出國報告(出國類別：開會)

參加國際醫藥法規協和會 108 年第二次會議-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：新加坡
出國期間：108 年 11 月 14 日至 108 年 11 月 21 日

壹、摘要

鑒於連續生產需有國際協和通用法規之需要，由美國 FDA 發起，ICH 同意於 107 年 9 月成立 Q13 工作小組，為制定及協和未來各國核准以連續生產（Continuous Manufacturing, CM）模式生產之產品查驗登記的一致性。本指引將由參與之官方及業界共同擬定，針對連續生產之特殊特性制定相關規範，做為製藥工業開發及應用連續生產製程及藥品許可證查驗登記機關審核之依據。

ICH Q13 工作小組透過面對面會議，及各次會後成員間之持續連繫討論，擬訂條文著重於連續生產所用設備及分析儀器之設計、系統整合及系統控制之科學面及法規面之草案內容。

本次會議討論達成下列任務：討論草案初版條文並調整其內容所需之章節範圍、決定另撰寫個別附則以說明本文內無法共通性說明之相關主題；成員已分組並將於會後分別合作完成初稿修正及指引撰寫。另，官方代表並赴 1 家連續生產製程原料藥廠做實地參訪。

關鍵字：Continuous Manufacturing、CM、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

鑒於近年來製藥工業已開始投入以連續生產（Continuous Manufacturing，簡稱 CM）模式之研發及實際量產，由美國 FDA 發起於 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。本工作小組已於 107 年 11 月及 108 年 6 月召開二次面對面會議，已訂定概念文件（Concept Paper）、工作計畫及工作時程表（附錄一、二、三）以因應經由連續生產之產品查驗登記申請趨勢之增加，目標為訂定一份官方及業界共同採用之法規指引，適用於採用連續生產模式之小分子及大分子藥品之原料藥及製劑。與傳統批次生產作業規範無異之查驗登記審查或 GMP 面向則不在本指引中重複制定。

本次會議目的包括：針對全體成員分工撰寫並予合併之草案初稿，討論各章節之增刪及依邏輯調整順序，並決定另撰寫個別附則以說明本文內無法共通性說明之相關主題，以適合未來連續生產之開發、量產及生命週期管理。官方代表並實地參訪 1 家採連續生產製程之原料藥工廠以增加對連續生產實際製程之了解。

參、過程

出國人員經奉派於 108 年 11 月 14 日至 21 日，參加國際醫藥法規協和會（International Conference of Harmonization, ICH）舉辦之「108 年第二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 11 月 15 日至 108 年 11 月 20 日。

三、 會議地點：新加坡。

四、 出席人員：

ICH Q13 專家工作小組領導人為美國 FDA 的 Dr. Sau Lee，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 30 人，成員如 ICH Q13 公布之單位及代表姓名（附錄四）。本工作小組，本次與會人員共計 30 人出席。

五、 出國人員行程及會議紀要：

第 1 天	11 月 14 日	啟程。
第 2 天	11 月 15 日	連續製程原料藥廠參訪。
第 3 天	11 月 16 日	上午：連續製程原料藥廠參訪。 下午：ICH Q13 官方代表會前會。
第 4 天	11 月 17 日	ICH Q13 指引草案初稿討論。
第 5 天	11 月 18 日	ICH Q13 指引草案初稿討論。
第 6 天	11 月 19 日	1. ICH Q13 指引草案初稿討論。 2. 向 ICH 大會簡報 Q13 工作小組目前進度及未來預定進度。
第 7 天	11 月 20 日	1. ICH Q13 初稿討論。 2. 分配修訂指引主文及附則之分組成員。
第 8 天	11 月 21 日	返程。

肆、會議內容重點摘要

本次會議完成討論成員分工撰寫之各章節內容之重複性，並檢討是否有遺漏需補上之必要主題，以確定草案撰寫之增刪及依邏輯調整章節順序。會中本工作小組向大會簡報工作進度，大會對於工作小組能於 6 個月間隔之 2 次面對面會議之間產出

草案初稿，給予高度肯定，並支持工作小組增加撰寫附則，以分別說明具差異性而無法納入本文之個別主題。

因草案初稿仍需重新統整且刪除重複性內容，故本次會議未進入對目前之草案初稿逐條文字討論，工作小組決定將俟本次會議討論修正後之大綱，才進行進一步之指引內容討論。

討論後 ICH Q13 大綱將調整為包括：簡介（Introduction）、連續生產概念（CM Concepts）、科學面向的建議（Scientific Approaches）及法規面向的期望（Regulatory Expectations）。整體內容則應滿足：基於現行對連續生產開發及量產之科學及技術層面之了解，充分敘明連續生產之獨特性及應注意事項，並依與現行法規面相配合之原則下制訂相關要求及查驗登記送審文件要項規範。章節內容應涵蓋：目的、範圍、操作模式（operation mode）、「批」定義、特性記述（characterization）、管控策略（control strategy）、良好製程控制狀態（State of Control）、變更管制等；法規面之送審文件要求應說明之項目則如：共同技術文件（CTD）、生命週期管理、產品品質系統、製程敘述、批與批量大小、管控策略、製程模式（operation mode）、製程確效、安定性、同產品由批次作業轉換為連續生產等。增加附則之目的為將不同類別之產品或重點技術加以個別說明，例如：製劑、原料藥、蛋白質治療藥物、製程模型（process model）及不合格品排除之控管等主題。

基於連續生產與批次生產有相當差異，連續生產之特殊性是否亦能適用於現行法規要求。例如：針對連續生產已使用很多線上分析監控 PAT (Process Analytical Technology)，是否即符合歐盟 21 November 2016 EMA 之「Guideline on Process Validation for

Finished Products - Information and Data to be Provided in Regulatory Submissions」（2016.11.21）內的「持續製程確認」（continuous process verification），可免除製程確效之要求？廠商初始查驗登記時應如何自行定義連續生產之「批量」，若實際確效之批量大小未達欲查驗登記之批量上限，而是輔以說明其設備維護能力可確保穩定運轉且能保持設備內無相關不純物之堆積時，是否可行？有別於傳統批次生產於放大批量時應重新執行製程確效；連續生產的製程如果不改變操作參數及投料速率，改變因素僅為延長投料時間時，視為一種批量放大，則廠商是否應申請查驗登記變更或得自行延長投料時間？與小分子化學物不同，生物製劑因其製程特性，所使用之設備能力即已固定批量大小，採延長時間方式執行批量放大並不適用，故在指引中需將大分子及小分子分開說明。上述待解決問題，在本次會議中略有討論，均仍待未來後續討論與解決。但唯有業者有責任對其連續生產製程有足夠知識與了解，能提供出科學依據及其製程設計上具相當控管能力，並於送審文件內有邏輯性之清晰說明，才能說服審查機關。本指引即為解決審查機關與業者之間的認知差異，以謀求雙方有共同之定義、語言及標準而制訂。

本工作小組於 107 年 11 月第一次實體會議完成概念文件（Concept Paper）及工作計畫（Business Plan），會後各成員完成草擬大綱決定須納入之主題；108 年 6 月第二次實體會議完成討論確認大綱之項目並將成員分組撰寫草案，各小組成員以定期電話會議及電子郵件聯繫、分享雲端共同編輯檔案等方式討論並草擬各章節內容，且經工作小組統整合併指引之草案初稿。

本次會議結束前，全體成員已重新分組，分工著手草案初稿之增刪與統整及附則之撰寫。雖本次增加撰寫附則之工作量，

工作小組擬仍暫維持原訂時程，目標以共 3 年時間（至 110 年 11 月）完成 ICH Q13 指引，後續主要時程目標如下表：

日期	預定工作目標
109 年 5 月	實體會議。 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、連續生產原料藥廠參訪重點摘要 【此節基於涉及與受訪藥廠保密協定，已刪除涉廠方產品資訊之內容不公開】

連續生產作業不同之處是需要嚴密管制投料原料、追蹤各批原料於生產設備之流動動向（利用混合、反應時間及流速計算）以利最終產品品質控管，故每桶原料之投料先掃描條碼以利追蹤，且不同原料之供應原廠批號不會混批以確保品質。

連續生產製程剛啟動一段時間內因為運轉尚未達穩定，或快結束前一段時間因為設備內的餘料逐漸消耗殆盡，所產出之品質不穩定均需自動排除。應採多少時間長度排除不穩定的產品，則於開發階段，因設備容積與生產流速固定，可以計算產品於各段設備之固定滯留時間，然後便可依據滯留時間於自動控制程式內設計拒用品排除與收集站。其餘不合監控規格之中間產品，亦可利用滯留時間排除至生產設備中之拒用品收集站。

原料藥連續生產之設計，應先了解原料之特性及製程中投料、溫度、流體等動力學如何影響化學反應、不純物之生成資訊等，透過製程模擬（Process stimulation）方式試驗，建立製程之設計空間（Design space）。設備方面，應了解原料或溶媒等在混合器內的混合特性避免阻塞或影響製程之穩定性；供料槽、緩衝槽大小、位置及各設備間之銜接與原料、半成品在設備內如何流動等，均影響滯留時間。設備如何設計將影響滯留時間分布，並與半成品品質監控及不良品排除有直接關係；另一方面，設備可以連續操作多久不至使設備內產生瘀塞致不純物增加，或當製程稍有不穩定但是經過即時監控可以立即自動調整相關參數仍可矯正品質。故，應定義並量化能容許之品質偏移程度及時間，且各階段半成品於設備內之流動均能完全被追蹤。與批次生產類似，製程間之取樣點及取樣頻率應妥善設計，因連續生產使用大量線上分析系統且互相回饋以隨時矯正相關參數，可多透過多變異數模型（Multivariate models）分析，且應取得足夠且有代表性的數據，以便量產時達穩固之製程之監控及作業控制，確保產品品質。至於應建立關鍵操作參數、關鍵品質屬性、不純物檔案等之建立，與批次生產之原料

藥要求相同。

陸、心得及建議

一、國際法規協和化不易，透明公開至為重要

ICH Q13 工作小組之討論至目前為止，官方及業界代表均能保持開放態度，充分溝通以拉近雙方認知之差異。在前一次面對面會議後成員分工撰寫草案初稿，雖各分組均分配有業界及官方代表，草案經整體全章節整合之後，及本次會議之討論中，仍可發現在部分觀點上業者希望有更大彈性，可能與官方亦有法規面之考量還是有段落差；或國家間之不同要求標準，例如製程確效、批量放大等規定，也是彼此要互相磨合的。僅有各方均將各自期待先公開及透明地表達，才能集思廣益討論出多贏之最適方案。

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

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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

August 02, 2019

Topic Adoption date: *June 2018*

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

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

Last Face-to-Face Meeting: *Amsterdam, The Netherlands, June 2019*

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*
May. 2019	*Outline for technical document developed*
Jun. 2019	*Face-to-Face Meeting in support of consensus building, outline finalization, and technical document drafting*

1.b. Future anticipated key milestones

Expected future completion date	Milestone
Nov. 2019	*Face to Face Meeting to develop the technical document*
Jun. 2020	*Face to Face Meeting to continue development of the technical document and Step 1 sign-off and Step 2 a/b endorsement, and initiate public consultation*
Nov. 2021	*Step 3 sign-off and Step 4 adoption of final guideline*

2. Timeline for specific tasks

Beginning date	End date	Task / Activity	Details
Jun. 2019	*Nov. 2019*	*Multiple EWG Meetings via Teleconference*	*Share and revise draft text for the 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 the technical document and consensus building; discuss potential 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)

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