出國報告(出國類別：出席研討會)

參加國際醫藥法規協和會 ICH Q13-工作小組第 1 次會議出國報告

服務機關：衛生福利部食品藥物管理署
姓名職稱：夏蓉蓉 技正
派赴國家：美國
出國期間：107 年 11 月 11 日至 107 年 11 月 20 日

壹、摘要

連續生產（Continuous Manufacturing）已於食品業或工業界有大量運用。製藥工業亦已開始採用連續生產，全球並已有少數產品已取得歐美日等國上市許可；未來並將有更多業者，基於連續生產可減少生產之廠房與人力成本，其自動控制及嚴密線上監控可更加確保產品品質等利基，開發更多藥品採用連續生產技術。由於連續生產尚未有國際協和通用法規，且有需求讓官方及業界有一個清楚的法規指引，故ICH Q13工作小組於107年9月成立，成員共有35人，來自官方稽查、審查或衛生單位、以及業界公協會代表。

ICH Q13非正式工作小組由美國FDA發起，以增進未來各國核准以CM生產之產品查驗登記的一致性，尤其要向全球查驗登記的原料藥及製劑產品更能受其益，使業者開發連續生產若能依循具一致性的指引，並減少業者對不同國家法規要求之顧慮，且更能確保一致之產品品質。

本次會議達成之任務包括：定版概念文件（Concept Paper）及工作計畫（Business Plan）、獲取同意撰寫ICH Q13指引、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、Q13非正式工作小組身分轉為專家工作小組，且透過本次面對面會議各與會官方民間代表已建立友誼及相互了解，有利未來進行充分及透明之溝通。

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

以連續生產（Continuous Manufacturing）方式製造原料藥及製劑，已經可被認同增加生產效率、靈活度及彈性。惟目前各國官方尚無既定的審查核准規範，國際間也尚未有協和通用法規。為讓官方及業界有針對連續生產技術製造的產品的明確法規指引可供參考，美國 FDA 發起 ICH Q13 非正式工作小組，目的為增進未來各國核准以 CM 生產之原料藥及製劑產品查驗登記的一致性、減少業者顧慮因各國不同的法規要求所增加的成本及風險導致業者卻步於投入開發連續生產製程，並使業者開發連續生產若能依循國際一致性的指引，進而更能確保產品於生命週期中之品質。

參、過程

出國人員經奉派於 107 年 11 月 12-15 日，參加國際醫藥法規協和會（International Conference of Harmonization, ICH）舉辦之「107 年第二次國際醫藥法規協和會，ICH Q13 非正式工作小組」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：107 年 11 月 12 至 107 年 11 月 15 日。

三、 會議地點：美國北卡羅萊納州夏洛特。

四、 出席人員：

ICH Q13 非正式工作小組於 107 年 9 月成立，成員共有 35 人，來自官方稽查、審查或衛生單位、以及業界公協會代表。工作小組領導人為美國 FDA 的 Dr. Sau Lee，本次與會人員共計 28 人出席。與會之會員國官方單位包括：我國本署 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 HAS、巴西 ANVISA、European Federation of Pharmaceutical Industries and Associations

（EFPIA）；與會業界公協會包括：美國 Pharmaceutical Research and Manufacturers of America（PhRMA）、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：哈薩克的 National Center for Expertise、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	11 月 12 日	1. 各國報告目前連續生產相關背景。 2. 討論修正概念文件（Concept Paper）。
第 2 天	11 月 13 日	1. 確認概念文件修正文字。 2. 討論修正工作計畫(Business Plan)。
第 3 天	11 月 14 日	1. 再次確認概念文件文字。 2. 確認工作計畫修正文字。 3. 討論向大會（Assembly Meeting）爭取同意撰寫 Q13 指引之簡報投影片。 4. 分組討論 Q13 連續生產定義及相關要素。
第 4 天	11 月 15 日	1. 於大會簡報 Q13 之概念文件及工作計畫，並獲大會同意成立為 Q13 專家工作小組（Expert Working Group）。 2. 討論 Q13 指引中連續生產之定義及範圍。 3. 討論本專家工作小組之未來工作。

肆、會議內容重點摘要

ICH Q13 最初概念文件及工作計畫之草稿係美國起草，並在本次會議前並經過 2 次電話會議（107 年 10 月 19 及 107 年 11 月 1 日）討論修正；本次會議即將重點放在與會代表逐字逐句討論文字表達是否合乎本工作小組之目的，且指引的內容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。

連續生產已經應用於化學合成及基因工程單株抗體製劑之上、下游製程。連續生產優點為製程時間之節省、廠房及設備所需空間大量減少、連續生產運用大量的製程中即時監控，能提高確保藥品品質、縮短製程增加供應量，如果有突發性之藥品大量需求時之其製程應變能力強並可增加用藥可近性。連續生產亦有缺點，例如：藥廠需有相當的研發及設備上的投資。

本工作小組面臨之挑戰包括：目前連續生產尚無統一定義及相關指引、各國之成熟度不一、各國或區域許有不同的考量及要求(regional concern)、指引如何涵蓋連續生產的完整生命週期等，需以目前現有技術及知識基礎，撰寫出在未來的技術發展進步中仍能繼續適用之通用指引。會中並初步指出應考量查驗登記之製程是否得接受同一產品得保留有批次製造及連續生產 2 種模式之可能，以保留生產與市場需求之彈性靈活度。

本次會議中，工作小組達成成果包括：互相了解各國目前管理情形及 Q13 指引需納入之技術層面、大致決定 Q13 指引中連續生產之定義及涵蓋範圍、取得概念文件（Concept Paper）及工作計畫（Business Plan）之共識、獲得 ICH 管理委員會（Management Committee）同意成立為 ICH Q13 專家工作小組（Expert Working Group）撰寫 Q13 指引。

第一天工作重點為各國先報告各國的目前發展，隨即逐字討論及修正 concept paper 草稿。當天已將原草稿修正成簡潔的文字

達官方及業界共識的 Q13 範圍，並能通用目前知識尚未達到但可能適用於未來發展的方向。各國已有藥品申請或通過連續生產之查驗登記，包括美國已通過 4 個藥品、歐盟通過 3 個藥品、日本通過 1 個藥品，其他國家也有 1 至 2 個通過或申請查驗登記中藥品，其中亦包括單株抗體藥品。我國目前尚無藥廠執行連續生產或申請連續生產之查驗登記，因應未來趨勢，亦有可能發展，故需要先增進此方面的知識及法規要求，並配合連續生產考量自動化控制之參數放行（parametric release）。

第二天工作重點為先行確認各代表是否對概念文件還有其他修正意見或需釐清疑義為討論修正工作計畫。大致確認連續生產之定義，未來指引涵蓋範圍將包括以及指引將涵蓋小分子化學產品、生物技術及生物藥品產品。並確認參與成員之國家若對連續生產有特殊的限制與要求，需傳達至工作小組中以利指引之撰寫。

第三天工作重點為最後確認概念文件及工作計畫之文字與內容，並逐一詢問與會各單位代表是否同意內容，獲得一致通過。會中並討論未來主管機關內部應有適當連續生產之教育訓練，訓練方式得包括透過參訪現有已投入連續生產量產之藥廠，來了解連續生產之技術及應用之可能性，但應謹慎避免指引撰寫內容因參訪特定藥廠而有偏頗。本日並討論修正隔日大會（Assembly Meeting）簡報以爭取同意撰寫 Q13 指引之簡報投影片內容。另外將成員代表分為 4 組，討論未來 Q13 指引中之應包括定義及相關要素。

第四天重點為起草大綱及專有名詞，全體與會人員再次針對目前業界連續生產的各種多樣化模式加以討論，以便確立未來 Q13 指引之範圍，例如：僅有單一製程步驟為連續生產，其餘製程步驟仍保留批次作業模式之定義，是否未來亦須遵守 Q13 指引，抑或 Q13 指引僅適用於製程從頭到尾均為連續生產之產品；此項討論尚未有結論，但成員均同意連續生產中製程、設備、自動控

制與品質監控反饋機制等之整合技術將成為 Q13 指引之重點。而連續生產將以「製程中連續投入之原料有持續進行轉化，且其產出物有連續被移出」為基礎概念，未來工作小組將再以此基礎來明定連續生產之定義。本日全員赴大會（Assembly Meeting）簡報於會上獲得同意且獲得管理委員會（Management Committee）同意成立為 ICH Q13 專家工作小組(Expert Working Group)撰寫 Q13 指引。

本工作小組預計以 3 年時間(自 107 年 11 月至 110 年 11 月）完成 ICH Q13 指引，其範圍將涵蓋小分子藥物及蛋白質治療藥物之新藥或既有藥品（均包括原料藥及製劑）的連續生產。指引之撰寫，將以現階段對法規單位對技術之了解與期待為撰寫方向。未來 3 年期間預計召開 6 次實體會議，並於需要時召開電話會議以便於時程內完成工作，主要時程目標如下表：

作。

日 期	預定工作目標
107 年 11 月	實體會議 概念文件定稿 工作計畫定稿 研擬大綱
108 年 6 月	實體會議 討論技術面或法規面可能面臨之問題 指引草案撰擬及討論
108 年 11 月	實體會議 指引草案撰擬及討論
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

伍、心得及建議

一、建立與國際官方及業界之技術交流及法規了解

ICH Q13 工作小組是一個 GMP 技術性的工作小組，能參與其中深感榮幸。未來將透過定期電話會議及實體會議，與各國稽查及審查官員以及業界先進共同討論連續生產相關之技術，以確立國際協和指引。本署則能藉由參與其中獲得第一手資訊，了解指引條文訂定的意旨，未來將有助於對法規解讀上更加明確。

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Final Concept Paper

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

Endorsed by the Management Committee on 13 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

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.

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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?*

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

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- *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. **The impacts of the project**

- *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、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)

3 December 2018

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ICH Secretariat, please use the contact form on the ICH website.