出國報告（出國類別：開會）

參加第四屆國際藥物監管者計畫－學名藥生體相等性工作組會議及國際醫藥法規協和會 (ICH) E12 工作組會議出國報告

服務機關：衛生福利部食品藥物管理署
姓名職稱：張連成科長
派赴國家：新加坡
出國期間：108 年 11 月 13 日至 108 年 11 月 21 日
報告日期：109 年 2 月

摘要

本次出國行程共參加兩場會議，在國際藥品監管者計畫（IPRP）學名藥生體相等性工作組（BEWGG）會議(4th International Pharmaceutical Regulators Programme – Bioequivalence Working Group for Generics Meeting)部分，主要由各國分享學名藥生體相等性試驗法規更新進展、技術審查所遇見的問題討論、BE 試驗的數據完整性、試驗設計等議題。

國際醫藥法規協和會 (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use，簡稱 ICH)係由美國、歐盟及日本三國藥政主管機關及製藥界共同於 1990 年發起成立之國際組織，目標是協和各國藥品法規與審查標準，致力於藥品品質、安全、有效等指引之制定，以加速新藥研發、藥品審查、藥品品質規範等標準一致化。2015 年 10 月，ICH 改組為非營利性之法律實體 (legal entity)，為接軌國際藥品法規與管理，臺灣積極參與 ICH 相關活動，並於 2018 年 6 月正式成為 ICH 藥政法規單位會員，是我國參與國際醫藥技術性合作組織之重要里程碑。

ICH 每年召開兩次會議，輪流於歐、美、亞地區舉行。2020 年 11 月 16 日至 21 日赴新加坡參加 E20 工作組第一次面對面會議，會議中完成概念文件(concept paper)及工作計畫(business plan) ，並對於指引草案重點與架構等議題討論，製作工作成果簡報檔提報大會，獲管理委員會同意繼續進行 E20 指引制定工作。

關鍵字：國際醫藥法規協和會(ICH)、生體相等性試驗(Bioequivalence)

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壹、背景說明及目的

學名藥的研發上市為降低日益增長的醫療費用，為保障民眾用藥可近性，因應國際醫藥衛生需求，國際學名藥藥監管者計劃（IGDRP）成立生體相等性工作組（BEWG）。 IGDRP 最近與國際藥品管理者論壇結合，形成國際藥品監管者計畫（IPRP），以學名藥生體相等性工作組（BEWGG）的名義持續 BEWG 工作。IPRP BEWGG 的目的是促進各國更大程度的合作，審查管理協和，該機構目前由以下各國家醫藥衛生主管機構組成：中國 NMPA、阿根廷 ANMAT，巴西 ANVISA、墨西哥 COFEPRIS，歐盟 EMA，加拿大衛生部（HC），新加坡 HSA，哥倫比亞 INVIMA，南非 SAHPRA，紐西蘭 Medsafe，大韓民國 MFDS，日本 PMDA，瑞士 Swissmedic，台灣 TFDA ，觀察員分別是澳洲 TGA，美國 USFDA 和世界衛生組織（WHO）。

國際醫藥法規協和會 (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use，簡稱 ICH)係由美國、歐盟及日本三國藥政主管機關及製藥界共同於 1990 年發起成立之國際組織，目標是協和各國藥品法規與審查標準，致力於藥品品質、安全、有效等指引之制定，以加速新藥研發、藥品審查、藥品品質規範等標準一致化。隨著 ICH 制定之規範逐漸影響全球，其他國家或地區，如加拿大、世界衛生組織等也陸續加入該組織。2015 年 10 月，ICH 改組登記為非營利性之法律實體 (legal entity)，名稱更改

為「The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use，簡稱 ICH」，對國際醫藥法規影響更深遠。為接軌國際藥品法規與管理，臺灣積極參與 ICH 相關活動，並於 2018 年 6 月正式成為 ICH 藥政法規單位會員,是我國參與國際醫藥技術性合作組織之重要里程碑。

ICH 每年召開兩次會議，輪流於歐、美、亞地區舉行。本次 ICH 會議聚集 16 會員機構、32 觀察會員機構等共 450 位參加者，14 項主題進行工作組面對面會議。會議首日由 ICH 秘書處舉行 ICH Briefing Session，介紹 ICH 背景、結構、目標與最新工作組運作方式及管理方針後，隨即開始為期 4-5 天的工作組會議，本次有 6 個工作主題提案獲得通過，由 Informal WG 正式成立 Expert WG。

貳、過程

一、行程表

日期	具體任務
2019.11.13	桃園機場出發，抵達新加坡樟宜國際機場 會場 Grand Copthorne Waterfront Hotel
2019.11.14-15	參加 4th International Pharmaceutical Regulators Programme – Bioequivalence Working Group for Generics Meeting
2019.11.16	後續 ICH 會議準備工作
2019.11.17-19	參加 ICH E20 Working group 會議
2019.11.20	由新加坡樟宜國際機場起飛，抵達台灣

二、會議摘要及重點摘錄

本次國際藥物監管者計畫－學名藥生體相等性工作組會議，首先邀請會員說明各自的法規更新，HC 將發布其口服吸入產品指引，將與 EMA 方法（具有體外理由和 PK 終點的分階段方法）更加相似。TGA 在2019年12月修訂其接受國外對照品的標準，如果國外對照品之規格，質量，形狀，顏色和標記與澳洲比較產品相同，則僅對需要分析體外溶離曲線與定性組成，不需要比較定量組成。TGA 還針對基於藥品溶解度及穿透性分類原則(Biopharmaceutical. Classification System, BCS)之生物豁免和其他強度生物豁免採用了 IPRP BEWGG 評估報告模板，計劃提供申請人產品研發階段之早期諮詢輔導，以尋求有關基於 BCS 的生物豁免，在數據可能含糊不清的情況下，使用國外對照品申請的科學建議。ANVISA 於 2019 年 6 月更新了其有關參考產品的決議，如果對照藥品（原廠藥品或境內核准藥品）不在巴西境內銷售，學名藥廠可在原廠聲明後，從國外市場購買與原廠相同之對照品用於生體相等性研究。目前 MFDS 所有劑型均需要證明生體相等性，過去僅用於比較測試藥品和對照藥品的 QC 測試結果，現在還需要比較其他理化特性（例如 pH 值，摩爾滲透壓濃度）。TFDA 預告藥品的主要和次要變更的清單，根據業界和專家的意見，2020年將對基於BCS的生物豁免進行詳細討論。PMDA 將在未來幾個月內發布其修訂的日文版 BE 指引。WHO 繼續在

其優先領域為藥物製定指引，包括沒有參考劑型的藥物。EMA 的 PK 工作組（PKWP）分享□ Liposomal doxorubicin、Dasatinib、Azacitadine 審查經驗，並與各國討論技術性問題。USFDA 2019 年 12 月更新其產品特定指南，且其生物分析方法驗證指南已於 2019 年 6 月完成。HSA 和 Swissmedic 最近沒有關於生體相等性的任何更新。BE 的試驗設計部分，出席代表討論各國制度，並撰擬成學術論文草案，包括有關研究對象的選擇，試驗設計和樣本數量章節。

本次 E20 工作組會議優先討論 ICH E20 指引適用範圍與適應性臨床試驗(adaptive clinical trials)定義、通用術語範圍、目錄，規劃實施的重要文件範圍，各國就其審查經驗分享評估試驗設計原則與標準、臨床試驗樣本變動導致偏差應如何處理等主題。會議第二天完成 Business Plan 與 Concept Paper，獲管理委員會同意正式成立之 E20 Expert Working Group，製作工作成果簡報檔提報大會(Assembly)。

參、心得與建議

一、推動學名藥查驗登記提供生體相等性試驗，為國際醫藥衛生主管機關審查趨勢

學名藥為各國應對公共衛生需求，普及醫療、對抗疾病，照顧民眾健康的重要治療工具，各國主管機關專家透過國際藥物監管者計畫－學名藥生體相等性工作組會議，分享實務審查經驗，也提出生體相

等性試驗對照品選用、試驗設計以及審查標準等各層面所面臨的挑戰，共同尋求解決方式，並將討論結果會集成研究論文發表有助於產業界了解各國法規更新與政策推動重點，有利於產品上市策略規劃與資料準備，加速學名藥上市。

二、ICH E20 臨床試驗研究，有助於臨床試驗設計創新，為藥品研發臨床試驗規劃提供更多選擇

適應臨床設計(Adaptive clinical designs) 的重要原則包括：控制錯誤結論的機會、估計治療效果的可靠性、試驗執行的盲性與數據的完整性必須被維持、試驗執行管理（即操作挑戰，決策，訊息和工作標準作業流程），都是新穎性試驗設計所面臨的挑戰。主管機關可利用諮詢互動的機會，為試驗委託者提出適應性試驗提供建議，並在需要時做出適當的決策，每個決策點應有足夠的資訊，針對 I 型錯誤預作規範，可以降低錯誤結論的風險。適當的預先計劃-應該完全預先指定設計細節，亦可納入其他原則。

肆、附錄

一、專家名單

(一)4th International Pharmaceutical Regulators Programme – Bioequivalence Working Group for Generics Meeting

單位	出席代表
ANVISA	Eduardo Agostinho Freitas Fernandes
EU	Henrike Potthast、Peter Bachmann、Abby (Yang) Yu
HC	Andrew Tam
Medsafe	Ben Jones (via teleconference)
MFDS	Kwansoo Kim
PMDA	Ryosuke Kuribayashi Kohei Shimojo
SAHPRA	Joy van Oudtshoorn (via teleconference)
SWISSMEDIC	Matthias Roost Chantal Walther
Taiwan FDA	Lien-Cheng Chang
TGA	Christopher Crane
USFDA	April Braddy
Observer	Philana Neo, My Nguyen

(二) 國際醫藥法規協和會 (ICH) E12 工作組會議

單位	出席代表
ANVISA	Ms. Carolina Pingret Cintra、Mr. Leonardo Fábio Costa Filho
BIO	Dr. Frank Bretz、Erik Pulkstenis
EC, Europe	Dr. Armin Koch、Mr. Frank Petavy
EFPIA	Bruno Flamion、Hans Ulrich Burger

FDA, US	Mr. John Scott、Gregory Levin
Health Canada	Dr. Roxana Alexa、Dr. Catherine Njue
HSA	Dr. Lisa Tan、Ms. Tan Hui Xing
IGBA	Dr. Kevinkumar A. Kansagra
JPMA	Dr. Hideki Suganami、Ms. Masayo Miyata
MFDS	Dr. Myung Ah Chung
MHLW/PMDA	Mr. Naoto Kotani、Dr. Yuki Ando
NMPA	Mr. Jianhong PAN、Mrs. Yunhong HUANG
PhRMA	Dr. Z. John Zhong、Mr. Paul Dearden
Swissmedic	Dr. Verena Gafner、Mr. Lorenzo Hess
TFDA	Dr. Lien-Cheng Chang、Wei-Lun Peng
IFPMA	Ms. Xiaoni Liu、Mrs. Zhihong (Sarah) LU
GHC	Dr. Turki Althunian
ICH Secretariat	Ms. Nadia Myers Biggs、Dr. Anne Latrive

二、會議照片

第四屆國際藥物監管者計劃－學名藥生物相等性工作組會議

ICH E20 工作組成員合影

TFDA 台灣代表團合影

Final Concept Paper
E20: Adaptive Clinical Trials
Dated 7 November 2019
Endorsed by the Management Committee on 18 November 2019

Type of Harmonisation Action Proposed

A new guideline on the design, conduct, analysis, and interpretation of adaptive clinical trials that provides a transparent and harmonized set of principles for the regulatory review of these studies in a global drug development program. These principles should also provide the flexibility to evaluate / discuss innovative approaches to clinical trial design throughout the development process. For the purposes of this document, adaptive clinical trials are defined as trials planned with an adaptive design.

Statement of the Perceived Problem

Although the European and US regulatory agencies have issued a reflection paper and draft guidance for adaptive clinical trials, respectively, these advisory documents themselves are not fully harmonized. Further adoption of such innovative clinical trials will be limited without a harmonized perspective from drug regulatory agencies, especially for confirmatory studies in global drug development programs. Different perspectives among regulatory agencies in different regions have resulted in uncertainty in the use of adaptive clinical trials in a global environment.

In particular, definitions related to adaptive clinical trials are sometimes inconsistent. There are no common principles for the design, conduct, analysis, and interpretation of adaptive clinical trials, especially in relationship to the risk of erroneous conclusions and maintenance of trial integrity. There are also no common expectations for documentation to support regulatory review of adaptive clinical trials. These issues hinder further adoption of adaptive designs across drug development. Without a harmonized perspective for adaptive clinical trials among the different ICH regions, sponsors and regulators are limited in their ability to build an efficient multi-regional prospective plan for drug development which incorporates these innovative designs.

Issues to be Resolved

This global harmonized regulatory guideline will address:

- A common terminology for adaptive clinical trials
- The potential benefits of adaptive clinical trials and areas (e.g., study settings and design features) of meaningful applications
- The principles for the design, conduct, analysis, and proper interpretation of adaptive clinical trials, including considerations of the risk of erroneous conclusions (e.g., control of false positive and false negative conclusions, and reliability of effect estimates), maintenance of trial integrity, and handling of operational challenges
- The documentation that is important for the planning and implementation of adaptive clinical trials and the interactions between sponsors and regulatory agencies.

While adaptive clinical trials throughout all stages of development are in scope, the primary focus of the guideline will be on confirmatory clinical trials.

Background to the Proposal

There is an increasing interest in using adaptive clinical trials in modern drug development. Potential advantages of adaptive designs include limiting patient exposure to unsafe or ineffective treatments, savings of trial resources, and accelerating the development process while ensuring that the adaptive clinical trials can provide the evidence for regulatory decision making. However, there are uncertainties due to the lack of common principles for the design, conduct, analysis, and interpretation of adaptive clinical trials and the lack of common expectations for documentation to support regulatory review. Hence, it is critical to develop a harmonized guideline to eliminate some of the limiting factors and ensure appropriate use of the potentially efficient designs in global development of effective treatments.

Type of Expert Working Group and Resources

The Expert Working Group (EWG) should consist of ICH Members and Observers in accordance with the applicable rules of procedure and standard operating procedures. The expertise should be a balance of clinical and statistical experts with experience in innovative clinical trial approaches.

Timing

An Informal Work Group was launched in June 2019 to finalize the Concept Paper prior to the formation of an ICH EWG. The work of the EWG will take approximately 3 – 4 years to complete.

Final Business Plan
E20: Adaptive Clinical Trials
Dated 7 November 2019
Endorsed by the Management Committee on 18 November 2019

1. The issue and its costs

- *What problem/issue is the proposal expected to tackle?*

  The European and US regulatory agencies have issued a reflection paper and draft guidances for adaptive clinical trials[1], respectively. However, in these advisory documents and even in the public literature, there are some differences with regards to, among others:
  - The terminology for adaptive clinical trials,
  - The principles for the design, conduct, analysis, and proper interpretation of adaptive clinical trials, and
  - The documentation that is important for the planning and implementation of adaptive clinical trials and the interactions between sponsors and regulatory agencies.

  The lack of harmonized guideline on adaptive clinical trials hinders the use of these innovative designs in global drug development programs in instances where they may be able to provide added value to drug development while maintiaining the evidence for regulatory decision making.

- *What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with "non action"?*

  The lack of harmonization related to adaptive clinical trials has created uncertainty and limited the ability of sponsors and regulators to build an efficient multi-regional prospective plan for global clinical development programs which incorporates these innovative designs. This can potentially result in delay in clinical development process, increase in development cost when different regulatory agencies have different requests, overexposure of inefficacious experimental treatments to patients, and different/inconsistent approval decisions among regulators.

2. Planning

- *What are the main deliverables?*

  The main deliverable is a harmonized guideline on adaptive clinical trials, which will provide clarity on
  - A common terminology for adaptive clinical trials
  - The potential benefits of adaptive clinical trials and areas (e.g., study settings and design features) of meaningful applications

[1] For the purposes of this document, adaptive clinical trials are defined as trials planned with an adaptive design.

- The principles for the design, conduct, analysis, and proper interpretation of adaptive clinical trials, including considerations of the risk of erroneous conclusions (e.g., control of false positive and false negative conclusions, and reliability of effect estimates), maintenance of trial integrity, and handling of operational challenges
- The documentation that is important for the planning and implementation of adaptive clinical trials and the interactions between sponsors and regulatory agencies.

Training materials will be developed to facilitate the implementation of the E20 guideline. Additional deliverables may include, for example, surveys of stakeholders, education, and a regional public workshop(s) to ensure appropriate use of adaptive clinical trials.

- *What resources (financial and human) would be required?*

  Formation of an Expert Working Group (EWG), which should consist of ICH Members and Observers in accordance with the applicable standard operating procedures. The EWG should be made up of clinical and statistical experts with experience in innovative clinical trials.

- *What is the time frame of the project?*

  The work of the EWG will take approximately 3 - 4 years to complete.

  The EWG plans to develop training materials while working on the E20 guideline document. In addition, we plan to engage stakeholders and if needed, conduct a survey(s) of stakeholders and hold regional workshop(s) during the consultation period to ensure sufficient training is available and that the guidelines are being implemented appropriately. To accomplish these goals, the work of the EWG will take approximately 3 - 4 years to complete.

- *What will be the key milestones?*

  The final concept paper will be submitted to the Management Committee (MC) in September 2019 with an expectation of an EWG face-to-face meeting in November 2019. Step 2 a/b document is planned to be completed by June - November 2021 and Step 4 is anticipated to be reached by November 2022 or 2023.

- *What special actions to advance the topic through ICH, e.g. stakeholder engagement or training, can be anticipated either in the development of the guideline or for its implementation?*

  Consultation with additional experts may be required to develop the guideline and provide training. Surveys of stakeholders may also be conducted to ensure sufficient training is available and that the guidelines are being implemented appropriately.

3. The impacts of the project

- *What are the likely benefits (social, health and financial) to our key stakeholders of the fulfilment of the objective?*

  It will eliminate some of the limiting factors and ensure appropriate use of the potentially more efficient designs in global development of effective treatments. This can potentially result in limiting patient exposure to unsafe or ineffective treatments, savings of trial resources, and accelerating the development process while maintaining evidentiary standards.

- *What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?*

  The proposal is consistent with current laws and regulations of the ICH regions. Regulatory authorities responsible for reviewing clinical development applications will need to agree globally on the principles for the design, conduct, analysis and proper interpretation of adaptive clinical trials as well as the recommendations for the documentation that are important for the planning and implementation of adaptive clinical trials and the interactions between sponsors and regulatory agencies. This guideline will supersede and update regional guidelines, enabling the appropriate use of adaptive designs in global clinical development based on the harmonised guideline.

- *Will the guideline have implications for the submission of content in the CTD/eCTD? If so, how will the working group address submission of content in the dossier? Will a consult be requested with the ICH M8 working group?*

  No, the E20 guideline will not have implications for the submission of content in the CTD/eCTD, which shall follow the ICH M8 guideline. The E20 guideline is expected to be aligned with other previous ICH guidelines.

4. Post-hoc evaluation

- *How and when will the results of the work be evaluated?*
  The results will be evaluated by:
  - Implementation of local regulations and/or guidance documents that align with the final guideline;
  - Surveys of stakeholders may also be conducted to ensure sufficient training is available and that the guidelines are being implemented appropriately.