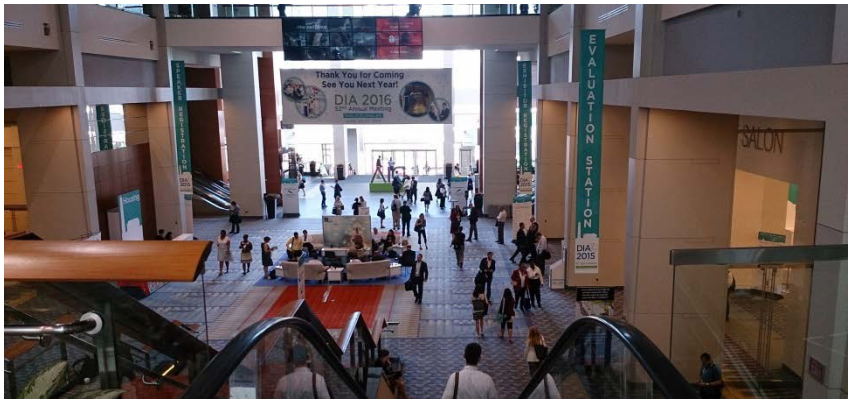
出國報告(出國類別：出席國際會議)

參加「第 51 屆藥物資訊(DIA)年會(DIA 2015)」出國報告



服務機關：衛生福利部

姓名職稱：葉明功技監、劉麗玲組長、祁若鳳簡技、黃琴嘵科長、楊雅婷審查員

派赴國家：美國

出國期間：104 年 6 月 13 日至 6 月 20 日

報告日期：104 年 8 月

摘要

「藥物資訊協會(Drug Information Association, DIA)」是一個由各國產、官、學、研等單位會員自發組成推動的科學協會，所舉辦之 DIA 年會為全球藥物研發資訊與藥政法規管理之最大會議，會員藉此機會交流溝通，促成合作。2015 年第 51 屆 DIA 年會於美國華盛頓舉行，本部食品藥物管理署藥品組劉組長麗玲受大會邀請，與美國參議院議員代表 Wade Ackerman 及 FDA 副局長 Robert Califf 同台演講，分享對複合性醫藥品(combination product)的管理觀點。另外，藥品組祁若鳳簡技也發表我國奈米藥品的管理現況與規劃，風險管理組黃琴喨科長發表我國執行 GMP/GDP inspection 的管理經驗。除分享我國對前瞻性新興醫藥品之零時差管理進度及國際合作經驗與成果，我方並藉著各國主管機關齊聚 DIA 年會的機會，與國際合作夥伴 EMA 及 PMDA 面對面洽談國際合作交流事項。

目次

壹、 目的與背景介紹

藥物資訊協會(Drug Information Association, DIA)成立於 1964 年，會員多達 1 萬 8 千多名，來自 80 餘國的政府主管、法規單位、學術單位、生技醫藥研發公司、製藥業者、委託研究(CRO)公司、醫藥軟硬體設備業者，與各種醫藥相關組織團體。每年 DIA 年會齊聚各國醫藥相關組織，在各論壇發表與討論研發及管理現況，擺設攤位展示成果，是全球藥物法規管理與產品研發之最大交流平台，甚受各國重視，我國也一向極為重視出席本會。

今(2015)年為第 51 屆藥物資訊協會年會，於 6 月 13~18 日於美國首府華盛頓舉行，參與者超過 7000 人，超過 450 個展商，研討主題分類計 20 項(20 tracks)，再區分議題超過 200 項，各議題分別由 2-3 位各界代表發表演講，，超過 700 場演講，重要藥政主管機關如歐盟 EMA、美國 FDA、日本勞動厚生省 MHLW 與 PMDA、加拿大 Health Canada 皆派員出席。我方今年受邀於會上演講 3 項議題，包括本部食品藥管理署藥品組劉組長麗玲受大會邀請，與美國參議院議員代表 Wade Ackerman 及 FDA 副局長 Robert Califf 同台演講，分享對複合性醫藥品(combination products)的管理觀點。藥品組祁若鳳簡技亦受邀發表我國奈米藥品的管理現況與規劃，風險管理組黃琴嘵科長也受邀發表我國執行 GMP /GDP inspection 的經驗。今年我國主管機關發表演講皆為前瞻性新興產品之管理議題，顯現我國與國際之零時差藥政管理進度，大幅提升我國藥政管理之國際能見度與影響力。

我國並依往例，由醫藥品查驗中心協助於展場設立攤位，發放文宣與影片，介紹我國醫藥品管理環境，今年宣傳主題為國內臨床試驗中心與成果，並於海報展示區張貼介紹我國藥品審查整合辦公室(iMPRO)的管理成果。醫藥品查驗中心劉文婷小組長與台大醫院林淑華教授也分別於會議中演講關於 CRO 查核注意事項及小兒罕見疾病用藥之開發經驗。

另外，我國並於年會期間，與國際合作夥伴歐盟 EMA 及日本 PMDA 面對面洽談國際合作交流事項，與日方確認今年底由我國主辦台日藥政大會之籌辦事項，並與 EMA 確認所舉辦之教育訓練課程，EMA 表示將知會我方有關教育訓練訊息，雙方並交換聯絡窗口。

貳、 行程表與過程紀要

一、行程表

日期	行程說明
104 年 6 月 13~14 日	桃園機場啟程至美國華盛頓
104 年 6 月 15	參加第 51 屆 DIA 年會 祁簡技若鳳受邀於「Next Generation Nanomedicines and Nanosimilars” Regulators’ Perspective」議題發表演講，講題為「Regulatory Convergence Challenge For Nanomedicines」。
	晚間與日本 PMDA 進行雙邊會談。
104 年 6 月 16 日	參加第 51 屆 DIA 年會 劉組長麗玲受邀於「Regulation of Combination Products」論壇發表演講，講題為「Regulation of Combination Products in the 21st Century」。
	法規科學專家學者聯誼餐會(台灣之夜)
104 年 6 月 17 日	早晨與 EMA 進行雙邊會談。
	參加第 51 屆 DIA 年會 黃科長琴喨受邀於「Risk-based Inspections and Compliance」論壇發表演講，講題為「GMP/GDP Management System for Medicinal Products in Taiwan」。
104 年 6 月 18 日	參加第 51 屆 DIA 年會
104 年 6 月 19~20 日	自美國華盛頓返抵台北

二、過程紀要

(一) 演說發表

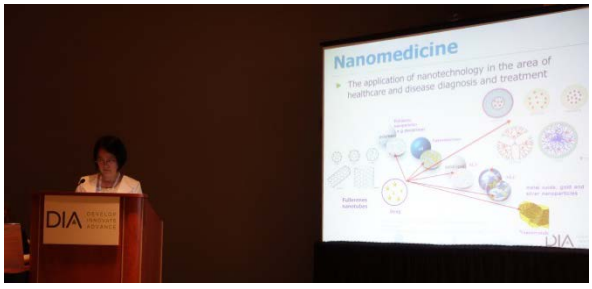
1. 劉麗玲組長發表在 APEC 推動複合性產品管理法規統整性(convergence)的成果 (6 月 16 日，session #247, track #19B) (簡報資料如附錄五)

我國自 2012 年在 APEC 會議倡議推動複合性產品管理法規統整性(convergence)計畫，獲得許多 APEC 會員國之回響與參與，其中包括美國。為了解 APEC 會員國的管理法規落差(gap analysis)，我國於 2012-2013 年間開展問卷調查及召開 APEC 研討會，發現歧異不僅在於國際間定義不同，藥品及醫材的管理要求也不同，譬如製造品質的標準，藥品有 GMP 規範，醫療器材則另有 Quality System Regulation (QSR)規範；審查標準也不同，藥品有化學藥品、生物藥品、或新藥與學名藥，醫療器材則以一、二、三級分類，可能產生之產品組合多達數十種；各國是否立有專法專章或專責審查管理單位，也不一致；雖然我國與先進國家是以主要作用機轉(primary mode of action)判定產品以藥品或醫療器材作為主要審查單位，但爭議性也隨者創新產品的開發及主要作用機轉解讀的不一致而越來越多；有關複合性產品的 CGMP 規定，僅美國有法律位階的明確規範。目前管理法規的挑戰有下列三點：(1)缺乏國際一致的產品分類，(2)缺乏正式的產品管理規定，(3)缺乏正式的產品審查框架。因此，我國認為國際法規管理的統整對於廠商的開發計畫與病患用藥有很大的幫助，極力呼籲各國正視複合性產品的管理與法規，應該建立整合審查小組，統合審查及修訂法規。另外，我國也藉機呼籲各界推展優良審查與送件規範，於藥品國際醫藥法規協和會議(ICH)及國際醫療器材法規管理論壇(IMDRF)聯合成立專家工作小組訂定指

引，並於 APEC RHSC 的法規科學訓練卓越中心納入複合性產品主題，以促進國際藥政法規的訓練活動、協和化與統整性。

各國對複合性產品定義各有不同，複合性治療的概念也不是新奇，美國 FDA 的複合性產品定義為含兩種(藥品、生物藥及醫療器材)以上的產品組合，FDA 副局長也從藥品合併治療開始導入複合性產品的治療效果，希望可以達到合併治療的加乘作用，希望啟發更多創新治療，如藥品與醫材的聰明結合達到對病人治療的最佳效果。同時也提到 FDA 有一個專屬辦公室 Office of Combination Products 可以指定複合性產品審查單位、判定非複合性產品的管理屬性、解決紛爭、訂定法規、回復內外界諮詢、舉辦訓練及提交年度報告給國會，管理挑戰性在於現在藥品與醫材的規範歧異極大，審查標準與要求不同，製造規範要求也不同，適應症/適用性(indication)觀點也不同，藥品是依據臨床成效(clinical outcome)，而醫材是做為醫療工具(tool)， 甚至收費標準、仿單標示及溝通都是挑戰，FDA 表示這些都需要更多的科學證據、資訊整合、多方溝通及流程改進，才能達到理想的管理目標。

2. 祁若鳳簡技發表我國的奈米藥品管理現況與規劃 (6 月 15 日，session #124, track 04)
(簡報資料如附錄五)



迄今，國際上對於是否給予奈米藥品定義仍未有定論，IPRF的奈米工作小組主席也在今年3月擴大工作小組成員電話會議中，開宗明義回復成員，不願對奈米提供定義。但國際對奈米醫藥品的工作定義(working definition) 共識為: 人為製造(engineered)產品的任一維介於1-100 nm之產品，但是如果其作用係借助其奈米特性，或即便超過100 nm, 但其物化特性顯現出與該物品原本不同而有奈米特性時，也屬奈

米科技產品 (係綜合參考EMA working definition of nanomedicine及FDA Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology)。

沒有定義並不代表各國沒有能力審查或管理奈米藥品，事實上，國際上對於奈米藥品的審查經驗不在少數，國際上奈米醫藥品核准上市的也有數十項，若把所有微脂體納入奈米藥品，則其開發與核准歷史已有數十年之久，加上在如果所有藥品都能在體內崩散溶解成真溶液的理想概念下，分子狀態與奈米並無二致，故各國主管機關都認為以現行安全、品質、療效的審查框架下，審查員有足夠的專業能力提供適切的審查判斷，無須在管理法規上訂定奈米藥品專章。

雖說國際上並未能給奈米醫藥品一個名分(相較於生物藥品或生物相似性藥品)，但仍無法切割其管理的必要性。起因於對奈米尺寸的產品的無孔不入可能性引起之病人、環境、過路人的安全副作用疑慮，但可能一則因為尺寸小難以監控觀察，一則可能因為奈米製程產品在人體或環境中並不如預期產生奈米效應，或其他原因，目前並未獲知奈米醫藥品的安全危害警訊。

基於科學的敬畏及管理者嚴謹態度，各國雖然說現今之審核架構已完全足以涵蓋奈米藥品，但預估未來仍可陸續見到各國有奈米醫藥品相關管理規範出爐，重點將先著重於檢驗與審查規格的訂定，主成分本身奈米化較無爭議，然現今奈米科技對醫藥品的貢獻多在於載體的開發，而載體屬於賦形劑，相較於其他藥品的賦形劑變更大多不影響藥品特性，奈米產品如微脂粒的雙層結構脂質的變更卻可能對藥品特性造成很大影響，故而現今也常聽到 nanosimilar 一詞，顯示相同主成分但不同賦形劑的奈米醫藥品之管理值得額外關注。至於安全與風險之監控規範，可能要再等一等。

在這次 DIA 年會中，祁若鳳簡技首先介紹我國國家型奈米計畫的推展與成果，我國已有好幾類(liposome, nanocrystal，nanoemulsion 等)與好幾項奈米產品已核准上市，在審查能量與品質標準上沒有疑慮，但是為了提供開發廠商可以簡易依循並與國際法規協和的審查規範，本部在我國國家型奈米科技計畫中，進行奈米法規之研究，並建置奈米藥品之最大類產品-微脂粒醫藥品的審查基準草案。另外，醫藥品查驗中心也在奈米國家型計畫中，規劃建立微脂粒學名藥品的審查基準草案。

會議中，美國 FDA-CDER 科學法規研究藥品品質辦公室 Office of Pharmaceutrial Quality (CDER/OPQ)組長 Katherine Tyner，也在會議上提供美國的管理現況，再次強調現行審查機制已足以審查奈米藥品，報告內容主要是 FDA 今年在期刊 *Advanced Review* 發表的奈米醫藥品品質管理的技術性資料審查經驗與觀點之文章，講述奈米尺寸引起的品質要求項目，包括產品如物化特性描述定性、分析方法、安定性試驗、非臨床試驗應執行項目、並強調 QbD 及 in vitro-in vivo 的重要性；也包括製程與管制要求，特別是製程放大必須考慮關鍵製程對產品品質的可能影響，奈米材料相容性與表面作用的影響，滅菌方法對奈米產品是一大挑戰，所以也要詳細論述與管控。總言之，了解關鍵品質參數(critical quality attributes)與做好品質製程管制是建立奈米藥品品質的重要因素。

會後，我方也與 FDA 代表討論雙方訂定奈米藥品基準的程序，並交換聯絡方式，Katherine Tyner 的業務直接涉及奈米藥品法規訂定，對我國日後修訂奈米藥品法規將可提供助益。

3. 黃琴喨科長發表我國實施 PIC/S GMP 與 GDP 的管理經驗 (6 月 18 日，sesson#363，track 12) (簡報資料如附錄五)

國際醫藥品稽查協約組織（The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme, 簡稱 PIC/S）」係由各國負責藥品 GMP 管理與稽查權責機關所組成的國際合作組織，現有 46 個會員，分屬 43 個國家，歐美醫藥先進國家 GMP 稽查單位皆積極參與；我國衛生福利部食品藥物管理署（Taiwan FDA）經藥廠查核單位人員積極努力，亦於 2013 年 1 月 1 日起正式成為 PIC/S 第 43 個會員。PIC/S

致力於促進藥品 GMP 法規標準國際協和、稽查品質一致化，為一個互助合作與資訊交流的國際合作組織。我國之實施 PIC/S GMP 與加入 PIC/S 組織亦帶動亞洲地區國家紛紛加緊步調實施 PIC/S GMP，繼我國加入 PIC/S 之後，日本、韓國亦相繼跟進，香港亦將於 2016 年 1 月入會。

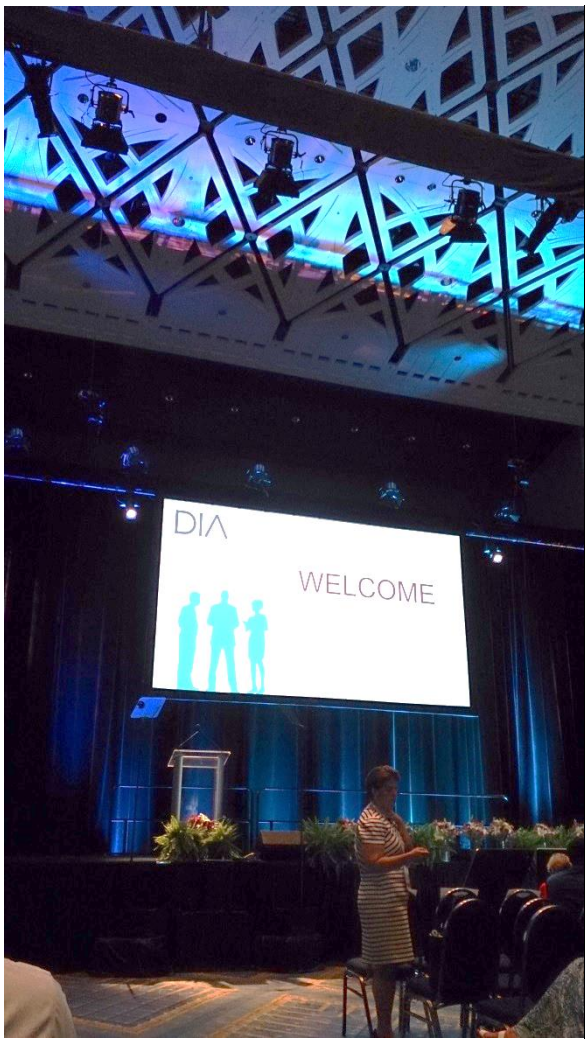
在這次 DIA 年會中，**黃琴喨科長**首先介紹，介紹我國推動藥廠實施 PIC/S GMP 的歷程，國內外藥廠查核之成果與現況，包括原要藥廠、製劑廠、醫用氣體廠及研發廠等。並從風險評估管理的角度，報告目前我國進行藥廠 GMP/GDP 查核之風險策略及未來執行策略。除 GMP 之外，黃科長亦報告推動藥品運銷規範 Good Distribution Practice GDP 之情形，有別於以往實施藥廠 GMP 之推動模式，我國目前於正式實施 PIC/S GDP 之前除與業者進行溝通外並先進行多項相關教育訓練課程及實地輔導性訪查，讓業者提前熟知規範內容與標準並進行改善。在加以舉辦頒獎方式表揚積極實施之藥廠、代理商、經銷商等業者，並以上台報告、壁報方式鼓勵已實施業者進行經驗分享，以加速推動 GDP 之實施。

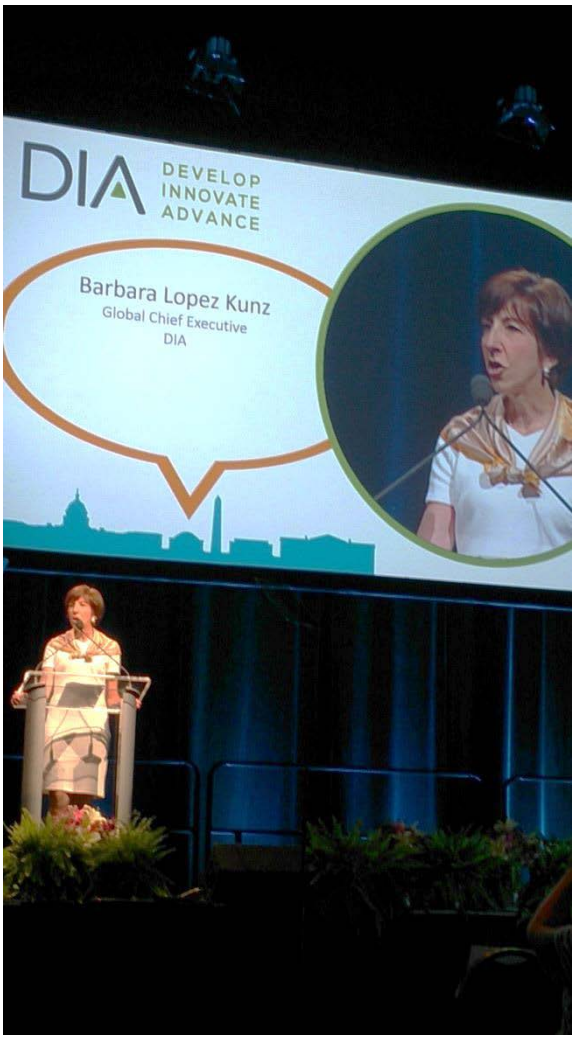
本次論壇中，美國 FDA-CDER_OC 科學法規研究藥品品質辦公室 Office of Manufacturing Quality 的 Deputy Director Mr. Richard L.Friedman，也在會中上報告美國的 GMP 管理現況，並從查核迷思角度分享 GMP 法規的看法。

Mr. Richard L.Friedman 與黃琴喨科長同為 APEC LSIF-RHSC GMP working group 的成員，平時只透過 e-mail 或電話會議方式一起討論有關 GMP 之議題，藉著 DIA 會議同一小組報告演講之際得以實際碰面，實屬難得。

(二) 其他議題介紹

1. **會議大會主題演講** welcome remarks/keynote speech/ plenary speech





繼會議開場由合唱團表演曲目: “You only get one shot”， 接續由 DIA 全球執行長(chief executive)Barbara Lopez Kunz 歡迎大家與會，並強調 DIA 在推動各專業合作以促進全球健康照護產品開發與創新的努力，激勵各界共同推動疾病治療、健康影響與生命拯救的完善體系。

年會共同主席(co-chair) Christopher P. Austen 很開心地分享美國 FDA 與 DARPA (Defense Advanced Research Projects Agency)在轉譯科學的研究成果:器官及器官系統之晶片技術，用於不適用動物或人體之藥品毒性檢測。晶片為器官的縮小版，可以模擬預測藥品毒性，未來可再擴充納入荷爾蒙系統，即可分析男性與女性對藥品的分別反應，將科幻化為事實。

年會共同主席(co-chair) Michael Rosenblatt 強調病人自始至終都是 DIA 的核心，現今病人又比以往更加活躍，我們需要結合病患組織協會、納入業界、醫護人員、

學術界的專業、加速創新研發與病患用藥。

另外，研發界代表 Daneil Burrus (Burrus Research associates, Inc 的 CEO)也總結鼓舞與會者積極投入創新，表示” you are the enablers of innovation”。

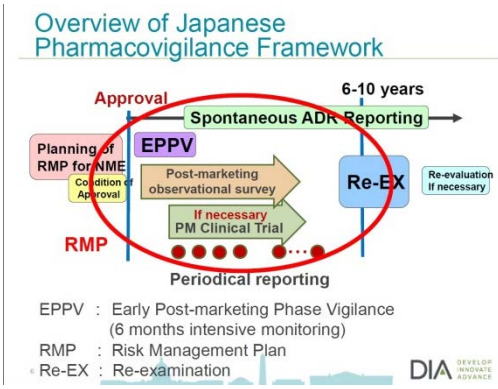
2. PMDA Town Hall 日本論壇

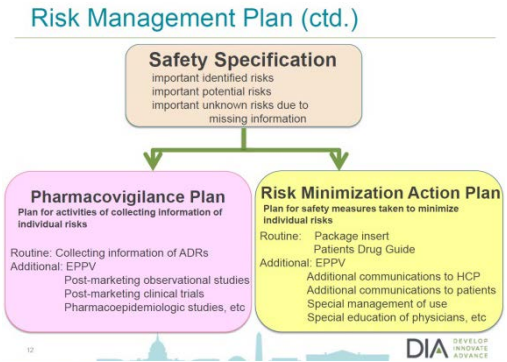
講者來自 PMDA 及 MHLW。PMDA 的管理依據藥品生命週期，演講主題包括創新鼓勵策略、安全管理策略及國際合作計畫。PMDA 介紹去年日本修訂之新藥事法，並提出六項創新管理: 從上市開發階段提供研發策略諮詢(consultation on R&D strategy)，至上市審查成立各式尖端(cutting edge)科學委員會(science board)，新增條件式核准(conditional approval)機制，推動 SAKIGAKE 策略，鼓勵日本首創之藥品核准，並規劃改善審查體系，到上市後安全評估之 MIHARI 專案，利用健康資料庫，建立上市後管理體系，未來將持續國際合作與法規協和化。重點如下:

(1) 日本並以該國之學術研究成功研發上市成產品 crizotinib (alectinib)、mogamulizumab(anti-CCR4 mAb)及近期很夯的 anti-PD1 mAb 為例，一方面推崇自國學術研發能力，也介紹 PMDA 諮詢機制與其成果。PMDA 提出科學計畫(sceicne-based initiative)，提供 R&D 策略的諮詢，希望幫助產品跨越開發之死亡谷(death valley)；更新及增加科學委員會，如生物產品、細胞組織產品、及醫療器材。建立進階審查諮詢系統(advanced review/consultation system)，以科學為基礎，逐步建立技術性電子資料庫(將建立電子送件系統)與模擬系統，作為未來新藥審查時利益風險評估與確立不良事件相關因素之參考，同時可作為有效諮詢的工具。

(2) 在風險管理方面，日本風險監控架構(pharmacovigilance framework)包含早期密

集監控(EPPV: early post-marketing phase vigilance, 核准後 6 個月內密集提交安全報告)、風險管理計畫(risk management plan)及 6-10 年後再審核(re-examination)，另外，藥品上市後仍要進行 ADR 自主通報，PMDA 每 5 個星期召開專家會議討論是否需要修改仿單，新藥與部分學名藥需檢送風險管理計畫(J-RMP)，定期交報告、執行上市後監控並採取額外安全措施。風險管理計畫包括 3 個元素: 安全規格(safety specification)、監控計畫 pharmacovigilance plan)及風險減少計畫(risk minimization action plan)，執行事項包括 ADR 通報、EPPV、上市後研究(post-marketing studies)、仿單修正、病人用藥指引(patient drug guide)、與醫護專家之教育訓練及溝通計畫等。J-RMP 會公布在 PMDA 網站上。PMDA 設有風險管理專員，由審查團隊與上市後安全團隊組成，負責研擬安全策略。另外值得關注的是，PMDA 自 2009 年開始 MIHARI 試辦專案，利用電子健康數據庫(healthcare data, 健保、病歷等)，以藥物流行病學研究方法，定量分析藥品風險及評估安全措施的影響。厚生勞動省(MHLW)也發起醫療資訊網計畫(Medical information database network project, MID-NET project)，納入 10 家醫院及醫院集團，以利 MIHARI 專案順利取得健康數據，進行分析與評估。預計在 2018 年可以全面採用該資料庫。其實我國採用健保資料庫進行藥物流行病學已經有好幾年，





(3) 日本藥事法(pharmaceutical and medical device act, PMD act)新法於 2013 年 11 月 27 日發布，於 2014 年 11 月 25 日正式生效，賦予醫療器材與再生醫學明確新地位，更加強藥品安全性規範。在推動基礎研究與實務應用之結合，MHLW 公布於 2015 年開始實施 SAKIGAKE 超跑策略(saki: 超越，gake: 跑)，對於在

日本首先申請藥證(或與國際同步申請)、且早期臨床試驗數據或非臨床試驗數據顯示有明顯療效的藥品，一旦通過認定(designation)，日本將優先審查。

(4) 日本也提到國際合作的進度，包括與歐盟 EMA 及美國 FDA 的三方密切合作，IGDRP 的學名藥合作計畫、ICH 的重組規劃、ICMRA 的合作。

3. CBER Town Hall: innovation and public health response CBER 論壇

CBER 介紹管理目標在鼓勵創新、促進民眾健康，並成為全球生物藥品的領導主管機關。在這次年會，CBER 以最新最吸引人的尖端生技產品為範例，說明對創新藥品的支持策略，顯示其成為全球生物藥品領導主管機關的使命與角色，包括疫苗與粒線體遺傳病及不孕症。

CBER 管理的產品包括過敏原、血品及血液製劑、醫療器材、基因治療產品、人類細胞組織產品、疫苗及異體移植。法規科學計畫目的在於提供科學專業與管理法規，鼓勵主動研究以解決法規缺口，提供公共健康與管理緊急議題之面對面溝通回應。CBER 介紹創新新藥的促進專案(expedited program)、法規科學的研究，舉例近年創新藥品之審查成果:疫苗及細胞基因治療，並提出適應性臨床試驗設計(adaptive trial design)及上市後監控。FDA 的新藥促進專案有四種機制，適用於發展治療嚴重疾病的藥品或生物藥品: (1) 治療嚴重或危及生命、且臨床前或臨床試驗數據顯示具有治療重大醫療需求潛力的新藥(含生物藥)，可以申請快速道路認定(fast track designation)，申請者可以與審查團隊頻繁互動；(2)突破性治療認定(breakthrough therapy designation，BT)，對於治療嚴重或危及生命、且初步臨床證據顯示該藥比現行治療具有臨床上極大改善效果者，在研發與審查階段都可以與 FDA 頻繁互動以加速產品開發；(3)加速核准路徑(accelerated approval pathway，AA pathway)，對於嚴重或危及生命的疾病，可以提供比現行治療更有效益(meaningful benefit)者，且必須提供可用以預測臨床效益的合理的替代性療效指標(surrogate endpoint)，或在死亡率或不可逆發病率之外的臨床終點(endpoint)的試驗結果顯示有效，另外，也必須執行上市後(post-approval)試驗以確認臨床效益；(4)優先認定(priority designation)，用於治療嚴重狀況，可望在安全與療效提供重大的改進，在審查方面，FDA 也會加速回應申請者，從一般 10 個月縮短為 6 個月。

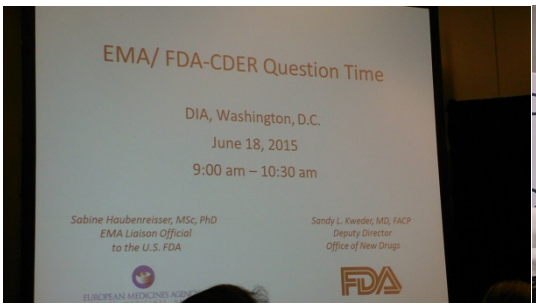
CBER 並以流行性腦脊隨膜炎疫苗(Meningococcal group B vaccine)為例，研發困難在於致病菌株之多樣性及低發生率，在 2013 年美國曾爆發校園大流行，2014 年 2 家製造廠送件申請，符合突破性治療認定(BT)、優先審查認定及加速核准路徑，所採用 AA 機制的 surrogated endpoint 是血清中抗菌抗體量，所選菌種則具美國盛行型菌株，FDA 分別於 2014 年 10 月 2015 年 1 月通過這 2 張藥證。另外 CBER 也提出伊波拉疫苗也可以 AA 機制與採用動物原則(animal rule)之方式核准，目前伊波拉疫苗研發進度約在 2-3 期臨床試驗，FDA 與國際如 EMA 及 WHO 專家都密集聯繫討論，但都需要執行上市後確認試驗。另外FDA 也以用於癌症等疾病治療的免疫T細胞治療、基因工程 T 細胞治療及預防母系遺傳粒線體疾病的新穎細胞工程技術為例，探討基因工程與細胞工程技術產品帶來的挑戰，並提出專責之各審查諮議會的工作重點。

另外，FDA CBER 也提出未來藥品(尤其是疫苗)以上市後大數據作為分析安全療效的新應用工具，FDA 以探討 65 歲以上使用高劑量與一般劑量的感冒疫苗的相對療效為例，因為老年人免疫力較弱，2009 年廠商提出提高老年人施打感冒疫苗劑量，以激活免疫反應，獲得 AA 方式核准，在後續 30000 人的確認試驗中，證實高劑量比一般劑量療效高 24.2%；另一方面，FDA 採用大數據(big data)回溯比較 2012-13 年間感冒季期間之觀察性數據(observational data)，看診及住院之數據，統計因感冒引發的人數，也發現相近的優勢比例(22%)，證實高劑量疫苗可以大幅減少老年人因感冒引發嚴重併發症的狀況。

FDA 於 2011 年提出適應性臨床試驗(adaptive design clinical trials)設計指引草案，在合理的範圍內可以修改臨床試驗計畫，廠商可依據中途統計數據，發現並修正假設，並重新設計試驗，以提高新藥試驗成功機率。在這過程中，CBER 也都與申請者合作已達良好設計。CBER 並以 2014 年 12 月核准的人類 papillomavirus vaccine Gardasil-9 為應用 adaptive design 之成功案例，並回溯分析 2008-2013 年間以適應性設計申請的試驗，計 140 件。FDA CBER 認為創新的分析方法可以幫助審查決定，上市後觀察性數據(observational data)可以廣泛應用於疫苗及生物藥品之監控，創新的統計方法可以改善疫苗及生物藥品的成功開發與上市。

4. **EMA 與 FDA 問答時間 An insider’s view of cooperation between the EMA and**

CDE/FDA: Question time (6 月 18 日)



本論壇為今年新增項目，在年會接近尾聲之時，邀集 EMA 及 CDER/FDA 雙方主管齊聚一堂，在各自簡述策略規劃與成果之後，開放與會會員發問。雙方主管來自包括國際合作、醫藥品審查、藥品監控、品質等部門單位，報告議題為(1)藥品監控(pharmacovigilance)、(2)適應性臨床試驗設計(adaptive pathway)、(3)品質來自於設計(quality by design)與 ICH-CMC 之規範，及(4)病人在醫藥品開發的角色、鼓勵納入病人相關團體參與藥品開發等議題，在表述各自近年來在全球醫藥品之開發與管理的理念與成果，及雙方共同合作的經驗與成果之後，開放所有參與 2015 DIA 年會的會員提出問題。對於有廠商提問如何設計藥品開發(臨床)試驗，EMA 及 FDA 都回復應早日納入病患團體，借助病患團體的力量與需求，協助規劃最適當的臨床試驗設計，並有效推動臨床試驗進行。另外，也歡迎病人向主管機關諮詢討論。

EMA 與 FDA 一向維持密切溝通聯繫，不論是在藥品審查溝通或是策略基準之訂定，或是緊急世界衛生健康事件，或是一些審查結束(predecisional review)前的資訊與意見交流(confidential information)。雙方之合作包括 QbD Pilot program, 希望能減少審查作業負擔、 增加統整性(convergence)、幫助全球醫藥發展、促進健康。

5. CDER Town Hall, CDER 論壇

CDER Town Hall 基本上延續前一場 CDE/EMA QA 時間的討論主軸，由與會會員提問，CDER 官員回復。本署劉組長也提問因為藥品要求規格越來越高，FDA 如何因應處理缺藥問題，FDA 也表示這確實是難題，但是處理的原則是以病患角度平衡風險 (balancing risk)，在藥品品質與藥品供需對病人之安全療效間的取捨，可能選擇替代性藥品(alternative drug)，或自國外進口藥品，FDA 也表示了解有些藥品短缺不是真的因為生產品質有問題，也希望廠商僅早報告，讓 FDA 有所安排，譬如加速審查藥證。可見我國之缺藥處理機制，與美國之作法其實相同。劉組長仍再次強調請 FDA 在推展全球法規新策略之規劃時(如 ICH 法規)，納入對缺藥議題的重視，避免造成全球性缺藥，危及病人用藥需求。FDA 再次表示有小組負責，所幸目前的缺藥事件仍屬地區性，尚無全球規模之缺藥情形發生。

另外，也有會員提出用藥資訊(medication inform)是否有工作會議等相關活動，FDA 表示美國有許多病患及消費者資訊，並非由廠商撰寫，也不需要經過 FDA 核准，鼓勵相關單位投入製作足以提供病患正確觀念又簡短的資訊，試問，有多少人會拿

來閱讀。

6. In vitro and in vivo Preclinical testing of biosimilars: what have we learned, 生物相似性藥品的臨床前試驗要求與技術開發

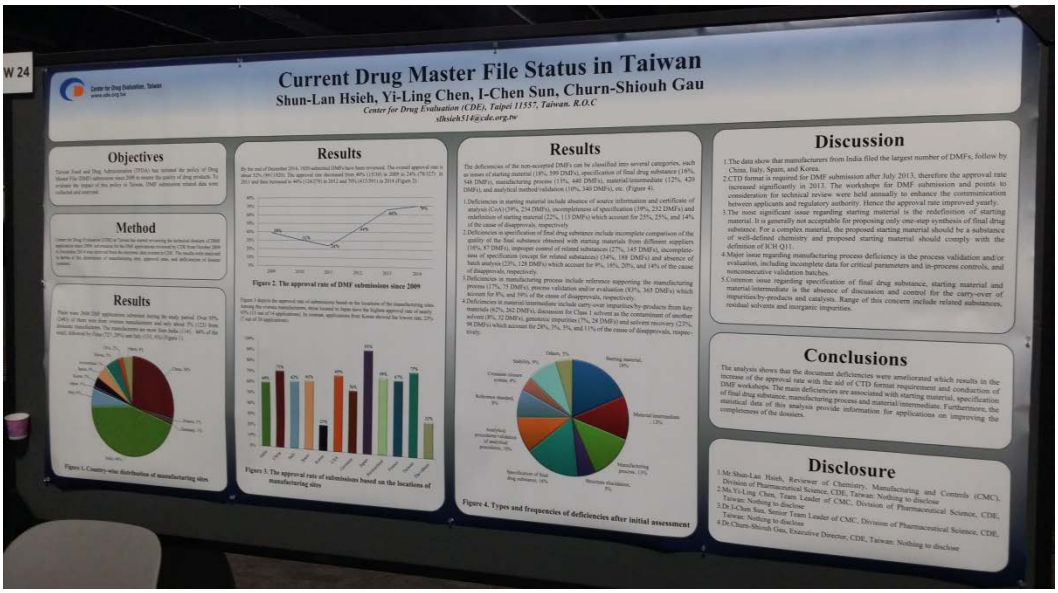
這場探討生物相似藥品所需要的臨床前試驗數據資料，比較各國對於生物相似性藥品的規範，揭示美國 FDA 與歐盟 EMA 對於刪減動物試驗的共識與趨勢，我國於去年七月公告的藥品非臨床試驗安全性規範第五版，也調整修正動物試驗要求，與國際同步。會議並邀請業界發表檢驗技術之創新應用，包括利用微晶片(microarray)分析基因表現形態(gene expression profile)，來比較藥品作用與效果。

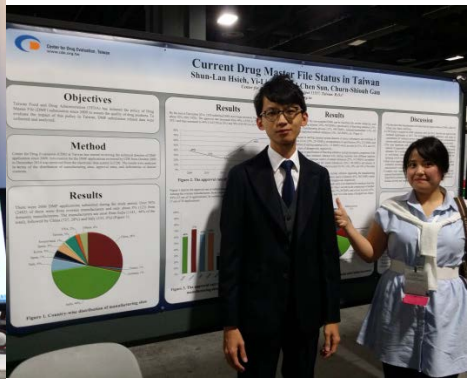
7. orphan drug development challenges: cases studies, 罕見疾病用藥的開發挑戰

這場由業界及臨床試驗研究單位主講的論壇，以開發者的角度，以案例分享罕見疾病用藥的開發困難點與策略，鼓勵應與罕見疾病團體、病患及其家屬、試驗團隊密切合作。

(三) 設立展場攤位與海報展示

今年 2015 DIA 年會，參與者來自產、官、學、研及醫藥相關組織團體，超過 7 千人，設立攤位超過 450 攤位，本部與財團法人醫藥品查驗中心共同設立展示攤位，以介紹我國卓越臨床試驗中心為主題，透過文宣、播放影片及工作人員解說，說明我國臨床試驗環境建置的成果，包括國際 AAHRPP 認證，多國多中心臨床試驗之聯合 IRB 審查機制等，展現「健康台灣 Health Taiwan」的目標，同時介紹食品藥物管理署與醫藥品查驗中心的組織架構與工作宗旨(展場文宣如附錄四)。海報展示區則張貼本署 iMPRO 藥品整合審查中心的成果。


W 24
Current Drug Master File Status in Taiwan
Shun-Lan Hsieh, Yi-Ling Chen, I-Chen Sun, Churn-Shiouh Gau
Center for Drug Evaluation (CDE), Taipei 11557, Taiwan. R.O.C
slhsieh514@cde.org.tw
Objectives
Method
Results
Figure 1. Country-wise distribution of manufacturing sites
Results
Figure 2. The approval rate of DMF submission since 2009
Figure 3. The approval rate of submissions based on the locations of manufacturing sites
Results
Figure 4. Types and frequencies of deficiencies after initial assessment
Discussion
1.The data show that manufacturers from India filed the largest number of DMFs, follow by China, Italy, Spain, and Korea.
2.CTD format is required for DMF submission after July 2013, therefore the approval rate increased significantly in 2013. The workshops for DMF submission and points to consideration for technical review were held annually to enhance the communication between applicants and regulatory authority. Hence the approval rate improved yearly.
3.The most significant issue regarding starting material is the redefinition of starting material. It is generally not acceptable for proposing only one-step synthesis of final drug substance. For a complex material, the proposed starting material should be a substance of well-defined chemistry and proposed starting material should comply with the definition of ICH Q11.
4.Major issue regarding manufacturing process deficiency is the process validation and/or evaluation, including incomplete data for critical parameters and in-process controls, and nonconsecutive validation batches.
5.Common issue regarding specification of final drug substance, starting material and material/intermediate is the absence of discussion and control for the carry-over of impurities/by-products and catalysts. Range of this concern include related substances, residual solvents and inorganic impurities.
Conclusions
The analysis shows that the document deficiencies were ameliorated which results in the increase of the approval rate with the aid of CTD format requirement and conduction of DMF workshops. The main deficiencies are associated with starting material, specification of final drug substance, manufacturing process and material/intermediate. Furthermore, the statistical data of this analysis provide information for applications on improving the completeness of the dossiers.
Disclosure
1.Mr.Shun-Lan Hsieh, Reviewer of Chemistry, Manufacturing and Controls (CMC), Division of Pharmaceutical Science, CDE, Taiwan: Nothing to disclose
2.Ms.Yi-Ling Chen, Team Leader of CMC, Division of Pharmaceutical Science, CDE, Taiwan: Nothing to disclose
3.Dr.I-Chen Sun, Senior Team Leader of CMC, Division of Pharmaceutical Science, CDE, Taiwan: Nothing to disclose
4.Dr.Churn-Shiouh Gau, Executive Director, CDE, Taiwan: Nothing to disclose



(四) 雙邊會談

1. 與 PMDA 會談

日方出席人員: Tatsuya Kondo (Chief Executive, PMDA)，Takao Yamori (Director of Center for Product Evaluation, PMDA)，Tomiko Tawaragi (Chief Safety Officer, PMDA)，Jun Kitahara (Division Director, Divison of Regulatory Cooperation , Office of International Programs, PMDA)，Hirofumi Suzuki, Division of Planning and Coordination, Pffice of International Programs, PMDA)。

我方與日本 PMDA 代表會談，就今年底台日雙邊藥政大會事項進行確認。今年是第三屆台日藥政大會，由我方主辦，於台北舉行，今年會議預計於 11 月舉辦 2 天，議題包括雙方推動鼓勵創新的政策與 GMP 政策等議題。


2. 與 EMA 雙邊會談

EMA 出席人員: Emer Cooke、Martin Harvey Allchurch (International Affairs)

我方與 EMA 主要就以下藥政管理相關議題進行交流討論並達成共識: (1) 我方提出精簡審查時，申請商所附之歐盟審查報告為公開版本，內容較為簡略，許多重要內容被遮蓋，無法閱覽，希望透過 EMA 提供完整版審查報告，以利了解審查觀點。EMA 表示可代為向廠商詢問，如廠商同意，將可提供詳細的審查報告予我方。(2) 我方詢問參與 EMA 人員教育訓練課程一事, EMA 表示我國已參加 GCP inspector training，目前 PV 查核員 training 目前僅提供 EU 會員國，未來不排除擴大受訓對象之可能性，日後可持續提供我方相關資訊，雙方並建立人員教育訓練之聯絡窗口。

(五) 法規科學專家學者聯誼餐會(台灣之夜):

我國主辦台灣之夜法規科學專家學者聯誼餐會(台灣之夜)，於華盛頓中國城 Tony Cheng’ s seafood restaurant 舉行，駐美國台北經濟文化代表處科技組趙衛武富組協助安排聯繫，駐美代表處副處長洪慧珠也到場致詞，宴請多國賓客，包括澳、法、日、韓、英、美等國藥政法規學者，約 80 多名貴賓與僑界代表與會，其中，著名的國際藥物資訊協會總裁 Per Spindler 也應邀出席。我方安排合唱團與古箏表演，透過輕鬆餐敘方式，促進彼此交流。海外媒體亦來進行採訪，包括華府新聞日報與世界新聞網，劉麗玲組長接受訪問時表示，參與 DIA 會議，經由各國產官學研界之相聚、交流，進行政策與科學之經驗分享，藉以再度提升我國製藥與法規國際化。CDE 執行長表示，此行之會議資訊，將可做為我國法規參考，使我國管理機制進一步與世界接軌。(當地新聞媒體報導如附件)。


Table 1

參、 心得與建議

一、心得

相較於 ICH 會議主要是探討藥品技術性審查基準與標準，DIA 可謂是國際上最重要之藥政管理會議，探討議題豐富，且不僅集結各國藥政主管機關，還有大小醫藥廠商，從開發商到大藥廠到委託公司(contract organization)，還設有展區提供各業者競相裝備競賽、各主管機關宣示管理策略的場地。今年大會開場主題演講強調 "只有一次機會 (You only get one shot)!”、及” You are the enabler!”，鼓勵各界積極投入創新、建立更完善的醫藥開發與管理系統。大會最後重頭戲，新增 FDA 與 EMA 的 QA 論壇，從所選之報告主題，可以看出現今國際上 2 個最重要的藥政主管機關的重點在於: (1)藥品生產製造品質(CMC、QbD)、(2)藥品上市後安全(Pharmacovigilance)、(3)鼓勵創新之新彈性策略 adaptive pathway、但同時不忘(4)創新開發是必須以病人為中心(patient involvement) 的。這些觀點顯現出國際藥政領導單位的高度。今年年會也有不少以病人為藥品開發中心的議題，尤其罕藥的開發可能要搭配家屬的安置，小兒用藥可能可以設計提高持續兒童參與的活動策略等，在國際藥廠紛紛提升病人在新藥開發與臨床試驗的角色時，反觀我國在執行藥品審查與管理時，大部分時候其實也是以病人為考量的，但面對各界對國產生技醫藥產業的關注與期待，主管機關常背負極大壓力，理應廠商積極提高產品品質與證明療效安全，但其實如同 PMDA 演講所提到 death valley，從基礎研發到臨床使用，許多藥品壯志未酬先身死於這中間的死亡谷，在我國醫藥品開發領域，傾向於有開發投資意願，研究學者熱心研究，但無法想像製造規格與研究時的差異，而業界對於後續失控的金額追加投注，很容易怯步轉而在研究檢驗規格上討價還價，在檢視科學證據以保護用藥安全及正視國產現實以扶植藥業發展的天平上，主管機關是深受挑戰的。

有幸參加 51 屆 DIA 年會，實感榮幸，並收穫良多。本次劉麗玲組長受邀與美國 FDA 官員及國會議員代表同台演講，顯示美國對複合性藥物管理的重視，不僅訂定給業界開發送件指引(guidance for industry)層級，更進一步探討立法鼓勵複合性藥物的開發，我國近年在 APEC 會議倡議呼籲各國正視複合性產品管理法規統整性

(convergence)，對於廠商的開發計畫與病患用藥有很大的幫助。加上我國近年在國際上推展藥品優良審查規範及優良送件規範，可以看到我國在藥政管理與國際合作的努力，主管機關的努力是相當值得肯定的。

二、建議

(一)國內廠商參與 DIA 年會

51 屆 DIA 年會有許多以病人為藥物開發為中心的論壇，與會之國際藥業代表們提供許多以人為中心的新藥開發觀點，納入病人團體的聲音，以專業與醫護人員、病人屬、及主管機關進行互動，帶動更完善的醫藥健康體系，業者代表不僅談論藥品品質、還有臨床試驗計畫，相當值得我國借鏡。我國以小型學名藥市場為主的藥業文化現況，更需要改變業界思維，導入提生產製造品質及增加病患用藥健康之概念，從而全面改變學名藥與新藥開發商的價值與使命感，提升我國醫藥健康環境，尤其 CRO 公司在台灣，不應只是藥品上市的附屬品，而是應對藥品上市具有更大輔助角色。今年我國參與 DIA 之廠商，除往例都會參加的輸入藥商代表，我們也欣見一家國產新藥廠商公司與會，希望藉由廠商的宣傳與彼此間互動，可以吸引更多國產廠商參加此類大型國際藥政會議。

(二)主管機關持續並擴大參與 DIA 年會

DIA 年會議題相當廣泛且有深度，討論議題豐富多元，從醫藥法規管理、新藥研發新知、臨床試驗管理、專案管理規劃，不僅提供主管機關許多新觀點與管理策略靈感，一方面是擷取各國優點的好機會，也是作為宣傳我國規劃與成果的好所在，應持續列為重點出國計畫，在預算許可前提之下，提供多位同仁出國與會的機會，分向參加各主題論壇，因為對於所提供之雖然年會議題很多，但聽者分身乏術，不能一一前往，儘管大會提供參加會員可以至 DIA 年會網頁下載會議簡報檔案，但無法補足當面提問的優點。

DIA 年會的主題相當廣泛，翻閱過去本署參加 DIA 年會，也不乏對藥品研究檢驗規格的探討與醫衛管理的討論，建議本部其他相關單位未來可以參酌與會。

另外，藉著出國之天時地利之便，積極建立雙邊會談機會，與歐、美、日等世界醫藥先進國家之藥政主管就藥品管理相關議題提出討論，實為提升我國能見度以及加強國際實質合作之良機。

(三)國內舉辦國際性醫藥法規或新藥研發等座談會議之參考

可參考 DIA 模式，廣泛邀請學界代表與學生參與，從基礎培養醫藥法規科學與新藥研發的精神，開放研發公司、CRO 公司參與，增加國內研究相關議題之風氣，促進產官學之間合作，增加專業人才投入法規科學與新藥研發領域，提升國內生醫產業競爭力。

肆、　附錄

一、　紀錄照片

本部成員攝於 DIA 會場

我國代表攝於 DIA 會場

Combination product 論壇講者: 左起: 美國參議員代表Wade Ackerman、劉麗玲組長、主持人 Michelle Taylor McMurry-Heath、FDA 副局長 Robert Califf

劉組長與 Robert Califf 演講前討論

劉組長與 EMA 官員 Enrica Alteri (Head of Human Medicines Evaluation)

劉組長與 FDA 官員 Theresa M. Mullin (Director, office of strategic programs, CDER)

Nanomedicine 論壇講者: 左起: FDA 官員 Katherine Tyner、祁若鳳簡技、主持人 Suzanne Sensabaugh

GMP compliance 論壇講者: 左起: 主持人 FDA 官員 Rick Friedman (Deputy Director)、黃琴嘵科長、Qing Shen

本部長官與 CDE 高純琇執行長於 DIA 會場合影


本部長官、CDE 與台灣業界代表於 DIA 展場合影

會議結束、要打包離開了……

長官說: “Jump!”

二、 美國華盛頓當地新聞媒體報導

(一) 華府新聞日報

Category: 華府新聞 DC News

美國藥物資訊協會在華府舉行第51屆國際年會

Created on Friday, 19 June 2015 12:57 Hits: 192

美國藥物資訊協會在華府舉行第51屆國際年會

2015/6/30 美國藥物資訊協會在華府舉行第51屆國際年會 - Washington Chinese Daily News 華府新聞日報

【本報記者衣遜華府報導】台灣衛福利部(Taiwan Food and Drug Administration .TFDA) 及財團法人醫藥品查驗中心(Center for Drug Evaluation Taiwan) 組團來華府參加美國藥物資訊協會(DIA) ，在華府舉行第51屆國際年會，該代表團成員共30餘位、來自產、官、學界代表，發表8場演說並藉此機會和歐美、日等藥政主管機關官員會面，商談合作事誼。

(二) 世界日報

世界新聞網 worldjournal.com

網頁列印

內容來自網址: http://www.worldjournal.com/3301609/article-shortlink/

台代表團出席DIA年會 台灣之夜聯誼

記者羅曉媛／華府報導

June 23, 2015, 6:00 am 136 次

台灣代表團出席「2015年國際藥物資訊協會」第51屆年會，駐美代表處副代表洪碧珠（左二），與TFDA及CDE代表合影。（記者羅曉媛／攝影）

桐花合唱團在台灣之夜獻唱。（記者羅曉媛／攝影）

三、會議議程

SCHEDULE AT-A-GLANCE

SATURDAY JUNE 13

Registration Hours:

9:00AM-5:00PM Exhibitor Registration

SUNDAY, JUNE 14

Registration Hours:

8:00-9:00AM Registration for Full Day, Morning Preconference Tutorials*
8:00AM-6:00PM Exhibitor Registration
12:30-1:00PM Registration for Afternoon Preconference Tutorials*
3:00-6:00PM Attendee and Speaker Registration

Schedule:

8:30am-12:00PM Half Day Preconference Tutorials*
9:00am-5:00PM Full Day Preconference Tutorials*
1:00-4:30PM Half Day Afternoon Preconference Tutorials*
4:00-5:00PM DIA 2015 51st Annual Meeting Orientation and Networking

**Space is limited for Preconference Tutorials. Onsite Registration is available, but not guaranteed*

MONDAY, JUNE 15

Registration Hours:

7:00AM-6:00PM Attendee, Speaker, and Exhibitor Registration

Schedule:

7:30-8:20AM DIA 2015 51st Annual Meeting Orientation/Networking and Coffee
7:45-8:30AM Coffee and Breakfast Breads
8:30-10:00AM Educational Opportunities
8:30-10:00AM Student Forum
9:30am-4:30PM Student Poster Session (Exhibit Hall Entrance A)
9:30am-6:00PM Exhibit Hall Open
10:00-11:00AM Coffee Break
11:00am-12:30PM Educational Opportunities
12:30-2:30PM Lunch (Exhibit Hall)
Innovation Theater Presentations (Exhibit Hall Entrance B)
2:30-4:00PM Plenary Session & Keynote Address
4:00-6:00PM Opening Reception (Exhibit Hall)

TUESDAY, JUNE 16

Registration Hours:

7:00AM-5:00PM Attendee, Speaker, and Exhibitor Registration

Schedule:

7:15-8:00AM Coffee and Breakfast Breads
8:00-9:30AM Educational Opportunities
9:00AM-4:00PM Professional Poster Session #1 (Exhibit Hall Entrance A)
9:00AM-5:00PM Exhibit Hall Open
9:30-10:30AM Coffee Break (Exhibit Hall)
Innovation Theater Presentations (Exhibit Hall Entrance B)
9:30-10:30AM Oral Presentations-Professional Poster Session #1A (Exhibit Hall Entrance A)
10:30AM-12:00PM Educational Opportunities
11:30AM-1:30PM Lunch (Exhibit Hall)
Innovation Theater Presentations (Exhibit Hall Entrance B)
11:30AM-1:30PM Oral Presentations-Professional Poster Session #1B (Exhibit Hall Entrance A)
12:30PM Student Poster Award Ceremony (DIA Booth #1523)
12:30-1:30PM Community Meet & Eat (Exhibit Hall)
1:30-3:00PM Educational Opportunities
1:30-3:30PM Exhibit Guest Passes
2:30-3:30PM Oral Presentations-Professional Poster Session #1C (Exhibit Hall Entrance A)
2:30-3:30PM Refreshment Break (Exhibit Hall)
Innovation Theater Presentations (Exhibit Hall Entrance B)
3:30-5:00PM Educational Opportunities

WEDNESDAY, JUNE 17

Registration Hours:

7:00AM-5:00PM Attendee, Speaker, and Exhibitor Registration

Schedule:

7:15-8:00AM Coffee and Breakfast Breads
8:00-9:30AM Educational Opportunities
9:00AM-4:00PM Professional Poster Session #2 (Exhibit Hall Entrance A)
9:00AM-4:00PM Exhibit Hall Open
9:30-10:30AM Coffee Break (Exhibit Hall)
Innovation Theater Presentations (Exhibit Hall Entrance B)
9:30-10:30AM Oral Presentations-Professional Poster Session #2A (Exhibit Hall Entrance A)
10:30AM-12:00PM Educational Opportunities
11:30AM-1:30PM Lunch (Exhibit Hall)
Innovation Theater Presentations (Exhibit Hall Entrance B)
11:30AM-1:30PM Oral Presentations-Professional Poster Session #2B (Exhibit Hall Entrance A)
1:30-3:00PM Educational Opportunities
1:30-3:30PM Exhibit Guest Passes
2:30-3:30PM Oral Presentations-Professional Poster Session #2C (Exhibit Hall Entrance A)
2:30-3:30PM Refreshment Break (Exhibit Hall)
Innovation Theater Presentations (Exhibit Hall Entrance B)
3:30-5:00PM Educational Opportunities

THURSDAY, JUNE 18

Registration Hours:

8:00-11:00AM Attendee and Speaker Registration

Schedule:

8:15-9:00AM Coffee and Breakfast Breads
9:00-10:30AM Educational Opportunities
10:30-10:45AM Coffee Break
10:45AM-12:15PM Educational Opportunities

四、我國之展場及攤位發放文宣

Innovative IRB Collaboration for Multi-Center Clinical Trials

Efficient Review with Quality Oversight

Authors: Ian Chen[1], Hsueh-Fen Fu[1], Chih-Liu Lin[2] | Organizations: [1]National Taiwan University Hospital, [2]Center of Drug Evaluation, Taiwan

Background

To synchronize IRBs review in multiple sites.

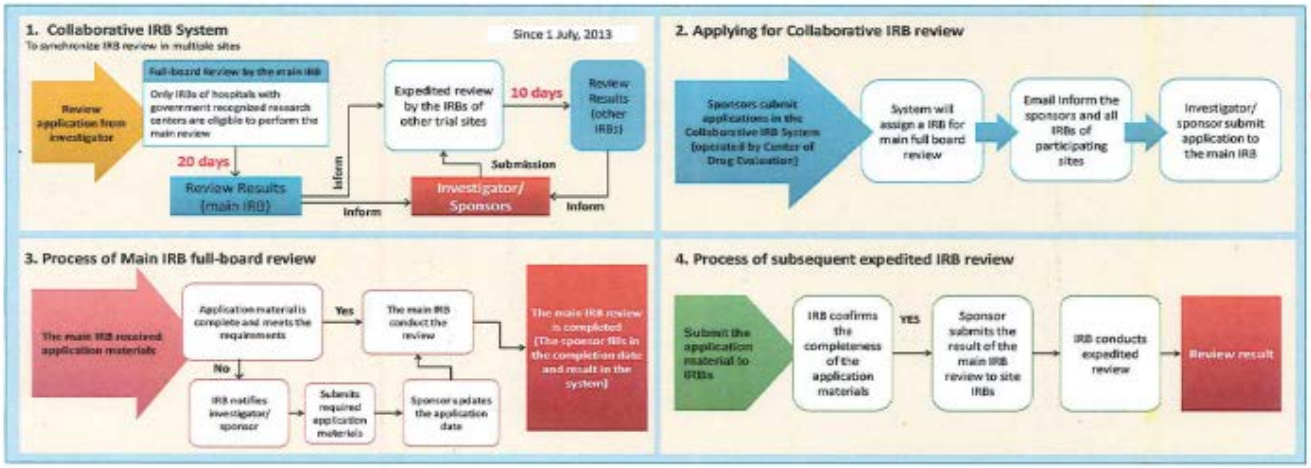
A multi-center clinical trial used to be reviewed by IRBs in all participating sites. A country-wide collaborative **IRB system** has been set up to minimize duplicated IRB full board review and to synchronize review timelines.

Method

A multi-center trial is registered to the Collaborative-IRB System and a main IRB is assigned to conduct full board review which will be completed in 20 days. The review records and results are then forwarded to other IRBs in all participating sites. These IRBs will conduct expedited review based which complete within 10 days.
The IRBs which can conduct main full board review for the system are listed by the Center of Drug Evaluation.

Features of the Collaborative IRB system

- Regulator led, top-down approach
- Only selected IRBs can perform the main full board review
- Use of the system is voluntary for investigators and sponsors
- Center of Drug Evaluation coordinates the whole system and holds bimonthly meetings with stakeholders to improve it
- Participation and application is voluntary for IRBs and sponsors



Results

Results: From July 2013 (when the Collaborative IRB system began) till December 2014

- 253 multi-center trials using the system
- 172 trials underwent main review (5 trials were not approved)
- Average of 8.1 days for main review
- 428 subsequent expedited reviews (2 trials did not secure approval)
- Average of 7.7 days for expedited review

Conclusion: Proven efficiency

The Collaborative IRB system reduced the duplication of full board review by 71.3%. This both reduces the use of IRB resources and shortens the time investigators spend obtaining approval from IRBs at all participating sites.

Acknowledgement

We thank Ms. Pei-Chin Yu in Center of Drug Evaluation for providing the statistical information.

五、本部之簡報資料

1. 劉麗玲組長發表在APEC推動複合性產品管理法規統整性(convergence)的成果 (6月16日，session #247, track #19B): **Regulation of Combination Products in the 21st Century**
2. 祁若鳳簡技發表我國的奈米藥品管理現況與規劃 (6月15日，session #124, track 04): **Regulatory Convergence Challenge For Nanomedicines**
3. 黃琴嘵科長發表我國實施PIC/S GMP與GDP的管理經驗 (6月18日，sesson#363，track 12): **Risk-Based Inspections and Compliance GMP/GDP Management System for Medicinal Products in Taiwan**

Regulation of Combination Products in the 21st Century

Li-Ling Liu
Director, Division of Medicinal Products, Food and Drug Administration, Ministry of Health and Welfare, Taiwan

Disclaimer

- The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. ("DIA"), its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates, or any organization with which the presenter is employed or affiliated.
-

Outline

- The two industries and regulatory oversight models in AP region
- The goal and progress of APEC regulatory convergence efforts
- Challenges for regulators when addressing CP regulatory issues
- Opportunities for regulatory confluence when regulating Combination Products (CPs) as devices or pharmaceuticals

The Growth Outlook for the Global Combination Products Market

- Global market
  - 2012: USD 66.0 billion
  - 2013 to 2019: grow at a CAGR of 7.9%
  - 2019: to reach USD 115.1 billion
- From the regional perspective, the market is dominated by North America in revenue terms. However, the most lucrative market is the Asia Pacific.

http://www.transparencymarketresearch.com/press release/drug-device-combination.htm

Examples of Combination Products

- Drug eluting stents
- Infusion pumps
- Bone graft implants
- Photodynamic therapy
- Wound care combination products
- Inhalers
- Transdermal patches, and
- Others (e.g. drug eluting beads)

Combination Products and the Two Industries

- The innovation in combination products has enhanced therapeutic benefit of medical products, but posed regulatory challenges.
- The pharmaceutical and medical device industries differ in culture, development process, and regulatory expertise. Bridging the two industries and promoting global regulatory convergence are crucial in this area.

Needs for Regulation of Combination Products

There is a need to

- establish a coordinated regulatory approach between the drug and device regulators for combination products, and
- promote greater convergence among APEC members' regulatory system for combination products.

Regulatory Convergence

- "Regulatory convergence" represents process whereby regulatory requirements across economies become more aligned over time as a result of the adoption of internationally recognized technical guidances, standards and best practices
- Does not require the harmonization of laws and regulations
- Broader concept than "harmonization"

The goal and progress of APEC regulatory convergence efforts (1)

- Combination product has been one of the priority work areas under the Regulatory Harmonization Steering Committee (RHSC) of APEC Life Science Innovation Forum (LSIF).
- Initial focus: Combination products regulated as medical devices or approved under the pathway for medical devices.

The goal and progress of APEC regulatory convergence efforts (2)

- Purpose: to share challenges and best practices in regulating combination products and identify opportunities for regulatory convergence
- Goals: to promote understanding of risk-based approaches for regulating combination products and provide tools to facilitate their regulatory convergence among APEC member economies

The goal and progress of APEC regulatory convergence efforts (3)

- Progress
  - 2012: (1) The priority work area was endorsed by RHSC; (2) Chinese Taipei hosted 2012 APEC-AHC-AHWP Joint Workshop on Medical Device Combination Workshop.
  - 2012-2013: A gap analysis survey was conducted among APEC member economies.
  - 2014: Chinese Taipei hosted 2014 International Forum on Medical Device Combination Products.

2012 APEC-AHC-AHWP Joint Workshop on Medical Device Combination Products

Date: November 4, 2012 (Taipei, Taiwan)

Agenda:

- Keynote: Updates on APEC
- Current Regulatory Perspectives and Challenges of APEC Economies
- Case Studies of Combination Products Regulated as Medical Devices
- Future direction: Potential Path Toward Convergence
- Summary and Outcome of Workshop

http://www.fda.gov.tw/EN/site.aspx?sid=3307

Gap Analysis Survey Conducted in 2012-2013

- Types of information requested:
  (1) implementation of regulation; (2) definition;
  (3) rule of classification; (4) pre-market review
  (5) post-approval modifications; (6) labeling;
  (7) GMP; (8) adverse events reporting;
  (9) major challenges
- 9 out of 21 economies responded to this survey, including Canada, Chile, China, Chinese Taipei, Japan, Mexico, Papua New Guinea, Singapore, and USA.

Observation from the Workshops and the Survey (1)

- Some APEC member economies have legal definition on combination products, whereas others don't. There is no consensus in definition of combination products.
- Most economies classify and regulate CPs under their existing regulatory framework for drugs, medical devices, and biologicals.

	USA	Other APEC member economies
Legal definition	21 CFR 3.2(e) • Single entity, co-packaged, or cross-labeled CPs	With or without legal definition • Single entity CPs • Single entity or co-packaged CPs
Regulations	21 CFR 3 and 21 CFR 4 Guidance documents	Guidance documents
Classification	Combination products	Drugs or Medical devices (or biologicals)

Observation from the Workshop and the Survey (2)

- Most APEC member economies classify CPs and assign the agency lead based on the primary mode of action (PMOA) of the CPs.
- CP regulations are evolving and remain undefined in many cases. Most APEC member economies look to US and EU models and trends in setting their requirements.

	USA	Other APEC member economies
Assignment of primary jurisdiction	Based on primary mode of action (PMOA)	
Regulatory requirements	In accordance with the requirements applicable to their constituent parts	
Pre-market review route	Depends on the nature of the combination product; Non-primary agency components involve in review procedures	

Observation from the Workshop and the Survey (3)

- **Pre-market review**
  - USA and some other economies have published some product-specific guidance documents (e.g. *drug-eluting stents, imaging devices and drugs, glass syringes for delivering drugs, injectors intended for use with drugs*) addressing the technical considerations for premarket submission.

Observation from the Workshop and the Survey (4)

- **GMP**
  - US FDA issued the final rule on CGMP requirements for combination products (final rule as codified in 21 CFR part 4) in 2013 and published a draft guidance for industry and FDA staff in 2015.
  - Other APEC economies require compliance with drug GMP or medical device GMP depending on the classification of the CPs.

17

Observation from the Workshop and the Survey (5)

- **Post-approval modifications**
  - US FDA published a drat guidance in 2013.
- **Adverse events reporting**
  - US FDA issued a concept paper for comment on the FDA website for Combination Products.
- **Labeling**
  - There is no published guidance for labeling.

18

Challenges for regulators when addressing CP regulatory issues (1)

- **Consistent product classification**
- **No formal regulatory requirement:**
  - Disagreements can arise on the level of evidence required to demonstrate that a CP is safe and effective.
  - Incomplete submissions and inappropriate classification can further delay the review timeline.

19

Challenges for regulators when addressing CP regulatory issues (2)

- Without a formal framework for evaluating CPs, it can be difficult to
  - ensure efficient evaluation and at times to identify and coordinate the regulatory roles and responsibilities amongst different agency components.
  - manage coordination between regulated entity to enable post-market development and ensure efficient post-market regulation.

20

Opportunities for regulatory confluence when regulating CPs as devices or as pharmaceuticals

- *The term 'confluence' relates to streamlining and alignment of regulatory requirements for combination products at the interface between device and pharmaceutical industries.*
- Opportunities for regulatory confluence:

Regulated areas	opportunities
CGMP	• A streamlined approach for manufactures to demonstrate compliance with the drug CGMPs and the quality system regulation
Clinical trials Marketing applications Postapproval modifications Adverse event reporting	• May have opportunities for regulatory confluence, but need guidance documents to address the considerations and requirements

21

Good Registration Management

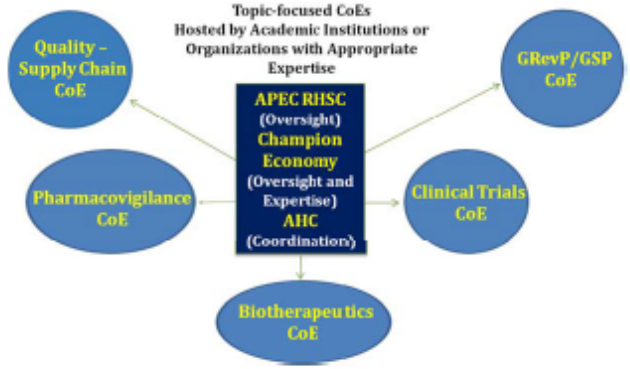
22

Contents of Good Review Practices Guidelines for Regulatory Authorities

1. INTRODUCTION
   - 1.1 Document Objective
   - 1.2 Context
   - 1.3 Definition
   - 1.4 Scope
2. PRINCIPLES OF A GOOD REVIEW
3. MANAGING THE REVIEW
   - 3.1 Project Management
   - 3.2 Quality Management
   - 3.3 Standard operating procedures
   - 3.4 Review process stages
4. COMMUNICATIONS
   - 4.1 Intra-agency
   - 4.2 Inter-agency
   - 4.3 With applicants
   - 4.4 With external experts
   - 4.5 With the public
5. REVIEW PERSONNEL
   - 5.1 Reviewer expertise, competency and training
   - 5.2 Critical thinking
6. CONDUCTING THE REVIEW
   - 6.1 Key elements in defining a review strategy
   - 6.2 Applying review strategy
7. GLOSSARY
8. REFERENCES

23

The Operating Model for APEC Training Centers of Excellence for Regulatory Sciences



24

附錄五-1

Recommendations

- Joint EWG of ICH-IMDRF→ develop guidelines.
- Incorporating combination product topic into CoEs, APEC RHSC→ promotion and training for member economies.
- Legislative changes or policies for health authorities.

DIA DEVELOP INNOVATE ADVANCE

Thank You

Li-Ling Liu

Director, Division of Medicinal Products, Food and Drug Administration, Ministry of Health and Welfare, Taiwan

LLL@fda.gov.tw

DIA DEVELOP INNOVATE ADVANCE

DIA 2015 51ST Annual Meeting
JUNE 14–18 | WASHINGTON, DC

Regulatory Convergence Challenge For Nanomedicines

--Next Generation Nanomedicines and Nanosimilars: Regulators' Perspective

Jo-Feng Chi
Senior technical specialist
Division of Medicinal Products, Taiwan FDA

June 15, 2015

FDA
衛生福利部食品藥物管理署
Food and Drug Administration
Ministry of Health and Welfare
http://www.fda.gov.tw/

Disclaimer

- The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. ("DIA"), its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates, or any organization with which the presenter is employed or affiliated.
-

Outline

- Nanotechnology and life
- National Program on Nano Technology (NPNT) in Taiwan
- TFDA's mission
- Regulatory and approval status of nanomedicine in Taiwan
- Challenges
- Suggestion

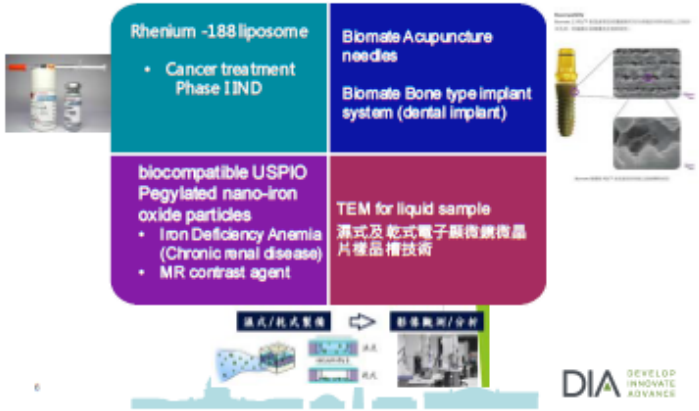
Nanotechnology and life

- The applications of nanotechnology

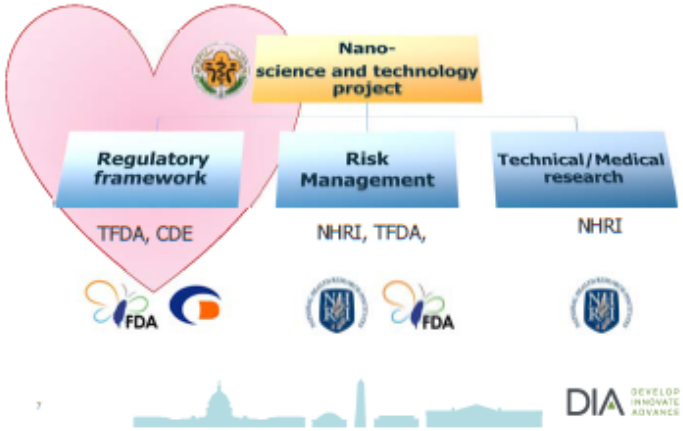
National Program on Nano Technology (NPNT) in Taiwan stage II: 2009-2014

National Program on Nano Technology (NPNT) in Taiwan stage II: 2009-2014

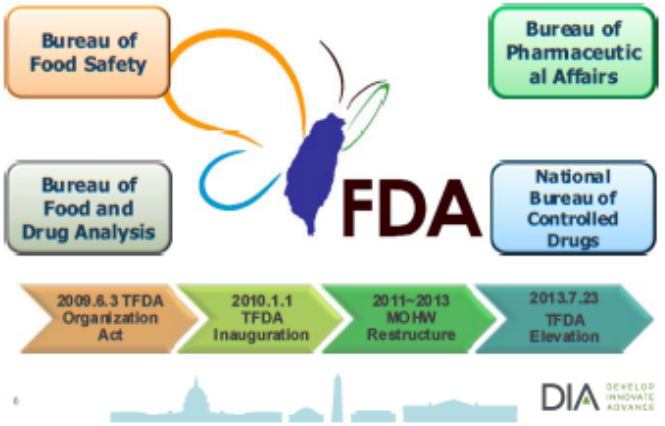
Achievement in Biomedicine development



MOHW in NPNT



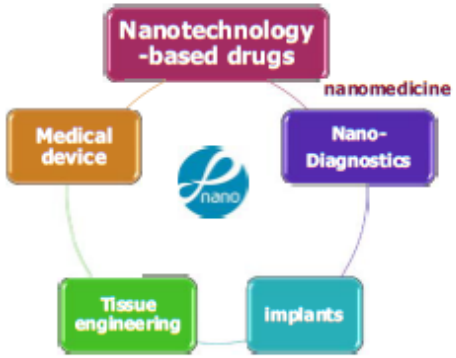
The TFDA organization



TFDA's mission

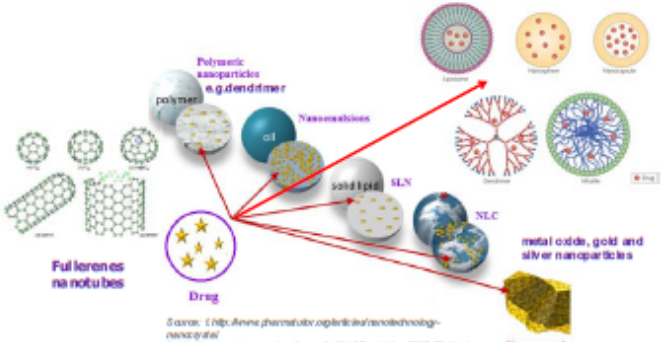
- **Protect the Public**
  - Pre-marketing review is Scientific evidence based and Good Review Practice (GRevP) followed
  - GCP inspection、PIC/S GMP standard
  - post-marketing surveillance
- **Promote the Science and Innovation**
  - Patients' need centered
  - Good Review Practice (GRevP) followed: streamlining, transparency, communication, internationally regulatory convergence

Nano medical products

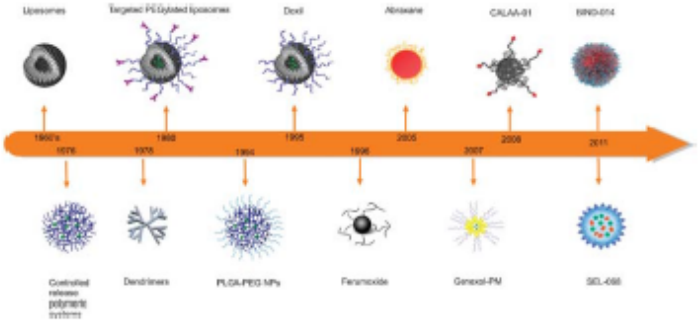


Nanomedicine

- The application of nanotechnology in the area of healthcare and disease diagnosis and treatment

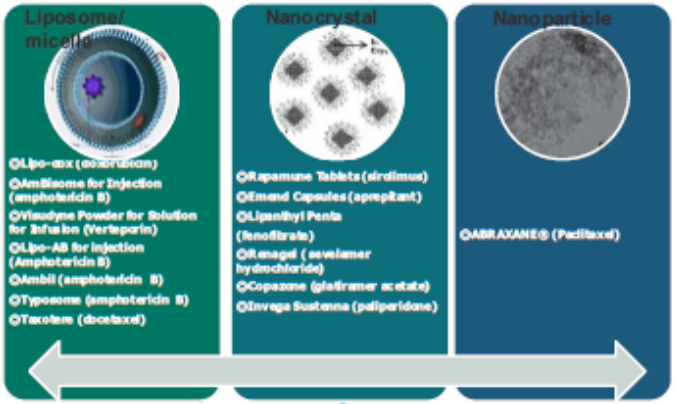


Time Line of Clinical Stage Nanomedicine



Source: Chem Soc Rev. 2012 Apr 7;41(7):2971-3010

Examples of approved nanomedicine in Taiwan



13

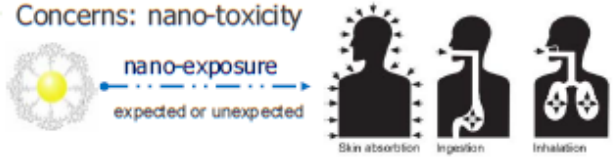
Nanomedicine

- Advantages:
  - Novel drug delivery system:
    - enhances solubility, stability, permeability, targeting, absorption, bioavailability,
    - Controlled release, drug exposure at action sites
  - Novel targeted therapies:
    - alters biodistribution, bioavailibility, etc
    - Controlled site release
  - Reduction in dose, toxicity, side effect and medical cost.

14

Nanotechnology-based drugs

- Concerns: nano-toxicity



- Nanotechnology might alter the physicochemical characteristics
  - Cell toxicity
  - Undesired tissue distribution
  - hypersensitivity reaction, oxidative stress,

15

Review Considerations in Taiwan

- Working definition of nanomedicine:
  - Nano-size: at least one dimension in the nanoscale range (1~100nm)
  - Nano-properties: physical or chemical properties or biological effects attributes to its dimensions, even outside the nanoscale range (up to 1 um)
- International reference guidances adapted-ICH, FDA
- Distinct features require evaluation practice on case-by-case base.
  - Thermodynamic properties, such as phase transition temperature of the lipid bilayer, are more critical for liposomes, but less for iron colloids.
- Drugs are evaluated for safety, efficacy and quality , not only its nanoscale parameter
- Risk-based assessment
  - Active ingredient, nanocrystal
  - Excipient, such as liposomal carrier

16

Review Considerations in Taiwan

Quality - CMC

- Size does matter
- Drug performance is dependent on its design and quality
  - Particle size distribution: agglomeration, aggregation
  - Chemical composition
  - shape
  - Surface characteristics: surface charge, surface area, surface chemistry
  - Other physicochemical properties: solubility/dispersability
- Manufacturing and process control
- Adequacy and justification of analytical methods
- Sterility challenge
- Stability: agglomeration, aggregation

Review Considerations in Taiwan

In vitro studies to support product quality-IVIVC

- In vitro stability: detection of premature release and dose dumping
- protein binding

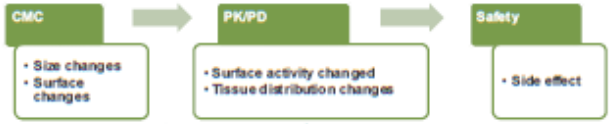
Safety and Efficacy-PK/ PD

- Absorption, Distribution, Metabolism, and Excretion
  - Mass balance study (radio-labeled), organ distribution
- Dose-proportionality study
- Drug-drug interaction, food effect, special population
- BA/BE

Review Considerations in Taiwan

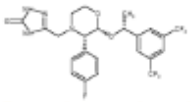
Safety and Efficacy-Pharm/Tox

- Unexpected toxicity to tissues, special concerns of immunotoxicity, reproduction toxicity, genotoxicity, and carcinogenic potential
  - –Complement activation
- Integrated approach is needed
- Test methods needs to be justified. Profile is different, however, methods of testing is similar.



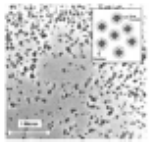
Review considerations-Example 1

- **Function/ benefit:**
  Solubility/bioavailability
  Example: Emend (aprepitant)



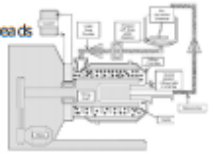
Drug substance: low solubility

Wet milling (micronized)



Decreased particle size · enhanced bioavailability

- **Review considerations:**
  - Particle size distribution
  - dissolution
  - Manufacturing process:
    - Production of a slurry of water, hydroxypropyl cellulose, and aprepitant
    - Pre-milling
    - Addition of aqueous sodium lauryl sulphate、sucrose dispersion
    - Media-milling to form a colloidal dispersion
    - spray-coating on beads
    - Selving
    - Encapsulation



EMA EPAR

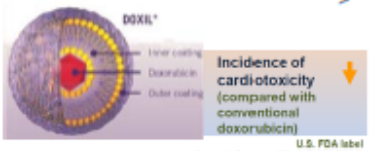
Eur. J. Pharm. Sci. 18, 113-120 (2003)

Review considerations-Example 2

- **Function/benefit:**

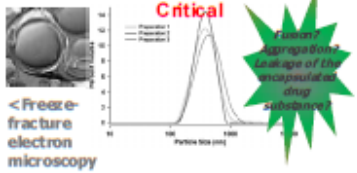
Reducing unacceptable toxicity
Example:lipo-dox (doxorubicin Hcl)
Long circulating, passive targeting to tumors

Encapsulated in liposome



U.S. FDA label
J. Control. Release 160, 117-134 (2012)
Ann. Oncol. 18, 1159-1164 (2007)

- **Review considerations:**



<Freeze-fracture electron microscopy>

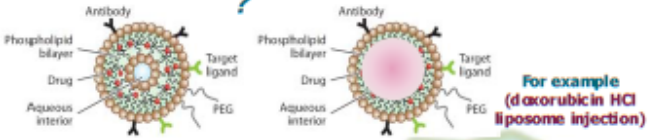
- ✓ Physicochemical parameters
- ✓ Assay for encapsulated and unencapsulated (i.e., free) drug substance
- ✓ Degradation products related to the lipids
- ✓ Assay of lipid components
- ✓ *In vitro* test for release of drug substance from the liposome

Nat. Protoc. 2, 547-576 (2007)
U.S. FDA: Guidance for Industry-Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (DOC)

21

Review considerations-Example 3 generic drug products/nanosimilars

Reference drug product ? Generic drug product



For example (doxorubicin HCl liposome injection)

Pharmaceutical comparability
Bioequivalence

Other studies?

Same drug product composition?
Manufactured by an active liposome loading process with an ammonium sulfate gradient?
Equivalent liposome characteristics?

U.S. FDA: Draft Guidance on Doxorubicin Hydrochloride (2013)
EMA: Reflection Paper on the Data Requirements for Intravenous Liposomal Products Developed with Reference to an Innovator Liposomal Product (2013)
Annu. Rev. Pharmacol. Toxicol. 54, 583-598 (2014)

22

Regulatory status in Taiwan

- Pharmaceutical Affairs Law
- Registration Guidance
- Registration Guidance Appendix :Technical document requirement for liposomal products
  - appendix 3: new drugs
  - appendix 5: generic products

23

Technical document requirement for liposomal products -Registration Guidance Appendix 3 New Drugs

	Design and development	Physico-Chemical	Safety								Pharmacology		ADME	Clinical study			
			acute	clonic	embryonic	dependency	immunogenicity	mutagenicity	carcinogenicity	Local reaction	有效性證明	一般藥理		BA	BE	others	literature
New molecular entity																	
Liposome	○	○	○	○	○	△	△	△	△	△	○	○	○	○	△	○	△
New administration route																	
Liposome	○	×	○	○	○	×	△	×	×	△	○	△	○	○	×	○	△
new indication																	
Liposome	○	×	×	×	×	×	×	×	×	×	○	△	△	△	×	○	△
new combination																	
Liposome	○	×	○	○	×	×	×	×	×	△	○	○	○	○	×	○	△
New dosage form																	
Liposome	○	×	○	○	○	×	△	×	×	△	○	×	○	◎	◎	◎	△
New administration doses																	
Liposome	○	×	△	△	×	×	×	×	×	△	○	×	○	○	×	○	△
New unit strength																	
Liposome	○	×	△	△	×	×	×	×	×	△	×	×	×	◎	◎	◎	×

24

Technical document requirement for liposomal products -Registration Guidance Appendix 5 Generic Drugs

	Design development	Physico-Chemical	Safety								Pharmacology	ADME	Clinical study			
			Acute tox	Chronictox	Embryogenic	dependency	immunogenicity	mutagenicity	carcinogenicity	Local reaction			BA	BE	others	literature
Generic																
Liposome																
Generic 1	×	×	△	△	×	×	×	×	×	△	×	△	◎	◎	◎	×
Generic 2	×	×	×	×	×	×	×	×	×	×	×	×	◎	◎	◎	×

○required
×not required
△case by case
◎either or : (1)Bioequivalence (BE) · (2)Bioavailability and clinical study (BA+CS)
Generic 1 : same API · different excipient or ratio
Generic 2 : same API and excipient (including component ratio)

25

Future plans for nanomedicine Regulations

- **Updating regulations in liposomal products:**
  - CMC guidance for liposomal products
  - Checking list for nanomedicine (adapted from US FDA Reporting format)
  - Guidance for Generic liposomal product
  - Revision of appendix 3 and 5

26

CMC guidance of liposomal products

(excluding adjuvant in vaccine or biological API or atypical lipid conjugates)

- Description and composition
  - Lipid, API, and other excipients
- Physicochemical properties
  - Structure description, particle size distribution, aggregate/agglomeration, surface charge, surface modification, internal compartment (volume, pH…), lipid bilayer transition, loading capadty, leakage, spectoscopic data, osmolality, light scattering
- Manufacturing process and process controls
  - Quality by design
  - Pharamaceutical Comparability
  - Validation, especially for sterility
- Control of excipients: lipid compo… NEW
  - As much required as API
  - Characteristics: lipid composition and ratio
  - Production (synthetic or natural): source, site, method
  - Specification
  - Stability
- Control of drug product
  - Physicochemical characteristics/specification
  - Stability
  - In vitro release

27

Checking list for nanomedicine

Form A – Chemistry, manufacturing, and controls (CMC) review checklist for nanotechnology*-related pharmaceuticals

1a) What nanomaterial is included in the product?
☐ Liposome* ☐ Micelle* ☐ Nanocrystal* ☐ Metal colloid*
☐ Polymer-drug conjugate ☐ Solid nanoparticle* ☐ Dendrimer*
☐ Other _____

1b) What is the source, manufacturing process and compositions of the nanomaterial? _____

2) Is the nanomaterial a reformulation of a previously approved product?
Yes _____ No _____

3) What is the nanomaterial functionality?
Carrier _____; Excipient _____; Packaging _____;
API _____; Other _____

4) Is the nanomaterial soluble (eg, nanocrystal) or insoluble (eg, gold nanoparticle) in an aqueous environment?
Soluble _____; Insoluble _____

5) Was particle size or size range of the nanomaterial included in the application?
Yes _____ (Complete 6); No _____ (Go to 7)

6) What is the reported particle size?
Mean particle size _____; Size distribution _____; Other _____

7) Please indicate the reason(s) why the particle size or size range was not provided:
_____
_____

8) Check all methods used to characterize the nanomaterial in Form B.

Checking list for nanomedicine

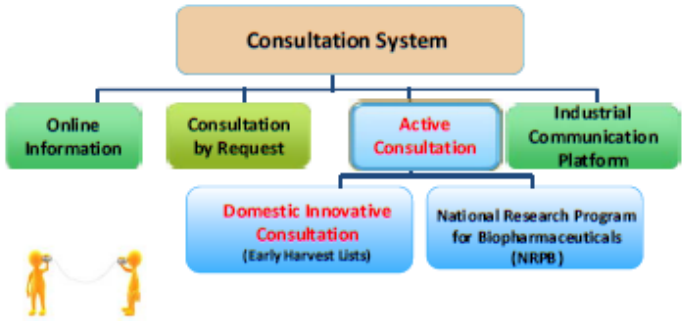
Form B – Methods used to characterize the nanomaterial[1]

Properties	Common techniques[2]
Chemical	
Chemical composition (core, surface)	☐ XPS ☐ MS ☐ AAS ☐ ICP-MS ☐ RS ☐ FTIR ☐ NMR ☐ Other _____ ☐ Not determined (please justify) _____
Purity	☐ ICP-MS ☐ AAS ☐ AUC ☐ HPLC ☐ DSC ☐ Other _____ ☐ Not determined (please justify) _____
Stability	☐ MS ☐ HPLC ☐ RS ☐ FTIR ☐ Other _____ ☐ Not determined (please justify)
Solubility	Please list the methods ☐ Not determined (please justify) _____
Structure	☐ NMR ☐ XRD ☐ Other ☐ Not determined (please justify) _____
Crystallinity	☐ XRD ☐ DSC ☐ Other _____ ☐ Not determined (please justify) _____
Catalytic activity	Please list the methods ☐ Not determined (please justify) _____

Checking list for nanomedicine

Morphology	
Size (primary particle)	☐ TEM ☐ SEM ☐ AFM ☐ XRD ☐ Other _____ ☐ Not determined (please justify) _____
Size (primary/aggregate/agglomerate)[3]	☐ TEM ☐ SEM ☐ AFM ☐ DLS ☐ FFF ☐ AUC ☐ CHDF ☐ XDC ☐ HPLC ☐ DMA (-) ☐ Other _____ ☐ Not determined (please justify) _____
Size distribution	☐ TEM ☐ SEM ☐ AFM ☐ DLS ☐ AUC ☐ FFF ☐ HPLC ☐ SMA ☐ Other _____ ☐ Not determined (please justify) _____
Molecular weight	☐ SLS ☐ AUC ☐ GPC ☐ Other _____ ☐ Not determined (please justify) _____
Structure/Shape	☐ TEM ☐ SEM ☐ AFM ☐ NMR ☐ Other _____ ☐ Not determined (please justify) _____
Stability (3D structure)	☐ DLS ☐ AUC ☐ FFF ☐ SEM ☐ TEM ☐ Other _____ ☐ Not determined (please justify) _____
Surface	
Surface area	☐ BET ☐ Other _____ ☐ Not determined (please justify) _____
Surface charge	☐ SPM ☐ GE ☐ Titration methods ☐ Other _____ ☐ Not determined (please justify) _____
Zeta potential	☐ LDE ☐ ESA ☐ PALS ☐ Other _____ ☐ Not determined (please justify) _____
Surface modification	☐ SPM ☐ XPS ☐ MS ☐ RS ☐ FTIR ☐ NMR ☐ Other ☐ Not determined (please justify)
Surface coating coverage	☐ AFM ☐ AUC ☐ TGA ☐ Other _____ ☐ Not determined (please justify) _____
Surface reactivity	Please list the methods ☐ Not determined (please justify) _____
Surface-core interaction	☐ SPM ☐ RS ☐ ITC ☐ AUC ☐ GE ☐ Other _____ ☐ Not determined (please justify) _____

Facilitate innovative medicine industry -Regulatory Consultation System



Conclusion

- TFDA review nanomedicine on **case-by-case** base
- The consideration in review of nanomedicine includes data of **quality, safety and efficacy**, not only its nanoscale parameter.
- **Current review approach is capable** of managing the potential risks associated with nanomaterials in drug products.
- TFDA is considering **including liposomal specification in the excipient** regulation for liposomal products.
- TFDA will adapt reporting formats of US FDA in nanomedicine review.
- TFDA is considering revising the regulation for nanosimilars (generic nanomedicine) products.
- TFDA will keep close interaction with the industry to facilitate nanomedicine development

Challenges

- Analytical methods and equipment/facilities are to be developed
- Safety/toxicity profile and Risk analysis methods for nanomaterials are to be generated
  - Different nanomaterials have distinct characteristics
  - Impact to the environment and health requires close monitoring
  - One rule/guidance for all is difficult

Suggestions

- Understanding the critical quality contributes, the interactions and the relations to drug performance
- Identifying and developing the appropriated and adequate analytical methods
- Close communication between the industry and the regulatory agents
- Regulation harmonization
  - Guidances for different, specific nanomedicines are suggested –IPRF WG
- Collaboration
  - Standard and norm creation –IPRF WG
  - information sharing, such as safety alert, authorized analytical facilities, activities

Thank you

Jo-Feng Chi
Senior technical specialist
pajfchi@fda.fov.tw