出國報告(出國類別：開會)

參加國際醫藥法規協和會 108 年第一次會議-ICH Q13-工作小組出國報告

服務機關：衛生福利部食品藥物管理署
姓名職稱：夏蓉蓉技正
派赴國家：美國
出國期間：108 年 6 月 1 日至 108 年 6 月 7 日

壹、摘要

鑒於近年來製藥工業亦已開始投入以連續生產（Continuous Manufacturing，簡稱 CM）模式之研發，全球並已有數項產品已取得歐美日等國上市許可並實際量產，未來趨勢將會有更多包含小分子及大分子藥物之原料藥及製劑，採用連續生產模式。由於連續生產尚未有國際協和通用法規，須制訂 ICH Q13 以增進未來各國核准以 CM 生產之產品查驗登記的一致性。

ICH Q13 條文內涵將著重於連續生產獨特面向制定相關規範，與傳統批次生產作業無異之審查或 GMP 要求則依原有法規，不訂在本指引之範圍內。因此 ICH Q13 之重點，將著重於連續生產所用設備及分析儀器之系統整合與控制面等要素。

本次會議達成下列任務：擬定 ICH Q13 目錄大綱且獲得共識、ICH Q13 內容將注意 ICH Q2(R2)及 ICH Q14 相關內容之關聯性，並於會後完成分段撰寫指引條文之成員分組。

關鍵字：Continuous Manufacturing、GMP、ICH、ICH Q13、連續生產、藥品優良製造規範、國際醫藥法規協和會

貳、目的

因應製藥工業近年開始研發及採用連續生產，由美國 FDA 發起訂定一份官方及業界共同採用之法規指引，於 107 年 9 月成立 ICH Q13 工作小組，成員來自官方稽查、審查或衛生單位、以及業界公協會代表。本工作組第一次會議於 107 年 11 月召開，已定版概念文件（Concept Paper）及工作計畫（Business Plan），指引範圍將涵蓋小分子藥物及蛋白質治療藥物之原料藥及製劑，預計自 110 年 11 月開始適用實施之目標時程。

連續生產之特性與優勢，為利用設備高度自動化以減少硬體設備空間及人力成本。連續生產設備之特色為其係利用嚴密線上監控分析及結合設備之自動化控制，再整合並連結各製程步驟之不同設備間的控制，並將監控與線上分析結果反饋於即時自動化調整設備操作參數，達到穩定產出一致性品質。

ICH Q13 條文內涵將將針對連續生產所運用之整體設備及線上分析儀器之系統整合及其連動之回饋控制機制之相關管理要求，及確保產出符合品質且品質一致之產品，不符合規格之產品則能經由系統自動監測與排除。與傳統批次生產作業無異之審查或 GMP 面向則將不再重複制定。

參、過程

出國人員經奉派於 108 年 6 月 1-7 日，參加國際醫藥法規協和會（International Conference of Harmonization, ICH）舉辦之「108 年第一次國際醫藥法規協和會，ICH Q13 專家工作小組」會議，詳細背景及會議內容如下：

一、 主辦與承辦單位：國際醫藥法規協和會。

二、 會議時間：108 年 6 月 3 至 108 年 6 月 6 日。

三、 會議地點：荷蘭阿姆斯特丹。

四、 出席人員：

ICH Q13 非正式工作小組於 107 年 9 月成立時成員來自官方稽查、審查或衛生單位、以及業界公協會代表共 35 人。後續增加來自 EDQM 及 PIC/S 之觀察員，部分會員國代表則因職務調動因素陸續變更參加成員。本工作小組領導人為美國 FDA 的 Dr. Sau Lee，本次與會人員共計 30 人出席。與會之會員國官方單位包括：我國 TFDA、美國 FDA、歐洲 EC/EMA、加拿大 Heath Canada、日本 MHLW/PMDA、韓國 MFDA、瑞士 SwissMedic、愛爾蘭 HPRA、新加坡 HSA、巴西 ANVISA；與會業界公協會包括：美國 Pharmaceutical Research and Manufacturers of America（PhRMA）、European Federation of Pharmaceutical Industries and Associations（EFPIA）、日本 Japan Pharmaceutical Manufacturers Association（JPMA）、Biotechnology International Organization（BIO）、International Generic and Biosimilar Medicines Association（IGBA）；與會 ICH 觀察員包括：International Federation of Pharmaceutical Manufacturers and Associations（IFPMA）、International Pharmaceutical Excipient Council（IPEC）、Active Pharmaceutical Ingredients Conference（APIC）、美國藥典（USP）。

五、 出國人員行程及會議紀要：

第 1 天	6 月 3 日	1. 取得 Q13 連續生產範圍共識。 2. ICH Q13 大綱逐條討論。
第 2 天	6 月 4 日	1. ICH Q13 大綱逐條討論。
第 3 天	6 月 5 日	1. ICH Q13 大綱逐條討論。 2. 討論未來工作進度。
第 4 天	6 月 6 日	1. 確定 ICH Q13 大綱。 2. 向 ICH 大會簡報 Q13 工作組目前進

		度及未來預定進度。 3. 分配撰寫不同章節之成員分組組別；各小組討論會後撰寫指引之合作方式。

肆、會議內容重點摘要

本次會議重點在討論並完成 ICH Q13 大綱，包括四大章節：簡介（Introduction）、定義（Definitions and Regulatory Concepts）、科學面向的建議（Scientific Approaches）及法規面向的期望（Regulatory Expectations）。該大綱所列之大標題及次標題係經彙整繼前次（107 年 11 月）實體會議後，各代表成員分別草擬所交出之大綱，產出綜整版本，然後提至本次會議逐條討論。會議每日均依序逐條討論並讓成員提出增減或意見，以便確定未來草擬本指引內容時，能符合會員國家的法規需求且不會阻礙藥廠連續生產技術之開發及運用。

會中明確溝通指引之撰寫規則，例如；應執著重於「做甚麼」而非「如何做」（”what” not “how”）、以精簡的文字敘述及表達、提供足夠科學資訊，但指引不是論文故無需過度贅述、需針對連續生產特點，例如系統整合為一大重點，以通則性撰寫，無須分述不同劑型或原料藥品項、必要時可以舉例通說明，但不能以特定公司狀況為例、須注意不與與其他 ICH 其他品質指引衝突或重複（例如：Q8、Q9、Q10、Q2(R2)/Q14）、需要涵蓋的範圍並使其為實際可行、容許各國間法規要求差異、並能使業者真正受益。在以上撰寫規則之外，工作小組並也面臨各會員國之間可能的差異性，例如技術發達程度、慣用名詞不同，法規差異、以及生命週期之管理。

由於會後將分工撰寫草案，對於連續生產定義之範圍於本次會議再次確定為涵蓋小分子藥物及蛋白質治療藥物之原料藥及製劑，且須為有至少 2 個製程步驟之設備系統整合（倘為可連續投料之單一製程步驟，例如連續打錠，不在本指引範圍）。

會議最後全體成員分為四組，以便會後分別撰寫四大章節，每個小組都有官方、業者、大分子、小分子專長人員。之後小組成員將以電子郵件傳遞資訊，以雲端檔案共同編輯草案內容，各小組長負責維繫小組進度並召開定期電話會議討論修正看法，小組長同時負責與其他小組間之溝通。

本工作小組自 107 年 11 月第一次實體會議起，預定 3 年時間（至 110 年 11 月）完成 ICH Q13 指引，主要時程目標如下表：

日期	預定工作目標
108 年 6 月	實體會議。 討論技術面及法規面須解決事項。 擬定指引草案大綱據以撰寫內容。
108 年 11 月	實體會議。 指引草案內容撰擬及討論。
109 年 6 月	ICH 文件完成 Step 1 - ICH Q13 經大會（Assembly Meeting）核定。 ICH 文件完成 Step 2 a/b－ a：大會同意進入下一階段的指引草案公告，b：法規主管機關針對指引草案採取他們認為必要的行動來制定基準的法規草案並簽署將採納基準草案。 公告草案徵詢大眾意見。
109 年 11 月	實體會議。 討論公開徵詢之回饋意見。

110 年 6 月	實體會議。 討論公開徵詢之回饋意見。
110 年 11 月	ICH 文件完成 Step 3 – 大會同意 ICH Q13 草案已達足夠共識將由各法規單位採用。 ICH 文件完成 Step 4 – 採用並將指引落實執行。

ICH Q13 工作組目前尚未寫出連續生產定義之完整文字，但是在本次會議上已有共識，連續生產需具備特性包括：有持續投「料」（material*）、投入的料在設備內轉化生成另一種「料」並且可以繼續投入下一個製程設備。因為許多傳統批次製造之設備，可以達到單一製程步驟之連續生產，例如連續打錠、連續粉碎等，故 ICH Q13 之範圍不含括單一製程步驟，須為有至少 2 個製程步驟且設備間之連動性有整合控制系統。（*：「料」（material）一詞的意義在此對生產製劑而言，除可為原料藥及賦形劑，亦包含繼續投入下一製程步驟之中間產品；對原料藥製造而言，除可為起始原料及其他反應物，亦可包含中間體或中間產品）。

連續生產的另外一個特性為，設備操作參數未必永遠恆定（Steady State），而是允許製程設計並確效的範圍內有動態的變化，此與傳統生產模式需為確效且固定之設備參數概念不同。原因係連續生產除了設備及線上分析儀器以自動控制系統整合期相互關聯以產生設備間之連動，經過分析儀器數據或各設備參數之監控，回饋至系統得以控制不同設備操作參數有動態（dynamic）的互相搭配，來達到產出符合品質的產品。因此會以「State of Control」來形容連續生產製程處於良好控制狀態，而 Steady State 一詞則較不適合用於連續生產。

一個連續生產製程一開始時整套設備需經過一段時間來互相調整參數達到穩定，快結束前則因為最前端已經停止投料而使製

程不穩定。因此生產作業剛一開始及結束前其製程未能達到 State of Control，所產出的產品不能符合規格須予排除；此外，連續生產期間若系統某環節出狀況，未能達到 State of Control，產出之「料」亦必須排除（material diversion）。

當製程中需要排除任何步驟產出的不符合規格「料」時，也是經自動化控制排除之，因此系統必須有一個機制來預測當有某一個監控點（設備參數或線上分析結果）超出規格時，不合格「料」何時會行進至系統建置的拒用品分岐排除站排出。該預測就是自監控點超出規格的時間至監控點回歸 State of Control 的這一段時間區間來定義。因此「料」在系統內的「行進速度」（Material flow rate）在連續生產製程至為重要，因為需了解從某一點至下一點間之 Material flow rate，才能經過參考監控點的回饋，準確預知這段未達到 State of Control 之時間區間內的「料」何時會行進到排除站並予排除之。「料」的排除的預測還牽涉到設計監控點的取樣計畫及頻率，達到對料在設備系統內移動的追溯性，以及排除站的點位設計。並且應先針對原料訂定嚴謹規格，來保障穩定的 Material flow rate，因為這對於是否能準確預測及排除不合格料非常重要。

由於連續生產有嚴密線上監控，不合格料亦能線上自動排除，產品品質的穩定性能透過使用連續生產模式而提高。然而業者有一想法，既然連續生產係具備線上監控所取得大量數據的優勢，製程變更時能不能不需經過事先審查核備就可直接進行變更並已報備方式送件備查。未來在 ICH Q13 會議將基於風險考量繼續探討此議題。

伍、心得及建議

一、增進國際連續生產製藥技術發展技術知識

由於 ICH Q13 為全新法規，官方單位普遍對連續生產之技術之設計開發理論、硬體設備建構及其操作情形無透徹之了解。期透過參與工作小組之研討，能增進對連續生產之相關技術知識，並期於未來能觀摩藥廠，實地獲取相關經驗與國內分享。

Final Concept Paper

ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products
dated 14 November 2018

Endorsed by the Management Committee on 15 November 2018

Type of Harmonisation Action Proposed

New Quality Guideline

Statement of the Perceived Problem:

There is a general consensus that continuous manufacturing (CM) has potential for improving the efficiency, agility, and flexibility of drug substance and drug product manufacturing. Regulatory agencies have seen more companies engaged in the development and implementation of CM in recent years than in the past. Although current regulatory frameworks allow for commercialization of products using CM technology, a lack of regulatory guidelines can make implementation, regulatory approval, and lifecycle management challenging, particularly for products intended for commercialization internationally. An ICH guideline would facilitate international harmonisation and could reduce barriers to the adoption of CM technology.

Issues to be Resolved:

- CM-related definitions and regulatory concepts: Due to differences from batch manufacture, many CM related definitions or terminologies require further clarification or explanation in the regulatory context, for example, definition of continuous manufacturing, startup/shutdown, state of control, process validation, and continuous process verification. Common understanding and consistent usage of terminology across different regions will lead to improved communication amongst stakeholders. Based on the current knowledge, the CM-related definitions and regulatory concepts covered in this guideline are intended to inform CM development and implementation for small molecules and therapeutic proteins. The general CM-related definitions and regulatory concepts therein may also apply to other biotechnological/biological entities.
- Key scientific approaches for CM: Fundamental scientific approaches for CM may differ from those encountered in batch processes, for example, concepts of system dynamics, monitoring frequency, detection and removal of non-conforming material, material traceability, process models, and advanced process controls. A common understanding of the scientific approaches will facilitate consistent science- and risk-based implementation and regulatory assessment of CM across different regions. Based on the current knowledge, the key scientific approaches covered in this guideline are intended to inform small molecules and therapeutic proteins. The general scientific approaches therein may also apply to other biotechnological/biological entities.
- CM-related regulatory expectations: Harmonised regulatory expectations for dossier approval and aspects of lifecycle management that are pertinent to CM can facilitate the adoption of CM and result in consistent regulatory assessment and oversight. Given the current maturity of the

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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technology, manufacturing of – drug substances and drug products – small molecules and therapeutic proteins for new and existing products will be addressed. The regulatory expectations with respect to marketing applications and post-approval changes, site implementation, and pharmaceutical quality systems will be addressed.

Background to the Proposal:

Objectives: The new ICH guideline document on CM will

- capture key technical and regulatory considerations that promote harmonisation, including certain CGMP elements specific to CM,
- allow drug manufacturers to employ flexible approaches to develop, implement, or integrate CM for the manufacture – drug substances and drug products – of small molecules and therapeutic proteins for new and existing products, and
- provide guidance to industry and regulatory agencies regarding regulatory expectations on the development, implementation, and assessment of CM technologies used in the manufacture of drug substances and drug products.

The working group will consider multiple approaches to CM, including end-to-end and hybrid approaches to drug substance and drug product manufacturing. This guideline will consider relevant ICH guidelines and how the content of those guidelines applies to CM.

Importance: The new ICH guideline will establish harmonised scientific and technical requirements needed to fulfill regulatory expectations for the implementation and assessment of CM to improve access to medicines.

Feasibility: The level of effort required to complete the ICH guidance on CM is medium with appropriate staffing of the working group. Both industry and regulatory agencies already have personnel with adequate background, expertise and/or experience to form a working group, and drug substances and drug products manufactured with continuous processes have been approved for multiple markets. Although CM is relatively new for pharmaceutical applications, there is sufficient information available to develop an ICH guideline. Fundamental scientific approaches and CM knowledge that is transferrable from other industries (for example, petroleum and food) will be used to develop the Q13 guideline. Additionally, some regulatory agencies are in the process of defining their own best practices for assessment of CM based applications. The benefit of the completed ICH guideline will be immediate as it will help to harmonise regulatory expectations and increase consistency in regulatory assessment and oversight across regions.

Type of Expert Working Group Recommended:

The EWG should include regulators and industry representatives with adequate background, expertise and/or experience in both technical and regulatory aspects of CM and with innovative thinking.

Timing:

The anticipated time to complete the guideline will be 3 years.

附錄二、ICH Q13 工作計畫 (已公布於 ICH 官方網頁 https://www.ich.org)

Final Business Plan

ICH Q13: Continuous Manufacturing for Drug Substances and Drug Products
dated 14 November 2018

Endorsed by the Management Committee on 15 November 2018

1. **The issue and its costs**

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

The current ICH Guidelines do not sufficiently address technical and regulatory requirements that are unique to Continuous Manufacturing (CM). A harmonised regulatory guideline can facilitate implementation, regulatory approval, and lifecycle management, particularly for products intended for commercialization internationally. This approach will benefit industry and regulators and improve access to medicines.

The proposed new quality guideline will:
- Harmonise CM-related definitions
- Articulate key scientific approaches for CM
- Harmonise regulatory concepts and expectations for CM across the regions

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

There is a general consensus that continuous manufacturing (CM) has potential for improving the efficiency, agility, and flexibility of drug substance and drug product manufacturing. Regulatory agencies have seen more companies engaged in the development and implementation of CM in recent years than in the past. Although current regulatory frameworks allow for commercialization of products using CM technology, a lack of regulatory guidelines can make implementation, regulatory approval, and lifecycle management challenging, particularly for products intended for commercialization internationally. An ICH guideline would reduce barriers for the adoption of CM technology.

Specific costs from lack of action by ICH include:
- Issuance of final regional guidelines/guidances with differing regulatory expectations.
- Multiple filing strategies required to comply with different regulatory expectations.
- Increased risk and costs for CM implementation due to the lack of harmonised regulatory expectations
- Uncertainty resulting in ad hoc special meetings and consultations between industry and regulators to resolve technical and regulatory questions, and
- Lost opportunities for patients to have improved access to medicines.

2. **Planning**

- *What are the main deliverables?*

The main deliverable is a new quality guideline, ICH Q13, on continuous manufacturing for drug substances and drug products.

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

The Expert Working Group includes approximately 35 experts. We anticipate the need for six face-to-face meetings and multiple interim teleconferences to complete the new guideline.

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

  The new guideline is anticipated to take three years to achieve Step 4, from November 2018 – November 2021.

- *What will be the key milestones?*

  The proposed timeline and milestones are below.

  - Final concept paper and business plan endorsed: November 2018
  - Step 2b: June 2020
  - F2F Meeting: June 2021
  - Step 4: November 2021

- *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?*

  The following are potential special actions that may be taken to advance development of the guideline:

  - Site-visits to CM facilities (coordinated regionally), for small and large molecules, by regulatory working group members.
  - Engage with suppliers to understand technologies' state-of-the-art capablities
  - Presentations at major technical conferences to promote engagement on the ICH guideline during the consultation phase.
  - Engagement with external, technical experts.

  The following are potential special actions that may be taken to advance or promote implementation of the guideline:

  - Creation of formal training materials related to the Q13 guideline and their distribution at inter-agency engagement activities and ICH-supported technical workshops.
  - Development of example case studies that cover the breadth of CM applications for distribution with the final guideline and to increase clarity for stakeholders. Small and large molecules manufacturing will be addressed.

3. <u>The impacts of the project</u>

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

  The proposed guideline will harmonise regulatory expectations for drug substance and drug product production using continuous manufacturing, which will increase the likelihood of its implementation by industry internationally. This will result in the following likely benefits:

  - Enable the development of new methods for production of new molecules to address therapeutic needs
  - Increased manufacturing options available to address public health needs
  - Improved access of medicines to patients
  - Development of new approaches for the control of drug manufacturing to enhance assurance of quality
  - Increase operator safety (process safety risk reductions) for manufacturing
  - Reduce resource consumption (for example, materials) and waste generation by shrinking equipment and facility footprints
  - Improve the robustness, efficiency, and capability of manufacturing processes

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

  The proposed work will assist regulatory bodies internationally. It will identify critical scientific and technical elements to be considered for CM to consistently and reliably manufacture products of the desired quality.

  The topic is feasible and implementable from a regulatory standpoint because there is adequate expertise and/or experience to draft a guideline, and pharmaceutical products manufactured with continuous processes have been approved for multiple markets.

- *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?*

  It is anticipated that any documentation related to CM would be incorporated into the relevant existing CTD/eCTD quality modules. Thus, the guideline would have no implications for the submission of content in the CTD/eCTD. Information may be provided within the guideline on the level of detail and documentation that could be submitted within those sections for CM-related dossiers.

4. Post-hoc evaluation

How and when will the results of the work be evaluated?
At the conclusion of each stage, we will determine whether deliverables and their timelines were met by comparison against our concept paper and business plan.

附錄三 ICH Q13 工作時程表(已公布於 ICH 官方網頁 https://www.ich.org)

ICH Q13 EWG Work Plan

February 21, 2019

Topic Adoption date: *November 2018*

Rapporteur: *Dr. Sau (Larry) Lee – FDA, United States*

Regulatory Chair: *Dr. Yoshihiro Matsuda - MHLW/PMDA, Japan*

Last Face-to-Face Meeting: *Charlotte, NC, USA, November 2018*

1. Key milestones

1.a. Current status of key milestones

Past completion date	Milestone
Nov. 2018	*Concept Paper and Business Plan Endorsement*
Nov. 2018	*Initiation of consensus building*

1.b. Future anticipated key milestones

Expected future completion date	Milestone
Jun. 2020	*Step 1 sign-off and Step2 a/b endorsement, and initiate public consultation*
Nov. 2021	*Step3 sign-off and Step 4 adoption of final guideline*

2. Timeline for specific tasks

Beginning date	End date	Task / Activity	Details
Nov. 2018	*May. 2019*	*Multiple EWG Meetings via Teleconference*	*Develop outline for technical document; initiate drafting process; identify sub-teams if required; identify potential sites for visits; discuss plans for face-to-face meeting*
Jun. 2019	*Jun. 2019*	*Face-to-Face EWG Meeting*	*Continue progress on drafting of technical document and consensus building; presentations on technical approaches/perspectives*
Jun. 2019	*Nov. 2019*	*Multiple EWG Meetings via Teleconference*	*Share and revise draft text for technical document; sub-team reports, if appropriate; discuss plans for next face-to-face meeting*
Nov. 2019	*Nov. 2019*	*Face-to-Face EWG Meeting*	*Continue progress on drafting of technical document and consensus building; discuss identified regional and/or technical concerns identified between face-to-face meetings*

附錄四、參與 ICH Q13 之相關單位及人員代表(已公布於 ICH 官方網頁 https://www.ich.org)

18 July 2019

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