出國報告(出國類別:參加國際會議)

參加2016「32屆國際藥物流行病學暨治療風險管理會議年會(ICPE)」之出國參加會議心得報告

服務機關:衛生福利部食品藥物管理署

姓名職稱:周靖 副審查員

出國期間:105年8月22日至28日

報告日期:105年10月19日

摘要:

國際藥物流行病學會(ISPE；International Society for Pharmaceutical Engineering)為一非營利的國際專業會員組織，其會員包括學術機構、藥商、政府單位及其他非營利組織專業人員，其致力於進藥物流行病學之科學信息交流，以流行病學研究方法，處理藥物於臨床上實際使用之相關資料、進一步分析藥物使用之效益、價值和安全性，並每年舉辦年會，邀請包括流行病學家、藥理學家、生物統計學家及政府衛生政策主管機關等，一同討論公衛政策、疾病防治及風險管理等各方面之研究成果，亦屬於國際政策交流之公共論壇，於會前舉辦教育訓練課程，並透過專業講師及會員間的相互交流達到教學相長之功用。

此次國際藥物流行病學會於8月24日-28日假愛爾蘭都柏林舉辦第32屆「國際藥物流行病學暨治療風險管理會議年會」，本次會議內容豐富，大會並舉辦多場會前教育訓練課程，邀請包括產官學界的專家擔任講師，如美國FDA CDRH的官員(Danica Marinac-Dabic)，且課程亦包括醫療器材風險效益評估，如醫療器材流行病學評估課程，即主要提供與會學員如何運用基礎醫療器材流行病學在真實世界進行風險評估。

本次會議期程共5天，前2天為會前基礎課程，後3天為正式會議，課程及研討會內容豐富，每日均安排不同主題可供選擇，藉由與各國藥物流行病學學者及藥政法規專家相互交流，有助提升我國藥品安全評估及風險管理政策之規劃。職主要透過前2天之基礎課程教育訓練，瞭解世界各國針對醫療器材產品之風險管理手段及措施，如美國FDA之醫療器材產品登錄制度，除可加速醫療器材上市前審查速度外，亦可強化可疑風險訊號之偵測。

職透過參與此次ISPE年會暨學術研討會，除可瞭解國際間最新法規及政策管理現況、流行病學研究方法的發展及應用外，未來並可致

力於提升國內藥物安全監視政策之發展，並與國際接軌，藉由積極瞭解國際間藥物安全監視現況，充實藥物安全監測方法的知識，達成完善我國醫療器材上市後管理政策。

目次:

一、 目的:

國際藥物流行病學會（International Society for Pharmacoepidemiology, ISPE）雖每年舉辦「國際藥物流行病學暨治療風險管理會議年會(Annual International Conference on Pharmacoepidemiology & Therapeutic Risk Management, ICPE)」，供各界交流藥物流行病學研究及各國藥物安全監測政策之進展，並提供教育訓練的機會，但以往主要針對藥品及疫苗的風險研究為主，少有醫療器材之相關課程或報告，或許鑑於醫療器材越來越精密複雜，使用風險也越來越高，故此次會前教育訓練，大會特別邀請 FDA 及相關專家開辦討論醫療器材之課程。

此次參加研討會之目的，除瞭解各國目前關注之醫療器材安全、政策發展動向，並藉由大會提供教育學習的機會，透過與各國交流平台增進藥物流病學知識與藥物安全訊息監控，達成國際間的藥物安全監視之規劃與用藥安全政策執行現況之互相學習與合作。另外我國對於醫療器材上市後之風險管理，雖已比照先進各國，建置藥物(含醫療器材)、食品、化粧品品質管理系統，透過主被動的方式蒐集醫療產品可疑風險訊號，並評估分析醫療機構、藥商通報之醫療器材不良事件，以求提早預防可能危害民眾健康的之醫療器材風險，藉由此次參加會議學習先進國家執行藥物安全監視政策之運轉模式，吸取經驗，進而強化我國醫療器材安全監視暨風險管理。

二、 ICPE 研討會行程:

(一) ICPE 大會議程:

日 期	擬參觀、考察、研習、進修國家之機關名稱及地點
105.8.22	由臺灣搭機前往愛爾蘭都柏林 台北-德國 法蘭克福-愛爾蘭 都柏林
105.8.23	
105.8.24	ICPE 開幕，參加 HALF-DAY-SESSIONS(Medical Device);Databases; Benefet Risk Assessment
105.8.25	參加 Pharmacoviligilance &Signal Detection
105.8.26	參加 Special Interest Group(SIG) Meetings (Medical Devices SIG)
105.8.27	搭機返回臺灣 愛爾蘭 都柏林-荷蘭 阿姆斯特丹 -台北
105.8.28	

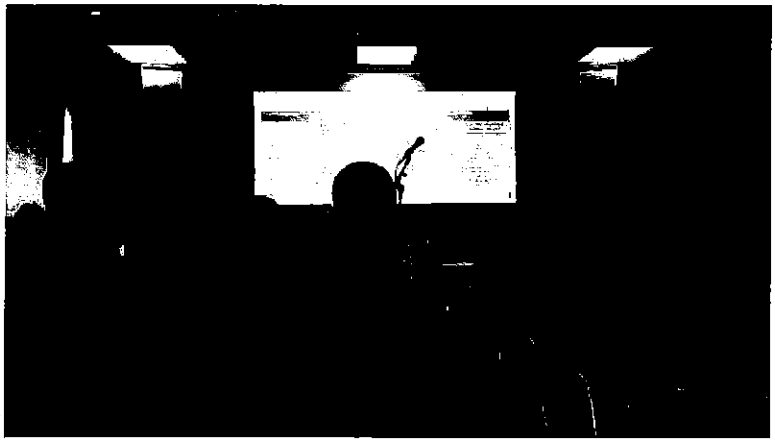
三、 研討會內容:

(一) **Pre-conference educational sessions(8/24-25)：**

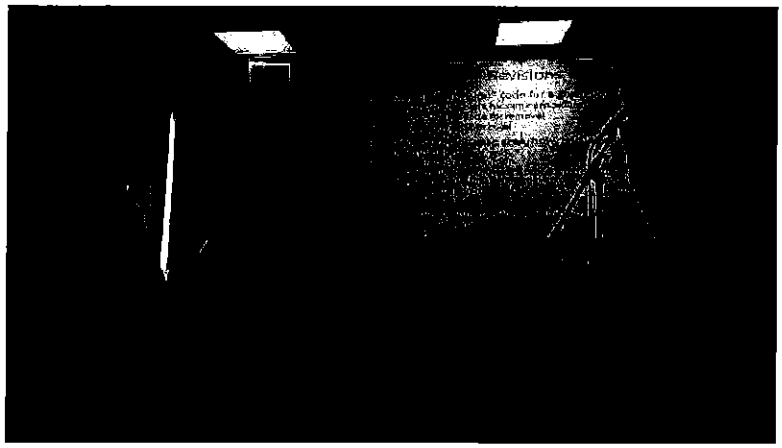
(1). Medical Device:

1. 該課程首位講者 Colin Anderson-Smith 為美國 FDA 官員，主要介紹介紹美國及及其他國家(包括歐盟、日本、加拿大等國)對醫療器材之風險管理架構，包括各國醫療器材風險等級分類及管制措施。在美國方面，其醫療器材主要依產品風險分為 I、II、III 等級，另外醫療器材製造商品質系統主要遵循 21 CFR Part 820 之品質系統規範（Quality System Regulation；QSR）要求；歐盟對醫療器材之管理，將醫療器材分為四個等級，製造商品質

系統則以 EN 46001/2:1996 標準，再遵循醫療器材指令(Medical Device Directive; MDD 93/42/EEC)之規定為要求；日本及加拿大針對醫療器材之風險分類與歐盟相同分為四個等級，製造商品質系統則以醫療器材優良製造規範(Good Manufacturing Practice；GMP) 規定為產品上市後之要求。

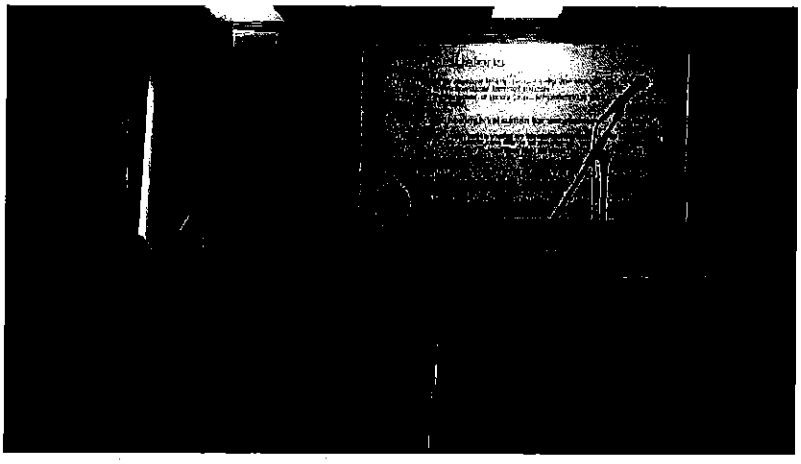


2. 第二位講者Jessica Jalbert博士，其主要講述如何研究植入式醫療器材之效果，該計畫主要是透過政府機關資料庫，去研究單一物件式植入式醫材(如心血管支架)或系統式植入式醫材(如骨科植入物)之使用效果，其透過各種資料代碼，國際疾病分類代碼(ICD-9)、Procedure codes及CPT-4 codes，追蹤分析研究植入效果,但目前仍有問題待解決，包括Procedure codes無法記錄手術位置(器官部位)，及高達4種的CPT-4 codes，並可能造成誤解，而且目前仍非常缺乏大型的資料庫可供研究或是偵測罕見的不良反應，且即使多數資料庫為電子病歷紀錄檔，年齡相關的臨床資訊也常記載不全，增加了研究的困難度。



3. 第三位講者Kade Etter博士，講題是患者自評結果(PRO: Patient Reported Outcomed)對醫療器材安全性評估的重要性，講者認為透過設計患者自評結果問卷，可有效分析評估醫療器材的安全性及有效性。對於新醫療器材而言，如果沒有患者自評結果，當進入市場後，產品可能會有顯著風險，但容易被忽略，造成民眾危害事件之發生。

本單元最後由Kade Etter帶領學員探討資料收集的方法、可能的優缺點與限制，並以分組討論報告的方式，由學員實際嘗試設計一個可行研究患者自評結果問卷，試著透過醫療器材的設計、目的及效能等，藉由問卷或面談的方式可以直接向病人收集第一手的資料，如果問卷設計優良，通常可以收集到較細節的醫材使用資訊，但可能會存在觀察性誤差，但可以透過一些問卷設計或諮詢技巧克服。另外為提高問卷的成效，針對患者的選擇，也是關鍵之一，除了要有明確的研究主題外，更要對各種醫療器材資料要有詳細的了解，後續並須針對蒐集病患之問卷回復進行分析，包含數據的品質、含括的族群、資料可近性及健康照護的體系等。

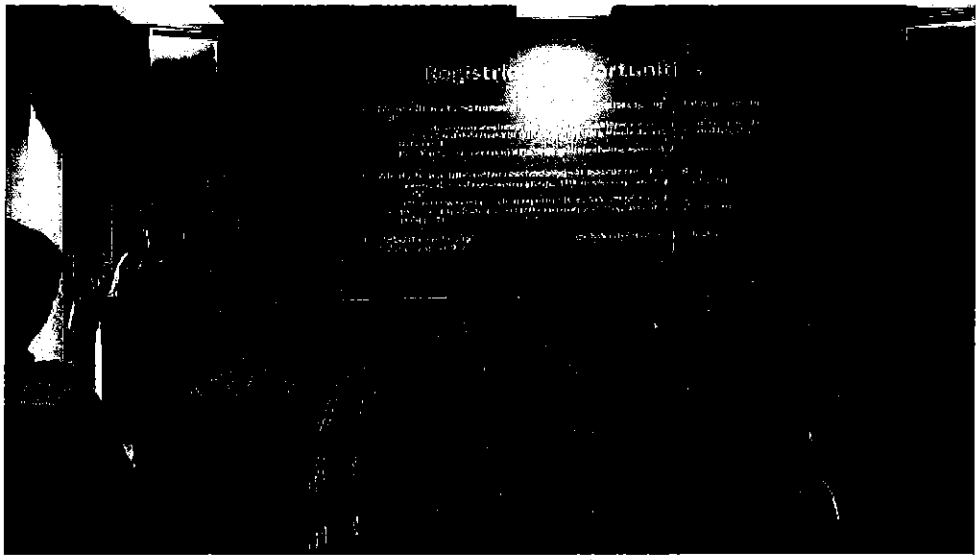


Compareative Effectiveness Research: CER and its Role in Adaptive Licensing:

1. 由美國 FDA CDRH 官員 Danica Marinac-Dabic 主講，美國在 2014 年公告「Medical Device Tracking Guidance for Industry and Food and Drug Administration Staff」(如附件 1)，針對部分高風險醫療器材之產品，要求藥商進行上市後追蹤制度，主要以心血管及骨科植入物類的醫療器材為主(共約 40 多項產品)，這套機制主要要求藥商可讓主管機關產品監控醫療器材發生不良事件或有產品風險時，可加速廠商針對產品回收或警訊發布的處理進度。

   除了上述產品追蹤制度外，另外 FDA 並在今(2016)年 6 月公布「Use Real- World Evidence to support Regulatory Decision-Making for Medical Device」(如附件 2)，其主要藉由醫療器材病患登錄資料庫，除可蒐集監控醫療器材不良事件的發生外，並可就所蒐集到醫材產品臨床效益及風險進行評估，作為未來同類新醫療器材辦理查驗登記時，需驗證審核的產品資料。Dr. Danica 強調當醫療器材上市後的安全資料

越來越齊全時，產品上市前所需繳交供審查的資料也就可能越來越少，同時也縮減上市前審查的時效。完善的醫材產品上市後監控制度可同時回饋至產品上市前審查。

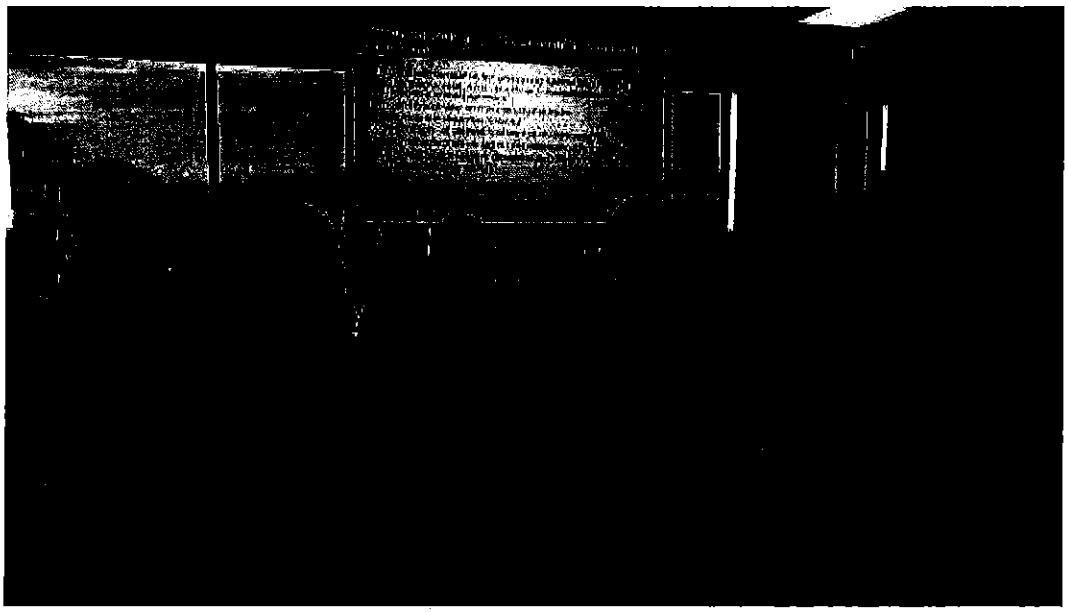


(二) **Pre-conference educational sessions(8/25):**

(1). **Pharmacovigilance& Signal Detection:**

主講者為 Andrew Bate 為輝瑞藥廠產品上市後管理部門主管，其主要講述透過不同種資料來源的比對達到藥物安全監視的方法，其表示針對藥物的安全監視可以透過流行病學的設計與研究，包括雙盲試驗、三盲試驗等找出產品上市後的安全訊號，並利用系統性及整體性的觀測藥物的生命週期，但此種研究方式要克服資料中偽陰性及偽陽性的問題，所以要透過多方資料的比對。另外藥商目前針對藥物上市後面臨的困難，包括產品本身的整體風險與效益的控管，必須精確且即時的對任何可能的風險作出反應，且也必須考量過度的反應可能會傷害利益。但在產品風險管理上，必須秉持透明的原則，並盡可能從不同的來源，充實科學的證據，作出最好的決策；並提到未來的風險管

理須要從被動轉化為主動監控。



(2). Regulatory Pharmacoepi:

美國及歐盟一向是全球藥物安全監視及政策制定的領頭羊，透Gerald 及June 的分享，可以了解先進國家在藥物安全監視的想法、決策的過程及面臨的挑。管理單位最重要的責任就是促進及保護大眾的健康，為了達成上述的目的所以須要執行藥物安全監視；藥物安全監視的目標是不斷的學習藥品在開發過程中所未知的知識，透過與藥廠、醫療人員及民眾的溝通，達到促進及保護大眾的健康的目的。自主性通報系統則是重要的監視工具。雖然一般認為自主性通報系統所提供的資料科學證據力就弱，但在缺乏其他研究證據時，仍常是形成決策的重要依據。故加強不良反應通報的質與量，以及提升評估的品質是非常重要的；應將所有的利益相關者都納入通報的來源，包含藥商、醫療人員及使用者。另外管理單位如何在較薄弱或具有衝突的科學證據下，依據風險管理原則，及時針對突發藥物不良反應事件做出回應，並與大眾溝通，這

是管理單位需要不斷精進研究的課題，

另外由倫敦大學 Stephen JW Evans 博士講述「**Introduction to, and epidemiology of, pharmacovigilance & signal detection**」，講述歐盟如何透過流行學、藥物上市後監控等，偵測藥物可疑危險訊號。其主要方法係透過蒐集藥品使用的病歷紀錄或透過專門研究計畫找出可能由藥物造成之不良反應事件，蒐集的資料來源包括美國 FDA 資料庫、或其他國家資料庫及藥商本身建置之產品資料庫，有關偵測藥物風險訊號的原則，可以先透過現有病例資料庫，透過統計學的方式找尋出該藥物可疑的不良事件比例， 並透過比對其他資料庫或臨床試驗研究確認藥物風險因子。

四、 心得及建議事項:

(一)ICPE 是利用上市後資料或臨床研究計畫蒐集資料進行研究分析，互相交流研究結果並探討風險管理之研討會，每年的都有許多精采的研究討論與發表，同時也兼具政策管理的分析探討，非常值得推廣國內相關藥物安全研究者及政府單位參與；有許多的SIG group 和教育課程，積極參與相信可以有許多的國際合作機會。此次參加第32屆ICPE國際研討會，職主要參與8/24-25之教育訓練課程為主，因目前國際間對藥物的上市後風險評估，以藥品為主的上市後風險評估相較於醫材，已有較完整的策略與評估模式，然而新興及高風險(植入式)醫療器材的蓬勃發展，目前國際間對醫療器材的風險研究已逐步展開，透過此次ICPE教育訓練，職透過學習藥品的風險管理及危險訊號偵測模式，評估未來是否可應用我國醫

療器材之風險因子之偵測。

（二） 本次會議有很多的討論都聚焦在data source 和data linkage 的部分。有好的研究才有好的科學證據，有好的科學證據才能進一步改善決策的品質；主管機關決策時常為沒有本土的研究資料所苦惱，而有好的資料來源是重要的第一步。在大數據的時代下，透過電腦科技的協助，將散落在各部門或個單位的資料庫串連，是相對容易獲得資料的方式，這也是目前全世界的藥物流行病學家在努力的方向之一。有幸衛福部統計室已在積極的串連相關健康資料，建議在小心維護資料安全性的前提下，要抱持更開放及透明的管理態度，積極導入相關科技輔助及協調各利益相關人士，畢竟這對國人健康及公共衛生有極大效益。

（三） 政策公開與透明化是regulator science 最重要的前提，尤其在藥物安全領域，積極的參與應是藥商的責任與義務，除了透過明確的法規要求外，主管機關透明化的政策討論，以及積極的與廠商合作參與，更能促進藥品上市後的安全管理與維護大眾的健康。此外，應該更加重視病人的意見與回饋，建議不良反應通報系統應該區分醫療人員/藥商及民眾的通報與宣導方式，更積極的蒐集使用者的報告。例如有關教育訓練課程中提及病人對醫療器材使用後之自評結果(PRO)之重要性，此節我國過往在此方面的研究並不多，由於部分高風險醫療器材係長時間植入人體，對人體的影響可能是長時間，故病患對醫療器材的風險危害感受最為真切，未來可透過PRO進行醫療器材長時間的風險評估之用。

（四） 另外這次大會中，美國FDA CDRH Danica Marinac-Dabic講述醫療器材上市後產品登錄制度及美國最新公告「「Use Real- World Evidence to support Regulatory Decision-Making

for Medical Device」，實可做為我國未來政策之參考，有關醫療器材上市後產品登錄制度部分，除可有效追蹤醫療器材產品使用後之安全、有效性外，亦可有效縮減未來同類型醫療器材上市前審查時效，降低不必要之臨床實驗，並可針對產品之使用風險，提早進行預警，美國最早是在1997年透過ACC(American College of Cardiology)就心血管照護病人進行追蹤，目前主要針對部分第三等級高風險醫療器材進行登錄，另外國際間瑞典、英國、澳洲、紐西蘭等先進國家，皆已推動人工植入物登錄制度資料庫，我國健保署亦於今年1月建置「人工關節登錄制度」，未來可以瞭解我國醫療器材上市後監控系統之可行性，有助於提升醫療器材風險訊號之偵測，並提早預防醫療器材危害事件之發生。

附件一

Medical Device Tracking

Guidance for Industry and Food and Drug Administration Staff

Document issued on March 27, 2014.

This document supersedes Medical Device Tracking issued on January 25, 2010.

For questions about this document contact Deborah Yoder at 301-796-6109 or by electronic mail at deborah.yoder@fda.hhs.gov or contact the Division of Analysis and Program Operations at 301-796-5530.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Analysis and Program Operations

Contains Nonbinding Recommendations

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to http://www.regulations.gov. Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, (HFA-305), Rockville, MD, 20852. When submitting comments please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 169 to identify the guidance you are requesting.

Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Medical Device Tracking
Guidance for Industry and Food and Drug Administration Staff

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

I. Introduction

The Food and Drug Administration (FDA) is issuing this guidance to announce that both the list of devices subject to medical device tracking requirements, and the list of medical devices released from tracking requirements, have been updated. This updated guidance identifies all affected devices (those tracked and those released from tracking) in table format. The table includes two fields to describe each device: (1) product code (procode) and (2) the standardized procode definition (product code – preferred term). These two descriptive fields are intended to provide clarity about which devices are tracked. The product code and preferred name are generally found in the approval or clearance letter issued by CDRH.

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

II. Background

The Food and Drug Administration Modernization Act (FDAMA) requires that manufacturers track certain devices when the Agency orders them to do so. Tracking is intended to facilitate notification and recall in the event a device presents a serious risk to health that requires prompt attention.

The tracking provisions of section 519(e) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 360i(e), were added in 1990 by the Safe Medical Devices Act (SMDA) and amended in 1997 by FDAMA. Device tracking enables FDA to require a manufacturer to promptly identify product distribution information and remove a device from the market.

Section 519(e) states the Agency may require tracking for a class II or class III devices

(A) the failure of which would be reasonably likely to have serious adverse health consequences; or

(B) which is

i. intended to be implanted in the human body for more than one year; or

ii. is a life sustaining or life supporting device used outside a device user facility.

FDA has issued letters to each manufacturer that currently makes and distributes a legally marketed device that must be tracked under the Act. An order to adopt a tracking method may also be issued by FDA for a "new" device as part of the premarket clearance process. FDA will issue an order to the sponsor of the submission when clearing a premarket notification submission (510(k)) or approving a premarket approval application (PMA). A tracking order issued as a result of a premarket review will be issued as a separate order; it will not be part of a 510(k) order or a PMA approval order.

FDA has discretion on whether to order tracking for devices that meet the statutory requirements or to release devices from tracking based on additional factors and other relevant information that comes to the Agency's attention. The following additional factors may be considered to determine whether a tracking order should be issued:

- likelihood of sudden, catastrophic failure;
- likelihood of significant adverse clinical outcome; and
- the need for prompt professional intervention.

The Agency may add or remove devices from the list of tracked devices and may consider the additional guidance factors in conjunction with the review of premarket applications, recall data, medical device reporting, inspections, petitions, postmarket surveillance or other information coming to its attention.

When FDA determines that a device should no longer be tracked, it will notify the manufacturer by direct communication.

Tracking of medical devices augments FDA's recall authority. Under section 518(e) of the FD&C Act, 21 U.S.C. 360h(e), FDA is authorized to order a mandatory recall. FDA's authority, under section 518(a) of the FD&C Act, 21 U.S.C.360h(a), enables us to require a manufacturer to notify health professionals and patients in the event of unreasonable risk of substantial harm associated with a device. Tracking enhances the impact of mandatory recalls or notifications when such actions concern tracked devices.

Additional information on tracked medical devices is also available on FDA's website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/MedicalDeviceTracking/default.htm

Questions about tracked medical devices, or the regulations and requirements associated with tracked medical devices, should be addressed to TrackedDevicesMailbox@FDA.HHS.GOV.

III. Scope

This guidance applies to manufacturers, importers, and distributors of tracked medical devices regulated by CDRH.

IV. Questions and Answers about Medical Device Tracking

The following questions and answers are provided to add clarity to the medical device tracking requirements of 21 CFR Part 821, available online at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=821

1. **How do I know if my device must be tracked?**
   When a new device receives FDA clearance or approval for marketing, and is on the tracked devices list, FDA will issue tracking orders to the manufacturer to confirm the tracking requirements for that device. No tracking obligations exist unless tracking orders have been issued.

   FDA will notify applicable manufacturers, in writing, when a device gets released from tracking requirements.

2. **What information must be tracked?**
   The required tracking information for a manufacturer of a tracked device is identified at 21 CFR 821.25. The required tracking information for a distributor of a tracked device is identified at 21 CFR 821.30.

   On July 10, 2012, FDA proposed that most medical devices distributed in the United States carry a Unique Device Identifier (UDI) (77 FR 40736). If implemented, the UDI requirement may impact your tracked device. We encourage you to visit our UDI website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/UniqueDeviceIdentification/default.htm for information about the proposed rule.

3. **Must I use a specific tracking method?**
   No. FDA understands that manufacturers will have different tracking methods and procedures. Manufacturers must have written standard operating procedures (SOPs) that define a method of tracking that will produce the information required by regulation.

4. **What must tracking methods do?**
   Tracking methods must provide certain critical information about the location of a tracked device within a short time frame. Manufacturers will have 3 working days to provide critical information about devices that have not yet been distributed to a patient and 10 working days for devices that have been distributed to patients.

5. **May I contract out management of my tracking program?**
   Yes. Manufacturers, however, remain responsible for making sure that the program complies with the tracking requirements. Manufacturers cannot alter, change, or in any way avoid their

tracking obligation unless FDA approves a manufacturer's written request for a variance or an exemption.

6. **Can a medical device registry satisfy the requirements of a tracking program?**
   Yes. If a registry collects information required by 21 CFR 821, a registry can manage a device firm's tracking program. Manufacturers, however, remain responsible for making sure that the program complies with the tracking requirements.

7. **What type of auditing am I expected to do on my tracking program?**
   Manufacturers must make sure that the tracking program works. Manufacturers must perform audits at 6 month intervals for the first 3 years after receiving tracking orders, and then annually after 3 years. Audits should verify that the tracking method actually works and that the information collected is accurate so that, in the event of a recall, the right persons are notified in a timely fashion.

   A recognized statistical sampling plan should be used, such as *Military Standard 105E: Sampling Procedures and Tables for Inspection by Attributes* (MIL STD 105E). A free download of this standard can be obtained at MIL-STD-105E.

   Audits may be conducted through on-site visits or through some other effective way of communication with the distributors, professionals, and patients.

8. **Will my tracking program be reviewed during any FDA inspections?**
   Tracking methods are subject to FDA inspection, which may include a review of the tracking system. FDA may review your tracking program to ensure that your tracking method actually tracks your device to the end user.

9. **Do my tracking obligations ever end?**
   Yes. Tracking is no longer required when you have evidence to confirm that the device has been (a) returned, destroyed, or explanted; or (b) that the patient died. Refurbishers and remanufacturers of tracked devices that remain in domestic commercial distribution are also subject to tracking requirements and should be able to ensure that the original manufacturer can promptly locate the devices.

   For devices with an approved PMA that are also subject to a tracking order, the need for continued tracking may be reassessed, at the sponsor's request or by the Agency's initiative, 10 years from the date of the original PMA's approval.

10. **What if someone else buys my business?**
    If you go out of business and a new person or entity acquires the right to manufacture or distribute the tracked devices, then these other persons or entities become responsible for continuing the tracking responsibilities.

11. **What if I just stop distributing tracked devices but stay in business?**
    If you stop distribution of a tracked device but continue to do other business, then you remain responsible for the tracking of devices that you previously distributed.

12. What if I go out of business completely and no one takes ownership of my manufacturing rights?

A manufacturer or distributor that goes out of business is required to notify FDA at the same time that it notifies of the business shutdown to any government agency, court, or supplier. With the notification to FDA, the manufacturer or distributor must provide FDA with a complete set of its tracking records and information.

13. Are there any special labeling requirements for tracked devices?

No. Special labeling is not required for tracked devices. FDA believes, however, that some form of identification should be provided with or on the device. This would enable users to easily recognize the device for tracking purposes.

14. If I'm not the original manufacturer and I just assemble kits and systems made by someone else, must I keep tracking records?

Yes. FDA considers a kit or system assembler to be a distributor. That means you must notify the manufacturer when a tracked device has been received. You should also ensure, when appropriate, that anyone who receives the kit or system knows that it contains a tracked device. The manufacturer's original labeling should remain on every tracked device included in a kit or system.

15. What if I work for the U.S. Government and distribute tracked device?

The U.S. Government (civilian or military) is subject to the tracking regulation and assumes the responsibilities of a distributor, final distributor, and multiple distributor.

16. Am I required to track exported devices?

A device distributed outside the U.S. would not subject to tracking (unless used on military bases or in consulates). Please remember, though, that manufacturers must track the device through the chain of distribution to the person or firm that physically exports the device. FDA does expect, in the event of a recall, that the manufacturer will make a reasonable effort to track implanted devices when the recipient has a foreign address.

17. Am I required to track imported devices?

Yes. An initial importer distributor assumes the role of a domestic manufacturer and, therefore, must track the device throughout its distribution in the U.S.

If the foreign manufacturer acts as its own initial distributor, then the foreign manufacturer maintains responsibility for device tracking. A failure to comply with U.S. tracking requirements may cause the imported device to be detained at the point of entry into the U.S.

18. What are my tracking responsibilities as a user facility?

User facilities, such as hospitals and nursing homes, have responsibilities as a final distributor when the device is for single use and otherwise have responsibilities as a multiple distributor when the device is for multiple use.

For example, a hospital that implants single-use tracked devices is the final distributor of those devices. A hospital outpatient clinic that rents, leases, or loans a multiple-use tracked device is the multiple distributor of those devices.

19. Does FDA have a specific reporting format that I must use?

No. There is no obligation to use a particular reporting format. Regardless of format, all required information must be provided to the manufacturer. Whenever possible, hospitals should consider using the manufacturer's format to facilitate the ease of tracking.

20. What are the tracking requirements associated with devices resterilized by the user facility?

The fact that a hospital sterilized, resterilized, or repackaged a tracked device does not make the hospital a manufacturer for tracking purposes; the user facility remains a final or multiple distributor.

21. What are the unique tracking obligations associated with external defibrillators?

FDA expects external defibrillators to be tracked to the vehicle, craft, or organization that purchased the device. Tracking information does not need to extend to the patient level.

22. What are the general tracking requirements for implants?

The manufacturer has the responsibility to track the implant through the chain of distribution to the patient and to update the address as necessary. How the manufacturer will update patient information should be specified in its tracking SOP.

23. Must I obtain written patient consent to obtain tracking information?

No. The regulation does not require that a patient give written consent to have a device tracked or to release their identity to the manufacturer.

24. What if a patient refuses to provide personal information needed for tracking?

Patients, but not user facilities, may refuse to provide personal information gathered for device tracking. Such refusals should be documented by the product, model, and serial number, and the information provided to the manufacturer. The manufacturer must maintain this record for the useful life of the device. A patient's refusal does not relieve the manufacturer of its obligation to account for the tracked device.

25. What are my responsibilities as a device importer or distributor?

While the primary responsibility for assuring a functional tracking system rests with the device manufacturer, any other person, including a device importer or distributer (whether final distributor or multiple distributor) who fails or causes others to fail to comply with the tracking requirements would be considered to be violating sections 301(e) and 301(q)(1)(B) of the FD&C Act. (These sections of the FD&C Act can be viewed at http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterIIIProhibitedActsandPenalties/default.htm)

26. Can I request an exemption or variance from tracking?

Yes. A manufacturer, importer, or distributor may request an exemption or variance from tracking in the form of a petition. Petitions should be submitted in compliance with the requirements of 21 CFR 10.30.

For devices with an approved PMA that are also subject to a tracking order, the need for continued tracking may be reassessed, at the sponsor's request or by the Agency's initiative, 10 years from the date of the original PMA's approval.

V. Medical Devices Requiring Tracking

FDA has issued tracking orders to manufacturers of the following devices, listed in alphabetical order according to the product code – preferred name:

Product Code - Preferred Name	*Procode*
Aortic valve prosthesis, percutaneously delivered	NPT
Breast prosthesis, non-inflatable, internal, silicone gel filled	FTR
Defibrillator, auxiliary power supply (AC OR DC) for low energy DC defibrillator	MPD
Defibrillator, automated, external, wearable	MVK
Defibrillator, automatic, implantable, cardioverter, with cardiac resynchronization (CRT-D)	NIK
Defibrillator, DC, high energy (including paddles)	DRK
Defibrillator, DC, low energy (including paddles)	LDD
Defibrillator, implantable cardioverter (NON-CRT)	LWS
Defibrillator, implantable, dual chamber	MRM
Defibrillator, over-the-counter, automated, external	NSA
Defibrillators, automated external (AEDs) (non-wearable)	MKJ
Electrode, pacemaker, permanent	DTB
Electrode, pacing and cardioversion, temporary, epicardial	NHW
Electrodes, defibrillator, permanent	NVY
Electrodes, pacemaker, drug-eluting, permanent, right ventricular (RV) or right atrial (RA)	NVN
Endovascular graft system, aortic aneurysm treatment	MIH
Heart valve, mechanical	LWQ

Heart valve, non-allograft tissue	LWR
Heart valve, replacement	DYE
Mandibular prosthesis, condyle, temporary	NEI
Monitor, apnea, home use	NPF
Monitor, breathing frequency	BZQ
Pacemaker battery	DSZ
Pacemaker, lead adapter	DTD
Pacemaker, pulse generator (NON-CRT) implantable	LWP
Pacemaker, pulse generator, implantable	DXY
Pulmonary valve prosthesis, percutaneously delivered	NPV
Pulmonic valved conduit	MWH
Pulse generator, pacemaker, implantable, with cardiac resynchronization (CRT-P)	NKE
Pulse generator, permanent, implantable	NVZ
Pulse generator, single chamber, single	LWW
Pulse generator, dual chamber, pacemaker, external	OVJ
Pulse generator, single chamber, sensor driven, implantable	LWO
Pump, infusion or syringe, extra-luminal	FIH
Pump, infusion, implanted, programmable	LKK
Shunt, protosystemic, endoprosthesis	MIR
Stimulator, autonomic nerve, implanted (depression)	MUZ
Stimulator, cerebellar, implanted	GZA
Stimulator, diaphragmatic/ phrenic nerve, implanted	GZE
Stimulator, diaphragmatic/phrenic nerve, laparoscopically implanted	OIR
Stimulator, electrical, implanted, for Parkinsonian symptoms	NHL
Temporomandibular joint, implant	LZD
Transmandibular implant	MDL
Ventilator, continuous, home use	NOU
Ventilator, continuous, non-life-supporting	MNS
Ventilator, continuous, minimal ventilatory support, facility use	MNT

Ventilator, continuous, minimal ventilatory support, home use	NQY
Ventilator, mechanical	ONZ

VI. Medical Devices Released from Tracking Requirements

The devices previously released from mandatory tracking requirements remain free of any tracking obligations.

With the issuance of this guidance, CDRH releases the following devices from mandatory tracking requirements, due to an updated risk assessment:

Product Code - Preferred Name	Procode
Condylar fixation plate, implant	JDP
Condyle prosthesis, mandibular; bone plate with mandibular condyle prosthesis; locking reconstruction plate with attachable condyle	MPL
Glenoid fossa prosthesis	MPI

Contains Nonbinding Recommendations

Draft – Not for Implementation

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on July 27, 2016.

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

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or Benjamin Eloff, Ph.D. at 301-796-8528 or Benjamin.Eloff@fda.hhs.gov, the Office of Device Evaluation at (ODE) at 301-796-5550 or Owen Faris, Ph.D. at 301-796-6356 or Owen.Faris@fda.hhs.gov, or the Office of Compliance (OC) at 301-796-5500 or James Saviola at 301-796-5432 or James.Saviola@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

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

Preface

Additional Copies

CDRH

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1500012 to identify the guidance you are requesting.

CBER

Additional copies are available from the Center for Biologics Evaluation and Research (CBER), by written request, Office of Communication, Outreach, and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Room 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, by email, ocod@fda.hhs.gov or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction and Scope

FDA is issuing this draft guidance to clarify how we evaluate real-world data to determine whether it may be sufficiently relevant and reliable to generate the types of real-world evidence that can be used in FDA regulatory decision-making for medical devices.

- **Real-World Data (RWD)** is data collected from sources outside of traditional clinical trials. These sources may include large simple trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and healthcare claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries (e.g., device, procedural, or disease registries). The data is typically derived from electronic systems used in health care delivery, data contained within medical devices, and/or in tracking patient experience during care, including in home-use settings.

- **Real-World Evidence (RWE)** is the evidence derived from aggregation and analysis of RWD elements.

RWD and associated RWE could constitute valid scientific evidence, depending on the characteristics of the data. This guidance should not be interpreted to convey that FDA is changing the evidentiary standards used in regulatory decision-making; rather, this guidance

describes the circumstances under which RWD may be used in different FDA contexts based on the existing evidentiary standards.

This guidance also clarifies when an Investigational Device Exemption (IDE) may be needed to prospectively collect and use RWD for purposes of determining the safety and effectiveness of a device. However, this guidance does not address the use of non-clinical data, adverse event reports, and secondary use of clinical trial data (e.g., post hoc analyses). In addition, this document does not provide guidance about good study design methods, conduct, or statistical methodology.

This guidance does not affect any federal, state or local laws or regulations or foreign laws or regulations that may otherwise be applicable to the use or collection of real-world evidence and that provide protections for human subjects or patient privacy. When finalized, this guidance should be used to complement, but not supersede, other device-specific and good clinical practice guidance documents.

FDA's guidance documents, including this draft 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 guidance means that something is suggested or recommended, but not required.

II. Background

To protect and promote the public health, FDA needs to understand and evaluate the available evidence related to regulated products.[1] For medical devices, available evidence is traditionally comprised of non-clinical and, in some cases, clinical studies conducted and provided to FDA by the device manufacturer or sponsor. However, FDA recognizes that a wealth of data covering medical device experience exists and is routinely collected in the course of treatment and management of patients. Data collected during clinical care or in the home setting may not have the same controls for data quality and against biased results as data collected within a clinical trial setting. However, under certain circumstances, RWD may be of sufficient quality to help inform or augment FDA's understanding of the benefit-risk profile of devices at various points in their life cycle. RWD, which are typically collected for non-regulatory purposes in electronic health records (EHRs), registries, and administrative and claims data, may provide new insights into the performance of medical devices. The information obtained could potentially be used to aid FDA in regulatory decision-making.

FDA has issued guidance on balancing premarket and postmarket data collection,[2] understanding benefit-risk determinations,[3] and expedited access to medical devices for unmet medical needs[4]

[1] FDA's What We Do

[2] Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval

in an attempt to streamline the process for bringing new technologies to market while assuring robust evidence generation and applying appropriate controls to ensure the continued safety and effectiveness of medical devices. FDA has also issued plans for and has begun implementation of a national evaluation system[5,6,7,8] that leverages RWD to more quickly identify safety problems, to better understand the benefit-risk profile of devices used in clinical care, and to reduce the time and cost of evidence generation to inform FDA premarket approval and clearance.

Routine clinical practice often involves the use of cleared or approved devices for uses or in patient populations not within the cleared or approved indications for use. However, the advances in knowledge that may result are often not realized because the data collected are not systematically characterized, aggregated, and analyzed in a way such that it can be relied upon to inform regulatory decision-making. By recognizing the value of RWE as an important contributing factor for understanding and regulating medical devices, we hope to encourage medical device researchers, manufacturers, physicians, hospitals and other stakeholders to learn more from routine clinical care than we do today.

FDA will use the criteria described in this guidance to help determine if RWD data sources are of sufficient quality to potentially generate valid scientific evidence.[9] FDA relies only upon valid scientific evidence to determine whether there is a reasonable assurance that a device is safe and effective. While it is required that this bar be met in all such cases, it is possible that RWD could meet this threshold under circumstances when important and necessary patient data were accurately and reliably captured at clinically relevant time intervals throughout the appropriate portions of the lifecycle of the medical device. For example, RWE may be suitable to support the expansion of the indications for use of cleared or approved devices through an appropriate premarket submission. RWE may also be suitable to augment the information needed to support clearance or approval of the next generation of a device. Other applications of RWE in premarket decision-making may be possible, as well, particularly as data systems and analysis methodology advance. Aggregation of RWD (e.g., in medical device registries) may

[3] Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications

[4] Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

[5] Strengthening Our National System for Medical Device Postmarket Surveillance

[6] Strengthening Our National System for Medical Device Postmarket Surveillance: Update and Next Steps - April 2013

[7] Strengthening Patient Care: Building a National Postmarket Medical Device Surveillance System

[8] Recommendations for a National Medical Device Evaluation System: Strategically Coordinated Registry Networks to Bridge the Clinical Care and Research - August 2015

[9] "Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use." [21 CFR 860.7(c)(2)]

also prove useful as a postmarket control suitable for providing ongoing information for device safety surveillance and for providing additional evidence for effectiveness. FDA has long applied postmarket controls as a way to reduce premarket data collection where appropriate, while assuring that the statutory standard of reasonable assurance of safety and effectiveness is still met.[10] FDA believes that applying postmarket controls to reduce premarket data collection, when appropriate, can help improve patient access to safe and effective medical devices.[11]

In some cases, a traditional clinical trial may be impractical or challenging to conduct, given the realities of medical device innovation and development cycles, ethical issues that may arise with treatment assignment, and other similar challenges in executing traditional trials with high quality. Analyses of RWD, using appropriate methods, may in some cases provide similar information with comparable or even superior characteristics to information collected through a traditional clinical trial. However, since not all RWD are necessarily collected and maintained in a way that provides sufficient reliability, the use of RWE for specific regulatory purposes will be considered based on criteria that assess the RWD's overall relevance and reliability, including the level of quality necessary for that type of regulatory action or decision. If a sponsor is considering the use of RWE to meet data requirements to support a regulatory decision by FDA, the sponsor should contact FDA through the pre-submission process.[12]

III. Real-World Evidence

RWE has the potential to contribute to a fuller understanding of the benefits and risks to patients when using a medical device. However, it must also be understood that RWE, as with other types of evidence, may be limited due to the underlying relevance and reliability of available data sources, which can impact the value of the gathered information. For example, because some RWD collections are designed for purposes of documenting delivery of care (e.g., EHR, administrative and claims data, quality improvement registries), they may not contain sufficient information to identify or evaluate the performance of a specific medical device. Furthermore, differences in data entry practices from institution to institution may lead to inconsistent data quality that can affect whether certain data is appropriate for regulatory use. Nevertheless, in some cases these data sources may be of sufficient quality and reliability to provide evidence that can be used to support regulatory decision-making.

Prospective clinical trials are designed to limit sources of bias and confounding factors, so that the association between the exposure (treatment) and outcomes can be assessed. In addition, well-controlled clinical trials provide a framework for inferring causal relationships. Similarly, collection and analysis of RWD should be performed in such a manner as to limit bias and assess the association between the exposure and outcome of interest. In some circumstances, RWD can provide information on real-world device use and performance from a wider patient population

10 The Least Burdensome Provisions of the FDA modernization Act of 1997: Concept and Principles
11 Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval
12 Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff

than a more traditional clinical trial, and thus provide information that cannot be obtained through a traditional clinical trial alone. However, retrospective analysis of RWD may have some inherent bias that could limit its value as RWE (e.g., the inability to draw causal inferences between medical device exposure and outcome). Therefore, at a minimum, a prospective analysis plan is needed and, in some circumstances, a prospective trial or a traditional clinical trial may be necessary to generate sufficient evidence for a regulatory decision. When considering a prospective trial, one should consider whether RWD collection instruments (e.g., registries) and analysis infrastructure are sufficient to serve as the mechanism for conducting the trial, and if they are not, whether it is possible to modify them for such a purpose. Ultimately, RWD collected using a prospective trial design may be used to generate or contribute to the totality of evidence needed to assess medical device performance if the sources of bias can be sufficiently mitigated. In many cases, this will require that the RWD sufficiently capture detailed device identifiers and other relevant variables to facilitate the analysis of specific devices and clinical contexts of use in a systematic manner.

Because of its nature, the quality (i.e., relevance and reliability) of RWD can vary greatly across sources. Likewise, there are many types of FDA regulatory decisions with varying levels of evidentiary needs. FDA's evidentiary standards for regulatory decision-making are not changing, and in each context we will evaluate whether the available RWD is of sufficient relevance and reliability to address the specific regulatory decision being considered. FDA believes that the increased use of electronic data systems in the healthcare setting has the potential to generate substantial amounts of RWD. However, because these systems can vary greatly in terms of quality, not all generated data will be sufficient evidence to support an FDA regulatory decision. Even so, these RWD may still provide a valuable contribution to the totality of evidence considered for the decision.

When RWE is intended to be used for purposes of evaluating a regulatory issue, it is important that the data not only follows the criteria described in section V, but is also presented in a standardized file format and data structure, and adhere to a recognized common data model, if applicable, as data would be presented from clinical trials. This includes discussions of the analytical methodology used to perform calculations related to statistically significant and clinically relevant differences between groups.

IV. Regulatory context in which RWE may be used

A. General considerations for the use of RWE

FDA will consider the use of RWE to support regulatory decision-making for medical devices when it concludes that the clinical data contained within RWD source(s) used to generate the RWE are of sufficient quality to provide confidence in the analyses necessary to inform or support the regulatory decision throughout the total product life cycle. The threshold for sufficient quality will depend on the specific regulatory use of the evidence. For example, a specific patient registry might be informative for postmarket surveillance, but not adequate for a premarket determination of safety and effectiveness, while another patient registry may be suitable to address both pre- and postmarket evidence requirements.

The collection or aggregation of RWD sources outside of the medical record is usually performed for specific pre-determined non-regulatory purposes, which may or may not be directly related to individual clinical care. For example, medical administrative claims data sources are typically populated to provide the information needed for billing/payment for medical care. Disease-specific RWD sources sponsored by patient advocacy organizations may be useful for tracking progression or outcomes of specific rare or poorly understood diseases. Treatment-specific RWD sources coordinated by one or more professional societies may have several primary purposes including assessment and tracking overall outcomes, providing data for quality assessment (QA), informing performance improvement (PI) initiatives, or allowing risk prediction and benchmarking for specific procedural or device therapies applied during one or more episodes of care for various specified conditions.

RWE may potentially be used in many ways to understand medical device performance at different points in the total product life cycle, including but not limited to:

- generation of hypotheses to be tested in a prospective clinical study;
- as a historical control, a prior in a Bayesian trial, or as one source of data in a hierarchical model or a hybrid data synthesis;
- in a setting where a registry or some other systematic data collection mechanism exists, RWD can potentially be used as a concurrent control group or as a mechanism for collecting data related to a clinical study to support device approval or clearance;
- in some circumstances where real-world use of a device is in a broader patient population or wider set of circumstances than described in the device labeling, it may be possible to use existing systematically collected RWD to expand the labeling to include additional indications for use or to update the labeling to include the new information on safety and effectiveness;
- for public health surveillance efforts. Under a surveillance paradigm, RWD is used to understand the evolution of the benefits and risks of medical devices after they have been approved or cleared in the United States. In some cases, ongoing surveillance will result in the identification of a signal that suggests there is an issue with a medical device. RWE may be used to refine these signals to inform appropriate corrective actions and communication;[13]
- to conduct post-approval studies that are imposed at the time of device approval or postmarket surveillance studies ordered under Section 522 of the FD&C Act. Traditionally, these studies have required developing and maintaining traditional clinical trial enterprises; however, as RWD methodology and infrastructure grow, RWE may be

[13] Strengthening Patient Care: Building an Effective National Medical Device Surveillance System

well-suited to address the issues identified by FDA; the availability of RWE would not lead to more required studies but could reduce the time and cost of evidence generation to meet postmarket requirements;

- RWE can, in certain circumstances, be used in lieu of submitting individual Medical Device Reports (MDRs); and

- to provide postmarket data in lieu of some premarket data under the Expedited Access Pathway (EAP) program. This may be facilitated through the building of an appropriate RWE generation and analysis system.[14]

B. Application of Investigational Device Exemption (IDE) requirements in 21 CFR 812 to the collection of RWD

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the FD&C Act that would apply to devices in commercial distribution. The purpose of this, per 21 CFR 812.1, "is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose." As explained in Part 812, the IDE regulations apply to all clinical investigations of devices to determine safety and effectiveness, with certain limited exceptions, and, in many cases, an approved IDE is required before initiating a clinical investigation. An investigation is defined as "a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.[15]"

Whether the collection of RWD could be subject to the IDE regulations depends in part on whether that collection constitutes a clinical investigation. Several factors can inform this determination, including the purpose for which the data is being gathered, whether the process for gathering the data would influence treatment decisions, and whether the rights, safety and welfare of human subjects are impacted, among other things. The collection of RWD that is initiated for the specific purpose of determining the safety and effectiveness of a device may be considered a clinical investigation as described above. For example, a registry designed to determine the safety and effectiveness of an approved device for a population solely outside the approved indication could be considered an investigation that could be subject to IDE regulations. Because the gathering of RWD is unique from traditional investigations, we believe that the determination of whether an IDE is required should be made on a case-by-case basis, and we recommend that you contact FDA about whether an IDE is required in cases where RWD collection is initiated for purposes of determining the safety and effectiveness of a device.

[14] Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

[15] See 21 CFR 812.3(h)

However, FDA does not regulate the practice of medicine,[16] and recognizes that some RWD is collected for purposes other than establishing the premarket safety and effectiveness of a device, such as the collection of information related to the actual use by clinicians of an approved or cleared device and/or treatment approaches for a particular disease or condition. Such observations may include RWD from a use of a medical device that was not within the cleared or approved indications for use. When such RWD collection is not intended to determine the safety and effectiveness of the device for purposes of supporting a marketing application to FDA, it would likely not meet the definition of a clinical investigation, and the IDE regulations would not necessarily apply. However, even if an approved IDE is not required for a certain data collection, depending on the factors described below, such data could still meet all the criteria to support use in FDA regulatory decision-making.[17]

Should a sponsor or Institutional Review Boards (IRB) be unclear regarding the applicability of the IDE regulations and need for submission and approval of an IDE for a given data collection activity, the sponsor or IRB should contact FDA. If an IDE is determined to be required for RWE generation activities, FDA will work with the IDE sponsor on the least burdensome approach to facilitate the efficient collection of high-quality data. Note that regardless of FDA's position related to the applicability of 21 CFR 812, FDA regulations at 21 CFR 56 (IRB review) and 21 CFR 50 (Informed Consent) may apply for RWE generation, as may other federal, state, and local laws regarding human subject protections.

V. Characteristics of RWD

FDA does not endorse one type of RWD over another. RWD sources should be selected based on the ability to address specific regulatory questions. Collection of RWD should not dictate, interfere with or alter the normal clinical care of the patient, including choice of treatment. Whether the RWD resides within paper or electronic medical records, is collected by administrative databases, is abstracted, aggregated and stored in disease- or treatment-specific observational databases (i.e., registries), or collected and aggregated through other means, accuracy when compared to verifiable source documentation is essential. Verifiable source documentation, which is the origin of RWD elements, includes, but is not limited to: paper or electronic inpatient and outpatient medical records and case histories, diagnostic laboratory and imaging data, patient-reported outcome measures, and medical device performance data that exists within the device such as self-diagnostics, error codes and patient diagnoses/treatments delivered (including unique device identifier (UDI)).

Important factors regarding RWD that FDA will assess include the relevance and reliability of the source and its specific elements. The underlying data should be robust (i.e., provide meaningful information under a variety of conditions) for the purposes and analyses for which it

[16] This means that FDA will not limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. Section 1006 of the FD&C Act, 21 USC 396.

was designed. These assessments will be used to determine whether the data source(s) and the proposed analysis generate evidence that is sufficiently robust to be used for a given regulatory purpose. That is, the threshold for whether RWD is sufficiently relevant and reliable for use will depend on the level of quality required and/or necessary to make a particular regulatory decision. These factors for assessing the value of RWD sources apply to all FDA regulatory uses of the data.

In cases where RWE is derived from multiple data sources, each data source will be evaluated individually and together in the aggregate to determine the relevance and reliability of the RWD to address the specific regulatory question. Assessments of RWD will be applied similarly to existing sources and to new collections of RWD. When developing a new RWD source, consultation with FDA and other stakeholders is recommended to ensure that relevance and reliability are addressed in the initial design.

A. Relevance

Regulatory relevance of RWD and the data source means that the data adequately addresses the applicable regulatory question or requirement, in part or in whole. FDA will assess the relevance of RWD and RWD sources as a part of the evaluation of the regulatory issue being addressed. Questions about the applicability of RWD to a specific case should be addressed to FDA through the pre-submission process[18]. Relevance of RWD for regulatory decision-making can be assessed either prior to a regulatory submission such as via the pre-submission process, or during the regulatory review process.

Since data elements for existing RWD sources are determined in advance and are primarily chosen for non-regulatory purposes (e.g., quality assurance (QA) and quality improvement (QI) in the case of clinical care registries), FDA will assess whether the individual data elements contained within the existing RWD source are sufficient (i.e., complete, well-defined, and appropriate in scope and timing) to fulfill a regulatory purpose. The overall assessment must conclude that the existing observational data source is reliable, complete, consistent, accurate, and contains all critical data elements necessary for evaluating the performance of a device in the applied regulatory context, including as a part of a larger set of evidence. The need for review or adjudication of specific outcomes of interest may also be assessed if this information is not provided. For collection and interpretation of RWD, it is critical to have a pre-defined common set of data elements, a common definitional framework (i.e., data dictionary), and pre-specified time intervals for data element collection and outcome analyses, in order to ensure the uniformity of data collection and its interpretation. The ability to reliably supplement the available data through linkage with other data sources (e.g., EHR and administrative claims data) to provide additional or confirmatory data will also be considered when assessing relevance of the RWD.

Important factors related to relevance that FDA will assess to determine if the RWD is suitable for use in regulatory decision-making include:

[18] Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff: Guidance for Industry and Food and Drug Administration Staff

417
418 **a.** the representativeness of the device use in a real-world population as captured
419 within the data source and the generalizability of the data to the relevant
420 population being evaluated;
421
422 **b.** the use and recognition of the RWD source regionally, nationally and/or
423 internationally, and the overall percentage of patient care encounters with the
424 device that are captured;
425
426 **c.** validation protocol and resultant data to evaluate how well the RWD source
427 reflects the patient population's experience;
428
429 **d.** whether the RWD contains elements to capture specific device identification
430 information (e.g., unique device identifier);
431
432 **e.** whether the data adequately captures the duration and extent of patient care
433 necessary to assess patient medical history and preexisting conditions, and follow-
434 up sufficient to evaluate the question being addressed (e.g., whether
435 administrative claims data has adequate continuity of coverage);
436
437 **f.** whether the data contains sufficient detail to capture the use of the device,
438 exposures, and the outcomes of interest in the appropriate population;
439
440 **g.** whether the data elements available for analysis will be capable of addressing the
441 specified question when valid and appropriate analytical methods are applied;
442
443 **h.** whether any linkages performed are scientifically appropriate and undertaken to
444 account for differences in coding and reporting across sources;
445
446 **i.** data source reporting schedule, including time interval between database close
447 and release, and length of reporting periods; and
448
449 **j.** the prior documented (e.g., peer reviewed publications or practice guidelines) use
450 of the data source for determining outcomes-based quality assessments, validated
451 predictive risk modeling, signal detection, performance improvement,
452 benchmarking, and other clinically-meaningful uses.

453 ## B. Reliability

454 FDA will assess the reliability of the data and the data sources by evaluating several factors as
455 outlined below. Primary factors FDA considers for assessing the reliability of RWD include
456 how the data were collected (data accrual), whether the data as collected are complete, accurate
457 and adequate for answering the question at hand (data adequacy), and whether the people and
458 processes in place during data collection and analysis provide adequate assurance that bias is
459 minimized and data quality and integrity are sufficient (data assurance). FDA will consider

existing data accrual and analysis infrastructure and methodology, as the fitness of a given data source is evaluated.

(1) Data accrual

A prospective protocol that pre-specifies the data elements to be collected, data element definitions (i.e., data dictionary to provide a common definitional framework), methods for data aggregation and documentation (e.g., common case report form, abstraction from verifiable sources), and the relevant time windows for data element utility and outcome assessments (i.e., common temporal framework) is essential to ensure reliability. Key factors FDA will assess include:

a. the preparedness of individual sites for complete and accurate collection of observational data (e.g., defined processes, site training and support, dedicated qualified personnel);

b. use of a common data capture form;

c. use of a common definitional framework (i.e., data dictionary);

d. adherence to a common temporal framework for collection of key data points;

e. the data collection procedures, data evaluation protocol or statistical analysis plan including when the data collection procedures were developed relative to actual data evaluation (i.e., prospective vs. retrospective);

f. the sources and technical methods used for data element capture (e.g., chart abstraction, point of care entry, EHR integration, UDI capture, data records from device, linkage to claims data);

g. patient selection and enrollment criteria that minimize bias and ensure a representative real-world population (e.g., all-comer's design, consecutive patient enrollment);

h. the timeliness of data entry, transmission, and availability;

i. whether the act of collection of data impacts the ability to measure treatment outcomes; and

j. whether necessary and adequate patient protections were in place (e.g., de-identified data, maintenance of privacy, and need for informed consent as determined by the reviewing IRB and in compliance with FDA regulations).

(2) Data assurance - Quality Control

Data quality control is essential for providing confidence in the reliability of RWD sources. To ensure sufficient reliability, data sources will also be evaluated with respect to the data QA plan and procedures developed for the data source itself. Since evaluation of RWD sources may not always permit specific line item source verification, important factors for consideration include:

a. assessments of data quality (e.g., abstracted from verifiable source);

b. adherence to source verification procedures and data collection and recording procedures for completeness and consistency;

c. completeness (i.e., minimized missing or out of range values);

d. data consistency across sites and over time;

e. evaluation of on-going training programs for data collection and use of data dictionaries at participating sites;

f. evaluation of site and data monitoring practices; and

g. the use of data quality audit programs.

The repurposing of routine medical care data for additional analyses often relies on data cleaning and cross-referencing. These techniques can confirm the data's internal consistency and identify missing values, but cannot determine data accuracy and authenticity. Comparing data from traditional clinical research to source documents through audits (i.e., external consistency) is an essential additional step in verifying the accuracy and completeness of the data. This type of verification is equally important for RWD that is intended to be used for regulatory analyses.

Regardless of the original purpose for collection of the RWD, requirements for data collection and quality assurance should be put into place during the data source design and development stages to optimize the reliability, quality and usefulness of the data. The data collection procedures should be clearly defined and described in a detailed data management standard operating procedures (SOP) manual. Standardizing procedures to ensure the use of uniform and systematic methods for collecting and cleaning data are vital to ensuring data quality. Adherence to the data quality assurance and control policies and procedures will be assessed.

VI. Examples Where RWE Can be Useful

The following examples are generalized from actual regulatory uses of RWE for regulatory decision making.

A. Expanded indications for use

The National Cardiovascular Data Registry (NCDR) was created in 1997 by the American College of Cardiology (ACC) as "an exploration into strategies for improving cardiovascular care through the use and application of clinical data." These registries are designed to help participants measure, benchmark, and improve cardiovascular care. In particular, the Registry for diagnostic cardiac CATHeterization and Percutaneous Coronary Intervention (Cath-PCI Registry) "assesses the characteristics, treatments and outcomes of cardiac disease patients who receive diagnostic catheterization and/or percutaneous coronary intervention (PCI) procedures, measuring adherence to ACC/AHA clinical practice guideline recommendations, procedure performance standards and appropriate use criteria for coronary revascularization." As a registry collecting data on consecutive patients and focused on quality assessment/performance improvement data related to real-world procedures and device use outcomes, an IDE is not required for routine data collection operations, even though a substantial volume of data is generated from use of a device, including data on use outside of the cleared or approved indications for use.

Another example is a Class III device with a narrowly defined indications for use that over time, has seen an expansion in clinically accepted use that is outside of the approved indications for use. In this example, recent technological advances in the design of these devices have also led to their rapid and widespread use for a new set of clinical applications that are not described in the approved labeling. There is little published data to support the effectiveness of this use that is outside of the approved indications for use, while there are recently published reports of high rates of adverse events with the use of the devices for any indication for use. To address the lack of data to support new indications for use for this device, relevant medical societies have established a national registry to collect safety and effectiveness information for all patients implanted with this specific Class III device at participating institutions. A study using the registry data collection and analysis infrastructure was initiated with an approved IDE application since the study focused on a use of this device that was not within the approved indications for use and imposed collection of specific follow-up data that might not otherwise be performed as part of standard medical care. FDA is hopeful that the data may address critical safety questions related to the use of these devices and may be of sufficient quality to help support labeling changes or other regulatory decisions for this device.

B. Postmarket Surveillance Studies (Section 522)

FDA has issued a series of postmarket surveillance study orders, related to investigating patient safety issues in a type of class II device, under the authority of Section 522 of the Federal Food, Drug, and Cosmetic Act. These 522 orders covered multiple devices from different manufacturers that are similar in intended use, design, and other characteristics, such that the surveillance questions were identical. To comply with the orders, many manufacturers decided to collaborate with a clinical professional society in this field and with FDA to develop a patient registry that would collect needed data to address the public health questions. The resultant registry was designed to collect data on all patients with the condition, including those treated with the devices of interest, other devices, and through medical management, and to follow their treatment outcomes. Manufacturers are able to share the comparator group consisting of

treatments that do not use the devices of interest. In addition, because the registry was designed at the outset to produce regulatory-quality data in addition to meeting research and quality improvement purposes, appropriate data quality checks and electronic controls were a part of the initial design and implementation. Since this registry development process took a substantial amount of time, FDA was willing to grant extensions to manufacturers to respond to the 522 orders as long as progress was being made. The registry was also designed to allow for its use (with additional protocols and other traditional study operational elements) in conducting premarket studies that could support future premarket submissions.

C. Post-Approval Device Surveillance as Condition of Approval

Permanent implants are typically designed to serve patients for a time period that is much longer than what can reasonably be captured in a premarket clinical trial. For example, a trial that follows patients for two years after implantation would not produce data for the designed life span of 7 to10 years for that implanted device. Traditionally, FDA would require extended follow-up of the premarket patient cohort and an additional new-enrollment study designed to capture hundreds to thousands of patients with follow-up for the life of the implanted device. Some clinical professional societies have developed registries that collect data on patients receiving these devices. FDA has worked with manufacturers and professional societies to evaluate the registries and has found that they can be reliable for certain health outcomes of interest. Should a registry exist that is capable of addressing the questions for which a Post-Approval Study (PAS) may be issued, FDA instead may issue a condition of approval that a manufacturer participate in and support collection/reporting of registry data on their device in lieu of a condition of approval specifying a formal PAS.

For example, a new breakthrough Class III medical device was recently approved based on prospective randomized controlled clinical trial data. Early in the PMA review process, the manufacturer began to consider postmarket commitments, and reached out to FDA, the Centers for Medicare & Medicaid Services (CMS), and the relevant clinical professional society. A registry was launched that provided data to support FDA and CMS data requirements and national quality assessment programs, in addition to the primary clinical quality assurance purpose desired by the clinical community. This registry has since been used to a) collect surveillance data on subsequent devices with similar designs and indications, b) collect and retrospectively analyze data on all uses of the devices to support new expanded indications for use, and c) support embedded prospective clinical investigations under IDE for new devices and new generations of approved devices. No IDE is necessary for the general data collection activities of the registry, as it collects data on all uses of otherwise approved medical devices. The retrospective analysis of data from uses that are outside the approved indications for use did not require an IDE, but was reviewed by an IRB for human subject protection issues. However, prospective enrollment of new patients into a clinical trial using the registry infrastructure meets the definition of a Clinical Investigation and is subject to 21 CFR 50 (Informed Consent) and 21 CFR 56 (IRB Review). Additionally, if the prospective enrollment is considered significant risk and is being used to determine safety and effectiveness of a medical device, an IDE approval will be required.

D. Control Group

A manufacturer approached FDA during the development of a new medical device that had substantial technological changes from previous iterations of that specific device and other similar devices from other manufacturers. FDA determined that additional clinical evidence was needed to support an approval decision for this device. A registry exists that captures all uses of medical devices in this clinical indication. The manufacturer designed a clinical study that compared the use of the new device to a non-randomized concurrent control group derived from the registry. The existing registry was evaluated by FDA and the manufacturer according to the factors cited in this guidance and was found to provide sufficient data on the control population, such that the manufacturer did not have to collect additional data from these patients or influence the course of their clinical care in any way.

E. Supplementary Data

FDA evaluates available evidence to make the best decision for patients and public health. In the case where RWD has been systematically collected, FDA has used these data, in combination with case reports, publications, adverse event reports, engineering and nonclinical test data, and other sources of information available to FDA to provide a full understanding of the severity of the issue, precipitating factors, affected population and alternative therapies. Periodically, FDA identifies an issue related to the safety of a marketed medical device that was not detected in premarket trials. The addition of RWD has proven extremely valuable to FDA, patients, physicians, and manufacturers to develop a course of action that best protects public health in these instances.

For example, a class III device was under review for a new indication. The manufacturer provided data from a prospective clinical trial with limited follow-up information and inadequate data from the control group that made interpretation of results difficult. A pre-existing observational registry collects and reports data on the control therapies. Subsequent analysis of these data supplemented the clinical trial data and assisted in the interpretation of the data, allowing FDA to come to an appropriate regulatory decision without requiring additional clinical trial data, precluding delays in regulatory decision-making. Without the RWE, additional study subjects could have been exposed to a device with a questionable risk-benefit balance. Coming to a final decision more quickly in this case protected subjects' health while also spurring development of new designs for the medical device.

F. Objective Performance Criteria and Performance Goals

An Objective Performance Criterion (OPC) refers to a numerical target value derived from historical data from clinical studies and/or registries and may be used in a dichotomous (pass/fail) manner by FDA for the review and comparison of safety or effectiveness endpoints[19]. An OPC is usually developed when device technology has sufficiently matured and can be based

[19] See Design Considerations for Pivotal Clinical Investigations for Medical Devices - Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff for more information on OPCs and PGs.

on publicly available information or on information pooled from all available studies on a particular kind of device. Similar to OPC, a performance goal (PG) refers to a numerical value that is considered sufficient by FDA for use in the evaluation of an investigational device regarding a safety and/or effectiveness endpoint. But, generally, the device technology is not as well-developed or mature for use of a PG as for an OPC, and the data used to generate a PG is not considered as robust as that used to develop an OPC. A PG might be considered for challenging patient populations or if there is no clinical equipoise for any control. From a sufficiently relevant and reliable observational data source, a PG can be constructed using appropriate statistical methods, such as a subject-level meta-analysis. As technology evolves over time, an OPC or PG could be updated using observational data.

VII. Glossary

The following definitions are supplied to provide the reader with an understanding of the specific terms used in this guidance. These definitions should not be construed to be new interpretations or clarification of the use of similar words or phrases in the Federal Food, Drug, and Cosmetic Act, related code or regulation, or other federal, state, or local laws, or other guidance documents.

- **Bias**—Bias is any systematic error in the design, conduct, analysis, interpretation, publication, or review of a study and its data that results in a mistaken estimate of a treatment's effect on disease. This systematic error results from flaws in the method of selecting study participants, in the procedures for gathering data, and in the decision of how and whether to publish the results. These flaws can lead to observed study results that tend to be different from the "true" results. Bias can be minimized by ensuring that the study design is appropriate for addressing the study hypotheses and establishing and carefully monitoring procedures of data collection that are valid and reliable.[20]
- **Confounding**—A situation in which a non-causal association between a given exposure or treatment and an outcome is observed as a result of the influence of a third variable designated as a confounder. The confounding variable needs to be related to both the treatment and the outcome under study. Confounding is distinct from bias because this association, while not causal, is real.[21]
- **Electronic Health Record (EHR)**—An electronic record of health-related information on an individual that conforms to nationally recognized interoperability standards and that can be created, managed, and consulted by authorized clinicians and staff across more than one health care organization. [22]

20 JM Last. A dictionary of Epidemiology (3rd edition). New York: Oxford University Press, 1995) (M Szklo & FJ Nieto. Epidemiology: Beyond the basics. Gaithersburg, MD: Aspen Publishers, Inc., 2000

21 L Gordis. Epidemiology. Philadelphia: WB Saunders, Co., 1996

22 The National Alliance for Health Information Technology Report to the Office of the National Coordinator for Health Information Technology on Defining Key Health Information Technology Terms April 28, 2008

- **Electronic Medical Record (EMR)**—An electronic record of health-related information on an individual that can be created, gathered, managed, and consulted by authorized clinicians and staff within one health care organization.[23]

- **Medical Administrative Claims Data**—"Claims data arise from a person's use of the health care system [and reimbursement of health care providers for that care]."[24]

- **Medically recognized standards of care**—Medically recognized standards of care are treatments or procedures that have been accepted by medical experts as appropriate treatments or procedures for a given type of disease or condition and are commonly used by health care professionals. The medical recognition of standards of care is typically represented by publication in a peer-reviewed journal or some form of recognition by a professional medical society. The evidentiary bases for these recognized standards of care vary.[25]

- **Observational Study**—In an observational study, investigators assess health outcomes in groups of participants according to a research plan or protocol. Participants may receive interventions, which can include medical products such as devices, or procedures as part of their routine medical care, but participants are not assigned to specific interventions (as in a clinical trial). For example, investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health.[26]

- **Prospective Study**—A prospective study (also called a *concurrent cohort study*) defines the original population of interest at the start of the study and collects exposure/treatment and outcome data from that time point forward. The start of the study is defined as the time the research protocol for the specific study question was initiated.[27]

- **Real-World Data (RWD)** is data collected from sources outside of traditional clinical trials. These sources may include large simple trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and healthcare claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries (e.g., device, procedural, or disease registries). The data is typically derived from electronic systems used in health care delivery, data contained within medical devices, and/or in tracking patient experience during care, including in home-use settings.

- **Real-World Evidence (RWE)**—RWE is the evidence derived from aggregation and analysis of RWD elements.

23 Ibid

24 Strom, Brian. Pharmacoepidemiology. Chichester, England: John Wiley and Sons, 2005.

25 Ethical Review and Oversight Issues in Research Involving Standard of Care Interventions: Workshop in Brief 2015, Institute of Medicine

26 Adapted from https://www.clinicaltrials.gov/ct2/about-studies/glossary

27 Ibid

- **Registry**—An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical or policy purposes.[28]

- **Retrospective Study**—A retrospective study (also called a *retrospective cohort study, a historical cohort, or non-concurrent prospective study*) defines the population and determines the exposure/treatment from historical data (i.e., data generated prior to the initiation of the study). The variables and outcomes of interest are determined at the time the study is initiated. Some studies are a combination of concurrent and retrospective cohort designs where the exposure/treatment is ascertained from existing objective records (e.g., medical records, claims data), and follow up and measurement of the outcome continues into the future.[29]

- **Surveillance**—Surveillance is a continuous and systematic process of collection, analysis, interpretation, and dissemination of descriptive information for monitoring health problems[30]. Postmarket surveillance is the active, systematic, scientifically valid collection, analysis and interpretation of data or other information about a marketed device.[31]

- **Traditional clinical trial**—Traditional clinical trials are typically conducted in specialized research settings and with specific populations, that often utilize measures designed to control variability and ensure data quality, such as lengthy eligibility criteria, detailed case report forms that exist apart from ordinary medical records, and intensive monitoring and auditing designed to ensure precise adherence to study procedures and rigorous precision in data collection. They may also include substantial efforts to assure compliance with treatments and avoid concomitant treatments that might influence the randomized treatment effect.

28 Registries for Evaluating Patient Outcomes: A User's Guide
29 Ibid
30 JW Buehler. Surveillance (Ch. 22) pages 435-458 in KJ Rothman & S Greenland (editors) Modern Epidemiology 2nd edition. Philadelphia: Lippincott-Raven Publishers, 1998
31 21 CFR 822.3