医師等が行うため、CADを適正に使用した場合の実際のリスクは高くない。これまでの承認前例において申請時に必要とされた臨床データはCADが持つリスクに対してあまりにハードルが高く、臨床データの収集と承認取得に莫大なコストと長期間を要した。

CADの定義や使用目的・使用方法の明確化と、薬事承認の審査基準をCADのリスクに見合った内容に見直し、かつその審査基準を周知し、申請者が投資回収や承認時期の見通しをもって申請することができるように改善願いたい。

■CAD等の医療用アプリケーションソフトウェアの医療機器化

現在、医療現場において IT 化が進んでおり、様々な情報機器が導入されている。CAD を臨床現場で利用する場合、すでに設置されている情報機器端末に CAD のソフトウェアだけを導入して、臨床に利用したいという要望が強い。しかし、現在の日本の薬事規制においては、CAD に代表される医療用アプリケーションソフトウェアを製造販売する場合は PC などの汎用ハードウェアに医療用アプリケーションソフトウェアを組み込んだ構成で薬事承認を取得し、同構成で製造販売しなければならない。そして、設置時及び導入後においても医療機器は厳格に構成品管理がなされるために、他の汎用 PC や他のソフトウェアとの組合せ変更が医療現場において実施できない。具体的には以下のような足かせ（デメリット）が医療現場で発生している。

- 医療現場のワークフローや操作性に最適な PC に CAD をインストールできない
- 複数ソフトウェアの同居による PC の削減による低コスト・省スペース化が困難
- 陳腐化した PC を最新鋭のものに交換することができない

一方、未承認の CAD は薬事規制を遵守する必要がないため、ソフトウェア単独で取り扱うことができ、これらの足かせ（デメリット）が一切ない。また、CAD は前述したように、最終的な読影や診断はオリジナル画像を見て医師等が行うので、実際の使用時のリスクはさほど高くないため、医師等も品質、有効性及び安全性が担保された医療機器としての CAD の必要性をさほど感じない。従って、同様な機能・性能を持った CAD であれば、足かせ（デメリット）のない安価な未承認の CAD が使用者に好まれ、足かせ（デメリット）のあるハードウェア込みの高価な

医療機器としてのCADは敬遠される。

CAD等の医療用アプリケーションソフトウェアの医療機器化を行い、ソフトウェア単独製品として製造販売できるようにして、医療機関での設置時及び導入後における上記のような足かせ（デメリット）の解消を切望する。

CADは診断支援の医療機器として、医療への貢献の潜在能力は大きい。是非、規制当局には日本におけるCADの発展の“行き詰まり感”を認識していただき、多くの企業がCADの研究開発に切磋琢磨し、品質、有効性及び安全性に優れた多くのCADが医療現場で使用されるように規制環境面での見直しと整備をお願いしたい。

6. 平成 22 年度の総括

開発ガイドライン策定のために、「CAD に対する性能評価項目の選定」「評価用データの収集代替法の検討」及び「CAD におけるソフトウェアの品質管理に対する評価項目の選定」について検討することを目的に、3 つのタスクフォース（TF）を設置した。各々、性能評価項目選定小委員会、評価用代替データ検討小委員会、CAD ソフトウェア品質管理評価項目選定小委員会とした。各々ＴＦにおいて詳細に検討した結果を、開発 WG 委員会にて総括討論した。その結果、開発 WG 委員会として、CADe（コンピュータ検出支援ソフトウェア）とソフトウェアの品質管理に関する開発ガイドライン(案)を提案することとした。

また、「性能評価用データ収集の代替法」及び「CADx（コンピュータ診断支援ソフトウェア）」に関しては、さらに詳細な検討と審議が必要であり、今後、開発ガイドラインの策定を検討していきたい。

参考資料

参考資料１：GHTF/SG1/N41R9:2005
GHTF FINAL DOCUMENT『Essential Principles of Safety and Performance of Medical Devices』

参考資料２：GHTF/SG1/N15:2006
GHTF FINAL DOCUMENT『Principles of Medical Devices Classification』

参考資料３：GHTF/SG1/N011:2008
GHTF FINAL DOCUMENT『Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)』

参考資料４: Draft Guidance for Industry and FDA Staff
Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions

参考資料５: Draft Guidance for Industry and FDA Staff
Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions

参考資料１：GHTF/SG1/N41R9:2005

GHTF FINAL DOCUMENT

『Essential Principles of Safety and Performanceof Medical Devices』

FINAL DOCUMENT

Title: Essential Principles of Safety and Performance of Medical Devices

Authoring Group: GHTF Study Group 1

Endorsed by: The Global Harmonization Task Force

Date: May 20, 2005

Abraao Carvalho, GHTF Chair

This document was produced by the Global Harmonization Task Force, a voluntary international group of representatives from medical device regulatory authorities and trade associations from Europe, the United States of America (USA), Canada, Japan and Australia.

The document is intended to provide *non-binding* guidance to regulatory authorities for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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Preface

The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory authorities and the regulated industry. The document is intended to provide non-binding guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

1 Introduction

The primary way in which the GHTF achieves its goals is through the production of a series of guidance documents that together describe a global regulatory model for medical devices. The purpose of such guidance is to harmonize the documentation and procedures that are used to assess whether a medical device conforms to the regulations that apply in each jurisdiction. Eliminating differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

This document has been developed to encourage and support global convergence of regulatory systems. It is intended for use by Regulatory Authorities, Conformity Assessment Bodies and industry, and will provide benefits in establishing, in a consistent way, an economic and effective approach to the control of medical devices in the interest of public health. It seeks to strike a balance between the responsibilities of Regulatory Authorities to safeguard the health of their citizens and their obligations to avoid placing unnecessary burdens upon the industry. Study Group 1 of the GHTF supports and encourages regulatory harmonization but recognises that some Regulatory Authorities may have to reflect different local needs when they introduce new regulations on conformity assessment. However, Regulatory Authorities that are developing conformity assessment schemes or amending existing ones are encouraged to consider the adoption of the system described in this document, as this will help to reduce the diversity of schemes worldwide and facilitate the process of harmonization.

The GHTF has identified as a priority the need to harmonize essential safety and performance criteria for a medical device that allow the manufacturer to demonstrate its product is suitable for its intended use. This goal was achieved through the publication of guidance on the subject entitled *Essential Principles of Safety and Performance of Medical Devices* (SG1/N020 of June 30, 1999) that applied to the majority of medical devices but not to *in vitro* diagnostic devices. **This current document supersedes that earlier one.** The major difference between them is the expanded scope; this document now includes medical devices for the *in vitro* examination of specimens derived from the human body.

The regulatory requirements of some countries do not, at this time, align fully with this guidance.

Study Group 1 of the Global Harmonization Task Force (GHTF) has prepared this guidance document. Comments or questions about it should be directed to either the Chairman or Secretary of GHTF Study Group 1 whose contact details may be found on the GHTF web page[1].

[1] www.ghtf.org

2 Rationale, Purpose and Scope

2.1 Rationale

Consistent identification, selection and application of safety and performance principles to a medical device offers significant benefits to the manufacturer, user, patient or consumer, and to Regulatory Authorities since it allows its manufacturer to design, manufacture and demonstrate the device is suitable for its intended use. Moreover, eliminating differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

2.2 Purpose

To describe six **general requirements** of safety and performance that apply to all medical devices.

To provide a comprehensive list of **design and manufacturing requirements** of safety and performance, some of which are relevant to each medical device. These are grouped as:

- Chemical, physical and biological properties.
- Infection and microbial contamination.
- Manufacturing and environmental properties.
- Devices with a diagnostic or measuring function.
- Protection against radiation.
- Requirements for medical devices connected to or equipped with an energy source.
- Protection against mechanical risks.
- Protection against the risks posed to the patient by supplied energy or substances.
- Protection against the risks posed to the patient for devices for self-testing or self-administration.
- Information supplied by the manufacturer.
- Performance evaluation including, where appropriate, clinical evaluation.

Note: the manufacturer selects which of the design and manufacturing requirements are relevant to a particular medical device, documenting the reasons for excluding the others. The Regulatory Authority and/or Conformity Assessment Body may verify this decision during the conformity assessment process.

2.3 Scope

This document applies to all products that fall within the definition of a medical device that appears within the GHTF document *Information Document Concerning the Definition of the Term "Medical Device"*, including those used for the *in vitro* examination of specimens derived from the human body.

3 References

GHTF final documents

SG1/N009 *Labelling for Medical Devices*

SG1/N012 *Role of Standards in the Assessment of Medical Devices.*

SG1/N020 *Essential Principles of Safety and Performance of Medical Devices*

GHTF documents available for public comment

SG1(PD)/N011 *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices.*

SG1(PD)/N029 *Information Document Concerning the Definition of the Term 'Medical Device'.*

SG1(PD)/N043 *Labelling for Medical Devices (revised).*

GHTF document being prepared for public comment

SG1(PD)/N040 *Principles of Conformity Assessment for Medical Devices.*

International standard

ISO 14971:2001 *Medical devices – Application of risk management to medical devices.*

ISO/TR 16142:2004 *Medical Devices – Guidance on the Selection of Standards in Support of the Recognized Essential Principles of Safety and Performance of Medical*

4 Definitions

Clinical evaluation: The review of relevant scientific literature and/or the review and assessment of data collected through clinical investigation.

Clinical investigation: Any designed and planned systematic study in human subjects undertaken to verify the safety and/or performance of a specific device. (Source – ISO/DIS 14155-1)

Device for self-testing/self-administration: Any device intended by the manufacturer to be able to be used by lay persons in a non-clinical environment. (Source – based on European Directive 98/79/EC)

Harm: Physical injury or damage to the health of people or damage to property or the environment. (Source – ISO/IEC Guide 51:1999)

Hazard: Potential source of harm. (Source – ISO/IEC Guide 51:1999)

Intended use / purpose: The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer. (Source – 21 CFR 801.4)

Medical device: Refer to GHTF guidance document: *Information Concerning the Definition of the Term "Medical Device"* (SG1/N029).

Performance evaluation: Review of the performance of a medical device based upon data already available, scientific literature and, where appropriate, laboratory, animal or clinical investigations.

Regulatory Authority (RA): A government agency or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and may take enforcement action to ensure that medical products marketed within its jurisdiction comply with legal requirements. (Source – EU-Canada MRA)

Risk: Combination of the probability of occurrence of harm and the severity of that harm. (Source – ISO/IEC Guide 51:1999)

Specimen: The discrete portion of a body fluid or tissue or other sample associated with the body taken for examination, study, or analysis of one or more quantity or characteristic to determine the character of the whole.

5 Essential Principles of Safety and Performance of Medical Devices

General Requirements

5.1 Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

5.2 The solutions adopted by the manufacturer for the design and manufacture of the devices should conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, the manufacturer should control the risk(s) so that the residual risk(s) associated with each hazard is judged acceptable. The manufacturer should apply the following principles in the priority order listed:

- identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse,

- eliminate risks as far as reasonably practicable through inherently safe design and manufacture,
- reduce as far as is reasonably practicable the remaining risks by taking adequate protection measures, including alarms,
- inform users of any residual risks.

5.3 Devices should achieve the performance intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions within the scope of the definition of a medical device applicable in each jurisdiction.

5.4 The characteristics and performances referred to in Clauses 5.1, 5.2 and 5.3 should not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.

5.5 The devices should be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected under transport and storage conditions (for example, fluctuations of temperature and humidity) taking account of the instructions and information provided by the manufacturer.

5.6 The benefits must be determined to outweigh any undesirable side effects for the performances intended.

Design and Manufacturing Requirements

5.7 Chemical, physical and biological properties

5.7.1 The devices should be designed and manufactured in such a way as to ensure the characteristics and performance referred to in Clauses 5.1 to 5.6 of the 'General Requirements'. Particular attention should be paid to:

- the choice of materials used, particularly as regards toxicity and, where appropriate, flammability,
- the compatibility between the materials used and biological tissues, cells, body fluids, and specimens, taking account of the intended purpose of the device.
- the choice of materials used should reflect, where appropriate, matters such as hardness, wear and fatigue strength.

5.7.2 The devices should be designed, manufactured and packed in such a way as to minimize the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to patients, taking account of the intended purpose of the product. Particular attention should be paid to tissues exposed and to the duration and frequency of exposure.

5.7.3 The devices should be designed and manufactured in such a way that they can be used safely with the materials, substances and gases with which they enter into contact during their normal use or during routine procedures; if the devices are intended to administer medicinal products they should be designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing these products and that their performance is maintained in accordance with the intended use.

5.7.4 Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product/drug as defined in the relevant legislation that applies within that jurisdiction and which is liable to act upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance should be verified, taking account of the intended purpose of the device.

5.7.5 The devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate the risks posed by substances that may leach or leak from the device.

5.7.6 Devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate risks posed by the unintentional ingress or egress of substances into or from the device taking into account the device and the nature of the environment in which it is intended to be used.

5.8 Infection and microbial contamination

5.8.1 The devices and manufacturing processes should be designed in such a way as to eliminate or to reduce as far as reasonably practicable and appropriate the risk of infection to patients, users and, where applicable, other persons. The design should:

- allow easy handling,

and, where necessary:

- reduce as far as reasonably practicable and appropriate any microbial leakage from the device and/or microbial exposure during use,
- prevent microbial contamination of the device, or specimen where applicable, by the patient, user or other person.

5.8.2 Where a device incorporates substances of biological origin, the risk of infection must be reduced as far as reasonably practicable and appropriate by selecting appropriate sources, donors and substances and by using, as appropriate, validated inactivation, conservation, test and control procedures.

5.8.3 In some jurisdictions products incorporating tissues, cells and substances of non-human origin may be considered medical devices. In this case, such tissues, cells and substances should originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues. National regulations may require that the manufacturer and/or the Regulatory Authority retain information on the geographical origin of the animals. Processing, preservation, testing and handling of tissues, cells and substances of animal origin should be carried out so as to provide optimal safety. In particular, safety with regard to viruses and

other transmissible agents should be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process.

5.8.4 In some jurisdictions products incorporating human tissues, cells and substances may be considered medical devices. In this case, the selection of sources, donors and/or substances of human origin, the processing, preservation, testing and handling of tissues, cells and substances of such origin should be carried out so as to provide optimal safety. In particular, safety with regard to viruses and other transmissible agents should be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process.

5.8.5 Devices labelled as having a special microbiological state should be designed, manufactured and packed to ensure they remain so when placed on the market and remain so under the transport and storage conditions specified by the manufacturer.

5.8.6 Devices delivered in a sterile state should be designed, manufactured and packed in a non-reusable pack, and/or according to appropriate procedures, to ensure that they are sterile when placed on the market and remain sterile, under the transport and storage conditions indicated by the manufacturer, until the protective packaging is damaged or opened.

5.8.7 Devices labelled either as sterile or as having a special microbiological state should have been processed, manufactured and, if applicable, sterilized by appropriate, validated methods.

5.8.8 Devices intended to be sterilized should be manufactured in appropriately controlled (e.g. environmental) conditions.

5.8.9 Packaging systems for non-sterile devices should keep the product without deterioration at the level of cleanliness stipulated and, if the devices are to be sterilized prior to use, minimize the risk of microbial contamination; the packaging system should be suitable taking account of the method of sterilization indicated by the manufacturer.

5.8.10 The packaging and/or label of the device should distinguish between identical or similar products placed on the market in both sterile and non-sterile condition.

5.9 Manufacturing and environmental properties

5.9.1 If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system should be safe and should not impair the specified performance of the devices. Any restrictions on use applying to such combinations should be indicated on the label and/or in the instructions for use.

5.9.2 Devices should be designed and manufactured in such a way as to remove or reduce as far as reasonably practicable and appropriate:

- the risk of injury, in connection with their physical features, including the volume/pressure ratio, dimensional and where appropriate ergonomic features;
- risks connected with reasonably foreseeable external influences or

environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, pressure, humidity, temperature or variations in pressure and acceleration;

- the risks connected to their use in conjunction with materials, substances and gases with which they may come into contact during normal conditions of use;
- the risks of accidental penetration of substances into the device;
- the risk of incorrect identification of specimens;
- the risks of reciprocal interference with other devices normally used in the investigations or for the treatment given;
- risks arising where maintenance or calibration are not possible (as with implants), from ageing of materials used or loss of accuracy of any measuring or control mechanism.

5.9.3 Devices should be designed and manufactured in such a way as to minimize the risks of fire or explosion during normal use and in single fault condition. Particular attention should be paid to devices whose intended use includes exposure to or use in association with flammable substances or substances which could cause combustion.

5.9.4 Devices must be designed and manufactured in such a way as to facilitate the safe disposal of any waste substances.

5.10 Devices with a diagnostic or measuring function

5.10.1 Devices with a measuring function, where inaccuracy could have a significant adverse effect on the patient, should be designed and manufactured in such a way as to provide sufficient accuracy, precision and stability for their intended purpose of the device. The limits of accuracy should be indicated by the manufacturer.

5.10.2 Diagnostic devices should be designed and manufactured in such a way as to provide sufficient accuracy, precision and stability for their intended use, based on appropriate scientific and technical methods. In particular the design should address sensitivity, specificity, trueness, repeatability, reproducibility, control of known relevant interference and limits of detection, as appropriate.

5.10.3 Where the performance of devices depends on the use of calibrators and/or control materials, the traceability of values assigned to such calibrators and/or control materials should be assured through a quality management system.

5.10.4 Any measurement, monitoring or display scale should be designed in line with ergonomic principles, taking account of the intended purpose of the device.

5.10.5 Wherever possible values expressed numerically should be in commonly accepted, standardised units, and understood by the users of the device.

Note: While SG1 generally supports convergence on the global use of internationally standardised measurement units, considerations of safety, user familiarity, and established clinical practice may justify the use of other recognised measurement units.

5.11 Protection against radiation

5.11.1 General

5.11.1.1 Devices should be designed and manufactured and packaged in such a way that exposure of patients, users and other persons to any emitted radiation should be reduced as far as practicable and appropriate, compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for therapeutic and diagnostic purposes.

5.11.2 Intended radiation

5.11.2.1 Where devices are designed to emit hazardous, or potentially hazardous, levels of visible and/or invisible radiation necessary for a specific medical purpose the benefit of which is considered to outweigh the risks inherent in the emission, it should be possible for the user to control the emissions. Such devices should be designed and manufactured to ensure reproducibility of relevant variable parameters within an acceptable tolerance.

5.11.2.2 Where devices are intended to emit potentially hazardous, visible and/or invisible radiation, they should be fitted, where practicable, with visual displays and/or audible warnings of such emissions.

5.11.3 Unintended radiation

5.11.3.1 Devices should be designed and manufactured in such a way that exposure of patients, users and other persons to the emission of unintended, stray or scattered radiation is reduced as far as practicable and appropriate.

5.11.4 Instructions for use

5.11.4.1 The operating instructions for devices emitting radiation should give detailed information as to the nature of the emitted radiation, means of protecting the patient and the user and on ways of avoiding misuse and of eliminating the risks inherent in installation.

5.11.5 Ionizing radiation

5.11.5.1 Devices intended to emit ionizing radiation should be designed and manufactured in such a way as to ensure that, where practicable, the quantity, geometry and energy distribution (or quality) of radiation emitted can be varied and controlled taking into account the intended use.

5.11.5.2 Devices emitting ionizing radiation intended for diagnostic radiology should be designed and manufactured in such a way as to achieve appropriate image and/or output quality for the intended medical purpose whilst minimising radiation exposure of the patient and user.

5.11.5.3 Devices emitting ionizing radiation, intended for therapeutic radiology should be designed and manufactured in such a way as to enable reliable monitoring and

control of the delivered dose, the beam type and energy and where appropriate the energy distribution of the radiation beam.

5.12 Requirements for medical devices connected to or equipped with an energy source

5.12.1 Devices incorporating electronic programmable systems, including software, should be designed to ensure the repeatability, reliability and performance of these systems according to the intended use. In the event of a single fault condition in the system, appropriate means should be adopted to eliminate or reduce as far as practicable and appropriate consequent risks.

5.12.2 Devices where the safety of the patients depends on an internal power supply should be equipped with a means of determining the state of the power supply.

5.12.3 Devices where the safety of the patients depends on an external power supply should include an alarm system to signal any power failure.

5.12.4 Devices intended to monitor one or more clinical parameters of a patient should be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health

5.12.5 Devices should be designed and manufactured in such a way as to reduce as far as practicable and appropriate the risks of creating electromagnetic interference which could impair the operation of this or other devices or equipment in the usual environment.

5.12.6 Devices should be designed and manufactured in such a way as to provide an adequate level of intrinsic immunity to electromagnetic disturbance to enable them to operate as intended.

5.12.7 Protection against electrical risks

Devices should be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided the devices are installed and maintained as indicated by the manufacturer.

5.13 Protection against mechanical risks

5.13.1 Devices should be designed and manufactured in such a way as to protect the patient and user against mechanical risks connected with, for example, resistance to movement, instability and moving parts.

5.13.2 Devices should be designed and manufactured in such a way as to reduce to the lowest practicable level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.

5.13.3 Devices should be designed and manufactured in such a way as to reduce to the lowest practicable level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.

5.13.4 Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle should be designed and constructed in such a way as to minimize all possible risks.

5.13.5 Accessible parts of the devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surroundings should not attain potentially dangerous temperatures under normal use.

5.14 Protection against the risks posed to the patient by supplied energy or substances

5.14.1 Devices for supplying the patient with energy or substances should be designed and constructed in such a way that the delivered amount can be set and maintained accurately enough to guarantee the safety of the patient and of the user.

5.14.2 Devices should be fitted with the means of preventing and/or indicating any inadequacies in the delivered amount which could pose a danger. Devices should incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy from an energy and/or substance source.

5.14.3 The function of the controls and indicators should be clearly specified on the devices. Where a device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information should be understandable to the user and, as appropriate, the patient.

5.15 Protection against the risks posed to the patient for devices for self-testing or self-administration

5.15.1 Such devices should be designed and manufactured in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to users and the influence resulting from variation that can reasonably be anticipated in user's technique and environment. The information and instructions provided by the manufacturer should be easy for the user to understand and apply.

5.15.2 Such devices should be designed and manufactured in such a way as to reduce as far as practicable the risk of use error in the handling of the device and, if applicable, the specimen, and also in the interpretation of results.

5.15.3 Such devices should, where reasonably possible, include a procedure by which the user can verify that, at the time of use, that the product will perform as intended by the manufacturer.

5.16 Information supplied by the manufacturer

5.16.1 Users should be provided with the information needed to identify the manufacturer, to use the device safely and to ensure the intended performance, taking account of their training and knowledge. This information should be easily understood.

Note: Further information is provided in *SG1/N009 Labelling for Medical Devices* and in SG1/N043 *Labelling for Medical Devices (revised).*

5.17 Performance evaluation including, where appropriate, clinical evaluation

5.17.1 All data generated in support of performance evaluation should be obtained in accordance with the relevant requirements applicable in each jurisdiction.

5.17.2 Clinical investigations on human subjects should be carried out in accordance with the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results. In addition, some countries may have specific regulatory requirements for pre-study protocol review or informed consent.

Note: Refer to SG1(PD)/N040 *Principles of Conformity Assessment for Medical Devices* and the work of GHTF Study Group 5 for further information on the use of clinical evaluation to demonstrate compliance with these Essential Principles.

参考資料２：GHTF/SG1/N15:2006

GHTF FINAL DOCUMENT

『Principles of Medical Devices Classification』

FINAL DOCUMENT

Title: Principles of Medical Devices Classification

Authoring Group: Study Group 1

Endorsed by: The Global Harmonization Task Force

Date: June 27, 2006

Georgette Lalis, GHTF Chair

Table of Contents

Preface

The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device Regulatory Authorities and the regulated industry. The document is intended to provide non-binding guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

1.0 Introduction

The objective of the Global Harmonization Task Force (GHTF) is to encourage convergence at the global level in the evolution of regulatory systems for medical devices in order to facilitate trade whilst preserving the right of participating members to address the protection of public health by those regulatory means considered the most suitable.

The primary way in which the Global Harmonization Task Force (GHTF) achieves its goals is through the production of harmonized guidance documents suitable for implementation or adoption by member Regulatory Authorities, as appropriate taking into account their existing legal framework, or by nations with developing regulatory programmes. Eliminating differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

This guidance document is one of a series that together describe a global regulatory model for medical devices. Its purpose is to assist a manufacturer to allocate its medical device to an appropriate risk class using a set of harmonized principles. Regulatory Authorities have the responsibility of ruling upon matters of interpretation for a particular medical device. Once assigned, such classification will prescribe how the manufacturer will demonstrate that its device complies with other documents in the series and, in particular, with those entitled *Essential Principles of Safety and Performance of Medical Devices* and *Labelling for Medical Devices* should it be required or requested so to do by a Regulatory Authority, Conformity Assessment Body, user or third party. It seeks to strike a balance between the responsibilities of Regulatory Authorities to safeguard the health of their citizens and their obligations to avoid placing unnecessary burdens upon the industry.

This document should be read in conjunction with the GHTF document on *Principles of Conformity Assessment for Medical Devices* that recommends conformity assessment requirements appropriate to each of the four risk classes proposed herein. This link between documents on classification and conformity assessment is important to ensure a consistent approach across all countries/regions adopting the global regulatory model recommended by the GHTF, so that premarket approval for a particular device may become acceptable globally. Regulatory Authorities who have different classification procedures are encouraged to adopt this GHTF guidance as the opportunity permits.

This document is intended for use by Regulatory Authorities, Conformity Assessment Bodies and industry, and will provide benefits in establishing, in a consistent way, an economic and effective approach to the control of medical devices in the interest of public health.

Regulatory Authorities that are developing classification schemes or amending existing ones are encouraged to consider the adoption of the system described in this document, as this will help to reduce the diversity of schemes worldwide and facilitate the process of harmonization.

At this time, classification requirements and other regulatory controls assigned to a medical device by different Regulatory Authorities have yet to be harmonized and may vary from the guidance provided in this document.

This guidance document has been prepared by Study Group 1 of the Global Harmonization Task Force (GHTF). Comments or questions about it should be directed to either the Chairman or Secretary of GHTF Study Group 1 whose contact details may be found on the GHTF web page.

2.0 Scope

This document applies to all products that fall within the definition of a medical device that appears within the GHTF document *Information Document Concerning the Definition of the Term 'Medical Device',* **other than those** used for the *in vitro* examination of specimens derived from the human body for which a separate document is being developed.

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3.0 References

GHTF final documents

GHTF/SG1/N12:2000 *Role of Standards in the Assessment of Medical Devices.*

GHTF/SG1/N29:2005 *Information Document Concerning the Definition of the Term 'Medical Device'.*

GHTF/SG1/N40:2006 *Principles of Conformity Assessment for Medical Devices.*

GHTF/SG1/N41:2005 *Essential Principles of Safety and Performance of Medical Devices.*

GHTF/SG1/N43:2005 *Labelling for Medical Devices.*

4.0 Definitions

Active medical device: Any medical device, operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Medical devices intended to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, are not considered to be active medical devices. (Source - European Directive 93/42/EEC)

Active therapeutic device: Any active medical device, whether used alone or in combination with other medical devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness, injury or handicap. (Source - European Directive 93/42/EEC)

Active device intended for diagnosis: Any active medical device, whether used alone or in combination with other medical devices, to supply information for detecting, diagnosing, monitoring or to support in treating physiological conditions, states of health, illnesses or congenital deformities. (Source – based on European Directive 93/42/EEC)

Central circulatory system: For the purpose of this document, central circulatory system means the major internal blood vessels including the following: pulmonary veins, pulmonary arteries, cardiac veins, coronary arteries, carotid arteries (common, internal and external), cerebral arteries, brachiocephalic artery, aorta (includes all segments of the aorta), inferior and superior vena cava and common iliac arteries.

Central nervous system: For the purpose of this document, central nervous system means brain, meninges and spinal cord. (Source - European Directive 93/42/EEC)

Duration of use

Transient: Normally intended for continuous use for less than 60 minutes.

Short term: Normally intended for continuous use for between 60 minutes and 30 days.

Long term: Normally intended for continuous use for more than 30 days.

NOTE: For the purpose of this document, continuous use means:

a) The entire duration of use of the device without regard to temporary interruption of use during a procedure or, temporary removal for purposes such as cleaning or disinfection of the device.

b) The accumulated use of a device that is intended by the manufacturer to be replaced immediately with another of the same type.
(Source - European Directive 93/42/EEC - modified)

Harm: Physical injury or damage to the health of people or damage to property or the environment. (Source – ISO/IEC Guide 51:1999)

Hazard: Potential source of harm. (Source – ISO/IEC Guide 51:1999)

Immediate danger: A situation where the patient is at risk of either losing life or an important physiological function if no immediate preventative measure is taken.

Intended use / purpose: The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.

Invasive devices

Invasive device: A device, which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.

Body orifice: Any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma or permanent tracheotomy.

Surgically invasive device: An invasive device which penetrates inside the body through the surface of the body, with the aid or in the context of a surgical operation.

NOTE: Devices other than those referred to in the previous subparagraph and which produce penetration other than through an established body orifice, should be treated as surgically invasive devices.

Implantable device: Any device, including those that are partially or wholly absorbed, which is intended: -

- to be totally introduced into the human body or,
- to replace an epithelial surface or the surface of the eye,

by surgical intervention which is intended to remain in place after the procedure.

Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device.
(Source - European Directive 93/42/EEC)

Life supporting or life sustaining: A device that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.

Medical device: See GHTF guidance document: *Information Document Concerning the Definition of the Term 'Medical Device'* (GHTF/SG1/N29:2005).

Reusable surgical instrument: Instrument intended for surgical use by cutting, drilling, sawing, scratching, scraping, clamping, retracting, clipping or other surgical procedures, without connection to any active medical device and which are intended by the manufacturer to be reused after appropriate procedures for cleaning and/or sterilisation have been carried out. (Source - European Directive 93/42/EEC – modified)

Risk: Combination of the probability of occurrence of harm and the severity of that harm. (Source – ISO/IEC Guide 51:1999)

5.0 General Principles

Regulatory controls are intended to safeguard the health and safety of patients, users and other persons by ensuring that manufacturers of medical devices follow specified procedures during design, manufacture and marketing.

The GHTF guidance documents *Essential Principles of Safety and Performance of Medical Devices* and *Labelling for Medical Devices* **apply to all devices whatever their risk class**.

Regulatory controls should be proportional to the level of risk associated with a medical device. The level of regulatory control should increase with increasing degree of risk, taking account of the benefits offered by use of the device. At the same time, the imposition of regulatory controls should not place an unnecessary burden on regulators or manufacturers.

Therefore:

- there is a need to classify medical devices based on their risk to patients, users and other persons; and
- there is benefit for manufacturers and Regulatory Authorities if a globally harmonized classification system is developed.

The risk presented by a particular device depends substantially on its intended purpose and the effectiveness of the risk management techniques applied during design, manufacture and use.

The risk presented by a device also depends, in part, on its intended user(s), its mode of operation, and/or technologies. In general, the classification rules are intended to accommodate new technologies. Without prejudice to these rules, Regulatory Authorities may wish to require the notification of new devices being placed on the market in their jurisdictions. Such notification may be used in assessing the evidence requirements for use in the conformity assessment process. It may also be used to consider the need, if any, for possible re-classification and/or changes in these harmonized classification rules.

6.0 Recommendations

6.1 Primary Recommendations

- Regulatory Authorities should work towards the establishment of a global classification system.
- This system should consist of four risk classes. Based on experience of GHTF Founding Members, this is sufficient to accommodate all medical devices and allows an efficient and graduated system of conformity assessment controls.
- The initial determination of class should be based on a set of rules derived from those features of devices that create risk. In most cases the initial rules based classification will also be the final classification.
- These rules should be sufficiently clear that manufacturers may readily identify the class of their medical devices, subject, as required, to final classification by the Regulatory Authority.
- The rules should be capable of accommodating future technological developments.
- The manufacturer should document its justification for placing its product into a particular risk class, including the resolution of any matters of interpretation where it has asked a Regulatory Authority and/or Conformity Assessment Body for a ruling.
- Decisions on final classifications, which deviate from the initial rules-based classification, should be weighed against the disadvantages of disharmonized international classification.

6.2 Factors Influencing Device Classification

A number of factors, including for example the duration of device contact with the body, the degree of invasiveness, whether the device delivers medicinal products or energy to the

patient, whether they are intended to have a biological affect on the patient and local *versus* systemic effects (e.g. conventional *versus* absorbable sutures) may, alone or in combination, affect device classification.

If, based on the manufacturer's intended purpose, two or more classification rules apply to the device, the device is allocated the highest level of classification indicated.

Where one medical device is intended to be used together with another medical device, that may or may not be from the same manufacturer, (e.g. a physiological monitor and a separate recorder, or a general purpose syringe and a syringe driver), the classification rules should apply separately to each of the devices.

Classification of an assemblage of medical devices that individually comply with all regulatory requirements depends on the manufacturer's purpose in packaging and marketing such a combination of separate devices. For example:

- If the combination results in a product that is intended by the manufacturer to meet a purpose different from that of the individual medical devices that make it up, the combination is a new medical device in its own right and should be classified according to the new intended use.
- If the combination is for the convenience of the user but does not change the intended uses of the individual medical devices that make it up (e.g. a customised kit that provides all the devices necessary to carry out a particular surgical procedure), the classification allocated to the assemblage for the purpose of a Declaration of Conformity is at the level of the highest classified device included within it.

If one or more of the medical devices that is in the assemblage has yet to comply with all the relevant regulatory requirements, the combination should be classified as a whole according to its intended use.

Accessories intended specifically by manufacturers to be used together with a 'parent' medical device to enable that medical device to achieve its intended purpose, should be subject to all the GHTF guidance documents as apply to the medical device itself (e.g. Essential principles for Safety and Performance, post-market surveillance etc.). For classification purposes an accessory may be classified as though it is a medical device in its own right.

While most software is incorporated into the medical device itself, some is not. Provided such standalone software falls within the scope of the definition for a 'medical device', it should be classified as follows:

- Where it drives or influences the use of a separate medical device, it should be classified according to the intended use of the combination.
- Where it is independent of any other medical device, it is classified in its own right using the rules in Section 8.0 of this document.
- Standalone software (to the extent it falls within the definition of a medical device) is deemed to be an active device.

Experience gained from the clinical use of a particular type of medical device may suggest that the rules appearing in Section 8.0 of this document are inappropriate. Current GHTF procedures require that all GHTF documents be reviewed at regular intervals. Such a review of this document will provide any participant with an opportunity to suggest a change of text that, in his/her opinion, will address any shortcoming.

The purpose of risk classification is to make sure that the regulatory controls applied to a medical device are proportionate to risk. Statutory conformity assessment authority provides Regulatory Authorities methods to assure compliance with regulatory controls. At this time, conformity assessment requirements and other regulatory controls assigned to each class of device by different Regulatory Authorities have yet to be harmonized and may vary. While Study Group 1 of GHTF continues to support and encourage regulatory harmonization, it recognises that some Regulatory Authorities may have to reflect different local needs or social considerations when they introduce new regulations on classification, for example, in the application of devices covered by the Additional Rules 13 to 16. Study Group 1 hopes any such differences will disappear in the course of time.

6.3 Proposed General Classification System for Medical Devices

Figure 1 indicates the four risk classes of devices. The examples given are for illustration only and the manufacturer must apply the classification rules to each medical device according to its intended purpose.

Figure 1: Proposed general classification system for medical devices

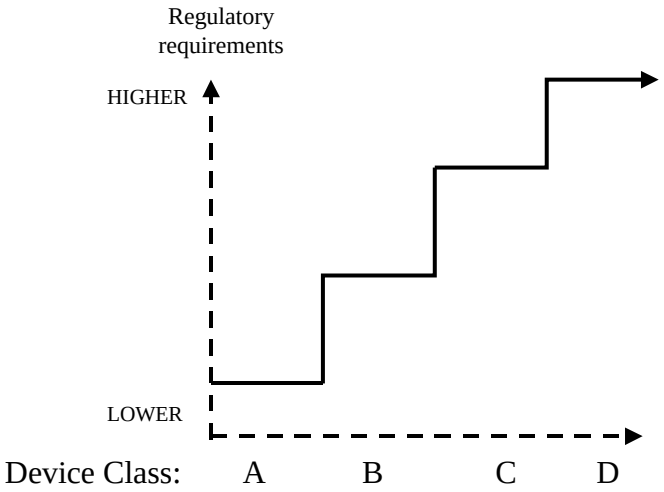
CLASS	RISK LEVEL	DEVICE EXAMPLES
A	Low Risk	Surgical retractors / tongue depressors
B	Low-moderate Risk	Hypodermic Needles / suction equipment
C	Moderate-high Risk	Lung ventilator / bone fixation plate
D	High Risk	Heart valves / implantable defibrillator

Figure 2 shows a conceptual illustration of increasing levels of regulatory requirements as the device risk class increases. These regulatory controls may include, for example: -

- operation of a quality system (recommended for all devices);
- technical data;
- product testing using in-house or independent resources;
- documentation of clinical evidence to support the manufacturer's claims;
- the need for and frequency of independent external audit of the manufacturer's quality system; and
- independent external review of the manufacturer's technical data.

The concept is expanded in the GHTF guidance document entitled *Principles of Conformity Assessment for Medical Devices*.

Figure 2: Conceptual illustration of regulatory controls increasing with device risk class



7.0 The Determination of Device Class using this Rules-based System

The manufacturer should:

1. Decide if the product concerned is a medical device, using the appropriate definition.

   NOTE: Medical devices that are used for the *in vitro* examination of specimens derived from the human body are not covered by the classification rules within this document (see Scope).

2. Document the intended use of the medical device.

3. Take into consideration all the rules that follow in order to establish the proper classification for the device, noting that **where a medical device has features that place it into more than one class, classification and conformity assessment should be based on the highest class indicated.**

4. Determine if the device is subject to special national rules that apply within a particular jurisdiction..

NOTES:

- Once a rules-based system has been adopted, modifications **may occasionally be required**. For example, where through post-market experience, a level of risk for a type of medical device, classified using the criteria found in this guidance document is

no longer appropriate, consideration should be given to re-classification of the device type by a change to the rules.

- Similarly, the historical knowledge of a device may necessitate a different class than the one assigned by the initial classification. Unlike the principle of reclassification after post-market experience with a device, this principle of historical knowledge should be applied immediately when the initial classification yields an inappropriate result.

- Where special national rules are applied, resulting in a device class other than that suggested by the present rules, then a different conformity assessment procedure may be indicated. This may have an effect on the acceptability of such devices for free movement in countries where these present rules have been adopted unless other, or additional, conformity assessment procedures are carried out.

8.0 Initial Classification Rules

The actual classification of each device depends on the claims made by the manufacturer and on its intended use. While the provision of illustrative examples in the table that follows is helpful when interpreting the purpose of each rule, it must be emphasised that the actual classification of a particular device must be considered individually, taking account of its design and intended use.

RULE	ILLUSTRATIVE EXAMPLES OF DEVICES THAT MAY CONFORM WITH A RULE
➢ ***NON-INVASIVE DEVICES***	
Rule 1. All non-invasive devices which come into contact with injured skin:	Devices covered by this rule are extremely claim sensitive.
- are in Class A if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates only, i.e. they heal by primary intent;	Examples: simple wound dressings; cotton wool.
- are in Class B if they are intended to be used principally with wounds which have breached the dermis, including devices principally intended to manage the microenvironment of a wound.	Examples: non-medicated impregnated gauze dressings.
unless they are intended to be used principally with wounds which have breached the dermis and can only heal by secondary intent, in which case they are in Class C.	Devices used to treat wounds where the subcutaneous tissue is as least partially exposed and the edges of the wound are not sufficiently close to be pulled together. To close the wound, new tissue must be formed within the wound prior to external closure. The device manufacturer claims that they promote healing through physical methods other than 'primary intent'. Examples: dressings for chronic ulcerated wounds; dressings for severe burns.

Rule 2. All non-invasive devices intended for channelling or storing • body liquids or tissues, • liquids or • gases for the purpose of eventual infusion, administration or introduction into the body are in Class A,	Such devices are 'indirectly invasive' in that they channel or store liquids that will eventually be delivered into the body (see comment for Rule 4). Examples: administration sets for gravity infusion; syringes without needles.
unless they may be connected to an active medical device in Class B or a higher class, in which case they are Class B;	Examples: syringes and administration sets for infusion pumps; anaesthesia breathing circuits. **NOTE:** "Connection" to an active device covers those circumstances where the safety and performance of the active device is influenced by the non-active device and *vice versa*.
unless they are intended for use of • channeling blood, or • storing or channeling other body liquids, or • for storing organs, parts of organs or body tissues, in which case they are Class B.	Examples: tubes used for blood transfusion, organ storage containers.
unless they are blood bags, in which case they are Class C.	Example: Blood bags that do not incorporate an anti-coagulant. **NOTE:** in some jurisdictions, blood bags have a special rule that places them within a different risk class.
Rule 3. All non-invasive devices intended for modifying the biological or chemical composition of • blood, • other body liquids, or • other liquids intended for infusion into the body are in Class C,	Such devices are indirectly invasive in that they treat or modify substances that will eventually be delivered into the body (see note to comment for Rule 4). They are normally used in conjunction with an active device within the scope of either Rule 9 or 11. Examples: haemodializers; devices to remove white blood cells from whole blood. **NOTE**: for the purpose of this part of the rule, 'modification' does not include simple, mechanical filtration or centrifuging which are covered below.
unless the treatment consists of filtration, centrifuging or exchanges of gas or of heat, in which case they are in Class B.	Examples: devices to remove carbon dioxide; particulate filters in an extracorporial circulation system.
Rule 4. All other non-invasive devices are in Class A.	These devices either do not touch the patient or contact intact skin only. Examples: urine collection bottles; compression hosiery; non-invasive electrodes, hospital beds.
➢ ***INVASIVE DEVICES***	
Rule 5. All invasive devices with respect to body orifices (other than	Such devices are invasive in body orifices and are not surgically invasive (refer to definition in

those which are surgically invasive) and which: • are not intended for connection to an active medical device, or • are intended for connection to a Class A medical device only.	Section 4). Devices tend to be diagnostic and therapeutic instruments used in ENT, ophthalmology, dentistry, proctology, urology and gynaecology. Classification depends on the duration of use and the sensitivity (or vulnerability) of the orifice to such invasion.
- are in Class A if they are intended for transient use;	Examples: examination gloves; enema devices.
- are in Class B if they are intended for short-term use;	Examples: urinary catheters, tracheal tubes.
unless they are intended for short-term use in the oral cavity as far as the pharynx, in an ear canal up to the ear drum or in a nasal cavity, in which case they are in Class A,	Examples: dentures intended to be removed by the patient; dressings for nose bleeds.
- are in Class C if they are intended for long-term use;	Example: urethral stent; contact lenses for long-term continuous use (for this device, removal of the lens for cleaning or maintenance is considered as part of the continuous use).
unless they are intended for long-term use in the oral cavity as far as the pharynx, in an ear canal up to the ear-drum or in a nasal cavity and are not liable to be absorbed by the mucous membrane, in which case they are in Class B.	Examples: orthodontic wire, fixed dental prosthesis.
All invasive devices with respect to body orifices (other than those which are surgically invasive) that are intended to be connected to an active medical device in Class B or a higher class, are in Class B.	Examples: tracheal tubes connected to a ventilator; suction catheters for stomach drainage; dental aspirator tips. **NOTE:** independent of the time for which they are invasive.
Rule 6. All surgically invasive devices intended for transient use are in Class B,	A majority of such devices fall into several major groups: those that create a conduit through the skin (e.g. syringe needles; lancets), surgical instruments (e.g. single-use scalpels; surgical staplers; single-use aortic punch); surgical gloves; and various types of catheter/sucker etc. **NOTE**: a surgical instrument (other than those in Class D) is in Class A if reusable and in Class B if supplied sterile and intended for single use. Also, a surgical instrument connected to an active device is in a higher class than A. **NOTE:** if the device incorporates a medicinal substance in a secondary role refer to Rule 13.
unless they are reusable surgical instruments, in which case they are in Class A; or	Examples: Manually operated surgical drill bits and saws.
unless intended to supply energy in the	Example: catheter incorporating/containing

form of ionizing radiation, in which case they are in Class C; or	sealed radioisotopes.
unless intended to have a biological effect or be wholly or mainly absorbed, in which case they are in Class C; or	**NOTES**: (a) the 'biological effect' referred to is an intended one rather than unintentional. The term 'absorption' refers to the degradation of a material within the body and the metabolic elimination of the resulting degradation products from the body. (b) This part of the rule does not apply to those substances that are excreted without modification from the body. Example: Insufflation gases for the abdominal cavity.
unless intended to administer medicinal products by means of a delivery system, if this is done in a manner that is potentially hazardous taking account of the mode of application, in which they are in Class C; or	Example: insulin pen for self-administration. **NOTE**: the term 'administration of medicines' implies storage and/or influencing the rate/volume of medicine delivered not just channelling. The term 'potentially hazardous manner' refers to the characteristics of the device and not the competence of the user.
unless they are intended specifically for use in direct contact with the central nervous system, in which case they are in Class D; or	
unless intended specifically to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class D.	Examples: angioplasty balloon catheters and related guide wires; dedicated disposable cardiovascular surgical instruments.
Rule 7. All surgically invasive devices intended for short-term use are in Class B,	Such devices are mostly used in the context of surgery or post-operative care, or are infusion devices, or are catheters of various types. Examples: infusion cannulae; temporary filling materials; non-absorbable skin closure devices; tissue stabilisers used in cardiac surgery. **NOTE:** includes devices that are used during cardiac surgery but do not monitor or correct a defect. **NOTE:** if the device incorporates a medicinal substance in a secondary role refer to Rule 13.
unless they are intended to administer medicinal products, in which case they are in Class C; or	**NOTE**: the term 'administration of medicines' implies storage and/or influencing the rate/volume of medicine delivered not just channelling.
unless they are intended to undergo chemical change in the body (except if the devices are placed in the teeth), in which case they are in Class C; or	Example: surgical adhesive.
unless they are intended to supply	Example: brachytherapy device.

energy in the form or ionizing radiation, in which case they are in Class C; or	
unless they are intended to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class D; or	Example: absorbable suture; biological adhesive. **NOTE**: the 'biological effect' referred to is an intended one rather than unintentional. The term 'absorption' refers to the degradation of a material within the body and the metabolic elimination of the resulting degradation products from the body.
unless they are intended specifically for use in direct contact with the central nervous system, in which case they are in Class D;	Example: neurological catheter.
unless they are intended specifically to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class D.	Examples: cardiovascular catheters; temporary pacemaker leads; carotid artery shunts.
Rule 8. All implantable devices, and long-term surgically invasive devices, are in Class C,	Most of the devices covered by this rule are implants used in the orthopaedic, dental, ophthalmic and cardiovascular fields. Example: maxilla-facial implants; prosthetic joint replacements; bone cement; non-absorbable internal sutures; posts to secure teeth to the mandibula bone (without a bioactive coating). **NOTE:** if the device incorporates a medicinal substance in a secondary role refer to Rule 13.
unless they are intended to be placed into the teeth, in which case they are in Class B; or	Examples: bridges; crowns; dental filling materials.
unless they are intended to be used in direct contact with the heart, the central circulatory system or the central nervous system, in which case they are in Class D; or	Examples: prosthetic heart valves; spinal and vascular stents.
unless they are intended to be life supporting or life sustaining, in which case they are in Class D; or	
unless they are intended to be active implantable medical devices, in which case they are Class D; or	Example: pacemakers, their electrodes and their leads; implantable defibrillators.
unless they are intended to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class D; or	Example: implants claimed to be bioactive. **NOTE**: hydroxy-apatite is considered as having biological effect only if so claimed and demonstrated by the manufacturer.
unless they are intended to administer medicinal products, in which case they are in Class D; or	Example: rechargeable non-active drug delivery system.

unless they are intended to undergo chemical change in the body (except if the devices are placed in the teeth), in which case they are in Class D; or	**NOTE**: bone cement is not within the scope of the term 'chemical change in the body' since any change takes place in the short rather than long term.
unless they are breast implants, in which case they are in Class D.	
➢ ***ACTIVE DEVICES***	
Rule 9(i). All active therapeutic devices intended to administer or exchange energy are in Class B,	Such devices are mostly electrically powered equipment used in surgery; devices for specialised treatment and some stimulators. Examples: muscle stimulators; TENS devices; powered dental hand pieces; hearing aids; neonatal phototherapy equipment; ultrasound equipment for physiotherapy.
unless their characteristics are such that they may administer or exchange energy to or from the human body in a potentially hazardous way, including ionizing radiation, taking account of the nature, the density and site of application of the energy, in which case they are in Class C.	Examples: lung ventilators; baby incubators; electrosurgical generators; external pacemakers and defibrillators; surgical lasers; lithotriptors; therapeutic X-ray and other sources of ionizing radiation. **NOTE**: the term 'potentially hazardous' refers to the type of technology involved and the intended application.
Rule 9(ii). All active devices intended to control or monitor the performance of active therapeutic devices in Class C, or intended directly to influence the performance of such devices, are in Class C.	Examples: external feedback systems for active therapeutic devices.
Rule 10(i). Active devices intended for diagnosis are in Class B:	Such devices include equipment for ultrasonic diagnosis/imaging, capture of physiological signals, interventional radiology and diagnostic radiology.
- if they are intended to supply energy which will be absorbed by the human body (except for devices used solely to illuminate the patient's body, with light in the visible or near infra-red spectrum, in which case they are Class A), or	Examples: magnetic resonance equipment; diagnostic ultrasound in non-critical applications; evoked response stimulators.
- if they are intended to image *in vivo* distribution of radiopharmaceuticals, or	Example: gamma/nuclear cameras.
- if they are intended to allow direct diagnosis or monitoring of vital physiological processes,	Example: electronic thermometers, stethoscopes and blood pressure monitors; electrocardiographs.
unless they are specifically intended for: a) monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for	Example: monitors/alarms for intensive care; biological sensors; oxygen saturation monitors; apnoea monitors.

instance variations in cardiac performance, respiration, activity of central nervous system, or b) diagnosing in clinical situations where the patient is in immediate danger, in which case they are in Class C.	Example: ultrasound equipment for use in interventional cardiac procedures.
Rule 10(ii). Active devices intended to emit ionizing radiation and intended for diagnostic and/or interventional radiology, including devices which control or monitor such devices, or those which directly influence their performance, are in Class C.	Example: these include devices for the control, monitoring or influencing of the emission of ionizing radiation.
Rule 11. All active devices intended to administer and/or remove medicinal products, body liquids or other substances to or from the body are in Class B,	Such devices are mostly drug delivery systems or anaesthesia equipment. Examples of Class B devices: suction equipment; feeding pumps; jet injectors for vaccination; nebuliser to be used on conscious and spontaneously breathing patients where failure to deliver the appropriate dosage characteristics is not potentially hazardous.
unless this is done in a manner that is potentially hazardous, taking account of the nature of the substances involved, of the part of the body concerned and of the mode and route of administration, in which case they are in Class C.	Examples: infusion pumps; anaesthesia equipment; dialysis equipment; hyperbaric chambers; nebuliser where the failure to deliver the appropriate dosage characteristics could be hazardous.
Rule 12. All other active devices are in Class A.	Examples: examination lamps; surgical microscopes; powered hospital beds & wheelchairs; powered equipment for the recording, processing, viewing of diagnostic images; dental curing lights.
➢ ***ADDITIONAL RULES***	
Rule 13. All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, and which is liable to act on the human body with action ancillary to that of the devices, are in Class D.	These medical devices incorporate medicinal substances in an ancillary role. Examples: antibiotic bone cements; heparin-coated catheters; wound dressings incorporating antimicrobial agents to provide ancillary action on the wound; blood bags incorporating an anti-coagulant. **NOTE:** Such medical devices may be subject to additional conformity assessment procedures according to the regional or national requirements of medicinal product Regulatory Authorities.
Rule 14. All devices manufactured from or incorporating animal or human	**NOTE:** In some jurisdictions such products: - are considered to be outside the scope of the

cells/tissues/derivatives thereof, whether viable or non-viable, are Class D,	medical device definition; - may be subject to different controls. It is likely the regulations controlling these devices will be the subject of future harmonization efforts. Examples: porcine heart valves; catgut sutures.
unless such devices are manufactured from or incorporate non-viable animal tissues or their derivatives that come in contact with intact skin only, where they are in Class A.	Examples: leather components of orthopaedic appliances.
Rule 15. All devices intended specifically to be used for sterilising medical devices, or disinfecting as the end point of processing, are in Class C.	Examples: devices for disinfecting or sterilising endoscopes; disinfectants intended to be used with medical devices. **NOTE:** This rule does not apply to products that are intended to clean medical devices by means of physical action e.g. washing machines.
unless they are intended for disinfecting medical devices prior to end point sterilisation or higher level disinfection, in which case they are in Class B; or	Example: washer disinfectors.
unless they are intended specifically to be used for disinfecting, cleaning, rinsing or, when appropriate, hydrating contact lenses, in which case they are in Class C.	In some jurisdictions solutions for use with contact lenses: - are considered to be outside the scope of the medical devices definition; - may be subject to different controls.
Rule 16. All devices used for contraception or the prevention of the transmission of sexually transmitted diseases are in Class C,	Examples: condoms; contraceptive diaphragms.
unless they are implantable or long-term invasive devices, in which case they are in Class D.	Example: intrauterine contraceptive device.

Decision trees illustrating how these rules may be used to classify specific devices are shown in Appendix A.

8.1 Rationale for the inclusion of the Additional Rules into this document

There are a small number of products that fall within the scope of the definition of a medical device and which may need to be classified to take account of factors other than those covered by the general rules (Rules 1 to 12). For the understanding of those countries that are not Founding Members of GHTF, it is felt important to offer guidance on the classification of such devices (see Clause 6.2, above). Therefore, four Additional Rules are provided (Rules 13 to 16).

Matters that may need to be considered are: -

Rule 13: Devices incorporating a medicinal product

- The regulations applying to medicinal products require different acceptance procedures to those for medical devices.
- The behavior of a medicinal product used in conjunction with a medical device may differ from that covered by its approved use as a medicinal product alone.

Rule 14: Devices incorporating animal or human tissues

- There is an absence of global regulatory controls for such devices.
- Classification needs to acknowledge the diversity of opinions on such devices, globally.
- The possible risks associated with the transmission of infectious agents through materials used in such devices, e.g. Bovine Spongiform Encephalopathies (BSE) and Creutzfeldt-Jacob disease (CJD), demand classification at a higher risk level.

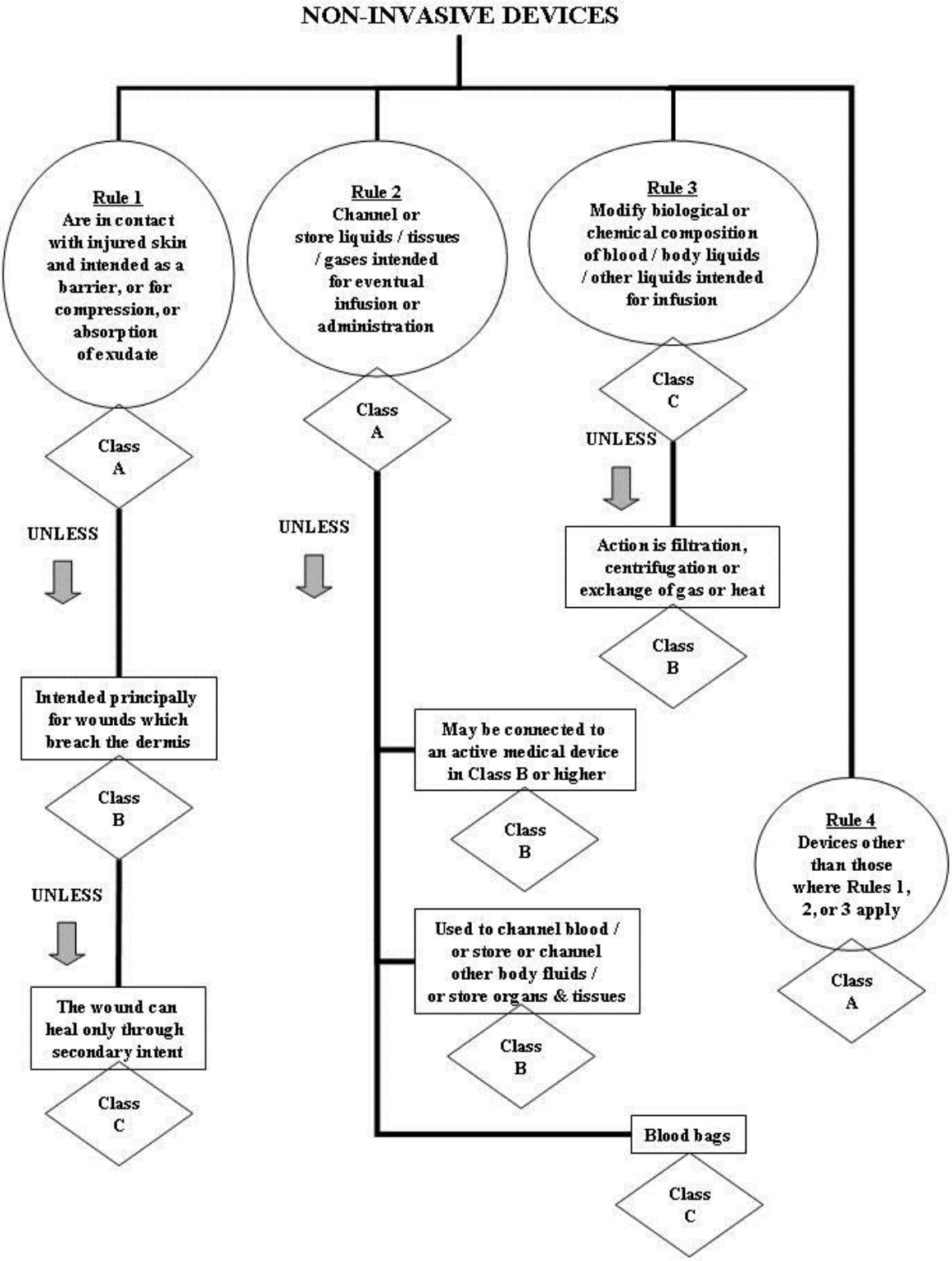
Rule 15 Disinfectants

- The particular concerns relating to those disinfectants that are used with contact lenses, due to sensitivity and vulnerability of the eye.

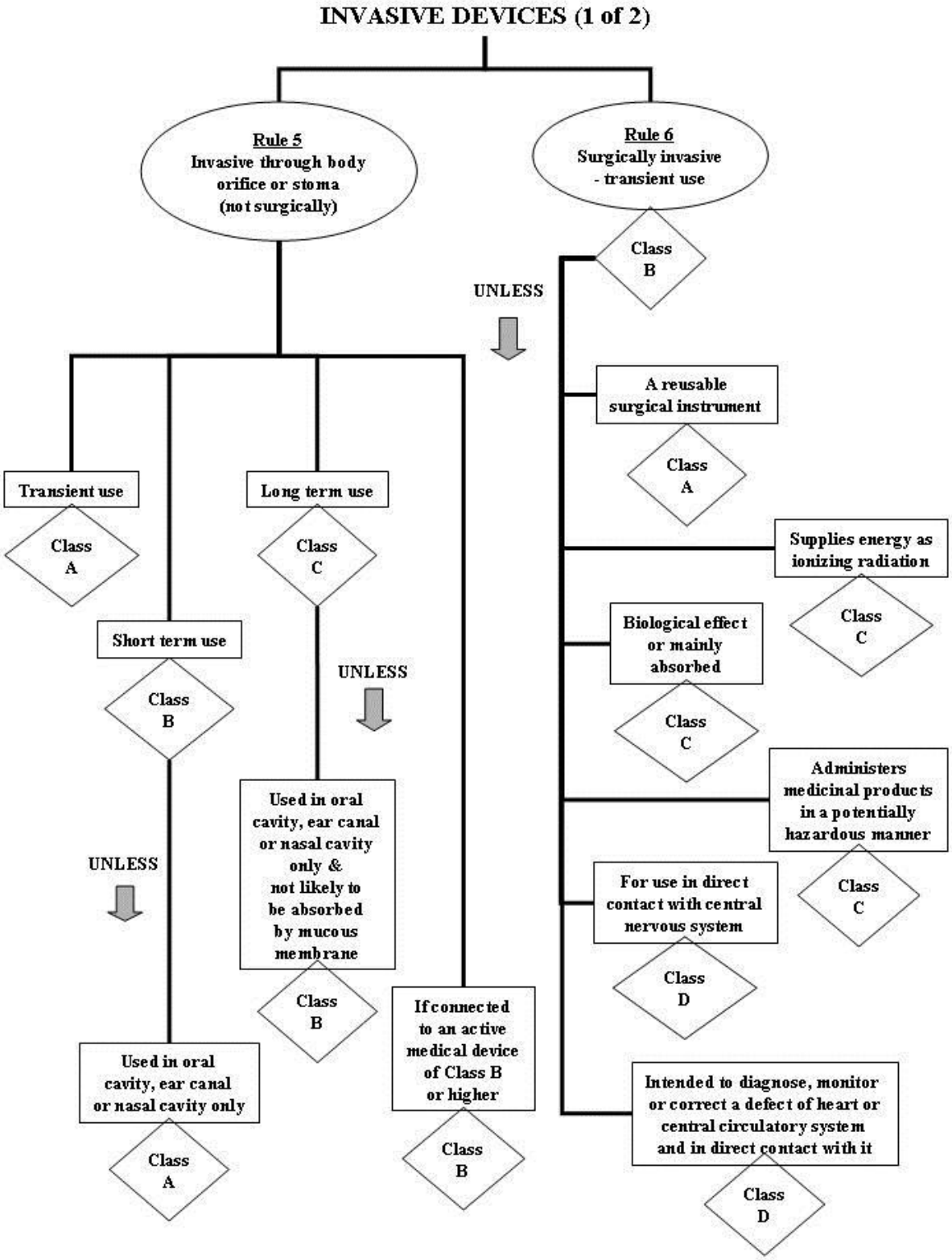
Rule 16 Contraceptive devices

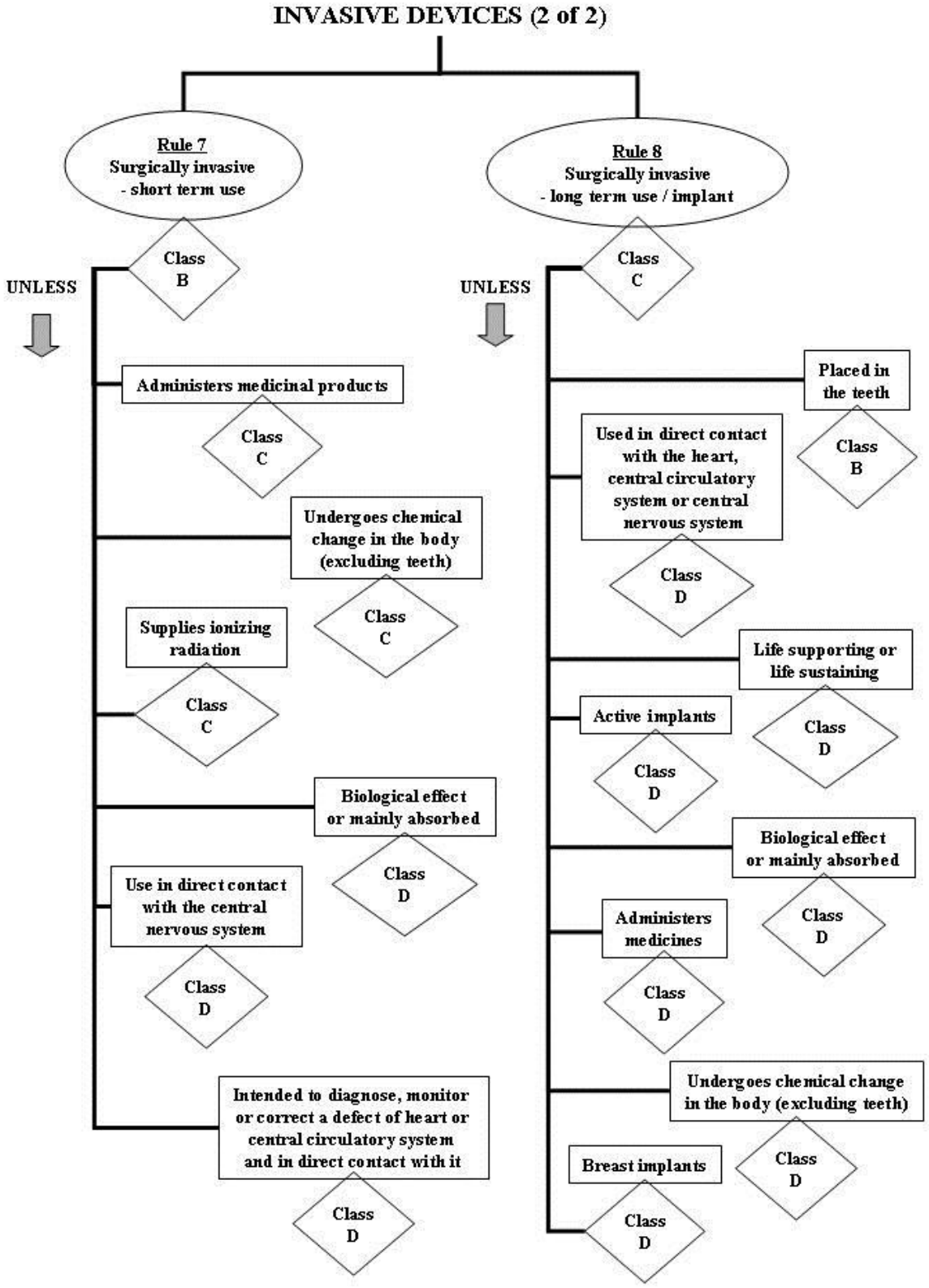
- The risks associated with unwanted pregnancy if caused by mechanical failure of the device.
- The need to safeguard public health through the use of condoms to reduce the prevalence of sexually transmitted diseases.
- User expectation that contraceptive devices are perfectly reliable and safe despite published data to the contrary.

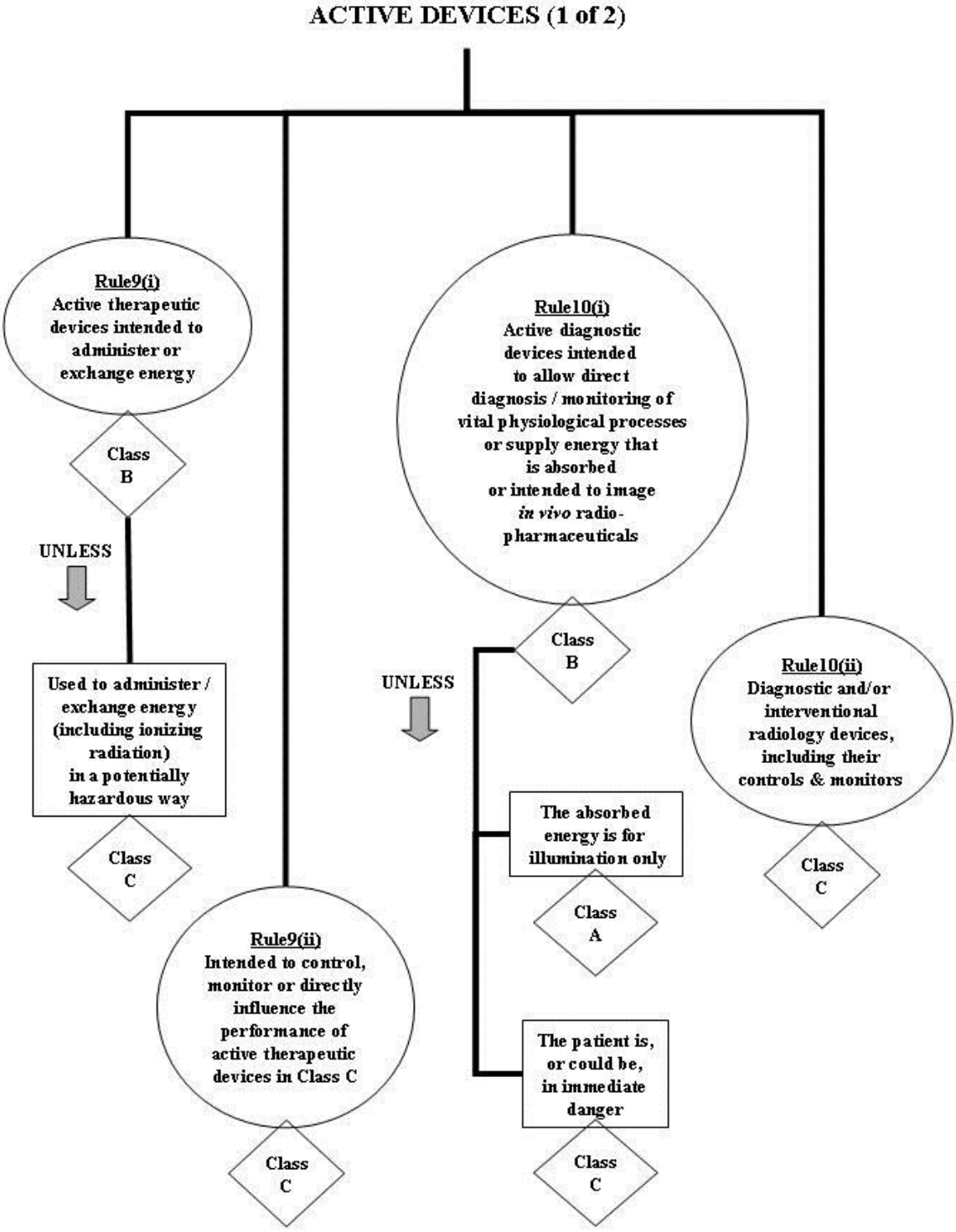
Appendix A: Decision trees to demonstrate how the rules may be used to classify specific devices.

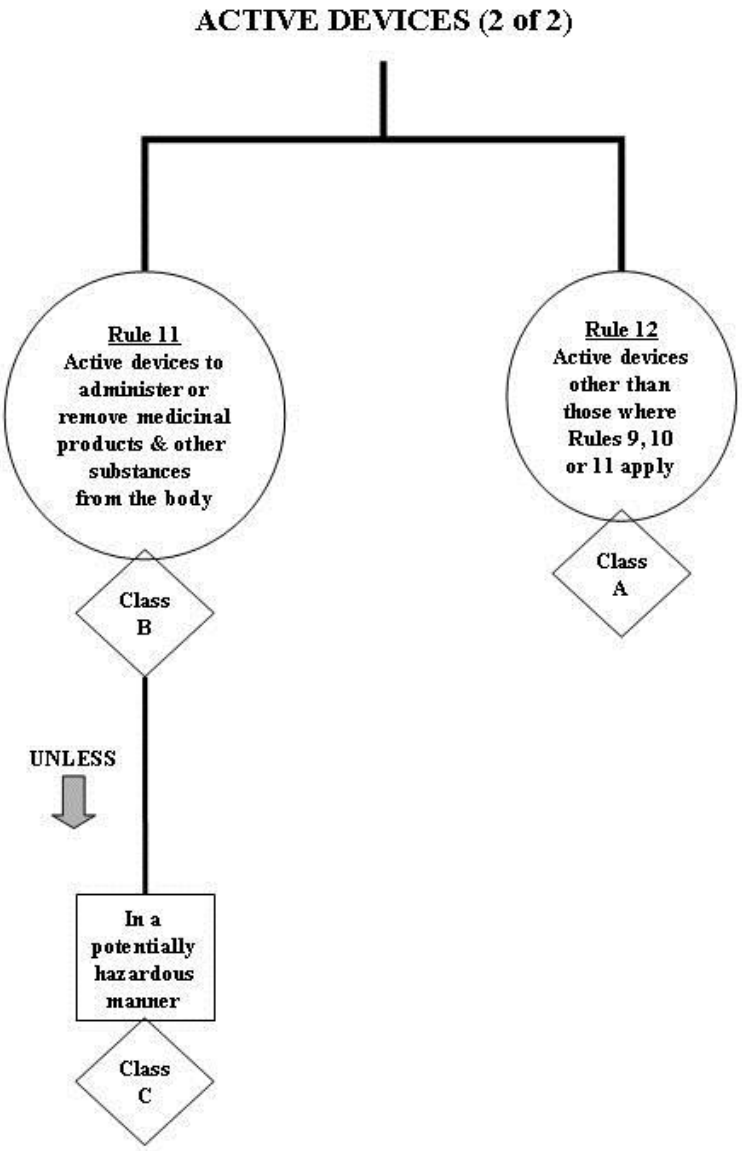


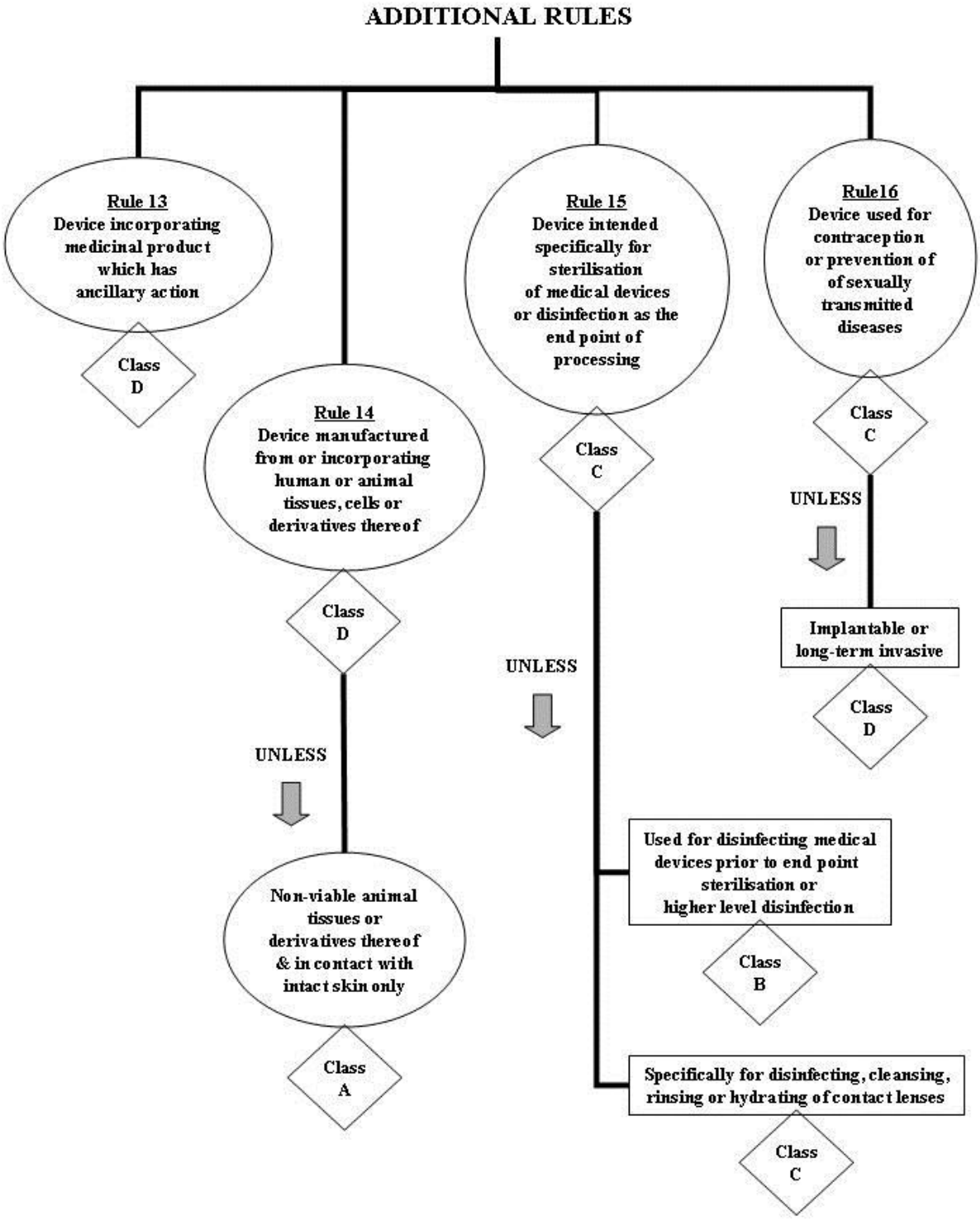
NOTE: This diagram and those that follow are for illustrative purposes only and the determination of risk class for a particular device should be made by referring to the rules themselves and not the decision trees. Where a medical device has features that place it into more than one class, conformity assessment should be based on the highest class indicated.


INVASIVE DEVICES (1 of 2)
Rule 5
Invasive through body orifice or stoma (not surgically)
Rule 6
Surgically invasive - transient use
Class B
UNLESS
A reusable surgical instrument
Class A
Supplies energy as ionizing radiation
Class C
Biological effect or mainly absorbed
Class C
Administers medicinal products in a potentially hazardous manner
Class C
For use in direct contact with central nervous system
Class D
Intended to diagnose, monitor or correct a defect of heart or central circulatory system and in direct contact with it
Class D
Transient use
Class A
Long term use
Class C
Short term use
Class B
UNLESS
Used in oral cavity, ear canal or nasal cavity only
Class A
UNLESS
Used in oral cavity, ear canal or nasal cavity only & not likely to be absorbed by mucous membrane
Class B
If connected to an active medical device of Class B or higher
Class B


INVASIVE DEVICES (2 of 2)
Rule 7
Surgically invasive
- short term use
Class
B
UNLESS
Administers medicinal products
Class
C
Undergoes chemical change in the body (excluding teeth)
Class
C
Supplies ionizing radiation
Class
C
Biological effect or mainly absorbed
Class
D
Use in direct contact with the central nervous system
Class
D
Intended to diagnose, monitor or correct a defect of heart or central circulatory system and in direct contact with it
Class
D
Rule 8
Surgically invasive
- long term use / implant
Class
C
UNLESS
Placed in the teeth
Class
B
Used in direct contact with the heart, central circulatory system or central nervous system
Class
D
Life supporting or life sustaining
Class
D
Active implants
Class
D
Biological effect or mainly absorbed
Class
D
Administers medicines
Class
D
Undergoes chemical change in the body (excluding teeth)
Class
D
Breast implants
Class
D


ACTIVE DEVICES (1 of 2)
Rule9(i)
Active therapeutic devices intended to administer or exchange energy
Class B
UNLESS
Used to administer / exchange energy (including ionizing radiation) in a potentially hazardous way
Class C
Rule9(ii)
Intended to control, monitor or directly influence the performance of active therapeutic devices in Class C
Class C
Rule10(i)
Active diagnostic devices intended to allow direct diagnosis / monitoring of vital physiological processes or supply energy that is absorbed or intended to image *in vivo* radio-pharmaceuticals
Class B
UNLESS
The absorbed energy is for illumination only
Class A
The patient is, or could be, in immediate danger
Class C
Rule10(ii)
Diagnostic and/or interventional radiology devices, including their controls & monitors
Class C


ACTIVE DEVICES (2 of 2)
Rule 11
Active devices to administer or remove medicinal products & other substances from the body
Class B
UNLESS
In a potentially hazardous manner
Class C
Rule 12
Active devices other than those where Rules 9, 10 or 11 apply
Class A


ADDITIONAL RULES
Rule 13
Device incorporating medicinal product which has ancillary action
Class D
Rule 14
Device manufactured from or incorporating human or animal tissues, cells or derivatives thereof
Class D
UNLESS
Non-viable animal tissues or derivatives thereof & in contact with intact skin only
Class A
Rule 15
Device intended specifically for sterilisation of medical devices or disinfection as the end point of processing
Class C
UNLESS
Used for disinfecting medical devices prior to end point sterilisation or higher level disinfection
Class B
Specifically for disinfecting, cleansing, rinsing or hydrating of contact lenses
Class C
Rule16
Device used for contraception or prevention of of sexually transmitted diseases
Class C
UNLESS
Implantable or long-term invasive
Class D

参考資料３：GHTF/SG1/N011:2008

GHTF FINAL DOCUMENT

『Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)』

FINAL DOCUMENT

Global Harmonization Task Force

Title: Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)

Authoring Group: Study Group 1 of the Global Harmonization Task Force

Date: February 21, 2008

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Preface

The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory authorities and the regulated industry. The document is intended to provide non-binding guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

1.0 Introduction

The primary way in which the GHTF achieves its goals is through the production of a series of guidance documents that together describe a global regulatory model for medical devices. The purpose of such guidance is to harmonize the documentation and procedures that are used to assess whether a medical device conforms to the regulations that apply in each jurisdiction. Eliminating differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

This document has been developed to encourage and support global convergence of regulatory systems. It is intended for use by Regulatory Authorities (RAs), Conformity Assessment Bodies (CABs) and industry, and will provide benefits in establishing, in a consistent way, an economic and effective approach to the control of medical devices in the interest of public health. It seeks to strike a balance between the responsibilities of Regulatory Authorities to safeguard the health of their citizens and their obligations to avoid placing unnecessary burdens upon the industry.

The GHTF has identified as a priority the need to harmonize the documentation of evidence of conformity to the essential principles of safety and performance. This guideline provides recommendations on the content of summary technical documentation (STED) to be assembled and submitted to a Regulatory Authority or Conformity Assessment Body. It should enable a manufacturer to prepare a STED and provide different Regulatory Authorities or Conformity Assessment Bodies with the same body of documentary evidence that its medical device conforms to the essential principles. The use of the STED should reduce costs for the manufacturer and reviewer, remove barriers to trade and facilitate timely international access to medical devices.

Where other guidance documents within the series are referenced within this text, their titles are italicised for clarity.

The regulatory requirements of some countries do not, at this time, align fully with this guidance.

Study Group 1 of the Global Harmonization Task Force (GHTF) has prepared this guidance document. Comments or questions should be directed to either the Chairman or Secretary of GHTF Study Group 1 whose contact details may be found on the GHTF web page[1].

2.0 Rationale, Purpose and Scope

2.1 Rationale

Manufacturers are expected to prepare, and either hold or provide timely access to, technical documentation that shows how each medical device was developed, designed and manufactured. This technical documentation, typically controlled in the manufacturer's

[1] www.ghtf.org

quality management system (QMS), is often extensive and sections of it may be held in different locations. The documentation is updated to reflect any changes made during the lifecycle of the device.

It is advantageous to both RAs/CABs and the regulated industry if a subset of this technical documentation is used for selected premarket and postmarket conformity assessment activities. This documentation subset is intended to be in a consistent, summarised or abridged form, with sufficient detail to allow the RA/CAB to fulfil its obligations. In the main, the documents contained within this subset are derived from the technical documentation held by the manufacturer and allow the manufacturer to demonstrate that the medical device to which it applies conforms to the *Essential Principles of Safety and Performance of Medical Devices*.

The availability of such Summary Technical Documentation (STED) should help eliminate differences in documentation requirements between jurisdictions, thus decreasing the cost of gaining regulatory compliance and allowing patients earlier access to new technologies and treatments.

2.2 Purpose

This document is intended to provide guidance on the content of the STED to be assembled and submitted to a RA or CAB for premarket review, and for use post-market to assess continuing conformity to the Essential Principles of Safety and Performance.

2.3 Scope

This document applies to all products that fall within the definition of a medical device that appears within the GHTF document *Information Document Concerning the Definition of the Term "Medical Device",* excluding those used for the in vitro diagnostic examination of specimens derived from the human body.

3.0 References

GHTF/SG1/N044:2008 *Role of Standards in the Assessment of Medical Devices.*

GHTF/SG1/N15:2006 *Principles of Medical Devices Classification.*

GHTF/SG1/N29:2005 *Information Document Concerning the Definition of the Term 'Medical Device'.*

GHTF/SG1/N40:2006 *Principles of Conformity Assessment for Medical Devices.*

GHTF/SG1/N41:2005 *Essential Principles of Safety and Performance of Medical Devices.*

GHTF/SG1/N43:2005 *Labelling for Medical Devices.*

4.0 Definitions

4.1 **Recognised standard:** standard deemed to offer the presumption of conformity to specific Essential Principles of Safety and Performance.

4.2 **Technical documentation:** the documented evidence, normally an output of the quality management system that demonstrates conformity of a device to the *Essential Principles of Safety and Performance of Medical Devices*.

PART 1 – PURPOSE OF THE STED

5.0 Preparation and Use of the STED

5.1 Preparation

Manufacturers of all classes of device are expected to demonstrate conformity of the device to the *Essential Principles of Safety and Performance of Medical Devices* (hereafter referred to as Essential Principles) through the preparation and holding of technical documentation that shows how each medical device was developed, designed and manufactured together with the descriptions and explanations necessary to understand the manufacturer's determination with respect to such conformity. This technical documentation is updated as necessary to reflect the current status, specification and configuration of the device.

For the purpose of conformity assessment, the manufacturer creates the STED from existing technical documentation to provide evidence to the RA/CAB that the subject medical device is in conformity with the Essential Principles. The STED reflects the status of the medical device at a particular moment in time (e.g. at the moment of premarket submission or when requested by a RA for post-market purposes) and is prepared in order to meet regulatory requirements. The flow of information from the technical documentation to the STED is illustrated in Figures 1 and 2.

The STED should be in a language acceptable to the RA/CAB.

The depth and detail of the information contained in the STED will depend on:

- the classification of the subject device;
- the complexity of the subject device.

It also depends upon whether the device has the following characteristics:

- it incorporates novel technology;
- it is an already marketed device type that is now being offered for an intended use different from the original one;
- it is new to the manufacturer;

- the device type has been associated with a significant number of adverse events, including use errors[2];
- it incorporates novel or potentially hazardous materials;
- the device type raises specific public health concerns.

The STED should contain summary information on selected topics, detailed information on certain specific topics (as indicated below) and an Essential Principles checklist (EP checklist). The information provided may include, for example, abstracts, high level summaries, or existing controlled documents, as appropriate, sufficient to communicate key relevant information and allow a reviewer to understand the subject. The EP checklist is created as part of the manufacturer's technical documentation and should be a controlled document within the manufacturer's QMS. It provides a tabular overview of the Essential Principles and identifies those that are applicable to the device, the chosen method of demonstrating that the device conforms to each relevant Essential Principle and the reference of the controlled document/s that is/are relevant to a specific Essential Principle. While many controlled documents are referenced in the EP checklist, only some are contained within the STED. The cited references to the controlled documents facilitate requests from a RA/CAB to provide additional information.

5.2 The Use of the STED in the Premarket Phase

In the premarket phase, the STED will be prepared and submitted to the RA/CAB for Class C and D devices. For Class A and B devices the STED will be prepared and submitted only at the request of a RA/CAB. (See Figure 1)

NOTES:

- For Class A and B devices where the STED is prepared on request, the manufacturer should be able to assemble and submit it in the timeframe indicated by the RA/CAB. This may be short.
- A copy of any submitted STED should be held by the manufacturer for future reference.

[2] See GHTF/SG2 guidance documents.

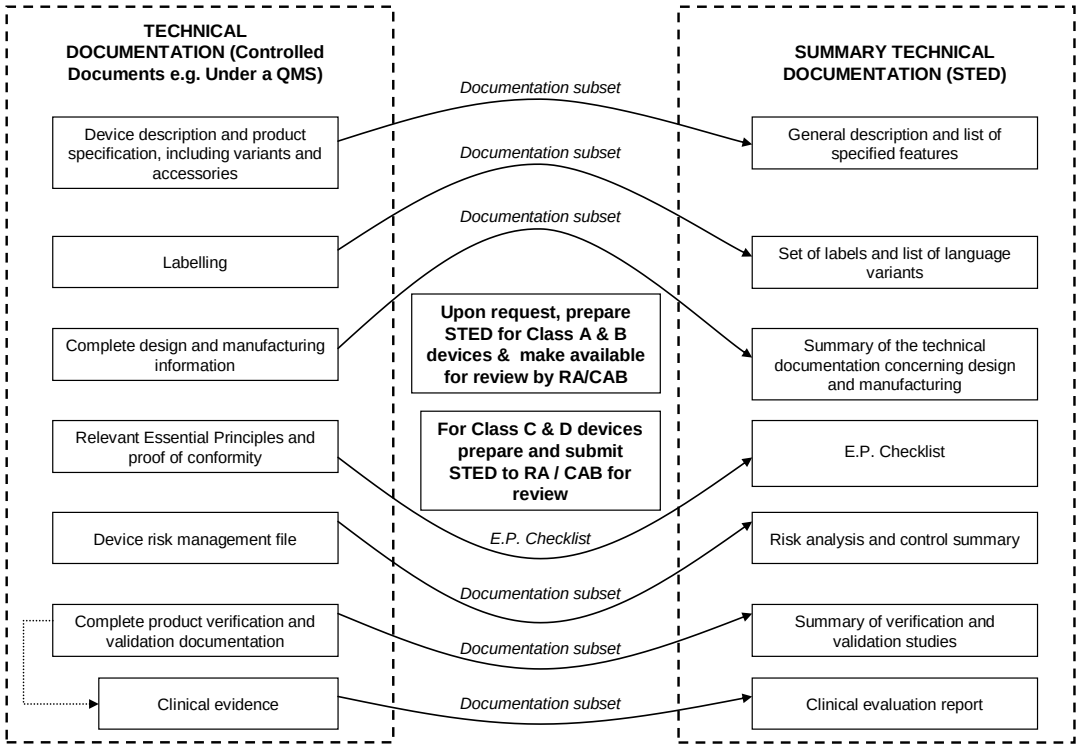


FIGURE 1: PREMARKET USE OF THE STED

5.3 The Use of the STED in the Post-market Phase

In the post-market phase, the RA/CAB may request submission of a STED for the device in question either to investigate conformity of a Class A or B medical device or the continued conformity of a Class C or D medical device (see Figure 2).

The STED would not typically be used to aid the postmarket investigation of adverse events, or the reporting of data from postmarket registries or studies, where different types of information are likely to be called for.

NOTES:

- The manufacturer should be able to prepare and submit the STED in the timeframe indicated by the RA/CAB. This may be short.
- A copy of any submitted STED should be held by the manufacturer for future reference.

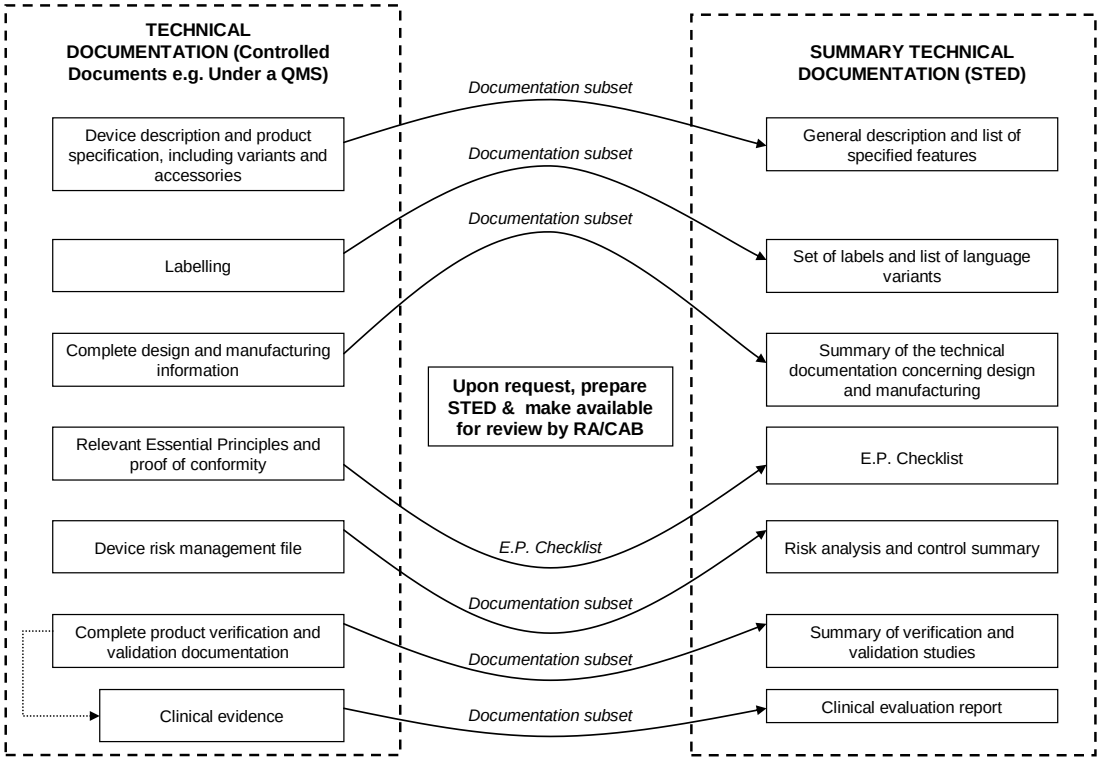


FIGURE 2: POST-MARKET USE OF THE STED

5.4 The Use of the STED to Notify Changes to the RA/CAB

Where prior approval of a proposed change to a medical device is required, the STED may be used in support of this process. Guidance on this case will be provided in the future

PART 2 – CONTENTS OF THE STED

6.0 Device Description and Product Specification, Including Variants and Accessories

6.1 Device Description

The STED should contain the following descriptive information for the device:

a) a general description including its intended use/purpose;
b) the intended patient population and medical condition to be diagnosed and/or treated and other considerations such as patient selection criteria;
c) principles of operation;
d) risk class and the applicable classification rule according to *Principles of Medical Devices Classification*;

e) an explanation of any novel features;
f) a description of the accessories, other medical devices and other products that are not medical devices, which are intended to be used in combination with it;
g) a description or complete list of the various configurations/variants of the device that will be made available;
h) a general description of the key functional elements, e.g. its parts/components (including software if appropriate), its formulation, its composition, its functionality. Where appropriate, this will include: labelled pictorial representations (e.g. diagrams, photographs, and drawings), clearly indicating key parts/components, including sufficient explanation to understand the drawings and diagrams.
i) a description of the materials incorporated into key functional elements and those making either direct contact with a human body or indirect contact with the body, e.g., during extracorporial circulation of body fluids.

6.2 Product Specification

The STED should contain a list of the features, dimensions and performance attributes of the medical device, its variants and accessories (if such are within the scope of the STED), that would typically appear in the product specification made available to the end user, e.g. in brochures, catalogues and the like.

6.3 Reference to similar and previous generations of the device

Where relevant to demonstrating conformity to the Essential Principles, and to the provision of general background information, the STED should contain an overview of:

a) the manufacturer's previous generation(s) of the device, if such exist; and/or
b) similar devices available on the local and international markets.

7.0 Labelling

The STED should typically contain a complete set of labelling associated with the device as described in GHTF guideline *Labelling for Medical Devices* and a list of language variants for the countries where the device will be marketed. Information on labelling should include the following:

- labels on the device and its packaging;
- instructions for use; and
- promotional material.

The labelling set should be in a language acceptable to the reviewing RA or CAB.

8.0 Design and Manufacturing Information

8.1 Device Design

The STED should contain information to allow a reviewer to obtain a general understanding of the design stages applied to the device. It is not intended to take the place of the more detailed information required for a QMS audit or other conformity assessment activity. The information may take the form of a flow chart.

8.2 Manufacturing Processes

The STED should contain information to allow a reviewer to obtain a general understanding of the manufacturing processes. It is not intended to take the place of the more detailed information required for a QMS audit or other conformity assessment activity. The information may take the form of a process flow chart showing, for example, an overview of production, assembly, any final product testing, and packaging of the finished medical device.

8.3 Design and Manufacturing Sites

For the activities in 8.1 and 8.2, the STED should identify the sites where these activities are performed. If QMS certificates, or the equivalent, exist for these sites, they should be annexed to the STED.

9.0 Essential Principles (EP) Checklist

The STED should contain an EP checklist that identifies:-

a) the Essential Principles;
b) whether each Essential Principle applies to the device and if not, why not;
c) the method(s) used to demonstrate conformity with each Essential Principle that applies;
d) a reference for the method(s) employed (e.g., standard), and
e) the precise identity of the controlled document(s) that offers evidence of conformity with each method used.

Methods used to demonstrate conformity may include one or more of the following:

a) conformity with recognised or other standards[3];
b) conformity with a commonly accepted industry test method(s);
c) conformity with an in-house test method(s);
d) the evaluation of pre-clinical and clinical evidence[4].
e) comparison to a similar device already available on the market.

The EP checklist should incorporate a cross-reference to the location of such evidence both within the full technical documentation held by the manufacturer and within the STED

[3] See GHTF/SG1/N044:2008 *Role of Standards in the Assessment of Medical Devices*
[4] See GHTF/SG5 guidance documents

(when such documentation is specifically required for inclusion in the Summary Technical Documentation as outlined in this guidance).

A template for a checklist is shown in Appendix A.

10.0 Risk Analysis and Control Summary

The STED should contain a summary of the risks identified during the risk analysis process and how these risks have been controlled to an acceptable level. Preferably, this risk analysis should be based on recognised standards and be part of the manufacturer's risk management plan.

11.0 Product Verification and Validation

11.1 General

The STED should contain product verification and validation documentation. The level of detail will vary (see Section 5.1).

As a general rule, the STED should summarise the results of verification and validation studies undertaken to demonstrate conformity of the device with the Essential Principles that apply to it. Such information would typically cover:

a) engineering tests;
b) laboratory tests;
c) simulated use testing;
d) any animal tests for demonstrating feasibility or proof of concept of the finished device;
e) any published literature regarding the device or substantially similar devices.

Such summary information may include:

a) declaration/certificate of conformity to a recognised standard(s) and summary of the data if no acceptance criteria are specified in the standard;
b) declaration/certificate of conformity to a published standard(s) that has not been recognised, supported by a rationale for its use, and summary of the data if no acceptance criteria are specified in the standard;
c) declaration/certificate of conformity to a professional guideline(s), industry method(s), or in-house test method(s), supported by a rationale for its use, a description of the method used, and summary of the data in sufficient detail to allow assessment of its adequacy;
d) a review of published literature regarding the device or substantially similar devices.

In addition, where applicable to the device, the STED should contain detailed information on:

a) biocompatibility;

b) medicinal substances incorporated into the device, including compatibility of the device with the medicinal substance;
c) biological safety of devices incorporating animal or human cells, tissues or their derivatives;
d) sterilisation;
e) software verification and validation;
f) animal studies that provide direct evidence of safety and performance of the device, especially when no clinical investigation of the device was conducted;
g) clinical evidence.

Detailed information will describe test design, complete test or study protocols, methods of data analysis, in addition to data summaries and test conclusions. Where no new testing has been undertaken, the STED should incorporate a rationale for that decision, e.g. biocompatibility testing on the identical materials was conducted when these were incorporated in a previous, legally marketed version of the device. The rationale may be incorporated into the EP checklist.

11.2 Biocompatibility

The STED should contain a list of all materials in direct or indirect contact with the patient or user.

Where biocompatibility testing has been undertaken to characterize the physical, chemical, toxicological and biological response of a material, detailed information should be included on the tests conducted, standards applied, test protocols, the analysis of data and the summary of results. At a minimum, tests should be conducted on samples from the finished, sterilised (when supplied sterile) device.

11.3 Medicinal Substances

Where the medical device incorporates a medicinal substance(s), the STED should provide detailed information concerning that medicinal substance, its identity and source, the intended reason for its presence, and its safety and performance in the intended application.

11.4 Biological Safety

The STED should contain a list of all materials of animal or human origin used in the device. For these materials, detailed information should be provided concerning the selection of sources/donors; the harvesting, processing, preservation, testing and handling of tissues, cells and substances of such origin should also be provided.

Process validation results should be included to substantiate that manufacturing procedures are in place to minimize biological risks, in particular, with regard to viruses and other transmissible agents.

The system for record-keeping to allow traceability from sources to the finished device should be fully described.

11.5 Sterilisation

Where the device is supplied sterile, the STED should contain the detailed information of the initial sterilisation validation including bioburden testing, pyrogen testing, testing for sterilant residues (if applicable) and packaging validation.

Typically, the detailed validation information should include the method used, sterility assurance level attained, standards applied, the sterilisation protocol developed in accordance with those standards, and a summary of results.

Evidence of the ongoing revalidation of the process should also be provided. Typically this would consist of arrangements for, or evidence of, revalidation of the packaging and sterilisation processes.

11.6 Software Verification and Validation

The STED should contain information on the software design and development process and evidence of the validation of the software, as used in the finished device. This information should typically include the summary results of all verification, validation and testing performed both in-house and in a simulated or actual user environment prior to final release. It should also address all of the different hardware configurations and, where applicable, operating systems identified in the labelling.

11.7 Animal Studies

Where studies in an animal model have been undertaken to provide evidence of conformity with the Essential Principles related to functional safety and performance, detailed information should be contained in the STED.

The STED should describe the study objectives, methodology, results, analysis and conclusions and document conformity with Good Laboratory Practices. The rationale (and limitations) of selecting the particular animal model should be discussed.

11.8 Clinical Evidence

The STED should contain the clinical evidence that demonstrates conformity of the device with the Essential Principles that apply to it. It needs to address the elements contained in the Clinical Evaluation Report described in guidance GHTF/SG5/N2.

12.0 Format of the STED

While this guidance document makes no specific recommendation for the format of the STED, it would be helpful to both manufacturers and reviewers if the STED was organized such that it incorporates the same sections as described in this guidance document e.g. device description, product specification etc..

13.0 Declaration of Conformity

The Declaration of Conformity is not part of the STED. However, it may be annexed to the STED once the conformity assessment process has been completed. The content of the Declaration of Conformity is described in GHTF/SG1/N40:2006 *Principles of Conformity Assessment for Medical Devices*.

Appendix **A**

Essential Principles (EP) Checklist

The EP checklist can be used by RAs, CABs and manufacturers to readily understand how the manufacturer demonstrates conformity to the essential principles for a particular device. The EP checklist also allows easy identification of relevant documents and data for conformity assessment purposes.

The contents of the checklist will vary from device to device. Complex devices are likely to reference a large number of standards, test reports and documents. The EP checklist in such cases may be many pages long. Very simple devices are more likely to have shorter EP checklists as many of the Essential Principles may not be applicable. In these cases, the supporting references to be incorporated into the checklist may be minimal.

The following is a recommended template for the EP checklist. Preparation of the EP checklist as outlined below will provide a useful overview of the device's conformity with the Essential Principles. The consistent use of this template will support harmonization across jurisdictions.

How to Complete the Checklist

a) Identity of the device

The manufacturer should identify the device, and where applicable the various configurations / variants covered by the checklist.

b) Applicable to the device?

Is the listed Essential Principle applicable to the device? Here the answer is either 'YES' or 'NO'. If the answer is 'NO' this should be explained briefly in the 'method used to demonstrate conformity' column.

> Example: For a device that does not incorporate biological substances, the answer to Essential Principle 5.8.2 would be 'NO' and, in the 'method used to demonstrate conformity' column, would include an explanation such as 'The device does not incorporate biological substances.'

c) Method used to demonstrate conformity

In this column the manufacturer should state the type(s) of method(s) that they have chosen to use to demonstrate conformity e.g. the recognised standard(s), industry or in-house test method(s), comparison study(ies) or other method used.

d) Method reference

After having stated the method in the previous column, here the manufacturer should now name the title and reference of the recognised standard(s), industry or in-house test method(s), comparison study(ies) or other method used to demonstrate conformity. For standards, this should include the date of the standard and where appropriate, the clause(s) that demonstrates conformity with the relevant EP.

e) Reference to supporting controlled documents

This column should contain the reference to the actual technical documentation that demonstrates conformity to the essential principle, i.e. the certificates, test reports, validation

reports, study reports or other documents that resulted from the method used to demonstrate conformity and its location within the STED.

NOTE: the Table that follows is for illustrative purposes only. The Essential Principles listed in the first column should be extracted from the latest version of GHTF's guidance document *Essential Principles of Safety and Performance of Medical Devices.* Those incorporated into this document are extracted from GHTF/SG1/N41:2005.

Essential Principle Checklist	
Device:	

Essential Principle	Applicable to the Device?	Method Used to Demonstrate Conformity	Method Reference	Reference to Supporting Controlled Documents
General Requirements				
5.1 Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.				
5.2 The solutions adopted by the manufacturer for the design and manufacture of the devices should conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, the manufacturer should control the risk(s) so that the residual risk(s) associated with each hazard is judged acceptable. The manufacturer should apply the following principles in the priority order listed: ▪ identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse, ▪ eliminate risks as far as reasonably practicable through inherently safe design and manufacture, ▪ reduce as far as is reasonably practicable the remaining risks by taking adequate protection measures, including alarms, ▪ inform users of any residual risks.				

Essential Principle	Applicable to the Device?	Method Used to Demonstrate Conformity	Method Reference	Reference to Supporting Controlled Documents
5.3 Devices should achieve the performance intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions within the scope of the definition of a medical device applicable in each jurisdiction.				
5.4 The characteristics and performances referred to in Clauses 5.1, 5.2 and 5.3 should not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.				
5.5 The devices should be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected under transport and storage conditions (for example, fluctuations of temperature and humidity) taking account of the instructions and information provided by the manufacturer.				
5.6 The benefits must be determined to outweigh any undesirable side effects for the performances intended.				

Design and Manufacturing Requirements				
5.7 Chemical, physical and biological properties				
5.7.1 The devices should be designed and manufactured in such a way as to ensure the characteristics and performance referred to in Clauses 5.1 to 5.6 of the 'General Requirements'. Particular attention should be paid to: ▪ the choice of materials used, particularly as regards toxicity and, where appropriate, flammability, ▪ the compatibility between the materials used and biological tissues, cells, body fluids, and specimens, taking account of the intended purpose of the device, ▪ the choice of materials used should reflect, where appropriate, matters such as hardness, wear and fatigue strength.				
5.7.2 The devices should be designed, manufactured and packed in such a way as to minimize the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to patients, taking account of the intended purpose of the product. Particular attention should be paid to tissues exposed and to the duration and frequency of exposure.				
5.7.3 ---------- etc. ----------				
5.7.4 ---------- etc. ----------				

参考資料４：

Draft Guidance for Industry and FDA Staff

Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data – Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions

Draft Guidance for Industry and FDA Staff

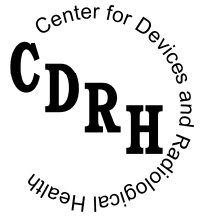
Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: October 21, 2009

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

For questions regarding this draft guidance document, contact Nicholas Petrick (OSEL) at 301-796-2563, or by e-mail at Nicholas.Petrick@fda.hhs.gov; or Joyce Whang (ODE) at, 301-796-6516 or by e-mail at Joyce.Whang@fda.hhs.gov.



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

Radiological Devices Branch
Division of Reproductive, Abdominal, and Radiological Devices
Office of Device Evaluation

Preface

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm187277.htm. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 240-276-3151 to receive a hard copy. Please use the document number (1698) to identify the guidance you are requesting.

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Draft Guidance for Industry and FDA Staff

Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. 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.

1. Introduction

This draft guidance document provides recommendations to industry, systems and service providers, consultants, FDA staff, and others regarding clinical performance assessment of computer-assisted detection (CADe[1]) devices applied to radiology images and radiology device data (often referred to as "radiological data" in this document). CADe devices are computerized systems that incorporate pattern recognition and data analysis capabilities (i.e., combine values, measurements, or features extracted from the patient radiological data) intended to identify, mark, highlight, or in any other manner direct attention to portions of an image, or aspects of radiology device data, that may reveal abnormalities during interpretation of patient radiology images or patient radiology device data by the intended user (i.e., a physician or other health care professional), referred to as the "clinician" in this document. In drafting this document, we considered the recommendations on documentation and performance testing for CADe devices made during the public meeting of the Radiological Devices Advisory Panel on March 4-5, 2008.[2] This draft guidance is issued for comment purposes only.

[1] The use of the acronym CADe for computer-assisted detection may not be a generally recognized acronym in the community at large. It is used here to identify the specific type of devices discussed in this document.

[2] http://www.fda.gov/ohrms/dockets/ac/cdrh08.html#radiology

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.

The Least Burdensome Approach

This draft guidance document reflects our careful review of what we believe are the relevant issues related to clinical performance studies for CADe devices applied to radiological data and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

2. Scope

This document provides guidance regarding clinical performance assessment studies for CADe devices applied to radiology images and radiology device data. Radiological data include those that are produced during patient examination with ultrasound, radiography, magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), etc.[3] As stated above, CADe devices are computerized systems intended to identify, mark, highlight, or in any other manner direct attention to portions of an image, or aspects of radiology device data, that may reveal abnormalities during interpretation of patient radiology images or patient radiology device data, by the clinician.

By design, a CADe device can be a unique detection scheme specific to only one type of potential abnormality, or a combination or bundle of multiple parallel detection schemes, each one specifically designed to detect one type of potential abnormality revealed in the patient radiological data. Examples of CADe devices that fall within the scope of this draft guidance include:

- a CADe algorithm designed to identify and prompt microcalcification clusters and masses on digital mammograms,
- a CADe device designed to identify and prompt colonic polyps on CT colonography studies,
- a CADe designed to identify and prompt filling defects on thoracic CT examination and,
- a CADe designed to identify and prompt brain lesions on head MRI studies.

This draft guidance does not cover clinical performance assessment studies for CADe devices that are intended for use during intra-operative procedures or for computer-assisted diagnostic devices

[3] For any use of a contrast imaging agent, we recommend that you verify that such comports with the regulation, labeling, and indications of the imaging drugs and devices. You may wish to consult the draft guidance **New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products (DRAFT)** (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126051.pdf) for new contrast imaging drugs and devices indications.

(CADx) and computer-triage devices, whether marketed as unique devices or bundled with a CADe device that, by itself, may be subject to this draft guidance. Below is further explanation of the CADx and computer-triage devices not covered by this draft guidance:

- CADx devices are computerized systems intended to provide information beyond identifying, marking, highlighting, or in any other manner directing attention to portions of an image, or aspects of radiology data, that may reveal abnormalities during interpretation of patient radiology images or patient radiology device data by the clinician. CADx devices include those devices intended to provide an assessment of disease or other conditions in terms of the likelihood of the presence or absence of disease, or devices intended to specify disease type (i.e., specific diagnosis or differential diagnosis), severity, stage, or intervention recommended. An example of such a device would be a computer algorithm designed both to identify and prompt potential microcalcification clusters and masses on digital mammograms and also to provide a probability score to the clinician for each potential lesion as additional information.

- Computer-triage devices are computerized systems intended to in any way reduce or eliminate any aspect of clinical care currently provided by a clinician, such as a device for which the output indicates that a subset of patients (i.e., one or more patients in the target population) are normal and therefore do not require interpretation of their radiological data by a clinician. An example of this device is a prescreening computer scheme that identifies patients with normal MRI scans that do not require any review or diagnostic interpretation by a clinician.

For any of these types of devices, we recommend that you contact the Agency to inquire about regulatory pathways, regulatory requirements, and recommendations about nonclinical and clinical data.

3. Rationale

This draft guidance makes recommendations as to how you should design and conduct your clinical performance assessment studies (i.e., well-controlled clinical investigations) for your CADe device. These studies may be part of your premarket submission to FDA.[4] The recommendations in this document are meant to guide you as you develop and test your CADe device; they are not meant to specify the full content or type of premarket submission that may be applicable to your device.[5] If you would like the Agency's advice about the classification and the

[4] This submission may be a premarket notification (510(k)), an application for premarket approval (PMA), an application for a product development protocol (PDP), an application for a humanitarian device exemption (HDE), or an application for an investigational device exemption (IDE).

[5] A 510(k) submission and a PMA application are the most common submission types for the CADe devices addressed in this draft guidance. As described in the draft guidance **Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions** (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm187249.htm), some CADe devices are Class II regulated under 21 CFR 892.2050 and require a

regulatory requirements that may be applicable to your device, you may submit a request under Section 513(g) of the Federal Food, Drug, and Cosmetic Act (the Act).[6]

Regardless of the type of premarket submission you are required to submit for your device, we recommend that you request the Agency's review of your protocols prior to initiating your standalone performance assessment and clinical performance assessment studies for your CADe device. To request the Agency's review of your protocols, you may submit a pre-submission to the Agency.

4. Clinical Study Design

The clinical performance assessment of a CADe device is intended to demonstrate the clinical safety and effectiveness of your device for its intended use, when used by the intended user and in accordance with its proposed labeling and instructions.

As described above in the scope, a CADe device, by design, is intended to identify data that may reveal abnormalities during interpretation of patient images or data by the clinician. There is a complex relationship between the CADe output and the clinician such that clinical performance may depend on a variety of factors that should be considered in any study design including:

- timing of CADe application in the interpretive process;
- physical characteristics of the CADe mark, i.e., size and shape, type of boundary (e.g., solid, dashed, circle, isocontour), and proximity of the CADe mark to the abnormality;
- user's knowledge of the type of abnormalities that the CADe is designed to mark; and
- number of CADe marks.

Your clinical performance assessment should be well-controlled especially if performed in a laboratory setting (i.e., off site of the clinical arena) to preclude or limit various biases that might impact conclusions on the device safety or effectiveness. Some various types of study designs that may be utilized to assess your CADe device include:

- A field test or prospective reader study (e.g., randomized controlled trial) that evaluates a device in actual clinical conditions. A field test may not be practical in situations, for example, where there is very low disease prevalence that may necessitate enrollment of an excessively large number of patients.
- A retrospective reader study consisting of a retrospective case collection enriched with diseased/abnormal cases is a possible surrogate for a field test.

510(k) while others are Class III and require a PMA. For more information on the various device classes, see Section 513(a)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360c(a)(1)).

[6] Section 513(g) of the Act (21 U.S.C. 360c(g)) provides a means for obtaining the Agency's views about the classification and the regulatory requirements that may be applicable to your device.

- A stress test is another option for the clinical performance assessment of some CADe devices. A stress test is a retrospective study enriched with patient cases that contain more challenging imaging findings (or other image data) than normally seen in routine clinical practice but that still fall within the device's intended use population (see **Section 5. Study Population**). Note that the use of sample enrichment will likely alter reader performance in the trial compared with clinical practice because of the differences in disease prevalence (and case difficulty for stress testing) between the trial and clinical practice.

The clinical performance assessment of CADe devices is typically performed by utilizing a multiple reader multiple case (MRMC) study design, where a set of readers evaluate image data under multiple reading conditions or modalities (e.g., readers unaided versus readers aided by CADe). The MRMC design can be "fully-crossed" whereby all readers independently read all of the cases. This design offers the greatest statistical power for a given number of cases. However, non-fully crossed study designs may be acceptable, for example in prospective studies where interpretations of the same patient data by multiple clinicians may not be feasible.

Whether you decide on a fully-crossed study design or not, we recommend the use of an MRMC evaluation paradigm to assess the clinical performance of a CADe device using one of the study designs described above. A complete clinical study design protocol should be included in your submission. Pre-specification of the statistical analysis is a key factor for obtaining consistent and convincing scientific evidence. We recommend you provide: [7]

- a description of the study design;
- a description of how the imaging data are to be collected (e.g., make and model of the imaging device imaging protocol) and the expertise of the person collecting the data (e.g., x-ray technician)
- a copy of the protocol, including the following:
  - hypothesis to be tested and study endpoints,
  - plans for checking any assumptions required to validate the tests,
  - alternative procedures/tests to be used if the required assumptions are not met,
  - study success criteria that indicate which hypotheses should be met in order for the clinical study to be considered a success,
  - statistical and clinical justification of the selected case sample size,
  - statistical and clinical justification of the selected number of readers,
  - image interpretation methodology and relationship to clinical practice,
  - randomization methods, and
  - reader task including rating scale used (see **Section 4**, subsection **Rating Scale**);
- the reader qualifications and experience;
- a description of the reader training;

[7] Precisely what information you should provide to FDA will depend largely on the type of premarket submission required for your device.

- a statistical analysis plan (i.e., endpoints, statistical methods) with description of:
  - the process for defining truth (see **Section 6. Reference Standard**),
  - the details of the scoring technique used (see **Section 4**, subsection **Scoring**), and
  - any results from a pilot study supporting the proposed design.

Valid estimation of clinical performance for CADe devices is dependent upon sound study design. Aspects of sound clinical study design should include the following:

- study populations (both diseased and normal cases) are appropriately representative of the intended use population;
- study design avoids confounding of the CADe effect, e.g., reading session effects
- sample size is sufficient to demonstrate performance claims;
- truth definition is appropriate for assessment of performance, and uncertainty in the reference standard is correctly accounted for in the study analysis, if applicable;
- appropriate data cohorts are represented in the data set;
- readers are selected such that they are representative of the intended population of clinical users; and
- imaging hardware are selected such that they are consistent with current clinical practice.

Evaluation Paradigm and Study Endpoints

Study endpoints should be selected to demonstrate that your CADe device is effective (i.e., that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results).[8] Selection of the primary and secondary endpoints will depend on the intended use of your device and should be fixed prior to initiating your evaluation. Performance metrics based on the receiver operating characteristic (ROC) curve or variant of ROC (e.g., free-response receiver operating characteristic (FROC) curve or location-specific receiver operating characteristic (LROC) curve), in addition to sensitivity (Se) and specificity (Sp) at a clinical action point will be likely candidates as endpoints. Considering Se/Sp and an ROC based endpoint allows evaluation of the device over the entire range of operating points as well as at the usual cut point a reader would act on in practice. Data collection for both sets of endpoints can be done simultaneously within a single reader study. Sensitivity (Se) is defined as the probability that a test is positive for a population of patients with the disease/condition/abnormality while Specificity (Sp) is defined as the probability that the test is negative for a population of normal patients (i.e., patients without the disease/condition/abnormality). An ROC curve is a plot of all sensitivities at all possible specificities. It is a summary of diagnostic performance of a device or a clinician. An FROC curve is a plot of sensitivity versus the number of false positive marks. FROC metrics summarize diagnostic performance when multiple disease

[8] See 21 CFR 860.7(e).

sites per patient are accounted for in the analysis. See Wagner, *et* al.[9] and the IRCU Report 79 [10] for additional details on these assessment paradigms.

Various summary performance metrics to assess the effectiveness of the use of your CADe device by readers may be employed (and may vary based on the specific device and clinical indication). Examples of these include:

- area, partial area, or any other measures, under ROC curve,
- area, partial area, or any other measures, under the FROC curve,
- area, partial area, or any other measures, under the LROC curve,
- reader Se/Sp (or recall rate[11]) pair, and
- reader localization accuracy.

We recommend the inclusion of lesion-based, patient-based, and any other relevant anatomical or image unit-based measures of performance in the assessment. The selection of lesion-based, patient-based or another unit-based measure of performance as a primary or secondary endpoint will depend on the intended use and the expected impact of the device on clinical practice.

For study endpoints based on the area under the ROC/FROC/LROC curve or partial area under the ROC/FROC/LROC curve, we recommend that you provide plots of the actual curves along with summary performance information for both parametric and non-parametric analysis approaches when possible. See Gur *et* al.[12] for potential limitations of relying on only one type of ROC analyses. As mentioned above, we also recommend that you include a sensitivity/specificity (or recall rate) endpoint in your analysis when an area-based endpoint is used because it is not always straightforward to translate the magnitude of an area under the curve (AUC) change into the magnitude of change expected in clinical practice. Reporting sensitivity/specificity (or recall rate) may provide additional information for understanding the expected impact of a device on clinical practice.

We recommend that you describe your statistical evaluation methodology, and provide results including:

- overall reader performance;

[9] Wagner, R. F., Metz, C. E., and Campbell, G., "Assessment of medical imaging systems and computer aids: A tutorial review," **Acad. Radiol.** 14:723–48, 2007.
[10] ICRU Report 79, "Receiver Operating Characteristic Analysis in Medical Imaging," Vol.8 No.1 (2008), Oxford University Press (ISSN 1473-6691).
[11] Recall rate refers to the percentage of patients (including diseased and non-diseased patients) that are called back or recalled for additional medical assessment.
[12] Gur, D., Bandos, A.I., and Rockette, H.E., "Comparing Areas under Receiver Operating Characteristic Curves: Potential Impact of the Last Experimentally Measured Operating Point," **Radiology** 247:12–15, 2008.

- stratified performance by relevant confounders or effect modifiers (e.g., lesion type, lesion size, lesion location, scanning protocol, imaging hardware, concomitant diseases) (see **Section 5**, **Study Population**); and
- confidence intervals (CIs) that account for reader variability, case variability, and truth variability or other sources of variability when appropriate.

We recommend that you identify and validate your analysis software.[13] You should provide a reference to the analysis approach used, clarify the software implementation, and specify a version number if appropriate. Certain validated MRMC analysis approaches, examples of which can be found in the literature or obtained online, may be appropriate for your device evaluation depending on its intended use and conditions of use.[14,15] If you plan to write your own analysis software we recommend you submit a copy of the code developed along with your validation data.

The definitions of a true positive, true negative, false positive, and false negative CADe mark should be consistent with the intended use of the device and the characterization of the reference standard (see **Section 6**, **Reference Standard**).

Control Arm

We recommend you assess the clinical performance of your CADe device relative to a control modality. For PMA submissions, a study control arm that uses conventional clinical interpretation (i.e., interpretation without the CADe device) should generally be the most relevant comparator in CADe performance assessment. For CADe devices intended as second readers, another possible control is double reading by two clinicians. For 510(k) submissions, direct comparison with the predicate CADe device may be useful for establishing substantial equivalence. Other control arms can be valid. We recommend you contact the Agency to discuss your choice of a control arm prior to conducting your clinical study.

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[13] For more information on MRMC analysis software, see, for example, Obuchowski, N. A., Beiden, S. V., Berbaum, K. S., Hillis, S. L., Ishwaran, H., Song, H. H., and Wagner, R. F., "Multi-reader, multi-case ROC analysis: An empirical comparison of five methods," **Acad. Radiol.** 11: 980–995, 2004.

[14] For MRMC literature references, see, for example: Metz, C. E., "Fundamental ROC analysis," **Handbook of Medical Imaging.** Vol. 1. Physics and Psychophysics. Beutel J, Kundel HL, and VanMetter RL (Eds.) SPIE Press, 751–769, 2000; Wagner, R. F., Metz, C. E., and Campbell, G., "Assessment of medical imaging systems and computer aids: A tutorial review," **Acad. Radiol.** 14:723–48, 2007; Obuchowski, N. A., Beiden, S. V., Berbaum, K. S., Hillis, S. L., Ishwaran, H., Song, H. H., and Wagner, R. F., "Multi-reader, multi-case ROC analysis: An empirical comparison of five methods," **Acad. Radiol.** 11: 980–995, 2004.

[15] For online access to software that analyzes MRMC data based on validated techniques, see, for example: LABMRMC software and general ROC software, The University of Chicago: http://xray.bsd.uchicago.edu/krl/roc_soft6.htm (for either quasi-continuous or categorical data); University of Iowa MRMC software: ftp://perception.radiology.uiowa.edu/PUBLIC (for categorical data); OBUMRM software: http://www.bio.ri.ccf.org/html/obumrm.html.

The study control arm should utilize the same reading methodology as the device arm and be consistent with clinical practice. The same population of cases, if not the same cases themselves, should be in all study arms to minimize potential bias. For designs that include distinct cases in each study arm, we recommend you provide a description and flow chart demonstrating how patients and readers were randomized into the different arms.

Reading Scenarios and Randomization

Reading scenarios should be consistent with the intended use of the device. We suggest the following as possible reading scenarios for inclusion as part of the clinical testing:

- a conventional reading without the CADe device (i.e., reader alone);
- a second-read in which the CADe output is displayed immediately after conducting a conventional interpretation; and
- a concurrent or simultaneous read in which the CADe output is available at any time during the interpretation process.

You should randomize readers, cases, and reading scenarios to reduce bias in performance measures. We recommend you describe your randomization methodology and provide an associated flowchart. One approach to randomization is to make use of the principle of Latin squares. For example, when evaluating both concurrent and second-reader modes with a set of 450 cases, a possible study design may consist of first dividing the cases into three groups of 150 cases, A, B and C. Each group is further divided into subsets of fifty cases, which are read with the same reading scenario. If α, β and γ are the index for the conventional reading, the second-read mode and the concurrent reading mode respectively, then reading scenarios and cases can be assigned as follows:

Image Group		Reading Session I	II	III
A	(150) (50)	α	β	γ
	(50)	β	γ	α
	(50)	γ	α	β
B	(150) (50)	β	γ	α
	(50)	γ	α	β
	(50)	α	β	γ
C	(150) (50)	γ	α	β
	(50)	α	β	γ
	(50)	β	γ	α

If the study enrolled four readers, the example above would result in 600=150x4 readings per group per reading session. The order in which the 150 cases are read should be randomized within each group and reading session. Note that the sample sizes used here are for illustrative purposes only. Generally, the sample sizes needed for clinical studies should be

representative of the intended use population. Likewise, this example study design illustrated above is not the only one that could be used to validate the effectiveness of your CADe device.

In case of multiple reading sessions where the same cases are read multiple times, we recommend that each reading session be separated in time by at least four weeks to avoid memory bias. However, longer time gaps may be advisable. For shorter or longer time gaps between reading sessions, we recommend you provide data supporting your proposed time gaps.

Rating Scale

You should use conventional medical interpretation and reporting for lesion location, extent, and patient management. ROC-based endpoints (see **Section 4**, subsection **Evaluation Paradigm and Study Endpoints**) may support collecting data with a finer rating scale (e.g., a 7-point or 100-point scale) when readers rate the lesion and/or disease status in a patient. We recommend providing training to the readers on the use of the rating scale (see **Section 4**, subsection **Training of Study Participants**).

Scoring

We refer to the procedure for determining the correspondence between the reader's interpretation and the truth (e.g., disease status) as the scoring process. The scoring process and the scoring definition are important components in the clinical assessment of a CADe device and should be described. We recommend you describe the process (i.e., rationale, definition, and criteria) for determining whether a reader's interpretation corresponds to the truth status established during the truthing process (see **Section 6. Reference Standard** for information on the truthing process).

In this document, we describe scoring in terms of the clinical performance assessment. A different type of scoring is used to evaluate device standalone performance which is described in the draft guidance entitled **Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions.**[16]

The scoring process for the clinical studies should be consistent with the abnormalities marked by the CADe and the intended use of your device. The scoring process should be described and fixed prior to initiating your evaluation. In your description of the scoring process, we recommend you indicate whether the scoring is based on:

- electronic or non-electronic means;
- physical overlap of the boundary, area, or volume of a reader mark in relation to the boundary, area, or volume of reference standard;

16 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm187249.htm

- relationship of the centroid of a reader mark to the boundary or spatial location of reference standard;
- relationship of the centroid of the reference standard to the boundary or spatial location of a reader mark;
- interpretation by reviewing reader(s); or
- other methods.

For scoring that relies on interpretations by reviewing readers, we recommend you provide the number of readers involved, their qualifications, their levels of experience and expertise, the specific instructions conveyed to them prior to their participation in the scoring process, and any specific criteria used as part of the scoring process. When multiple readers are involved in scoring, you should describe the process by which their interpretations are combined to make an overall scoring determination or how their interpretations are incorporated in the performance evaluation, including how any inconsistencies are addressed.

Training of Study Participants

We recommend you specify instructions and provide training to study participants on the use of the CADe device and the details on how to participate in the clinical study. Training should include a description of the device and instructions for how to use the device. For specialized reading instructions or rules (e.g., rules for changing initial without-CADe interpretation when reviewing the CADe marks), we recommend you justify their clinical relevance according to reading task, clinical workflow, and medical practice.

We also recommend that training be provided to the readers on the use of the rating scale (see **Section 4**, subsection **Rating Scale**), especially if such a rating scale is not generally utilized in clinical practice. Such training helps avoid incorrect or un-interpretable results. We recommend that reader training include rating a representative set of normal and abnormal cases according to the study design methodology, and making use of cases that are not part of the testing database.

5. Study Population

Patient data (i.e., cases) may be collected prospectively or retrospectively based on well-defined inclusion and exclusion criteria. We recommend that you provide the protocol for your case collections. Note that cases collected for your clinical trial should be independent of the cases used during your device development and should be new to the readers participating in the clinical assessment of the device. An acceptable approach for acquiring data is the collection of consecutive cases that are within the inclusion and outside of the exclusion criteria from each participating collection site.

Enrichment with diseased/abnormal cases is permissible for an efficient and less burdensome representative case dataset. You may also enrich the study population with patient cases that contain imaging findings (or other image data) that are challenging to clinicians but that still fall within the device's intended use population. This enrichment is often referred to as stress testing.

For example, if assessing a CADe device designed to assist in detecting colon polyps, the study population may be enriched with cases containing small polyps. Enrichment may affect reader performance so the extent of enrichment should be weighed against the introduction of biases into the study design.

The sample size of the study should be large enough such that the study has adequate power to detect with statistical significance your proposed performance claims. If performance claims are proposed for individual subsets, then the sample sizes for these subsets should be determined accordingly to detect these claims with statistical significance. For formal subset analysis, a pre-specified statistical adjustment for the testing of multiple subsets would be statistically necessary.

The study population should be representative of the intended use population for your device. Your study dataset should include the full range of diseased/abnormal and normal cases. The study should also contain a sufficient number of cases from important cohorts (e.g., subsets defined by clinically relevant confounders, effect modifiers, and concomitant diseases) such that clinical performance estimates can be obtained for these individual subsets. As stated above, powering these subsets for statistical significance may not be recommended unless specific subset performance claims are being included.

When describing your study population, we recommend you provide specific information, where appropriate, including:

- the patient demographic data (e.g., age, ethnicity, race);
- the patient medical history relevant to the CADe application;
- the patient disease state and indications for the radiologic test
- the conditions of radiologic testing, e.g. technique (including whether the test was performed with/without contrast, contrast type and dose per patient, patient body mass index, radiation exposure, T-weighting for MRI images) and views taken
- a description of how the imaging data were collected (e.g., make and model of imaging devices and the imaging protocol) and the expertise of the person collecting the data (e.g., x-ray technician)
- the collection sites;
- the processing sites if applicable (e.g., patient data digitization);
- the number of cases:
  - the number of diseased cases
  - the number of normal cases
  - methods used to determine disease status, location and extent (see **Section 6. Reference Standard**);
- the case distributions stratified by relevant confounders or effect modifiers, such as lesion type (e.g., hyperplastic vs. adenomatous colonic polyps), lesion size, lesion location, disease stage, organ characteristics (e.g., breast composition), concomitant diseases, imaging hardware (e.g., makes and models), imaging or scanning protocols, collection sites, and processing sites (if applicable); and

- a comparison of the clinical, imaging, and pathologic characteristics of the patient data compared to the target population.

Data Poolability

Premarket approval applications based solely on foreign data and otherwise meeting the criteria for approval may be approved if, among other requirements, the foreign data are applicable to the United States (U.S.) population and U.S. medical practice and the studies have been performed by clinical investigators of recognized competence (21 CFR 814.15). You should justify why non-U.S. data reflects what is expected for a U.S. population with respect to disease occurrence, characteristics, practice of medicine, and clinician competency. In accordance with good clinical study design, you should justify, both statistically and clinically, the poolability of data from multiple sites. We recommend that premarket notification applications follow similar quality data practices with regard to foreign data and data poolability. You are encouraged to contact the Agency if you intend to make use of foreign data as the basis of your premarket submission.

6. Reference Standard

For purposes of this document, the reference standard (also often called the "gold standard" or "ground truth" in the imaging community) for patient data indicates whether the disease/condition/abnormality is present and may include such attributes as the extent or location of the disease/condition/abnormality. We refer to the characterization of the reference standard for the patient, e.g., disease status, as the truthing process.

We recommend that you provide the rationale for your truthing process and indicate if it is based on:

- the output from another device;
- an established clinical determination (e.g., biopsy, specific laboratory test);
- a follow-up clinical imaging examination;
- a follow-up medical examination other than imaging; or
- an interpretation by a reviewing clinician(s) (i.e., truther(s)).

We also recommend that you describe the methodology utilized to make this reference standard determination (e.g., based on pathology or based on a standard of care determination). For truthing that relies on the interpretation by a reviewing clinician(s), we recommend you provide:

- the number of truthers involved;
- their qualifications;
- their levels of experience and expertise;
- the instructions conveyed to them prior to participating in the truthing process;
- all available clinical information from the patient utilized by the truthers in the identification of disease/condition/abnormality and in the marking of the location and extent of the disease/condition/abnormality; and

- any specific criteria used as part of the truthing process.

When multiple truthers are involved, you should describe the process by which their interpretations are combined to make an overall reference standard determination and how your process accounts for inconsistencies between clinicians participating in the truthing process (truth variability) (see **Section 4**, subsection **Evaluation Paradigm and Study Endpoints**). Note that clinicians participating in the truthing process should not be the same as those who participate in the core clinical performance assessment of the CADe device.

7. Reporting

Reporting of performance results may be guided by the FDA Guidance entitled **Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests; Guidance for Industry and FDA Reviewers**.[17] We recommend submitting electronically the data used in any statistical analysis in your study including the following:

- patient information,
- disease or normal status,
- concomitant diseases,
- lesion size,
- lesion type,
- lesion location,
- disease stage,
- organ characteristics.
- imaging hardware,
- imaging or scanning protocol,
- imaging and data characteristics (e.g., characteristics associated with differences in digitization architectures for a CADe using scanned films),
- and statistical analysis.

For more information on submitting data electronically, please see the FDA white paper entitled **Clinical Data for Premarket Submissions**.[18]

[17] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm

[18] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm

8. Postmarket Planning for PMAs

FDA applies the "Total Product Life Cycle (TPLC)" model to promote and protect the public health. Premarket approval (PMA) applications should include a postmarket plan to assess the continued safety, effectiveness, and reliability of an approved device for its intended use.

One potential piece of a postmarket plan is a post-approval study (PAS). FDA may require you to conduct a post-approval study as a condition of approval in a PMA approval order (21 CFR 814.82(a)(2)). A post-approval study is not always necessary as a condition of approval. FDA determines whether one is necessary on a case-by-case basis.

In the event your PMA approval order does require a post-approval study, we suggest that the study population characterization include race, age and target population baselines. FDA recommends that the target population include baselines for prevalence of the abnormality to be detected, as well as current screening method sensitivity, positive predictive value (PPV), specificity, negative predictive value (NPV), biopsy rate, and recall rate. FDA further recommends that you include in your study protocol, at a minimum, the following:

- Radiologist training and experience for those participating in the PAS
- User training with the CADe device
- Adjustments to CADe systems that may occur during the study period
- Types of abnormalities detected
- Type of imaging center
- Consecutive enrollment of subjects
- Study sensitivity, PPV, specificity, NPV, biopsy rate, recall rate, false-negative rate, number of missed abnormalities (may consider evaluation of readings at next exam for comparison of missed abnormalities)
- Area under of curve and/or ROC analysis

FDA will work interactively with you to finalize the postmarket plan and/or any post-approval study protocol prior to approval decisions so that they are ready to implement if the device is approved.

For additional information, please refer to the FDA Guidance entitled **Procedures for Handling Post-Approval Studies Imposed by PMA Order; Guidance for Industry and FDA Staff.**[19]

[19] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm

参考資料５：

Draft Guidance for Industry and FDA Staff

Computer-Assisted Detection Devices Applied to Radiology Images

and Radiology Device Data - Premarket Notification [510(k)] Submissions

Draft Guidance for Industry and FDA Staff

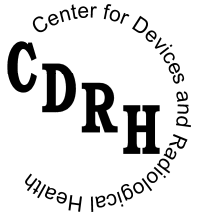
Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: October 21, 2009

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

For questions regarding this draft guidance document contact Nicholas Petrick (OSEL) at 301-796-2563, or by e-mail at Nicholas.Petrick@fda.hhs.gov; or Joyce Whang (ODE) at 301-796-6516, or by e-mail at Joyce.Whang@fda.hhs.gov.



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

Division of Imaging and Applied Mathematics
Office of Science and Engineering Laboratories

Radiological Devices Branch
Division of Reproductive, Abdominal, and Radiological Devices
Office of Device Evaluation

Preface

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm187249.htm. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-847-8149 to receive a hard copy. Please use the document number (1697) to identify the guidance you are requesting.

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Guidance for Industry and FDA Staff

Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. 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.

1. Introduction

This draft guidance document provides recommendations to industry, systems and service providers, consultants, FDA staff, and others regarding premarket notification (510(k)) submissions for computer-assisted detection (CADe[1]) devices applied to radiology images and radiology device data (often referred to as "radiological data" in this document). CADe devices are computerized systems that incorporate pattern recognition and data analysis capabilities (i.e., combine values, measurements, or features extracted from the patient radiological data) and are intended to identify, mark, highlight, or in any other manner direct attention to portions of an image, or aspects of radiology device data, that may reveal abnormalities during interpretation of patient radiology images or patient radiology device data by the intended user (i.e., a physician or other health care professional), referred to as the "clinician" in this document. In drafting this document, we considered the recommendations on documentation and performance testing for CADe devices made during the Radiology Advisory Public Panel on March 4-5, 2008.[2] This draft guidance is issued for comment purposes only.

[1] The use of the acronym CADe for computer-assisted detection may not be a generally recognized acronym in the community at large. It is used here to identify the specific type of devices discussed in this document.

[2] http://www.fda.gov/ohrms/dockets/ac/cdrh08.html#radiology

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.

The Least Burdensome Approach

This draft guidance document reflects our careful review of what we believe are the relevant issues related to computer-assisted detection on radiological data and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

2. Background

This draft guidance applies to the CADe devices identified in **Section 3. Scope** by their classification regulation (21 CFR 892.2050) and product codes (NWE, OEB, OMJ). A manufacturer who intends to market one of these devices must:

- conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E;
- conform to the special controls designated for this device (see 21 CFR 892.2050(b)); and
- obtain a substantial equivalence determination from FDA prior to marketing the device. (See also 21 CFR 807.81 and 807.87.)

This document provides recommendations regarding premarket notifications (510(k)s) for these devices. It supplements the requirements in 21 CFR 807.87 and other FDA documents concerning the specific content of a premarket notification submission, including the guidance, **Format for Traditional and Abbreviated 510(k)s**.[3]

Under "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications**,"[4] a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA has issued a guidance document addressing

[3] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm

[4] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm

that device. Manufacturers considering certain modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. Scope

This document provides guidance regarding premarket notification (510(k)) submissions for CADe devices applied to radiology images and radiology device data. Radiological data include those that are produced during patient examination with ultrasound, radiography, magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), etc.[5] As stated above, CADe devices are computerized systems intended to identify, mark, highlight, or in any other manner direct attention to portions of an image, or aspects of radiology device data, that may reveal abnormalities during interpretation of patient radiology images or patient radiology device data by the clinician. This draft guidance covers CADe devices marketed as a complete package with a review workstation, or as an add-on software to be embedded within imaging equipment, an image review platform (for example, a PACS (picture archiving and communications system)), or other imaging accessory equipment.

This draft guidance document applies to the CADe devices under 21 CFR 892.2050 Picture archiving and communications systems, and the following current product codes:

- NWE (Colon computed tomography system, computer-aided detection),
- OEB (Lung computed tomography system, computer-aided detection), and
- OMJ (Chest x-ray, computer-aided detection).

This draft guidance does not address non-CADe device components or capabilities, including the many non-CADe devices that are covered by 21 CFR 892.2050, i.e. product codes LLZ (System, Image Processing, Radiological) and NFJ (System, Image Management, Ophthalmic).

21 CFR 892.2050 Picture archiving and communications system.

(a) *Identification.* A picture archiving and communications system is a device that provides one or more capabilities relating to the acceptance, transfer, display, storage, and digital processing of medical images. Its hardware components may include workstations, digitizers, communications devices, computers, video monitors, magnetic, optical disk, or other digital data storage devices, and hardcopy devices. The software components may provide functions for performing operations related to image manipulation, enhancement, compression or quantification.

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[5] For any use of a contrast imaging agent, we recommend that you verify that such comports with the regulation, labeling, and indications of the imaging drugs and devices. You may wish to consult the draft guidance **New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products (DRAFT)** (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126051.pdf) for new contrast imaging drugs and devices indications.

(b) *Classification.* Class II (special controls; voluntary standards--Digital Imaging and Communications in Medicine (DICOM) Std., Joint Photographic Experts Group (JPEG) Std., Society of Motion Picture and Television Engineers (SMPTE) Test Pattern).

By design, a CADe device can be a unique detection scheme specific to only one type of potential abnormality or a combination or bundle of multiple parallel detection schemes, each specifically designed to detect one type of potential abnormality that is revealed in the patient radiological data. Examples of CADe devices that fall within the scope of this draft guidance include:

- a CADe device designed to identify and prompt colonic polyps on CT colonography studies,
- a CADe designed to identify and prompt filling defects on thoracic CT examination, and
- a CADe designed to identify lung nodules on MRI studies.

This draft guidance does not cover devices in the Class III product code MYN (Analyzer, Medical Image), any CADe devices that are intended for use during intra-operative procedures, or any computer-assisted diagnostic devices (CADx) or computer-triage devices, whether marketed as unique devices or bundled with a computer-assisted detection device that, by itself, may be subject to this draft guidance. Below is further explanation of the CADx and computer-triage devices not covered by this draft guidance:

- CADx devices are computerized systems intended to provide information beyond identifying, marking, highlighting, or in any other manner directing attention to portions of an image, or aspects of radiology device data, that may reveal abnormalities during interpretation of patient radiology images or patient radiology device data by the clinician. CADx devices include those devices that are intended to provide an assessment of disease or other conditions in terms of the likelihood of the presence or absence of disease, or are intended to specify disease type (i.e., specific diagnosis or differential diagnosis), severity, stage, or intervention recommended. An example of such a device would be a computer algorithm designed both to identify and prompt lung nodules on CT exams and also to provide a probability score to the clinician for each potential lesion as additional information.

- Computer-triage devices are computerized systems intended to in any way reduce or eliminate any aspect of clinical care currently provided by a clinician, such as a device for which the output indicates that a subset of patients (i.e., one or more patients in the target population) are normal and therefore do not require interpretation of their radiological data by a clinician. An example of this device is a prescreening computer scheme that identifies patients with normal MRI scans that do not require any review or diagnostic interpretation by a clinician.

For any of these types of devices, we recommend that you contact the Agency to inquire about premarket pathways, regulatory requirements, and recommendations about nonclinical and clinical data.

4. Describing the Device in a 510(k) Premarket Notification

We recommend you identify your device by the regulation and product code described in **Section 3. Scope**, and provide an overview of your CADe algorithm and a detailed description of the following:

- the algorithm design and function,
- processing steps,
- features,
- models and classifiers,
- training paradigm,
- databases,
- reference standard, and
- scoring methodology.

General Information

In accordance with 21 CFR 807.87, provide proposed labels, labeling, and advertisements sufficient to describe the device, the intended use, directions for use, a complete description of the operational principles for your device, and a 510(k) summary or a 510(k) statement (see 21 CFR 807.87(e), (f) & (h) and **Section 8. Labeling**). In providing a description of your device, we recommend you include the following information:

- target population information including patient population, organs of interest, diseases/conditions/abnormalities of interest, and appropriate clinician intended to use the device (e.g., radiologist, family practice physician, nurse);
- radiological data used as input and compatible with your CADe design, including imaging modalities (e.g., computed tomography, magnetic resonance), make, model and specific trade name for each modality/system if applicable, specific image acquisition parameter ranges (e.g., kVp range, slice thickness), and specific clinical imaging protocol(s) (e.g., oral contrast studies, magnetic resonance imaging (MRI) sequence);
- current clinical practice relevant to the diseases/conditions/abnormalities of interest;
- proposed clinical workflow (as compared to the predicate device) including a description of:
  - how your device is labeled for use in clinical practice,
  - when your device should be utilized within the proposed workflow,
  - effects on interpretation time as it relates to specific claims;

- device impact (as compared to the predicate device), including:
  - the impact on patient health from additional medical procedures resulting from an unnecessary patient recommendation or follow-up by the clinician based on the information provided by the device (e.g., an incorrect follow-up determination would likely result in short term surveillance imaging for the patient or an incorrect follow-up determination would likely result in a biopsy),
  - the impact on the patient associated with device performance for true positive and true negative marks, separately, and
  - the impact on the patient associated with device performance for false positive and false negative marks, separately;
- device limitations (as compared to the predicate device) including diseases/conditions/abnormalities for which the device has been found ineffective and should not be used; and
- supporting data from the scientific literature.

Algorithm Design and Function

We recommend you provide information on the algorithm design and function including details on the following:

- algorithm implementation:
  - a description of the format of all CADe marks available, including all relevant geometric and other properties such as shape, size, intended location in relation to region of interest (e.g., overlap, adjacent), border (e.g., solid, dashed), and color.

We recommend you provide a detailed flowchart identifying the processing, features, models, and classifiers utilized by your algorithm. We suggest your flowchart include the following:

- all manual operations and associated predefined default settings (e.g., selection of rules or thresholds by the physician);
- all semi-automatic operations and associated predefined default settings (e.g., selection of seed points for region segmentation); and
- all automatic operations that do not involve direct interaction with the clinician.

You should include other algorithm information including:

- name,
- version and important characteristics of the software platform,
- operating system, and
- programming language.

We also recommend you describe the design and function for each stage of your algorithm, where a stage is an independent or well-defined functional unit within the CADe algorithm. Your description may likely include a discussion of the following:

- purpose of the stage,
- processing steps,
- features,
- classifiers and their estimated complexity,
- training paradigm,
- development and training databases utilized, and
- reference standard.

Processing

Processing refers to any image or signal normalization, filtering, and segmentation of areas or structures of interest. Examples of filtering and segmentation processes are the use of a smoothing filter for noise reduction or the delineation of an organ of interest from its surroundings, respectively. We recommend that you provide a description of all processing as well as relevant algorithm flowcharts, equations, and references.

Normalization processing refers to calibration or transformation of image or signal characteristics to that of a reference image or signal. We recommend you provide a description of the technique used to establish the proper calibration or transformation, as well as the characteristics of the reference.

Features and Feature Selection

Features are computer or human estimated quantities characterizing images, regions, or pixels within radiological data, including any specific patient characteristics (e.g., age, sex, ethnicity). Feature selection includes any processes used to cull a set of candidate features. Feature selection or dimensional reduction may be accomplished by manual selection of important features by a user or by an automated selection algorithm (e.g., through the use of a genetic algorithm). For each stage of your algorithm, we recommend you provide:

- the total number of features computed and evaluated during algorithm development, and
- the number of features retained after feature selection, if appropriate.

For each feature, we recommend you provide:

- a description of how the feature is determined (e.g., mathematical expression),
- the feature class (e.g., demographic, biological, morphological and geometrical features), and

- the feature type (i.e., computer estimated feature value or reader estimated feature value).

Models and Classifiers

We define a model as any method or rule used to rate or categorize information within an image. A classifier is a human- or statistically-defined model used to rate or categorize regions within an image with respect to disease, condition, or abnormality. This model is an assumed relationship between image features and the rating or categorization of disease, condition, or abnormality, and depends on a specific set of parameters that are determined in processing steps either manually or automatically. Models and classifiers typically perform some type of pattern recognition procedure. They can vary from a single threshold on a uniquely extracted feature to a complex classifier (i.e., a weighted combination of feature values). For each stage of your algorithm, we recommend you provide the following:

- the number of different models and classifiers utilized; and
- the types of models and classifiers used (e.g., simple threshold, decision tree, linear discriminant, neural network, support vector machine), including specific parameters and values being utilized.

Algorithm Training

Algorithm training is a procedure used to set algorithm parameters and thresholds. This procedure includes the adjustment of filter parameters, the selection of the most discriminant features, and the adjustment of classifier weights and model parameters. Training may be done manually by humans (e.g., the programmer or a medical professional), automatically using a specialized training algorithm, or by a combination of both. For the individual stages as well as the overall algorithm, we recommend you describe your algorithm training paradigm, including the technique employed for feature selection, and indicate if it is performed:

- manually by humans;
- automatically using a computerized training method; or
- by a combination of manual and computerized techniques.

If algorithm training is performed manually, we recommend you provide the number and qualifications of the individuals performing the training. Whether the training is performed manually, automatically, or by a combination of techniques, we recommend you describe the criteria and performance metrics used to determine the settings (i.e., thresholds, weights, or parameters) of each individual stage and provide a summary of the resulting observed performance.

We further recommend you provide history of the accrual and use of data in the training and evaluation of the CADe device.

Databases

Databases refer to the sets of radiology images or radiology device data used in training and testing your device. These databases may contain computer simulated data, phantom data, or patient data depending on the nature of the evaluation.

For a database of computer simulated or phantom data (i.e., training and testing cases), we recommend you provide:

- a description of the phantom or simulation methodology; and
- any data characterizing the relationship between the simulated or phantom data and actual patient data for the imaging technique, organ, and disease of interest.

For each database of patient data (i.e., training and testing cases), we recommend you provide specific information including:

- the patient demographic data (e.g., age, ethnicity, race);
- the patient medical history relevant to the CADe application;
- the patient disease state and indications for the radiologic test;
- the conditions of radiologic testing, for example technique (including whether the test was performed with/without contrast, contrast type and dose per patient, patient body mass index, radiation exposure, T1-weighting for MRI images) and views taken;
- a description of how the imaging data were collected (e.g., make and model of imaging devices and the imaging protocol) and the expertise of the person collecting the data (e.g., x-ray technician);
- the collection sites;
- the processing sites, if applicable (e.g., patient data digitization);
- the number of cases:
  - the number of diseased cases,
  - the number of normal cases,
  - any methods used to determine disease status, location and extent (see **Section 4**, subsection **Reference Standard**);
- the case distributions stratified by relevant confounders or effect modifiers, such as lesion type (e.g., hyperplastic vs. adenomatous colonic polyps), lesion size, lesion location, disease stage, organ characteristics, concomitant diseases, imaging hardware (e.g., makes and models), imaging or scanning protocols, collection sites, and processing sites (if applicable);
- a comparison of the clinical, imaging, and pathologic characteristics of the patient data compared to the target population; and
- a history of the accrual and use of both training and test databases.

For CADe devices intended to be used with proprietary imaging devices, we recommend you provide the trade names, regulatory status, and physical characteristics of these proprietary imaging devices.

Reference Standard

For purposes of this document, the reference standard (also often called the "gold standard" or "ground truth" in the imaging community) for patient data indicates whether or not the disease/condition/abnormality is present and may include such attributes as the extent or location of the disease/condition/abnormality CADe device development and evaluation often relies on databases of a radiology images or radiology device data with a reference standard addressing whether or not the disease/condition/abnormality is present within an individual patient and if so, its location and extent. We refer to this characterization of the reference standard for the patient, e.g., disease status, as the truthing process.

The methodology utilized to establish the reference standard can impact reported performance. The types and nature of the abnormalities marked or not marked by your CADe device should be consistent with the intended use of your device. You should provide the rationale and describe the procedure for defining if a disease/condition/abnormality is present and the location and extent of the disease/condition/abnormality (e.g., based on pathology or based on a standard of care determination). You should also indicate if the reference standard is based on:

- the output from another device;
- an established clinical determination (e.g., biopsy, specific laboratory test);
- a follow-up clinical imaging examination;
- a follow-up medical examination other than imaging; or
- an interpretation by reviewing clinician(s) (i.e., truther(s)).

The methodology utilized to make this reference standard determination should be described and should be fixed prior to initiating your evaluation. For truthing that relies on the interpretation by reviewing clinician (i.e., truther), we recommend you provide:

- the number of truthers involved;
- their qualifications;
- their levels of experience and expertise;
- the instructions conveyed to them prior to participating in the truthing process;
- all available clinical information from the patient utilized by them in the identification of disease/condition/abnormality and in the marking of the location and extent of the disease/condition/abnormality; and
- any specific criteria used as part of the truthing process.

When multiple truthers are involved, you should describe the process by which their interpretations are combined to make an overall reference standard determination and how your process accounts for any inconsistencies between clinicians participating in the truthing process (truth variability). Clinicians participating in the truthing process should not be the same as those who participate in the core clinical performance assessment of the CADe device because doing so would introduce bias into the study results.

Scoring

In addition to determining the reference standard for the location and extent of the disease/condition/abnormality, CADe device development and evaluation often rely on determining whether the spatial location and extent of a CADe mark correspond to the location and extent of the disease/condition/abnormality. We define the procedure for determining the correspondence between the CADe output and the reference standard (e.g., disease location) as the scoring process. The scoring procedure and the scoring definition are important components for interpreting standalone device performance and for appropriately labeling the device.

In this document we describe the scoring used to evaluate device standalone performance. A different type of scoring is used in the clinical performance assessment which is described in the draft guidance entitled **Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions**.[6]

The scoring process should be consistent with the abnormalities being marked by the CADe and the intended use of your device. The scoring process should be described and primary and secondary endpoints should be fixed prior to initiating your evaluation. In your description of the scoring process, we recommend you indicate whether the scoring is based on:

- electronic or non-electronic means;
- physical overlap of the boundary, area, or volume of the mark in relation to the boundary, area, or volume of the reference standard;
- relationship of the centroid of the mark to the boundary or spatial location of the reference standard;
- relationship of the centroid of the reference standard to the boundary or spatial location of the mark;
- interpretation by reviewing readers; or

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6 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm187277.htm

- other methods.

For scoring that relies on interpretations by reviewing readers, we recommend you provide the number of readers involved, their qualifications, their level of experience and expertise, the specific instructions conveyed to them prior to participating in the scoring process, and any specific criteria used as part of the scoring process. When multiple readers are involved in scoring, you should describe the process by which their interpretations are combined to make an overall scoring determination or how their interpretations are incorporated in the performance evaluation, including how any inconsistencies are addressed.

Other Information

We recommend that you include information for software-controlled devices described in **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices**[7] and in **Guidance for Off-the-Shelf Software Use in Medical Devices**.[8] The kind of information we recommend is determined by the "level of concern," which is related to the risks associated with a software failure. The level of concern for a device may be minor, moderate, or major. Based on prior CADe device submissions, the level of concern for a CADe system is generally moderate or major.

If the CADe system is an add-on software to be installed within a third party image review platform, we recommend you also provide the names, version/model numbers, and characteristics of these third party platforms as well as a description of the file format of the CADe output that is generated by your device. If applicable, we recommend you refer to **Guidance for the Submission of Premarket Notifications for Medical Image Management Devices**.[9]

We recommend submitting electronically the data used in any statistical analysis in your study. For more information on submitting data electronically, please see the FDA white paper entitled **Clinical Data for Premarket Submissions**.[10]

[7] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm

[8] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073778.htm

[9] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073720.htm

[10] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm

5. Standalone Performance Assessment

Because each new CADe device represents a new implementation of software, FDA expects that each new CADe device (as well as software and other design, technology, or performance changes to an already cleared CADe device) will have different technological characteristics from the legally marketed predicate device even while sharing the same intended use. Accordingly, under section 513(i)(1)(A) of the Act, determinations of substantial equivalence will rest on whether the information submitted, including appropriate clinical or scientific data, demonstrate that the new or changed device is as safe and effective as the legally marketed predicate device and does not raise different questions of safety and effectiveness than the predicate device.

To support a substantial equivalence determination for a new CADe device, or for changes to an already cleared CADe device that could significantly affect safety or effectiveness, we recommend you measure and report the performance of your CADe device by itself, in the absence of any interaction with a clinician (i.e., standalone performance assessment). These measurements estimate how well the CADe device, by itself, marks regions of known abnormalities and how well the CADe device avoids marking regions other than the abnormalities (e.g., normal organ and structures). Study endpoints should be selected to establish meaningful and statistically significant performance for the device.

To support substantial equivalence, we recommend comparing the standalone performance of your CADe device to the standalone performance of the predicate device on the same dataset, if possible. Otherwise, the characteristics or makeup of the database used to assess standalone performance should be comparable to the characteristics or makeup of the database used in assessing the predicate device.

The types and nature of the abnormalities marked or not marked by your CADe device should be consistent with the intended use of your device. To measure standalone performance, the true location of abnormalities should be determined through some well-described truthing process (see **Section 4**, subsection **Reference Standard**). The location and extent of a CADe mark should be compared to the truthed location and extent of an abnormality using the established scoring process (see **Section 4**, subsection **Scoring**). The reference standard definition, scoring process, and analysis methodology, including primary and secondary performance endpoints, should be established prior to the collection of the standalone performance assessment data and analysis of these data. Any performance claims based on a covariate analysis should be demonstrated through a prespecified analysis plan.

We recommend that you perform standalone testing in a way that will provide good estimates of performance stratified by important covariates, such as lesion type, size or shape. This stratified standalone performance is useful in labeling by providing the end users with additional information to better interpret the meanings of the CADe marks.

Study Population

We recommend you assess and report your device standalone performance on testing data that is independent and sequestered from the data on which the CADe was developed and trained. Reusing test data (i.e., conducting multiple tests on the same data) is problematic for interpreting the results. Test data, used once before, does not constitute independent data for testing a CADe device because the CADe algorithm may have become trained to that data, either implicitly or explicitly. If you intend to reuse test data, we recommend that you contact the Agency to discuss the scientific validity of your proposed methodology and seek advice on the reuse of test data.

Your testing database should be representative of the target population and the target disease, condition, or abnormality for which your device is intended. We recommend that you provide the protocol for your case collections. An acceptable approach for acquiring data that is representative of the intended use population is the collection of consecutive cases from each participating collection site that fall within the inclusion and outside the exclusion criteria. The full range of diseased/abnormal and normal cases should be sufficiently represented in the testing database.

Enrichment with diseased/abnormal cases is permissible for an efficient and least burdensome representative case dataset but may affect standalone performance estimates (e.g., the performance estimates may not generalize to the intended use population). You may choose to enrich the study population with patient cases that contain imaging findings (or other image data) that are known to challenge clinicians but that still fall within the device's intended use population (i.e., stress testing). For example, if assessing a CADe device designed to detect colon polyps, the study population may be enriched with cases containing smaller polyps. The study should contain a sufficient number of cases from important cohorts (e.g., subsets defined by clinically relevant confounders, effect modifiers, and concomitant diseases) such that standalone performance estimates can be obtained for these individual subsets (e.g., performance estimates for different nodule size categories when evaluating a lung CADe device). Powering these subsets for statistical significance may not be necessary unless specific subset performance claims are being included. A good study design might include and report results for both an enriched data set containing relevant confounders as well as a set of consecutive cases from each participating collection site where the consecutive cases may better represent the standalone performance in clinical practice.

The sample size of the study should be large enough such that the study has adequate power to detect with statistical significance your proposed performance claims. If performance claims are proposed for individual subsets, then the sample sizes for these subsets should be determined accordingly to detect these claims with statistical significance. For formal subset analysis, a pre-specified statistical adjustment for the testing of multiple subsets would be statistically necessary.

As part of the device standalone performance assessment, you should describe the testing database (**see Section 4**, subsection **Databases**). We recommend your performance testing include:

- detection accuracy testing,
- localization accuracy testing,
- reproducibility testing,
- stability analysis, and
- algorithm training performance.

Detection Accuracy

We recommend you estimate and report the CADe standalone performance following the scoring process (see **Section 4**, subsection **Scoring**). The definition of a true positive, true negative, false positive, and false negative CADe mark should be consistent with the intended use of the device. For example, if the device is intended to detect all abnormalities (e.g., benign and malignant), then a true positive CADe mark should be defined as "marking" any abnormalities. On the other hand, if a device is intended to detect only a subset of abnormalities (e.g., only those lesions with certain imaging features), then a true or false CADe mark should be defined accordingly.

For truthing (e.g., disease type, location, and extent) that relies on the interpretation by reviewing readers, we recommend that you account for reader variability in the truthing process and for various consensus or agreement rules between expert readers, in the CADe standalone performance estimates. One method of accounting for variability in the reference standard is to resample the expert truthing panel. See Miller *et* al.[11] for details on one approach.

We recommend you report the overall lesion-based, patient-based, and any other relevant anatomical or image unit-based sensitivities, and average number of false positives per case (FPs/case) or other relevant measure of specificity, at each device operating point as well as stratified analysis per relevant confounder or effect modifier as appropriate (e.g., lesion size, lesion type, imaging or scanning protocols, imaging or data characteristics). FPs/case or other relevant measure of specificity should be derived from normal and abnormal patient data separately. If your device allows the clinician to select or manipulate the device operating point, we recommend you provide the device performance for each selectable operating point or for the range of possible operating points. The detection accuracy assessment methodology, including the selection of primary and secondary performance endpoints, should be determined and fixed prior to initiating your evaluation.

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[11] Miller, D. P., O'Shaughnessy, K. F., Wood, S. A., and Castellino, R. A., "Gold standards and expert panels: A pulmonary nodule case study with challenges and solutions," Proc. of the **SPIE**, Medical Imaging; 5372: 173–184, 2004.

All performance measures should be reported with associated confidence intervals (CIs). We recommend you provide a description of your methodology for estimating these CIs and the clinical significance associated with these CIs.

We also recommend you provide graphs of the free-response receiver operating characteristic (FROC) curves (i.e., a plot of patient-based sensitivity vs. average number of FPs/case as a function of operating point) when reporting detection accuracy and the clinical interpretation of this analysis. Associated FROC CIs should be reported when appropriate. Resampling techniques, such as bootstrapping,[12] are potential methodologies for estimating these CIs.

Localization Accuracy

Localization accuracy depends upon the scoring criteria used to determine the nature of each CADe detection, i.e., true positive (TP) or false positive (FP). Using only one scoring criterion, i.e., the criterion used for the device performance reported in the labeling (see **Section 4**, subsection **Scoring**), may not be sufficient to evaluate localization accuracy. We recommend you report the CADe localization accuracy by reporting the overall lesion-based, patient-based, and any other relevant anatomical or image unit-based sensitivities, and the average number of FPs/case or other relevant measure of specificity, using multiple scoring criteria. Common scoring criteria used to determine the nature of each CADe detection include:

- centroid of the CADe detection area or volume falling in the reference standard area or volume;
- distance between centroids of the CADe detection and the reference standard;
- ratio of the distance between centroids of the CADe detection and the reference standard, relative to the maximum width of the reference standard region;
- ratio of the area (A) or volume (V) intersection between the CADe detection and the reference standard, with the total area or volume of the reference standard defined as follows:

$$\frac{\mathrm{A}(CAD) \cap \mathrm{A}(Ref)}{\mathrm{A}(Ref)} \quad \text{or} \quad \frac{\mathrm{V}(CAD) \cap \mathrm{V}(Ref)}{\mathrm{V}(Ref)}$$

- ratio of the area (A) or volume (V) intersection between the CADe detection and the reference standard, with the total area or volume of the CADe detection, defined as follows:

$$\frac{\mathrm{A}(CAD) \cap \mathrm{A}(Ref)}{\mathrm{A}(CAD)} \quad \text{or} \quad \frac{\mathrm{V}(CAD) \cap \mathrm{V}(Ref)}{\mathrm{V}(CAD)}$$

[12] Efron, B., and Tibshirani, R., "Bootstrap methods for standard errors, confidence intervals and other measures of statistical accuracy," **Statistical Science** 1, 54–77, 1986.

- ratio of the area (A) or volume (V) intersection between the CADe detection and the reference standard with the total area or volume union of the reference standard and the CADe detection, defined as follows:

$$\frac{\mathrm{A}(CAD) \cap \mathrm{A}(Ref)}{\mathrm{A}(CAD) \cup \mathrm{A}(Ref)} \quad \text{or} \quad \frac{\mathrm{V}(CAD) \cap \mathrm{V}(Ref)}{\mathrm{V}(CAD) \cup \mathrm{V}(Ref)}$$

We recommend you estimate and report location accuracy performance of your device using various values of the distance and ratio criteria and, if applicable, plots showing the performance change as a function of overlap criteria. The location accuracy assessment methodology, including the selection of primary and secondary performance endpoints, should be determined and fixed prior to initiating your evaluation.

We also recommend you supplement this evaluation by examining the impact of relevant confounders or effect modifiers, such as:

- lesion size,
- lesion type,
- lesion location,
- disease stage,
- organ characteristics,
- imaging hardware,
- imaging or scanning protocol, and
- image or data characteristics (e.g., characteristics associated with differences in digitization architectures for a CADe using scanned films).

We recommend you report all performance measures with associated CIs.

Reproducibility Testing

We recommend you report device reproducibility testing. These testing processes provide insight into the stability of the algorithm and its dependency on parameters usually related to the image acquisition protocol. For example, for digitized image data, the placement of the film in the scanner or the time when the scanning occurs could produce data differences that may affect how the algorithm performs. Providing standalone performance from the same patient and from multiple scans acquired using the same (or a different) acquisition protocol will provide information regarding the reproducibility and stability of the algorithm, with respect to the expected variation in data collection methods. We recommend you provide the following:

- description of the reproducibility study;
- parameters expected to introduce variability in the results (e.g., scanning characteristics, make and model of the imaging devices, acquisition protocol parameters such as contrast agent or probe positioning);

- effects to be monitored (e.g., effect on the segmentation accuracy, feature extraction, overall CADe performance accuracy); and
- results and statistical analysis.

Algorithm Stability Testing

We further recommend you conduct algorithm stability testing including:

- algorithm stability with respect to training set changes (i.e., invariance of the CADe algorithm with respect to the datasets used in its design and training) (e.g., see Yousef *et* al.[13]),
- algorithm stability over time (e.g., invariance to changes in the imaging system, acquisition conditions, operator settings), and
- algorithm stability with respect to other relevant covariates.

For assessment of the stability of your CADe algorithm, we recommend that you describe your methodology and provide results. Such evaluation may be performed, for example, by resampling using multiple bootstrap sets of the training database.

Algorithm Training Performance

We recommend you measure and report standalone performance of your CADe device on the dataset used to train the algorithm. Assessment of the algorithm training performance may include measures such as lesion-based, patient-based, and other relevant anatomical or image unit-based sensitivities, and the average number of false positives per case (FPs/case) or other relevant measure of specificity, at each device operating point. If your device allows clinicians to select or manipulate the device's operating point, we recommend you provide the device performance for individual selectable operating points or the range in performance for continuously varying parameters.

Other Information

In addition to all device performance assessment testing described above, we reiterate our recommendation that you provide a comparison of the performance testing results to the corresponding performances testing results of the legally marketed predicate device to which you are claiming substantial equivalence (e.g., a previously released version of the device), if applicable. Valid comparison of device performance is dependent upon sound study design in the collection of your testing database. We recommend that you describe your comparison analysis, hypothesis to be tested, sample size estimation, and endpoints, and that you provide

[13] Yousef, W. A., Wagner, R. F., and Loew, M. H., "Estimating the uncertainty in the estimated mean area under the ROC curve of a classifier," **Pattern Recognition Letters,** 2005 (http://www.sciencedirect.com/science/article/B6V15-4GTW8JJ-1/2/58c02b75531e668fbcbcd7810c7034b7).

comparison results. For example, when using a common database sequestered from the development and training of both your device and the predicate device, a comparison of the CADe standalone performance may include a measure of the:

- difference in area under the FROC curves with associated statistical analysis (e.g., see Samuelson *et* al.[14]), and
- difference in detection sensitivity and number of FPs/case at the device operating points.

Reporting of standalone performance results may be guided by the FDA Guidance entitled **Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests; Guidance for Industry and FDA Reviewers**.[15]

We again recommend submitting electronically[16] the data used in any statistical analysis in your study including patient information, disease or normal status, lesion size, lesion type, imaging and scanning setting, and imaging and data characteristics.

We also recommend you provide all data on a CD-ROM.

6. Clinical Performance Assessment

As described above, because each new CADe device represents a new implementation of software, FDA expects that each new CADe device (as well as software and other design, technology, or performance changes to an already cleared CADe device) will have different technological characteristics from the legally marketed predicate device even while sharing the same intended use. Accordingly, under section 513(i)(1)(A) of the Act, determinations of substantial equivalence will rest on whether the information submitted, including appropriate clinical or scientific data, demonstrate that the new or changed device is as safe and effective as the legally marketed predicate device and does not raise different questions of safety and effectiveness than the predicate device.

Because the reader is an integral part of the diagnostic process for CADe devices, we believe that a standalone performance assessment without a clinical performance assessment (i.e., a reader study) will usually not be adequate to demonstrate that the diagnostic performance of the CADe device is as safe and effective as the legally marketed predicate. Therefore, you should assume that a clinical assessment will be necessary to demonstrate substantial equivalence between your

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[14] Samuelson, F. W., and Petrick, N., "Comparing image detection algorithms using resampling," in Proceedings of the IEEE International Symposium on Biomedical Imaging. **IEEE**, pp. 1312–1315, 2006.

[15] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm

[16] See footnote 10.

CADe device and its predicate for its intended use, when used by the intended user and in accordance with its proposed labeling and instructions. This clinical performance assessment should provide an estimate of the clinical effect of the CADe device on clinician performance. If you believe a clinical assessment may not be necessary for demonstrating substantial equivalence of your device with the predicate, we recommend that you contact the Agency to seek advice prior to conducting your studies.

For clinical assessment, various control arms can be employed, including reading aided by the predicate device and unaided reading. The use of the predicate device as the control, with both devices evaluated on the same data set, allows for direct comparison of your device with the predicate for assessing substantial equivalence. The use of unaided reading as the control provides an assessment of the clinical effectiveness of your device, which, in 510(k) studies, should be compared with the clinical effectiveness of the predicate device, as estimated in a prior study. For this comparison to be unbiased, the two studies would ordinarily have to be calibrated on the distributions of important covariates, which can require that the data be available at the patient level in both studies. In addition, the comparison can be problematic to make if different sets of readers, different reference standards, or different scoring methods are used in the two studies.

For further detail on potential clinical assessment methodologies, we recommend that you consult the draft guidance entitled **Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions**.[17]

Examples of changes to an already cleared CADe device for which we recommend submitting a clinical performance assessment include:

- characteristics or makeup of the database used to assess standalone performance (see **Section 5**) cannot be demonstrated to be comparable to the characteristics or makeup of the database used in assessing the predicate device and these difference raises clinical concerns (i.e., could significantly affect safety or effectiveness);
- the results of the standalone performance assessment (see **Section 5**) are different from those of the predicate device, and the significance and effect on the clinician or patient for these different levels of performance are not well-known or well-described in the literature;
- the reference standard definition, scoring process, analysis methodology, or performance endpoints are different from those of the predicate device, and the significance and effect on the clinician or patient of these differences are not well-known or well-described in the literature;

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17 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm187277.htm

- the algorithm design is different from that of the predicate device and this difference raises clinical concerns (i.e., could significantly affect safety or effectiveness);
- the device design has different human factors from those of the predicate device (e.g., clinician's interaction with a different CADe output display); or
- a new precursor technology or acquisition protocol is employed, changing the nature of the inputs to the CADe (e.g., the current CADe device is applied to digital radiographs whereas the predicate device was applied to film-based radiographs).

There may be situations where a standalone performance assessment without a clinical performance assessment (i.e., a reader study) may be sufficient to demonstrate substantial equivalence. If you believe that a standalone performance assessment without a clinical performance assessment (i.e., a reader study) may suffice to show substantial equivalence, we recommend you contact the Agency to discuss your proposed approach.

7. User Training

We recommend you provide a summary of the procedure that will be used to train the intended users of your device when marketed. The goal of this training should be to help clinicians use the CADe device in an appropriate manner and to provide training so that they can achieve the expected device effectiveness. Training should include both the expected advantages and known limitations of the device (e.g., the CADe does not identify calcified nodules). An aspect of the training may be provided in the form of a self-test for the clinician. This self-test should provide feedback to the clinician on how well he/she performs before and after the integration of the CADe device and guidance on how to improve his/her performance. Training should be based on a broad set of patient data including normal cases. This training data should include typical true positives (TPs) and false positive (FPs) that the device tends to output, as well as typical true negatives (TNs) and false negatives (FNs).

For CADe devices allowing multiple thresholds or operating points, the training should help clinicians identify the most appropriate device setting for their practices. In addition, the training should help allow clinicians to identify suitable CADe reading scenarios.

8. Labeling

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR Part 801.[18]

[18] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR Part 801 before a medical device is introduced or delivered for introduction into interstate commerce. In addition, final labeling for prescription medical devices

Your user manual should include the information described below.

Indications for use

We recommend that the indications for use (IFU) address how the device will be used, for example:

> *The device is intended to assist [target users] in their review of [patient/data characteristics] in the detection of [target disease/condition/abnormality] using [image type/technique and conditions of imaging]*.

Directions for use

There must be adequate directions for use as described in 21 CFR 801.5; the requirements applicable to prescription devices are described in 21 CFR 801.109. You should submit clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patient images/data. Instructions should encourage local/institutional training programs designed to familiarize clinicians with the features of the device and how to use it in a safe and effective manner. The direction should also clearly define the intended user of the device.

Warnings

The warnings should address limitations of the device. For example:

> [*target user*] should not rely solely on the output identified by [*device trade name*], but should perform a full systematic review and interpretation of the entire patient dataset.

Another example may be:

> This CADe device has been found to be ineffective for patients with [*disease/condition/ abnormality*]. This CADe should not be utilized with patients presenting with this [*disease/condition/abnormality*].

Precautions

The precautions should discuss the potential for adverse events associated with the use of the device and recommend mitigation measures. The adverse event discussion should at least include a discussion of potential adverse events associated with an increased workup rate (i.e., events from false-positives) and missed disease/condition/abnormality.

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must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of 21 CFR Part 801.

Device Description

We recommend you include the following in your device description:

- an overview of the algorithm design and features,
- an overview of the training paradigm and the training or development database, and
- a description of the reference standard used for patient data utilized in the development and adjustment of the algorithm.

Clinical Performance Assessment

When appropriate, we recommend you include a summary of the clinical performance assessment including:

- study objectives,
- study design,
- patient population, e.g., age, ethnicity, race,
- number of clinicians and their qualification,
- description of the methodology used in gathering clinical information,
- description of the statistical methods used to analyze the data, and
- study results.

Additional information on reporting clinical performance results can be found in the draft guidance entitled **Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions**.[19]

Standalone Performance Assessment

We recommend you provide a summary of the device standalone performance and reproducibility testing including:

- the scoring criteria used to determine the nature of each region marked by your CADe device;

[19] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm187277.htm

- the overall lesion-based, patient-based, and any other relevant anatomical or image unit-based sensitivities, and the average number of FPs/case or other relevant measure of specificity, at each available device operating point;
- the stratified analysis per lesion size, per lesion type, per imaging or scanning protocols, per imaging or data characteristics, as appropriate;
- the confidence intervals (CIs) on each measure; and
- the free-response receiver operating characteristic (FROC) performance, as appropriate.

この報告書は、平成２２年度に独立行政法人　産業技術総合研究所が、経済産業省からの委託を受けて実施した成果を取りまとめたものです。

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