出國報告(出國類別：出席研討會)

參加國際醫藥法規協和理事會(International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICH)
ICH 有效性基準工作小組: ICH E19 安全數據收集優化(Optimisation of Safety Data Collection) 研討會出國報告

服務機關：衛生福利部食品藥物管理署

姓名職稱：林邦德科長

派赴國家：新加坡

出國期間：108 年 11 月 16 日 至 108 年 11 月 21 日

報告日期：109 年 2 月

壹、 摘要

國際醫藥法規協和理事會(International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICH) 安全性資料收集最佳化基準(ICH E19 Optimization of Safety Data Collection)草案的制定係源起美國食品藥物管理局(FDA)於 2016 年 2 月公布的臨床試驗安全資料收集最佳化規範(Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post approval Clinical Investigations) ，由 ICH 於 2016 年 11 月在日本舉行的會議上宣布將訂定 ICH E19，目的在於對於藥品查驗登記之上市前後期及上市後臨床研究，通過適當的篩選，減少全面性的收集一些不影響統計結果之安全性資料(非嚴重不良事件 Non-serious adverse event、檢驗資料及其他對於評估藥品安全性不重要的資料等)，對於已充分表徵之非嚴重不良事件的安全數據加以選擇性地收集(優化)，可減少病人接受試驗多餘檢測項目或次數等負擔與試驗之醫療資源，藉以將資源有效地運用在其他臨床試驗上，可獲得更多安全資訊。

ICH E19 工作小組成員包括由美國 FDA 官員擔任主導報告員(Rapporteur)，歐盟(EC)官員擔任法規主席(Regulatory Chair)及其他 ICH 法規單位與國際業者公協會員代表透過電話會議及電郵來討論修訂意見，於 2017 年 5 月加拿大蒙特利爾舉行的面對面(face-to face)會議，完成“概念文件”和“工作計劃”草案，同年 11 月於瑞士日內瓦的大會公布，會後繼續透過網路共同編輯平台(SharePoint)及進行多次電話會議，在於 2018 月 5 月底完成草案初稿，同年 11 月簽署完成草案初稿，於今年(2019)2 月完成步驟 1 (Step 1)，同年 2 月進入步驟 2 由各衛生主管機關公告基準草案階段。

本次面對面會議為基準制定步驟 3 (Step 3: Regulatory Consultation and Discussion)的開始，就各主管機關公告草案期間所收集之各界意見內容進行討論， 共計有 78 項一般意見及 622 項針對特別章節之意見，就彙整意見強度分類為優先修訂、須追加修訂及一般文具修訂等 3 類，再依序持續進行草案增修，預計於明年(2021)年底能完成草案修訂。

關鍵字: 國際醫藥法規協和理事會(ICH)、安全數據收集優化(Optimization of Safety Data Collection)、非嚴重不良事件(non-serious adverse event)等

目次

目的

衛生主管機關和業者在減少臨床試驗參與者的負擔及為了促進臨床研究可能產生的重要新醫學知識和促進公共衛生上有著共同的關注。儘管在臨床研究期間對患者進行安全監控至關重要，但是不必要和繁瑣的數據收集，例如頻繁且費時的回診、醫學檢驗及/或體檢等可能阻礙患者參加臨床試驗研究的意願。在醫藥產品開發的整個過程中，以及隨後在藥物上市期間，廠商都收集大量與安全相關的數據，包括所有生命體徵，醫學檢驗數據和不良事件。隨著安全數據的積累，有關藥品安全性概況的知識也在不斷發展。在藥物開發的後期階段，如果對於藥品的安全性得到了很好的理解和記錄，則全面收集所有安全性數據可能僅會提供有限的臨床重要性知識，在這種情況下，只要不損害研究目標和研究參與者的福利，對安全性數據收集採取更具選擇性的方法可能是適當且最佳的。

重要的是，廠商和研究者應確保本基準概述的選擇性安全性數據收集方法不會損害患者常規的醫療照護。安全監視是公認保護研究受試者所必須的項目，並將繼續同時依照標準的治療一併執行。

本基準旨在就某些後期的上市前臨床試驗或上市後研究中何時採用選擇性方法來收集安全數據提供國際協和的實施方法。 通過收集選擇性安全性數據，減免產生有限的附加信息，可以減輕患者的負擔，並以更高的效率進行大量的信息豐富的臨床研究及在更大的全球參與度下進行研究試驗，並且可以更好地為民眾提供醫療服務。基準草案提供了一些關於在一些藥品研發後期階段的藥品上市前或上市後研究中安全數據收集中適當使用選擇性方法的建議，這些研究充分了解並記錄了關於常見不良事件的安全性。 通過收集相關患者數據的臨床研究來推進重要的臨床研究問題，使該藥物可按預期用途進行充分的獲益風險評估，同時減輕不必要的測試對患者的負擔。

過程紀要

時間	行程
11 月 **16** 日	啟程：台北/桃園–新加坡 住宿：Grand Copthorne Waterfront
11 月 **17** 日 - **11** 月 **20** 日 **(4** 天**)**	出席 ICH 有效性指引工作小組: ICH E19 安全性資料收集優化(Optimization of Safety Data Collection)研討會 會議地點：Grand Copthorne Waterfront 會議室 (E19 工作小組) 住宿： Grand Copthorne Waterfront
11 月 **21** 日	回程;新加坡-桃園/台北

工作小組研討會議進行 4 天，草案內容討論摘要如下:

議程:

第 1 天(2019 年 11 月 17 日/週日)

- 歐盟代表提供歐盟公告草案所收集的意見概述。
- 小組分組討論，就 E19 基準草案各特定的章節所收集到的意見或建議，綜合整理出高重要性的議題。

第 2 天(2019 年 11 月 18 日/週一)

- 完成小組分組討論。
- 各小組向工作小組(EWG)報告。
- 綜合討論。

第 3 天(2019 年 11 月 19 日/週二)

- 綜合討論。
- 開始進行基準草案增修。

第 4 天(2019 年 11 月 20 日/週三)

- 繼續進行基準草案增修。
- 向大會(ICH Assembly)報告。
- 在下一次 2020 年 6 月於加拿大溫哥華舉行的會議之前，討論臨時行動項目。

討論結果:

綜整各主管機關草案公告期間所蒐集的意見,認為具重大影響的三個主要議題為:

1. 什麼時候可以充分表徵藥物的安全性/ When is a drug's safety profile sufficiently characterized?

2. 範圍 : 關於 E19 所適用試驗類型的內容(例如上市前,上市後,臨床試驗類型-大型結果試驗,非干預性研究等/ Scope- What does E19 cover with respect to the type of trial (e.g. premarket, post-market, type of clinical trial-large outcome trial, Non-interventional studies)
3. 文句及詞語內容之釐清/Clarification。

相關問題及擬議的解決方案彙整如下表:

主題 **Theme**	問題 **Problem**	擬議的解決方案 **Proposed Solutions**
2	非干預性研究不在概念文件範圍內 範圍 1.3	• 建議的單獨部分（建議單獨的部分，包括僅出於學術目的的非介入研究） • 或從 E19 中移除 • 澄清主要和次要數據收集
1	什麼時候可以充分表徵藥物的安全性/ When is a drug's safety profile sufficiently characterized 2.2 的新標題	提供一些定量閾值/Provide some quantitative threshold
2/3	產品開發階段-在藥品研發後期的預先核准階段，永遠無法充分表徵藥物的安全性” 在 2.2 下增列批准藥物和未批准藥物新的章節/ Stage of development of product- “In late stage pre-approval phase, safety profile	核准藥品上市前，核准上市後和非干預研究分別列在不同的章節中/ Difference sections for preapproval, post approval and Non-interventional studies

	of a drug is never sufficiently characterized” Add new subsection under 2.2 sec for approved drugs and non-approved drugs	
	問題：給患者帶來負擔	• 改寫 • 真正的負擔是計畫研究員/ Real burden is with investigator
2	範圍	• 何謂藥品研發後期階段的預先核准(可能新增一個章節來說明/What is late stage pre-approval (possible section of its own) • 指定與 E19 相關的臨床試驗類型？(例如，大型的結果試驗(研究疾病對於人體健康影響)或持續時間較長的臨床試驗)/Specify types of trials that E19 would be relevant? (e.g. large outcome trials or longer duration trials)
3	非嚴重不良事件 Non-serious adverse events (NSAE) - 在藥物開發的上市前階段，非嚴重不良事件始終很重要 - 需要區分預期和意外的非嚴重不良事件 - 需要區分與研究藥物產品相關的非嚴重不良事件 -不應排除強度中等至嚴重的那些不良事件	• 重新編排第 2 節，以討論何時首先充分表徵藥物的安全性 • 釐清非嚴重不良事件 • 所謂的充分表徵是什麼意思 What do we mean sufficiently characterized? • 提供主管機關足夠的科學證據/Bring scientific justification to Regulatory Authority

1/3	不應停止或限制收集伴隨藥物的安全性資料/Collection of concomitant medications should not be stopped or limited in collection -與評估藥物的不良反應 (即藥品交互作用) 的因果關係有關 relevant to assess causality of an adverse drug reaction (i.e., DDI)	• 明確指出必須充分評估具有足夠特徵的藥物安全性，並對目標人群的藥物代謝和藥物動力學等特徵進行評估/ Make clear that a sufficiently characterized drug safety profile must have undergone extensive evaluation of the drug's metabolic profile and pharmacokinetic characteristics in population of interest • 明確指出當發生嚴重不良事件時，有必要收集包括伴隨用藥在內的全面安全數據，以評估 SAE，AESI 和 DDI 是否存在，並確定與研究藥物有關的因果關係/ Make clear that when a serious adverse event arises, comprehensive safety data collection, including concomitant medications, will be necessary to assess whether SAE, AESI, and DDI and determine causality with the investigational drug product • 釐清是否有關有已知藥物代謝的臨床前/體外數據 Clarification of pre-clinical/in vitro data on drug metabolism if known • 確保在臨床試驗計畫書中清楚地包括或排除伴隨藥物/ In protocol make sure clearly identify inclusion/exclusion on concomitant medications

3	特別需要關注的不良事件/Adverse events of special interest	• 釐清 AESI 仍將與伴隨藥物一起收集/Clarify that AESI would still be collected with concomitant medications
3	針對於不同適應症採用選擇性的安全資料收集/Applying SSDC in different indications	• 提供更清楚的說明/Provide more clarification • 參考相關的章節 Back reference (i.e. see relevant section) • 重新整理基準架構 Restructure/reorganize section 2
3	針對於不同的人口採用選擇性的安全資料收集 Applying SSDC in different populations	• 提供更清楚的說明/Provide more clarification • 參考相關的章節 Back reference (i.e. see relevant section) • 重新整理基準架構 Restructure/reorganize section 2
1/3	藥品曝露量的程度/Extent of Exposure	• 清楚說明我們的意思-是否按劑量或患者人數常規服用藥物（個人對上患者人數）Provide clarity on what we mean - is it drug exposure wrt dosing or patient numbers (in a person vs population) • 想要提供數字的評論 Comments want numbers provided
3	如何在臨床試驗計畫書中寫有關選擇性的安全性資料收集/ How to spell this out in the protocol	• 計劃書裡應說明一些相關準備事項及擬執行的試驗計畫內容 Logistics and protocol issues which should be addressed in protocol

3	如果我們不全面性的收集所有的安全性資料，我們可能會疏忽掉一些訊號/ If we don't collect everything we may miss something	• 見上述的非嚴重不良事件 See above for non-serious AEs • 定量的範例(一般的原則與特定的數字)/Quantitative example (general principles vs specific numbers) • 在基準文件開頭優先的強調這個意見/Preemptively address this comment early in the document
3	安全通報與安全資料收集/ Reporting vs collecting	• 釐清及如何定義這二者的不同(可能加到" 範圍"的章節中)/ Clarification and how we define each (possibly add to Scope section)
1	充分的表(特)徵指的是藥品或是一組不良事件/ Is well-characterized referring to product or set of AEs	• 如果有潛在的風險，如何將其表(特)徵化得很好 How can it be well-characterized if you have potential risk
3	多國(區域)多中心的差別/ Multiregional differences	• 待進一步補充
3	統計上的議題 /Statistical issues	• 待進一步補充

肆、心得與建議事項

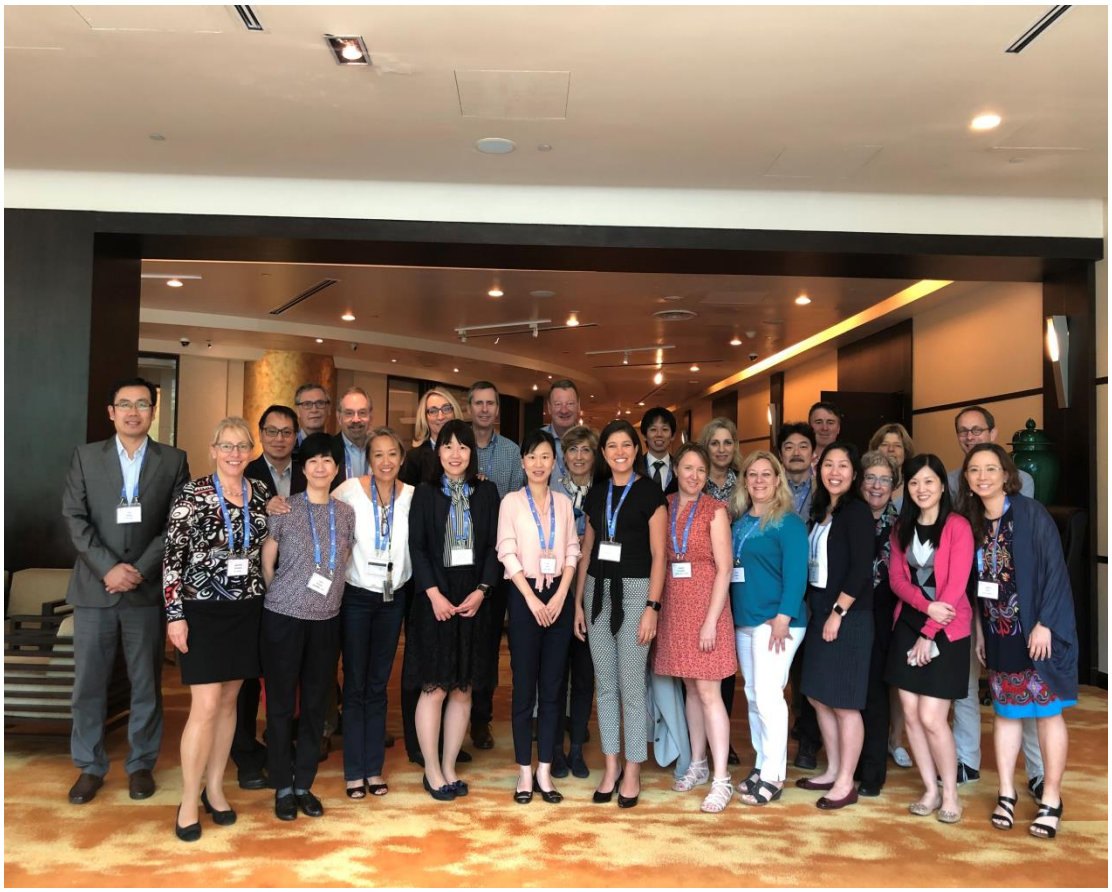
職很榮幸能被長官推薦代表本署加入此一工作小組，透過持續參與會議及提供技術文件基準制定的意見，使得我們能和 ICH 國際醫藥先進主管機關及業者代表們一起進行討論及增藥品查驗登記相關的技術文件基準，進一步的提升我國藥品法規環境與及製藥國際化。

本基準制定工作計畫的進度為於今(2019)年 2 月底完成步驟 1：技術文件經專家小組成員(EWG)充份討論並獲得共識後作成草案，提交給大會 Assembly (Step 1: Consensus building-Technical Document)，同年 2~3 月進入步驟 2，包括步驟 2a:大會根據 EWG 所提交對於草案的技術問題達成充分的科學共識的報告來同意進入下一階段的法規草案公告，及步驟 2b: ICH 法規主管機關採認基準草案(Step 2a/b：2a ICH Parties consensus on Technical Document, 2b Draft Guideline adoption by regulators)，並於今年 4 月起進入步驟 3 草案公告、蒐集意見及討論(Step 3: Regulatory consultation and discussion)的第 1 階段:各區域間公告草案來徵詢意見(Stage I - Regional regulatory consultation)，再於 10 月份就草案公布所收集各界之意見，進行進一步修訂(附件 3)。

此次面對面會議為基準制定步驟 3 的第 2 階段:EWG 討論收到的意見，就基準草案修訂達成共識(Stage II - Discussion of regional consultation comments)，討論內容為各主管機關公告草案期間所收集之意見，共有 78 項一般意見及 622 項意見針對特別之章節。會議依照草案章節分為 4 組進行討論，就所蒐集意見強度分類為須優先修訂、須追加修訂及一般修訂等 3 類，其中主要意見為歐盟對於 E 19 所規範選擇收集安全性資料是否牴觸到歐盟現行臨床試驗相關法規仍有部分疑義(附件 4)，如歐盟臨床試驗規定(Risk proportionate approaches in clinical trials)要求所有臨床試驗軍需收集所有的不良反應(adverse events)，除非在試驗計畫書中(protocol)事先提供有充分的理由得以減免。

會議結論為將依公告蒐集意見優先順序分類結果，由 EWG 分工持續進行草案修訂，預計於明年(2020)再進行 2 次面對面會議來確定完成第 3 步驟:基準草案修訂,再於後年(2021)完成第 4 步驟:完成 ICH 協和化的基準並將由各 ICH 法規單位採用(Step 4)。

附件 1:工作小組合照



附件 2: 工作小組人員名單
E19 EWG Membership List

ANVISA, Brazil
Ms. Fanny Nascimento Moura

EC, Europe
Mr. Peter Mol
Ms. Gabriele Schwarz

FDA, United States
Dr. Karen Farizo
Dr. Ellis Unger

Health Canada,Canada
Dr. Nashwa Irfan
Dr. Fannie St-Gelais

IFPMA
Dr. Dan Zhang

JPMA
Dr. Hironori Sakai
Ms. Yukiko Watabe

NMPA, China
Dr. Ying Chen
Mr. Tao Wang

Swissmedic, Switzerland
Dr. Renate Essen

WHO
Dr. Shanthi Pal

BIO
Ms. Kathleen Beyrau
Ms. Amy Lau

EFPIA
Mr. Anthony Beardsworth
Dr. Guy Demol

Global Self-Care Federation
Dr. Barbara de Bernardi

HSA, Singapore
Ms. Jalene Poh
Dr. Choo Qiuyi

IGBA
Dr. Karin A. Heston-Greenberg
Dr. Christina Mahl

MHLW/PMDA, Japan
Dr. Kinue Nishioka
Hiroyuki Takatoku

PhRMA
Dr. Leslie Dondey-Nouvel
Dr. Jeremy Jokinen

TFDA, Chinese Taipei
Dr. Hsin-Jung Lee
Mr. Pang-Te Lin

Disclaimer:
Expert Working Groups members are appointed by their nominating ICH Member or Observer party and are responsible for representing the views of that party, which may not necessarily reflect their personal views. Working Group experts do not respond personally to external inquiries but are directed to forward any inquiries they receive to their nominating party or the ICH Secretariat for a response on behalf of either their ICH party or the ICH Association as appropriate. For questions to the ICH Secretariat, please use the contact form on the ICH website.

附件 3　各主管機關公告草案期間

Public consultation dates:

ANVISA, Brazil - Deadline for comments by 19 September 2019

EC, Europe - Deadline for comments by 29 September 2019

FDA, United States - Deadline for comments by 25 September 2019

MHLW/PMDA, Japan - Deadline for comments by 18 August 2019

NMPA, China - Deadline for comments by 30 September 2019

TFDA, Chinese Taipei - Deadline for comments by 31 July 2019

附件 4　歐盟(EC)對於 E19 的意見

Draft ICH-E19 guideline – EU Comments

Singapore 17 -20 November 2019

Outline

- Overview EU requirements on interventional clinical trials and non-interventional studies
  - Legal requirements and guidance
  - Safety data management requirements
- Summary of main comments from EU stakeholders
- Suggestions for improvement

1

Outline

- Overview EU requirements on interventional clinical trials and non-interventional studies
  - Legal requirements and guidance
  - Safety data management requirements
- Summary of main comments from EU stakeholders
- Suggestions for improvement

1

EU Requirements - Interventional clinical trials

- Art. 41(2) Reg. EU No 536/2014 (Implementation new CT Regulation pending portal development finalisation)

Reporting of adverse events and serious adverse events by the investigator to the sponsor:

- *(…) The investigator shall record and document all adverse events, **unless the protocol provides differently**. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, **unless the protocol provides differently**.*
- *The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events, **unless, for certain serious adverse events, the protocol provides that no immediate reporting is required**. (…).*

- Risk proportionate approaches in clinical trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, 25 April 2017.

Chapter 4.2 provides a clear and unambiguous framework as to when and how a risk proportionate approach in interventional clinical trials can be considered for adverse event recording and reporting.

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_04_25_risk_proportionate_approaches_in_ct.pdf.

4

EU Requirements - Non-interventional studies

- Art 107 Dir. 2001/83/EC:
  - "***Marketing authorisation holders** shall **record all suspected adverse reactions** in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, **or occurring in the context of a post-authorisation study**."*
- Chap VI.C.1.2.1.1. GVP Module VI:
  - "***Information on all adverse events should be collected and recorded** (…) in the course of the study **unless the protocol provides with a due justification for not collecting certain adverse events**."*
  - *"For all collected adverse events, **comprehensive and high quality information should be sought** (…). **Cases of adverse reactions,** which are suspected to be related to the studied medicinal product by the primary source or the notified organisation, **should be recorded in the pharmacovigilance database and submitted as ICSRs** (…)."*
  - *"**All fatal outcomes** should be considered as adverse events which **should be collected**. (…) In certain circumstances, suspected adverse reactions with fatal outcome may not be subject to submission as ICSRs (…)."*
  - ***For adverse events** specified in the study protocol which are **not systematically collected, healthcare professionals and consumers should be informed** in the protocol (or other study documents) **of the possibility to report adverse reactions** (for which they suspect a causal role of a medicine) to the marketing authorisation holder of the suspected medicinal product (studied or not) or to the concerned competent authority via the national spontaneous reporting system.*

5

Summary of main comments

- Better characterise the issues addressed with selective safety data collection approach.
  - Statement that collection of safety data can be burdensome to study participants and a disincentive to their participation is misleading and should be removed.
- Better outline main purpose and importance of the collection of safety information
  - In clinical development process: to provide a broad safety data basis for the assessment of a product related risks to patients as a fundamental part of its benefit-risk assessment.
  - In post-authorisation setting: to gather further knowledge about a medicinal product risks
    - to allow healthcare professionals and patients to make individual benefit-risk judgements,
    - to permit competent authorities to put in place further measures to minimise such risks.
- New guideline should not contradict and jeopardise implementation of EU legislation.
  - Legal requirements and guidance in EU provide definitive framework to selective collection of adverse events in clinical trials and studies based on a risk proportionate approach:

    All adverse events are required to be collected unless the protocol provides differently requiring a sound justification.

6

Summary of main comments

- Better define conditions to apply selective safety data collection without compromising the required knowledge on product safety profile and collection of significant adverse events.
- Better distinguish proposals related to the collection of adverse events from those applying to clinical safety monitoring set out in study protocols (e.g. ECGs, lab tests, blood pressure)
  - To avoid current confusion on type of data concerned by selective collection.
- Better distinguish situations applying to different settings of drug development
  - Pre- and Post-authorisation.
  - Interventional clinical trials and non-interventional studies.
- Better examples should be provided with adequate details and context to explain if and how a selective safety data collection could be implemented in a particular situation.
  - Current examples compromise guideline understanding, exposing the risk of misinterpretations in its implementation.
  - Examples mix-up non-interventional studies based on the primary or secondary use of data with interventional clinical trials in pre or post-authorisation setting.

7

Comments on proposals for interventional clinical trials

Interventional clinical trials = most robust approach to collect reliable data on incidence of serious as well as non-serious adverse reactions.

- In pre-authorisation clinical trials: Limiting safety data collection is difficult to support.
  - Drug development programmes increasingly shortened to speed-up patient access to newly developed medicines; therefore additional reduction of available safety data should be avoided.
  - Selective safety data may bias benefit-risk assessment and introduce further uncertainties while available safety data are not comprehensive:
    - Limited patients' exposure; Excluded populations, comorbidities or co-medications.
- In post-authorisation clinical trials: Full safety data collection not always necessary depending on extent of characterisation of safety profile.
  - Selective data collection approach to be considered for well-known and well characterised adverse reactions in line with existing EU guidance.
    - When patient exposure to product large enough,
    - For reactions observed across multiple trials with same severity and seriousness,
    - If no regulatory interest in collecting more precise incidence data or risk factors for reactions.
    - Selective safety data collection should not prevent identification of less common adverse reactions.

8

Comments on proposals for non-interventional studies

- Non-interventional studies based on primary or secondary use of data do not entail any additional burden to study participants.
  - Use of medicinal products does not diverge from clinical practice and no additional intervention is envisaged.
  - Study objective is often to collect large amount of safety data concerning use of medicinal product in real life in line with marketing authorisation.
  - It allows identification and characterisation of safety concerns not fully explored/observed
    - in a pre-approval closely controlled environment with limited number of patients exposed, and also
    - in patients groups that had been excluded from clinical trials.
  - These studies are often conducted for safety reasons and data collection is determined by study objectives.

9

Comments on definitions

- Guideline is inconsistent on terms used to define the type of information for which selective safety data collection could be applied.
  - Need to better define what is meant by safety data for which it may be appropriate to limit or stop the collection. Document currently groups non-serious adverse events with safety data, routine laboratory tests, concomitant medications, physical examinations, electrocardiograms.
    - Their managements and documentations differ depending of the circumstances.
- Guideline is inconsistent on data to be collected in association with adverse events.
  - Complete and comprehensive collection of information on cases of adverse events is important requirement to allow meaningful assessment of medicinal product causal role.
    - Documentation of information on co-administered medicinal products, medical histories, concurrent conditions and investigations is required to allow the identification of confounders.

10

Comments on implementation of selective collection

- Guideline should better explain the conditions of implementation of selective collection in the different phases of the drug development process.
  - Better explanations and guidance defining the conditions when product safety profile can be considered sufficiently characterised should be included.
    - Patients characteristics, dosage, treatment duration, route of administration, indication
- Selective collection implementation should be agreed with the competent authorities / ethics committees prior to the study initiation.
- Protocol should always provide
  - detailed scientific justification & documentation on risk assessment and mitigation activities (based on approved Risk Management Plan or development Risk Assessment & Mitigation Plan),
  - plan to revert to comprehensive safety data collection if unexpected safety issues arise.

11

Comments on implementation of selective collection

- Guideline should better address complexity introduced on
  - statistical analysis of the safety data and estimation of adverse reactions frequency,
  - conduct of meta-analysis from published studies, with varying selective collection approaches introduced throughout the product life cycle.
  - Reporting of safety data in DSUR, PSUR (PBRER) for studies with selective safety data collection.

12

Suggestions for improvement

- Collate information on safety data management requirements across ICH regions in interventional clinical trials and non-interventional studies (as supporting document for E19 update).
- Add a Glossary (as appendix?) with established terms, in particular AE, ADR, AE of Special Interest, Important Medical Event, SAE, SADR (SSAR = SADR), SUSAR.
- Non-interventional studies with a design based on primary data collection should remain in the scope but put in an extra chapter.
  - Non-interventional studies based on secondary use of data should be excluded of scope.
- Include section with explanations on the outline of a scientific and ethical justification to be provided by the sponsor to get a protocol with a selective approach to safety reporting approved by the Competent Authorities (CA) and the Ethics Committee (EC) /Institutional Review Boards (IRB).
- EC/IRB should be mentioned in the guideline in addition to CA as the second party that needs to provide a favorable opinion on the selective safety reporting approach within a particular clinical trial.

13

Suggestions for improvement

- Include detailed explanations on when a safety profile is well-characterized, **defining minimal number of patients exposed and** taking into **consideration patients' characteristics** (race, age, gender, co-morbidities, co-treatments etc.), **treatment details** (doses, route of administration, treatment duration), indication.
  - Exclude certain products classes from guideline scope (e.g. advanced therapy, gene therapy).
- Provide explanations on what constitutes an adverse event e.g. based on abnormal lab data or based on the addition of new concomitant medication with emphases that an event is only an AE if there is a change in conditions (e.g. lab data) compared to baseline.
  - Comprehensive information should be collected for cases of adverse events to assess medicinal product causal role.
- Add explanations on when SAE collection can be waived, i.e. if the primary endpoints are safety endpoints and SAE are collected as endpoints.
- Structured justification document/ template should be included in guideline (annex).

14

Any questions?

Further information

Temporary visiting address Spark building . Orlyplein 24 . 1043 DP Amsterdam . The Netherlands
For deliveries refer to www.ema.europa.eu/how-to-find-us
Send us a question via www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Follow us on **@EMA_News**