出國報告（出國類別：會議）

第54屆藥物資訊年會(DIA)及TFDA藥政專題論壇

服務機關：衛生福利部食品藥物管理署
姓名職稱：吳秀梅署長、張連成科長
派赴國家/地區：美國/波士頓
出國期間：107年6月23-30日
報告日期：107年9月

摘要

第 54 屆「藥物資訊協會」年會(54th Drug Information Association Annual Meeting)於 107 年 6 月 24 至 28 日在美國波士頓舉行，全球產、官、學界近萬人出席。台灣由衛生福利部食品藥物管理署吳秀梅署長率代表團約 40 人參與此一盛會。除設置主題攤位，介紹「臨床試驗資訊平台」（TaiwanClinicalTrials.TW），具體呈現台灣臨床試驗充沛研發能量與國際競爭力外，另於 6 月 25 日首次舉辦「TFDA Town Hall」主題論壇，向國際宣傳我國優良藥政管理制度，並於 6 月 27 日舉辦“台灣之夜“晚會，DIA 現任理事 Angelika Joos、Alberto Grignolo、我國波士頓台北經濟文化代表處徐佑典處長及美、德、日、韓、加拿大等國專家學者出席交流，透過交換新藥研發優質法規環境及藥政管理經驗，各國代表及國際藥廠均肯定我國政府精進藥品管理、推動醫藥法規環境與國際接軌之成效。

關鍵字: 「藥物資訊協會」 (Drug Information Association, DIA)、衛生福利部食品藥物管理署（Taiwan Food and Drug Administration, TFDA）

目次

壹、 目的

藥物資訊協會(Drug Information Association，簡稱 DIA)為一世界性組織，由政府藥物法規機關、學術單位、生技醫藥研發公司、製藥公司、受託研究(CRO)公司等會員組成。該協會每年辦理全球藥物研發與法規執行之最大會議，不僅提供專業的藥物研發新知，參加會員也能藉此交流藥物研發經驗與藥政管理趨勢。

本年度為第 54 屆藥物資訊協會年會， 6 月 24~28 日於美國波士頓舉行，參與者超過 8000 人，會場同時有 470 個展覽攤位 ，研討主題分類計 22 項(2 2 tracks)，再區分議題超過 200 項，各議題分別由 2-3 位各界代表發演講超過 800 場次演講，重要藥政主管機關如：美國 FDA、歐盟 EMA、日本勞働厚生省 MHLW 與 PMDA、加拿大 Health Canada 皆派資深官員出席。

我國於藥政管理成果及創新議題投稿獲 DIA 大會肯定，邀請本署於大會期間舉辦「TFDA Town Hall」主題論壇，由吳秀梅署長擔任主持人，與各國分享台灣推動國際化醫藥品法規管理體系之成果，台大醫院腫瘤醫學部楊志新主任說明「多國多中心藥品臨床試驗與資料解釋之挑戰」；財團法人醫藥品查驗中心高純琇執行長分享我國「應用真實世界證據於法規決策經驗」；行政院科技會報辦公室劉祖惠主任介紹「台灣藥品產業之開發優質環境與政策」。會議期間我國亦有壁報論文發表，包括說明新藥開發新穎性臨床試驗設計、細胞治療諮詢輔導措施及台灣轉移性黑色素瘤治療之成本效益。

貳、 過程

一、行程:

日期	具體任務	說明
107.6.23	啟程往美國波士頓	高雄小港機場出發，經香港轉機至波士頓
107.6.24	參加 DIA short course	#20: Real World Evidence Studies #34: Japan Regulatory Environment: Overview of the Organization
107.6.25	舉辦 TFDA Town Hall 並參加 DIA 各項課程及研討會，參觀大會展覽	
107.6.26		
107.6.27		
107.6.28		
107.6.29-30	返程	由波士頓轉香港，抵達台灣

二、會議情況

(一) DIA short course

1. Real World Evidence Studies

   US FDA局長Scott Gottlieb博士,於2017年提出對未來各國藥品主管部門的期許，為節省研發成本、爭取時效，各國應審視現實世界證據對醫療產品開發的影響，掌握現實世界證據推展公共衛生機會,尤其 RWE 的廣泛使用可以使醫療產品開發過程更加有效率，並有助於降低開發成本。更重要的是，它可以幫助確保醫師和病人更好地了解新產品的臨床應用，以做出更有效、最適合病人的醫療選擇，也可幫助更安全，更有效技術或產品應用於臨床治療。藥品主管部門需要縮小用於製定決策所需資訊，與醫療界、醫療保險付款人以及醫療保健決策的其他人員間的訊息差距。

   本課程由 US FDA CDER OND 心血管和腎臟產品部主任 Norman Stockbridge、美國 IQVIA Sci 事務全球主管 Nancy Dreyer、ICON 藥物開發服務副總裁兼 TA 主任 Mary Jane Geiger 及北卡羅來納大學吉林斯全球公共衛生學院流行病學系教授 Alan Brookhart 擔任講座，探討真實世界證據（Real World Evidence，RWE）如何補充和擴展從隨機對照試驗(RCT；Randomized Controlled Trial)獲得的藥物的安全性和有效性知識，描述解釋 RWE 研究品質和有效性的關鍵流行病學設計，主要以心血管安全性研究的案例，評估 RWE 用於討論關鍵研究設計原則，通過評估和討

論應用安全評估的演練，認識主管部門何時可基於 RWE 的方法，引用具有足夠的品質來實現決策。

課程中提出 RWE 數據以可用於產品上市核准的幾個案例，說明如下：

(1) Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia.

急性淋巴細胞白血病（ALL）是一種罕見疾病，年齡標準化率在不同地區從大約 1 到 2/10 萬。成年病人開發的前線治療通常採用兒科方法改編，改善疾病預後，然而，如果復發，結果非常差。Blinatumomab 是一種 BiTE 重組抗體，可將表達 CD3 的 T 細胞重定向至表達 CD19 的白血病細胞，誘導 T 細胞活化，增殖，Blinatumomab 先前獲得 US FDA 批准用於 R 患者/ R ALL 主要基於 189 名成年患者的第 2 期 single-arm study (MT103-211)，有許多潛在的方法可用於評估僅使用 single-arm 或非對照研究的直接證據的新療法之相對益處和風險。因此，US FDA 在審查這些方法的優點和缺點時，對文獻綜述，meta-analysis、大型治療中心的臨床證據進行評估，並從多個機構收集的個體病人數據整理分析結果後，發現在選擇使用外部歷史對照來證明新的治療效果，在現階段無令人滿意的治療方式的情況下，基於初步數據，新治療似乎非常有希望，因此 US FDA 和 EMA 進行了一項「歷史比較」研究，進而批准 blinatumomab single-arm study 結果的方法。這是一個 RWE 數據比較研究，幫助主管機關核准藥品新適應症的經典案例。

(2) US FDA expands access to artificial heart valve to inoperable patients

US FDA 批准通過股動脈插入瓣膜（經股動脈入路），通過腿部或心臟下端（經心尖路徑），可用於需要備用接入點無法操作的患者。為了支持該產品仿單標籤變更，Edwards Lifesciences Corp.提出美國經導管瓣膜治療登記處（TVTR）和歐洲 THV 設備登記處的數據，以及 US FDA 批准的臨床研究數據和醫學期刊。TVTR 數據來自使用替代接入點的病人執行的數千個程序，並且沒有證據表明該設備表現不同，或接入點具有不同的風險與利益。在 THV 進入特定病人市場僅僅兩年後，來自 TVTR 的 RWE 數據被用於支持 US FDA 批准醫療器材新適應症，擴大了患者獲得挽救生命的治療的機會，製造商將繼續使用來自 TVTR 的數據，替代醫療機構研究 THV 程序的短期和長期病人使用結果。

2. Japan Regulatory Environment: Overview of the Organization

本課程由日本行政法人醫藥品醫療機器綜合機構（PMDA）醫學資訊學和流行病學辦公室 Yoshiaki Uyama 主任、PAREXEL Consulting 公司副總裁 Alberto Grignolo 博士主持，討論日本製藥法規和程式的重大變化正在影響日本新藥的開發以及全球發展計畫，討論過程中發現日本厚生勞動省（MHLW）和 PMDA 藥政管理系統的主要驅動因素，包括藥物開發過程中的監管程序（與 PMDA 和臨床試驗通報的

磋商）， 日本藥物開發與東亞和全球藥物開發，孤兒藥物管理、J-NDA 準備和審查的整合，也討論日本醫藥產業發展戰略，以滿足日本對新藥批准的要求，以及選定的批准後要求。

(二) TFDA Town Hall 與「台灣之夜」晚會

此次 TFDA Town Hall，由本署吳秀梅署長主持，與各國分享台灣推動國際化醫藥品法規管理體系之成果，台大醫院腫瘤醫學部楊志新主任說明「多國多中心藥品臨床試驗與資料解釋之挑戰」；財團法人醫藥品查驗中心高純琇執行長分享我國「應用真實世界證據於法規決策經驗」；行政院科技會報辦公室劉祖惠主任介紹「台灣藥品產業之開發優質環境與政策」。會議期間我國亦有壁報論文發表，包括說明新藥開發新穎性臨床試驗設計、細胞治療諮詢輔導措施及台灣轉移性黑色素瘤治療之成本效益。

「台灣之夜」晚會有 DIA 現任理事 Angelika Joos、Alberto Grignolo、我國波士頓台北經濟文化代表處徐佑典處長及美、德、日、韓、加拿大等國專家學者出席交流，透過交換新藥研發優質法規環境及藥政管理經驗，各國代表及國際藥廠均肯定我國政府精進藥品管理、推動醫藥法規環境與國際接軌之成效。

(三)專題演講

1. Regenerative Medicine Advanced Therapies Facilitating Product Development and Approval

本專題由神經科學負責人，Athersys 再生醫學副總裁 Robert W. Mays 博士，講述將早期臨床試驗的經驗應用於 RMAT 指定的 III 期 MASTERS-2 研究，Athersys 公司正著重於 MultiStem 研發，此為一種具專利技術，成人「現有」幹細胞的產品平臺，用於神經，心血管，炎症和免疫疾病領域的多種疾病適應症。MultiStem 開發過程中對於安全性，執行 GLP Toxicology and Clinical Pathology、Genetic Stability and Tumorigenicity Testing、Long Term GLP Histopathology Analysis、Immune Sensitization Analysis 及 Gene Expression, Protein Expression and SNP Array Analysis。在已發表的急性中風臨床前動物實驗結果中，發現在較早時間點接受幹細胞治療的動物在神經保護方面表現出統計學上顯著的改善，較高劑量的靜脈輸注細胞具持續且統計學上顯著的神經系統改善。隨機雙盲第二期臨床試驗結果顯示，受試者具備較佳耐受性與安全性，接受 MultiStem 治療的和安慰劑治療的受試者相比，觀察到較低的死亡率，目前 FDA 與 EMA 皆已核准進行第三期樞紐試驗中，預計收納 300 位缺血性中風受試者。如何能夠“降低”新興再生醫學領域臨床

開發中涉及的一些未知因素，Robert W. Mays 博士歸納出以下幾點，也可稱為「細胞療法的經驗與教訓」，以「降低」新興再生醫學領域臨床開發中的不確定因素：

(1) 簡化和直接進行臨床工作（對醫院臨床工作要深入瞭解）
(2) 考慮配方和劑量參數作為臨床轉譯的一部分
(3) Potency Assay的開發愈早開始愈有利後續研究選擇
(4) 再生醫學產品應注重於治療嚴重或危及生命的疾病，以獲得藥政單位加快審查，凸顯產品的發展潛力
(5) 訂定後期臨床試驗和商業化的時間表

美國 FDA CBER 臨床評估和藥理學/毒理學部，組織和先進治療辦公室主任 Tejashri Purohit-Sheth 醫師，說明 FDA 審查再生醫學產品的經驗，CBER 架構及負責管理的產品列表如圖 1-4 所示。

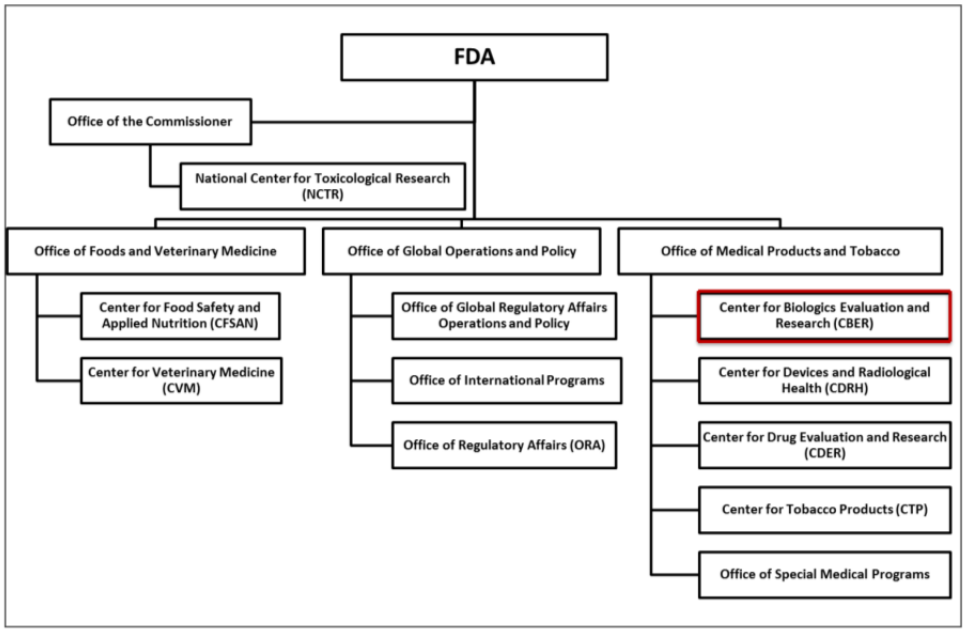


圖 1、FDA Organization 2018

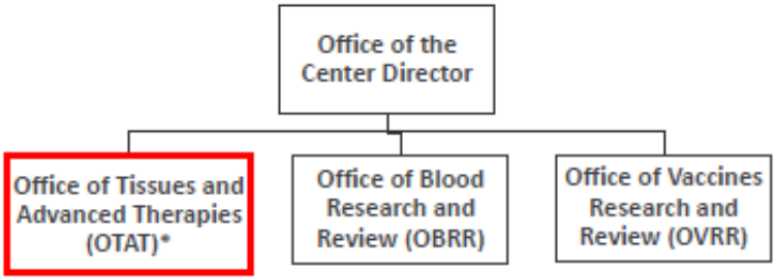


圖 2、Center for Biologics Evaluation and Research (CBER) - Product Review Offices

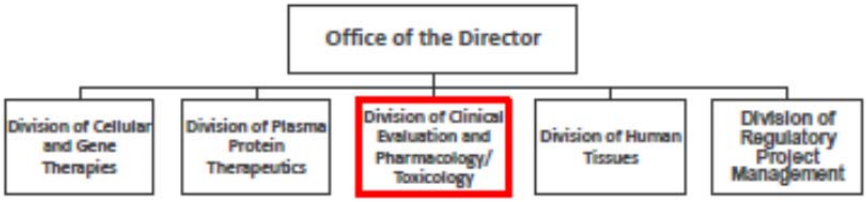


圖 3、Office of Tissues and Advanced Therapies (OTAT)

- **Gene therapies (GT)**
  - Ex vivo genetically modified cells
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
  - Microbial vectors (e.g., Listeria, Salmonella)
- **Stem cells/stem cell-derived**
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Fetal (e.g., neural)
  - Embryonic
  - Induced pluripotent stem cells (iPSCs)
- **Products for xenotransplantation**
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
  - Cellular Immunotherapy
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulins
  - Anti-toxins
  - Snake venom antisera
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

圖 4、Diversity of OTAT-Regulated Products

美國國國會通過的 21 世紀醫療法案(21st Century Cures Act) Section 3033 要求 US FDA 對於 Regenerative Medicines Advanced Therapy(RMAT) 須提出加速審查計畫，可適用之條件包括：再生醫學療法(Regenerative medicine therapy)、治療，改變，逆轉、治愈嚴重或危及生命的疾病，初步臨床證據表明，該藥物有可能解決此類疾病或病症的未滿足的醫療需求。研發機構或藥廠可藉此計畫與 FDA 互相討論，以獲得進行優先審核 (priority review)的資格，加快再生醫學療法的開發和審查。

在歐盟，主要對於 ATMP (Advanced Therapy Medicines Product)的法規主要是 ATMP Regulation (1397/2007)，除規範產品定義、審查程序、品質、療效與安全(GMP、GCP)，以及上市後風險監測計畫(RMP)以外，也成立了 Committee for Advanced Therapies (CAT)，其組成如圖 5 所示。

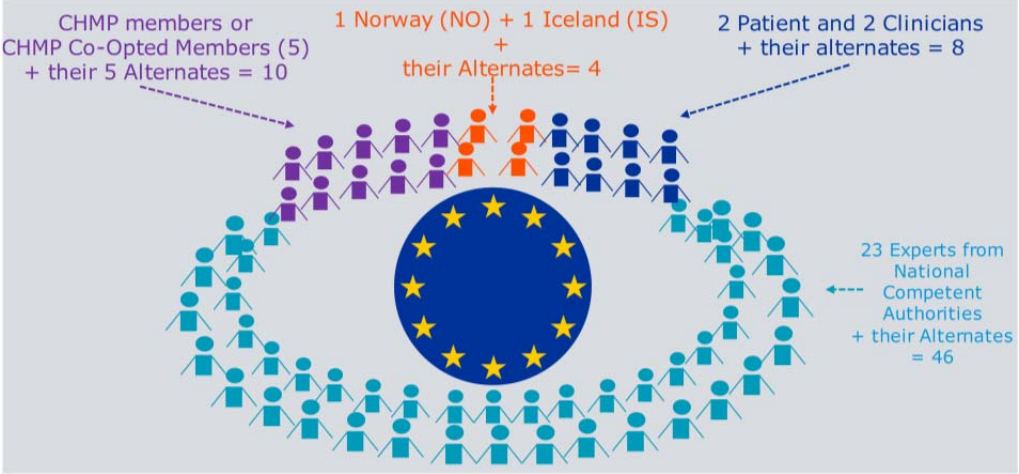


圖 5、Committee for Advanced Therapies

在歐盟法規 Legal base-accelerated assessment (Recital 33 and Article 14(9) of Regulation (EC) No 726/2004)，提供歐盟主管部門支持創新產品的授權，因此 EMA 提出 PRIority Medicines (PRIME) scheme，適用 PRIME scheme 產品的條件有：具有重大公共衛生意義，特別是從治療創新的角度研發的藥品，可能在很大程度上解決未滿足的醫療需求，必須基於非臨床和臨床開發的數據和證據，為解決未滿足的醫療需求提供科學依據。進入 PRIMEscheme 的資格和所需證據如圖 6。PRIMEscheme 的特點有：

(1) 書面確認 PRIME 資格和加速評估的潛力
(2) 在開發期間 CHMP(The Committee for Medicinal Products for Human Use)報告，人員可被早期任命
(3) 可啟動與歐盟網絡的多學科專業會議
(4) 加強關鍵發展里程碑/決策點的科學建議
(5) EMA 會提供專職聯絡人員及關於科學建議要求的中小企業和學者的獎勵措施

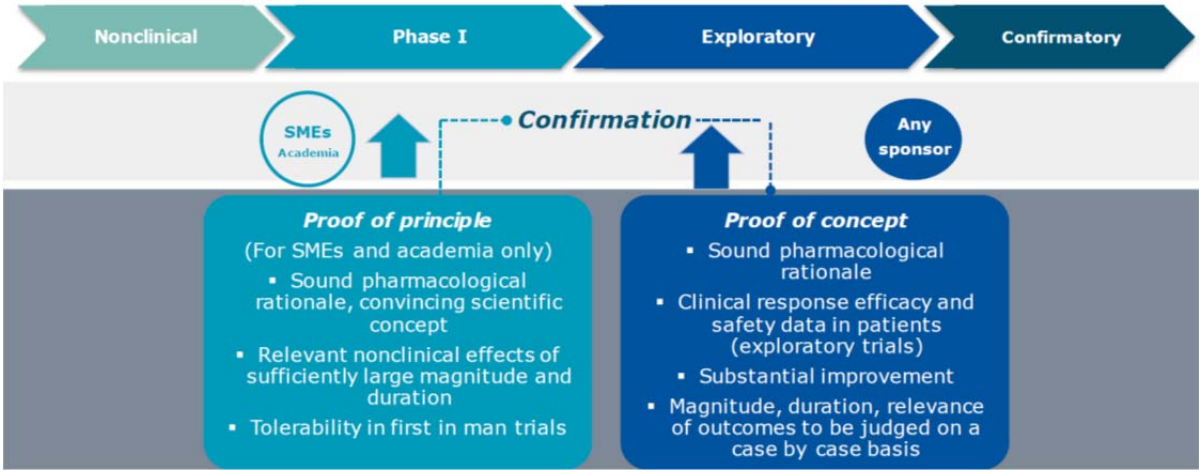


圖 6、Entry points PRIME eligibility and required evidence

EMA 對於基因與細胞治療的基準整理如圖 7。

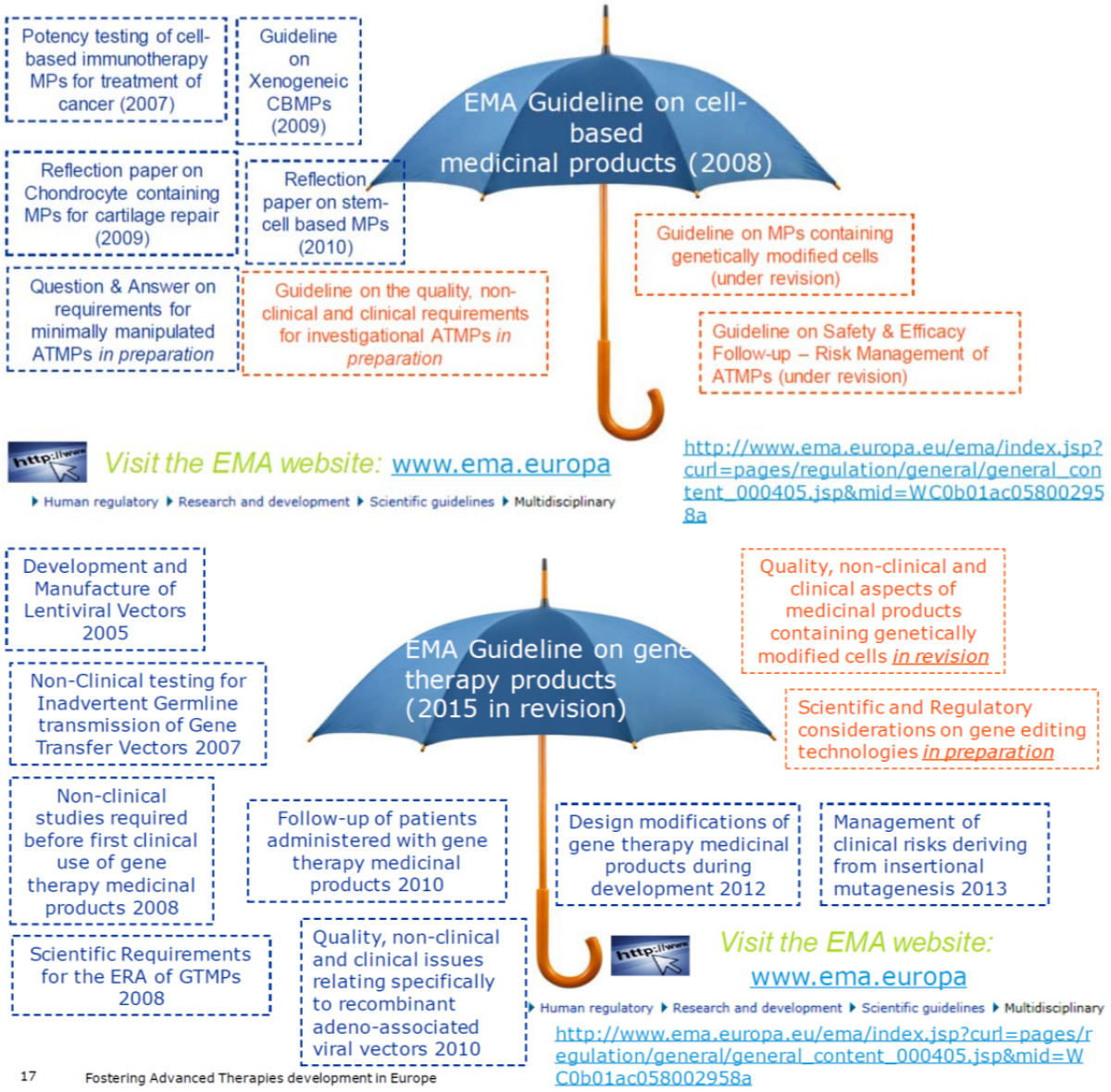


圖 7、Guidelines for gene and cell-based medicinal products

2. Gene Therapy Clinical Trials Current Challenges

基因療法和轉基因生物對臨床試驗的進行，面臨特殊的管理挑戰。有些國家對這些產品有明確的管理架構，隨著對進行全球臨床試驗的日益重視，本次會議邀請 PRA 健康科學臨床科學家 Venkata Jaggumantri 博士、PPD 法規部門首席科學家 Kirsten Messmer 博士、Ultragenyx 基因治療法規事務全球主管副總裁 Janet Rae 博士，分享先進國家審查程式，並以業界觀點陳述管理部門所遭遇之挑戰。

基因治療含有活性物質，由人類使用或給予人類的重組核酸組成，以調節、修復、替換、添加或刪除基因序列。治療、預防或診斷效果直接與其所含的重組核酸序列，或該序列的遺傳表達產物有關，其中也涉及遺傳信息的修改，最終目標是治療或預防疾病。將基因治療中最重要的組成「重組核酸（例如基因）」轉移到人體或細胞中通常需要支援額外的核酸序列（即啟動子），並且需要更高級的生物結構（即病毒或細胞）扮演傳遞的角色。因此，基因治療有幾種產品形式必須要在藥政管理審查過程中被考量：核酸載體本身(Nucleic-acid vectors)、將載體包覆在細胞中的最終產品，例如：轉基因細胞 (CAR-T cells)。在開始基因治療試驗之前的考慮因素有：

(1) 特定場所的倫理和生物安全/環境審查政策與時間表。
(2) 環境風險評估相關規定即須備妥的文件，例如：風險組（RG）分類、生物安全要求（Biosafety Level）或污染防治規定（Containment Level）。
(3) 積極開發研究支持計畫，例如活動流程圖，確定備份資源，備援計畫，參與試驗人員培訓，受試者收納說明文件等。

於美國執行基因治療臨床試驗需經研究構 IRB，以及美國 NIH RAC(Recombinant DNA Advisory Committee)委員會審查，流程如圖 8 所示，試驗需於審查會議前 8 周備齊資料提出申請，IRB 審查會議召開時，試驗主持人需到場簡報，計畫書(含執行機構設施環境要求)必須依據美國 NIH 基準撰擬並備妥相關文件。

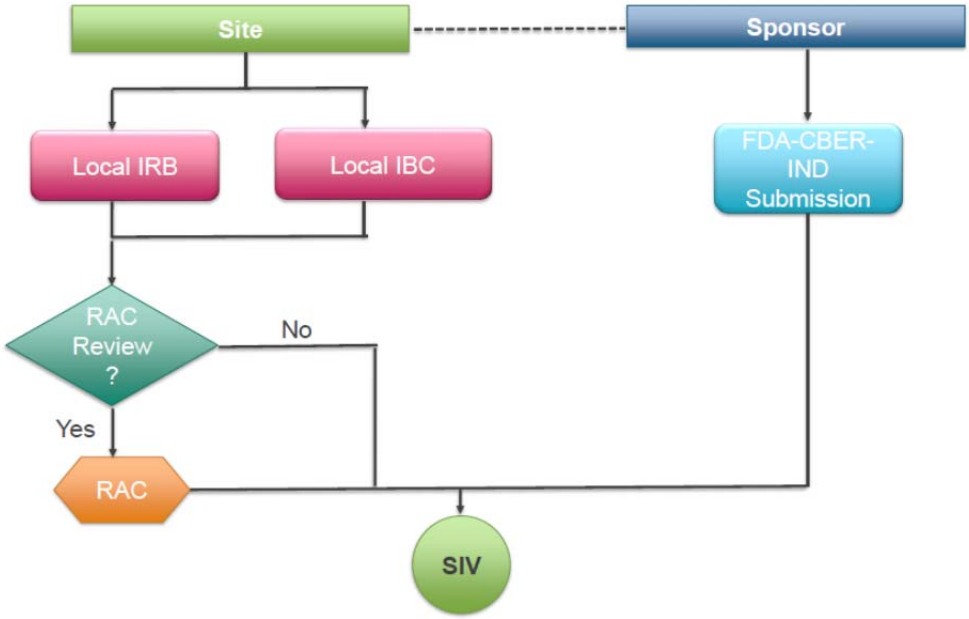


圖 8、Study Start Up – US

英國對於基因治療臨床試驗的審查流程如圖 9，主要的挑戰是英國面臨脫歐議題，因此對基因治療臨床試驗管理造成的可能衝擊有：鼓勵基因治療臨床試驗的資金來源未明確、審查單位與 EMA 的權責與程序正在談判中，審查費用能否減免、送審資料需重複提報給英國與 EMA，未來如雙方審查意見紛歧該如何處理等。在執行層面，也面臨諸多挑戰，例如：受試者招募的試驗機構、受試者團體的因應與合作是否受到影響，跨境受試者要如何登記追蹤，嚴重不良反應的通報等等。

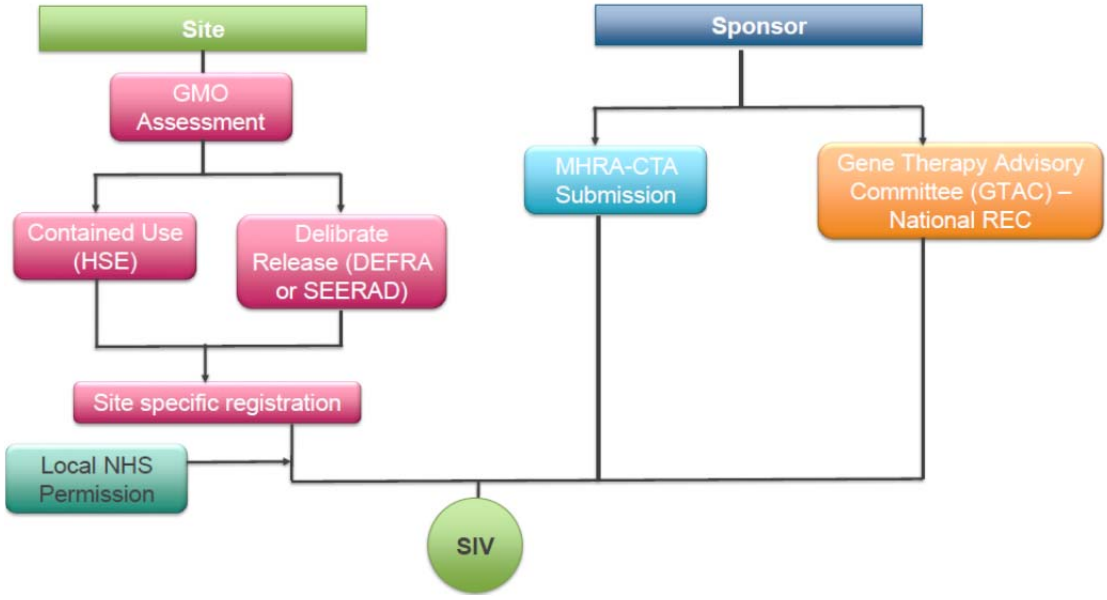


圖 9、Study Start Up – UK

全球核准執行的基因治療臨床試驗情況整理如圖 10。

Product name	Originator	Country (Year) Approved	Indication(s)
Gendicine (recombinant p53 gene)	Shezhen SiBiono Gene Tech	China (2004)	Head and neck cancer
Oncorine (E1B/E3 deficient adenovirus)	Shanghai Sunway Biotech	China (2005)	Head and neck cancer; nasopharyngeal cancer
Rexin-G (mutant cyclin-G1 gene)	Epeius Biotechnologies	Philippines (2006)	Solid tumors
Neovasculgen (vascular endothelial growth factor gene)	Human Stem Cells Institute	Russia (2011)	Peripheral vascular disease; limb ischemia
Glybera (alipogene tiparvovec)*	uniQure	EU (2012) – Withdrawn 2017	Lipoprotein lipase deficiency
Imlygic (talimogene laherparepvec)	Amgen	USA and EU (2015)	Melanoma
Strimvelis (autologous CD34+ enriched cells)	GSK	EU (2016)	Adenosine deaminase deficiency
Zalmoxis (T-cells genetically modified to express herpes simplex I virus thymidine kinase)	MolMed	EU (2016)	Graft-versus-host disease
Invossa (tonogenchoncel-L)	Kolon TissueGene	South Korea (2017)	Osteoarthritis
Kymriah (tisagenlecleucel-t)	Novartis	USA (2017)	Acute lymphocytic leukemia
Yescarta (axicabtagene ciloleucel)	Kite Pharma	USA (2017)	Diffuse large B-cell lymphoma; non-Hodgkin's lymphoma; follicular lymphoma
Luxturna (voretigene neparvovec)	Spark Therapeutics	USA (2017)	Vision loss due to biallelic RPE65-mediated inherited retinal disease

Source: Pharmaprojects® Informa, 2018

圖 10、Gene Therapies Approved Globally

3. Harmonizing Regulatory Science Through the International Council for Harmonisation (ICH)

自 1990 年成立以來，國際醫藥品法規協和會（ICH）將藥品管理部門和醫藥產業聚集在一起討論藥物開發、製造和申請上市的科學和技術基準。2015 年 ICH 完成的一系列加強管理與可持續性的改革，目的為實現進一步的全球醫藥法規與管理措施的協和化，希望節省研發資源、加快藥品研發與審查時效，為病人提供有效、安全與高品質的藥品，本專題演講由 International Generic and Biosimilar Medicines Association (IGBA) Nicholas Cappucino 博士、Health Canada Celia Lourenco 博士、US FDA Theresa Mullin 博士、Biotechnology Innovation Organization (BIO) Wassim Nashabeh 博士、Pharmaceutical Research and Manufacturers of America (PhRMA)副總裁 Jerry Stewart 先生及日本 PMDA Toshiyoshi Tominaga 博士共同與談，首先說明 ICH 主要管理架構如圖 11。

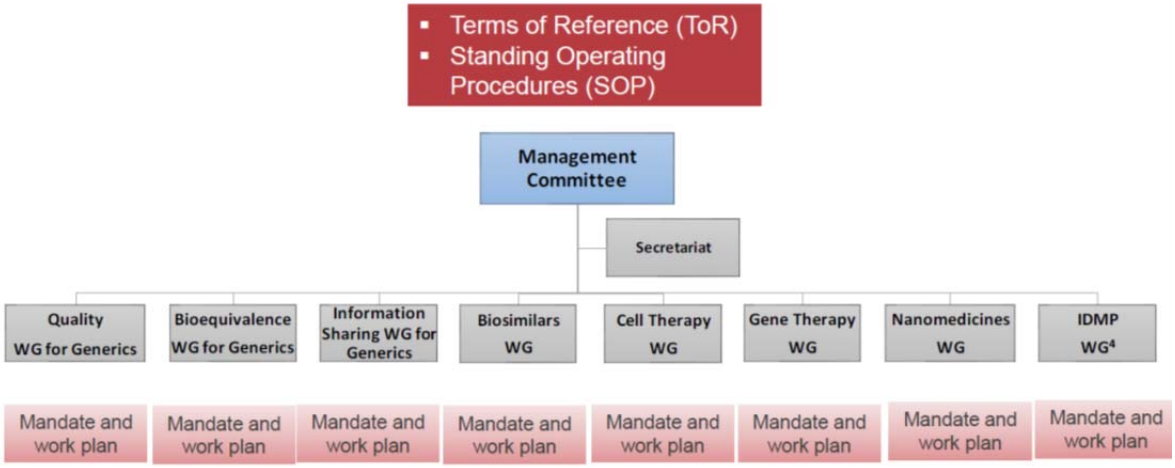


圖 11、Governance of ICH

US FDA Theresa Mullin 博士報告未來 ICH 應如何選新的主題， ICH 每年都會選擇新主題提案，ICH 會員和觀察員被邀請每年 12 月提出制定新的或修訂現有審查基準方案，近期的經驗每年平均會有 15 個基準被提報討論，會員提出的審查提案，需由 ICH 管理委員會新主題小組委員會協調，向 ICH 大會提出審查建議，ICH 大會每年都會核准 2-5 個主題提案，向 ICH 提案的程序如圖 12。

ICH 對藥品技術審查基準調和的步驟包括：新主題的選擇、就技術草案達成共識、草案提交 ICH 大會同意、法規單位諮詢與討論、再次提報大會通過，然後才是個會員國落實在國內管理或審查制度。

正式的 ICH 流程可讓 ICH 實現更大範圍的醫藥法規全球協和，整理如下：

(1) 在品質，功效，安全和多學科領域制定新的 ICH 基準-由專家工作組（EWG）開發。

(2) 問答文件-由實施工作組（IWG）制定，工作組進行討論。

(3) 自 2015 年以來，ICH 已經建立了「reflection papers」的做法，以描述特定領域的基準撰擬工作，隨著 ICH 會員資格變得更大，更多樣化，這些“reflection papers”支持更有效率的討論，讓主題能夠採取優先順序的方式進行融合，可以允許從大多數「一次性」主題提案，轉變為按主題組織的新主題規劃，也允許採用策略性的方法選擇新的 ICH 主題提案。

(4) 「reflection papers」由 ICH 成員撰擬和提報，然後由 ICH MC 和大會進行審查和討論。如果該文件得到了 ICH 大會的認可，「reflection papers」中概述的擬辦理討論工作，將包含的個別主題納入新的主題提案過程。

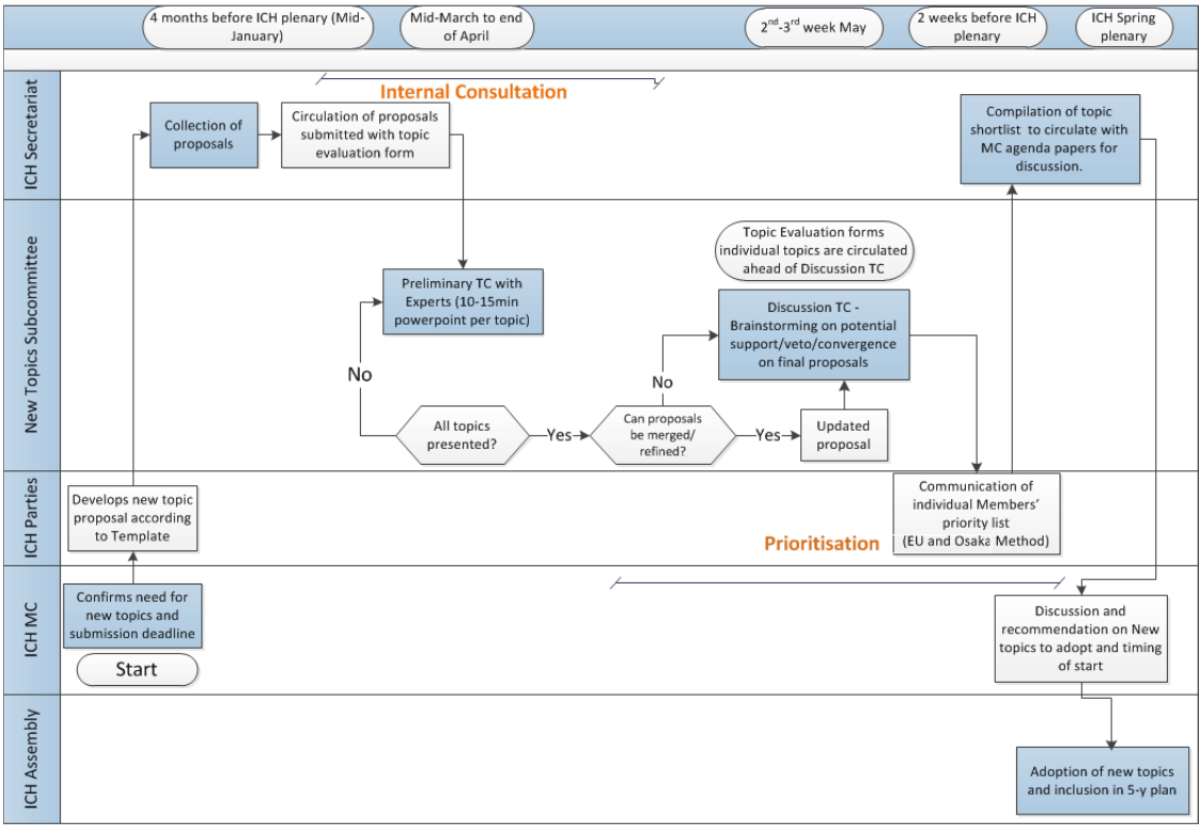


圖 12、New Topic Selection Process

4. FDA Town Hall

本專題演講由 OHOP 法規事務副主任(ADRA)Tamy Kim 博士、US FDA 生物藥品審查與研究中心(CBER) Peter Marks 博士、藥品審查研究中心(CDER) Janet Woodcock 醫師共同與談。主要說明 US FDA 依據 21 世紀醫療法案，於 2017 年成立腫瘤卓越中心(Oncology Center of Excellence; OCE)，通過創新和合作實現以病人為中心的決策管理模式，2017 年 OCE 參與 3 個中心的藥物、生物製劑和設備的癌症產品的審查和批准，提供主題和管理專業知識，包括來自所有 3 個中心的審核人員（CDER，CBER 和 CDRH）創建跨中心論壇。OCE 簡化突破性產品的監管審查流程，例如：seamless trial designs、Real world evidence，以加快腫瘤產品開發的新管理模式，OCE 2017 年批准用癌症治療用藥整理如圖 13。

Cancer type	Drugs
Breast	abemaciclib, palbociclib, ribociclib, pertuzumab, neratinib
Bladder	pembrolizumab, avelumab, durvalumab, nivolumab
Gastric	pembrolizumab, nivolumab, regorafenib
Kidney	cabozantinib, sunitinib
Lung	alectinib, dabrafenib and trametinib, ceritinib, pembrolizumab, brigatinib, osimertinib
Melanoma	nivolumab
Merkel Cell	avelumab
Ovarian	olaparib, niraparib
Tissue agnostic	pembrolizumab
Leukemia	gemtuzumab ozogamicin, liposome-encapsulated daunorubicin and cytarabine, enasidenib, tisagenlecleucel, inotuzumab ozogamicin, blinatumomab, midostaurin, bosutinib, dasatinib
Lymphoma	acalabrutinib, axicabtagene ciloleucel, pembrolizumab, brentuximab vedotin, copanlisib, obinutuzumab, rituximab and hyaluronidase
Multiple Myeloma	lenalidomide
Biosimilars	Ogivri (trastuzumab-dkst), Mvasi (bevacizumab-awwb)

圖 13、OCE Regulatory Review: 2017 Approvals in Cancer

Peter Marks 博士報告 US FDA CBER 加快再生醫學先進療法的開發和審查措施，適用於某些細胞療法，治療組織工程產品，人體細胞和組織產品以及組合產品，包括產生持久效果的轉基因細胞療法和基因療法等，用於嚴重或危及生命的疾病或病症，初步臨床證據必須表明有可能解決未滿足的醫療需求，經過事前認可者，可適用優先審查和加速批准，此一措施擴大了加速審查的選項範圍，正在開發或通過 CBER 批准的新產品如圖 14。

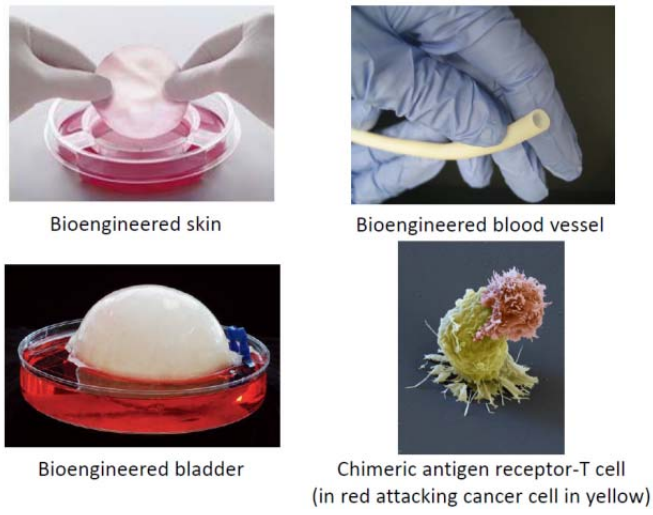


圖 14、Novel Products in Development or Approved through CBER

另外，CBER 考量到學術研究人員，醫藥產業或研發機構在開發生物製品的過程中可能會有疑問，如果能夠建立早期討論機制，將可消除產品開發障礙，例如，幫助研發者避免不必要的臨床前研究，同時，使審查人員有機會熟悉開發中的新產品和技術，為患者提供安全有效的產品。因此提出「INitial Targeted Engagement for Regulatory Advice on CBER producTs，INTERACT Program」，進一步鼓勵支持藥廠與審查單位的互動，未來會建置外部網頁詳細描述該程序。各種與發展相關的主題皆可成為 INTERACT 會議的主題，一般而言，INTERACT 會議期間提出的問題將側重於產品臨床前測試的要求、第一次人體試驗所需的產品製造議題、初始臨床開發策略、設備或化驗設計考慮因素等主題。INTERACT 會議取代了 CBER 之前所有產品的 IND 前會議流程，但 INTERACT 會議不會取代正式的產品特定會議，例如 IND 之前的會議或 BLA 之前的會議。

US FDA 提出學名藥競爭力行動計畫的三個目標如下：

(1) 簡化 ANDA 審核流程，以提高審查的效率，有效性

(2) 加強複雜產品 ANDA 的開發和審查。

(3) DCAP 協調了 GDUFA II 的主要目標：提高安全，高品質和低成本仿製藥的第一次批准率，減少審查批准的週期。

在新藥管理現代化的部分含括 OND，OSE，OTS，OPQ 等領域，專注於強化藥物開發和患者，衛生專業人員，科學家，醫藥產業界的互動，改善資訊流通，政策與流程管理，維持法規科學品質，因此，未來會著重於精進法規與審查程序、提出技術指引等文件，以及規劃長期安全性監測計畫。

(四)與醫藥產業及各國主管機關互動

本次會議美國 FDA、日本 PMDA 及許多來自歐美國家的學者專家、國際醫藥大廠與醫藥品研發服務公司、臺灣醫藥產業、臺大醫院、臺北榮民總醫院、長庚紀念醫院、臺北醫學大學附設醫院臨床試驗中心、陽明大學及景康藥學基金會等醫藥學研機構均派員參與，吳署長秀梅亦與 US FDA、EMA(European Medicines Agency)、Health Canada 及 PMDA 等國代表會談，深入討論未來如何深化醫藥法規合作，加強法規科學審查人員交流，並邀請各國代表來台參加 2018 年台灣東協藥政管理論壇及 APEC GRM 活動，台灣各大醫學中心臨床試驗部門與來參加會議之醫藥研發服務公司接觸，外交部駐波士頓代表處也積極給予協助，共同拓展台灣醫藥法規國際化、審查透明與效能之知名度。

參、心得及建議

本次 DIA 年會，TFDA 嘗試以「Regulatory Challenges in Reviewing MRCT Data: The TFDA Perspective」及「Using Real World Evidence in Regulatory Decision Making」為主題投稿，首次獲大會邀請於會議期間主辦 TFDA Town Hall，分享台灣在創新藥品議題的藥政管理革新成果，並以「An Adaptive Seamless Phase II/III Design in Drug Development for Binary Endpoints」為題投稿大會專題海報，或邀請於海報期間派員說明臨床試驗設計考量，學習非常寶貴的經驗。

TFDA 於 2018 年 6 月已成為 ICH 正式會員，大會期間多場 ICH 主題論壇接提及此一最新概況，US FDA、EMA、Health Canada 及 PMDA 等國代表也於會場向吳署長秀美表達祝賀，未來期待與我國能夠有更進一步的法規人員交流，也非常樂意支持我國深化參與國際醫藥法規協和活動，吳署長表達我國將更積極推動 ICH 法規基準落實，促進我國醫藥產業轉型升級，提高民眾用藥的可近性，為全球醫藥衛生作出有效貢獻。

本次出席會議有別於一般國際研討會，除參加 DIA short course 與專題演講吸取國際醫藥品創新研發經驗外，亦學習到主辦 TFDA Town Hall、於會場設展覽攤位，向世界宣揚台灣醫藥衛生法規管理經驗，也邀請各國代表參加台灣之夜晚宴深入交流，過程從議程設計、講員邀請、與大會秘書處接洽聯繫、安排布置會議場地，邀請國內外業界貴賓出席、文宣作業等，都是新的嘗試與突破。會議期間，各國藥政主管機關也於雙邊會談時，表達希望派員參加我國即將舉辦之「2018 年台灣東協藥政管理論壇」及 APEC GRM 活動，EMA 派質量和專業科學學科主管 Ragini Shivji 博士，配合「2018 年台灣東協藥政管理論壇」生物藥品主題，以「Perspectives on Current Quality Issues for Biologicals」為題向我國產官學研界分享 EMA 對生物製品品質管理問題的觀點，展現我國出席第 54 屆「藥物資訊協會」年會，實質增進我國與各國互動機會，未來希望進一步藉由此類出席國際醫藥法規專題會議的場合，積極爭取各國認同台灣藥品管理制度，促進醫藥產業進軍國際市場。

附錄 1- 會議活動照片

1. 健康台灣展示攤位前合影

2. 吳署長與 US FDA 代表會談

3. 吳署長與 EMA 代表會談

4. 吳署長與 PMDA 代表會談

5. 吳署長主持 TFDA Town Hall

6. 吳署長與 TFDA Town Hall 講員合影

7. TFDA Town Hall 台灣代表團

8. 吳署長與我國波士頓台北經濟文化代表處徐佑典處長一行合影

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

TFDA Perspective on Regulatory Management of Drug Development

Shou-Mei Wu
Director General
Ministry of Health and Welfare TFDA, Taiwan

Disclaimer – Content Slide

- 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.
- For work prepared by US government employees representing their agencies, there is no copyright and these work products can be reproduced freely. Drug Information Association, Drug Information Association Inc., DIA and DIA logo are registered trademarks. All other trademarks are the property of their respective owners.

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

Taiwan Profile

- Area: about 36,000 sq.km.
  (14,400 square miles)
- Capital: Taipei City
- Population: 23 million
- **99.9% Citizen Covered by NHI**
  – a Single Payer and Single Database (IC Card)
- Pharmaceuticals Market:
  NT$ 145.9 Billion (US$ 4.86 Billion) in 2017
- **TFDA has been made an ICH official member**





Review Process for Clinical Trial (IND) Applications

A standard review process: 45 calendar days

Aug 10th 2017
- ***Streamline first-in-human IND Review Process***
- ***Refine IND Amendment Management based on degree of changes***

Hospital, Sponsor, CRO

TFDA

Integrated Medicinal Products Review Office (iMPRO)

Administrative Section	Technical Section				
	CM	Phar	PK/P	Clinic	Statistic

Assessment Report

IRB

Ethnic/Ethical concern, Cell/Gene Therapy, etc.

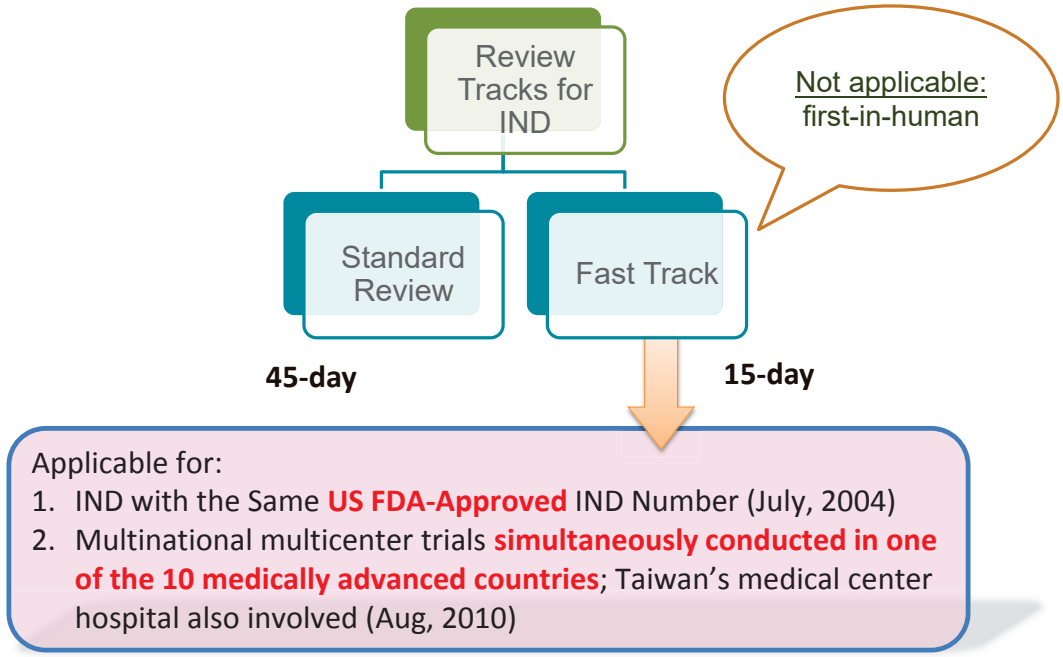
Advisory Committee

Consult with AC experts if needed

TFDA decision

Hospital, Sponsor, CRO

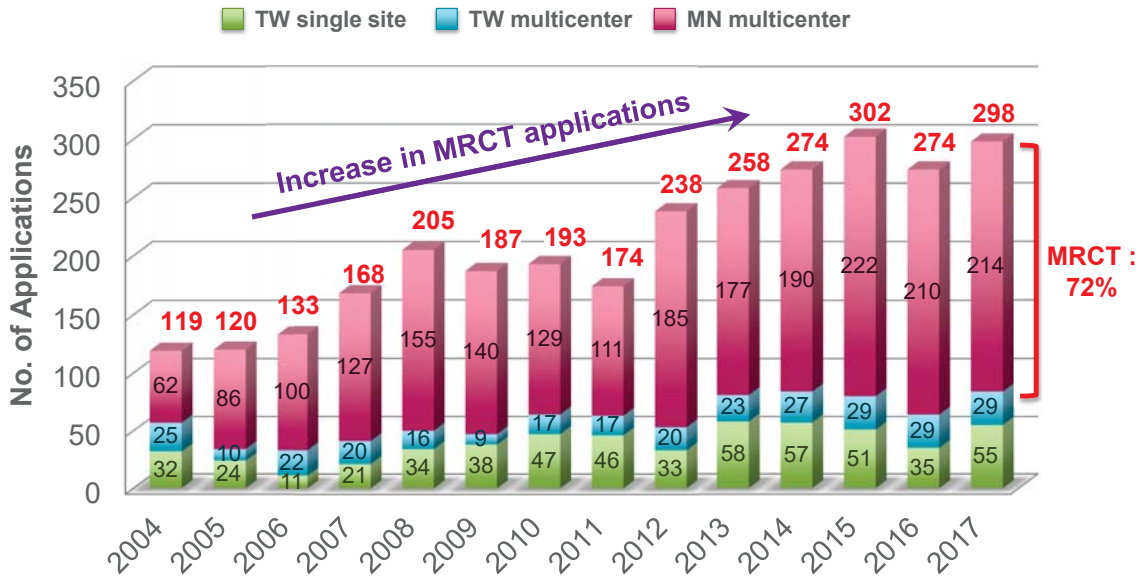
Enhance IND Review Efficacy-Fast Tract Review for Pharmaceutical Product



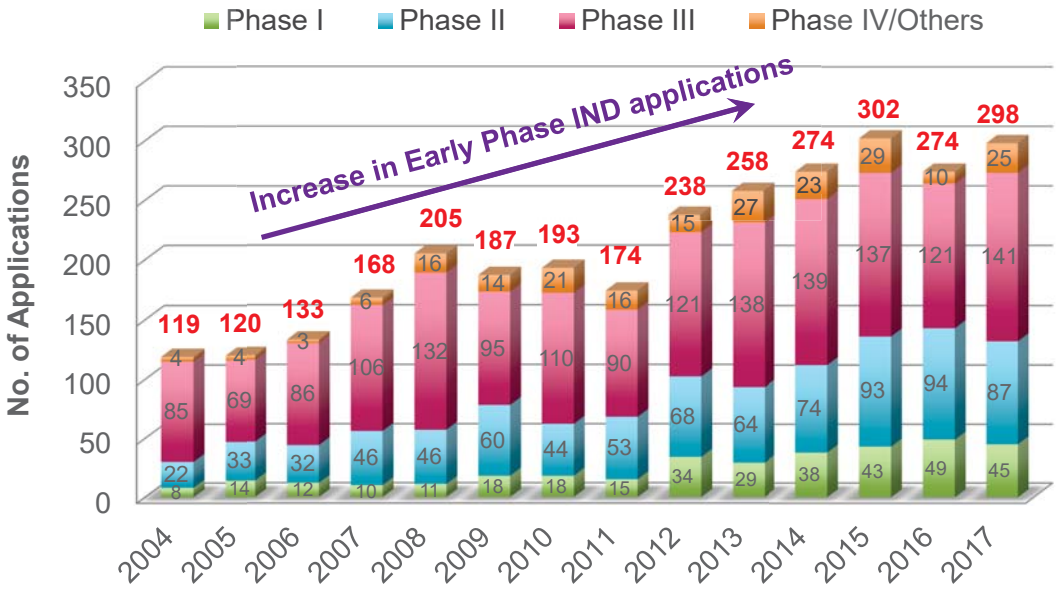
Applicable for:

1. IND with the Same **US FDA-Approved** IND Number (July, 2004)
2. Multinational multicenter trials **simultaneously conducted in one of the 10 medically advanced countries**; Taiwan's medical center hospital also involved (Aug, 2010)

IND Applications in Taiwan by Local/MRCT Type



IND Applications in Taiwan by Study Phases



The Improvement of IND Review

2017.08.10

Streamlining first-in-human (FIH) IND review process

Case-by-case consultation waived, shortening review time to 45 days from 120 days

Cell therapy/gene therapy clinical trials fast-track review mechanism

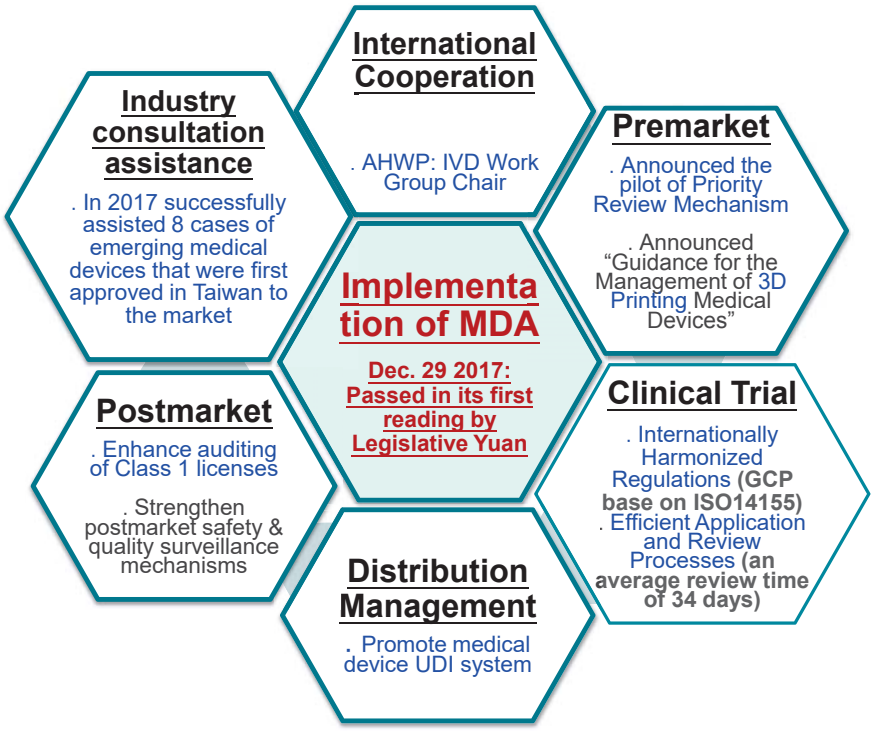
Review process shortened to 30 days

Refining IND amendment management based on the degree of changes

Review process based on risk assessment

- Accelerate new drug development
- Early access to innovative medicine
- Facilitate Taiwan's development on biotechnology and pharmaceutical industries

Important Achievements of Medical Device



Future Prospects

Thank You

Shou-Mei Wu
Director General
Ministry of Health and Welfare TFDA, Taiwan




DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

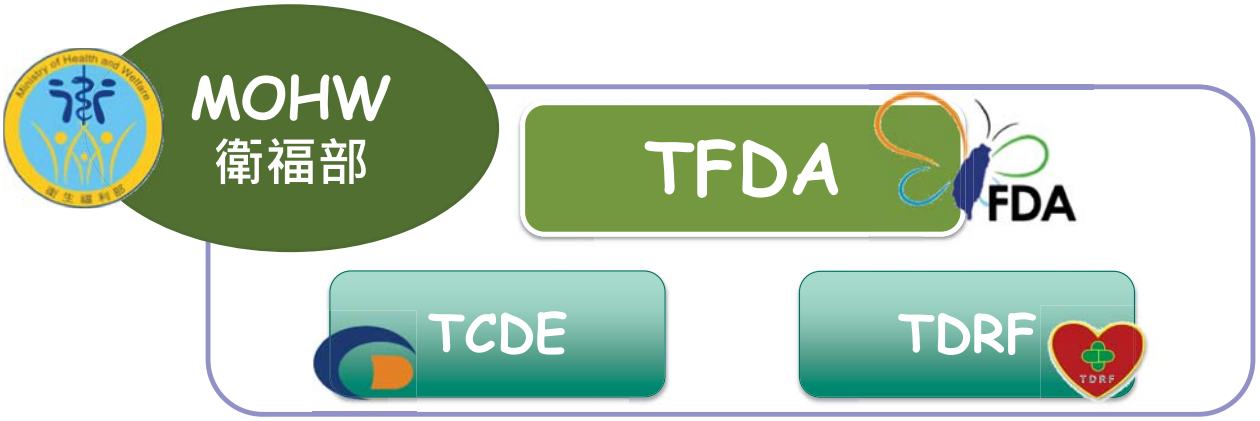
Using Real-World Evidence in Regulatory Decision Making

Churn-Shiouh Gau, Ph.D.
Executive Director
Center for Drug Evaluation,
Taiwan

Disclaimer – Content Slide

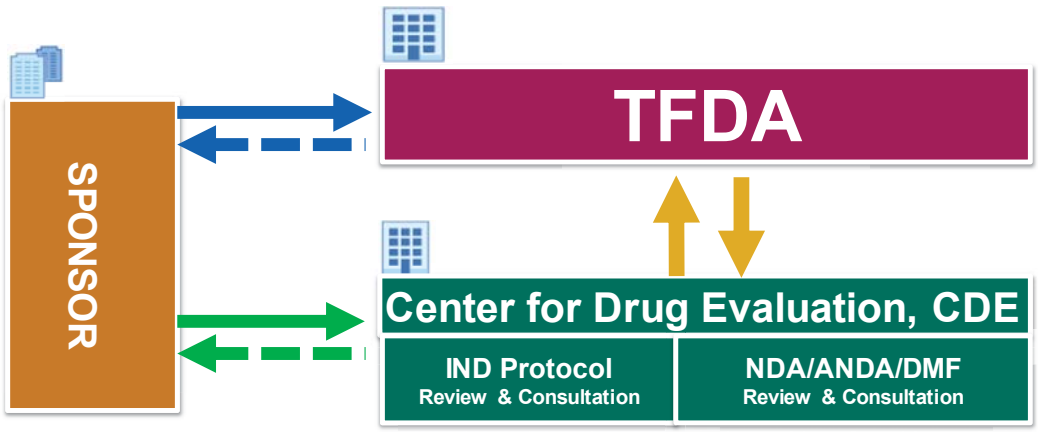
- The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. ("DIA"), its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates, or any organization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

Regulatory Infrastructure in Taiwan



MOHW: Minister of Health and Warfare, Taiwan
TFDA: Taiwan Food and Drug Administration,
TCDE: Taiwan Center for Drug Evaluation,
TDRF: Taiwan Drug Relief Foundation

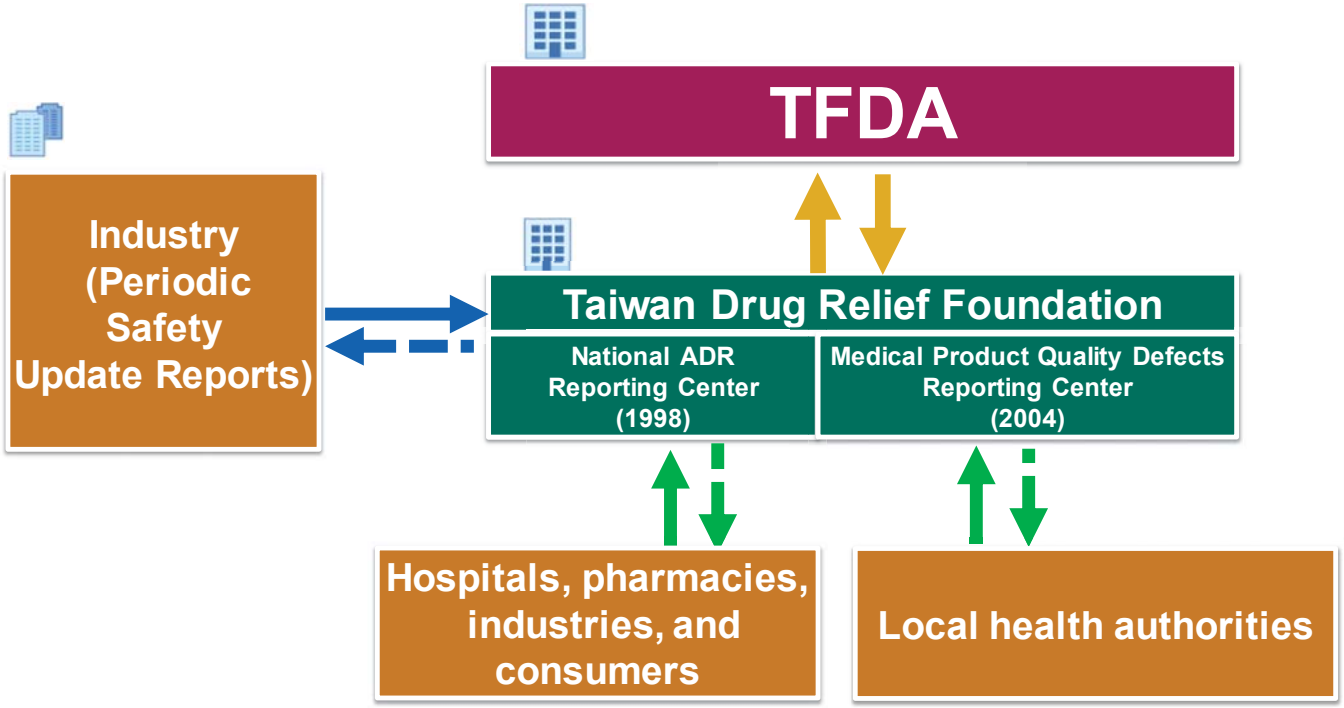
TFDA/CDE in Taiwan



Arrows in blue are for IND and NDA application.
Arrows in green are consultation.

CDE was established at 1998 by DOH (now MOHW) to assist TFDA to evaluate pharmaceuticals for marketing authorization.

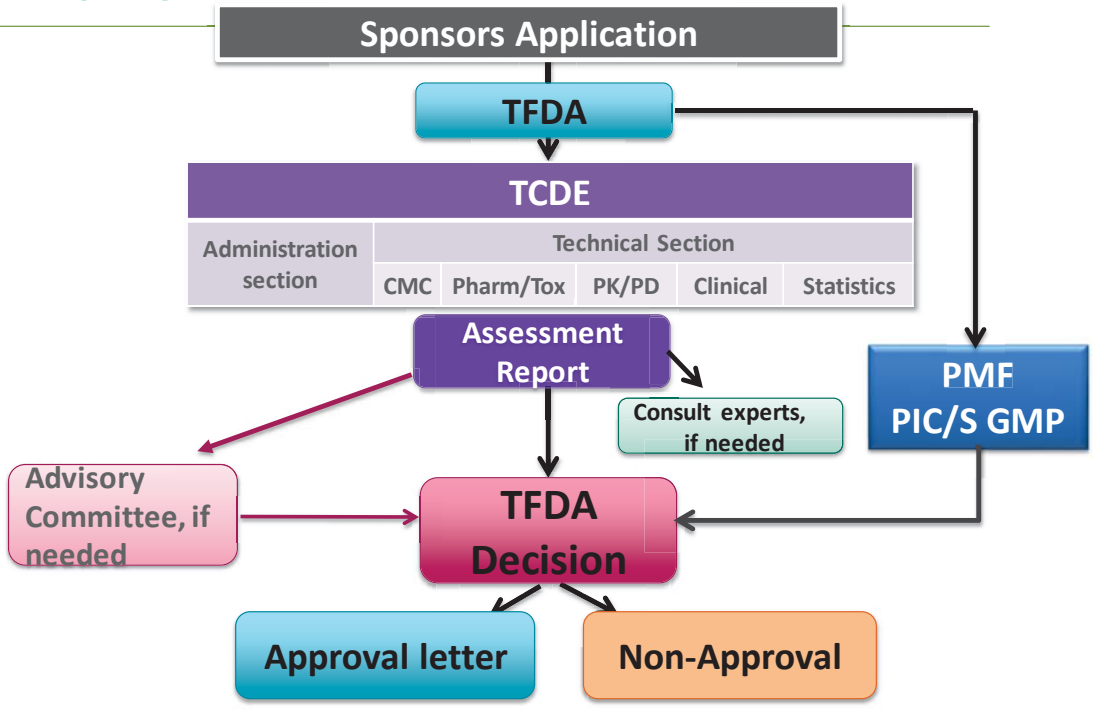
Framework of Drug Safety/Quality Surveillance



DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

5

NDA Review



DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

6

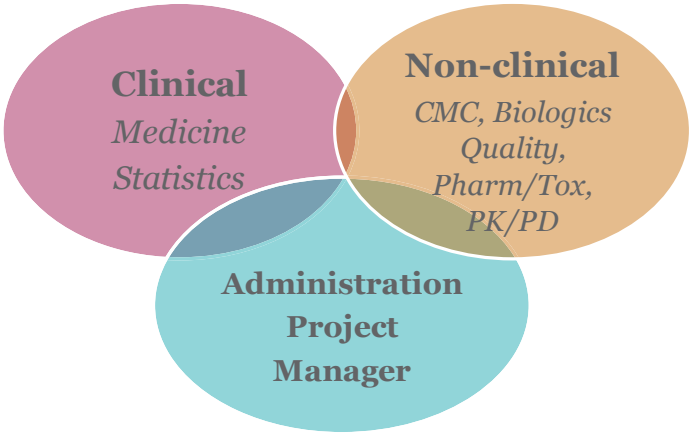
Comprehensive and Multidisciplinary NDA Review

Team Approach

- Multidisciplinary
- Communication
- Consensus building

Decision Making

- Evidence-based
- Benefit-Risk Assessment

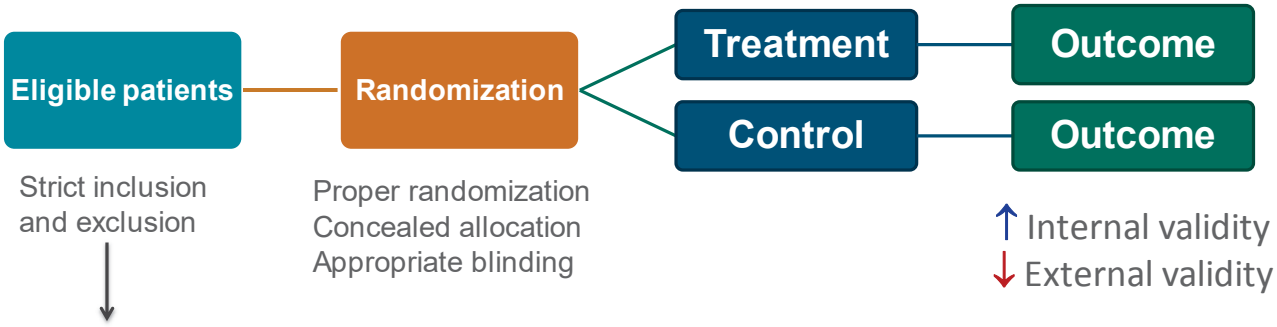


NDA Review Team in CDE

Evidentiary Standards for Drug Approval

Is there substantial evidence of drug safety and efficacy for the claimed indication?

Confirmatory randomized controlled trials (RCTs) – **An ideal Setting**



Artificially homogeneous

Minimize the chance of bias from
patient selection, treatment assignment, patient evaluation and data analysis

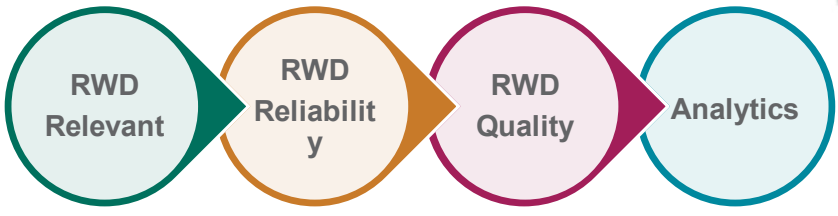
Increasing use of real-world evidence to support decision making

Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD

US FDA guidance, 2017

Ability of RWD to generate RWE depends on



Sufficient? Sufficient? Assured? Adequate?

Minimize source of bias?

Translate RWD into RWE

Define a meaningful question

Setup an appropriate design and/or choose an adequate RWD source

Protocol and analysis plan

Conduct study
Analyze RWD

Complete study report
RWE

Taiwan experience with RWD/RWE

Change of approved product label

- Update label information of drug-drug interaction and safety

Post-market safety surveillance

- Phase IV safety study requested by regulatory
- Post-marketing pharmacovigilance

Pre-market safety assessment

- PSURs/PBRERs from other countries could be one of the sources of pre-marketing safety evaluation in Taiwan

Pre-market efficacy assessment

- Provide critical efficacy evidence (e.g. rare disease)
- As a historical control for single arm control

Case study 1 – The approval of Sapropterin Tablet for Hyperphenylalaninemia (HPA)

- HPA is diagnosed as an abnormal elevation in blood phenylalanine level (>120 μmol/L)
- Caused by
  - Phenylalanine hydroxylase (PAH) deficiency, also phenylketouria (PKU), or
  - **Tetrahydrobiopterin (BH4) deficiency**
- Incidence

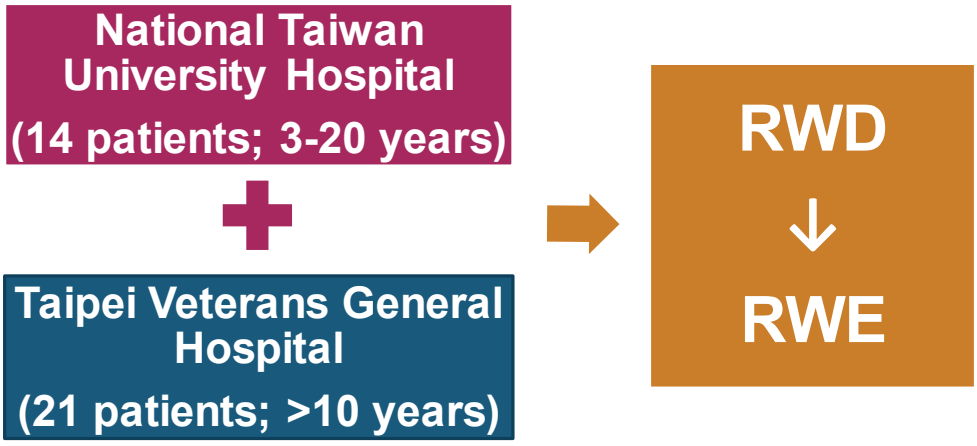
  Caucasian: ~ 1 in 10,000 & 1.5-2% of HPA are BH4 deficiency type

  Taiwanese: ~ 1 in 34,000 & 30% of HPA are BH4 deficiency type
- In Taiwan, Sapropterin tablets have been imported and used for the treatment of BH4 deficiency for many years without registration.

Clinica Chimica Acta 313 Ž2001. 157–169

Case study – Sapropterin Tablets ("Excelsior" BH4)

- Well collected patient clinical data derived from two retrospective observational studies in patients with BH4 deficiency.



Case study – Sapropterin Tablets ("Excelsior" BH4)

- The "Excelsior" BH4 Tablet (sapropterin) was approved for the treatment of hyperphenylalaninemia due to tetrahydrobiopterin (BH4) deficiency, based on following consideration:
  - Claimed indication is a rare disease
  - Clear mechanism of action
  - Surrogate endpoint (blood Phenylalanine (Phe) level)
  - **Well-collected patient clinical data (real world data)**

Case study 2 – Oral Ketoconazole vs. Hepatotoxicity

- In Taiwan, oral ketoconazole was indicated for the treatment of fungal infections, advanced prostate cancer and Cushing's syndrome.
- Concerns raised internationally on **liver toxicity** associated with oral ketoconazole

EMA: Suspended

FDA: Restrict & lots of warnings

DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

15

Oral Ketoconazole vs. Hepatotoxicity

- **Taiwan National ADR Reporting Database**

Item	Hepatobiliary disorders	All
No. of cases	31	58
Age（year）		
Mean ±SD	45±15	51±20
Range	16-86	16-94
Gender（N）		
Male	8	18
Female	23	40
Outcome of adverse reaction（N）		
Death	1	2
Life threatening	4	5
Hospitalization	20	25
Non-serious	6	26

ADR=Adverse drug reaction

- ✓ Some uses without prescription
- ✓ Use due to mild skin conditions

DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

16

Oral Ketoconazole vs. Hepatotoxicity

- **Taiwan National Health Insurance (NHI) Claim Database**

Medical care institute	No. of prescription (%)
Medical centers	280 (1.1%)
Regional hospitals	354 (1.4%)
District hospitals	1,103 (4.5%)
Primary care clinics	19,103 (77.3%)
Pharmacy	3,864 (15.6%)
Total	24,704 (100.0%)

- ✓ **Difficulty in providing intense liver function and adrenocortical function monitoring**
- ✓ **Liver function test within 30 days before treatment: 2.7%**

DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

17

Case study – Oral Ketoconazole vs. Hepatotoxicity

- Literatures
  - Within the recommended dosage, the incidence and severity of liver injury caused by oral ketoconazole are higher than those of other azoles
  - Liver injury occurs mostly between 1 and 6 months, but there are still many case reports occurring within 1 month (including few days).

Cannot reduce the risk by limiting the dosage/duration

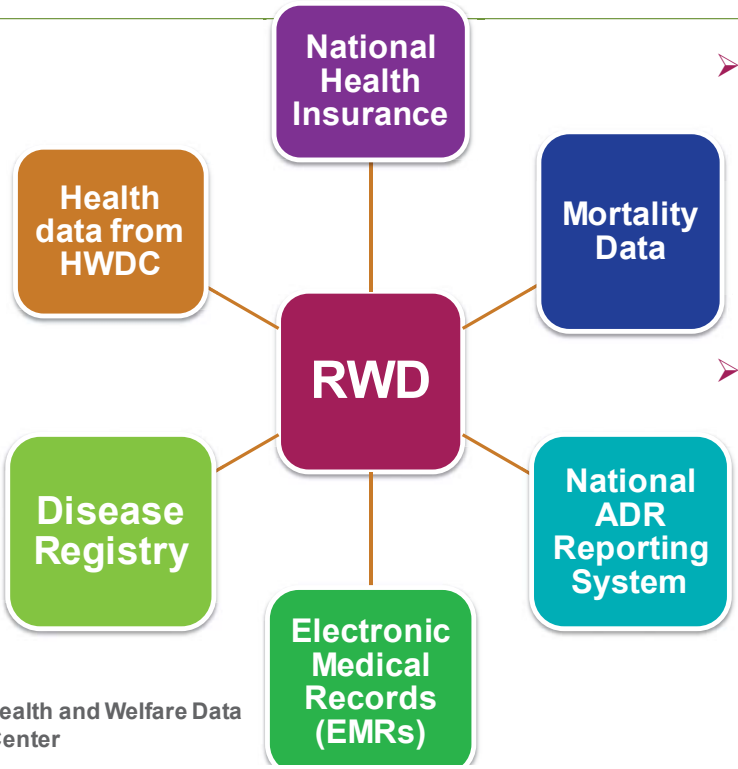
- **There are other available medicines in the market.**

Taiwan: withdrawal

DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

18

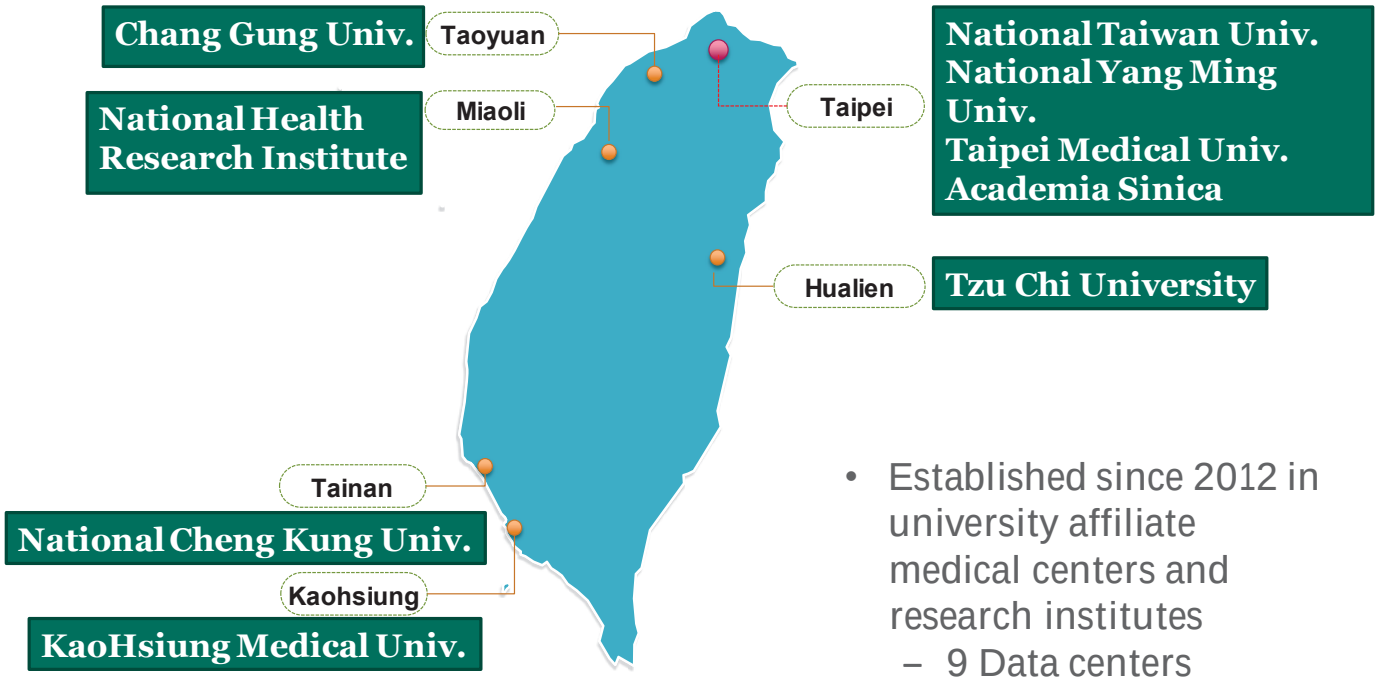
RWD Collections in Taiwan



HWDC= Health and Welfare Data Science Center

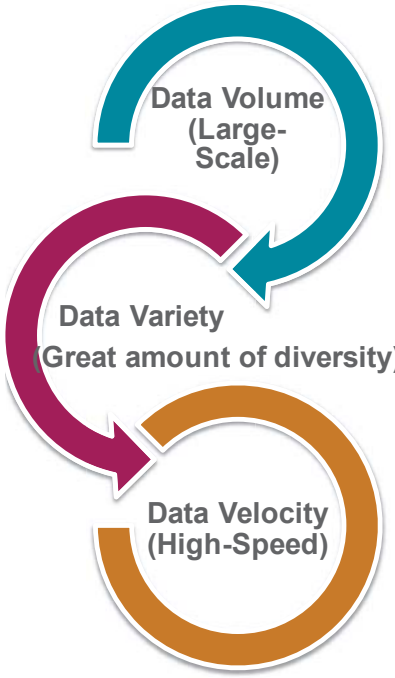
- National Health Insurance (NHI)
  - Established in 1995
  - Large database: 99% of Taiwan's population (23 million)
  - Real-world practice
    - Medical service utilization
    - Prescription drug use
  - Longitudinal RWD (since 1995)
- National Adverse Drug Reactions (ADR) Reporting System
  - Established in 1998
  - Post-marketing Surveillance
    - Mandatory reporting serious adverse reactions of all approved medical products
    - Voluntary reporting of non-serious adverse reactions
    - Obligatory PSUR for medical products under monitoring stage

HWDC Centers in Taiwan



- Established since 2012 in university affiliate medical centers and research institutes
  - 9 Data centers

Facts and Opportunities



Data value

Ask right questions
↓
Collect high-quality data
↓
Conduct proper analyses
↓
Generate reliable and robustness evidence

Regulatory

- Pharmacovigilance
- Safety label changes
- Drug-drug interactions
- Conditional approval requiring collection of on-market data
- Extension of indication

Industry

- Discover drug pathways
- Identify unmet clinical need, profile target populations
- Uncover new indication
- Profile patient compliance/adherence

DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

21

Challenges

- **Data challenge**
  - Sources/heterogeneity in collection systems
  - Completeness, validation and quality
  - Uncontrolled biases due to time, site, and other study-specific effects
- **Processing and exploration challenge**
  - Data collection
  - Data analysis
- **Management challenges**
  - Data privacy and security
  - Patient protection

Consultation with the regulatory authority if RWE is intended to be submitted

DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

22

Thank You

Churn-Shiouh Gau, Ph.D.
Executive Director
Center for Drug Evaluation, Taiwan

TFDA as an ICH new member, June 7, 2018. (poster from ICH website)

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

Global Challenges in Conducting MRCT and Interpreting Data

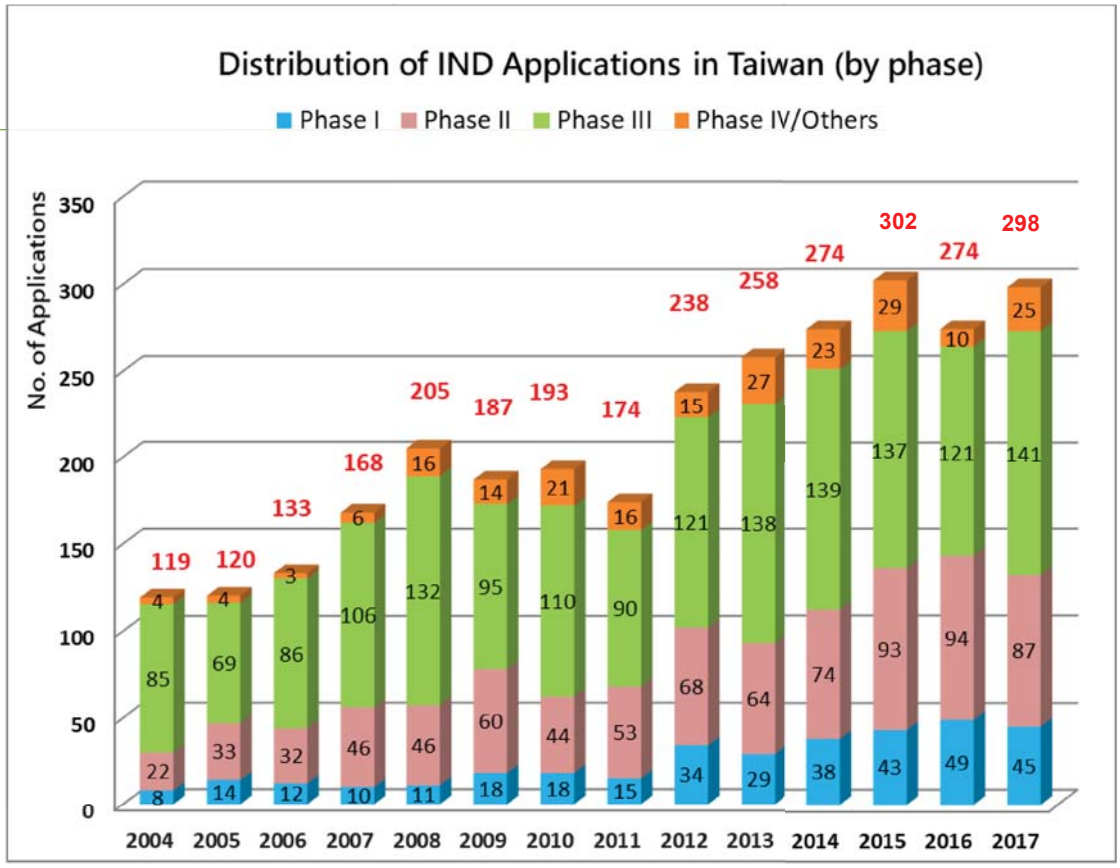
James Chih-Hsin Yang M.D., Ph.D.
楊志新教授
Professor and Director,Graduate Institute of Oncology,NTU
台灣大學醫學院腫瘤醫學研究所所長
Director,Department of Oncology,National Taiwan University Hospital
台大醫院腫瘤醫學部主任

Disclaimer – Content Slide

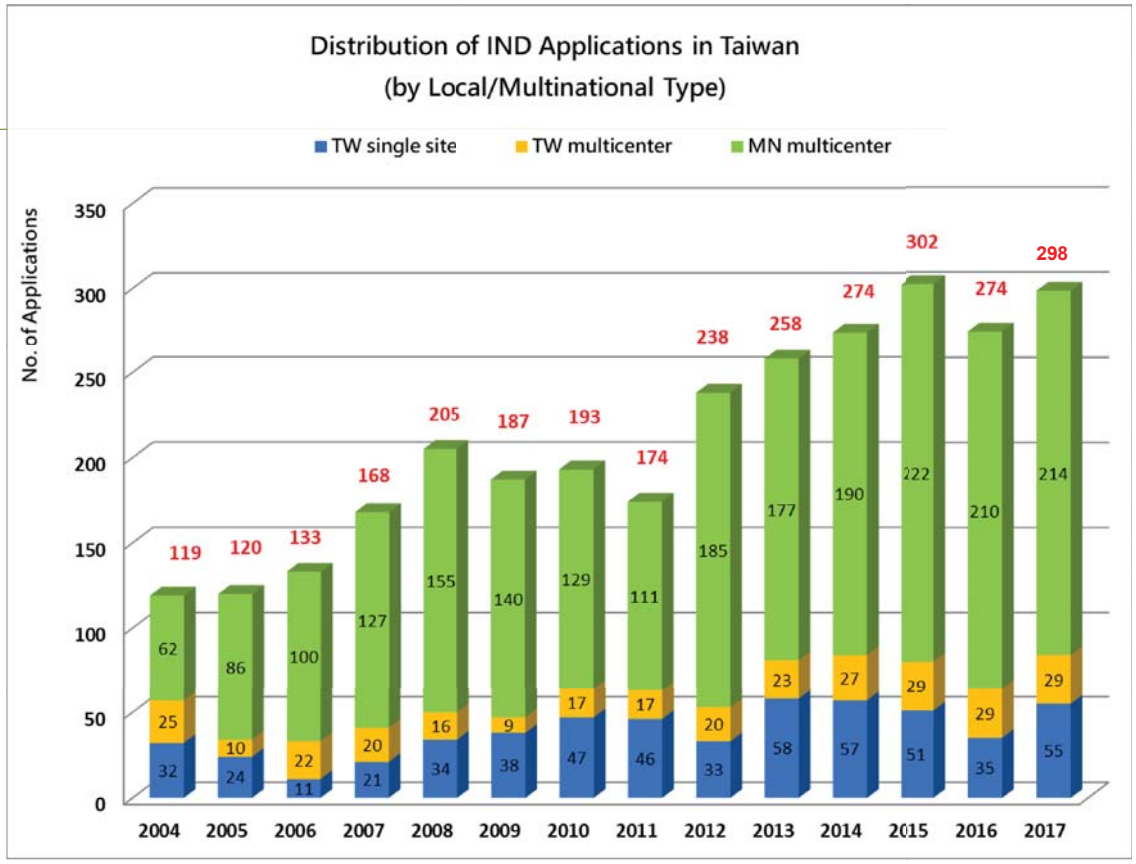
- The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates, or any organization with which the presenter is employed or affiliated.
- For work prepared by US government employees representing their agencies, there is no copyright and these work products can be reproduced freely. Drug Information Association, Drug Information Association Inc., DIA and DIA logo are registered trademarks. All other trademarks are the property of their respective owners.

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

2


Distribution of IND Applications in Taiwan (by phase)
Phase I
Phase II
Phase III
Phase IV/Others
No. of Applications
0
50
100
150
200
250
300
350
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
119 120 133 168 205 187 193 174 238 258 274 302 274 298
8 14 12 10 11 18 18 15 34 29 38 43 49 45
22 33 32 46 46 60 44 53 68 64 74 93 94 87
85 69 86 106 132 95 110 90 121 138 139 137 121 141
4 4 3 6 16 14 21 16 15 27 23 29 10 25

DIA2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28
3


Distribution of IND Applications in Taiwan
(by Local/Multinational Type)
TW single site
TW multicenter
MN multicenter
No. of Applications
0
50
100
150
200
250
300
350
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
119 120 133 168 205 187 193 174 238 258 274 302 274 298
32 24 11 21 34 38 47 46 33 58 57 51 35 55
25 10 22 20 16 9 17 17 20 23 27 29 29 29
62 86 100 127 155 140 129 111 185 177 190 222 210 214

DIA2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28
4

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

5

Clinical trials (related to drugs) registered in NTUH IRB (2017)

Number	Multi-regional		Domestic		Total
	PI -Initiated	Sponsor	PI- Initiated	Sponsor	
Phase I	1	79	8	25	113
Phase II	6	107	22	27	162
Phase III	5	368	7	16	396
Phase IV	1	13	51	7	72
Others	1	3	83	5	92
Total	14	570	171	80	835

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

6

New Clinical trials (related to drugs) registered in NTUH IRB

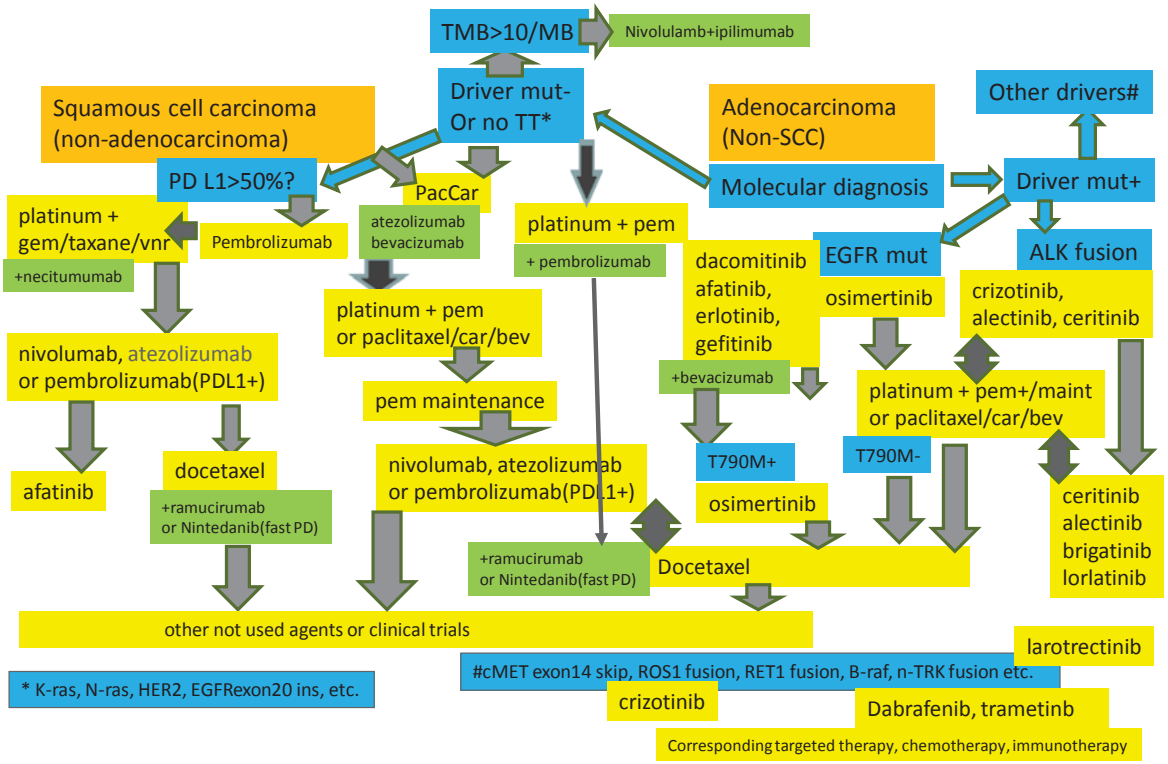
Phase\年度	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Phase I	4	12	12	7	9	19	18	29	26	40	30
Phase II	28	32	41	30	41	49	34	34	67	41	40
Phase III	79	74	59	68	63	104	72	101	114	90	101
Phase IV	86	41	34	29	25	29	16	21	15	16	13
Others	2	4	15	23	14	16	16	25	21	17	26
總計	199	163	161	157	152	217	156	210	243	204	210

DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

7

2018 April

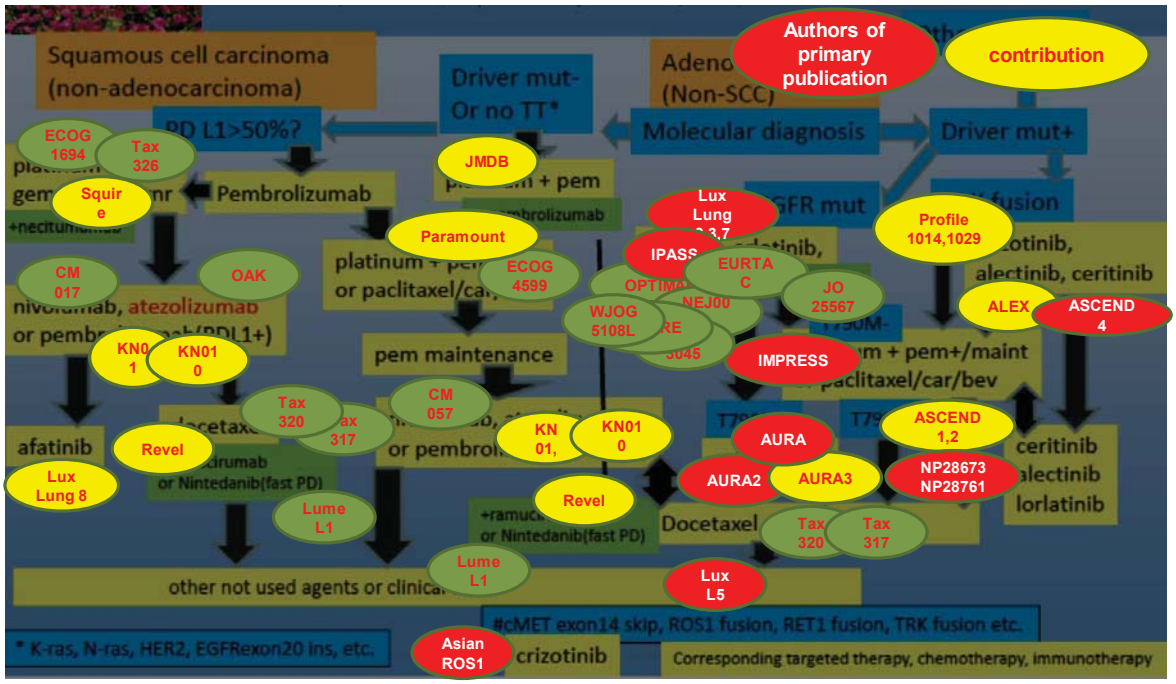
New Paradigms For the treatment of stage IV nonsmall cell lung cancer



DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

8

Taiwan Lung Cancer Clinical Trial Consortium contribution to new drug approval and new therapy in advanced lung cancer



Pre- ICH E17

- MRCT conducted in ICH or non-ICH
- No guidelines for regulatory agencies to review MRCT
- MRCT may be planned/designed for multi-country approval, however, there is no guidelines for the design
- Ethnicity sensitivity assessment was applied, but lack consistency or harmonized regulations

Phase 3 CheckMate 057
Study Design: Nivolumab vs Docetaxel in Previously Treated NSQ NSCLC

Key eligibility criteria
- Stage IIIB/IV NSQ NSCLC
- ECOG PS 0–1
- 1 prior platinum-based chemotherapy
- Prior TKI therapy allowed for known *ALK* translocation or *EGFR* mutation
- Prior maintenance therapy allowed
- Pretreatment tumor samples required for PD-L1 analysis

(N = 582)

Randomize 1:1

Nivolumab
3 mg/kg IV Q2W until PD or unacceptable toxicity
(n = 292)

Docetaxel
75 mg/m² IV Q3W until PD or unacceptable toxicity
(n = 290)

- **Primary endpoint**
  - –OS
- **Additional endpoints**
  - –ORR
  - –PFS
  - –Efficacy by tumor PD-L1 expression
  - –Safety
  - –Quality of life

Randomization stratified by prior maintenance therapy and line of therapy (second-line vs third-line)

ClinicalTrials.gov number NCT01673867
NSQ = non-squamous; TKI = tyrosine kinase inhibitor

DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

11

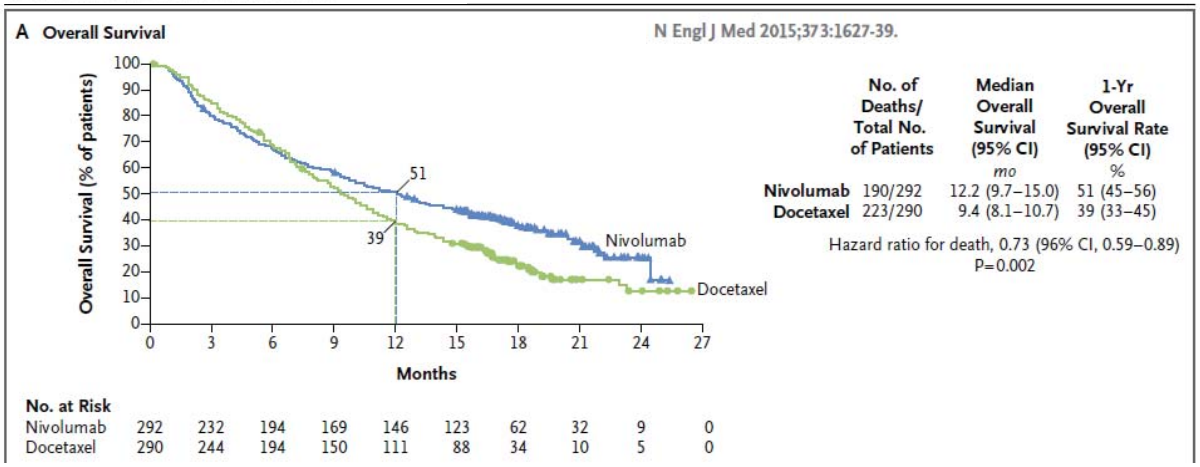
Nivolumab vs. Docetaxel 2nd line non-sq NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer



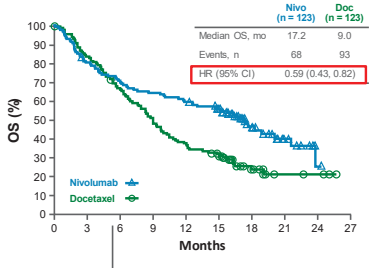
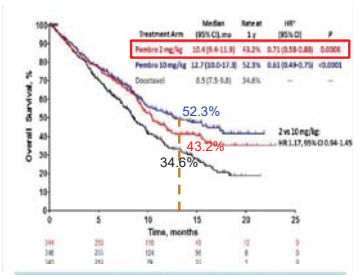
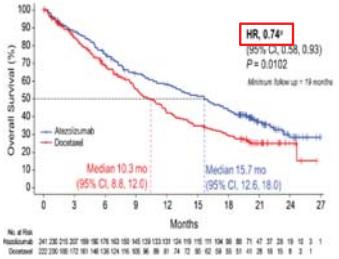
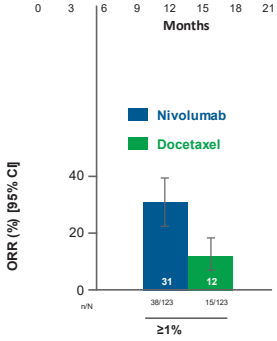
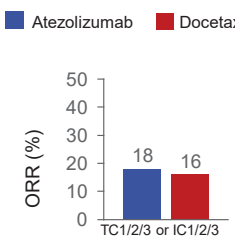
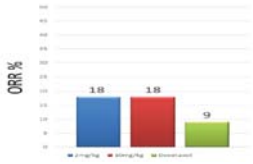
DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

12

Checkpoint inhibitors in 2L NSCLC (PD-L1≥1%)

OS

ORR

Nivolumab NSQ (CheckMate 057)	Pembrolizumab (Keynote 010)	Atezolizumab (OAK)
		
		
		
	ASIAN	
3% (N=9)	21% (N=145)	20% (N=85)

MRCT Drug development
E17: lack definition of "regions"

- True global MRCT
- Global MRCT in limited regions: any of the combinations

North America + Europe,

East Asia

Mainland China + Hong Kong + Taiwan Japan+Korea .....

Mainland China+Korea+Taiwan+…….

Japan+Korea+Taiwan+…….

Korea+Taiwan+Hong Kong+Singapore+…..

Korea+Taiwan

Japan only

Mainland China only

ICH E17 : scope

- Guidelines for planning/designing MRCT

No guidelines for data interpretation

--- leading to multi-countries drug approval

– Planning: examples

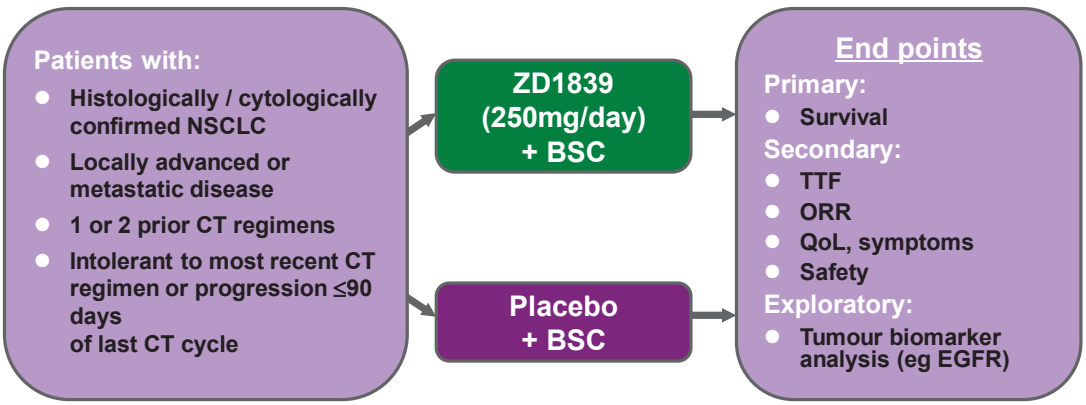
1. usefulness,
2. essential points (e.g. GCP),
3. ethnic factors (extrinsic, intrinsic) for safety or efficacy

– Designing: examples

4. Dose determination
5. Control concomitant medication (or treatment)
6. How to define a population, sample size estimation

ISEL Trial Design

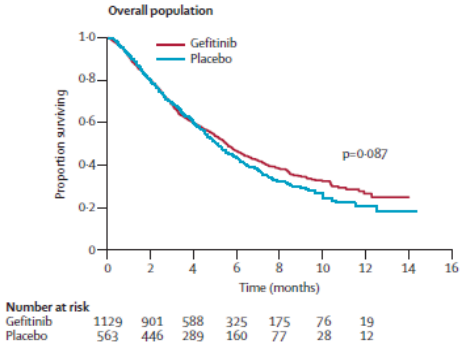
- 1692 patients in 210 centres across 28 countries
- Stratified for histology, gender, intolerant / refractory, PS and smoking history



CT, chemotherapy; BSC, best supportive care;
TTF, time to treatment failure; ORR, objective response rate; QoL, quality of life

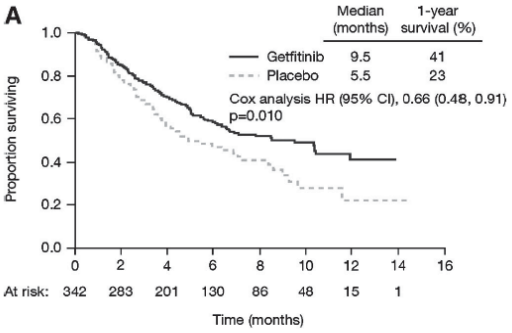
Thatcher N et. al. Lancet 2005

ISEL : AZD1839 (gefitinib) vs. placebo

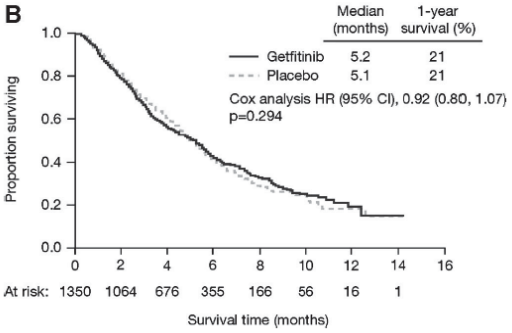


Thatcher N et. al. Lancet 2005

Asian



Non-Asian



Chang A. et. al. JTO 2006

Sample size

- Sample size to regions or pooled regions should be determined

: but without substantial increasing the sample size

E17 guidelines

- Simultaneous global drug development
- Promoting acceptance of MRCT to regulatory authorities, considering ethnic sensitivity and applicability, sponsors should plan and design and prepare for individual region evaluation
- Pre-specified Pooled population :

1. regions with similar ethnic factors,
2. defined subsets in populations across regions with similar intrinsic or extrinsic factors

Phase III trial of afatinib (2nd generation irreversible EGFR TKI in EGFR mutation-positive NSCLC

Stage IIIB (wet)/IV lung adenocarcinoma (AJCC version 6)

EGFR mutation in tumour
(central lab testing; Therascreen EGFR29* RGQ PCR)

Randomization 2:1
Stratified by:
EGFR mutation (Del19/L858R/other)
Race (Asian/non-Asian)

Afatinib 40 mg/day†

Cisplatin + Pemetrexed
75 mg/m^2 + 500 mg/m^2
i.v. q21 days, up to 6 cycles

Primary endpoint: PFS (RECIST 1.1, independent review)‡
Secondary endpoints: ORR, DCR, DoR, tumour shrinkage, OS, PRO§, safety, PK

*EGFR29:19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.
†Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10 mg decrements in case of related G3 or prolonged G2 AE.
‡Tumor assessments: q6 weeks until Week 48 and q12 weeks thereafter until progression/start of new therapy.
§Patient-reported outcomes: Q-5D, EORTC QLQ-C30 and QLQ-LC13 at randomization and q3 weeks until progression or new anti-cancer therapy.

Participating regions

133 sites in 25 countries

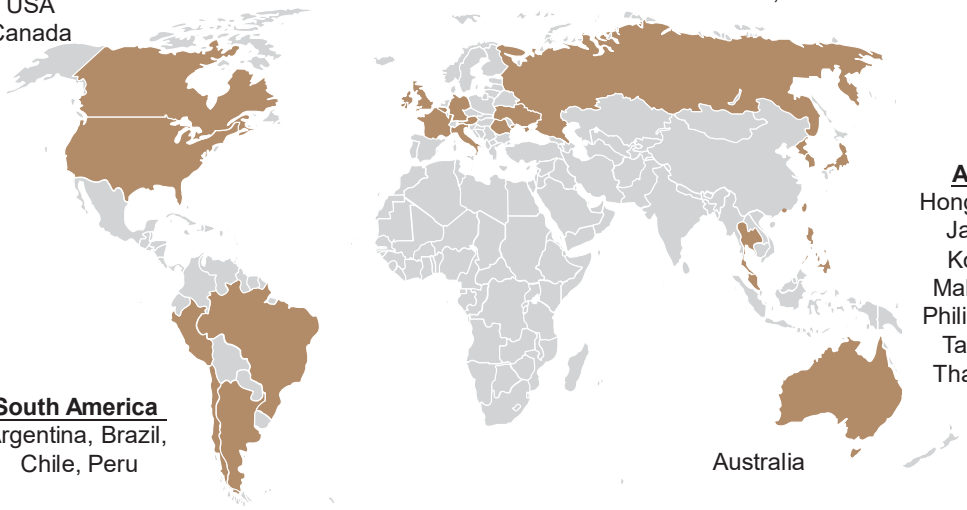
North America
USA
Canada

South America
Argentina, Brazil,
Chile, Peru

EUROPE
Austria, Belgium, France, Germany,
Hungary, Ireland, Italy, Romania, Russia,
Ukraine, UK

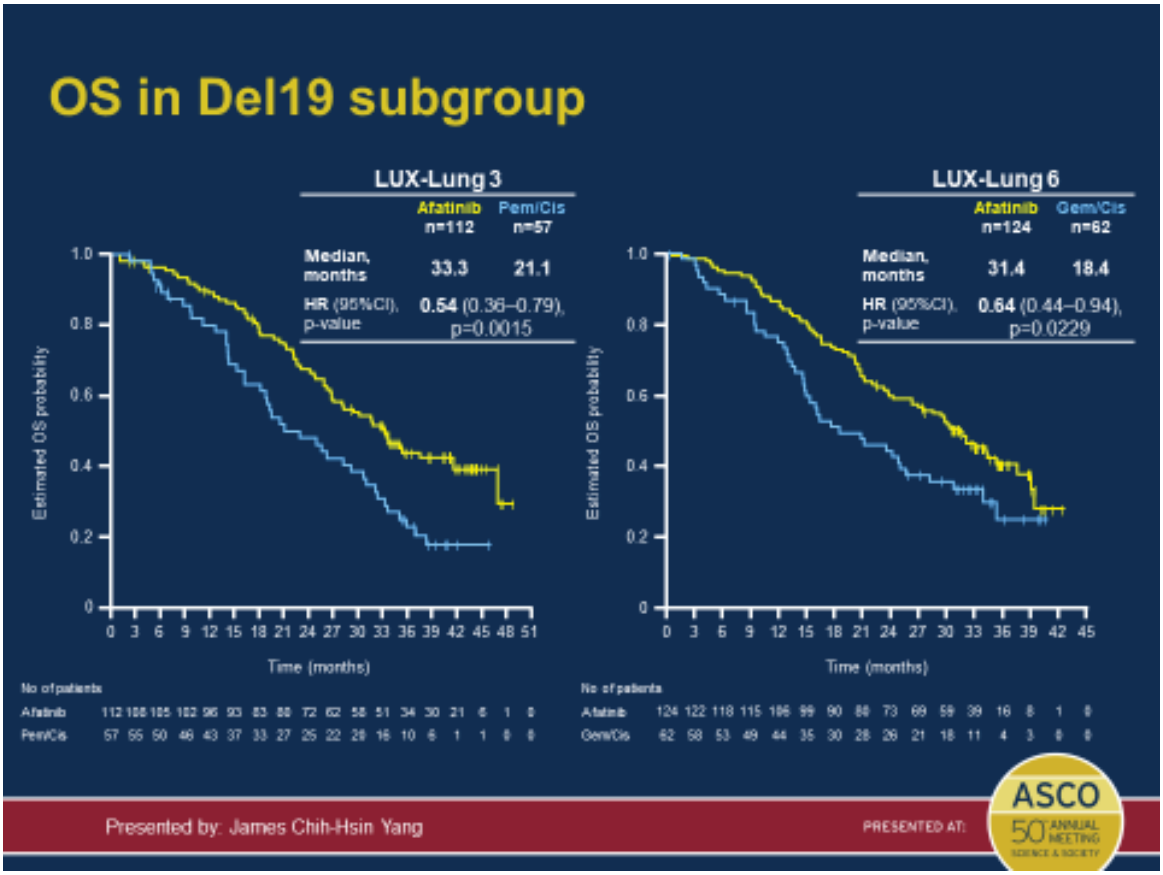
ASIA
Hong Kong
Japan
Korea
Malaysia
Philippines
Taiwan
Thailand

Australia



DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

21



DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

22

OS by race/ethnicity in the *EGFR* Del19 mutation subgroup

Non-Asian

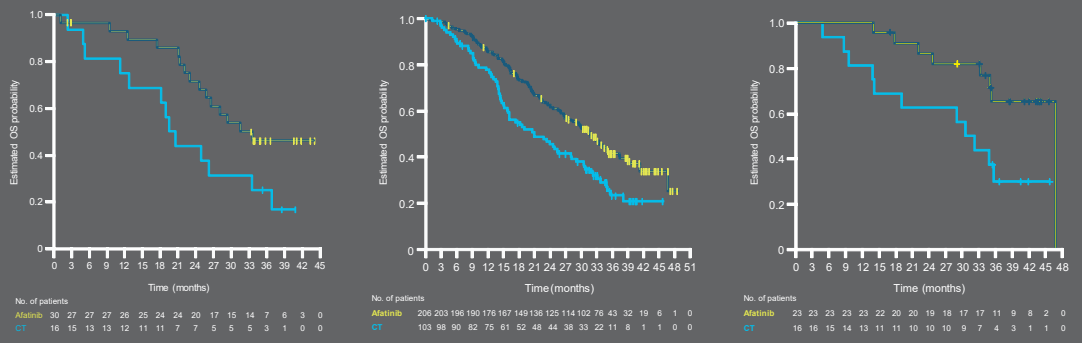
	Afatinib n=30	CT n=16
Median, mo	33.6	20.0
HR (95% CI)	**0.45** (0.21–0.95)	
p value	p=0.031	

Asian

	Afatinib n=206	CT n=103
Median, mo	31.7	21.1
HR (95% CI)	**0.61** (0.46–0.82)	
p value	p=0.001	

Japanese

	Afatinib n=23	CT n=16
Median, mo	46.9	31.5
HR (95% CI)	**0.34** (0.13–0.87)	
p value	p=0.018	



DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

23

Quality control

- In addition to usual required Quality
- Adequate evaluation of ethnic intrinsic and extrinsic factors by the same standard
- Building up high quality MRCT sites

DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

24

Afatinib vs. Gefitinib : Drug-related AEs

	Afatinib (n=160)		Gefitinib (n=159)		Afatinib (n=94)		Gefitinib (n=88)	
	All	Grade 3	All	Grade 3	All	Grade 3	All	Grade 3
Diarrhea	90.0	11.9†	61.0	1.3	88.3	5.3	59.1	1.1
Rash/acne*	88.8	9.4	81.1	3.1	88.3	8.5	79.5	2.3
Stomatitis*	64.4	4.4	23.9	-	70.2	7.4	29.5	-
Paronychia*	55.6	1.9	17.0	0.6	64.9	2.1	19.3	-
Dry skin	32.5	-	37.1	-	31.9	-	33.0	-
Pruritus	23.1	-	22.6	-	25.5	-	28.4	-
Fatigue*	20.6	5.6	14.5	-	10.6	1.1	9.1	-
Decreased appetite	16.3	0.6	11.9	-	18.1	-	17.0	-
Nausea	16.3	1.3	13.8	-	8.5	-	9.1	-
Alopecia	10.6	-	15.1	-	6.4	-	11.4	-
Vomiting	10.6	-	3.8	0.6	6.4	-	1.1	-
ALT increased	9.4	-	23.9	7.5‡	14.9	-	31.8	11.4
AST increased	6.3	-	20.8	2.5	9.6	-	29.5	2.3

Non-Asian ALT Gr 3 : 3%

FLEX

Adv NSCLC

First-L

EGFR(+)

RANDOMIZE

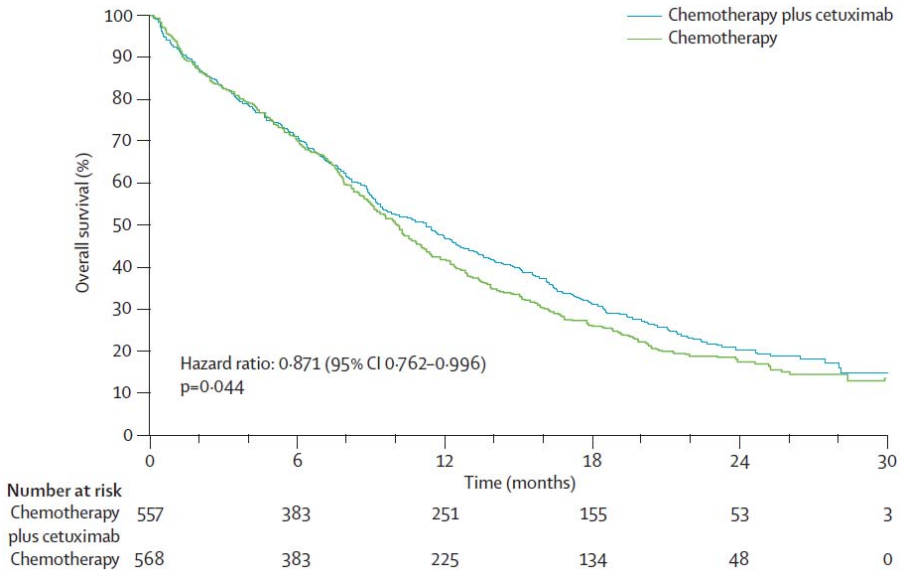
VNB / Cis + Cetuximab

Monoclonal Antibody to EGFR

VNB / Cis

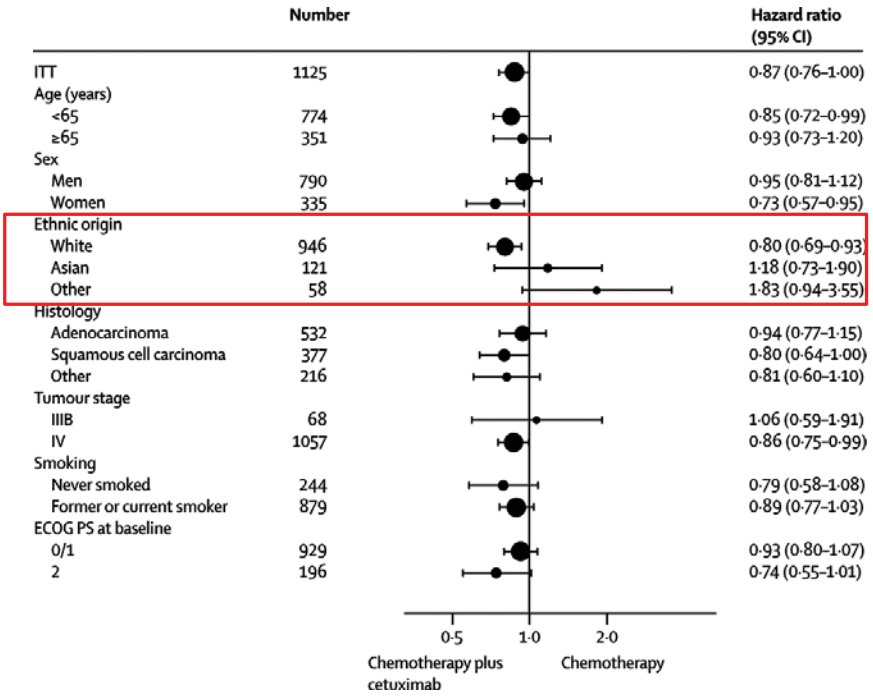
175 hospitals in 28 countries

FLEX: Overall Survival



Pirker R et al. Lancet 2009, 373, 1525

FLEX
ethnic sensitivity



Pirker R. et al. Lancet 2009

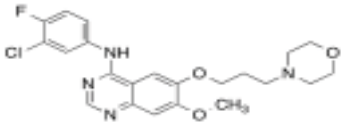
MRCT in exploratory stage

- Encourage early global MRCT
- Exploratory MRCT can collect scientific data (ethnic factors, PK/PD) to facilitate confirmatory MRCTs
- Exploratory MRCT can serve as the basis for regional approval

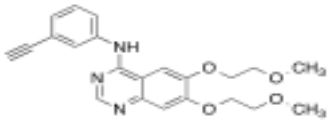
New TKI Recipe ? Early develop in multiple regions

3rd Generation mutant specific EGFR TKI

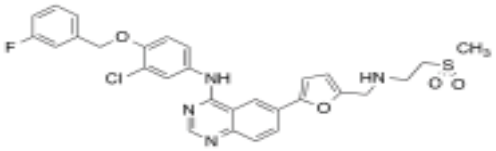
First generation (anilino-quinazolines)



Gefitinib

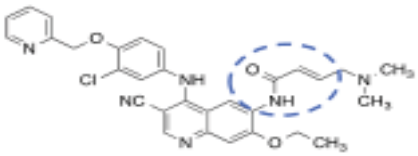


Erlotinib

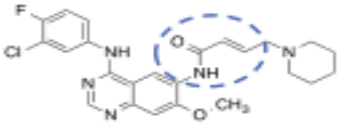


Lapatinib

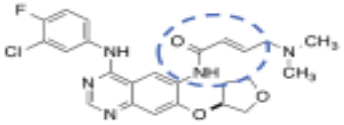
Second generation (anilino-quinazolines)



Neratinib (anilino-cyanoquinoline)

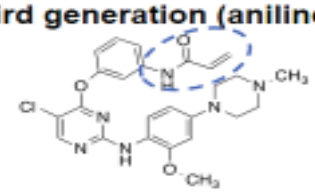


Dacomitinib

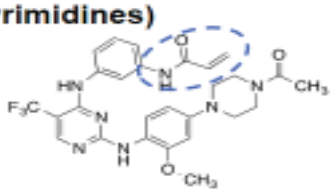


Afatinib

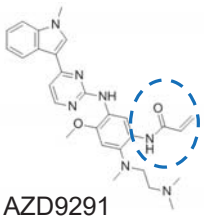
Third generation (anilino-pyrimidines)



WZ4002



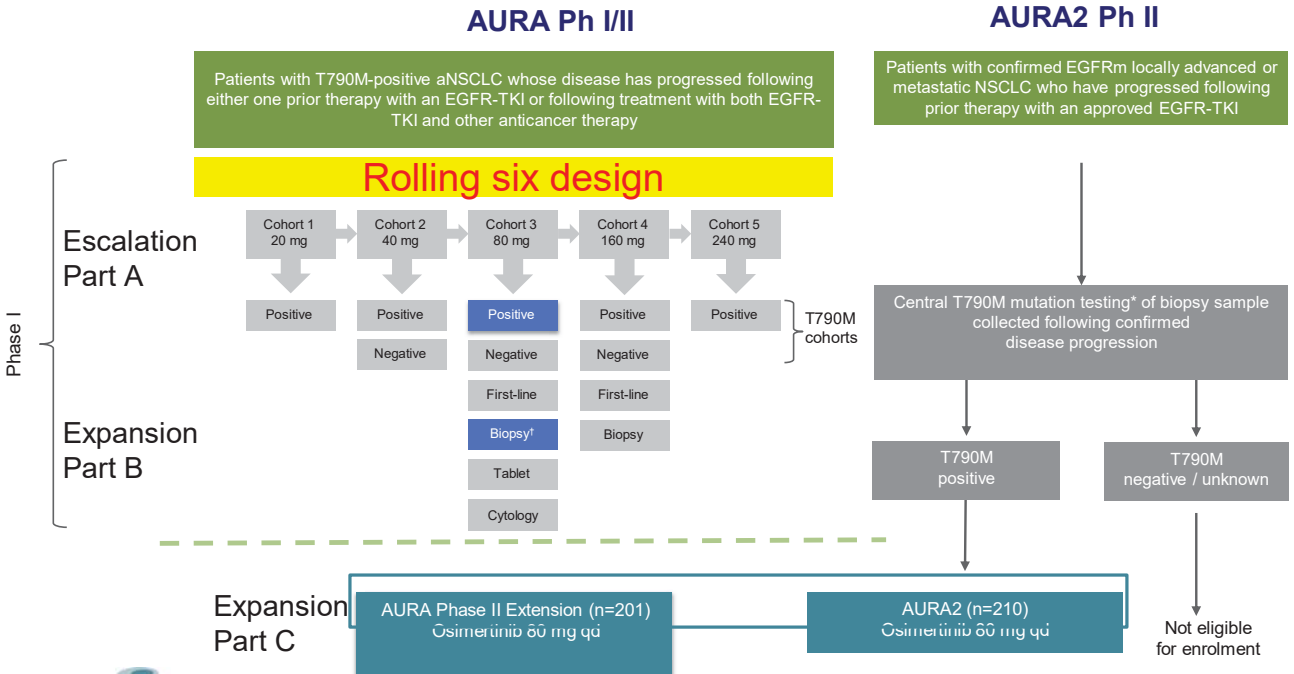
CO-1686



AZD9291

Alex Waterson

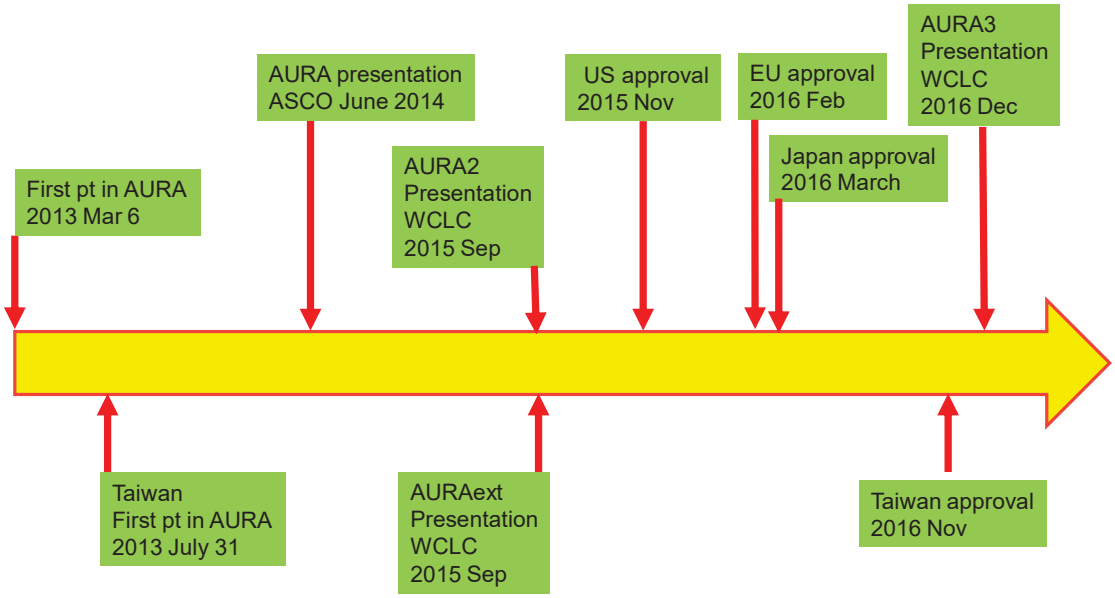
AZD9291 (Osimertinib) Early phase development



EUROPEAN LUNG CANCER CONFERENCE 2016

Yang JC et. al. ELCC 2016

Osimertinib Clinical Development



MRCT : E17

- May improve our ability to plan and design studies, answering scientific questions of intrinsic and extrinsic ethnic factors
- May impact small countries' participation in MRCT !!!
- Efficiency will become the most important issue for small countries to compete in MRCT.

Thank You

James Chih-Hsin Yang M.D., Ph.D.

楊志新教授

Professor and Director,Graduate Institute of Oncology,NTU

台灣大學醫學院腫瘤醫學研究所所長

Director, Department of Oncology, National Taiwan University Hospital

台大醫院腫瘤醫學部主任

Join the conversation #DIA2018

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

The Development of Pharmaceutical Industry in Taiwan

Annie Tsu-Hui Liu, Ph.D.
Director
Biotechnology, Health, Medicine and Agriculture Division,
Office of Science and Technology, Executive Yuan
Taiwan, ROC

Disclaimer – Content Slide

- 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.
-

DIA 2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

Taiwan Quick Facts

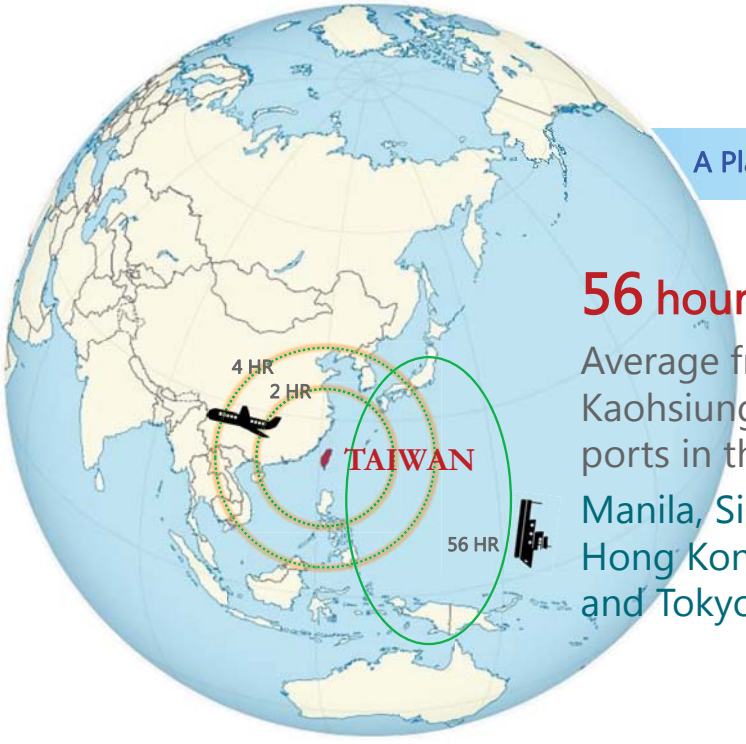
- Location
- Competitiveness
- Population & Healthcare
- Bio-Clusters
- And More .....

Taiwan – Asia-Pacific Transportation Hub

2.55 hours

Fly average from Taipei to six major cities in the western Pacific:

Tokyo, Seoul, Beijing, Shanghai, Hong Kong, and Singapore



A Platform Linking to the World

56 hours

Average from Kaohsiung to five major ports in the region:

Manila, Singapore, Hong Kong, Shanghai, and Tokyo

Why Taiwan Matters

No. / Asia

No. 4	WEF	Global Competitiveness Report 2017-2018 No. 15 / 137 countries
No. 2	BERI	Environmental Risks of Investment 2017 No. 4 / 50 countries
No. 2	GEDI	Global Entrepreneurship and Development 2017 No. 16 / 137 countries
No. 3	EIU	Global Business Environment 2014-2018 No. 14 / 82 countries
No. 4	IMD	Global Competitiveness 2018 No. 17 / 63 countries

Biopharmaceutical Innovation

5

DIA2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

Government Policies and Measures

5 + 2

Industry Innovation Program

Bio-Pharmaceuticals

- Build the Biomedical Corridor
- Upgrade Industry Infrastructure and Ecosystem
- Connect with the World
- Pursue the Industries of the Future

Asia. Silicon

Smart Machinery

Green Energy

National Defense

Circular Economy

New Agriculture

DIA2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

Population and Healthcare

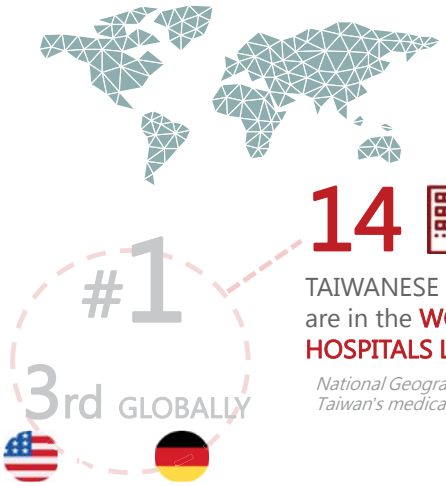
- **23 mil** people
  - Life Expectancy – Males>**77** ; Females: >**83**
  - Population over 65-**14%**
- "National Health Insurance Plan"
  - **One** single buyer and **one** single database
  - ~**99%** citizens covered by NHI since 1995
  - Low personal medical expanse, wide coverage with reimbursement restriction, an efficient system
  - Over **27,000** contracted medical care institutions

Source: : MOHW, 2017

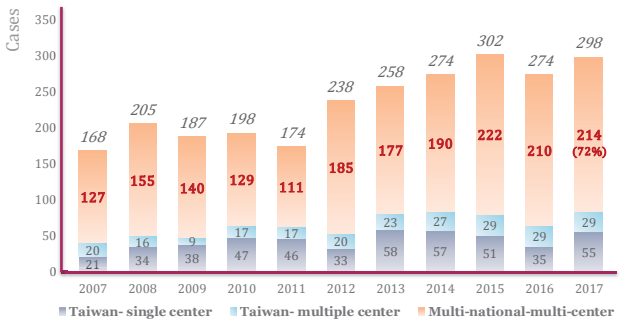
DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

7

Excellent Clinical Practices



Taiwan has demonstrated its ability to participating **multinational clinical trials** with the international community



Taiwan Clinical Trial Consortium (TCTC)

c-IRB Mechanism (Collaborative IRB Review)

Source: : TFDA, 2018

DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

8

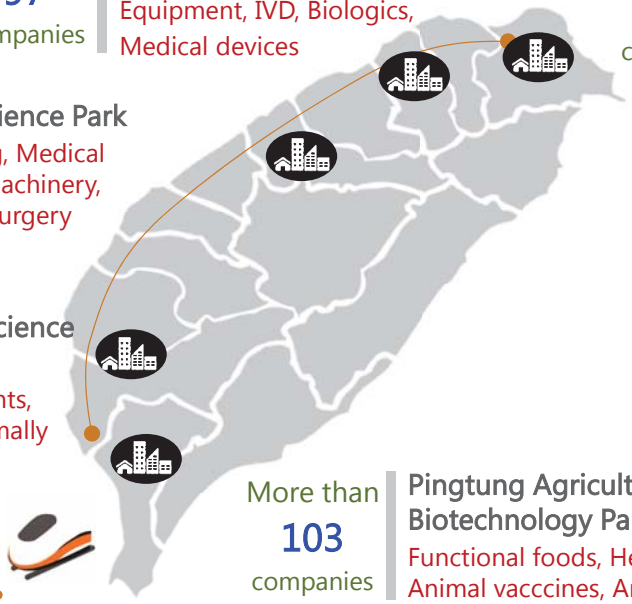
Comprehensive Bio-industrial Clusters

More than **97** companies
Hsinchu Science Park
Hsinchu Biomdeical Park
Equipment, IVD, Biologics, Medical devices

More than **178** companies
Nankang Biotech
Neihu Technology
R&D for New Drugs, Medical devices

More than **39** companies
Central Taiwan Science Park
Drug manufacturing, Medical devices, Precision machinery, Minimally invasive surgery

More than **74** companies
Southern Taiwan Science Park
Genetic drugs, Implants, Instruments for minimally invasive surgery



Taipei—Kaohsiung
1.5 hrs. by High Speed Rail

More than **103** companies
Pingtung Agricultural Biotechnology Park
Functional foods, Herbal medicine, Animal vacccines, Animal breeding

DIA2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

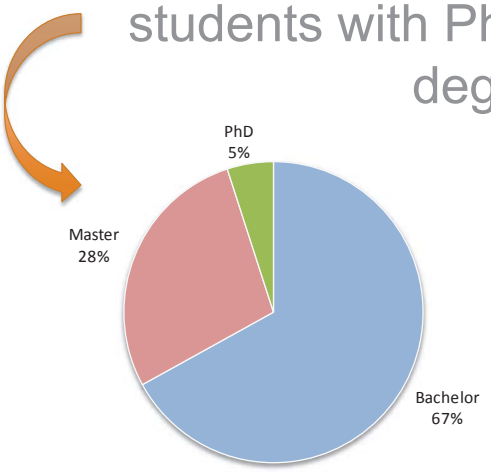
9

Well-trained Young Professionals Are Assets to the Industry

160+ universities and colleges

750+/yr graduate students with Ph.D. degree

> 30,000/yr
students in life science, health & medical fields



Source: : MOE, 2017

DIA2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

10

Sound Intellectual Property Protection

IP Protection

Intellectual Property Protection Laws

- Patent Law
- Trademark Law
- Copyright Law
- Fair Trade Act
- Copyright Collective Management Organization Act
- Integrated Circuit Layout Protection Act
- Trade Secrets Law

Actions

- Criminal liability
- Increased penalties of extraterritorial misuse
- Intellectual Property Rights Protection Police Force prevents and counter pirated products
- Improve professionalism of judgments by technical review officers of the Intellectual Property Court

New

Patent Linkage

The amendment of Pharmaceutical Affairs Act that relate to intellectual property, namely drug data exclusivity and patent linkage, was made by Presidential decree on January 31, 2018

Driving Forces to Innovation

Special Regulation for Promoting Technology-Based Enterprise Entering Taiwan's Capital Market

If an issuer obtains a clear written assessment issued by the TPEx-designated professional institution for a technology based enterprise, and that its products or technology have marketability, shall not be subject to the restriction of duration of corporate existence and financial requirements.

Tax Benefits for Biotech & New Pharmaceutical Company

Act for the Development of Biotech & New Pharmaceuticals Industry

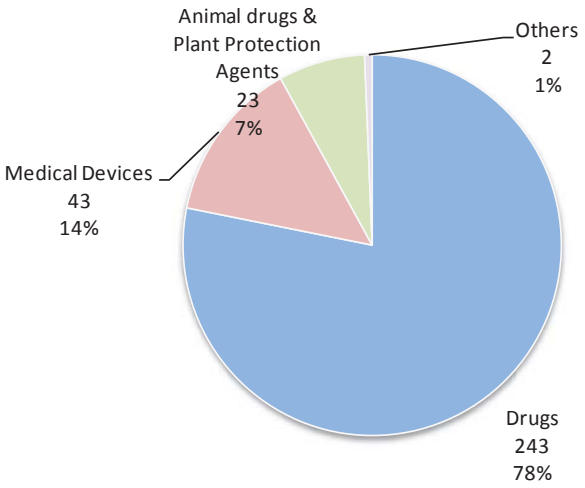
- ✓ **Research & development incentive:** 35% of R&D spending may be offset
- ✓ **Incentive for personnel training:** 35% of employee training may be offset
- ✓ **Shareholder investment offset:** Investors may be offset 20% of the original cost of shares
- ✓ **Tax deferral for technology appraised as capital stock**
- ✓ **Tax deferral for stock option certificates**

Over 130 Companies Receive Tax Benefits

132 qualified companies by Mar. 2018

311 qualified products by Mar. 2018

> 70 % are pharmaceutical companies



Source: : BPIPO, 03/2018

Active Capital Markets

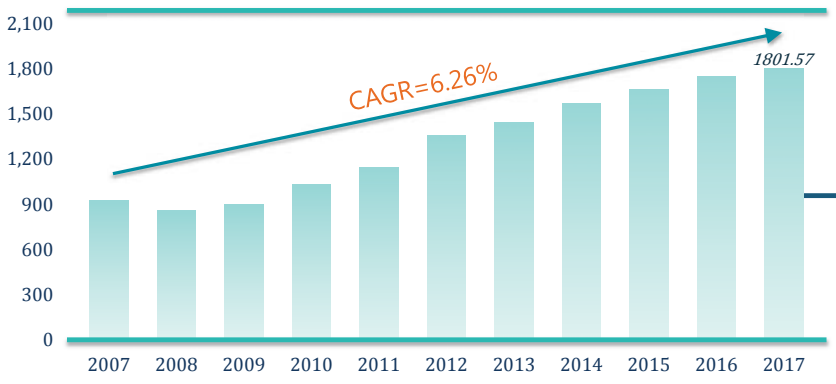
113 Bio-related stock-listed companies, No. 1 in Asia

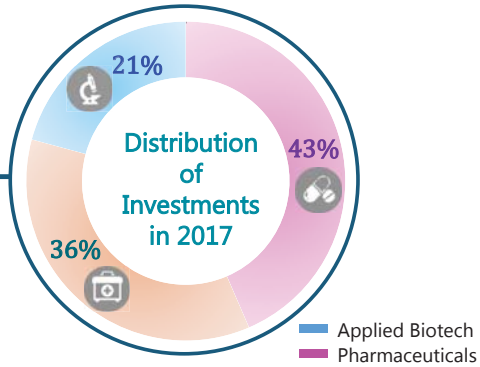
USD **24** billion Market Cap in total

USD **7.6** billion Revenue in total (+3.7%)

USD **1.8** billion Private investments in Bio

*Genetic Engineering & Biotechnology News (GEN's) 2016





Source: : BPIPO, 03/2018

Strong Support by the Government

The **Fantastic 4** in Taiwan are all biomed-related

President Tsai:
Cofounded TaiMed Biologics in 2007 (antibody treatment for HIV, Trogarzo, FDA approval granted, Mar. 2018)

Vice President Chen:
- Scientist in Epidemiology
- Former Minister of Health
- VP of Academia Sinica

Premier Lai of Executive Yuan: Physician and Lawmaker on Public Health Policy for many years

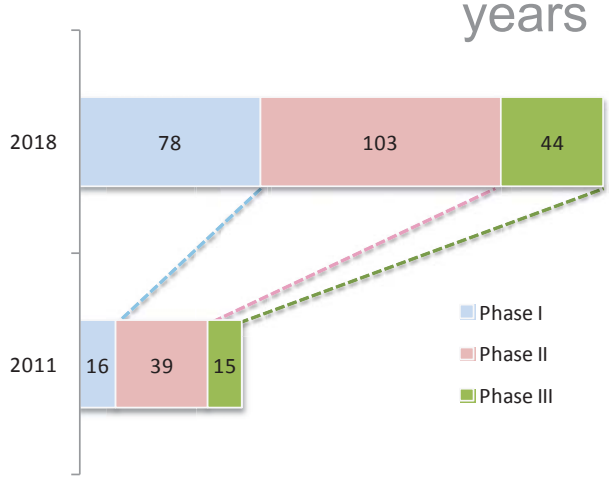
Mayor Ko of Taipei City: Well-known Trauma Surgeon in National Taiwan University Hospital

New Drug Pipelines Are Increasing

270+ new drugs by May, 2018

> 57 % filed US IND

Pipelines tripled in **7** years

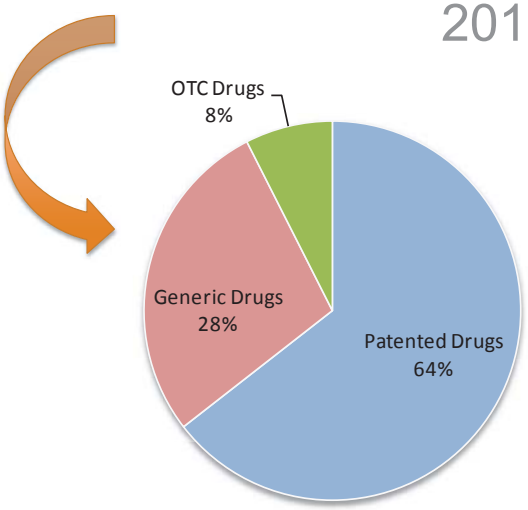


Source: : DCB, 03/2018

Steady Growth of Pharmaceutical Market

6.2 billion USD by 2017

CAGR **4%** in 10 years



Germany, USA, Ireland, France and Switzerland are **top 5** import countries by 2017

Source: : DCB, 03/2018

DIA2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

17

Increasing Exports Are Vital to Industry Expansion

- **130+** PCS/GMP domestic drug companies by 2018
- USA, China and Japan are **top 3** export countries by 2017
- CAGR **3.8%** in 6 years

- **5** new drugs are entering in global markets
- 100M USD and **124%** growth in international licensing by 2017

Source: : DCB, 03/2018

DIA2018
GLOBAL ANNUAL MEETING
BOSTON | JUNE 24-28

18

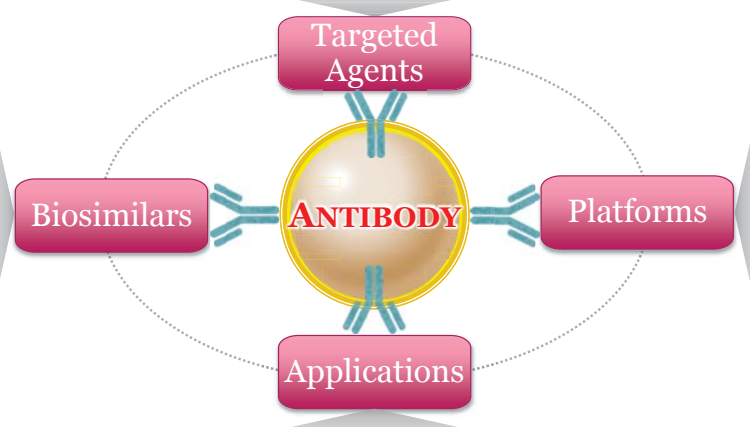
Biologics Are Right on the Spots

Taiwan Has Comprehensive Antibody Drug Development Pipelines

SSEA-4 | EGFR | PSGL-1（CD162） | glyco-variant of CD71 | TNF alpha | HER2 | NEO1 | PDGFRα | HSV gD

PD-1 | PD-L1 | CD4 | CD20 | CD23 | HIV-gp | HSV gD | CεmX | IL-6 | Globo H | IgE | SNS01 | VEGF

Herception (trastuzumab)
Humira (adalimumab)
Avastin (bevacizumab)
Rituxan (rituximab)
Xolair (omalizumab)
Actemra (tocilizumab)
Trogarzo (ibalizumab)
Perjeta (pertuzuma)



ADC / BsAB / Glycans

- Research Institutions
  - Academia Sinica
  - DCB
  - ITRI
- Comapies
  - TaiMed
  - CHO Pharma
  - Immunwork
  - EirGenix
  - AbGenomics
  - Henlix

Autoimmune diseases	Cancer	Infectious disease
Rheumatoid arthritis、Allergy	Pancreatic cancer、Lung cancer	AIDS、Anti-HSV

Source: : DCB, 05/2018

Catching the Trends

Taiwan's Efforts in Precision Medicine Development

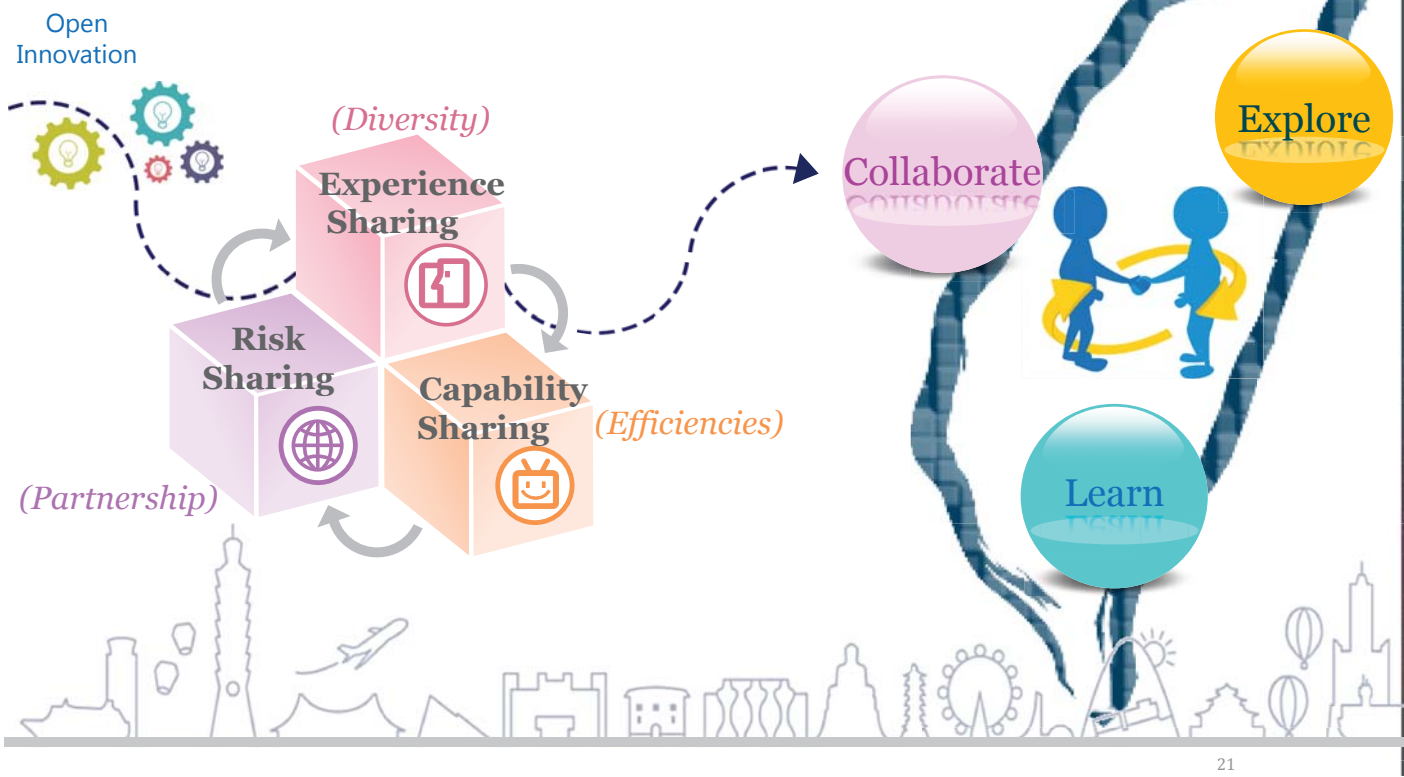
	Diagnostics				Medicine			
	Database	Reagent, Chips....	Software	Service	Antibody	Platform	New Therapeutics	CRO/CDMO
Companies	•ACT Genomics •Full Hope Biomedical •Vita Genomics	•General Biologicals •Personal Genomics •Pharmigene •Quark Bio	•ACT Genomics •GGA	•ACT Genomics •Libogene •Gene on Link •Genomics	•Glyconex •OBI •Tanvex •TaiMed •United Biopharma	•EirGenix •Glyconex •Henlix •Immun-work •OBI	•Celtec •Humorigin •Medigen •UBI •Vax Genetics	•Abnova •LASCO •Level •Mycenax •PPC •Tanvex •TPG
R&D	•NHRI •Academia Sinica	•ITRI	•NHRI •Academia Sinica		•DCB	•DCB •ITRI	•DCB •NHRI	

Resources

- Taiwan BioBank (Database)
- Laboratory Developed Tests
- National Health Insurance Database
- Taiwan Clinical Trial Consortium
- Strong Government Support

Source: : DCB, 05/2018

Taiwan Is Ready for the Future

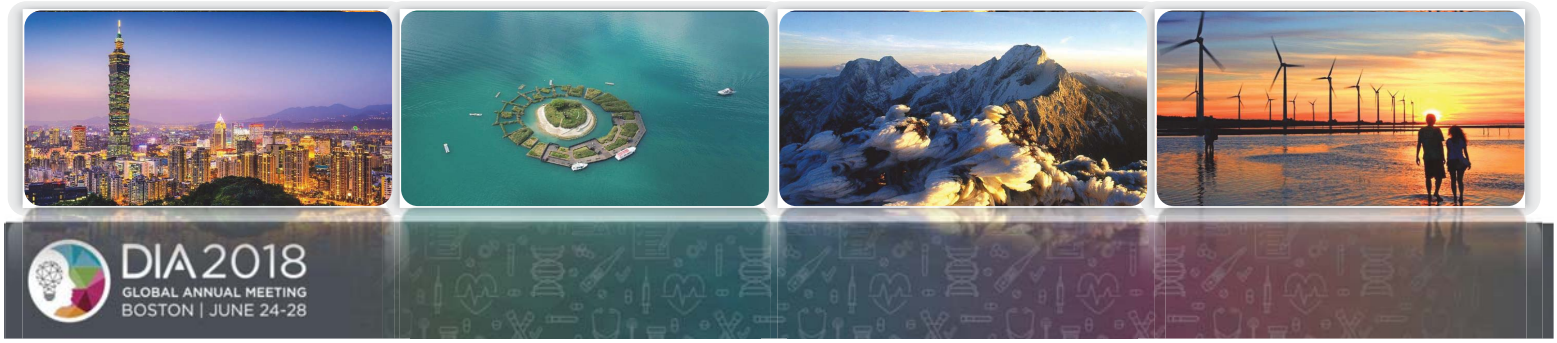


DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

21

Thank You for Your Attention

Annie Tsu-Hui Liu, Ph.D.
Director
Biotechnology, Health, Medicine and Agriculture Division,
Office of Science and Technology, Executive Yuan
Taiwan, ROC



DIA 2018 GLOBAL ANNUAL MEETING BOSTON | JUNE 24-28

An Adaptive Seamless Phase II/III Design in Drug Development for Binary Endpoints

張連成[1], 張敏琪[2], 蕭金福[*2,3], 陳惠芳[1], 吳秀梅[*1]

Lien-Cheng Chang[1], Min-Chi Chang[2], Chin-Fu Hsiao[*2,3], Hwei-Fang Cheng[1], Shou-Mei Wu[*1]

[1]Food and Drug Administration, Ministry of Health and Welfare, Taipei 115, Taiwan.
[2]Department of Statistics, National Chiao Tung University, Hsinchu 300, Taiwan.
[3]Institute of Population Health Sciences, National Health Research Institutes, Miaoli 350, Taiwan.

Abstract

Objective:
To use adaptive methodology to combine separated phase II and phase III clinical trials into a single trial.

Method:
We propose an adaptive seamless phase II/III design based on dichotomous data with controlling overall type I and II error rates. Sample sizes and critical values for each stage will also be determined.

Results:
Drug development is risky, complex, time-consuming and costly, often taking more than 10 years and costing over 800 million US dollars from start to regulatory approval for marketing. The current drug development paradigm may not be suitable today. New concepts, strategies, and methodologies are needed to encourage growth and investment in the pharmaceutical industry. We propose a seamless, adaptive phase II/III design for clinical trials with binary endpoints. In the phase II stage patients are randomly assigned to either receive one of several doses of the test drug or to the control group, If one or more doses are found more superior than the control group these doses are selected for the phase III stage. Patients of the selected dose groups and control group continue through to the confirmation stage. New patients recruited randomly receive a selected dose of either group. Critical value is found at each stage to determine whether the treatment should continue. Then traditional phase II and III trials are combined into a single trial. Data collected from phase II will be included in the final analysis, thus sample size reduction and time saving may be possible.

Conclusion:
This design could be used in regions with similar ethnicity, e.g. the greater Chinese area. Then the phase II stage can be conducted in one region, whereas the phase III stage can be conducted in all regions. This may help in harmonizing clinical trial data from all regions, and save time and money for drug development.

A Seamless Adaptive Phase II/III Design

Let K be the number of doses for the test drug, n_2 be the number of patients assigned to each of the K doses and the control group, X_i^{II} be the total number of response observed from the n_2 patients for the i^{th} group at the phase II stage respectively. Here $i = 0$ indicates the control group.

Assume that the responses are dichotomous and

$$X_i^{II} \sim B(n_2, r_i),$$

where r_i is the response rate for the i^{th} group and B represents a binomial distribution. It is desired to test the following hypothesis:

$$\mathrm{H_0}: r_i - r_0 \le 0 \text{ vs. } \mathrm{H_A}: r_i - r_0 > 0.$$

Let $T_i^{II} = \hat{r}_i^{II} - \hat{r}_0^{II}$ be the estimate of $r_i - r_0$. The accrual of another n_3 patients for each group will continue to the phase III stage for the control group and dose groups for which $C_1 \le T_i^{II} \le C_2$.

We also let X_i^{III} be the number of response observed from the n_3 patients in each group, $T_i^{III} = \hat{r}_i^{III} - \hat{r}_0^{III}$, where $\hat{r}_i^{III} = (X_i^{II} + X_i^{III})/(n_2 + n_3)$, and

$$X_i^{II} + X_i^{III} \sim B(n_2 + n_3, r_i).$$

The i^{th} dose is declared to be superior to the control group if $T_i^{III} > C_3$.

The probability of "accepting" the i^{th} dose group is

$$\begin{aligned}
&\varphi(r_i, r_0, n_2, n_3, C_1, C_2, C_3) \\
&= Pr\left(T_i^{II} > C_2\right) + \sum_{x=\lfloor n_2 C_1 \rfloor}^{\min(\lfloor n_2 C_2 \rfloor, n_2)} Pr\left(T_i^{III} > C_3 | n_2 T_i^{II} = x\right) \times Pr\left(n_2 T_i^{II} = x\right) \\
&\approx Pr\left(T_i^{II} > C_2\right) + \int_{C_1}^{C_2} Pr\left(T_i^{III} > C_3 | T_i^{II} = t\right) \times g(t)\, dt\,,
\end{aligned}$$

where $g(.)$ represents the probability density function of T_i^{II}. Under the null hypothesis, the expected total sample size is

$$\mathrm{E(N)} = (K+1)n_2 p_0 + \sum_{j=1}^{K} [(j+1)n_3 + (K+1)n_2]\, p_j,$$

where p_0 is the probability of stopping accrual at phase II stage, p_j is the probability of the accruals for j of the dose groups and control group are continued to phase III stage.

Result

- Since the ratio in Tables is less than 1, the phase II/III design can reduce the sample size compared with the traditional design.
- If the difference between the treatment group and the control group increases, both the sample size required for each stage and E(N) decrease.
- The required sample sizes per group for each stage increases as C_1 increases.
- Larger value of C_1 will produce higher probability of early stopping, and thus reduce the expected total sample size. It can also increase the success probability of the phase III stage for the clinical development.

Table1. $r_i - r_0$=0.20, K=1, (α, β) = (0.05, 0.2)

r_0	r_i	C_1	C_2	C_3	n_2	n_3	E(N)	n_2'	n_3'	*ratio*
0.05	0.25	0	0.22	0.08	11	26	47.53	40	40	0.46
		0.05	0.18	0.08	13	26	39.47	40	40	0.49
0.1	0.3	0	0.27	0.10	14	35	62.32	50	50	0.49
		0.05	0.21	0.09	18	36	57.04	50	50	0.54
0.2	0.4	0	0.30	0.11	19	49	86.06	65	65	0.52
		0.05	0.25	0.11	24	50	79.64	65	65	0.57
0.3	0.5	0	0.32	0.12	22	56	98.94	75	75	0.52
		0.05	0.26	0.12	28	57	93.19	75	75	0.57
0.4	0.6	0	0.34	0.13	23	59	103.88	78	78	0.53
		0.05	0.28	0.12	29	60	97.99	78	78	0.57
0.5	0.7	0	0.35	0.13	23	56	101.06	75	75	0.53
		0.05	0.29	0.13	28	58	95.32	75	75	0.57
0.6	0.8	0	0.37	0.14	20	49	88.18	65	65	0.53
		0.05	0.30	0.13	25	50	84.51	65	65	0.58
0.7	0.9	0	0.40	0.15	15	37	66.37	50	50	0.52
		0.05	0.33	0.14	19	37	64.27	50	50	0.58

Table2. $r_i - r_0$=0.15, K=1, (α, β) = (0.05, 0.2)

r_0	r_i	C_1	C_2	C_3	n_2	n_3	E(N)	n_2'	n_3'	*ratio*
0.05	0.25	0	0.17	0.07	18	42	77.31	61	61	0.49
		0.05	0.13	0.06	22	45	61.82	61	61	0.55
0.1	0.3	0	0.21	0.08	24	59	105.97	80	80	0.52
		0.05	0.15	0.07	31	63	91.47	80	80	0.59
0.2	0.4	0	0.23	0.09	33	83	147.43	110	110	0.53
		0.05	0.17	0.08	45	89	135.75	110	110	0.61
0.3	0.5	0	0.24	0.09	40	99	177.26	129	129	0.54
		0.05	0.18	0.08	53	105	162.22	129	129	0.61
0.4	0.6	0	0.25	0.09	42	106	188.04	138	138	0.54
		0.05	0.19	0.09	57	112	175.39	138	138	0.61
0.5	0.7	0	0.26	0.10	41	104	184.05	135	135	0.54
		0.05	0.20	0.09	57	110	175.37	135	135	0.62
0.6	0.8	0	0.27	0.10	37	93	165.29	121	121	0.54
		0.05	0.20	0.09	51	98	157.95	121	121	0.62
0.7	0.9	0	0.28	0.10	30	74	132.75	96	96	0.54
		0.05	0.22	0.10	41	77	127.27	96	96	0.61

Table3. $r_i - r_0$=0.15, K=2, (α, β) = (0.05, 0.2)

r_0	r_i	C_1	C_2	C_3	n_2	n_3	E(N)	n_2'	n_3'	*ratio*
0.05	0.25	0	0.19	0.07	20	53	147.27	77	77	0.47
		0.05	0.14	0.07	25	56	113.56	77	77	0.53
0.1	0.3	0	0.22	0.08	27	75	204.51	101	101	0.50
		0.05	0.17	0.08	36	78	170.61	101	101	0.56
0.2	0.4	0	0.25	0.09	38	106	288.59	140	140	0.51
		0.05	0.19	0.09	51	109	249.46	140	140	0.57
0.3	0.5	0	0.26	0.10	45	125	340.89	164	164	0.52
		0.05	0.20	0.09	61	129	301.42	164	164	0.58
0.4	0.6	0	0.27	0.10	48	134	364.72	174	174	0.52
		0.05	0.21	0.10	65	137	323.90	174	174	0.58
0.5	0.7	0	0.28	0.10	47	131	356.78	171	171	0.52
		0.05	0.22	0.10	64	134	320.58	171	171	0.58
0.6	0.8	0	0.29	0.11	42	118	320.35	154	154	0.52
		0.05	0.22	0.10	58	120	291.48	154	154	0.58
0.7	0.9	0	0.30	0.11	34	93	255.35	122	122	0.52
		0.05	0.24	0.11	46	94	232.87	122	122	0.57

n_2' and n_3': total sample sizes per group required for traditional phase II and phase III design, respectively. E(N): expected total sample size for phase II/III design.

Figure1. $r_i - r_0$=0.20, K=1, (α, β) = (0.05, 0.2), C_1=0

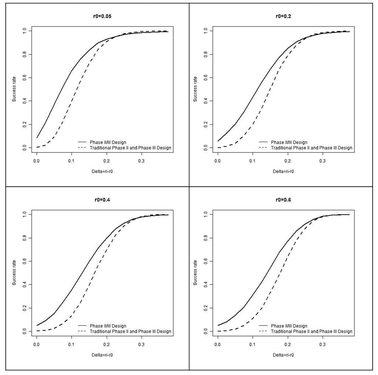


Figure2. $r_i - r_0$=0.15, K=1, (α, β) = (0.05, 0.2), C_1=0

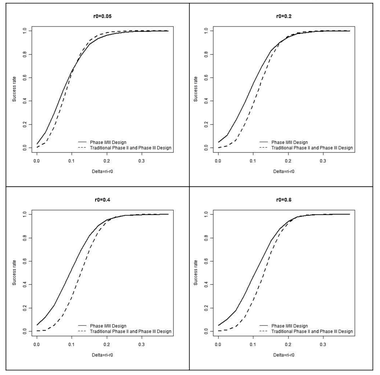


Figure3. $r_i - r_0$=0.15, K=1, (α, β) = (0.05, 0.2), C_1=0.5