出國報告（出國類別：開會）

參加國際醫藥法規協和會 (ICH) S12 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：甘偉君審查員
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 1 月

摘要

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，以期加速新藥研發、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 改組並於瑞士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，多年的耕耘與努力，於 107 年 6 月 ICH 會議中正式成為 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。108 年 6 月之 ICH 大會通過「基因治療產品的非臨床生物分佈研究(Nonclinical Biodistribution Considerations for Gene Therapy Products)」指引制定提案，成立安全(Safety) 群組下的 S12 Informal Working Group。出國人員奉派於 108 年 11 月 16 日至 21 日赴新加坡參加 S12 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 S12 指引制定工作。正式成立之 S12 Expert Working Group 下階段目標是在明(2021)年上半年完成第一階段(Step 1)工作，產出 S12 技術文件(Technical Document)。

關鍵字：國際醫藥法規協和會(ICH)、基因治療、生體分佈(Biodistribution)

目 次

壹、背景說明及目的

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，以期加速新藥研發、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 改組並於瑞士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，多年的耕耘與努力，於 107 年 6 月 ICH 會議中正式成為 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。108 年 6 月 ICH 大會通過「基因治療產品的非臨床生物分佈研究(Nonclinical Biodistribution Considerations for Gene Therapy Products)」指引制定提案，目標完成以動物模式研究基因治療產品的分子在動物體內的器官分佈情形的試驗規範，於是成立安全(Safety)群組下的 S12 Informal Working

Group (IWG)。此工作組部分專家係來自國際藥品法規計畫(International Pharmaceutical Regulators Programme，簡稱 IPRP)基因治療工作組，有豐富的基因治療製劑審查經驗，進行中的技術文件則是以 IPRP 在 2018 年發表的 Reflection paper「主題：Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products」作為基礎。其他專家是多國法規單位及日本、美國、歐洲產業協會代表，為此工作組貢獻最新的法規及研發考量。工作組於 108 年 11 月 16 日至 21 日赴新加坡進行第一次面對面(Face to Face)會議之前，進行了兩次電話會議，經由主席說明工作組成立背景、成員介紹，成員針對新加坡會議擬完成之工作項目「概念文件(concept paper)」及「工作計畫 (business plan)」初稿進行討論，順利讓 4 天的面對面會議有效率地完成上述文件，成立正式 Expert Working Group (EWG)。

貳、過程

一、行程表

日期	具體任務
108 年 11 月 16 日	桃園機場啟程，抵達新加坡 會場 Grand Copthorne Waterfront Hotel
108 年 11 月 17 日至	參加 ICH S12 Informal WG 工作組會議

108 年 11 月 20 日	向 ICH 大會報告工作進度
108 年 11 月 21 日	新加坡啟程，返抵桃園機場

二、會議摘要及重點摘錄

本次ICH會議聚集16會員機構及32觀察會員機構共450參加者，有 14 項主題進行工作組面對面會議。會議第一天早上由 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。Session 結束隨即開始為期 4-5 天的工作組會議。有 6 個工作主題提案獲得通過，由 Informal WG 正式成立 Expert WG。

S12 基因治療產品的非臨床生物分佈研究指引制定工作組在新加坡進行首次面對面會議，深入討論指引應該適用哪些 GT 產品、BD 研究追蹤的分子種類、使用藥品劑量、如何選擇動物模式等大項目。於會議第二天完成並繳交概念文件及工作計畫，獲管理委員會同意正式成立之 S12 Expert Working Group，繼續執行 S12 指引制定工作。另外，編列技術文件目錄、製作工作成果簡報檔提報大會(Assembly)。會議最終分工開始文件初稿撰寫工作，目標 109 年初完成初稿，110 年上半年完成第一階段(Step 1)工作，產出 S12 技術文件。

參、心得與建議

一、學習國際間基因治療產品審查考量，增進我國審查能量，使法規及標準與國際接軌

本次為 S12 工作組第一次面對面討論，各國主管機關專家分享與交流管理上的實務經驗與所面臨的挑戰，共同尋求解決方式，而產業代表提出研發或是向法規單位申請時遇到的難題，說明其堅持和經驗談，成員們在會議中逐漸互相理解建立共識。藉由 ICH S12 工作組三年期工作，將可與各國專家共同制定 ICH 第一個基因治療相關指引，保持與國際專家交流的良好管道，持續掌握國際最新脈動，達成法規國際協和化，並可向國際宣達我國積極推動先進醫療及完善法規環境。

二、輔導產業細胞與基因治療非臨床試驗設計，提升我國再生醫療產業發展

參與 ICH 會議掌握國際間對基因治療製劑審查標準，用於輔導產業細胞與基因治療非臨床試驗設計，有助提升國內相關產業發展的水平，設計符合國際規範的試驗，縮短研發時程及藥政單位的審查時間。期能協助病人及早接受相關治療，且有助國內研發生產市場擴展至全球。

肆、附錄

一、S12 專家名單

S12 EWG Non-clinical Biodistribution Studies for Gene Therapy Products

Expert list

ANVISA, Brazil
Dr. Francielli Cristine Cunha Melo

BIO
Nicholas Buss
Dr. Jim McNally

CDSCO, India
Mr. Sanjeev Kumar

EC, Europe
Claire Beuneu
Rune Kjeken

EFPIA
Dr. Manuela Braun
Timothy MacLachlan

FDA, United States
Dr. Ying Huang
Dr. Kim Schultz

Health Canada, Canada
Dr. Sharon Choi

IFPMA
Mr. Tian XU

JPMA
Dr. Takanori Ikeda

MFDS, Republic of Korea
Dr. So-Young Lee

MHLW/PMDA, Japan
Dr. Mizuho Nonaka
Mr. Yuto Takishima

NMPA, China
Mr. Xuan YE

PhRMA
Amita Joshi
Laurence O. Whiteley

Swissmedic, Switzerland
Dr. Andreas Marti

TFDA, Chinese Taipei
Dr. Wei-Chun Daphne Kan

TGA, Australia
Dr. Anne Field

WHO
Dr. Si Hyung Yoo

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.

二、S12 Final Concept Paper

ICH
harmonisation for better health

Concept Paper
S12: Nonclinical Biodistribution Considerations for Gene Therapy Products
Dated 18 November 2019
Endorsed by the Management Committee on 18 November 2019

Type of Harmonisation Action Proposed

The field of gene therapy (GT) is progressing at an exponential pace. There are many investigational GT products in the development pipeline, starting with the research/discovery stage and extending to all phases of clinical trials. Several GT products are now approved in various global regions for the treatment of oncology and non-oncology medical conditions. As such, the field (industry and regulators) recognises that international harmonisation regarding aspects of the nonclinical development programme for GT products is needed. Therefore, a Safety Guideline discussing the biodistribution (BD) considerations in nonclinical studies to support the development of GT products is proposed. The conduct of BD studies is considered an important component of the nonclinical programme for a GT product. The BD data are considered informative and necessary to support GT product administration and safety monitoring in early clinical trials. This guideline will provide recommendations on the elements of nonclinical studies performed that include BD assessment, and will contribute to the streamlined development of the GT products, while maintaining scientific rigor and minimising the unnecessary use of animals.

Statement of the Perceived Problem

Existing regulatory guidance documents released by various regulatory authorities contain different expectations on the BD assessment of GT products. This creates a challenge for both regulators and industry when developing a GT product. Examples of areas in which harmonisation is currently lacking, but is needed, include:

1. GT products that will be covered under this guideline;
2. The definition of BD;
3. The need for and timing of the conduct of BD studies;
4. BD study design components;
5. Assay methodologies for assessing BD;
6. BD data required to justify the selection of most relevant species for nonclinical pharmacology and safety studies; and
7. Interpretation of BD data to help inform aspects of clinical trial design.

Lack of harmonisation in the above areas may lead to divergent nonclinical BD study designs, unnecessary use of animals, and the delay of the overall nonclinical development programme and subsequent administration of an investigational GT product in clinical trials.

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S12 Final Concept Paper (續)

Issues to be Resolved

The guideline will address the areas in which harmonisation is needed as identified above. It will provide a transparent, consistent, and harmonised approach across regulatory regions.

1. The scope of this guideline will specify the GT product types and the objective and definition of BD, as these factors are critical to effective implementation of the guideline.
2. The guideline intends to address the timepoint in a product development programme when BD studies should be performed, as well as any circumstance where a BD study would not be required.
3. The guideline will provide recommendations for the overall design of nonclinical BD studies, such as test article identification, animal species selection, dose levels, sample collection time intervals, and types of samples to be collected.
4. The guideline will provide considerations for when a BD study is incorporated into nonclinical pharmacology and safety studies or conducted as an independent study.
5. The guideline will discuss considerations in assay methodologies.
6. The guideline will discuss considerations for investigational GT products that are modified during product development and the potential need to conduct additional BD studies.
7. The guideline will discuss application of the nonclinical BD data to inform the clinical trial design (*e.g.*, monitoring, long-term follow-up).

Background to the Proposal

Existing nonclinical regional guidances for GT products differ in scope and their descriptions for BD study considerations. This topic has been discussed by regulatory authorities within the framework of the International Pharmaceutical Regulators Programme (formerly International Pharmaceuticals Regulators Forum) Gene Therapy Working Group (GTWG), which formed in 2013. This WG released a Reflection Paper in 2018 titled, "Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products" (http://www.iprp.global/working-group/gene-therapy). This paper also reflects a public discussion that occurred in a dedicated session at the annual American Society of Gene and Cell Therapy meeting in 2015. The interactive discussion that occurred in this session was also summarised in a publication titled, "Biodistribution studies: understanding international expectations" (Huang et al. Molecular Therapy Methods and Clinical Development Volume 3, 16022, 2016; https://doi.org/10.1038/mtm.2016.22). These documents provide a starting point for the proposed S12 guideline.

Type of Expert Working Group (EWG) and Resources

The EWG should be composed of nonclinical experts in the fields of toxicology, pharmacology, and biology of GT products, nominated by ANVISA, Brazil; BIO; EFPIA; EC, Europe; FDA, United States; Health Canada, Canada; JPMA; MFDS, Republic of Korea; MHLW/PMDA, Japan; NMPA, China; PhRMA; Swissmedic, Switzerland; TFDA, Chinese Taipei, as well as other regulatory members if requested. Additional observer members can be nominated by WHO, as well as other observer organisations, if requested.

Timing

After the Concept Paper and Business Plan are endorsed by the Assembly, the EWG will be formally established in early 2020. It is expected that this project could be completed in 3 years (*Step 4* in 2Q 2023), which includes the public consultation period.

三、S12 Final Business Plan

Final Business Plan
S12: Nonclinical Biodistribution Considerations for Gene Therapy Products
Dated 18 November 2019
Endorsed by the Management Committee on 18 November 2019

Background

Understanding the distribution, persistence, and clearance profiles (biodistribution assessment) of gene therapy (GT) products following *in vivo* administration is an important element of the nonclinical development programme for investigational GT products. These data contribute to the design of safety studies in animals, as well as provide insight and supportive information for pharmacology/proof of concept studies. In addition, the biodistribution (BD) data can inform dose levels, dose-escalation paradigms, dosing schedules, and monitoring plans for clinical trials in the target clinical population. In July 2018, the International Pharmaceutical Regulators Programme (IPRP) Gene Therapy Working Group (GTWG) published a Reflection Paper titled "Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products" (http://www.iprp.global/working-group/gene-therapy). The purpose of this document was to communicate current thinking of global regulators regarding: 1) when BD studies are necessary; 2) the timing for conduct of BD studies; and 3) the design of nonclinical BD studies. While this document is generally informative in content, regulators and sponsors/investigators in this field recognise that existing nonclinical regulatory guidances for GT products authored by various regulatory bodies differ in the classification of a GT product, the scope of the respective guidance, the definition of BD, and overall considerations for BD assessment. Therefore, a harmonised guideline is needed that will address these issues, as well as provide discussion and recommendations regarding the timing, design and analysis tools of BD assessment, and its application to clinical trial design.

1. The issue and its costs

Existing regional guidances address nonclinical BD studies and relevant technical aspects, including the need for, scope, timing and design of BD studies, as well as overall application of resulting BD data in product development. However, there is a lack of consistency between regions. Due to global development of GT products, there is a need for harmonisation.

The consequences of this issue include unnecessary use of animals, repeating studies due to differing regulatory requirements, and inconsistencies in study design and data quality that may affect understanding the product safety profile. This can lead to increases in the cost of development programmes for GT products and delays in clinical trial initiation. Of note, many of the investigational GT products are intended for the treatment of diseases/medical conditions for which no effective therapy exists. Thus, lack of harmonisation can be deleterious for the regulators, the sponsors/investigators, and the patients.

2. Planning

- *What are the main deliverables?*

  A harmonised guideline on nonclinical BD assessment for GT products will provide clarity and transparency for the following critical elements:
  - GT products that will be covered under this guideline;
  - The definition of BD;

S12 Final Business Plan (續)

- The need for and timing of the conduct of BD studies;
- BD study design components;
- Assay methodologies for assessing BD;
- BD data required to justify the selection of most relevant species for nonclinical pharmacology and safety studies;
- Interpretation of BD data to help inform aspects of clinical trial design; and
- Application of the "3Rs" (Replacement/Reduction/Refinement) principles of animal use.

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

  Formation of an expert working group (EWG) (maximum of two experts nominated by ANVISA, Brazil; BIO; EFPIA; EC, Europe; FDA, United States; Health Canada, Canada; JPMA; MFDS, Republic of Korea; MHLW/PMDA, Japan; NMPA, China; PhRMA; Swissmedic, Switzerland; TFDA, Chinese Taipei, and other regulatory members as requested). One member designated as an observer can also be nominated by WHO, as well as other observer organizations, and active/dedicated participation by industry, regulatory, and *ad hoc* advisory members as necessary. The EWG members are expected to have expertise in nonclinical toxicology, pharmacology, and biology of GT products, as well as an understanding of the regulatory process in their respective regions. Technical support for EWG activities that include teleconferences and online information exchange will be necessary.

- *What is the time frame of the project? What will be the key milestones?*

  The Concept Paper and this Business Plan will be submitted to the ICH Management Committee (MC) and placed for endorsement by Assembly on November 18, 2019. Establishment of EWG is to be in early 1Q 2020, with the expectation of the first face-to-face meeting of the EWG in May 2020. It is anticipated that a Step 2b guideline will be completed by 2Q 2021, with Step 4 reached by 2Q 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?*

  Training materials, such as a slide presentation, that explain the S12 guideline background and document contents, will be generated as needed, for critical phases of guideline development (*i.e.*, Step 2b and Step 4).

3. The impact of this guideline

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

  A harmonised guideline will result in more streamlined and efficient GT product development programmes, minimise animal use, and provide a basis for consistent scientific evaluation of investigational GT products. These factors will also inform elements of clinical study design and contribute to overall development of safe and effective GT products.

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

  The guideline will be consistent with current laws and regulations of the ICH regions. A primary objective of the document is to achieve consistent recommendations on BD assessment for GT products that are in keeping with the regional regulations. The guideline will supersede regional guidances and is intended to reduce the burden on resources needed for regulatory authorities responsible for application review.

四、會議照片

ICH S12 工作組成員合影