計畫編號：DOH95-DC-1415

行政院衛生署九十五年度科技研究計畫

建立我國新型流感疫苗製劑臨床試驗管理機制及規範

研 究 報 告

執行機構：財團法人醫藥品查驗中心

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執行期間： 95 年 1 月 1 日至 96 年 12 月 31 日

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建立我國新型流感疫苗製劑臨床試驗管理機制及規範

朱夢麟、王蓉君、李元鳳、蔡承恩、李逸琦、廖紫歆、詹美華

財團法人醫藥品查驗中心

醫藥品查驗中心接受委託執行「建立我國新型流感疫苗製劑臨床試驗管理機制及規範」計畫，計畫全程二年；九十五年計畫執行目標及工作重點包括：(1) 設立新型流感專案工作小組「Pandemic Task Force Working Group (PTFWG)」；(2) 建立問題導向之專家諮詢委員會議「Issue-Oriented Advisory Committee Meeting (IOACM)」制度；(3) 提供疫苗相關產品研發的法規諮詢輔導；(4) 提出「新型流感疫苗查驗登記之審查注意要點」之草案。本計畫九十五年一月至十一月上旬重要成果摘錄如下：

(一) 成立新型流感專案工作小組；由三位臨床醫師、一位生醫博士、二位專案經理、一位企劃經理，共同負責規劃、推動業務及計畫之執行。

(二) 成立專家諮詢委員會並成立專家諮詢委員會 (IOAC)，並已召開二次專家會議。二次會議分別針對「新型流感疫苗查驗登記之審查注意要點草案 (95 年 6 月 8 日版)」及「國家衛生研究院新型流感疫苗研發過程臨床前試驗」應符合之法規要求等議題

進行討論。

（三）受理 6 件新型流感疫苗研發相關之法規諮詢輔導案。除 1 件仍進行輔導外，其餘均依據現行法規科學之要求，函文完成答覆諮詢。

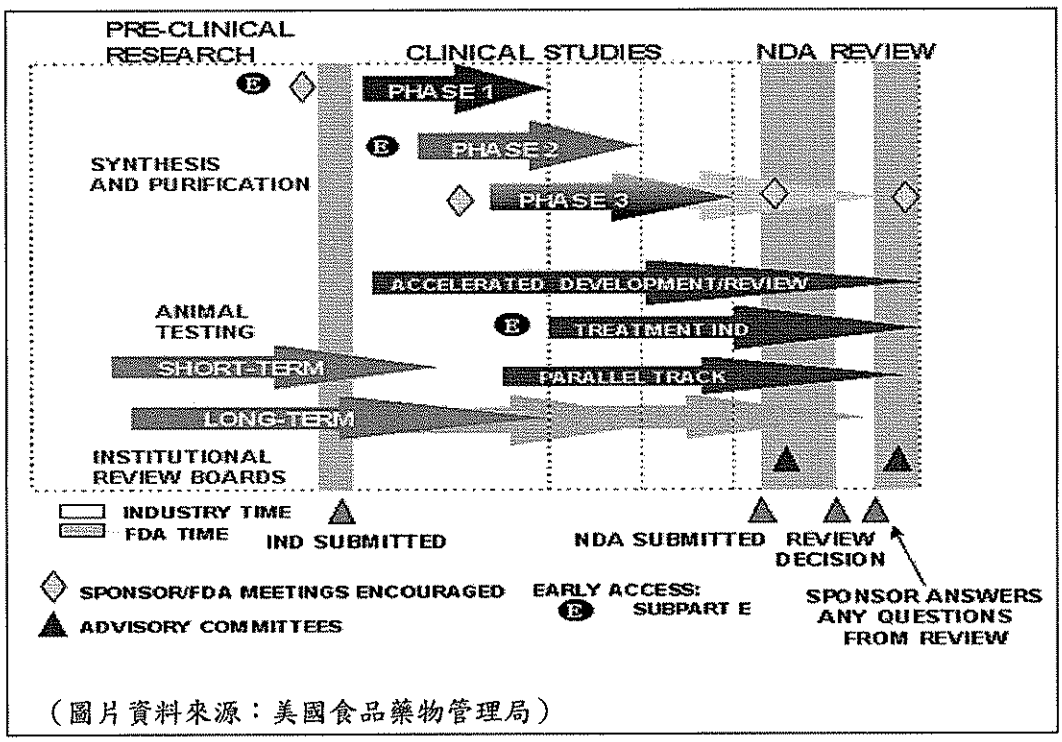
（四）已提出「新型流感疫苗查驗登記之審查注意要點」建議草案（8 月 28 日）；現正協助衛生署藥政處進行草案法條化公告作業。

本計畫 95 年度執行現況良好；原列年度工作目標及預期績效均已如期完成。96 年將依計畫原訂內容，持續運作新型流感專案工作小組以及專家諮詢委員會，並進行法規研擬、法規諮詢輔導等工作，以協助新型流感疫苗臨床試驗之進行。

關鍵詞：臨床試驗、查驗登記、新型流感專案工作小組

壹、前言

一、目前在流感疫苗生產技術方面主要以胚胎蛋培養與細胞培養二種製程為主。疫苗產品上市前之研發過程非常冗長（品質管制及臨床前研究約需 5-7 年、臨床研究約需 3-5 年），在經由胚胎蛋製程與細胞培養技術製備初型流感疫苗後，需進行臨床前研究（Pre-Clinical Research）及臨床研究（Clinical Studies）；研發單位在進行臨床研究之前，需要送臨床試驗計畫書以進行「臨床試驗計畫審查」（Investigational New Drug Application Review, IND Review），並在完成 phase III 臨床試驗之後、產品上市前要進行新藥查驗登記審查（New Drug Application Review, NDA Review）以取得產品上市許可。研發者需要提供完整詳細的資料，包括：試



（圖片資料來源：美國食品藥物管理局）

驗設計、化學製造管制、藥物動力學、藥理、毒理、臨床及統計等資料，IND 及 NDA 的審查。

二、流感疫苗研發過程的每一步驟，均需要相關環境之配合，除試驗設計外，更需要跨領域專業人員提供臨床試驗、查驗登記等相關法規之指導。流感疫苗無論是國內自行研發或引進國外廠商於國內研發，研究單位及業者在研發的關鍵性階段如果能獲得法規諮詢及相關輔導服務，解決研發過程所遭遇之困難，將能有效縮短產品上市時間、降低疫苗開發的成本。

三、在流感疫苗相關管理機制方面：國內有關疫苗查驗登記部分之法規，目前僅有「藥品查驗登記審查準則－疫苗藥品之查驗登記」，主管單位並未針對流感疫苗產品之查驗登記訂定相關規範，此外，在臨床試驗部分，目前也沒有特別針對流感疫苗訂立之相關管理機制。國內流感疫苗之自製，除疫苗研發生產外，極需配合研發現況，進行臨床前階段及臨床試驗管理機制與規範之建立，以協助政府儘快達成流感疫苗自製之目標。

四、本計畫在防疫工作上之重要性：

（一）本計畫將設立新型流感專案工作小組「Pandemic Task Force

Working Group (PTFWG)」，該小組主要負責疫苗相關產品研發的法規諮詢輔導及協助衛生署設立相關法規管理結構及框架之工作。此外，本計畫將建立問題導向之專家諮詢委員會議「Issue-Oriented Advisory Committee Meeting (IOACM)」制度，提供研發單位及廠商與製程、病毒、醫學等專家進行科學討論之機會，以解決研發過程所遭遇之困難。

（二）查驗中心協助衛生署提供生技製藥產業業者諮詢服務，自88年至94年5月底止，已受理諮詢案件共計640件。查驗中心累積多年新藥研發之諮詢輔導服務經驗，執行本項計畫將可有效協助新型流感疫苗產品開發之臨床試驗的進行。故本計畫的施行在自製流感疫苗的工作上佔有關鍵性的重要地位，能實際協助台灣發展流感疫苗相關產業，以加強台灣的防疫工作。

貳、實施方法

一、計畫總目標：

（一）設立新型流感專案工作小組「Pandemic Task Force Working Group (PTFWG)」，並建立問題導向之專家諮詢委員會議「Issue-Oriented Advisory Committee Meeting (IOACM)」制度。

（二）提供疫苗相關產品研發的法規諮詢輔導。

（三）協助衛生署建立疫苗相關產品研發過程的法規管理結構及框架。

（四）協助衛生署建立緊急情況下之疫苗相關產品查驗登記審查流程。

二、實施方法及進行步驟：

（一）第一年（95 年）：

1. 成立新型流感專案工作小組「Pandemic Task Force Working Group (PTFWG)」

（1）工作小組核心成員由查驗中心一位熟悉相關法規專業人員、一位生醫領域博士及一位臨床醫師組成。

（2）工作內容：

a. 負責計畫推動及執行。

b. 負責法規諮詢輔導服務工作、協調召開諮詢會議。

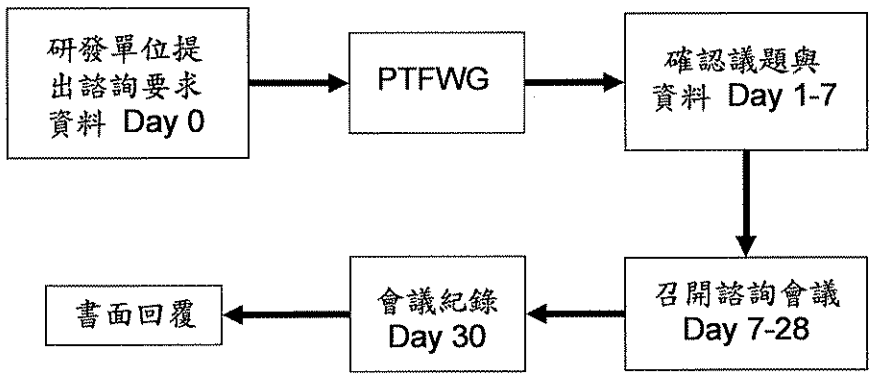
c. 負責專家諮詢委員會議「Issue-Oriented Advisory Committee Meeting」相關工作。

d. 負責相關法規及指引研擬工作。

e. 參加國內外與疫苗產品研發及管理相關會議，並與國內外研發及法規、管理相關單位及機構進行交流合作。

2. 提供問題導向之諮詢輔導服務：

（1）諮詢流程：



（2）研發單位及廠商應提供諮詢必要的資訊：

a. 明確之議題。

b. 背景說明、國內外相關文獻或資料，如有 Investigator's brochure 為佳。

c. 如為臨床試驗相關，應附 Synopsis。

(3) 運作重點：

a. 廠商或研究單位在向查驗中心提出諮詢服務時，需以書面方式提供與諮詢議題相關之初步研究結果。

b. 查驗中心之 PTFWG 應就廠商或研究單位提出之問題開會討論，並回覆。

c. 各項會議記錄將成為未來廠商或研究單位提出疫苗相關產品上市申請審查時的重要參考。

3. 建立專家諮詢委員會「Issue-Oriented Advisory Committee (IOAC)」制度

(1) 由查驗中心邀請 20-25 位國內外製程、病毒、醫學、法規等專家擔任諮詢委員會委員。

(2) 當 PTFWG 對廠商或研究單位提出之問題需徵詢其他專家意見時，由查驗中心負責召開「Issue-Oriented Advisory Committee Meeting」。

(3) 會議運作方式：

a. 由 PTFWG 向委員會提出案件將討論之特定議題。

b. 委員會將包括有法規科學實務經驗之專家，以便提供可行之建議。

c. 疫苗相關產品的實質快速審查可經由諮詢服務的充份溝通而達成。

4. 研擬管理法規及指引：

（1）瞭解國內研發及法規現況

a. 參加各界舉辦與疫苗研發及產品相關之研討會及專題演講。

b. 與國內衛生主管機關、研發單位、醫生、生物醫學及法界專家舉辦座談會。

c. 進行國內研發現況資料蒐集及追蹤。

（2）瞭解國外研發及法規現況

a. 參加國外與疫苗產品研發及管理相關之會議。

b. 與國內外研發及法規、管理相關單位及機構進行交流合作。

c. 邀請國外與疫苗產品研發及管理相關主管機關人員、研發單位專家、學界來訪。

d. 進行國外研發現況及法規研擬相關資料之蒐集及

追蹤。

（3）協助衛生署草擬流感疫苗相關產品之臨床試驗管理法規及指引。

（4）協助衛生署建立 Mock-up Vaccine 之審查規範與流程。

（二）第二年（96 年）：

1. 維持新型流感專案工作小組「Pandemic Task Force Working Group (PTFWG)」之運作

（1）工作小組核心成員由查驗中心一位熟悉相關法規專業人員、一位生醫領域博士及一位臨床醫師組成。

（2）工作內容：

a. 負責計畫推動及執行。

b. 負責法規諮詢輔導服務工作、協調召開諮詢會議。

c. 負責專家諮詢委員會議「Issue-Oriented Advisory Committee Meeting」相關工作。

d. 負責相關法規及指引研擬工作。

e. 參加國內外與疫苗產品研發及管理相關會議，並與國內外研發及法規、管理相關單位及機構進行

交流合作。

2. 持續配合國內疫苗研發階段，提供各研究單位及廠商流感疫苗相關試驗設計及法規諮詢輔導服務，以協助臨床試驗之進行。(流程及運作方式詳如第一年所述)

3. 維持專家諮詢委員會「Issue-Oriented Advisory Committee (IOAC)」之運作

(1) 由查驗中心邀請 20-25 位國內外製程、病毒、醫學、法規等專家擔任諮詢委員會委員。

(2) 當 PTFWG 對廠商或研究單位提出之問題需徵詢其他專家意見時，由查驗中心負責召開「Issue-Oriented Advisory Committee Meeting」。

(3) 會議運作方式：

a. 由 PTFWG 向委員會提出案件將討論之特定議題。

b. 委員會將包括有法規科學實務經驗之專家，以便提供可行之建議。

c. 疫苗相關產品的實質快速審查可經由諮詢服務的充份溝通而達成。

4. 研擬管理法規及指引：

(1) 持續瞭解並追蹤國內研發及法規現況

a. 參加各界舉辦與疫苗研發及產品相關之研討會及專題演講。

b. 與國內衛生主管機關、研發單位、醫生、生物醫學及法界專家舉辦座談會。

c. 進行國內研發現況資料蒐集及追蹤。

(2) 持續瞭解並追蹤國外研發及法規現況

a. 參加國外與疫苗產品研發及管理相關之會議。

b. 與國內外研發及法規、管理相關單位及機構進行交流合作。

c. 邀請國外與疫苗產品研發及管理相關主管機關人員、研發單位專家、學界來訪。

d. 進行國外研發現況及法規研擬相關資料之蒐集及追蹤。

(3) 協助衛生署草擬流感疫苗相關產品研發過程之管理法規及指引。

(4)協助衛生署建立新型流感疫苗 fast track approval 之查驗登記審查流程，並建立送審資料要求。

三、預定進度：

（一）第一年：

1. 成立新型流感疫苗專案工作小組 Pandemic Task Force Working Group (PTFWG)。(95.03)

2. 建立專家諮詢委員會 Issue-Oriented Advisory Committee (IOAC)。(95.05)

3. 提出新型流感疫苗適用之「藥品查驗登記審查準則－疫苗類藥品之查驗登記」修改建議版本。(95.06)

4. 提出「新型流感疫苗查驗登記之審查注意要點」建議草案。(95.12)

（二）第二年：

1. 持續運作新型流感專案工作小組(PTFWG)以及專家諮詢委員會(IOAC)會議。(96.06)

2. 配合國內疫苗研發階段，提供各研究單位及廠商流感疫苗相關試驗設計及法規諮詢輔導服務。(96.06)

3. 提供臨床試驗計畫書之快速審查流程，以協助臨床試驗之進行。(96.12)

4. 協助衛生署建立新型流感疫苗 fast track approval 之查驗登記審查流程。(96.12)

四、執行進度控管及追蹤：

（一）本計畫執行期間由計畫主持人全程負責執行進度的協調及督導。每年召開至少二次專家諮詢委員會（IOAC）會議。PTFWG 每一個月召集工作會議，會中除就主要工作項目依產學發展可能性擬定執行方法外，並進行執行進度的追蹤管理，以期完成計畫預定目標。

（二）為執行本項計畫，除直接參與計畫執行之人員外，查驗中心其他成員，包括：（1）負責化學、藥理、毒理、以及藥物動力學等各項「臨床前」試驗的審查工作的基礎醫學組、（2）負責臨床試驗審查的臨床組、（3）負責控制案件審查時程、提供案件審查所需參考的法規資料、擔任對外溝通窗口的專案組，都將適時支援。

參、結果

本計畫九十五年一月至十一月上旬的執行成果敘述如下：

一、成立新型流感專案工作小組

（一）工作小組已於 1 月成立。核心成員由查驗中心三位臨床醫師及一位生醫領域博士組成，並由二位專案經理及一位企劃經理協助業務推動及計畫執行。

（二）基於計畫執行需要，已分別於 2 月 7 日及 3 月 15 日召開二次工作會議，以進行分工及進度控管。

（三）工作小組於 3 月 3 日進行第一次法規草案研擬的內部討論會；會中確認目前衛署公告之「藥品查驗登記審查準則－疫苗類藥品之查驗登記」可補充或更新之內容，並交換法規草擬意見（內容詳附件一）。會中決議；原衛生署公告的審查準則，(1)就疫苗有關化學製造管制部份已相當完備，只需參考歐盟法規資料以重點說明及補充方式撰寫即可，(2) 臨床部分闕如，需重新撰寫。會中並決議將新增部分之「新型流感疫苗之查驗登記注意要點」以附件補充方式增列於原衛生署已公告之審查準則之後。

（四）於台灣醫誌（2006; Vol. 49 (3): 40-42）刊載「醫藥品

查驗中心於禽流感防疫中所扮演之角色」一文（附件二），並由小組成員於 2 月 24 日「2006 年台灣禽流感研討會暨台北市生物產業協會年會」針對「藥物法規科學在禽流感防治上的角色」（附件三）發表演講。主要介紹查驗中心將在（1）提供流感抗病毒學名藥物上市之法規依據，（2）提供 H5N1 新型流感疫苗研發之諮詢及法規服務，及（3）禽流感預防及治療相關新藥臨床試驗計畫書之快速審查流程，三部分扮演重要角色，以期擴大計畫執行效益。

（五）內部人員專業訓練（CDE In-house Staff Training）：

將邀請專家演講，於 11 月 6 日及 7 日舉辦。訓練主題包括：Development of HPV vaccine（附件四）、Development of immunologic adjuvants（附件五）、Regulatory Routes to Expedite Vaccine Approval（附件六）及 Development and evaluation of plasmid DNA and therapeutic vaccines（附件七）。

二、提供問題導向之諮詢輔導服務：

（一）已於 2 月提供查驗中心諮詢服務申請說明，向參與新型流感疫苗研發的專家及單位書面介紹查驗中心的諮詢服務機

制。研發的專家及單位透過網路線上申請（http://www.cde.org.tw）或撥打查驗中心諮詢專線（02-23224567 轉 888），將有專人提供服務。查驗中心期透過諮詢服務以協助減少產品研發、上市過程可能會遇到的法規問題（附件八）。

（二）受理 LT Mucosal adjuvant for nasal influenza vaccine、Adenovirus-vectored influenza vaccine、Adjuvant for H5N1 mock-up vaccine、Cell substrate for H5N1 mock-up vaccine 等與流感疫苗研發及臨床試驗有關之諮詢服務申請。

三、建立專家諮詢委員會「Issue-Oriented Advisory Committee (IOAC)」制度：

（一）已邀請國內 8 位學者專家（包括：何美鄉研究員、李慶雲教授、林文理總經理、施信如教授、張上淳主任、黃立民教授、黃昭蓮研究員、熊昭主任）擔任「新型流感疫苗專家諮詢委員會」核心委員。並邀請李啟仁博士(Supervisory Research Chemist, Center for Biologics Evaluation and Research, Food and Drug Administration, U.S.A.）擔

任法規諮詢顧問。

（二）查驗中心將於研擬新型流感疫苗產品研發上市相關法規，及特定議題之諮詢輔導等業務，徵詢委員意見。

四、研擬管理法規及指引：

（一）瞭解國內外研發及法規現況：

1. 國家衛生研究院疫苗中心及衛生署疾病管制局相關人員於1月19日來訪，由查驗中心召開「新型流感疫苗製劑與新型流感防治計畫溝通會議」(紀錄詳附件九)。會中由李敏西博士介紹「Guidelines for Developing Human Influenza H5 Vaccines」。本項會議促使國家衛生研究院及查驗中心瞭解彼此工作內容，並釐清在新型流感疫苗研發工作上未來的合作方向。

2. 蒐集並研讀EMEA及WHO的guidance共12份，以瞭解國外法規管理內容及現況。

3. 工作小組部份成員於3月4日在台大醫院國際會議中心與應「International Avian Symposium」邀請來台之講員Prof. Martine Denis進行會談，借重其在疫苗研發的經驗，就「一般原則」、「化學製造管制」、「臨床」等面向，討論疫苗相關管理法規的重要之點（附件十）。

4. 查驗中心工作小組邀請衛生署相關單位，包括：藥政處、疾病管制局、藥物食品檢驗局，於5月26日同赴國家衛生研究院疫苗研發中心訪視其新型流感疫苗研發及生產現況（紀錄詳附件十一）。

5. 籌辦研討會及round table discussion：

(1)查驗中心於11月3日假台大醫院國際會議中心301會議室（台北市徐州路2號3樓），辦理「新疫苗之發展及法規科學現況研討會」(Vaccine Symposium: The Evaluation and Regulatory Consideration on New Vaccine in the United States and Taiwan)。研討會邀請Chi-Jen Lee, ScD（CBER, FDA）、Lucia H. Lee, MD（CBER, FDA）、莊再成主任（國家衛生研究院疫苗研發中心）及劉定萍主任（行政院衛生署疾病管制局血清疫苗中心）於會中發表演說，研討會內容以美國的疫苗發展狀況、新疫苗臨床試驗的品質要求、新疫苗安全性及有效性的評估，及國內疫苗發展策略及現況等議題為主題，介紹美國及國內有關新疫苗的發展及法規科學現況，並由本中心資深審查員分享國內疫

苗產品的審查經驗，以供國內各界參考。本項會議總計約有 220 人次參加。（會議手冊詳附件十二）

（2）查驗中心於 11 月 6 日下午假廣電基金會放映室以「Development of pandemic influenza vaccines」（附件十三）、「Clinical evaluation of vaccines for pandemic influenza」為題（附件十四），邀請專家、政府及研發單位召開：「Round Table Discussion on Pandemic Influenza Vaccines」。現正進行相關籌備工作。本項會議總計約有 45 人參加。

（二）查驗中心正以衛生署公告之「藥品查驗登記審查準則－疫苗類藥品之查驗登記」為基礎，參考 European Agency for the Evaluation of Medicinal Products（EMEA）的相關規定，研擬針對新型流感疫苗適用之修改建議草案（暫稱：「新型流感疫苗查驗登記之審查注意要點」草案）。本項建議草案第二版已於 5 月底完成，並由專家針對草案內容提供修改建議後清稿，業於 8 月 28 日行文衛生署以為法規研擬參考（附件十五）。目前刻正協助衛生署藥政處進行草案法條化公告作業。

（三）查驗中心已於6月30日上午邀請所有「新型流感疫苗專家諮詢委員會」委員、國家衛生研究院相關研發人員、及衛生署藥政處、疾病管制局、藥物食品檢驗局相關官員，舉辦新型流感疫苗專家諮詢委員會暨第一次專家會議（會議紀錄詳如附件十六），針對草案內容提供建議及指導，以協助查驗中心順利完成法規草案研擬事宜。

（四）新型流感疫苗專家諮詢委員會暨第二次專家會議已於10月26日下午召開；會議針對國內疫苗發展現況、國家衛生研究院疫苗研發現況及問題、研發過程的法規需求等議題進行報告及討論。（會議紀錄詳如附件十七）

肆、結論與建議

本兩年之計畫執行總目標為「建立我國新型流感疫苗製劑臨床試驗管理機制及規範」。九十五年之計畫執行目標及工作重點包括：(1) 設立新型流感專案工作小組「Pandemic Task Force Working Group (PTFWG)」；(2) 建立問題導向之專家諮詢委員會議「Issue-Oriented Advisory Committee Meeting (IOACM)」制度；(3) 提供疫苗相關產品研發的法規諮詢輔導；(4) 提出「新型流感疫苗查驗登記之審查注意要點」之草案。九十五年一月至十一月上旬之執行現況良好，分別已達成下列成果：

一、已於年初成立新型流感專案工作小組（三位臨床醫師、一位生醫博士、二位專案經理、一位企劃經理），共同負責規劃、推動業務及計畫之執行。

二、九十五年經由專家諮詢委員會議之運作，分別於 (1) 95 年 6 月 30 日針對「新型流感疫苗查驗登記之審查注意要點（草案；95 年 6 月 8 日版）」，法規內容之九項討論議題召開專家會議進行討論，並完成會議紀錄，函文與會單位參存（95 年 7 月 20 日藥查企字第 950544 號函文）；並於 (2) 95 年 10 月 26 日針對「國家衛生

研究院新型流感疫苗研發過程臨床前試驗」應符合之法規要求，召開第二次專家會議並獲得初步之共識，會議紀錄並函文與會單位參存。

三、有關於疫苗相關產品，廠商於研發過程的法規諮詢輔導，於本年度則已承辦下列的案件：（1）CDC's influenza A/H5 IVD，諮詢有關查驗登記法規之需求；（2）DCB's LT mucosal adjuvant for nasal influenza vaccine，諮詢有關研發過程之輔導，本案件仍持續於關鍵途徑輔導中；（3）Vaxin's adenovirus-vectored influenza vaccine，諮詢臨床試驗相關議題；（4）NHRI's adjuvant for H5N1 mock-up vaccine，諮詢新疫苗佐劑之法規要求以及相關之試驗設計；（5）NHRI's cell substrate for H5N1 mock-up vaccine，諮詢以細胞培養病毒製造新型流感疫苗之相關法規要求；以及（6）Akzo Nobel's endemic/pandemic influenza vaccine 臨床試驗相關議題之諮詢案件。上述諮詢案件，除第（2）案仍於關鍵途徑輔導中（諮詢者提供的資料簡陋有限），其餘均依據現行法規科學之要求，函文完成答覆諮詢。

四、新型流感專案工作小組並透過讀書討論會以及與專家諮詢委員會之專家互動的方式，初步草擬完成「新型流感疫苗查驗登記之審

查注意要點（草案；95 年 8 月 28 日版）」，呈報衛生署藥政處（95 年 9 月 6 日藥查企字第 950671 號函文），並經衛生署藥政處函文（95 年 9 月 14 日衛署藥字第 0950340179 號）指示，於未來繼續協助其完成草案之法條化公告作業。

五、此外，查驗中心並積極舉辦以及派員參加疫苗相關之研討會，如：（1）派員於 95 年 2 月 24 日「台灣禽流感研討會暨台北市生物產業協會年會」中演講，講題為「藥物法規科學在禽流感防治上的角色」；（2）派員參加「2006 DIA Vaccine Workshop, May 16-17, 2006; Vienna, Austria」研討會，並撰寫成出國報告書及建議事項呈報主管機關;（3）派員參加 95 年 9 月 1-3 日於台南舉行之「Pasteur/NHRI/CDC Symposium on Re-Emerging Virus Infections」，了解目前相關新興疾病之疫苗研發現況;（4）查驗中心並邀請 FDA CBER 資深官員來台，於 95 年 11 月 3 日舉辦 Vaccine Symposium 「The Evaluation and Regulatory Consideration on New Vaccine in the United States and Taiwan」，以及 95 年 11 月 6 日舉辦「新型流感疫苗」議題之圓桌討論會議。上述研討會之舉辦與參與，有助於法規人員對於國內/國際上疫苗之研發進展的現況與未來之瞭解，更充實相關人員於法規科學工作上的內涵。

六、查驗中心人員並積極撰寫與新疫苗相關之法規科學現況介紹之文章，刊載於期刊中，共計有：(1) 王蓉君、陳恆德、朱夢麟；醫藥品查驗中心於禽流感防疫中所扮演之角色。台灣醫界雜誌 2006; Vol.49, No.3 p.40-42；(2) 王蓉君、李明亮、莊再成；新型流感疫苗之臨床試驗。Acta Paediatrica Taiwanica. 2006; Vol. 47 Suppl. p.18-22；以及 (3) 王蓉君、朱夢麟、陳恆德；新疫苗法規科學現況之簡介 (submitted)。查驗中心期望透過上述文章的刊載，能獲得各界先進的廣泛討論與指導，共同為本國的生物科技發展貢獻心力。

綜上所陳，本計畫未來仍應繼續推動執行之業務內容尚且包括：(1) 持續運作新型流感專案工作小組以及專家諮詢委員會會議，針對未來特定議題進行討論，並取得專家委員們符合國情之共識；(2) 配合國內疫苗研發各個階段，繼續提供各研究單位及廠商流感/新型流感疫苗相關試驗設計及法規諮詢輔導服務；(3) 提供新型流感疫苗臨床試驗計畫書之快速審查流程，以協助臨床試驗之進行；(4) 協助衛生署藥政處完成「新型流感疫苗查驗登記之審查注意要點 (草案)」法條化公告作業，並建立起「新型流感疫苗緊急情況下之快速查驗登記審查流程」機制。預期未來藉由上述各個工作要項的達成，將有助於我國生

物科技產業的發展，並達到防疫的功能。

而對於法規科學單位言之，雖位居於產業（產品由研發至上市的過程）之下游，但業者於研發過程中（上、中游），若有法規單位適時的參與並提供諮詢建議，則不僅可以提高產品成功問世的機率，更可以加快查驗登記的審查流程。新型流感疫苗於研發製造之過程中使用大量新的生產技術（manufacturing technology），法規單位欲提供關鍵性諮詢建議的角色，則必須更主動積極的瞭解其相關的研發新知，亦即對於產業的上、中、下游，需要能全盤的掌握。因此，唯有藉由不斷的參與國際性會議獲取及時的新知，法規單位才能適時的提供關鍵性之諮詢建議；而對於未能加入世衛組織的我國而言，此即部分困難之所在。

伍、參考文獻

1. Cell Culture Inactivated Influenza Vaccines - Annex to note for guidance on harmonisation of requirements for influenza vaccines (CPMP/BWP/2490/00)
2. Core SPC for Pandemic Influenza Vaccines (EMEA/CHMP/VEG/193031/2004/draft)
3. Development of influenza vaccine reference viruses by reverse genetics (WHO, July 2005)
4. Draft Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications - 2/17/2005
5. Draft Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications - 9/8/2000
6. Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines - 3/12/2001
7. Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials - 4/29/2005
8. EMEA pandemic influenza crisis management plan for the evaluation of and maintenance of pandemic influenza vaccines and vaccines (EMEA Nov 2005 (draft))
9. FEDERAL REGISTER Biological Products; Bacterial Vaccines and Related Biological Products; Implementation of Efficacy Review; Proposed Order - 5/15/2000

10. FEDERAL REGISTER Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Proposed Rule and Proposed Order - 12/29/2004
11. Federal Register Notice; Biological Products; Bacterial Vaccines and Related Biological Products; Revocation of Biologics Licenses - 5/29/2001
12. Guidance for Industry for the Evaluation of Combination Vaccines for Preventable Diseases: Production, Testing and Clinical Studies - 4/10/1997
13. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product - 1/5/1999
14. Guidance for Industry: FDA Review of Vaccine Labeling Requirements for Warnings, Use Instructions, and Precautionary Information - 10/1/2004
15. Guidance for Industry: How to Complete the Vaccine Adverse Reporting System Form (VAERS-1) - 9/8/1998
16. Guidance for Reviewers: Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol - 11/20/2000
17. Guideline on adjuvants in vaccines for human use (CPMP/VEG/134716/2004)
18. Guideline on dossier structure and content for pandemic influenza vaccine marketing authorization application (CPMP/VEG/4717/03)
19. Guideline on submission of marketing authorization applications for pandemic influenza vaccines through the centralized procedure (CPMP/VEG/4986/03)

20.National Vaccine Advisory Committee. "United States Vaccine Research: A Delicate Fabric of Public and Private Collaboration." Pediatrics, Vol 100(6), Dec.1997, pp. 1015-1020.

21.Note for guidance on harmonisation of requirements for influenza vaccines (CPMP/BWP/214/96)

22.Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95)

23.Note for Guidance on the Clinical Evaluation of New Vaccines (CPMP/EWP/463/97)

24.Note for Guidance on the Clinical Safety Data Management

25.Parkman PD, Hardegree MC. "Regulation and Testing of Vaccines." In Plotkin SA, Orenstein WA, [eds.]. Vaccines, 3d ed. Philadelphia: Saunders; 1999, pp.1131-1143.

26.Production of pilot lots of inactivated influenza vaccines from reassortants derived from avian influenza viruses (WHO, Nov 2003)

27.Stehlin, Isadora. "How FDA Works to Ensure Vaccine Safety." FDA Consumer Magazine, March 1996.

28.US CDC National Immunization Program

29.因應禽流感可能入侵防治對策（940819 國安會議簡報）

30.因應禽流感可能入侵防治對策（941031 國安會議簡報）

31.我國因應流感大流行準備計畫 (2005/9/23)

32.流感疫苗研究發展計畫（2005/9/22）

33.規劃流感疫苗自製計畫（2005/9/22）

34.藥品查驗登記審查準則－疫苗類藥品之查驗登記

陸、附錄

一、 法規草案研擬的內部討論會會議紀錄（3 月 3 日）

二、 醫藥品查驗中心於禽流感防疫中所扮演之角色／台灣醫誌 Vol. 49 (3): 40-42, 2006

三、 藥物法規科學在禽流感防治上的角色／2006 年台灣禽流感研討會暨台北市生物產業協會年會（2 月 24 日）

四、 Development of HPV vaccine／Lucia H. Lee, M.D.

五、 Development of immunologic adjuvants／李啟仁博士

六、 Regulatory Routes to Expedite Vaccine Approval／Lucia H. Lee, M.D.

七、 Development and evaluation of plasmid DNA and therapeutic vaccines／李啟仁博士

八、 查驗中心諮詢服務申請說明

九、 新型流感疫苗製劑與新型流感防治計畫溝通會議紀錄（1 月 19 日）

十、 與 Prof. Martine Denis 會談紀錄／International Avian Symposium（3 月 4 日）

十一、赴國家衛生研究院疫苗研發中心訪視紀錄（5 月 26 日）

十二、新疫苗之發展及法規科學現況研討會(Vaccine Symposium: The

Evaluation and Regulatory Consideration on New Vaccine in the United States and Taiwan）會議手冊

十三、 Development of pandemic influenza vaccines／李啟仁博士

十四、Clinical evaluation of vaccines for pandemic influenza ／Lucia H. Lee, M.D.

十五、新型流感疫苗查驗登記之審查注意要點草案（8月28日版）

十六、新型流感疫苗專家諮詢委員會暨第一次專家會議紀錄（6月30日）

十七、新型流感疫苗專家諮詢委員會暨第二次專家會議紀錄(10月26日）

流感防治計畫工作會議

（讀書會第一次會議）

會議紀錄

時　　間：民國 95 年 3 月 3 日（星期五）上午 11：00～12：00

地　　點：本中心第五會議室

出席人員：朱夢麟、王蓉君、李元鳳

記　　錄：李逸琦

說明事項：

本讀書會為因應新型流感疫苗工作小組 95 年度預定工作內容中，「法規建立」之工作項目，主要在於確認目前衛署公告之「藥品查驗登記審查準則－疫苗類藥品之查驗登記」中，建議可補充或更新之內容，並收集討論可參閱之國外公佈法規。

決議事項：

- CMC 部分法規：

  由於「藥品查驗登記審查準則－疫苗類藥品之查驗登記」之 CMC 部分相當完整，故將參考歐盟法規資料以重點說明及補充方式撰寫。

- 臨床部分法規：

  1. 由於「藥品查驗登記審查準則－疫苗類藥品之查驗登記」之臨床部分幾乎闕如，而「SARS 疫苗審查注意要點（草案）」與臨床相關部分為條列式簡述；因此，臨床部分法規需重新撰寫。
  2. 於 2006/01/19 與 NHRI communication meeting 中，達成共識參考歐

盟現行法規為主：

a. EMEA/CPMP/VEG/4717/03 Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application;
b. EMEA/CPMP/BWP/214/96 Note for Guidance on harmonization of Requirements fro Influenza Vaccines.

- 朱醫師指示：將新增部分之「新型流感疫苗之查驗登記注意要點」以附件補充方式增列於衛生署已公告之「藥品查驗登記審查準則－疫苗類藥品之查驗登記」之後。

醫藥品查驗中心於禽流感防疫中所扮演之角色

王蓉君 陳恆德 朱夢麟

截至 2005 年 12 月 23 日為止，經 WHO 確定之禽流感累積病例已有 141 例，並且已經造成 73 人的死亡 (表1)[1]。目前於防疫之疫情等級上，國內尚在 0 級：即國外發生高病原性家禽流行性感冒感染人之確定病例 (表2)[2]；而專家一致認為禽流感已不是「會不會來的問題」，而是「什麼時候來的問題」。世界衛生組織秘書長更呼籲民眾：「以目前的疫情來看，全球爆發人類禽流感疫情只是時間早晚問題。」世界衛生組織更保守估計，若爆發人傳人的禽流感流行，全球可能有 200 萬到 700 餘萬人死於禽流感，威力遠勝於只死亡 700 餘人的 SARS。台灣和已有病例之亞洲各國往來極為頻繁 (中國有 30 萬台商，越南有 9 萬台商，台灣有 3 萬越籍新娘)，疫情之傳播隨時可能襲台，不得不加緊防備。

我國在針對禽流感的防治措施上，衛生署將禽流感流行情況分為 0 級、A1 級、A2 級、B 級、C 級 (表2)，疾病管制局等相關單位依據疫情等級而訂有不同的應變措施。就防疫上措施訂有：我國因應流感大流行三大策略 (傳染阻絕手段、流感抗病毒藥劑、新型流感疫苗) 和四道防線 (阻絕境外、邊境檢疫、社區防治、醫療體系之保全)[2]。

財團法人醫藥品查驗中心 (簡稱查驗中心) 正式成立於民國 87 年 7 月 13 日，其目的是藉網羅醫藥學相關訓練背景之高科技人員，進行醫藥品審查專業訓練，以建立嚴謹之新藥 (含生物製劑) 審核團隊，為國人用藥安全把關。查驗中心組織架構精簡，各組人員專業分工，包含化學製造及管制、藥理/毒理、藥動，生物製劑、臨床各專科領域、統計、藥政法規等專業人才，以及美國 FDA 中具新藥研發、藥品審查經驗專長的專家顧問群。查驗中心之主要業務即在於以專業之法規科學 (regulatory science) 協助衛生署建立公開、透明的審查流程，提昇審查品質與效率，提供業界有關研發及法規諮詢的服務，更進而配合我國生技製藥產業之促進發展；故查驗中心之角色不僅在為國人的用藥安全做為守護者，同時更是做為健康產業之促進者。因此，財團法人醫藥品查驗中心於禽流感防疫中所扮演之角色，主要在於 1. 提供流感抗病毒學名藥物上市之法規依據，2. 提供 H5N1 新型流感疫苗研發之諮詢及法規協助，以及 3. 禽流感預防及治療相關新藥臨床試驗計畫書之快速審查流程。

財團法人醫藥品查驗中心

抗病毒藥物之背景

在疫苗可被普遍使用做為防疫工具之前，目前有數種抗病毒藥物，經 WHO 專家認為是可以做為有效的預防或治療 H5N1 病毒。二種屬於 neuraminidase 抑制劑類的藥物：oseltamivir (商品名 Tamiflu 克流感) 以及 zanamivir (商品名 Relenza 瑞樂沙)，在臨床研究顯示其可以減少由季節性流行性感冒病毒所造成疾病的嚴重性和縮短患病的期間。值得注意的是 neuraminidase 抑制劑類的藥物，其藥理機轉乃抑制病毒由受感染細胞中釋出，因此早期使用可減輕症狀及降低傳染力，其有效性必需在症狀出現後 48 個小時之內投予藥物。Neuraminidase 抑制劑被預期對於 H5N1 病毒仍屬有效；因此對於感染到 H5N1 的人而言，此類藥物如果早期投予的話，預期應該可以降低疾病的嚴重度以及提高其存活率，但在臨床上的資料 (經驗) 目前是非常有限的。另一類抗病毒藥物：M2 抑制劑 amantadine 和 rimantadine，應該亦具有對抗流行性感冒病毒的能力，但病毒可能很快即發展出對這些藥物的抗藥性，因而限制了他們臨床上的療效。目前已知一部分流行的鳥類 H5N1 病毒已經對 M2 抑制劑產生完全的抗藥性，另一部分則否[3]。

抗病毒藥物之臨床試驗報告

在一項對健康且未接種過疫苗、年齡 12~65 歲的受試者所進行的預防流行性感冒臨床試驗之結果顯示，克流感以 75 毫克一天一次投與連續 42 天，在社區性的爆發流感期間可以有效降低經實驗室證實之流行性感冒發生率，其中使用克流感預防組發生率為 1.2% (6/520)，而未使用之對照組發生率為 4.8% (25/519)。同樣的，對於居住在護理之家的老年人 (約 80%曾接種疫苗，14% 患有慢性呼吸道阻塞性疾病，

表1　通報 WHO 之確定禽流感 A/(H5N1) 累積病例；至 2005 年 12 月 23 日止[1]

病例發生年份	柬埔寨		中國		印尼		泰國		越南		總合	
	個案數	死亡人數	個案數	死亡人數	個案數	死亡人數	個案數	死亡人數	個案數	死亡人數	個案數	死亡人數
2003	0	0	0	0	0	0	0	0	3	3	3	3
2004	0	0	0	0	0	0	17	12	29	20	46	32
2005	4	4	6	2	16	11	5	2	61	19	92	38
總合	4	4	6	2	16	11	22	14	93	42	141	73

表2　流行疫情等級

分級	啓動時機
0 級	國內檢出 H5 或 H7 型家禽流行性感冒病毒或 國外發生高病原性家禽流行性感冒感染人之確定病例。 1. 國內禽鳥發生低病原性家禽流行性感冒。 2. 國內禽鳥發生高病原性家禽流行性感冒。
A1 級	國外發生人傳人之新型流行性感冒確定病例。
A2 級	國內發生禽畜類傳染至人、境外移入、實驗室感染等新型流行性感冒疑似病例。
B 級	國內發生新型流行性感冒人傳人之確定病例。
C 級	國內進人新型流行性感冒人傳人確定病例之大規模流行。

43% 患有心臟病)，給予上述之預防性藥物，臨床試驗之結果顯示可以降低流行性感冒的發生率，對照組爲 4.4% (12/272) 而克流感預防組爲 0.4% (1/276)[4,5]。

對於患有流行性感冒患者的其他家庭成員，給予接觸患者 (暴露) 後的預防性藥物，在接觸患者兩天之內以克流感 75 毫克一天一次投予連續七天，可以降低經實驗室證實之流行性感冒的發生率，其中對照組爲 12% (24/200) 而克流感預防組爲 1% (2/205)[4,5]。

流感抗病毒學名藥物上市之法規要求

目前國衛院逐步完成國產之第一批克流感藥物，預計於明年 3 月可以投入量產。與原廠羅氏藥廠生產之克流感相比較，國產之克流感可視爲是學名藥。除於重大緊急危難情形之外，學名藥在取得上市之前，必需證明其與原廠藥物於藥劑上之相等性 (pharmaceutically equivalent) 以及生體上的相等性 (bioequivalent)，才能引用羅氏藥廠生產之克流感相關數據。因此國產之克流感藥粉需於未來證明其與原產之克流感口服懸浮液具有生體上的相等性後才可以上市。此外，由於未來國產克流感藥粉可能被泡製成溶液調劑使用，因此也需證明克流感藥物在溶液狀態的藥物安定性[6-10]。

H5N1 新型流感疫苗研發之國際現況

賽諾菲藥廠於 2005 年 12 月 15 日宣佈該公司研發之 H5N1 疫苗於人體試驗的初步結果。此項添加了疫苗輔佐劑 alum 的 H5N1 疫苗初步顯示其於受試者可以產生不錯的免疫反應。此人體臨床試驗是在 300 個志願者的身上進行測試 H5N1 疫苗，志願者被分成爲六個小組，使用三種不同劑量分別爲 7.5、15 和 30 微克 (microgram)，添加或不添加疫苗輔佐劑 alum 之 H5N1 疫苗，在間隔 3 週給予兩次注射。其中以添加了疫苗輔佐劑之 30 微克劑量 H5N1 疫苗兩次注射後所產生的免疫反應，得以達到歐盟法規單位 (European Agency for Evaluation of Medicinal Products) 對於流感疫苗注射後需產生免疫反應之標準的要求。初步資料顯示此「原型」(prototype) 疫苗具有預防 H5N1 病毒的效果[11]。

疫苗研發之諮詢及法規協助

由於 H5N1 疫苗屬於全新研發的「原型」疫苗，因此必須要有完整的臨床前 (pre-clinical) 的資料，以及人體的第一、二階段試驗結果的學理依據，才得以進入第三階段的臨床試驗。全新的疫苗在人體 phase III 臨床試驗驗證其療效 (亦即：臨床上對傳染性疾病之保護性) 時，其療效指標應該以「疾病的預防」爲其目標；但由於 H5N1 原型疫苗之研發階段，並未發生眞正的人類大規模禽流感爆發，因此要偵測「疾病的預防」有其實際執行層面上的困難；因此，在法國賽諾菲藥廠研發的 H5N1 原型疫苗，是以替代免疫力生成指標 (surrogate immunogenicity endpoint) 取代，做爲其臨床保護效果之評估，此點目前爲歐盟法規單位所接受的。我國若有相關研發 H5N1 疫苗之試驗，基本上參考此一精神應可以被接受[12-14]。

相關新藥臨床試驗計畫書之快速審查流程

財團法人醫藥品查驗中心曾於 2003 年我國 SARS 流行期間，在網站上公告有關 SARS 新藥臨床試驗計畫書之快速審查流程要點。對於禽流感之防疫基本上也是相同，即相關之臨床試驗計畫書也將提供快速審查的流程。世界衛生組織也一再呼籲大眾，在

禽流感尚未爆發大的疫情之前，即應事先草擬準備好相關臨床試驗計畫書，一但疫情不幸眞正爆發時，即可立即使用上[13,15]。

參考文獻

1. http://www.who.int/csr/disease/avian_influenza/country/cases_table_2005_12_23/en/index.html/ 2005 年 12 月 23 日。
2. http://flu.cdc.gov.tw/ 2005 年 12 月 23 日。
3. http://www.who.int/csr/disease/avian_influenza/antivirals2005_11_3/en/print.html/ 2005 年 11 月 3 日。
4. Tamiflu New Drug Application: Registration's Clinical Study Reports.
5. Tamiflu: Micromedex, Drugdex Drug Evaluations.
6. http://www.fda.gov/cber/gdlns/drugcmc.pdf/ 2005 年 12 月 16 日。
7. http://www.fda.gov/cber/gdlns/drugsubcmc.pdf/ 2005 年 12 月 16 日。
8. http://www.fda.gov/cber/gdlns/stabdft.pdf/ 2005 年 12 月 16 日。
9. http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf/ 2005 年 12 月 16 日。
10. http://www.fda.gov/cder/guidance/index.htm/2005 年 12 月 16 日。
11. http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/news/dec1505sanofi.html/ 2005 年 12 月 16 日。
12. http://www.emea.eu.int/pdfs/human/ewp/046397en.pdf/ 2005 年 12 月 20 日。
13. http://www.emea.eu.int/pdfs/human/vwp/471703en.pdf/ 2005 年 12 月 20 日。
14. http://www.emea.eu.int/pdfs/human/bwp/021496en.pdf/ 2005 年 12 月 20 日。
15. http://www.who.int/csr/disease/avian_influenza/en/index.html/ 2005 年 12 月 20 日。

藥物法規科學在禽流感防治上之角色

財團法人醫藥品查驗中心
王蓉君/陳恒德/朱夢麟 醫師
24 February, 2006

藥物法規科學在禽流感防治上之角色

- 防疫：
  - 傳染阻絕：口罩、防護衣
  - 新型流感疫苗
- 治療：
  - 流感抗病毒藥劑
- 診斷：
  - Influenza A/H5 (Asian Lineage) Virus Real-time RT-PCR Primer and Probe Set 體外診斷試劑及其他

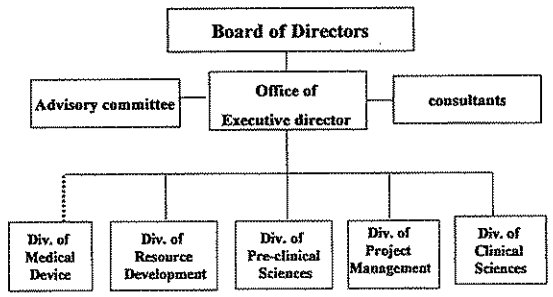
2

財團法人醫藥品查驗中心

- 正式成立於民國八十七年七月十三日
- 查驗中心組織架構精簡，各組人員專業分工：
  - 包含化學製造及管制、藥理/毒理、藥動，生物製劑、臨床各專科領域、統計、藥政法規等專業人才，
  - 美國FDA中具新藥研發、藥品審查經驗專長的專家顧問群。
- 查驗中心之主要業務在於以專業之法規科學：
  - 協助衛生署建立公開、透明的審查流程
  - 提昇審查品質與效率
  - 提供業界有關研發及法規諮詢的服務
  - 進而配合我國生技製藥產業之促進發展
- 查驗中心之角色不僅在為國人的用藥安全做為守護者，同時更是做為健康產業之促進者。

3

查驗中心組織圖



http:// www.cde.org.tw

4

醫藥品查驗中心禽流感工作小組之任務

- 小組成員：
  - 3 MD, 3 PhD, 1 Statistician, 2 Project manager, 1 Strategic planning manager
- 任務：

  法規環境Guideline之研擬，專家委員會之建立，並承接行政院衛生署疾病管制局研究計畫。

5

醫藥品查驗中心禽流感工作小組之任務

- 提供流感抗病毒學名藥物上市之法規要求。
- 提供H5N1新型流感疫苗研發之諮詢及法規協助
  1. 研擬Mock-up vaccine上市之法規要求。
  2. 成立Fast track approval之查驗登記審查流程機制。
- 提供禽流感預防及治療相關之新藥臨床試驗計畫書的快速審查流程。
- 提供禽流感快速診斷試劑、醫療器材之研發上市的法規諮詢與審查。

6

流感抗病毒學名藥物上市之法規要求

- 與原廠羅氏藥廠相比較，國人自行研發生產的克流感應視為是學名藥。
- 學名藥在上市前，必需證明其與原廠藥物之相等性(pharmaceutically equivalent)以及生體上的相等性(bioequivalent)；但於重大緊急危難情形則除外。
- 若調劑成溶液使用，需證明國產克流感藥物在溶液狀態的藥物安定性。

7

新型流感疫苗研發之法規要求

- H5N1疫苗屬於全新研發的疫苗，因此必須要有完整的臨床前的資料，以及人體的第一、二階段試驗結果的學理依據，才得以進入第三階段的臨床試驗。
- 全新的疫苗在人體第三階段臨床試驗驗證其療效(亦即：臨床上對傳染性疾病之保護性)時，其療效指標應該以「疾病的預防」為其目標。
- 以替代免疫力生成指標(surrogate immunogenicity endpoint)取代，做為其臨床保護效果之評估，此點目前為歐盟法規單位所接受的。
- 參考歐盟法規單位以 mock-up vaccine 之NDA完整資料先行送審，再以pandemic variation方式經fast track approval上市。

8

臨床試驗計畫書之快速審查流程

- 世界衛生組織一再呼籲大眾，在禽流感尚未爆發大的疫情之前，即應事先草擬準備好相關臨床試驗計畫書，一但疫情不幸真正爆發時，即可立即派上用場。
  1. 克流感對於治療禽流感的臨床療效評估，事先建立相關之臨床試驗計畫書。
  2. 其他相關之臨床試驗計畫書，醫藥品查驗中心也將提供快速審查的流程。

9

研發過程之諮詢服務

- 為提昇臨床試驗品質，並輔導國內生技製藥產業研發，查驗中心提供業者及研發單位在新藥研發過程中之相關法規諮詢服務，協助解決疑難，以促進產業研發與提昇競爭力。
- 例如：
  1. 國衛院諮詢有關 NDA Requirement of Pandemic Flu Vaccine 之要求。
  2. CDC諮詢有關Influenza A/H5 (Asian Lineage) Virus Real-time RT-PCR Primer and Probe Set 體外診斷試劑之法規要求。

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研發過程之諮詢服務

相關諮詢申請方式如下:

- 請直接網路線上申請，填妥相關內容後點選"儲存與送件"，本中心收到您的申請後，將主動與您連繫。
- 也可撥打本中心諮詢專線02-23224567轉888，將有專人提供服務，協助您釐清問題以填寫諮詢申請表。

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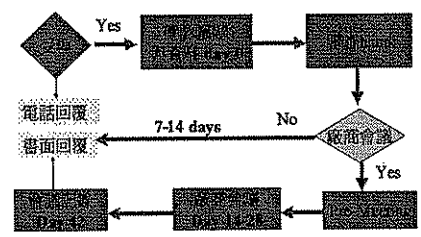
目前查驗中心諮詢案件審理流程



對於諮詢資料之準備及中心受理諮詢案原則說明皆可參考中心網站http://www.cde.org.tw 點選「諮詢業務」

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Recent Development of New Vaccines: HPV vaccine [Gardasil]

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Outline

- Composition
- Indications
- Efficacy
  - CIN2/3
    - HPV 16/18 naïve women (per-protocol)
    - Regardless of HPV baseline status (naïve + non-naïve)
    - Non-vaccine HPV types
  - Genital warts
    - HPV 6/11 naïve women (per-protocol)
    - Regardless of HPV baseline status (naïve + non-naïve)
    - Non-vaccine HPV types
- Safety
- Concomitant vaccine evaluation: Hep B
- Immunological Bridging to girls 9-15y
- Phase 4 commitments
- Taiwan regulatory review perspective

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Gardasil: Description

- Each 0.5 mL dose contains
  - 20 mcg HPV 6 L1 VLP
  - 40 mcg HPV 11 L1 VLP
  - 40 mcg HPV 16 L1 VLP
  - 20 mcg HPV 18 L1 VLP
  - Adjuvant: 225 mcg aluminum
- Administered 0, 2, and 6 months IM

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Gardasil: Proposed Indications

- **Prevention of HPV 16/18 related:**
  - Cervical cancer
  - Cervical AIS
  - CIN 2 and CIN 3
  - Vulvar and vaginal cancer
  - VIN 2 and VIN 3
  - VaIN 2 and VaIN 3
- **Prevention of HPV 6/11/16/18 related:**
  - CIN grade 1
  - Genital warts (condyloma acuminata)
  - VIN grade 1 and VaIN grade 1
  - HPV infection

AIS = Adenocarcinoma in situ; CIN = Cervical Intraepithelial Neoplasia;
VIN = Vulvar Intraepithelial Neoplasia; VaIN = Vaginal Intraepithelial Neoplasia

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Efficacy Endpoint for Preventive HPV Vaccines (Cervical Cancer)

Nov 2001 VRBPAC:

– CIN 2/3 histology, AIS, or worse with virology

- Serology:
  - Less sensitive than molecular techniques in establishing that a new, or incident, infection
  - Does not distinguish persistent infection from an infection that has resolved. Both incident and persistent infections (starting during the trial) have been proposed as endpoints in HPV vaccine trials.

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Cont. Efficacy Endpoint for Preventive HPV Vaccines (Cervical Cancer)

Cont. choice of efficacy endpoints

- Incident HPV infection
  - Few thousand participants, rapid cases accruement
  - Short duration of follow-up + time to trial completion
  - However, extensive PAP smear + HPV testing on all trial participants, plus colposcopy and biopsy
- Prevention of HPV infection
  - Decrease in circulating HPV in a population would be difficult to quantify in the context of an efficacy study
  - HPV infection: asymptomatic, transient
  - It is usually symptomatic disease that brings patients to clinicians and trial participants to the attention of clinical investigators. Difficult to determine whether a vaccine prevents the infection of interest, or whether the vaccine induces an immune response that contains and clears HPV infection, before disease becomes apparent.

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Cont. Efficacy Endpoint for Preventive HPV Vaccines (Cervical Cancer)

Cont. choice of efficacy endpoints

- Persistent HPV infection
  - Same reasons as for prevention of HPV infection
  - Optimal interval in which infection would be considered 'persistent' not readily apparent
- Cytology (i.e., Low-grade squamous intraepithelial lesion (LSIL) atypical squamous cells (ASC) on PAP smear)
  - Prevention of persistent LSIL would translate into fewer repeat Pap smears, colposcopies and biopsies [clinical benefit]
  - In U.S, LSIL cytology by itself is an insufficient basis to treat

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Cont. Efficacy Endpoint for Preventive HPV Vaccines (Cervical Cancer)

Cont. choice of efficacy endpoints

- Histology
  - Dx of CIN1 is more definitive than cytology results, but required bx
  - risk of CIN 1 progressing to cancer is low. Vaccine efficacy overestimated for prevention of CIN1
- Cervical cancer not feasible due to long duration of follow-up (7-12y) + standard of care to treat CIN 2/3

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Gardasil BLA: Protocols Contributing to Combined Efficacy Analysis

- **005:** "Proof of Concept" Phase II Trial for HPV 16
- **007:** Quadrivalent Dose-Ranging, efficacy for prevention of HPV infection
- **013:** CIN/Warts Efficacy Study
- **015:** CIN 2/3 Efficacy Study

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Gardasil: Protocol 013 Substudies

Subset

- Hepatitis B concomitant use
- HPV 16 immunological bridging study to girls 9-15y

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HPV [Gardasil®]: Efficacy studies

- Four studies (Protocols -005, -007, -013, -015)
  - Double blind, randomized, placebo-control studies
  - Multinational
    - Uniform eligibility criteria: age, life time partners, no abnormal PAP
    - Consistent surveillance methods:
      - Algorithm for PAP tests + colposcopy referral
      - Centralized laboratory processing
      - Standard case definition
      - Interpretation by designated pathology panel
    - Prospectively defined statistical analysis plan

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Comparison of Study Design: Number of Subjects, Median Age, and Duration of Follow-up in Efficacy Population

Subjects	Protocol 005	Protocol 007	Protocol 013	Protocol 015
N # Vaccine # Placebo	2391 1193 1198	551 276 275	5442 2717 2725	12157 6082 6075
Median Age (Range)	20 yr. (16-25)	20 yr. (13-24)	20 yr. (16-24)	20 yr. (15-26)
Mean duration of follow-up	3.1 years	2.4 years	1.7 years	1.4 years

Total number of subjects with data for cervical disease efficacy = 20541

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Role of Baseline HPV Status and Endpoint Counting for Prophylactic Vaccine Efficacy Analyses

Baseline HPV Status	HPV 6- related	HPV 11- related	HPV 16-related	HPV 18- related
Naïve to all 4 vaccine HPV types	Yes	Yes	Yes	Yes
Positive HPV 6 or 11, Naïve 16/18	No	No	Yes	Yes
Positive HPV 16, Naïve for 6/11/18	Yes	Yes	No	Yes
Positive HPV 18, Naïve 6/11/16	Yes	Yes	Yes	No

Naïve: Subjects seronegative Day 1 and PCR negative Day 1 through Month 7 13

Role of Baseline HPV Status and Endpoint Counting for Prophylactic Vaccine Efficacy Analyses

Baseline HPV Status	HPV 6- related	HPV 11- related	HPV 16-related	HPV 18- related
Naïve to all 4 vaccine HPV types	Yes	Yes	Yes	Yes
Positive HPV 6 or 11, Naïve 16/18	No	No	Yes	Yes
Positive HPV 16, Naïve for 6/11/18	Yes	Yes	No	Yes
Positive HPV 18, Naïve 6/11/16	Yes	Yes	Yes	No

Note: Non-HPV 6, 11, 16, 18 related disease not included in analyses. 14

Efficacy Analysis Populations

- Per Protocol Population for Efficacy (PPE): Received all 3 vaccinations, naïve to relevant vaccine HPV type through Month 7, did not deviate from protocol; cases counted after Month 7.
- **Modified Intent to Treat-3 Population (MITT-3):** Received at least one vaccination and had any follow-up visit one month after dose 1. Cases were counted from 30 days after dose 1.

  Subjects were included regardless of baseline HPV status (naïve + non-naïve)

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Endpoints from Efficacy Protocols (Protocols 005, 007, 013, and 015)

Primary Endpoints:

- HPV 16/18 related CIN 2/3 or worse [-015, combined analysis]
- HPV 6/11/16/18 related CIN [-013]
  - CIN grade 1
  - HPV infection
- HPV 6/11/16/18 related External Genital Lesions (EGLs) [-013]

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Other Endpoints

Other Endpoints of Interest:

- HPV 16/18 related EGLs
- CIN 2/3 due to any HPV type and non-vaccine HPV types
- EGL due to any HPV type and non-vaccine HPV types

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Efficacy Against HPV 16/18 CIN 2/3 or Worse

- Cervical AIS
- CIN 2 and CIN 3
- Cervical cancer

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Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse (Protocol 015)

	Gardasil N=6082			Placebo N=6075			
Population	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
PPE	5301	0	0.0	5258	21	0.3	100% (75.8, 100%)
MITT-3	5947	67	0.6	5973	111	1.0	39.2% (16.9, 55.8%)

Incidence Rate: Calculated per 100 person years at risk.

PPE: Naive to relevant HPV type, received three doses of vaccine, cases counted after Month 7.
MITT-3: Included regardless of baseline HPV status; received at least one dose of vaccine, cases counted 30 days post-dose 1.

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Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse (Protocols 005, 007, 013, 015)

	HPV L1 VLP Vaccine N=10268			Placebo N=10273			
Population	N	No. of Cases	Incidence	N	No. of Cases	Incidence	Efficacy (95% CI)
PPE	8487	0	0	8460	63	0.4	100% (92.9, 100%)
MITT-3	9831	122	0.6	9896	201	0.9	39.0% (23.3, 51.7%)

PPE: Naive to relevant HPV type, received three doses of vaccine, cases counted after Month 7.
MITT-3: Included regardless of baseline HPV status; received at least one dose of vaccine, cases counted 30 days post-dose 1.

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Analysis of Efficacy of Against HPV 16/18 Related CIN 2/3 or Worse by HPV Type – MITT 3 Analysis (Protocols 005, 007, 013, 015)

	Gardasil N=10268			Placebo N=10273			
HPV Type	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
HPV-16	9831	115	0.5	9896	184	0.9	37.2% (20.3, 50.7%)
HPV-18	9814	7	0.04	9846	33	0.2	76.7% (51.0, 92.0%)

MITT-3: Included regardless of baseline HPV status; received at least one dose of vaccine, cases counted 30 days post-dose 1.

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Efficacy Against HPV 6/11/16/18 CIN

- CIN grade 1
- HPV infection

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Analysis of Efficacy Against HPV 6/11/16/18 Related CIN (Protocol 013)

	Gardasil N=2717			Placebo N=2725			
Population	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
PPE	2240	0	0	2258	37	1.0	100% (87.4, 100%)
MITT-3	2607	65	1.2	2611	113	2.0	42.9% (21.9, 58.6%)

PPE: Naive to relevant HPV type, received three doses of vaccine, cases counted after Month 7.
MITT-3: Included regardless of baseline HPV status; received at least one dose of vaccine, cases counted 30 days post-dose 1.

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Analysis of Efficacy Against HPV 6/11/16/18 Related CIN (Protocols 007, 013, 015)

	Gardasil N=9075			Placebo N=9076			
Population	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
PPE Combined	7858	4	0.03	7881	83	0.7	95.2% (87.2, 98.7%)
MITT-3 Combined	8814	170	1.0	8846	317	1.8	46.4% (35.2, 55.7%)

PPE: Naive to relevant HPV type, received three doses of vaccine, cases counted after Month 7.
MITT-3: Included regardless of baseline HPV status; received at least one dose of vaccine, cases counted 30 days post-dose 1.

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Cases of HPV 6/11/16/18 Related CIN in PPE Population

- Four cases occurred in the Gardasil group for the PP analysis (Protocol 015).
- All four cases had HPV 16 related CIN 1 at Month 12-13.
  - One subject had anti-HPV 16 level just below level of detection and LSIL at Day 1 and HSIL at Mo 7, and possibly had prior exposure to HPV 16; also non-naive to HPV 18 at Day 1 and colposcopy triggered by the HSIL at Mo 7, led to a diagnosis of HPV 18 related CIN 3 at Mo 9.
  - Three other subjects developed LSIL at Mo 7 and Mo 12, which led to colposcopies with the resulting diagnoses. One had anti-HPV 16 level at Mo 7 higher than GMT seen in Per Protocol Immunogenicity (PPI) population.

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Efficacy Against Any HPV Type and Non-Vaccine HPV Type Related CIN

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Overall Impact on CIN 2/3 or Worse Due to Any HPV Type (Protocols 007, 013, and 015)

	Gardasil N=9075			Placebo N= 9075			
Population	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
MITT-3	8814	287	1.6	8846	328	1.9	12.2% (-3.2, 25.3%)

MITT-3: Included regardless of baseline HPV status; received at least one dose of vaccine, cases counted 30 days post-dose 1.

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Analysis of Efficacy Against Non-HPV 6/11/16/18 Related CIN 2 or CIN 3 Among Subjects in All MITT-1 Population (Protocols 007, 013, 015)

	Gardasil N=9075			Placebo N= 9075			
	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
CIN 2	5993	69	0.7	5766	49	0.6	-16.1% (-73.2, 21.8%)
CIN 3	5993	36	0.4	5766	27	0.3	-28.5% (-120.1, 24.1%)

All MITT-1 Population: Naive to all four vaccine HPV types through Month 7, received three doses of vaccine.
Source: Additional Efficacy Analyses Requested by CBER

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Efficacy Against HPV 6/11/16/18 Related External Genital Lesions (EGLs)

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Analysis of Efficacy Against HPV 6/11/16/18 EGL (Protocol 013)

	Gardasil N=2717			Placebo N=2725			
Population	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
PPE	2261	0	0.0	2279	40	1.8	100% (88.4, 100%)
MITT-3	2671	26	0.5	2668	80	1.4	67.8% (49.3, 80.1%)

PPE: Naive to relevant HPV type, received three doses of vaccine, cases counted after Month 7.
MITT-3: Included regardless of baseline HPV status; received at least one dose of vaccine, cases counted 30 days post-dose 1.

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Analysis of Efficacy Against HPV 6/11/16/18 Related EGLs by HPV Type (Protocols 007, 013, 015)

	Gardasil N=9075			Placebo N= 9075			
	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
MITT-3 HPV 6/11	8954	59	0.3	8962	194	1.1	69.6% (59.2, 77.7%)
MITT-3 HPV 16	8954	11	0.1	8962	55	1.1	80.0% (61.3, 90.5%)
MITT-3 HPV 18	8954	2	0.01	8962	20	0.1	90.0% (58.7, 98.9%)

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Analysis of Efficacy Against HPV 16/18 Related EGLs (Protocols 007, 013, 015)

	Gardasil N=9075			Placebo N= 9075			
Population - EGL type	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
PPE - Condyloma, VIN 1 or VaIN 1)	7769	0	0.0	7741	24	0.2	100.0% (83.4, 100.0%)
PPE - VIN 2/3 or VaIN 2/3 or worse)	7769	0	0.0	7741	10	0.1	100.0% (55.5, 100.0%)
MITT-3 - Condyloma, VIN 1 or VaIN 1)	8954	7	0.04	8962	51	0.3	86.2% (69.6, 94.7%)
MITT-3 – VIN 2/3 or VaIN 2/3 or worse)	8954	8	0.05	8962	26	0.1	69.1% (29.8, 87.9%)

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Analysis of Efficacy Against HPV 6/11/16/18 Related EGL by Severity of Disease – PPE Population (Protocols 007, 013, 015)

	Gardasil N=9075			Placebo N= 9075			
Population - EGL type	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
PPE - Condyloma	7897	1	0.0	7899	91	0.8	98.9% (93.7, 100.0%)
PPE – VIN 1	7897	0	0.0	7899	10	0.1	100.0% (55.4, 100.0%)
PPE-VIN 2/3	7897	0	0.0	7899	8	0.1	100.0% (41.4, 100.0%)
PPE-VaIN 2/3	7897	0	0.0	7899	5	0.04	100.0% (<0.0, 100.0%)

PPE: Naïve to relevant HPV type, received three doses of vaccine, cases counted after Month 7.

Source: Response to CBER request 5/1/06.

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Analysis of Efficacy Against HPV 6/11/16/18 Related EGL by Severity of Disease – MITT-3 population (Protocols 007, 013, 015)

	Gardasil N=9075			Placebo N= 9075			
Population - EGL type	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
MITT-3 Condyloma	8954	52	0.3	8962	164	1.0	68.5% (57.5, 77.0%)
MITT-3 VIN 1	8954	8	0.05	8962	19	0.1	57.8% (<0.0, 84.0%)
MITT-3 VIN 2/3	8954	7	0.04	8962	22	0.1	68.1% (22.7, 88.5%)
MITT-3 VaIN 2/3	8954	2	0.01	8962	9	0.1	77.7% (<0.0, 97.7%)

MITT-3: Included regardless of baseline HPV status; received at least one dose of vaccine, cases counted 30 days post-dose 1.

Source: CBER Additional Request for analyses, 5/1/06

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Efficacy Against Non-HPV 6/11/16/18 Related EGL in All MITT-1 Population (Protocols 007, 013, 015)

	Gardasil N=9075			Placebo N=9075			
	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
EGL not related to HPV 6/11/16/18	5999	62	0.6	5773	49	0.6	-2.1% (-54.1, 32.2%)
Condyloma, VIN 1, VaIN 1	5999	46	0.5	5773	49	0.6	9.7% (-37.9, 40.9%)
VIN 2/3 or VaIN 2/3	5999	5	0.1	5773	6	0.1	19.8% (-216.3, 85.5%)
Vulvar or vaginal cancer	5999	1	0.01	5773	0	0.0	NA

MITT-1: same as PPE population, but includes pts with pti violations

Source: Additional Efficacy Analyses Requested by CBER

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Safety

- Safety Population
- Safety Surveillance
- Deaths
- SAEs
- Pregnancies/Lactation

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Safety Population: Detailed and General

Safety Population	Gardasil	Placebo
Detailed Safety Population	6160	4064
General Safety Population	11778	9686

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Gardasil recipients 9-15 Year Old Female Subjects (Protocols 016 and 018)

Age	Females Gardasil
9	85
10	158
11	196
12	165
13	190
14	192
15	137
Total	1123

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Safety Surveillance (Detailed Safety Cohort)

- Vaccine Report Cards for 14 days after each vaccination (Protocols 005, 007, 013 + NSAE 015)
  - Solicited local AEs: Pain, tenderness, redness for 5 days after vaccination
  - Temperatures for 5 days after vaccination ≥ 100° F oral
  - Solicited and unsolicited systemic AEs: Sore muscle, sore joints, headache, rash, diarrhea for 14 days after vaccination

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Pregnancy and Lactation Reporting

- All pregnancies were to be followed to outcome
- SAEs were reported for mothers and infants
- Lactation outcomes were followed

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Safety Results

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Deaths (Protocols 007, 013, 015, 016, 018)

	Gardasil (N=11, 0.9%)	Placebo (N=7, 0.7%)
Trauma	5	3
DVT/PE	1	1
Sepsis, DIC	1	
Sepsis, pneumonia	1	
Arrythmia	1	
Pancreatic Cancer	1	
Convulsion, drug use	1	
Suicide		2
Asphyxiation post-C-section		1

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Serious Adverse Events (Protocols 007, 013, 015, 016, 018)

SAE (Organ system)	Gardasil N=11778	Placebo N=8020
Gyn or Obstetrical	42	41
GI	11	8
Appendicitis	4	1
Injury	5	5
Neurological	4	7
Immune mediated	2	4
Coagulation/DVT	2	1
Pulmonary	2	0
GU	5	5
Endocrine	1	0
Injection site reaction	1	0
Psychiatric	0	2
Cardiovascular	1	1
Musculoskeletal	1	1
ENT	1	0
Administration of access study vaccine	16	20
Total	101 (0.9%)	97 (1.0%)

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Pregnancy Outcome Summary (Protocols 013, 015, 016, 018)

	Gardasil (N=10416)	Placebo (N=9120)
Subjects with pregnancies	1115 (10.7%)	1151 (12.6%)
Number of pregnancies	1244	1272
Number of fetuses/infants with known outcomes	996	1018
Number of pregnancies with unknown outcomes	258	263
Live Births	621 (62.3%)	611 (60.0%)
Spontaneous miscarriage	249 (25%)*	257 (25.2%)*
Late fetal deaths	11 (1.2%)	8 (0.9%)

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Distribution of Congenital Anomalies by Estimated Dates of Conception (EDCn) Timing in Relation to Vaccination (Protocols 013, 015, 016, 018)

	Gardasil	Placebo
Congenital Anomalies	15	16
EDCn within 30 days of study vaccine	5**	0
Live birth reported in neonatal period	5	0
EDCn beyond 30 days of study vaccine	10	16
Live birth reported in neonatal period	8	12
Live birth reported beyond neonatal period	1	1
Fetal Loss	0	2
Intra-uterine diagnosis	1	1

**Diagnoses included hip dysplasia, ankyloglossia and pyloric stenosis, congenital hydronephrosis, club foot, and congenital megacolon

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Adverse Events in Pregnancy/Lactation (1) (Protocols 013, 015, 016, 018)

- A similar pattern and occurrence of SAEs and AEs in pregnancy were reported in women who were vaccinated with Gardasil (N=40, 4.2%) or placebo (N=41, 4.3%).
  - These events included conditions leading to C-section, premature labor, and conditions associated with pregnancy.

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Adverse Events in Pregnancy/Lactation (2) (Protocols 013, 015, 016)

- Higher proportion of children with SAEs in women who received Gardasil while breastfeeding in the vaccination period (Gardasil N=17, 3.4%; placebo N=9, 1.8%); the events were of similar nature in both groups.
  - In both the vaccine and placebo groups, these included respiratory infections, gastroenteritis, and asthma.

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Safety Conclusion

- Although no obvious safety signal was identified, post-marketing pharmacovigilance activities will continue to collect AEs that occur post-vaccination in a larger population.
- Congenital anomalies: No apparent pattern

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Immunogenicity

- Bridging immune response in adolescent girls to adult women
- Duration of immune response
- Co-administration with Hepatitis B vaccine

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Bridging Immune Response from Females 16-26 Years to Females 9-15 Years of Age

- Females naïve to the four vaccine HPV types are expected to benefit most from the vaccine.
- Efficacy studies cannot be conducted in preadolescent girls.

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Immunogenicity Bridging Between 9-15 Year Old Females in the Immunogenicity Studies to 16-26 Year Old Women in the Efficacy Studies

	9-15 Year Old Females in Protocols 016 and 018			16-23 Year Old subjects in Protocols 013 and 015		
Assay (cLIA)	n	GMT mMU/mL	95% CI	n	GMT mMU/mL	95% CI
Anti-HPV 6	927	931.3	876.9, 989.2	2827	542.4	526.6, 558.7
Anti-HPV 11	927	1305.7	1226.2, 1390.4	2827	766.1	740.5, 792.6
Anti-HPV 16	929	4944.9	4538.5, 5334.8	2707	2313.8	2206.2, 2426.7
Anti-HPV 18	932	1046.0	971.2, 1126.5	3040	460.7	443.8, 478.3

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Duration of Immune Response

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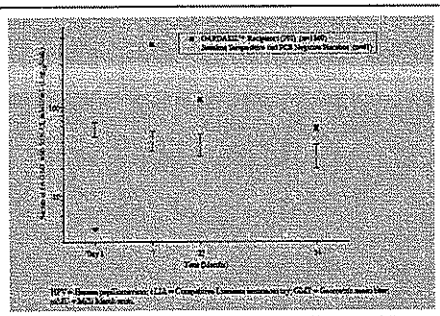
Persistence of Anti-HPV 18 Immune Responses in 18 to 26 Year Old Female Recipients of Gardasil (Seronegative at Day 1 and PCR Negative Through Month 7) Versus Placebo Recipients (Seropositive and PCR Negative at Day 1)



Source: Figure 5.3.5.3.3:16, p. 69, Integrated Summary of Immunogenicity

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Seropositivity Rates for Anti-HPV 6, 11, 16, and 18 at Month 24 (Vaccinated Women 18-26 years) with Serology Data at All Time Points (N=2818)

HPV type	Seropositivity rate at Month 24 (95% CI)
Anti-HPV 6	**95.7%** (94.5, 96.6%)
Anti-HPV 11	**97.6%** (96.8, 98.3%)
Anti-HPV 16	**99.6%** (99.2, 99.9%)
Anti-HPV 18	**73.9%** (71.8, 75.9%)

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Co-administration of Gardasil with Hepatitis B Vaccine

- Anti-HPV 6, 11, 16, and 18 immune responses were non-inferior when Gardasil was given with or without Recombivax (Seroconversion rate, GMT ratios)
- Anti-Hepatitis B immune response was similar when Recombivax was given with or without Gardasil (SC rates)
  - Anti-Hep B GMTs lower in coadministration group

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Applicant's Proposed Post-marketing Commitments

- Routine pharmacovigilance
- Phase 4 studies
- Other studies

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Routine Pharmacovigilance

- Passive reporting of adverse events (AEs) including:
  - Monthly submission of non-serious AE reports
  - Regular FDA-CDC-Sponsor conference calls
- Pregnancy registry

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Phase 4 Studies

- Observational safety surveillance study in U.S.
  - Investigation of serious AEs that occur in close temporal association with vaccination (60 days follow-up)
- Nordic Long Term Follow-up Study
  - Longitudinal evaluation of subjects in Protocol 015 enrolled in Nordic countries using national registries

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Nordic Long Term Follow-up Study: Outcomes

- HPV-related diseases
- Long term effectiveness and duration of immune response
- Potential safety signals
- Pregnancy outcomes

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Conclusions

- The efficacy, safety, and "bridging" immune response data submitted to the BLA support licensure of Gardasil in females 9-26 years of age naïve to the relevant vaccine HPV type for prevention of the following diseases/events:
  - HPV 16/18 related cervical cancer, CIN 2/3 and AIS.
  - HPV 6/11/16/18 related VIN 2, VIN 3, VaIN 2, VaIN 3
  - HPV 6/11/16/18 related CIN 1, genital warts, VIN 1 and VaIN 1

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Gardasil: FDA Review Concerns

- **Applicant's Per Protocol HPV type-specific analyses that indicated a very high level of efficacy in naïve subjects may not reflect the efficacy of Gardasil for all HPV related disease on a population basis.**
- **HPV related disease occurred in Gardasil recipients.**
  - **Some vaccine recipients were non-naïve at baseline for one or more vaccine HPV type(s), and some of these subjects developed HPV disease related to that HPV type(s).**
  - **Subjects who were naïve to all four vaccine HPV types could still develop disease related to an HPV type not included in the vaccine.**

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Gardasil: FDA Review Concerns

- Longer-term efficacy
  - Study 005 results suggest favorable longer term efficacy
- Duration of immune response
  - Post-licensure commitments

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Questions/Discussion points

From Tw review perspective:

- Gardasil BLA review:
  - Data submitted
  - safety or efficacy concerns
- Gardasil (2005) vs. Cervarix (2006)
  - Multinational clinical data
  - Quality and conduct of the studies
  - Intrinsic and extrinsic factors
  - Need for additional studies

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Development of Immunologic Adjuvants

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Immunologic Adjuvants

I. Adjuvants are agents that act to enhance, accelerate, modify, or prolong specific immune responses to vaccine antigens.

II. Aluminum salt (Alum) remain the only adjuvant in U.S.-licensed vaccine formulation. MF59 is licensed in Europe.

III. Many new adjuvants have been shown to be more effective than gel-type adjuvants in enhancing Ab and cell-mediated immune responses.

Types of Immunologic Adjuvants

Adjuvant Type	General and Specific Examples
1. Gel-type	Al-hydroxide/phosphate
2. Microbial	Murqmyl dipeptide (MDP), Cholera toxin (CT), E. coli heal-labile toxin (LT), Mono-P-lipid A, CpG oligonucleotide
3. Particulate Liposome	Immunostimulatory complex (ISCOMS),
4. Oil-emulsion & Surfactant	MF59, QS-21
5. Cytokines	IL-2, IL-12, GM-CSF, IFN-gamma
6. Others (genetic & synthetic)	

Adjuvant Mechanism

I. Effects on antigen delivery and presentation.
- "depot effect"
- improved delivery of antigen to APCs and to the secondary lymphoid organs.

II. Induction of immunomodulatory cytokines, and

III. Effects on antigen presenting cells (APCs).
- The Ag is released into cytoplasm and processed through MHC class I to induce cytotoxic T-cells and class II to enhance Ab responses.

Need of Effective Adjuvants in Changed Targets of Vaccines

Changed targets of vaccines:

- Therapeutic vaccines for allergy, autoimmunity, cancer, and new infection preventive vaccines.
- Required childhood immunization, with pneumococcal conjugate, Hib conjugate, and varicella vaccines.
- Multicomponent acellular pertussis vaccines, and an injectable inactivated poliovirus (IPV) vaccine.
- New combination vaccines.

Adjuvant Safety Testing

I. Local adverse reactions – inflammation at the injection site, or induction of granulomas or sterile abscesses.

II. Systemic reactions in animals include malaise, fever, arthritis, and anterior chamber uveiitis (such models may not reflect expected toxicity in humans).

III. Such reactions may be due to synergy between exotoxins or endotoxins and the adjuvant.
Therefore, safety evaluation of the vaccine should be conducted in Phase I clinical trial.

Formula for A CpG Adjuvant Motiff

I. $X_1X_2CGY_1Y_2$ X_1 = purine X_2 = Purine or T
Y = pyrimidine

II. CpG motiff can be species-specific:
-- Mice -- *TGACGTT*
ODN #1826 -- 5'TCCAT *GACGTT* CCT GACGTT3'
Non-CpG#1982 -- 5'TCCAG *GACTTT* TCT CAGGTT3'
-- Human -- *TGTCGTT* (Davis et al. J. Immunol., 1998).

III. CpG -- TGACTGTG *AACGTT* CGAGATGA
Non-CPG -- TGACTGTG *AAGCTA* CGAGATGA

CpG ODN as a Mucosal Adjuvant

I. Protein antigens:
-- Influenzae virus -- Moldoveanu et al., Vaccine 1998.
-- HBsAG -- McCluski et al., J. Immunol., 1998.

II. Polysaccharides:
-- Pn 19F PS-CRM197
Pn 6B-CRM197 Conjugate -- Chu et al I&I, 2000.
-- H. influenzae PS-TT or PS-CRM197 conjugate
- Hunolstein et al., Vaccine, 2001
-- Meningococcal Gr C PS
- Davis, Curr Top Microbiol & Immunol., 2000

Adjuvant Effect of CpG on Ab Responses to Pn 9V PS –Ply conjugate

Antibody response (9V PS)	CpG ODN (ug/ml serum)	Non-CpG ODN	Control (Conj alone)
IgG	**9.71±1.34	0.84±0.01	1.17±0.03#
IgA	** 12.0 ±1.14	1.36±0.08	0.92±0.03

#, Mean of 8 samples ± standard error.
**, P < 0.01 when mice injected with 9V PS-Ply plus CpG ODN are compared with the controls given 9V PS-Ply alone.

Ab Responses to Pn 9V PS-Ply Conj and 9V PS

(A). 9V PS IgG Ab

Immunogen	Blood (ug/ml)	Spleen	Intestine (ug/ mg protein)	Lung	Peyer's patch
(1) 9V PS-Ply + CpG	**1.57±0.10#	0.89±0.07	2.10±0.01	2.19±0.78	3.78±0.60
(2) 9V PS-Ply alone	0.38±0.04	0.99±0.15	1.42±0.19	2.40±0.73	3.89±0.36
(3) 9V PS + CpG	**0.83±0.06	1.19±0.24	1.47±0.17	1.89±0.42	4.73±0.68
(4) 9V PS alone	0.38±0.01	1.13±0.14	1.06±0.03	2.14±1.06	4.41±0.35
(Saline control	0.30±0.06	0.63±0.03	0.64±0.03	0.19±0.03	0.57±0.09)

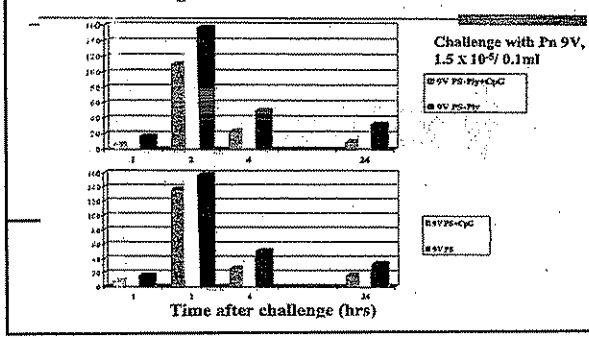
#, Mean of 4 samples ± standard error.
*, P < 0.05; **, P < 0.01, when antibody response of mice immunized with 9V PS-Ply or 9V PS was compared with the immunogen alone.

Ab Responses

(B). 9V PS IgA antibody

Immunogen	Blood (ug/ml)	Spleen	Intestine (ug/ mg protein)	Lung	Peyer's patch
(1) 9V PS-Ply +CpG	*1.12±0.27#	1.52±0.35	**3.23±0.49	1.35±0.07	3.78±0.60
(2) 9V PS-Ply alone	0.28±0.03	0.87±0.18	0.77±0.07	1.97±0.61	3.89±0.36
(3) 9V PS + CpG	**0.72±0.09	1.84±0.48	**2.39±0.41	1.37±0.29	4.73±0.68
(4) 9V PS alone	0.34±0.01	0.98±0.14	0.82±0.08	1.76±0.83	4.41±0.35
(Saline control	0.32±0.05	0.70±0.10	0.44±0.07	0.19±0.02	0.48±0.04

Bacterial Clearance from Blood in Mice Challenged with 9V Pneumococci



Future Adjuvant Research and Development

I. More effective adjuvant for improving licensed single and combination vaccine constructed of subunit antigens.

II Adequate selection of adjuvants for use in vaccine formulation.

III. Establish standardized methods for safety testing in human candidate vaccines

Regulatory Routes to Expedite Vaccine Approval

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The Fundamental Challenge

Regulations and the applications of regulations are dependent on the existing level of science that will support a particular action.

The challenge for all of us is to identify the gaps in our knowledge, to identify the pathways – the Critical Path - to addressing those gaps, and to define the criteria for acceptability.

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Need for Expedited Pathways for Regulatory Approval

- Public health importance
  - Emerging and re-emerging diseases [e.g. SARS]
  - Pandemic strains of influenza
  - Vaccine shortages: e.g., seasonal influenza
  - New vaccines of local and global public health importance: e.g.,HPV

  Efficient, rapid development and approval of vaccines
- Emergency use
  - Anthrax, smallpox vaccine
  - Ciprofloxacin for anthrax post-exposure prophylaxis

  Regulations pertaining to counter-terrorism products

3

Formal Regulatory Mechanisms

- Request for fast track development
- Priority review of biologics license application
- Treatment IND
  - accelerated approval of licensure process
- Emergency IND
  - Emergency Use Authorization

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Fast Track Development:
Ex. FT Approved

- Meningococcal conjugate vaccine
- Request: development for
  - Indication: Active immunization of children < 2 years old
- Serious/life-threatening disease:
  - invasive *N. meningitidis* disease: meningitis, sepsis, bacteremia
  - substantial morbidity: 11%–19% of survivors have sequelae (e.g., neurologic disability, limb loss, or hearing loss)
  - 10-14% of cases can be fatal

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Fast Track Development:
Ex. FT Approved

- Current options available for prevention of invasive meningococcal disease
  - Antibiotic chemoprophylaxis
  - Currently available meningococcal polysaccharide vaccine is not effective nor indicated in children <2 years old
- Does the vaccine show potential (given its stage of development) to prevent this serious aspect of the condition?
  - Early Phase II data: immunogenic in target population, proposed dose and dosing regimen
  - If proposed basis of licensure anticipated to be based on immune criteria: *in vitro* assay available? Quantitative assessment? Correlate identified? Antibody level/titer associated with protection?

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Fast Track Development:
Ex. FT Approved

- Is the clinical development program designed to determine whether the vaccine will affect the proposed serious aspect of the medical condition?
  - Placebo-controlled trial
  - Demonstration of protective antibody titer
  - Proposal + rationale for selected antibody titer
- How does the vaccine offer benefit over the existing therapy?
  - Prevents serious manifestations and consequences of the disease
  - Avoids toxicities associated with currently available antibiotic chemoprophylaxis. It is possible, however, that vaccine-related serious adverse events could occur.
  - If included in the routine childhood immunization schedule, vaccination offers better compliance compared to chemoprophylaxis

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Fast Track Development

- Designed to facilitate the development new vaccines to prevent serious or life-threatening conditions and that demonstrate the potential to address an unmet medical need
- 60 days to review + issue written response
- Benefit to Industry:
  - Press release
  - More meetings with FDA
  - Granting designation of fast track development often implies priority review of BLA

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Fast Track Development:
Ex. FT

- Pneumococcal conjugate vaccine (PnC): 10 serotypes
  - 7 common serotypes with Prevnar
  - 3 new serotypes account for an additional 3% of cases of invasive pneumococcal disease
  - Conventional carrier protein
- Request: development for
  - Indication: Active immunization of children < 2 years old
- Serious/life-threatening disease
  - invasive pneumococcal disease

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Fast Track Development:
Cont. Ex. FT

- Current options available for prevention of invasive meningococcal disease
  - Antibiotic chemoprophylaxis
  - Currently available PnC vaccine is highly effective for 7 of 10 serotypes in children <2 years old
  - Currently available pneumococcal polysaccharide vaccine is not effective nor indicated in children <2 years old
- Does the vaccine show potential (given its stage of development) to prevent this serious aspect of the condition?
  - Early Phase II data: previous human experience from a similar, related PnC: immunogenic in target population when given at 2-3-4 and 12 months, proposed dosing regimen is 2-4-6 and 12-15 months
  - No clinical data with the proposed formulation

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Fast Track Development:
Cont. Ex. FT

- Cont.

  Does the vaccine show potential (given its stage of development) to prevent this serious aspect of the condition?
  - ethical difficulty in conducting efficacy trials with an un-vaccinated control group while an efficacious vaccine is available
  - Proposed basis of licensure based on immune criteria:
    - *In vitro* assay available? 22F vs. non-22F ELISA
    - Correlate identified? IgG antibody
    - Antibody level/titer associated with protection?

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Derivation of Immune correlate

- A threshold Ab level that predicts protection
  - Not a precise Ab concentration
  - Sources of inherent variability associated a statistical estimate:
    (1) variability of the efficacy estimate (i.e. wide confidence limits)
    (2) variability due to number of specimens sampled for immunogenicity evaluation (n=6000 samples for pooled aggregate)
  - The step function used to establish the proposed PnC threshold levels is considered a population-based correlate rather than an individual-based correlate

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Cont. Derivation of Immune correlate

- 3 trials
  - NCKP: general U.S. pop'n; 7 valent formulation
    - # total cases IPD in ctl:test 39:1
  - Navajo: American Indian; 7 valent formulation
    - # total cases IPD in ctl:test 8:2
  - S Afr: HIV (-), S. African pop'n; 9 valent formulation
    - # total cases IPD in ctl:test 10:1

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Cont. Derivation of Immune Correlate

Efficacy Estimate (Aggregate of 7 Serotypes)			
	Estimated Protective	95% Confidence Limits	
	Level (µg/mL)	Lower	Upper
NCKP	0.20	0.03	0.67
Navajo	1.00	0.25	> 50.00
SA	0.68	0.03	6.00

Basis of aggregate efficacy estimate:
NCKP trial: per protocol serotype-specific efficacy was only shown for 4 of the 7 serotypes included in the vaccine.

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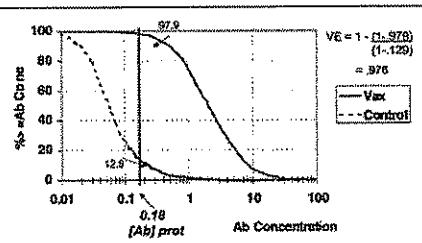
Cont. Derivation of Immune Correlate



Ignoring Ab levels in controls obtains [Ab] prot = .20 µg/ml

-- Non-22F ELISA assay
Ab threshold = 0.18 ug/mL using NCKP data only
Ab threshold = 0.35 ug/mL using pooled data from 3 trials

Jodar et al. Vaccine. 2003; 21: 3265-3272

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Fast Track Development:
Ex. FT

- Is the clinical development program designed to determine whether the vaccine will affect the proposed serious aspect of the medical condition?
  - Bridging study: current formulation vs. proposed formulation; dosing regimen
  - Confirmatory study: controlled trial compared to 7v PnC
    - 7vPnC: non-inferiority comparison
    - New serotypes:?
- How does the vaccine offer benefit over the existing therapy?
  - Prevents serious manifestations and consequences of the disease. However, vaccine would only prevent an additional 3% of IPD cases compared to Prevnar immunization.
  - Avoids toxicities associated with currently available antibiotic chemoprophylaxis. It is possible, however, that vaccine-related serious adverse events could occur.
  - Vaccination offers better compliance compared to chemoprophylaxis

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Formal Regulatory Mechanisms

Priority Review of BLA

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Priority Review of BLA:
7-valent pneumococcal conjugate vaccine [Prevnar®]

- Priority review status to the application granted
  - the severity of disease for which the vaccine would be indicated, i.e., "invasive pneumococcal disease (meningitis and bacteremia)"
  - lack of alternative licensed vaccines for use among infants and small children
  - preliminary results indicating substantial evidence of efficacy.
- Preliminary efficacy data
  - presented at the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting on November 19,1998

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7-valent pneumococcal conjugate vaccine [Prevnar®]

- Indication for priority review

  "For active immunization of infants and children beginning as early as 6 weeks of age for the prevention of invasive pneumococcal disease caused by capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, 23F)"

- Prevention of acute otitis media and pneumonia
  - secondary and tertiary endpoints
  - not the focus of the initial license application

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7-valent pneumococcal conjugate vaccine [Prevnar®]

Regulatory Timeline

Nov 1994	IND filed
Oct 1995	Confirmatory efficacy trial initiated
Apr 30, 1998	Safety data base of efficacy trial locked
Aug 20, 1998	Primary efficacy analysis
Apr 20, 1999	Efficacy trial unblinded, case ascertainment ends
May 17, 1999	Manufacturing-bridging study complete
Jun 1, 1999	BLA submitted
Jul 13, 1999	FDA/CBER accepts BLA as complete
Nov 5, 1999	Advisory Committee (VRBPAC) meeting
Feb 17, 2000	BLA approved

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Priority Review of BLA

- Granted for biological products considered to be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease
  - 6 month review of the BLA
  - Allows for submission of the application by section, i.e., review by segments of the application (product chemistry-manufacture-control, statistical, clinical, etc.)
  - The review clock does not begin until the applicant has informed FDA that a complete BLA has been submitted

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HPV vaccine [Gardasil®]

- Indication for fast track designation: significant impact on prevention of cervical cancer, based on current epidemiological data
  - Cervical cancer: an important public health problem
    - HPV types 16 and 18: estimated to be responsible for more than 50% of cervical cancer
- Indication for priority review: significant improvement, compared to existing methods, to prevent cervical cancer caused by HPV types 16 and 18.

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Priority Review of BLA: HPV vaccine [Gardasil®]

Regulatory Timeline

2000	IND filed
2002	Fast track development designation granted
Dec 01	Ptl 013 initiated
Jun 02	Ptl 015 initiated
May 05	Pre-BLA Meeting; agreement for priority review of BLA
Jun05	Ptl 015 completed
Jul 05	Ptl 013 completed
Aug 2005	BLA submitted
Dec 2005	FDA/CBER accepts BLA as complete
May 2006	Advisory Committee (VRBPAC) meeting
June 2006	BLA approved

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Priority Review of BLA:

Ex.

- Taiwan application for rotavirus vaccine
  - Rotateq
  - Rotarix
- Epidemiology: circulating rotavirus serotypes in Tw
- Clinical spectrum of rotavirus disease in Tw
- Current available treatments for RV disease in Tw
- Recommendations for routine RV immunization
- Vaccine uptake
- Physician/Parental acceptance of risk:benefit ratio

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Should we take a coffee break?

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Investigational drug for treatment use

- Facilitate availability of promising drugs prior to market approval
  - Ex. drugs for AIDS, cancer [terminal illnesses]
  - ~granting indication but product still investigational & being evaluated under IND
- Manufacturer is IND sponsor: physician obtains drug from sponsor via enrolling pt in controlled trial [treatment protocol]
- If a manufacturer is not willing to establish a treatment protocol, then the licensed medical practitioner may seek to obtain the drug from the sponsor and submit a treatment **IND**
  - requesting authorization to use the investigational drug for treatment use
  - Treatment IND submitted by licensed practitioner

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Cont. Treatment IND

- Treatment protocol
  - Intended use of the drug
  - Rationale for use of the drug
  - Brief description of the criteria for patient selection.
  - Method of administration of the drug and the dosages.
  - Description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimize risk.
- Written informed consent

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Cont. Treatment IND

- § 312.34 Treatment use of an investigational new drug
  - Treat a serious or immediately life- threatening disease
  - No comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population
  - The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed
  - The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence

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Formal Regulatory Mechanisms

Accelerated Approval of Licensure

Original intent of regulation: rising mortality due to acquired immunodeficiency syndrome (AIDS), prior to availability of highly active antiretroviral agents.

-- Drugs for treatment of HIV infections
-- Drugs and biologics for the treatment of cancer

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Accelerated Approval

- Serious or life-threatening disease
- Basis for Approval
  - Controlled clinical trial results establish vaccine effect based on a surrogate endpoint
  - Assumption that the surrogate endpoint is reasonably likely to predict clinical benefit
- Post-licensure clinical endpoint study is required as a conditional commitment for approval
  - Adequate and well-controlled

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Accelerated Approval:
Ex. Approval Denied

HPV vaccine

- Cervical cancer is a serious and life-threatening medical condition
- Interest in accelerated approval for HPV vaccines is understandable given the duration of trials [~3y] that may be required to document unequivocal histologic evidence of high-grade cervical dysplasia or cancer
- Available options for preventing cervical cancer
  - cytologic screening with appropriate interventions, e.g., colposcopy, biopsies, and excisional or ablative procedures as indicated
  - Continued screening will be necessary, even if an HPV vaccine is effective and become available, in order to prevent cervical lesions caused by HPV types not included in the vaccine

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Accelerated Approval:
Ex. Approval Denied

- Confirmatory clinical endpoint study
  - Difficult to conduct placebo-controlled study if widely available and routinely used
  - long duration of follow-up that may be required to accrue sufficient cases of high-grade lesions
  - the confirmatory trials would need to be fully accrued and well underway at the time of an accelerated approval in order to assure that the confirmatory trials would yield a definitive result
- Traditional approval: no clinical efficacy trial required

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Emergency IND

- Investigational drug needed for an **emergency** situation that does not allow time for submission of an **IND**
  - immediate life-threatening illness

§ 312.36 Emergency use of an investigational new drug

- Call designated contact person
- Granted on the condition that the requestor will submit an **IND** submission as soon as practicable

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Formal Regulatory Mechanisms

Emergency Use Authorization

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Project Bioshield

- May 2004: legislation to encourage drug & vaccine manufacturers to develop ways to counter bioterror attacks
  - 5.6 billon over 10yrs; $900 million granted in 1st yr
  - ~100 of 1000 biotech companies are working on biodefense products
- Biological products: e.g. anthrax, smallpox
- Govt. stockpile
- Guidance document
  - FDA authorization for use of unapproved products in emergencies

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Guidance for Industry

- Emergency use authorization of medical products
  - Allows the FDA Commissioner to strengthen the public health protections against biological, chemical, radiological, and nuclear agents that may be used to attack the American people or the U.S. armed forces.
  - FDA commissioner, rather than the HHS Secretary, can declare the emergency + no requirement for IND application during emergency use

www.fda.gov/cber/gdlns/emonuse.pdf - 06-21-2006 -

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Guidance for Industry:
Emergency use authorization of medical products

- Declaration of Emergency
  - Secretary of Homeland Security: domestic emergency involving a heightened risk of attack with a specified biological, chemical, radiological, or nuclear agent or agents
  - Secretary of Defense: military emergency
  - Health and Human Services Secretary: public health emergency
- Once an emergency is declared
  - Assistant Secretary of Public Health Emergency Preparedness (ASPHEP) forms Working Group (FDA, NIH, CDC, others)
  - *Scope:* The FDA Commissioner can issue ≥1 Emergency Use Authorizations (EUA) on the basis of a single declaration of emergency provided that the EUAs are intended for use in the same emergency. Authorization good for at least one yr.

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Guidance for Industry:
Emergency use authorization of medical products

- Cont. Once an emergency is declared
  - Federal Register (FR) notice: describes the reason for authorization, a description of the intended use of the EUA product, and its indications and contraindications. FR notice also needed for termination of an authorization, with an explanation of the reasons for the decision.

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Guidance for Industry:
Emergency use authorization of medical products

- Eligible products: investigational drug, device or biological product, or, unapproved indication for a licensed product
- Criteria for EUA product
  - Based on available data it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing the serious or life- threatening disease or condition.
    - *in vitro*, animal or ± controlled clinical data
    - lower standard of effectiveness than used for std product approval
  - Known + potential benefits > known + potential risks
  - No adequate, approved and available alternative
    - contraindications in a special pop'n can be interpreted as inadequate
    - inadequate supply can be interpreted as unavailable

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Guidance for Industry:
Emergency use authorization of medical products

- Content of EUA request
  - Product
    - Description, fulfillment of criteria to be a EUA product
    - Status of product development: investigational, if licensed ≥1 countries
  - Manufacturing
    - CMC information
    - Sites where the product, if authorized, would be (or was) manufactured and the Good Manufacturing Practices (GMP) status of the manufacturer
  - Approved alternative products, including their availability and adequacy for the proposed use (if known)
  - Available safety and effectiveness information
  - Risk: benefit assessment
  - Instructions for use of the EUA product (e.g., if follow-up treatment is required)

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Guidance for Industry:
Emergency use authorization of medical products

- Effectiveness data:
  - Proposed mechanism of protection
  - Pre-clinical data: immunogenic
  - Clinical data (e.g., in published case reports, uncontrolled trials, controlled trials, if available, and any other relevant human use experience)
- Risk: benefit assessment
  - Measures taken to mitigate risk or optimize benefit
  - Limitations, uncertainty, and data gaps
  - A description of circumstances, if any, under which the product should not be used (e.g., contraindications)

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CONDITION OF AUTHORIZATION	UNAPPROVED PRODUCT	UNAPPROVED USE OF AN APPROVED PRODUCT
Information for Health Care Providers and Authorized Dispensers	Mandatory for manufacturers and others*	Mandatory for manufacturers'
Information for Recipients	Mandatory for manufacturers and others*	Mandatory for manufacturers'[1]
Adverse Event Monitoring/Reporting	Mandatory for manufacturers and others*	Discretionary for manufacturers
Recordkeeping/Access	Mandatory for manufacturers; discretionary for others*	Discretionary for manufacturers
Compliance with GMPs	Discretionary for manufacturers and others*	Discretionary for manufacturers and others*
Advertising	Discretionary for manufacturers and others*	Discretionary for manufacturers and others*
Restricted Distribution	Discretionary for manufacturers and others*	Discretionary for manufacturers and others*
Restricted Administration	Discretionary for manufacturers and others*	Discretionary for manufacturers and others*
Data Collection/Analysis	Discretionary for manufacturers and others*	

* Others may include, for example, the U.S. government.

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Guidance for Industry:
Emergency use authorization of medical products

- **No liability protection to manufacturer!**
- **Timeline for Review**
  - In an emergency situation that is occurring or believed imminent, a request for consideration for an EUA will be acted upon within a matter of hours or days.

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Project Bioshield:
Industry Perspective

- Development of counter terrorism vaccines remains risky
  - Long development time
  - Slim profit margin
  - Limited liability coverage: possible pt lawsuit against manuf if vaccine failure
  - Possibility that another biotech company will develop better product that the govt will ultimately prefer to include in stockpile

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Development and Evaluation of Plasmid DNA an Therapeutic Vaccines

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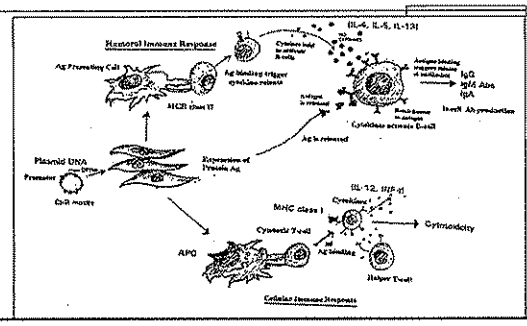
Plasmid DNA Vaccine

1. It contains plasmid DNA necessary for selection and replication in bacteria. In addition, it contains eukaryotic promoters and enhancers, and transcription termination sequences to promote gene expression in vaccine recipients.
2. Some DNA vaccines contain a mixture of plasmids, with each plasmid carrying a gene encoding a different antigenic protein.

Status of DNA Vaccine

1. Early stage of DNA vaccine research.
   Plasmid DNA to express protein Ag of influenza.
   – Hemagglutinin (HA)
   – Nucleoprotein (NP)
2. DNA vaccines successfully tested in animal models.
   Viruses – HIV, hepatitis B, bov herpes virus, herpes simplex, papilloma virus, hepatitis C.
   Parasites – Malaria, leishmania.
   Bacteria – TB, mycoplasma.
3. Immune responses: Humoral – IgM, IgG (2a), IgA.
   CMI response – CTL and TH1-like cytokine response.

Immunization of DNA Vaccine



Safety Concerns on DNA Vaccine

1. Potential for insertion into the host genome, thereby increasing the risk of malignancy.
2. To trigger the development of autoimmune disease.
3. Induces immunologic tolerance.
4. Low immunogenicity, particularly in larger animals and humans.

Clinical Trials of DNA Vaccines

Disease or pathogen	Proteins encoded by genes
Hepatitis B virus	HBsAg
Herpes simplex	Herpes glycoprotein, BD, ICP-27
HIV	Envelope (*env*) and regulatory (*tat, rev, gag, pol*). Core protein and enzymes involved in HIV replication.
Influenza Hemagglutinin, HA	
Malaria	Circumsporozoite protein, CSP, SSP2, PyHEP17

DNA Vaccines to Prevent Infectious Diseases

I. CBER approach to regulation.
   - Case-by case basis
   - Antibiotic resistant marker: use kanamycin or neomycin

II. IND submission
   A. Product manufacture and characterization
      MCB and WCB – PTC in Characterization of cell lines used to produce biologics (1993).
   B. Specifications for bulk plasmid product.
   C. Final product lot release testing.

DNA Vaccines to Prevent Infectious Diseases cont.

III. Animal studies
   A. Immunogenicity
      - Ab response, proposed dose, duration of Ag expression, cell-mediated immune response.
   B. Adverse reactions
      - Clinical pathology, gross change, histopathology, immunotoxic effect.
   C. Genetic toxicity.
      - Integration into host genome, mutagenesis, chromosomal instability, overexpression of Ag.
      - Autoimmunity and tolerance.
   D. Reproductive toxicity and tumorigenicity.

Manufacturing Issues

A. Product manufacture
   - detailed descriptions of the plasmid construction,
   - DNA sequence of the entir plasmid present in the MCB.
   - describes the genotype, phenotype, source of bacterial cells, and the procedures to construct MCB and WCB.

B. Bulk plasmid product release testing
   - in-process testing to ensure manufacturing consistency, product safety and stability.
   - establish specification on bacterial host contaminants, nucleic acids and protein. Pyrogen test.
   - identification and potency assay.

Manufacturing Issues

C. Final product release testing
   - Potency
   - General safety; mice and guinea pig
   - Sterility
   - Purity and quantity
   - Identity
   - Residual moisture
   - Endotoxin

Pn 19A Pneumolysin Gene and Expressed Protein

N-terminal
ATG GCA AAT AAA GCA GTA AAT GAC TTT ATA .....
Met Gly Asn Lys Ala Val Asn Asp Phe Ileu
TAT CCT CAG GTA GAG GAT AAG GTA GAA AAT
Try Pro Glu Val Glu Asp Lys Val Glu Asn
1413 nucleotide/3 = 471 amino acids C-terminal

Functional Domains of Ply

N Asn His Asp C

142, oligomerization
367, oligomerization
385, C' activation
427-437, cytotoxicity
465-471, cell binding

Expression of 19A ply Gene in Cells

19A *ply* gene was amplified by PCR, subcloned and transformed into *E.coli* cells. *Ply* DNA was inserted into JW4303 vector containing CMV promotor. The plasmid *ply* DNA was transformed into human Rhabdomyosarcoma cells for gene expression.

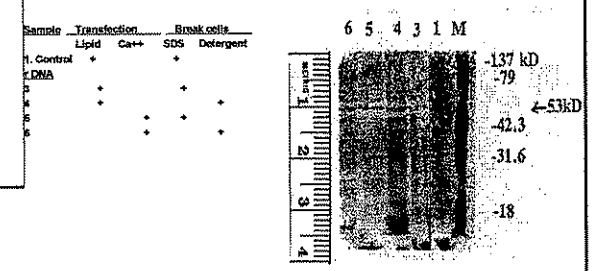
Transfection and Expression of ply DNA in Human cells

Cationic lipid or
Ca-phosphate + *ply* Gene DNA → Complex →

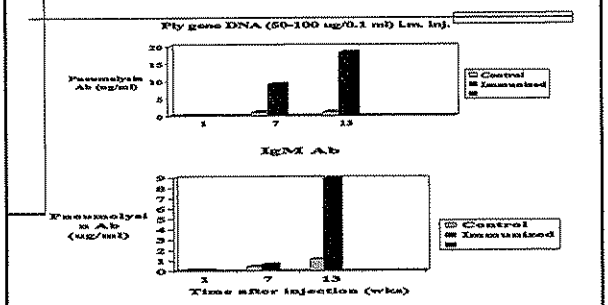
Add transfection medium Incubate 72 hrs
+ Human rhabdomyosarcoma → at 37° C
cells

→ Break cells by → Analyze by immunoblot
SDS or detergent

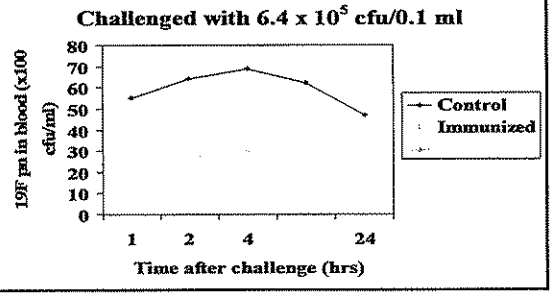
Immunoblot of Expressed Ply in Human Cells



Ab Response in Mice Immunized with *ply* Gene DNA



Bacterial clearance in Mice Immunized with *ply* Gene DNA



Prospectives of DNA Vaccine R & D

1. **DNA vaccines may not be sufficiently immunogenic for the therapeutic vaccination of patients with infectious diseases or cancer in clinical trials.**

2. **To increase the immunogenicity of genetic vaccines.**
   - **using effective adjuvants.**
   - **making them "self replicating" using a gene encoding RNA replicase.**
   - **Ags can be modified to make them better immunogen.**
   - **exogenous cytokines can enhance or direct the immune response.**

Therapeutic Vaccines for Infectious Diseases

Recent research and development:

Li, JM. Therapeutic DNA vaccines against TB. Chin Med J, 2006.

Lowrie, DB. DNA vaccines for therapy of TB. Vaccine, 2006.
DNA vaccines are also effective in therapeutic use.

Crameri R. DNA vaccines for allergen-specific immunoterapy. Curr Opin Immunol, 2006. DNA vaccines are used for both prophylaxis and treatment of allergic disease.

Sun W. DNA vaccines induce protective and therapeutic activities in tumors. Immunol Cell Biol, 2006.

Developmental Toxicity Studies

A. General considerations
- case-by-case basis
  - species-specific differences in immune response, different development time lines.

B. Previous non-clinical and clinical experience.
- perform the non-clinical development toxicity on the same lot as proposed for the clinical trial.
- if the combination vaccine is formulated with new adjuvant, preservative, additional developmental toxicity studies are needed.

Evaluation of Therapeutic Vaccines

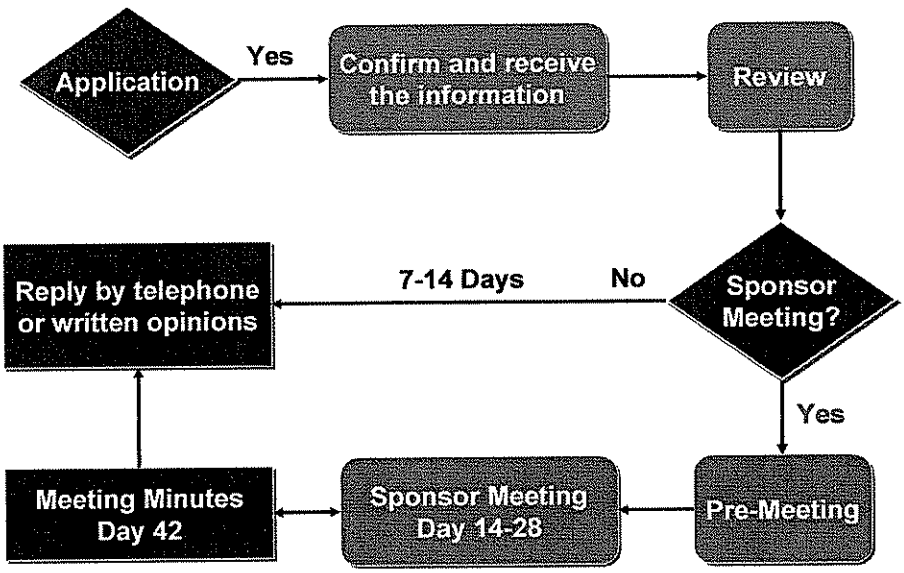
1. Effectiveness
   - antibody assessments.
   - induction of cytokines and cytotoxic T cells.

2. Experimental procedure and dosage
   - assess a single dose level and the maximum human dose.
   - give one or several additional doses during organogenesis.

財團法人醫藥品查驗中心諮詢申請

財團法人醫藥品查驗中心（以下簡稱查驗中心）提供免費之新藥研發法規諮詢服務。諮詢資料之準備及查驗中心受理諮詢案之原則說明，請參考查驗中心網站 http://www.cde.org.tw，由「業務概況」點選【諮詢服務】進入。

1. 相關諮詢申請方式如下：
   1.1 網路線上申請：進入「諮詢服務」後，點選上方之【諮詢服務網路線上申請】進入；填妥相關內容後點選表格下方之【儲存與送件】送出。查驗中心收到您的申請後，將有專人主動與您連繫。
   1.2 或撥打查驗中心諮詢專線（02-23224567 轉 888）：將有專人提供服務，協助您釐清問題以填寫諮詢申請表。
2. 目前，查驗中心諮詢案件審理之流程如下：



新型流感疫苗製劑與新型流感防治計畫溝通會議

（一）

會議紀錄（稿）

時　　間：民國 95 年 1 月 19 日（星期四）下午 2：00～4：40

地　　點：本中心第一會議室

主　　席：朱夢麟

出席人員：（敬稱略；依姓氏筆劃序）

疾病管制局：劉定萍、江正榮、張正鵬、連偉成

國家衛生研究院：Yan C. Kwok、包中怡、池榕穗、李敏西、胡勇誌、張瑞原、陳念慈、蔡浩鵬、羅淑婷

醫藥品查驗中心：王蓉君、李元鳳、林治華、陳恆德、陳淑儀、詹美華、劉涓（另有會議）、盧青佑

記　　錄：詹美華

壹、報告：（略）

一、Guidelines for Developing Human Influenza H5 Vaccines／李敏西

二、建立我國新型流感疫苗製劑之臨床試驗管理機制及規範／王蓉君

貳、結論：

一、本項會議有助於瞭解彼此工作內容，並釐清未來合作方向。

二、預計每季召開工作會議，以追蹤國家衛生研究院及醫藥品查驗中心計畫的執行進度。

三、醫藥品查驗中心原則上將以 EMEA 有關新型流感疫苗(Pandemic Influenza Vaccine)相關法規為主，並參考 FDA 的規定、配合國內現況，以進行規範研擬。

四、產品製造工廠查核現由藥檢局負責，且最後核准產品上市之權責

單位為藥政處。故新型流感疫苗計畫的執行，需要藥檢局及藥政處等政府單位的參與。

五、研發單位在新型流感疫苗製程中應與法規單位保持密切的討論及溝通，以達成 Fast track approval 的目標。醫藥品查驗中心將邀請國內、FDA、EMEA 與疫苗研發或法規有關之專家，組成 IOAC (Issue-Oriented Advisory Committee)，以協助研發單位解決產品研發上市過程可能發生的困難。

六、由疾病管制局於 6 月前協調組成 site visit team 拜訪國家衛生研究院，就其新型流感疫苗的研發及產製情況進行實地瞭解。

流感防治計畫工作會議

(International Avian Flu Symposium Meeting Minute with Prof. Martine Denis)

會議紀錄

時　　間：民國 95 年 3 月 4 日（星期六）上午 12：00～13：30

地　　點：臺大醫院國際會議中心 3 樓貴賓室

出席人員：Prof. Martine Denis、唐海文、王靜文、朱夢麟、王蓉君、李元鳳、蔡承恩（敬稱略）

記　　錄：王蓉君

討論事項：

GENERAL ISSUE:

Dr. Chu: First, I would like to introduce our reviewers in CDE: Dr. Tsai, Dr. Li and Dr. Wang. There is a working group for pandemic flu vaccine task force in CDE. Three of us in this task force will attend the 2006 DIA Workshop on Vaccines which will be held on Vienna, May 16-17. In the mean time, it will be a great interesting for us to visit GSK R&D center for flu vaccine in Rixensart, Belgium. As you know, there is a lot of issues on the research and development of pandemic flu vaccine. We hope that we can learn something from you by this visiting. Thank you for arranging this visiting for us. Will we meet you there?

Prof. Martine Denis: Yes, of course. Concerning about the visiting to Rixensart R&D center, please confirm the items which could be presented to you and the items expand beyond flu vaccine.

CMC ISSUE:

1. Q: What is the established animal model used for evaluation of the potency of flu vaccine

   A: Ferret is a fairly good model.

2. Q: In WHO guidance, optimal cell line for reverse genetics of reassortant derivation is discussed. What is you experience and recommendation in developing the cell line for such use?

   A: The history and control of the cell line must be very careful and the requirements are just like those of the other biologics. Validation of the cell line for flu vaccine products require detailed evaluation and validation. (In the GSK vaccine, now in phase I trial, MDCK is used).

3. Q: In case the reference virus is genetically modified to obtain better potency, what is the process in getting approval for the modified virus to be used for the vaccine production?

   A: It is best to manufacture the vaccine as it is obtained from WHO or the approved laboratory. Genetic modification creates a different strain and new issues, thus is probably not suitable for the vaccine production.

CLINICAL ISSUE:

1. Q: We know that GSK has submitted the 1st "mock-up" vaccine dossier into EMEA regulatory authority. Is this mock-up vaccine

an egg-based, whole virion and with adjuvant vaccine?

A: Yes, it is.

2. Q: We are quite interesting in the clinical trial design of this mock-up vaccine. Have this "core pandemic dossier" completed the Phase I, II and III studies?

   A: No. actually, we call these studies of the mock-up vaccine as feasibility studies. We do have the immunogenicity response data at this moment.

3. Q: What is the number of subjects enrolled in these trials?

   A: The simple size is few hundred, not large; but we have about 1,000 subjects enrolled. Of course, the subjects enrolled in these studies were adult less than 60 years of age. The immunological response of children and the elderly need to be further evaluated.

4. Q: What is the primary endpoint in this mock-up vaccine?

   A: We use the immunogenicity response to be the endpoint. Considering about the assessment criteria for the immunological response on this mock-up vaccine, we evaluate the seroconversion rate $\geqq$ 40%, GMT> 2.5, subjects with HI titer $\geqq$ 1:40 should $>$ 70% in adult less than 60 years of age.

5. Q: Do they need to fit all of the three immunological criteria or one of them?

   A: We use all of three criteria as the co-primary endpoint.

6. Q: We have learned that 2 doses of vaccination are necessary for the protective immunological response at this moment. Is

that true?

A: Yes.

7. Q: Do you consider that the 3rd dose (booster) vaccination will be needed during the outbreak of pandemic?

A: We don't know now. This is the issue proposed to be studied on the post-approval commitments trial.

流感防治計畫
國家衛生研究院疫苗中心參訪會議紀錄

一、時　　間：民國95年5月26日（星期五）10：00～14：00

二、地　　點：國家衛生研究院

三、主　　席：莊再成主任

四、出席人員：

疾病管制局：劉定萍主任、江正榮科長、連偉成科長、繆柏齡科長、李正道科長

藥物食品檢驗局：楊若英技正

藥政處：黃淑萍薦任技士

醫藥品查驗中心：朱夢麟特聘研究員、王蓉君醫師、李元鳳博士、蔡承恩醫師、李逸琦專案經理、廖紫歆專案經理

國家衛生研究院：莊再成主任、周文祥副主任、李敏西副研究員、李信廠務經理、郭恩澤品管經理、李慧敏法規經理、包中怡法規助理、趙欣如研究助理、顧倩君研究助理、蔡浩鵬助技術師、陳信偉助研究員、周愛湘博士後研究員、蕭佳欣研究助理、黃鈴華研究助理、馮臺貞研究助理、吳佳翰研究助理、伍鳳碧研究助理陳念慈專案管理助理、許惠鈞品保助管理師、江東榮執行秘書、張素芝主任、羅麗珠主任、黃玉燕、賴瑨瑄

五、記　　錄：廖紫歆專案經理、李逸琦專案經理

六、會議討論事項：

1. 疾病管制局：

1.1. 對於目前的研究現況cell-based或是egg-based兩者皆有進行培養，目前是否有確定的時間點，決定選擇其一進入臨床試驗？

1.2. 不論是cell-based或是egg-based，目前國內都還沒有完善的場所可生產，對於國衛院而言兩個系統皆須從頭開始建立相關製程，因此是否應考量於未來法規審查上何者是較易被審查單位接受？

回覆：目前國衛院於執行上發現cell-based的培養效果較佳，但因egg-based為傳統方式較易follow，因此仍為現行國際上較普遍的執行方式。但於今年美國NIH已有提出計畫，將以cell-based的方式進行研發，因此這兩個方式皆可執行，主要是在於未來製造廠的設備與技術的配合。

1.3. 目前的進度規劃為預計今年第四季完成manufacture of clinical trial material，但於 safety test 的檢測進度，目前是否有規劃？

回覆：目前有與美國的實驗室聯繫，若可行，經於今年8月份將 cell bank 及 virus bank 直接送檢。並想詢問：於台灣是否有CRO公司可執行 safety test，並且試驗數據是可被接受的？擬提專家會議討論。

1.4. 於目前 bulk vaccine 的檢測項目中，有多種的virus的活性檢測似乎有重覆的現象；應可將一些檢測列於 in-process control中檢測之，如 Hemagglutinin inhibition assay。

2. 醫藥品查驗中心：

2.1. 臨床部分：

2.1.1. 查驗中心已成立「新型流感疫苗工作小組」。

2.1.2. 95年4月：本工作小組已初步完成「新型流感疫苗查驗登記之審查注意要點（草稿）」。

2.1.3. 95年6月30日：將邀請國內專家蒞臨查驗中心舉辦之專家諮詢會議，針對上述審查注意要點提出建議。

2.1.4. 95年下半年：擬邀請國外專家蒞臨指導。

2.2. 【CMC and Pharm/Tox】部分：

2.2.1. For an innovated and first time vaccine manufacturer

(1) Can the CMC dossier be provided in a divided, but orderly, process?

回覆：將來與查驗中心聯繫後，再商量如何有系統將CMC資料陸續送入。

(2) CMC minimal requirements for a phase I study, in general:

a. Source, history, and control of the cell substrate and cell bank system;

b. Source and control of the ancillary materials and excipient/adjuvant;

c. Manufacturing process (and control) and description;

d. (Preliminary) specification of the DS and DP, including the test methods;

e. Batch analytical result(s);

f. Validation of the safety related process and analytical methods, e.g., viral inactivation, sterility, endotoxin;

g. e.g., (Preliminary) stability data.

2.2.2. Reproductive organs, depends on the subjects or prevention of pregnancy in phase I trial, be evaluated in the repeated dose toxicity study.

回覆：若國衛院來不及執行臨床試驗前完成Reproduction toxicity，則會先於臨床試驗時先排除有相關疑慮之受試者，例如：婦女（含懷孕／授乳）。擬提專家會議討論。

2.2.3. 若依照EU法規的方式，以mock-up flu Vaccine為基礎，當新的pandemic strain出現時，如何以現有之mock vaccine資料來支持新的pandemic strain，值得考量。

回覆：因各病毒特性不同所以希望經驗可以擴充，目前國衛院所取得的是2004年越南株，目前疾病管制局已向WHO索取新的病毒株（2005年印尼株），將來更希望可以建立平台，以在緊急情況下自行建立國內病毒株。

2.2.4. 根據國衛院於950526之進度報告，提及細胞株之Madin-Darby Canine Kidney (MDCK) 係購自食工所，擬將MDCK細胞株送至國外實驗室進行檢測，國內尚無單位或實驗室經過認證執行細胞及病毒種批系統之QC測試。擬提專家會議討論。

2.2.5. 關於品管技術之建立：

(1) Bulk vaccine檢測項目，可參考歐盟相關法規。某些檢測項目可考慮是否與 in-process control test合併。

(2) 以SDS-PAGE檢測出相對濃度後，建議仍應測試MDCK之residual protein，可放入in-process control中。

回覆：

(1) 目前可以 in-house antibody 檢測MDCK之Residual protein。國衛院會搜尋是否有已建立之檢驗方法。

(2) 疾管局專家建議分析Formaldehyde對cell toxicology的影響，可考慮利用flu. Virus對Hema-absorption的特性分析，係Formaldehyde或是virus造成的細胞毒性。

(3) 建議Validation應納入 Kinetic monitoring data。

2.2.6. 建議除了CMC以及safety issue以外，before Phase I clinical trial之前，應有小型動物之初步的immunogenicity data，才可以進入人體臨床試驗。

3. 藥物食品檢驗局：

3.1. 目前就已完成的cell culture 製備方式來看，以PM培養基而言，Scale從1L、2L、10L到40L，放大產量後其HA的檢測值似乎無一致性，未來量產時是否可控制產品品質之一致性。

3.2. 本次簡報中未說明，製程中病毒不活化確效何時執行。

3.3. 本次簡報中未說明，製程中之不活化劑含量、無菌試驗等檢測，以及一般cell來源的疫苗製劑大多會檢測DNA殘量等檢測項目，未來是否會執行。

回覆：相關的CMC檢測會照法規要求執行，於 safety test 方面計畫請CRO或DCB協助執行，並想請問藥檢局是否可協

助這方面的檢測？

3.4. 製造單位理應建立完整之製程及成品檢驗規範以管制自家產品，藥檢局歷年來執行封緘檢驗業務係針對Final Products進行檢驗並負責審核批次檢驗紀錄及成績書。

3.5. 歐盟EDQM於2005年已提出「Official Control Authority Batch Release of A Pandemic Influenza Vaccine」，可作為未來產品管制之參考。

（以下空白）

附件十二

Vaccine Symposium

11.3
2006

- The Evaluation and Regulatory Consideration on New Vaccine in the United States and Taiwan
  新疫苗之發展及法規科學現況
- Venue: Conference Room 301, NTUH International Convention Center
  地點：台大醫院國際會議中心 301 會議室
- Organizer: Center for Drug Evaluation, Taiwan
  主辦單位：財團法人醫藥品查驗中心



新疫苗之發展及法規科學現況

Vaccine Symposium: The Evaluation and Regulatory Consideration on New Vaccine in the United States and Taiwan

時　　間：95 年 11 月 3 日（星期五）

地　　點：台大醫院國際會議中心 301 會議室（台北市徐州路 2 號 3 樓）

主辦單位：財團法人醫藥品查驗中心

時　間	講　題	講　員	主持人
08:30-08:50	Registration		
08:50-09:00	Opening Remark / 廖繼洲處長 / 陳恆德執行長		
09:00-09:50	The vaccine development in the United States	Chi-Jen Lee, ScD CBER, FDA	朱夢麟 特聘研究員 醫藥品查驗中心
09:50-10:40	Quality data requirements in clinical trials of new vaccine	Lucia H. Lee, MD CBER, FDA	
10:40-11:10	Coffee Break		
11:10-12:00	National vaccine development strategies and current status in Taiwan	劉定萍 主任 衛生署疾病管制局 血清疫苗中心	
12:00-13:30	Lunch		
13:30-14:20	Safety and efficacy evaluation on new vaccines	Lucia H. Lee, MD CBER, FDA	林奏延 院長 長庚兒童醫院
14:20-15:10	FDA's critical path on development of drug, vaccine, and other biologics	Chi-Jen Lee, ScD CBER, FDA	
15:10-15:30	Coffee Break		
15:30-16:20	Current status of NHRI on new vaccine development in Taiwan	莊再成 主任 國家衛生研究院 疫苗研發中心	
16:20-16:50	The experiences of vaccine products review in Taiwan	王蓉君 審查員 醫藥品查驗中心	
16:50-17:30	Panel Discussion		

Contents

INVITED SPEAKERS

The Vaccine Development in the United States

Chi-Jen Lee, Sc.D

（李啓仁 博士）

Supervisory Research Chemist

Center for Biologics Evaluation and Research

Food and Drug Administration

U.S.A.

The Vaccine Development in the United States

Chi-Jen Lee, Sc.D（李啓仁 博士）

Center for Biologics Evaluation and Research, FDA
Bethesda, MD, U.S.A.

The development of vaccines has been one of the most important achievement in immunology and preventive medicine. Recently, various driving forces have promoted the development of vaccine. New technologies, increased demands on safe and more effective products an global efforts have stimulated the development of new vaccines and improvement of existing vaccines.

The Institute of Medicine has reported the priority of important vaccine candidates for development in the U.S. Several of recommended vaccines have been licensed and widely used. In addition, recent efforts have focused on developing therapeutic vaccines directed against chronic diseases, such as cancers, Alzheimer's disease, and autoimmune diseases. Global cooperations among U.S. government, WHO, and other organizations have been exerted toward vaccine development.

Advanced analytical methods such as HPLC, NMR, and nephelometry have been applied for evaluation of physico-chemical characteristics of bacterial glycoconjugate vaccines and detection of impurities in the products. Specifications provide limits for contamination as well as accuracy and reliability of the assay to ensure uniformity of properties of the product. The future perspectives and changes impacting vaccine development will be discussed.

Quality Data Requirements in Clinical Trials of New Vaccine

Lucia H. Lee, M.D.

Medical Officer
Center for Biologics Evaluation and Research
Food and Drug Administration
U.S.A.

Quality Data Requirements in Clinical Trials of New Vaccine

Lucia H. Lee, M.D.

Center for Biologics Evaluation and Research, FDA
Bethesda, MD, U.S.A.

Overview: Clinical Testing of Vaccines

Vaccine evaluation is based on three underlying principles:

- The proposed population is often healthy children. If a vaccine is licensed, and routinely recommended, the potential number of vaccine recipients could involve the entire birth cohort.
- From a public perspective, there is less tolerance of adverse safety outcomes for a healthy population. The proven benefit of the vaccine, i.e., disease prevention, is assessed relative to the risk of an adverse event. As more information becomes available about the recognized benefits of the vaccine or detection of vaccine-associated adverse events, the risk:benefit ratio can change over time.
- Vaccines are complex biological products, which require specialized assays, and testing to ensure product quality.

Pre-clinical:

Study results provide the safety and immune response data that the vaccine candidate, as formulated for clinical use, can safety be given to human subjects.

Pre-licensure studies:

Phase II studies, which involve testing in a small number of individuals, are to primarily evaluate safety of the investigational vaccine. In phase II studies, the vaccine is evaluated in a few hundred individuals that are representative of the intended target population. The study design is typically a randomized, controlled trial. Immune response for a range of vaccine doses is studied, and dose escalation proceeds in a step-wise manner. The vaccine formulation, dose and dosing regimen are optimized for use in a phase III trial. Phase III trials are large-scale studies which constitute the essential data for demonstrating efficacy and safety in the intended population. Inclusion of a control group, appropriate primary endpoint, statistically justified hypothesis maximize the chance that the

observed outcome is due to the true effect of the vaccine.

Post-licensure studies:

Continued monitoring of vaccine performance provides ongoing assurance of product quality, safety and effectiveness. Post-marketing surveillance may be the only means to detect rare serious events that occur too infrequently to be identified in pre-licensure trials.

National Vaccine Development Strategies and Current Status in Taiwan

劉定萍 主任

(Christine Ding-Ping Liu, M.T., M.S.)

行政院衛生署

疾病管制局血清疫苗中心

Director

Vaccine Center, Center for Disease Control

Department of Health, Taiwan, Republic of China

Human Vaccine Research & Development in Taiwan

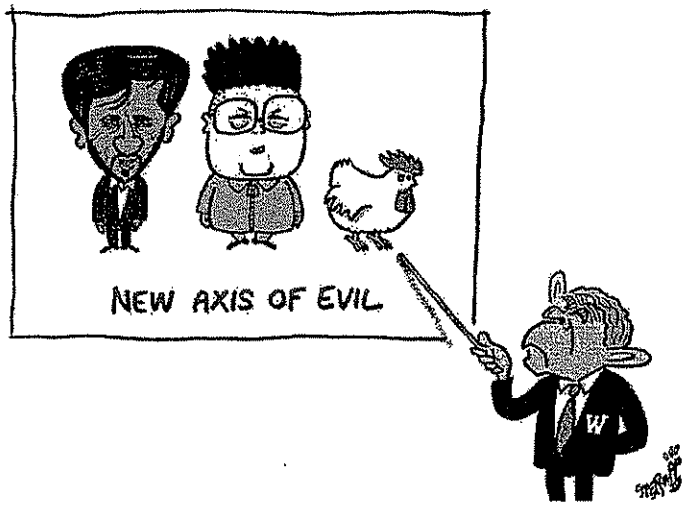
Christine Ding-Ping Liu
Vaccine Center, Taiwan CDC

Vaccine ~

High-Cost, Risky and Fragile Industry

我國疫苗研製政策~ Past

- 疫苗以外購為主
  - 台灣人口規模不足以維持工廠營運，不符成本效益及發展性
- 僅國外不易購得，或屬我國地方性傳染病者始進行研製
  - EV71, JE...
- 保生失敗經驗使得產官學界均為之卻步



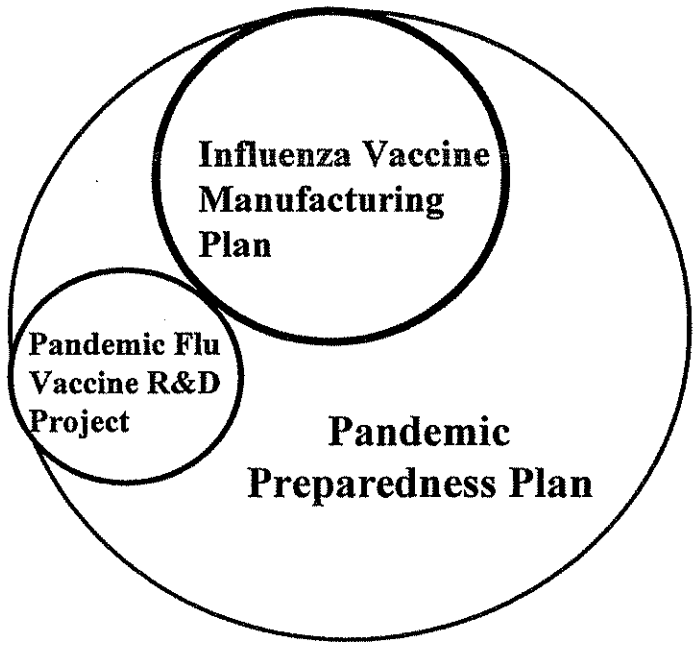
我國疫苗研製政策~ Present

- 流感大流行的威脅使政府認知到，研製疫苗能力實為維護國家安全，民眾健康之無價資產
- 2004年底，李遠哲前院長在APEC資深官員會議倡議國際間進行禽流感疫苗之研發工作
- 2006年開始三年期之流感疫苗研發計畫;辦理流感疫苗BOO案
- 2007年起併入五年期之人用疫苗(含量產技術)研發計畫，包括Meningococcus B, cell based JE, EV71,第一年經費3.5億元

Taiwan Vaccine Strategy for Pandemic

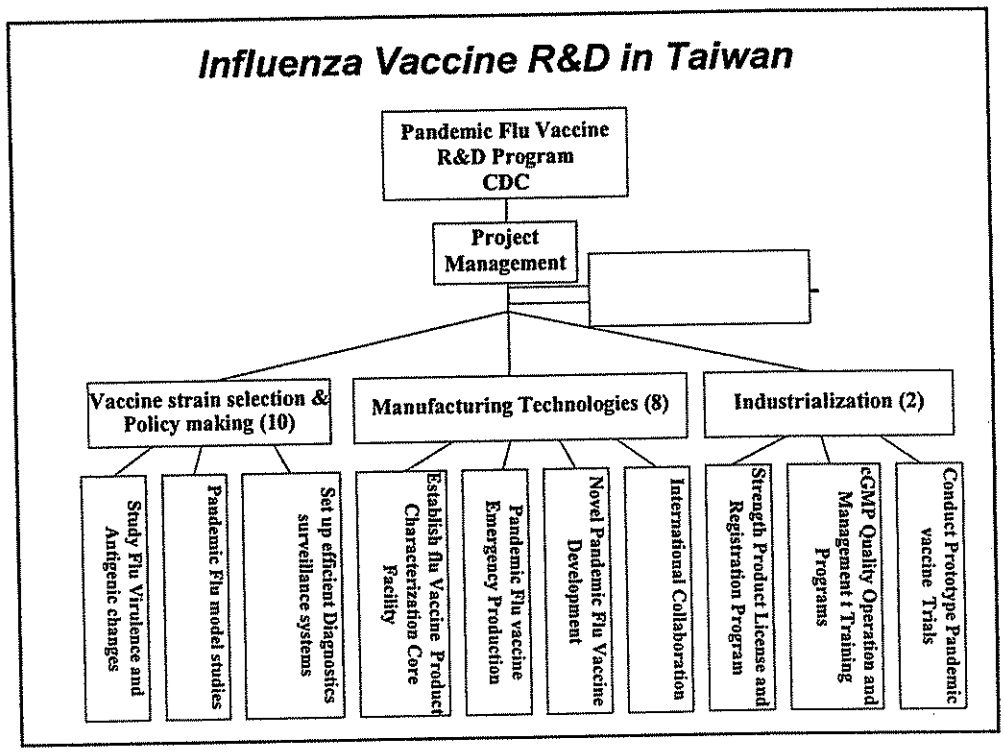
- **Short term: stockpile for the first line workers**
  - Purchase from foreign companies
  - Obtain the best vaccine available before the end of 2006
- **Mid term:** Influenza Vaccine R&D Project
  - construct production line for emergency use
- **Long term: Self-manufacturing "BOO" project:**
  - Begin Operations in Taiwan within 3 years of contract
  - 16 M doses capacity required; 10-year purchasing contract guaranteed
  - Negotiation with the Nobilion completed, **waiting for signatures and approval**

Influenza vaccine R&D in the national preparedness plan



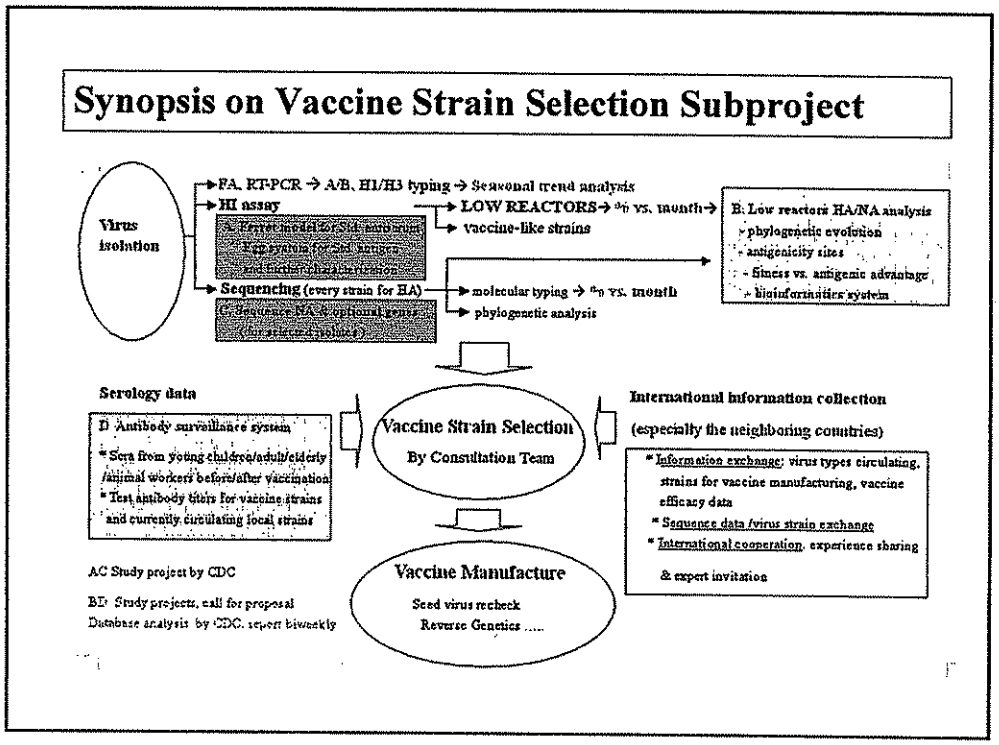
Influenza Vaccine R&D Project

- Dr. YJ Lee pledged 20 million USD for influenza vaccine manufacturing R&D at APEC in November 2004
- Year 2006: $4 M USD approved
- Year 2007: compiled with "Human Vaccine and Scale-Up Production Technology R&D Project", $7 M USD for flu vaccine in 2007
- Three branches, including 20 subprojects



選定疫苗株及疫苗政策研究

- 目的- 瞭解本土流感病毒演化狀況，建立疫苗株選擇能力;
- 研究重點
  - 產製病毒標準抗原及抗血清: 建立雪貂及雞胚蛋接種動物模式(疾管局/劉銘燦)
  - 本土流感病毒抗原性相關基因之定序與分析(中研院/何美鄉; 疾管局/吳和生)
  - 建置基因庫生物資訊系統(陽明/楊永正,張傳雄)
  - 建立國人社區血清抗體監測系統(台大/黃立民;榮總/李建賢; 中山/陳志豪)
  - 流感疫苗及防疫政策之數理模式研究 (中興/謝英恆; 交大/孫春在)



選定疫苗株及疫苗政策研究(一)

- 已建立雪貂免疫模式，製備流感病毒3個分離株 A/Taiwan/7702/2004 (H3N2), B/Taiwan/8578 /2004, A/Taiwan/ 0071/2006(H1N1)之抗血清
- 進行94年度50株A型流行性感冒病毒分離株之HA(已完成100%)、NA(60%)、PA(60%)以及NP(100%)等四個基因片段PCR實驗及定序。95年度150株A型流行性感冒病毒分離株之HA (40%)及NA(8%)基因片段PCR實驗及定序
- 完成HA半自動化的統計分析程式並試用，已完成1-5月的流行資料分析

選定疫苗株及疫苗政策研究(二)

- 進行台灣1~4月A型流感病毒之M及NA gene 氨基酸有無抗流感藥物變異之測定
- 完成病毒序列資料庫及使用者搜尋介面之軟體架構
- 完成美國NCBI 及 IRV 與LANL之Influenza Sequence Database (ISD) 序列資料之整合

建立疫苗基礎技術-
建立病毒核心實驗室

- 新型流感基因體鑑定及反轉基因法製備疫苗種株技術之建立與運用(長庚/施信如)
- 建立標準化免疫分析技術平台(陽明/謝世良)
  - 病人免疫受體特定基因序列選殖，比對與分析
  - 病毒基因變異對宿主免疫反應之影響
- 建立病毒學、免疫病理學技術平台(成大/王貞仁)

建立核心實驗室-成果

- 對已公布之HA與NA流感病毒基因序列，進行分析人與禽類病毒之基因特異性。同時，針對本土病毒株進行基因定序，且序列資料收集中。目前已有30株病毒株之完整資料
  - Scanning for *"Species-associated"* amino acid residue in avian vs. human influenza viruses
- 已選殖reverse genetics system所需之質體。將此12個質體轉染至293細胞, 可以成功產出病毒顆粒
- 分析91至95年13株H3，7株H1流感病毒的NS基因。大量培植8株流感病毒及純化HA, NA, M之單株抗體，初步證實可偵測influenza A感染的細胞

建立疫苗基礎技術-
新型病毒原型疫苗之先導生產

- 建置我國新型流感疫苗緊急應變生產線 (NHRI/莊再成)
  - 疫苗株純化，篩選; 馴化，製備方法建立
  - 安全性檢測
  - 建立滾動瓶培養產製技術
  - 執行原型疫苗先導生產及無毒化製備與檢驗
  - 建立量產病毒純化技術
  - 建立製程檢驗分析品管技術與制度，及相關SOP
  - 先進國家種庫建置管理，品保品管制度等技術轉移

緊急疫苗未來執行規劃

- 2006 Q3 開始持續進行H5N1流感疫苗先導生產與儲備，並以每年儲備10萬劑為目標（每劑含15μg HA蛋白）
- 2006 Q4 完成5000劑臨床試驗用 H5N1 mock-up vaccine生產
- 2007 Q2 開始進行臨床試驗IND申請
- 2007 Q3 規劃開始進行臨床試驗

建立疫苗基礎技術-

疫苗之改良與技術開發

- 研發以新型醣脂佐劑結合抗人類流感及禽流感之DNA雙效疫苗(中研院/翁啟惠，何大一，陳玲津; DCB/黃瑞蓮，紀威光)
- 以無血清微載體細胞培養量產新型流行性感冒疫苗(NHRI/李敏西)
- 新型流感次單元疫苗及新型高分子疫苗緩釋劑之研發(NHRI/冷治湘)
- 改良哺乳動物細胞與篩選病毒複製促進劑以增加流行性感冒病毒(疫苗株)之產量(NHRI/徐祖安)

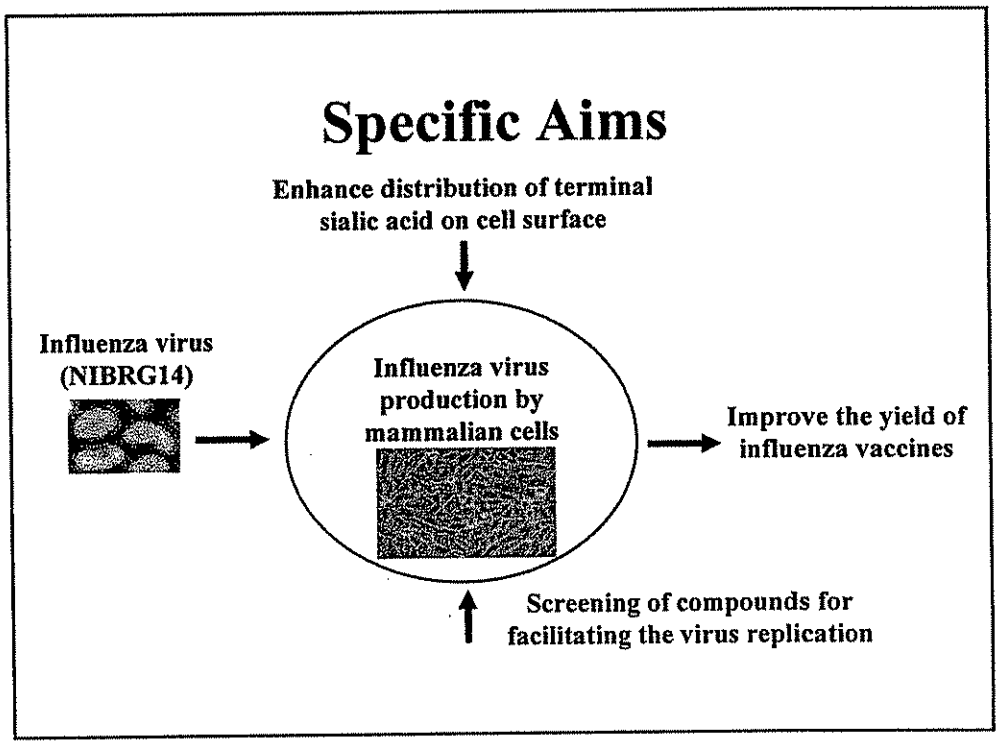
➢ 選取2-3件有潛力標的，3年內進入臨床前試驗

疫苗之改良與技術開發-成果

- 合成第一代的H5 DNA plasmid。並製作去除transmembrane domain的H5 plasmid，藉以轉染293細胞株，可使細胞大量產生重組H5蛋白並分泌至細胞外; 將進行動物攻毒試驗
- 佐劑: 已產製3毫克以上的醣脂alpha-GalCer與7種新型類似物；同時已研製另外10種新型醣脂類似物。其中醣脂alpha-GalCer的產量已達10毫克，並完成臨床前試驗，將測試其作為H5 DNA疫苗的佐劑效能
- 生物技術開發中心已規劃抗病毒疫苗ADVAX的產程，並已進行高產量E. coli 菌株篩選及小規模 (20公升) 醱酵測試

疫苗之改良與技術開發-成果II

- 利用基因重組的技術，研發安全有效的次單元抗原。目前完成抗原基因HA1_H5及NtM2-NP之合成並得到含H5_HA1抗原基因的重組桿狀病毒株
  - 由大腸桿菌表達系統，可以表達NtM2-NP的重組蛋白並完成純化
- 建立哺乳動物細胞表面醣蛋白質分析系統，加強Vero cells 表面 α-2,3-linked sialic acid的分佈， 並進行穩定細胞之篩選
- 利用anti-virus assay 和NA assay建立小分子化合物對流感並養之篩選系統，每月篩選80-100小分子化合物，找出能促進病毒繁殖的化合物



推動產業發展及臨床試驗-
強化人用疫苗評估與執照申請管理機制

- 由醫藥品查驗中心 (CDE) 辦理
- 建立我國疫苗製劑管理機制與規範，以及緊急應變用疫苗之執照申請規範
- 成立新型流感專案工作小組 (Pandemic Task Force Working Group)，任務導向顧問小組會議 (Issue-Oriented Advisory Committee Meeting)
- 建立臨床前階段及臨床試驗管理機制與規範
- 協助進行新型流感疫苗臨床試驗

推動產業發展及臨床試驗-

技術與營運管理人才培育計畫

- 由國家衛生研究院辦理
- 與國內外相關機構合作開設“cGMP- 生物製藥認證”課程
- 針對產業界，學術界與政府單位提供至少20名學員之人才培育
- 課程內容包含產程規劃與設施施工管理，確效認證，生產管理，法規管理等主題

推動產業發展及臨床試驗-

執行新型流感疫苗臨床試驗

- 引進國際藥廠在我國執行臨床試驗
- 第一或第二期臨床試驗，標的物為--
  - 改良劑型流感疫苗
  - H5N1等新型流感疫苗
  - 佐劑應用
  - 接種方式改良
  - 細胞培養劑型
- 需已於歐美日或澳洲等先進國家執行臨床試驗

推動產業發展

- 法規訂定: 業由醫藥品查驗中心完成新型流感疫苗查驗登記作業之初稿，以應後續疫苗採購，研製及臨床試驗之需
- 技術與營運管理人才培育: cGMP生技製藥認證學程已於7/14開課，引入加拿大Wateroo University學程，全程學員共34人; 並於7/13召開開訓前研討會，超過120人參加

推動產業發展及臨床試驗-

國際合作研究與技術移轉

- MTA
  - CDC-NHRI-IOMAI: H5N1 patch animal test
- Cooperative Agreement
  - CDC-NHRI-IVI: H5N1 vaccine R&D
- MOU
  - National Center for Epidemiology, Hungary-Taiwan CDC: influenza vaccine R&D (洽談中)

台灣人用疫苗研發(含量產技術)暨產業生根計畫

- 行政院衛生署及經濟部技術處
- 計畫期程為5年，96年預計投入經費3.5億
- 研究標的:禽流感、腸病毒71型、細胞培養日本腦炎、B型流行性腦脊髓膜炎疫苗
- 目標：於5年內進入臨床試驗並取得多項專利

細胞培養日本腦炎疫苗(一)

- 已完成細胞培養日本腦炎病毒生產量產製程的建置。
- 完成臨床前動物試驗(包含小鼠、兔子、豬、馬匹及猴子等)、原型疫苗安定性試驗、安全性試驗(包含異常毒性試驗、亞急性毒性試驗)。
- 細胞種庫與病毒種庫已分別通過24、32項安全性測試確效，包含無菌測試、黴漿菌測試、病毒污染測試等項目，尚須補充細胞種庫致癌性研究與病毒種庫外來物污染測試項目

細胞培養日本腦炎疫苗(二)

- **國衛院疫苗研發中心**
  - 94/12/13與本局簽訂生物製劑生產技術及研發合作契約
  - 台灣人用疫苗研發（含量產技術）計畫
- **國光公司**
  - 經濟部科專計畫
  - 日本腦炎疫苗細胞培養製程技術平台開發
  - 94年11月1日與本局簽訂合作研究契約
- **International Vaccine Institute (IVI), Korea**
  - 95/6/29本局與國衛院、IVI完成三方16項合作備忘錄簽署
  - 本局與國衛院完成臨床前試驗，並技轉下游廠商
  - IVI負責尋找下游廠商並協助規劃與執行臨床試驗

腸病毒EV71疫苗研發

- 已利用交叉中和試驗篩選出適當之疫苗株，並建立病毒母種庫與工作病毒庫各400支。
- 已完成產程的開發，並已執行20批次量產，依據蛋白質濃度與抗原回收率證實批次純化產物品質具有相當的穩定性。
- 抗原蛋白質含量為2 μg/mL以上配合鋁鹽佐劑配方免疫小鼠時，中和抗體力價可達1:40以上，原型疫苗具有相當穩定之免疫產生性。
- 94年12月13日本局與國衛院簽訂生物製劑生產技術及研發合作契約
- 台灣人用疫苗研發（含量產技術）計畫

B群腦膜炎球菌重組次單元疫苗研發

- 以抗B群腦膜炎球菌（NMB）單株抗體篩選出一新的表面抗原Ag473，此抗原在所有的NM菌株皆有表現
- 表面抗原標的物Ag473所引發的抗體能辨識NM全菌，顯示Ag473具有成為廣效性疫苗的潛力
- 在初步建立的老鼠試驗研究中，Ag473抗原能誘發產生免疫反應，抵抗腦膜炎球菌的感染
- 台灣人用疫苗研發（含量產技術）計畫
- GSK and Sanofi Pasteur公司均表達合作意願，且會將協助我們進行第3期臨床試驗與產品的製造

Vaccines produced by Taiwan CDC- Past

- Tuberculin（2001 stop supply）
- Japanese encephalitis vaccine（1999 stop production）
- Smallpox vaccine（1983 stop production）
- Plague vaccine（1983 stop production）
- Typhoid & paratyphoid mixed vaccine（1983 stop production）
- Whopping cough vaccine（1983 stop production）
- DP vaccine （1980 stop production）

Vaccines Produced by Taiwan CDC- Present

- Bacterial Vaccine
  - freeze-dried BCG vaccine, cholera vaccine
- Toxoids
  - tetanus toxoid alum precipitated, TD, Td
- Antitoxin
  - Tetanus and diphtheria
- Antivenin
  - 百步蛇，雨傘節與飯匙倩，龜殼花與赤尾鮐，鎖鏈蛇

國衛院疫苗研發中心與先導工廠

- 鞏固國內疫苗產業發展基礎架構
- 研製台灣本土性疫苗
- 發揮cGMP生物製劑先導工廠的功能
- 提供國內疫苗研製量能
- 培育生物製劑產業人才
- 防範生物恐怖，保障國人安全

我國疫苗產業的願景

- 疾管局與國衛院的角色
- BOO案的成功達成帶頭作用
  - 帶動週邊軟硬體與人才的需求
  - 母雞帶小雞，促進國內外廠商合作
- 政府獎助方式的變革
  - 以保證收購取代缺乏管考及責任的專案補助或變相補助方式

疾管局與國衛院的願景(一)

- 強化本局血清疫苗研製中心組織功能，於疫苗產製及確效流程中導入風險管理機制，以期所生產之生物製劑符合cGMP標準。
- 通過美國FDA審核標準之生物製劑先導工廠，提供業或學界研究成果製程量化與產品化評估。
- 有效整合上游產、官、學之研究成果與資源，並建立跨平台垂直合作模式，著重中游量產技術之開發與應用，輔導協助將技術移轉至下游民間廠商。

疾管局與國衛院的願景(二)

- 以預防法定傳染病之疫苗為目標，提供三種技術平台(technology platforms): (1)生物製劑之製程(2) 生物製劑之檢驗方法(3)生物製劑之確效
- 開發本土性、特殊性生物製劑之領航角色
- 成立亞太抗毒素血清製品開發中心

Safety and Efficacy Evaluation on New Vaccines

Lucia H. Lee, M.D.

Medical Officer
Center for Biologics Evaluation and Research
Food and Drug Administration
U.S.A.

Safety and Efficacy Evaluation on New Vaccines

Lucia H. Lee, M.D.

Center for Biologics Evaluation and Research, FDA
Bethesda, MD, U.S.A.

Factors in the Acceptability of Foreign Clinical Data

Vaccines are increasingly being developed for a global market. Sections in the Code of Federal Regulations (CFR) as well as the ICH E5 guidance document provide a framework for accepting foreign clinical data from supportive or confirmatory studies.

21 CFR §312.120 describes the conditions in which international data can support initiation of clinical studies in the United States.

- The study goals, methods of assessment and analysis are clearly defined, and the study, as proposed, can achieve its stated objectives.
- The investigator(s) responsible for the trial have the training and expertise to conduct clinical trials.
- The study was performed in accordance with ethical principles.

21 CFR §314.106 and *§314.126* describe the conditions in which international data can support approval of a biologic licensure application.

- Clinical conditions applicable to the U.S. population and medical practice
- Data validated by FDA inspection or other appropriate means
- Design includes a valid comparison to a control group, if supporting efficacy

ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data:

A bridging study is a supplemental study performed in the new region (e.g. Taiwan, U.S.) to provide clinical data on efficacy, safety, dosage and dose regimen. The need for a bridging study depends on the similarity of intrinsic factors (e.g., genetic, race, disease conditions) and extrinsic factors (e.g., epidemiology, medical practices, conduct of the trial) among two populations.

A situation in which the use of non-U.S. data frequently does not fulfill regulatory requirements, without the need for additional studies conducted in a U.S. population,

are development plans for infant/toddler vaccines. The study design and conduct of these trials, for example, provide necessary data to demonstrate applicability to U.S. population in the context of epidemiologic factors and appropriate control group. In addition, the data are relevant to medical practice with regard to dosing schedule and concomitant vaccine evaluation.

Examples of recently licensed vaccines, in which the application contained confirmatory and/or supportive clinical data from non-U.S. trials, are vaccines for the prevention of influenza [Fluarix®], HPV [Gardasil®] and Rotavirus [RotaTeq®].

References:

1. ICH Guidance E5 (R1): Ethnic Factors in the Acceptability of Foreign Clinical Data http://www.ich.org.
2. International Conference on Harmonisation (ICH); Guidance for Industry: E5 - Ethnic Factors in the Acceptability of Foreign Clinical Data - Questions and Answers – 9/28/06. www.fda.gov/cber/gdlns/iche5ethnic.htm

FDA's Critical Path on Development of Drug, Vaccine, and Other Biologics

Chi-Jen Lee, Sc.D

（李啓仁 博士）

Supervisory Research Chemist

Center for Biologics Evaluation and Research

Food and Drug Administration

U.S.A.

FDA's Critical Path on Development of Drug, Vaccine, and Other Biologics

Chi-Jen Lee, Sc.D (李啓仁 博士)

Center for Biologics Evaluation and Research, FDA
Bethesda, MD, U.S.A.

The U.S. FDA's mission is to protect the public health by assuring the safety, efficacy and purity of drugs and biologics. However, there is growing concern that new science discoveries may not quickly produce more effective and safe medical products for treatment and prevention of diseases. This is because the present product development path becomes inefficient, and costly. During past years, the number of new drug and biologic applications submitted to FDA has declined. In contrast, the costs of product development have increased greatly.

What is the problem? In FDA's view, the applied sciences needed for medical product development have not kept pace with the rapid advances in basic sciences. Not enough applied scientific work has been done to create new tools to better demonstrate the safety and effectiveness of new products. As a result, the majority of investigational products that enter clinical trials fail.

New product development approaches, involving powerful new scientific and technical methods including computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques, are urgently needed to improve predictability and efficiency for the critical path from laboratory concept to commercial product. Many scientists in academia, government, and industry are working on these challenges, and there has been much success in recent years. FDA is uniquely positioned to help identify the challenges to product development. Its standards and guidances are often used to guide development programs.

FDA is planning an initiative that will identify and prioritize (a) the most pressing development problems, and (b) the areas that provide the greatest opportunities for rapid improvement and public health benefits. This will be done for all three dimensions along the critical path – safety assessment, evaluation of medical utility, and product industrialization.

Current Status of NHRI on New Vaccine Development in Taiwan

莊再成

特聘研究員兼主任

(Pele Choi-Sing Chong, Ph.D.)

國家衛生研究院疫苗研發中心

Vaccine R&D Center of National Health Research Institute, Taiwan

Current Status of NHRI on New Vaccine Development in Taiwan

莊再成 主任（Pele Choi-Sing Chong, Ph.D.）

Vaccine R&D Center of National Health Research Institute
Zhunan Town, Miaoli County, Taiwan, ROC.

NHRI Vaccine Research and Development Center (VRDC) established since June, 2003, now has 57 permanent staff including Center Director and Deputy Director, 9 PI, 3 section managers, 1 Research Associate, and 43 technical specialists and research assistants (RAs) for Production, Research and Administration in VRDC. In addition, we have 7 postdoctoral fellows (PDFs), 3 students and 29 project-specific contracted RAs. The Research section of Vaccine Center had been rapidly expanded in the Zhunan NHRI main campus. The product development and manufacturing section is still remaining in CDC Kun Yang site as the Vaccine Center cGMP pilot plant is being built. The newly hired PIs bring in different expertise and skill set to the Vaccine Center where now has enough critical mass in the Genetic Engineering, Molecular Immunology and Vaccine Formulation and Delivery Systems platform technologies to support projects involved in studying human immuno-modulation mechanism from stem-cell to dendritic cells, producing Asian-specific HLA tetramer, investigating novel dendritic cell (DC)-based cancer immunotherapeutics, identifying tumor associate antigens (TTAs), performing vaccine R&D to meet Taiwan needs such as avian flu, EV-71, JEV, meningococcal group B, dengue, and RSV for elderly. During the last 10 months a P2+ facility for avian flu vaccine development had been set up that has 40 liters capacity. At the same time, Virology and Bioanalytical laboratories are being set up to perform product characterization to assist avian flu vaccine development. In addition, Clinical and Regulatory Affair section has been implemented to help design clinical trials of new vaccines, understand age-specific disease burden and epidemiological characteristics, compile documents for filing Investigational New Drugs (IND) and work with Institutional Review Board (IRB) for initiating phase 1 and 2 clinical trials.

In this presentation, we shall describe "state of the art" platform technologies developed by the PIs, the tools of project management helping the new vaccines development and a business development model that could support the Vaccine Center in future.

Current Status of New Vaccines Development in NHRI

NHRI Vaccine Center
Established Since June/2003

Pele Chong (PhD), Director
Vaccine Research And Development Center
National Health Research Institutes
E-mail pelechong@nhri.org.tw

NHRI 國家衛生研究院

Current Status of New Vaccines Development in NHRI

- Mission and mandates of NHRI Vaccine Center
- Infra-structure of NHRI Vaccine Center
- Research and Development at NHRI Vaccine Center
  - Platform technologies
  - Project Management
  - JEV vaccine development
  - EV71 vaccine development
  - Meningococcal group B vaccine development
  - H5N1 vaccine development
- cGMP Pilot Plants
- Strategy of Business Development

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The challenges of the 21st century

Nelson Mandela

Life or death for a young child too often depends on whether he is born in a country where the vaccines are available or not. The issue is of fundamental fairness.

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Mission of NHRI Vaccine Center

NHRI Vaccine Research and Development Center (VRDC) strives to be the leader in developing novel vaccines and immunotherapeutic candidates to fulfill Asian health care needs.

We aim to nurture open door and sense of urgency policies, proactive and transparent teamwork to sustain productive and innovative Research and Development environment.

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Mandates of NHRI Vaccine Center

To Complete the Missions, Vaccine Center will:

- Be built within the NHRI Zhu Nan campus, completed and validated by Dec/2007
- Have infra-structure and facilities to conduct vaccine research and development to meet local needs
- Have cGMP facilities that have capability to produce cGMP-grade traditional vaccines and anti-venom serum for local use
- Assist local Universities or Biotech to produce GMP-grade vaccine candidates and initiate phase 1 and 2 clinical trials in Taiwan and Asia
- Be the forum for training and educating local young scientists in vaccine-related biotechnology, and
- Have the ability to respond to Taiwan government emergency request for vaccines against pandemic diseases and bioterrorism.

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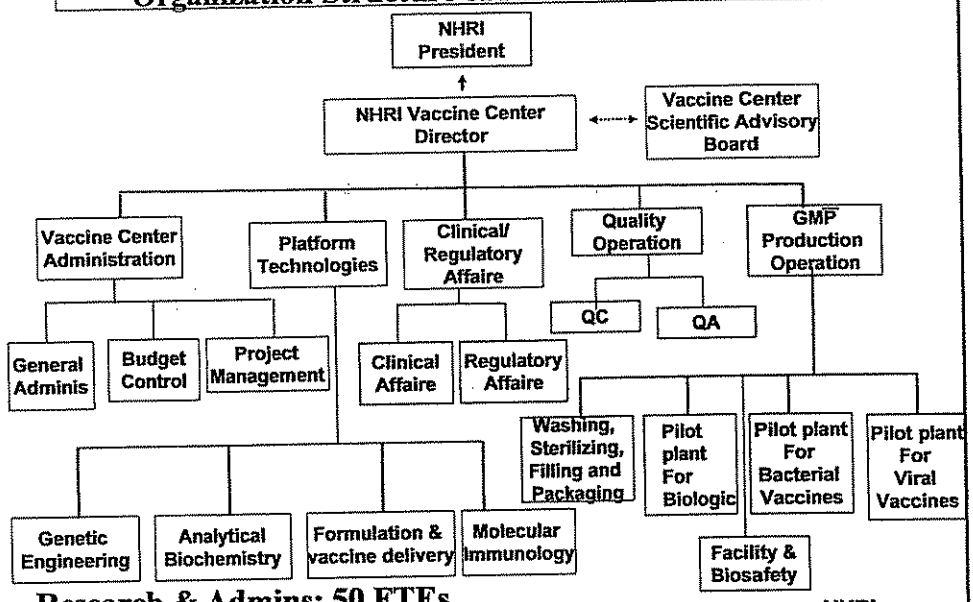
Organization Structure of NHRI Vaccine Center



Research & Admins: 50 FTEs

Development & production: 70 FTEs

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Members of Scientific Advisory Board

Members	Nationality	Expertise
Dr. Michel Klein	Canada	Vaccinology
Dr. Steve Kuo	Taiwan	Public Health
Dr. Leaf Huang	US	Formulation
Dr. Ih-Jen Su	Taiwan	Infectious Diseases and Clinical Trials
Dr. Monto Ho	US	Infectious Diseases and Clinical Trials
Dr. Mong-Ling Chu	Taiwan	Regulatory Affaire
Dr. Michael Lai	Taiwan	Molecular Virology
Dr. Albert Osterhaus	Netherlands	Virology and Infectious Diseases
Dr. Hans Wigzell	Sweden	Vaccinology

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Product Development or Academic Exercises?

A Question is often asked by Senior Management.

Why?

They are accountable for U$200 millions R&D expenses and NO product?

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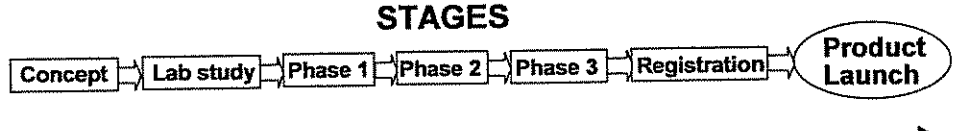
Research to Product Launch

STAGES



7 to 13 years

Development of Healthcare Products

Products	Successful rate (%)	Cost (millions US$)
Pharmaceutical	0.01 to 0.5	100 to 600
Biologics	0.1 to 5	100 to 400
Vaccines	0.5 to 2	50 to 200

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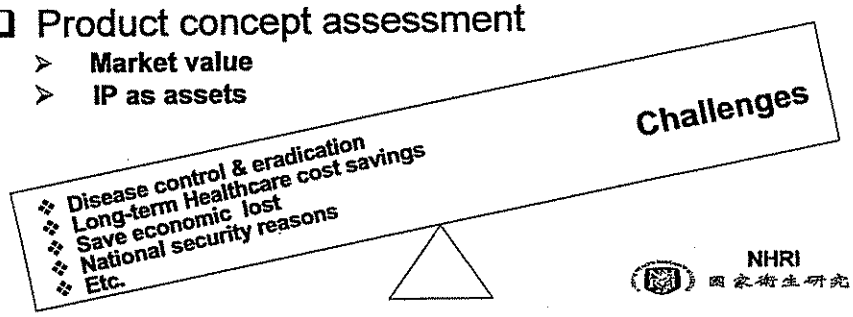
Vaccine Development: Points of Considerations

- ***Specific Industrial Challenges***
  - Complexity of the Vaccine development & Clinical Trials
  - Sustained R and D Investment
  - Balance High-risk Projects
  - Yields of Immunogens (Cost Driver)
  - Large Investments in Manufacturing Facilities
  - Liability Issues (IP, Regulatory and Safety issues)
- Product concept assessment
  - Market value
  - IP as assets



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BUSINESS CRITERIA OF A VACCINE

- **Statement of Interests**
  - **Purpose**
    - **Market needs (local and/or global)**
  - **Product Information**
    - **The Disease and its epidemiology known?**
    - **Potential product profile or specifications**
      - **Scientific rationale (animal model?)**
      - **Potential end-points indications for phase III**
      - **Minimum product requirements (compliance with Regulatory Guidelines)**
      - **Optimum profile (Multiple Indications)**
    - **Competition (SWOT analysis, IP issues)**
    - **Market description (EU, US and International)**
    - **Opportunities**
    - **Potential Problems/Hurdles/Potential solutions**
    - **Consistency with Company Portfolio?**
- **Project Prioritization Ranking (3 years)**
- **Return of Investment (ROI)**

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SCIENTIFIC CRITERIA OF A VACCINE

- ***Safety***
  - ***Compliance with cGMP guidelines***
- ***Efficacy***
  - Elicit cross-neutralizing Abs against divergent serotypes of the disease-causing pathogen
  - Elicit effector T cell responses, eg. Anti-viral CTLs
  - Elicit other necessary effector mechanisms (Th1 or Th2)
  - Offer Long-term protection (Memory B- and T-cells)
- ***Cost Effectiveness***
  - Simple Proudction processes
  - Good Stability Profile, Minimum Cold Chain Storage
  - If possible, single dose

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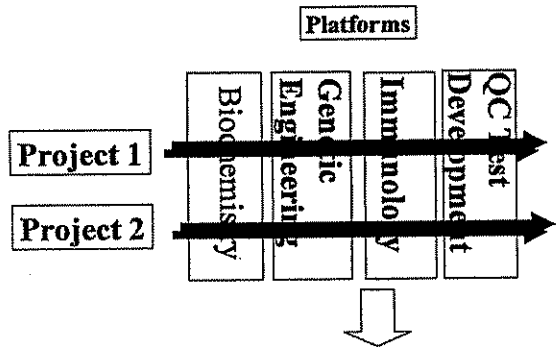
High Performance Matrix Systems for Project operations



Project Team

- Defines the project plan
- Negotiates resources
- Manages the project plan
- Deliver milestones on time
- Develop conflict resolution
- Synthesizes all alternatives
- Calculates risks
- Recommend possible solution

Platform Managers

- Defines tasks to be conducted
- Cost analysis and allocates resources
- Negotiates resources, budget and timelines for milestones
- Is responsible for the work done on time within budget
- Provides supports to the project when requested by the Project Leaders

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Platform Technologies

Genetic Engineering

- E. coli, yeast, CHO and Vero cell expression systems
- Bacterial and Viral vectors for mucosal vaccine development
- Host modification for high virus titer production
- Plasmid-based Chimeric Reassortant for live vaccine and vectors

Molecular Immunology

- HLA reagents for Asian populations
- Molecular monitoring systems for human immune responses to Vaccines
- Human dentritic cell technology for Cancer vaccines

Formulation and Vaccine Delivery Systems

- Controlled-release microencapsulation technology for multivalent vaccine development
- Develop novel DNA vaccine delivery systems
- Synthetic Adjuvant development

Bioanalytical and Product Characterization

- "State of the art" Bioanalytical and Serological core facility
- GLP/GMP QC testing systems
- Product characterization according to ICH guidelines

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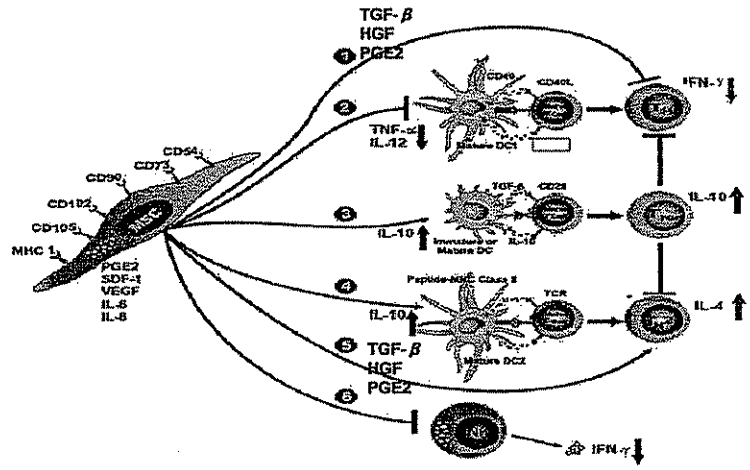
Team Studies Immunomodulation



Stem Cell: Dr. Hsu-Ching Hsu
Dendritic Cell: Dr. Ching-Liang Chu
Antigen presentation: Dr. Stephen Hsu
Vaccine Formulation: Drs. Liu & Chong

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Team Studies Immunomodulation

Stem Cell (PI Dr. Shu-Ching Hsu)

- Reconstitute human SC into NOD/SCID mouse as xenograft model to study infections and immune responses
- Identify factors switching SC to Treg cells and biological fucntions

Dendritic Cell (PI Dr. Ching-Liang Chu)

- Establish human DC technology for antigen processing and presentation study
- DC platform for adjuvants and vaccine delivery systems screening

Antigen presentation (PI Dr. Stephen Hsu)

- Identify cellular immune responses using natural infection model
- Modify epitopes to enhance vaccine potency

Vaccine Formulation (PIs Drs. Liu & Chong)

- Synthetic adjuvants development
- Liposomes and emulsion based vaccine delivery systems
- Lipopeptides for CTL induction
- Controlled-release microencapsulation technology for single dose vaccines
- Develop novel DNA vaccine delivery systems

External Collaborators:

Taiwan: Drs. Edmond Hsieh, Mei-Wah Tao, Sui-Li Chen
International: CANVAC, Dr. Leaf Huang, IVI

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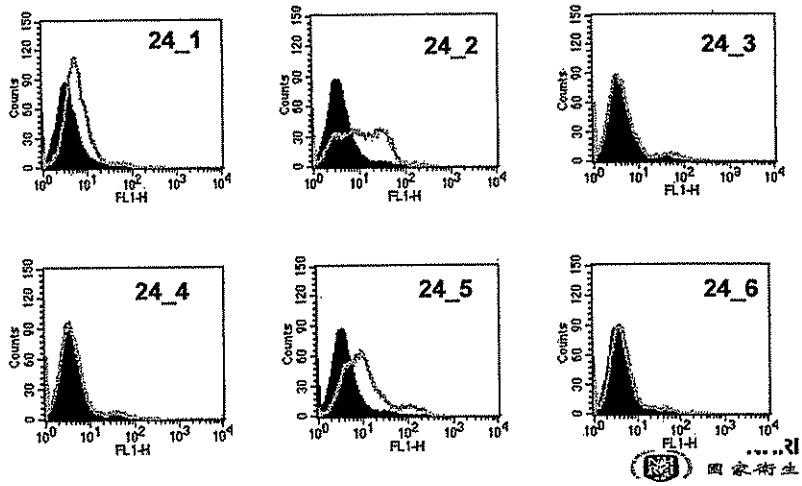
Vaccine Center Research Team

国家衛生研究院

Expression of HLA-A24 transgenic mice



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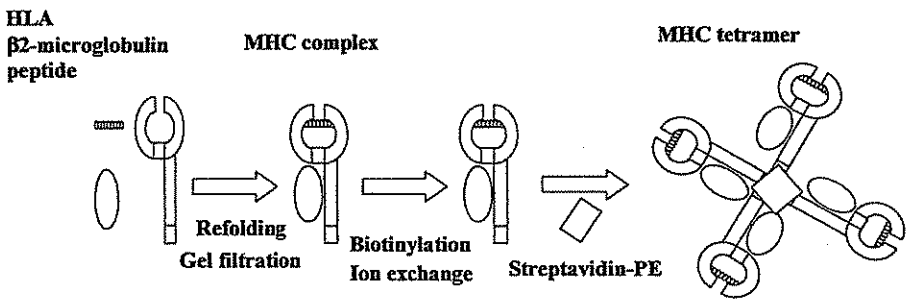
Procedure for generating MHC tetramer



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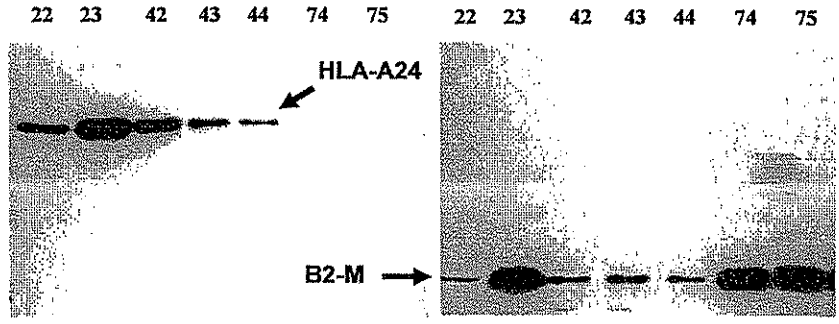
MHC complex was confirmed by western blot



Anti-his Anti-b2-microglobulin

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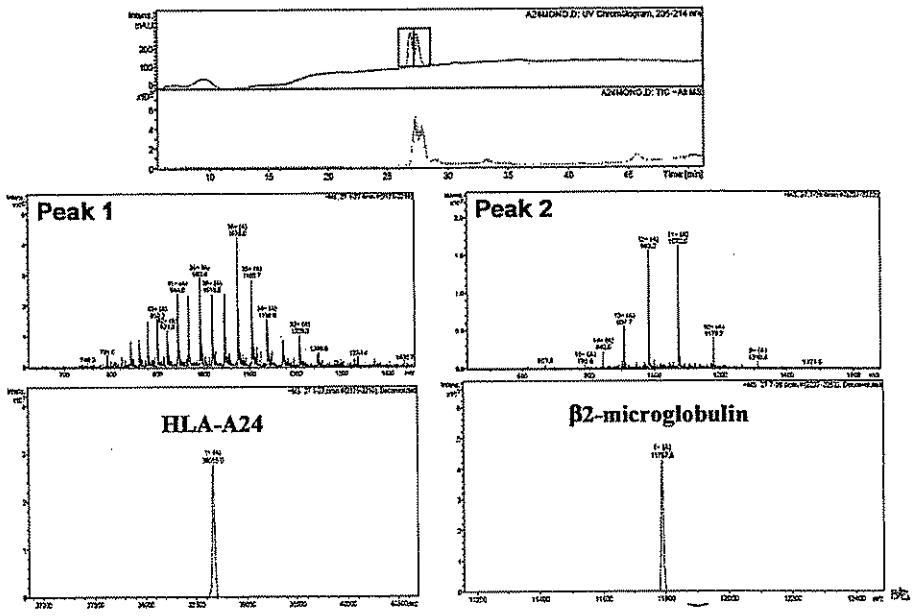
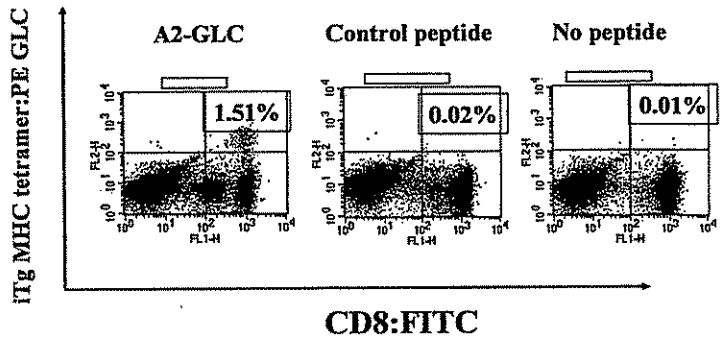
File:940805

HLA-A24 complex was analyzed by LC-Mass



Establishment of peptide-specific CTL cells from healthy volunteer-tetramer staining



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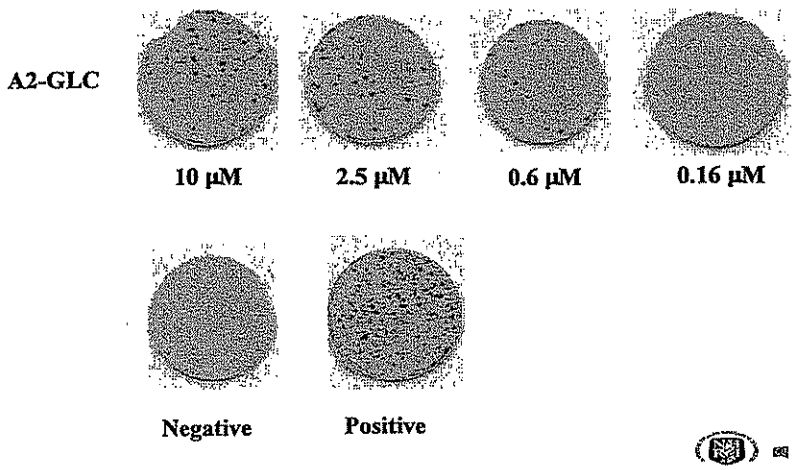
Establishment of peptide-specific CTL cells from healthy volunteer-ELISPOT assay



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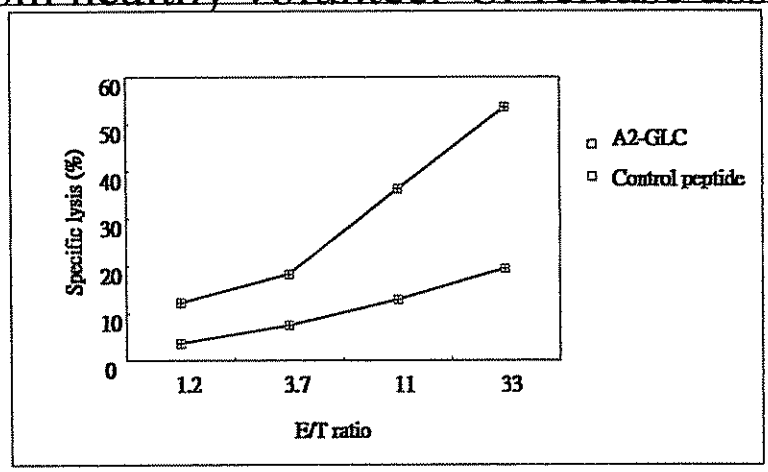
Establishment of peptide-specific CTL cells from healthy volunteer-Cr release assay



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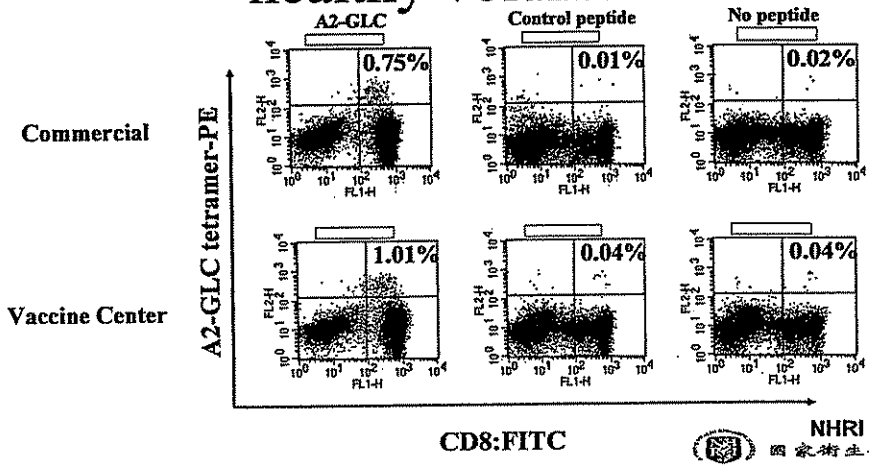
Validation of VC tetramer on ~~peptide-specific CTL cells in~~ healthy volunteer



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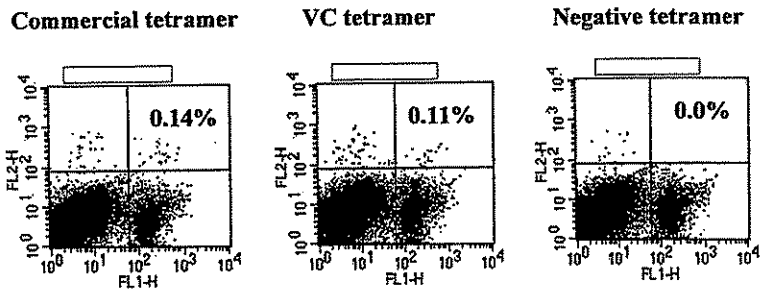
Validation of VC tetramer on EBV-~~specific CTL cells in HLA-A2~~ transgenic mice



NHRI 國家衛生研究院

The Product Portfolio of NHRI Vaccine Center

Vaccines	Stages of Development			Strategic Partners
	Research	Clinical	Licensed	
DT, TT			Taiwan	CDC
BCG			Taiwan	CDC
Horse anti-Snake venom IgG			Taiwan	CDC
EV-71	Completed	Master virus seed 2007		CDC
JEV	Completed	Master virus seed, 2006		Adimmune, IVI
Cell-based Avian flu vaccine	Pre-clinical	Master virus seed 2007		CDC, IVI, IOMAI
Meningococcal group B	Exploratory	Master cell bank 2008		CDC, Aventis Pasteur
RSV Subunit (F, SH & M)	Exploratory	2009		
Dengue Vaccine (D3 of E protein)	Exploratory	2009		

NHRI 國家衛生研究院

Development of Cell Culture Derived JEV Vaccine

CDC/NHRI

Vaccine Centers collaborations

NHRI 國家衛生研究院

JEV & EV71 Team Members

NHRI
國家衛生研究院

Aims

- **Replace traditional JEV vaccine prepared from mouse brain**
- **Set up cell culture technology to produce viral vaccine**

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Flow Chart for the Production of Cell Culture Derived JEV

Vero Cell
Master seed
Working seed

Cell Bank | **Virus Bank** — Master seed, Working seed

↓

Virus Scale-up Production & Harvest — 40-80 Liter capacity (Roller Bottle)

↓

Virus Concentration — Microfiltration, Ultrafiltration

↓

Virus Purification — Benzonase, Liquid chromatography

↓ In-process assay system

Virus Inactivation — Formalin

↓

Immunization — Alum adjuvant

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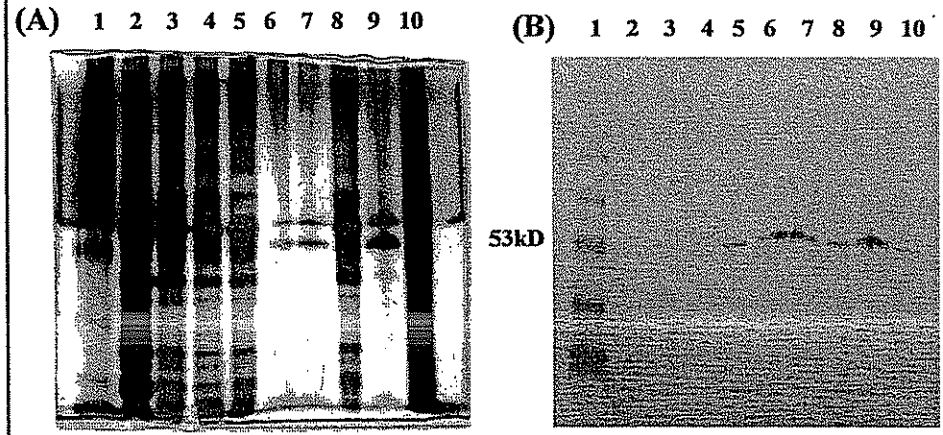
Purity



SDS/PAGE with silver staining (A) and Western blot (B) of Japanese encephalitis virus in different purified steps and methods

1. Marker 2. BSA 3.Ori. 4. MF 5. UF 6. UF-LC
7. UFB-LC 8. UFB-D 9. UFB-D-LC 10. Kitasato

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Residual cellular DNA content

Concentration of Residual Cellular DNA in Different Treatment for Cell Culture Derived Japanese Encephalitis Virus Vaccine

Lot	1-1	1-2	2-1	2-2	3-1	3-2	4
Harvest (Ori)	18.4	18.4	24	24	35.8	35.8	36
No treatment (Ori-MF-UF-LC)							43.5
Ori+Benzonase-MF-UF-I.E-LC	5.32		1.25		0.82		
Ori+Benzonase-MF-UF-D-LC		<0.003		<0.003		<0.003	

Unit: ng/ml

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Potency test

- Mouse
- Monkey
- Horse
- Swine

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Potency test (I)-Mouse

Table 2 Assessment of neutralization antibodies elicited by cell culture derived JE vaccine prepared from Beijing strain JE virus

Sample/Vaccine	Protein Conc.(μg)/Dose	Relative Antigen Content [Sample O.D.(Dose)/184-P O.D.(Dose)]	PRNT Titer The 22nd Day serum	PRNT Titer The 29th Day serum
RB79	12.38	1	45	76
RB81	12.2	1	42	25
RB89	13.94	1	57	92
RB90	12.73	1	19	87
RB93	12.32	1	33	22
RB94	11.88	1	37	49
RB95	17.96	1	25	54
Biken	19.57	1.132	45	83
Kitasato	40.46	2.014	63	32
184-P	25.3	1	5	1

- **Neutralization virus : Beijing strain JE virus**
- **184-P : JE vaccine from Japan NIH, 1ml/Dose**
- **Kitasato & Biken : Commercial JE vaccine from Japan, 0.5ml/Dose**
- **Immunization Method : I.P. 0.5ml/Dose (Human dosage dilute 8 times), inoculate 2 times, every week**
- **Immunization Animal : ICR strain mouse**

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Assessment of neutralization antibodies elicited by cell culture derived JE vaccine against Nakayama strain JE virus

Sample/Vaccine	Protein Conc.(μg)/Dose	Relative Antigen Content [Sample O.D.(Dose)/184-P O.D.(Dose)]	PRNT Titer The 29th Day serum
RB79	12.38	1	40
RB81	12.2	1	26
RB89	13.94	1	23
RB90	12.73	1	40
RB93	12.32	1	16
RB94	11.88	1	12
RB95	17.96	1	47
Kitasato	40.46	2.014	4
JE018702	62	ND	45
184-P	25.3	1	2

- **Neutralization virus : Nakayama strain JE virus**
- **184-P : JE vaccine from Japan NIH, 1ml/Dose**
- **JE018702 : JE vaccine from Taiwan NIPM, 1ml/Dose**
- **Kitasato : Commercial JE vaccine from Japan, 0.5ml/Dose**
- **Immunization Method : I.P. 0.5ml/Dose (Human dosage dilute 8 times), inoculate 2 times, every week**
- **Immunization Animal : ICR strain mouse**

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Comparison of Protective efficacy of cell culture derived JE vaccine prepared from Beijing strain by intracerebral challenge

Sample/Vaccine	Protein Conc.(μg)/Dose	Relative Antigen Content [Sample O.D.(Dose)/184-P O.D.(Dose)]	ED_{50}
RB89LC	20.91	1.5	$4^{1.53}$
RB93LC	18.49	1.5	4^{2}
RB95LC	26.98	1.5	$4^{1.5}$
Kitasato	41.47	2.09	4^{2}
184-P	16.41	1	$4^{1.14}$

- **LD50 of Beijing strain JE virus : 107.5/0.03 ml**
- **Challenge dose : 39.5 LD50**
- **184-P : JE vaccine from Japan NIH, 1ml/Dose**
- **Kitasato : Commercial JE vaccine from Japan, 0.5ml/Dose**
- **Immunization Method : I.P. 0.5ml/Dose , inoculate 4 times, every other day.**
- **Challenge method : I.C. 0.03 ml virus**
- **Immunization Animal : ICR strain mouse**

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Comparison of Protective efficacy of cell culture derived JE vaccine prepared from Beijing strain by intraperitoneal challenge

Sample/Vaccine	Protein Conc.(μg)/Dose	Relative Antigen Content [Sample O.D.(Dose)/184-P O.D.(Dose)]	ED_{50}
RB89LC	11.82	0.848	$4^{3.78}$
RB93LC	10.45	0.848	$4^{3.5}$
RB95LC	15.23	0.848	$4^{3.06}$
Kitasato	36.38	1.697	$4^{3.28}$
184-P	24.41	1	$4^{2.14}$

- **LD50 of Beijing strain JE virus : 103.93/0.5 ml**
- **Challenge dose : 646 LD50**
- **184-P : JE vaccine from Japan NIH, 1ml/Dose**
- **Kitasato : Commercial JE vaccine from Japan, 0.5ml/Dose**
- **Immunization Method : I.P. 0.5ml/Dose , inoculate 4 times, every other day.**
- **Challenge method : I.P. 0.5ml/dose virus , I.C. 0.03 ml PBS**
- **Immunization Animal : ICR strain mouse**

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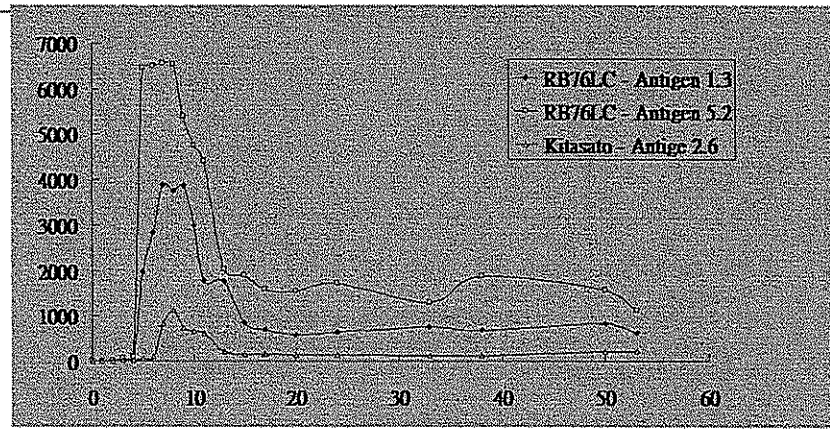
Potency test (II)-Monkey

Neutralizing antibody responses in monkeys innoculated with 4 dosage of cell culture derived JE vaccine



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Neutralizing antibody responses in monkeys innoculated with 2 dosage of cell culture derived JE vaccine

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Potency test (III)-Horse

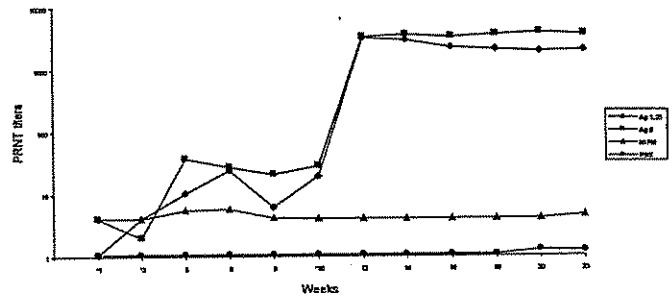

Figure 1.

.Time course of neutralizing antibody titers in the program of three times immunization. Four groups of three horses were inoculated with antigen ELISA units 1.25, 5, NIPM and PBS at weeks 1, 3 and 10. Reciprocal titers of neutralizing antibody were showed as plaque reduction neutralization test (PRNT) titers as the highest serum dilution yielding a 50% reduction in plaque number. The symbol, *, was used in the figure for representing vaccina

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Potency test (IV)- Swine

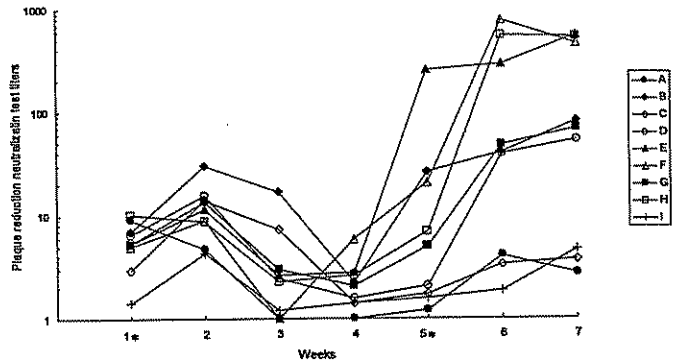

Fig. 1

Plaque reduction neutralization test antibody titers in groups of swine after immunization. Experimental programs of groups of swine listed in Table 1. The second immunizations were performed at 5 weeks just for groups of A, B, D, F, H, and L The symbol, ∗, indicates at 1 and 5 weeks for representing immunization.

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Safety Tests

- Master Cell Bank Testing
- Working Cell Bank Testing
- End of Production Cell Bank
- Master Virus Bank Testing
- Working Virus Bank Testing

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Enterovirus (EV) 71 Vaccine Development

Aim:

- Implement Taiwan Government policy
- Establish a biologic development model from R&D to product launch
- Set up cell culture technology and infrastructure for viral vaccines production

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Diseases caused by Enterovirus in Thailand (Bangkok Post 09/06)

Hand Foot and Mouth Disease

This common childhood illness is found mostly in children age less than 5 years. It appears world-wide and all year round. It is caused by a group of virus called enteroviruses. Common features of this disease include spots and vesicles on the hands, feet, legs, and inside the mouth, accompanied by fever. Symptoms appear 3 to 6 days after exposure to the virus. Fever may precede the rash by 1 to 2 days. Lesions inside the mouth may become painful ulcers. Symptoms usually subside in about one week

During large outbreaks in recent years in Taiwan and Malaysia, fatalities attributable to this disease have been reported. Statistically the number of fatal cases amount to less than 1 in 10,000 of all cases.

The disease is transmitted through contact with saliva, bodily fluids, or feces of infected children. Outbreaks are common in kindergartens and schools.

Diagnosis is made by observation of the typical clinical features. Confirmatory laboratory tests are possible but rarely required.

Serious complications of this disease are rare. The type of complication that is of the most concern is involvement of the brain and nerves which may cause brain damage, paralysis, and death.

Treatment consists of general supportive measures and reduction of fever. There are no specific treatments for this condition. Appearance of more sinister symptoms such as persistent vomiting, drowsiness or altered consciousness, weakness, or breathlessness is an indication for seeking medical attention.

The spread of the disease can be prevented by basic hygiene such as hand washing, avoiding shared use of utensils, and avoiding contact with infected individuals

Diseases caused by Enterovirus in Taiwan

Year	1998	1999	2000	2001	2002	2003	2004	July, 2005
Confirmed Cases	405	35	291	393	162	70	49	131
EV71	77	6	152	187	58	44	19	74
EV71/Confirmed Cases	(19.0%)	(17.1%)	(52.2%)	(47.6%)	(35.8%)	(62.9%)	(38.8)	(56.5%)
Death	78	9	41	58	30	8	4	12
	19.30%	25.70%	14.10%	14.80%	18.50%	11.40%	8.16%	9.16%
EV71	34	1	25	27	8	4	4	5
EV71/Death	(43.6%)	(11.1%)	(61.0%)	(46.6%)	(26.7%)	(50.0%)	(100%)	(41.7%)

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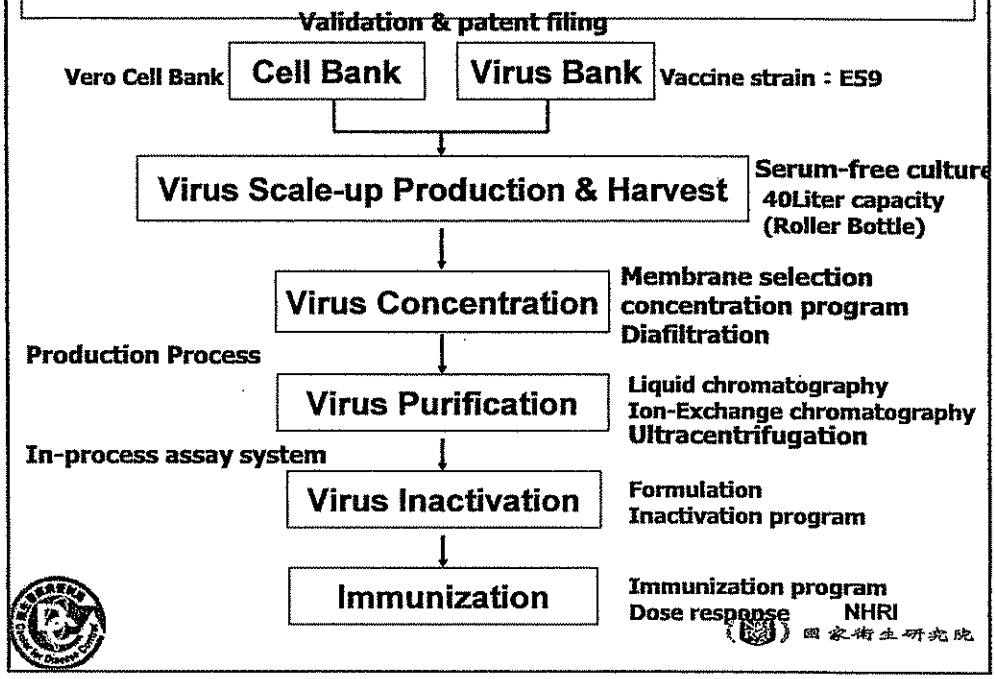
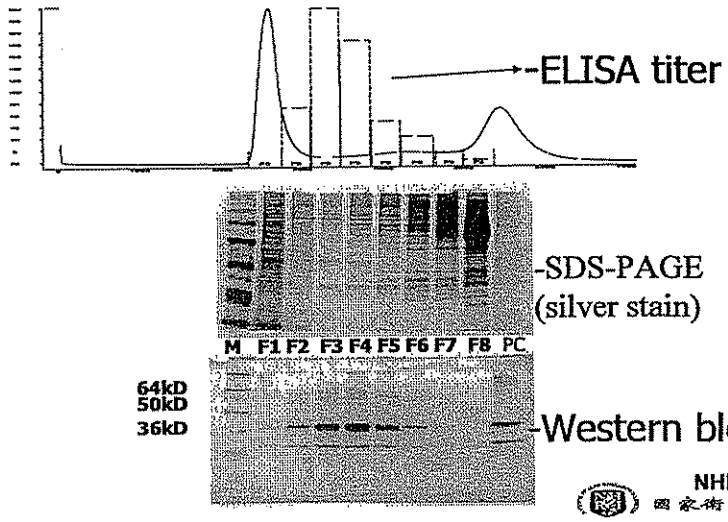
Flow Chart for the Cell-Culture Based EV71 Vaccine Production



EV71 Cross Neutralization (1998-2005)

Year	virus strain	Neutralization Titer (Immunogen 50 OD/ml)							
		E259-V5	1207-rabbit	1207-V5	YN3H-V4	1341-V5	459-V4	236-V5	1295-V4
1998	E815-V5	40<X<160	—	10<X<40	40<X<160	40<X<160	40<X<160	10<X<40	40<X<160
	1207-V5	160<X<640	X>12800	160<X<640	40<X<160	10<X<40	10<X<40	10<X<40	10<X<40
	1225-V4	160<X<640	—	160<X<640	40<X<160	10≤X<40	10<X<40	10<X<40	10<X<40
	1232-V5	40<X<160	—	10<X<40	40<X<160	10<X<40	40<X<160	10<X<40	40<X<160
	1263-V5	10<X<40	X<100	X<10	X<10	10<X<40	10<X<40	10<X<40	10<X<40
	1341-V5	40<X<160	—	40<X<160	40<X<160	40<X<160	40<X<160	10<X<40	40<X<160
	YN3-V7	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
	YN3H-V4	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
2000	E43-V5	40<X<160	—	10<X<40	40<X<160	40<X<160	10<X<40	10<X<40	40<X<160
	E92-V5	40<X<160	—	40<X<160	40<X<160	40<X<160	40<X<160	40<X<160	40<X<160
	E259-V5	640<X	—	160<X<640	40<X<160	10<X<40	40<X<160	10<X<40	10<X<40
2002	E73-V5	40<X<160	—	40<X<160	40<X<160	10<X<40	10<X<40	10<X<40	10<X<40
	E75-V5	40<X<160	—	40<X<160	40<X<160	10<X<40	40<X<160	10<X<40	10<X<40
	E117-V5	40<X<160	—	40<X<160	40<X<160	10<X<40	40<X<160	10<X<40	40<X<160
	E119-V6	40<X<160	—	10<X<40	10<X<40	10<X<40	10<X<40	X<10	X<10
	E120-V4	640<X	—	640<X	40<X<160	40<X<160	40<X<160	10<X<40	10<X<40
	E122-V6	10<X<40	—	10<X<40	10<X<40	10<X<40	10<X<40	10<X<40	10<X<40
2003	2161-V3	160<X<640	—	40<X<160	40<X<160	40<X<160	40<X<160	10<X<40	10<X<40
	1762-V3	640<X	—	160<X<640	40<X<160	40<X<160	40<X<160	10<X<40	10<X<40
	1763-V4	40<X<160	—	40<X<160	160<X<640	10<X<40	160<X<640	40<X<160	160<X<640
2004	236-V5	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
	459-V4	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
	624-V4	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
	798-V4	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
	887-V5	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
	912-V4	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
	1049-V4	10<X<40	X<100	X<10	10<X<40	10<X<40	10<X<40	10<X<40	10<X<40
	1116-V5	10<X<40	X>12800	10<X<40	10<X<40	10<X<40	40<X<160	10<X<40	10<X<40
	1118-V4	X<10	X<100	X<10	10<X<40	X<10	10<X<40	X<10	10<X<40
	1276-V4	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
	1295-V4	X<10	X<100	X<10	X<10	X<10	X<10	X<10	10<X<40
	1623-V4	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
	1627-V4	X<10	X<100	X<10	X<10	X<10	X<10	X<10	X<10
1970	BrCr-V4	X<10	—	X<10	X<10	X<10	X<10	X<10	X<10

Analysis of LC Fractionation



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Batch Production

Batch No./Step		Volume(mL)	OD_{450}/ug	ELISA OD_{450} /100uL	Total ELISA OD_{450}	Recovery(%)	Purification fold	$TCID_{50}$/mL	Total $TCID_{50}$
05EV04	ori	20000	0.39	19.67	3933333	100.00	1.00	$1.0x10^5$	$2.0x10^9$
	uf	1300	0.71	312.80	4066400	103.38	1.82	$1.0x10^6$	$1.3x10^9$
	ufdi-fin	1300	2.03	441.60	5740800	145.95	5.24	$3.98x10^6$	$5.17x10^9$
	LC	2600	20.52	80.96	2104960	53.52	53.04	-	-
05EV05	ori	20000	0.53	26.53	5306667	100.00	1.00	$3.16x10^5$	$6.32x10^9$
	uf	1300	0.87	468.80	6094400	114.84	1.66	$3.16x10^6$	$4.1x10^9$
	ufdi-fin	1200	1.75	515.20	6182400	116.50	3.32	$3.16x10^6$	$4.1x10^9$
	LC	2400	23.16	99.63	2391040	45.06	44.11	-	-
05EV06	ori	20000	0.35	13.36	2672000	100.00	1.00	$1.38x10^6$	$2.76x10^{10}$
	uf	1300	0.70	217.07	2821867	105.61	1.97	$8.6x10^6$	$1.18x10^{10}$
	ufdi-fin	1200	2.20	242.13	2905600	108.74	6.22	$6.13x10^6$	$7.36x10^9$
	LC	2400	15.45	43.73	1049600	39.28	43.62	-	-

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Immune period: 1st & 4th week

EV 71-E59 017 UFB LCP 2-1	Adjuvant						
	$AlPO_4$			$Al(OH)_3$			
Immune ELISA unit (OD/0.5ml)	132	33	16.5	132	33	16.5	$TCID_{50}$
Immune protein (μg/0.5ml)	13	3.3	1.65	13	3.3	1.65	
Neutralization titer	809.1	446.68	142.88	285.1	101.86	94.4	56.2

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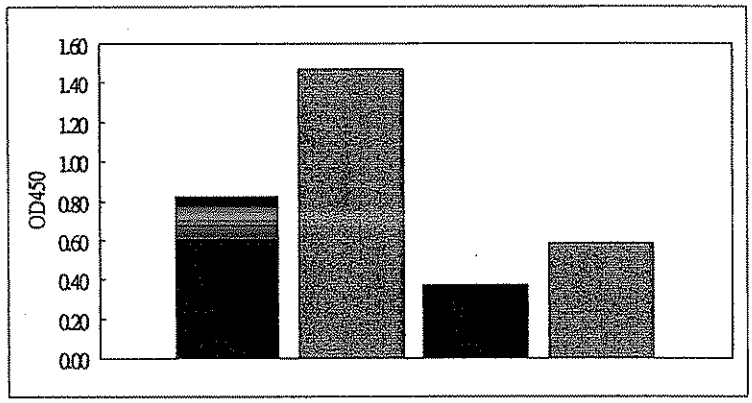
Comparison of Antigen content of EV71 production cultured by M199 and DMFA Medium



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Comparison of neutralization response of EV 71 prototype vaccine cultured by M199 and DMFA Medium

Immunogen	Inactivated E59	
Prepared by	Culture Media	
Media Type	M199 + 1%FBS	DMFA
Immunization concentration (ug)	301.73	263.29
Neutralization Titer	208.9	188.36

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N. Meningococcal group B Proteins Based Vaccine Development

Collaboration with Dr. Chiou-Ying Yang

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Characteristics of monoclonal antibodies against Nm22209

Hybridoma	Isotype	ELISA					BC50 (μg/ml)[a]
		NMB	BMW 135	NMC	NMY	IMR-32[b]	
4-13-227	IgG3	38/38	4/4	1/1	6/6	-	~30
4-7-3	IgG3	80/80	50/50	3/3	20/20	-	~30
5-1-7	IgM	+	ND[c]	ND	ND	+	ND
5-4-48	IgM	+	ND	ND	ND	+	ND
5-4-46	IgM	+	ND	ND	ND	+	ND
5-4-48	IgM	+	ND	ND	ND	+	ND
172-3	IgG2b	3/38	-	-	-	-	ND

[a] BC50, amount of monoclonal antibody that when incubated for 30 min with Nm22209 cells (~1 x 10^4 CFU) and 20% of 50-fold diluted human complement (Sigma) yielded a 50% decrease in CFU compared to that without complement. The bactericidal activities of mAbs 4-7-3 and 4-13-227 against Nm22209 are week compared to that of 210-06 (~0.05 μg/ml), an antibody against the P1.2 epitope on the outer membrane PorA protein.

[b] IMR-32, a human neurablastoma cell line.

[c] ND, not determined.

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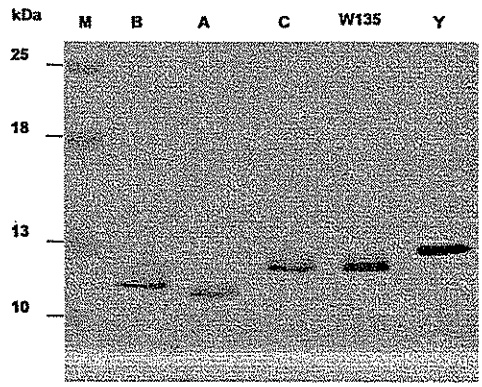

Fig. 1. Western blot of total proteins from N. meningitidis serogroups B, A, C, W135, and Y probed with monoclonal antibody 4-7-3. M, prestained protein markers.

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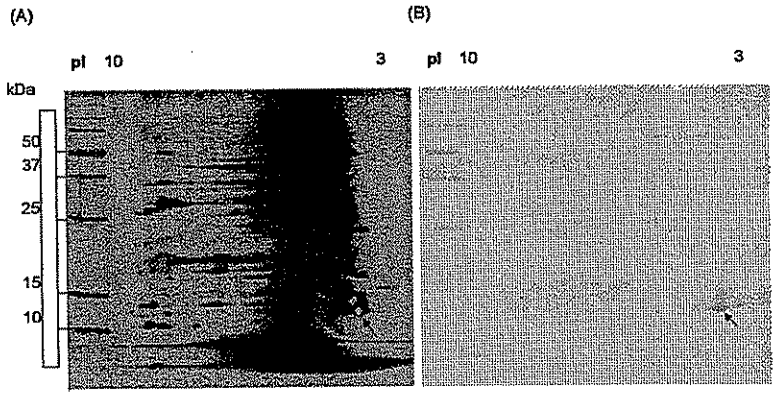

Fig.2. Silver staining (A) and 2D-Western blot (B) of the total proteins isolated from *N. meningitidis* serogroup B (Nm22209). Ag473 is indicated with an arrow.

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Fig. 4. Western blot analysis of the total proteins from *E. coli* expressing the indicated recombinant proteins. Ag473(S),the cysteine in the leader sequence was changed to serine.

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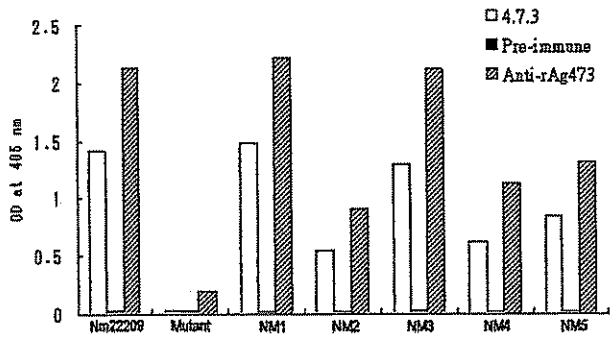

FIG.6 Binding of anti-rAg473 antiserum to intact *N. meningitidis* determined by ELISA.

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Protection of BALB/c mice by Immunization of recombinant Ag473 against Nm22209 Challenged

Immunogens	# of mice survived / # of mice Challenged	# of mice with bacteremia in the survival group	Relative level of bacteremia
Naive	3/9	1/3	100%
rAg473	9/9	3/9	7 to 34%
rAg473	10/10	0/10	0

1st dose 15 ug of rAg473/ CFA
2nd dose 15 ug of rAg473/ IFA
3rd dose 15 ug of rAg473/ IFA

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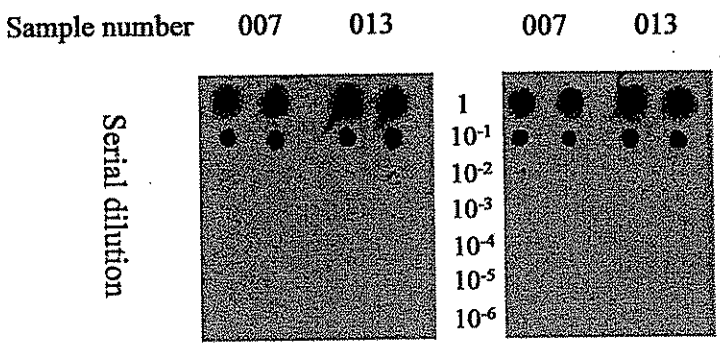
Immunodotting of Fresh Neisseria meningitidis isolates using anti-Ag473 antibody



Left: First antibody(4-7-3 ascites)1:10000 dilution, second antibody (goat anti mouse)1:3000.**Right:** First antibody(4-7-3 ascites)1:5000 dilution, second antibody(goat anti mouse)1:3000 dilution.

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Prototype H5N1 Flu Vaccine Development

Part of Taiwan Pandemic Flu Preparedness

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Cell culture base flu vaccine development team 國家衛生研究院

Prototype of H5N1 vaccine preparation from cell culture-based processes

Master Seed Preparation (3 weeks)

↓

MDCK cells ——→Inoculation (5 -7 days)

↓

Upstream Process (2 days)
Harvest, Centrifugation, Microfiltration, Ultrafiltration

↓

Downstream Processes
Zonal Centrifugation, Diafiltration (2 days)

↓

Inactivation (2 days at 37⁰ C)

↓

QC Assay, Formulation, Filling (7 - 10 days)

Max production capacity → 40L / batch / 3 weeks (4 roller racks)

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Cell Culture Flu Vaccine Development

Lot No.	Scale / Batch	HA / 50μL (火鳥RBC)
D/F P64 20060106	1L	512
PM P64 20060122	1L	1024
D/F P64 20060121	6L	512
D/F P64 20060218	2L	512
D/F P64 20060222	2L	512
D/F P64 20060301	2L	512
PM P64 20060219	2L	1024
PM P64 20060226	2L	1024
D/F P64 20060322	10L	512
D/F P64 20060323	10L	512
PM P64 20060322	10L	512
PM P64 20060329	4L	256
PM P64 20060511	40L	256
D/F P64 20060524	20L	128

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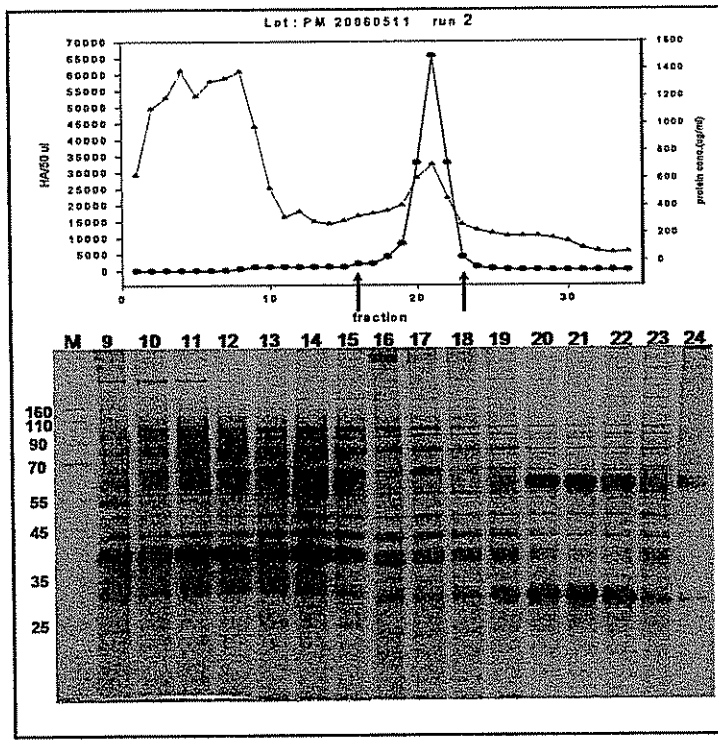

Well	HA/50mL	Total Protein (μg)
9	1024	974.3
10	1024	528.4
11	1024	318.5
12	1024	358.5
13	1024	284.4
14	1024	267.4
15	1024	290.7
16	2048	325.3
17	2048	342.7
18	4096	363.2
19	8192	402.8
20	32768	601.0
21	65536	699.9
22	32768	454.5
23	4096	262.7
24	8192	360.1

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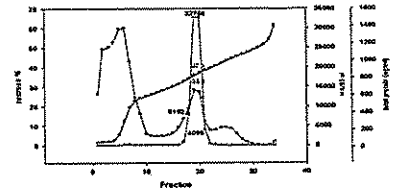
Production batches

	Batch Scale (Liter)	HA titer of harvest(/50uL)	Total HA antigen of final bulk (μg)
Serum-containing culture	20	256	30,908
	20	128	24190
Serum-free culture	10	512	11961
	40	256	98,040

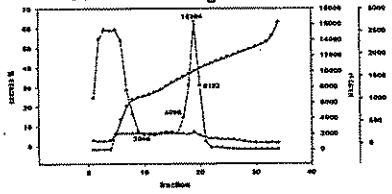
➢ We have successfully grew WHO vaccine strain, NIBRG-14, in MDCK cells at 40L scale.

Zonal Centrifugation

serum-free culture



serum-containing culture



➢ We have developed the centrifugation condition to purify the virus consistently in sucrose concentration between 35%~40%.

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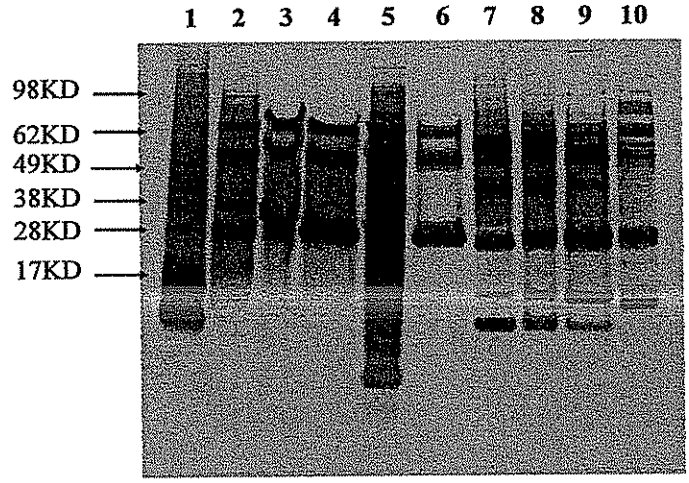
SDS-PAGE (Silver Stain)



1 Marker
2 PM ori
3 PM mix
☆ 4 PM dia
5 DF ori
☆ 6 DF dia
7 06Flu04 ori
8 06Flu04 mix
☆ 9 06Flu04 dia
10 KKB/KI Flu

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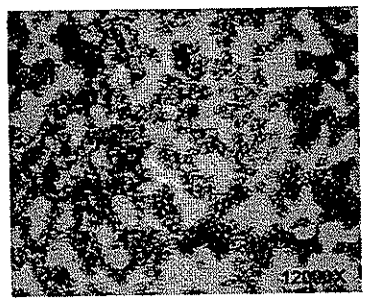
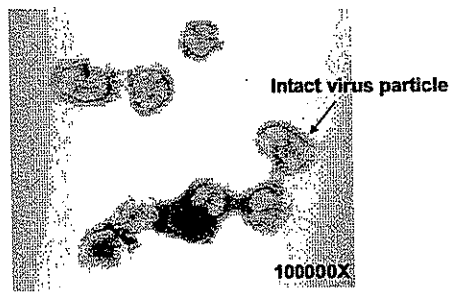
Whole Virion Observation by Electrical Microscope





➢ These figures showed that the vaccine bulk we produced was INACTIVATED WHOLE VIRION.

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Development of QC Tests

Tests	Seed	In-Process	Bulk
Mycoplasma test (PCR)	V		
Sequence analysis (PCR)	V		
Hemagglutination assay		V	
Hemagglutination inhibition assay			V
Neutralization assay ($TCID_{50}$)			V
Plaque Assay	V		V
Virus titration ($TCID_{50}$)	V		V
SDS-PAGE		V	V
Protein content assay		V	V
SRD assay			V
Residual DNA content			V

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Virus Bank

	Quantity	Sterility	Mycoplasma test (by PCR)	HA titer (HA/50uL)	HA sequencing	TCID50 (/mL)	Plaque assay (PFU/mL)
Master virus bank	400 vials, 0.5mL/vial	PASS	Negative	256	correct	$1x10^7$	$5x10^8$
Working virus bank	410 vials, 0.5mL/vial	PASS	Negative	256	correct	$1x10^8$	$9.5x10^7$

Cell Bank

	Quantity	Sterility	Mycoplasma test (by PCR)
Master cell bank	350 vials, $1x10^6$cells/mL/vial	PASS	Negative
Working cell bank	400 vials, $1x10^6$cells/mL/vial	PASS	Negative

- We have established master and working banks for both NIBRG-14 virus and MDCK cell.
- All of the virus and cell banks have passed in-house preliminary tests and will be validated in the future.

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NHRI Vaccine Center cGMP Pilot Plants

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Schedule of Plant Construction

Task	2003	2004	2005	2006	2007
Early Assignment	———				
Research on Plan & Feasibility		—			
Conceptual Design		—			
Plans approved by Government		—			
Public Bidding and Review			—		
Detailed design			—		
Obtain Construction License			—		
Construct、Install、Operate			—	———	
Obtain Operation License				—	—
Execute Validation of Hardware					—
Execute Validation of Production					———

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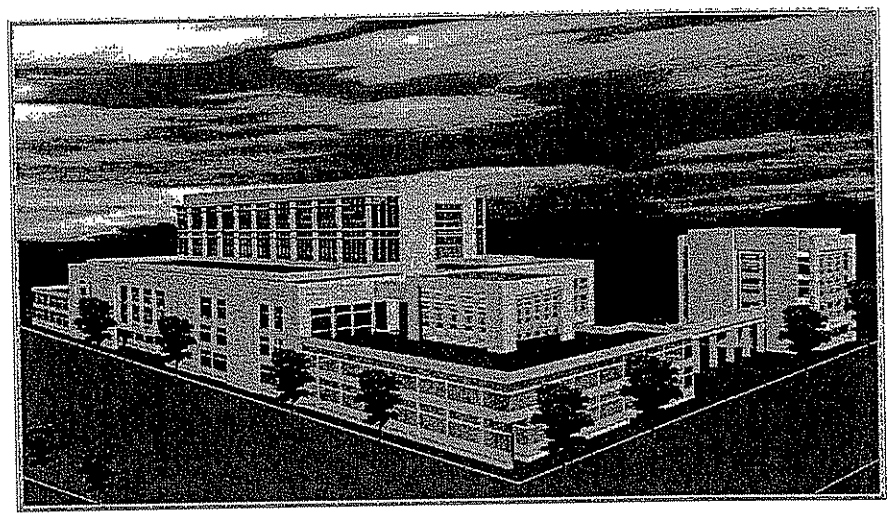
造型與色彩



西北向外觀 NHRI

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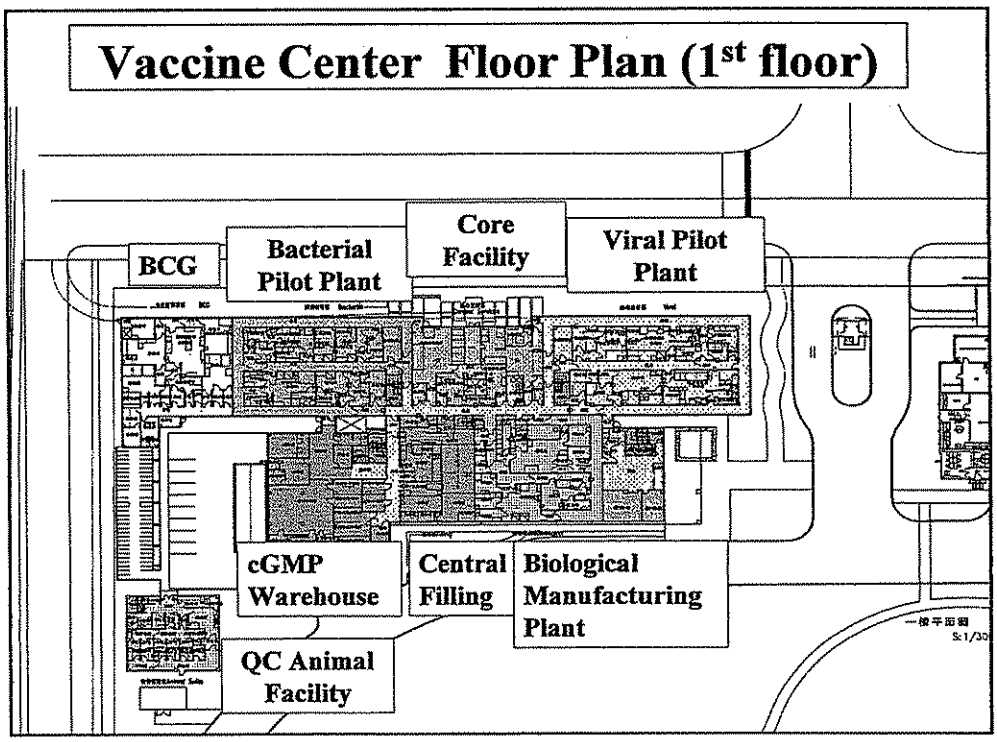
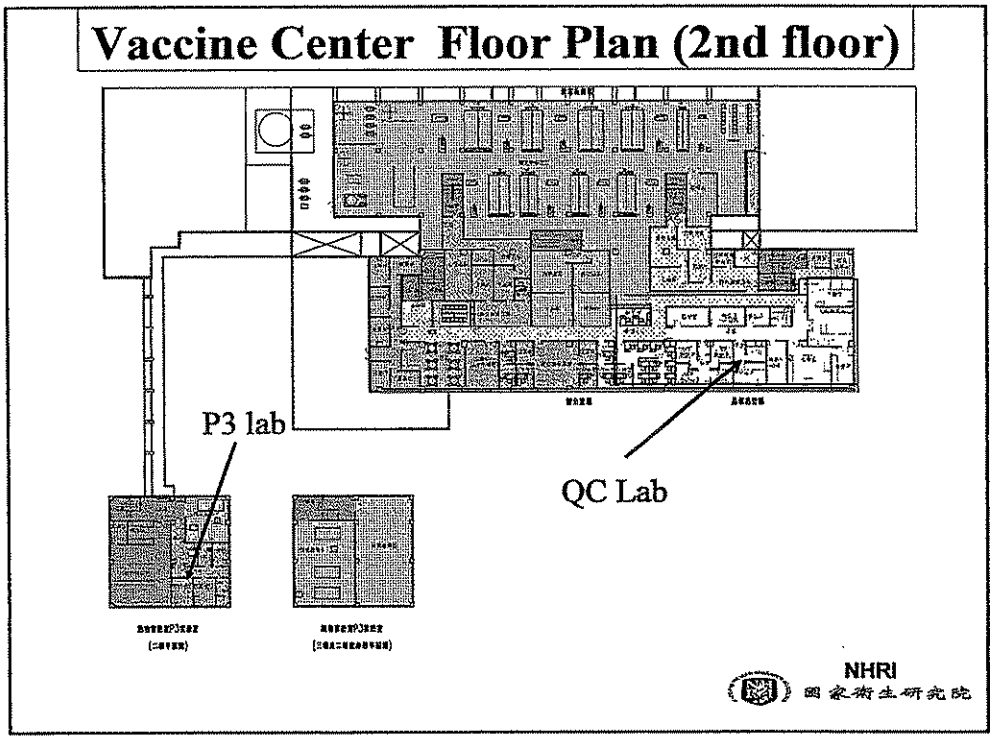

Vaccine Center Floor Plan (1st floor)
BCG
Bacterial Pilot Plant
Core Facility
Viral Pilot Plant
cGMP Warehouse
Central Filling
Biological Manufacturing Plant
QC Animal Facility


Vaccine Center Floor Plan (2nd floor)
P3 lab
QC Lab
NHRI
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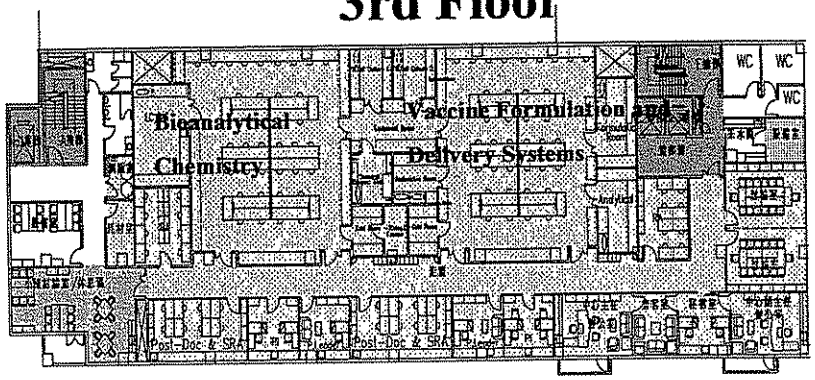
廠區配置-三樓配置

3rd Floor



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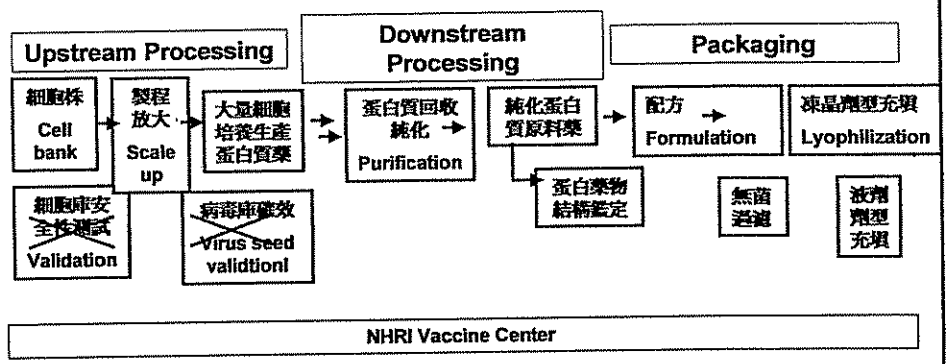
NHRI CRO & CMO之能力



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NHRI Vaccine Center
As
Biotechnology Training Forum

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『生技製藥CGMP認證學程』
成立目的

建立國際接軌的合作機制：與國外cGMP教育與認證機構（University of Waterloo, PharmEng Technology Inc.）合作開設「cGMP-生物製藥認證」課程與實務並重之訓練課程。

提出長期cGMP人才培養模式：於國外，建立合作管道。於國內，橫向擴大產官學研參與層面，向下延伸提供在學學生教育機會。

擴大強化國際認證基礎：營造國際化的訓練環境，實施國際化同步的課程內容，採取國際化相同的認證程序，將增加與世界先進國家cGMP交互認證之基礎層面。

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NHRI Vaccine Center Business Development Model

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Roles of NHRI Vaccine Center

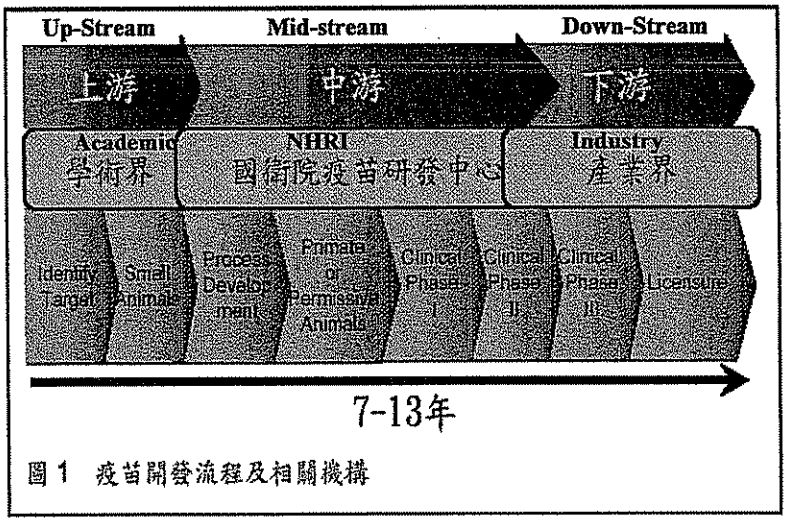

圖 1　疫苗開發流程及相關機構

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Strategies For Business Development

NHRI/University Strategic Alliance
- Identify, evaluate & secure patent rights
- Marketing & technical feasibility analysis
- Collaborate & complete pre-clinical studies
- Production of Phase 1 & 2 clinical-grade materials
- Quality and Regulatory training
  - IND dossier preparation
  - Draft Clinical Protocols
  - QA audit
- Initiate Clinical trials
  - NHRI clinical trials division
  - Trial sites
- Perform Immunological monitoring and Biostatistic

NHRI
Vaccine Center

Before Phase III trials
Identify and negotiate
- Up-front payment
- Manufacturing rights
- Marketing rights
- Royalty

Risk & Profit Sharing

Business Partners
International Pharma
Local Manufacturers

Small Biotech
&
University/Institutes
in Taiwan

Risks Sharing with Business Partners
- Financial contribution bases on Regional rights
- US/Canada; EU; Asia
- Define top limit of financial supports

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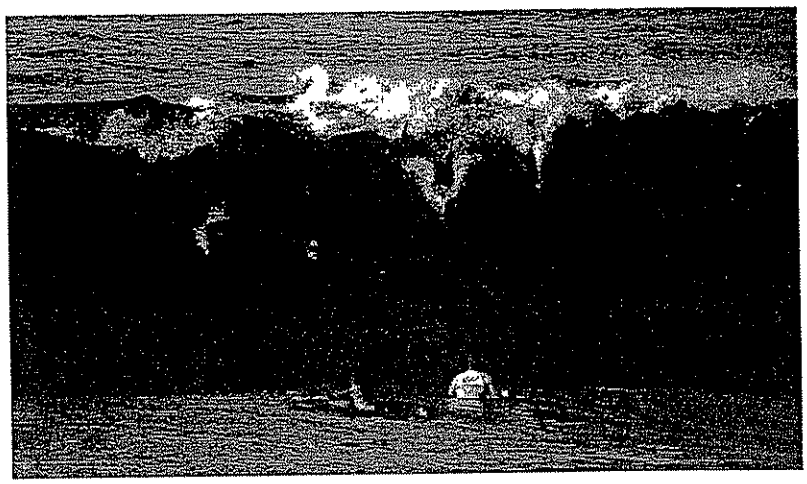


謝謝 Thank you!!

NHRI
國家衛生研究院

The Experiences of Vaccine Products Review in Taiwan

王蓉君 審查員

(Jung-Chun Wang, M.D.,M.P.H.)

財團法人醫藥品查驗中心

Center For Drug Evaluation, Taiwan

The Experiences of Vaccine Products Review in Taiwan

王蓉君 審查員（Jung-Chun Wang, M.D.,M.P.H.）

Division of Clinical Sciences, Center For Drug Evaluation
Hangjou S. Rd., Taipei, Taiwan, ROC.

Vaccines play the major irreplaceable roles for the prevention of infectious diseases. Recently, the research and development of manufacture technology on vaccines have made great progresses on the antigen selection, cell substrates, new adjuvants, as well as new administration routes.

Taiwan's Center for Drug Evaluation, CDE, has conducted reviews on 6 new vaccine products and has completed 8 R&D consultations during 2005-6. There are currently two guidelines for vaccine product reviews, but the clinical evaluation of new vaccines is unavailable at this moment in Taiwan. Nonetheless, Taiwan's CDE takes into consideration the CMC, pre-clinical safety, immunogenicity, the efficacy and safety of clinical studies, post-licensure studies and surveillance. The reviewers usually met the lack of stability test, incomplete records of in-process control/ validation, improper schedules and doses for repeated doses toxicities. On the other hands, more serious concerns were on reproductive and developmental toxicity, the correlation between immunologic response and clinical protection, the persistence of antibody response, ethnic immunologic bridging studies, the interaction between concurrently administered vaccines and the post-licensure planning etc.

CDE also carries its mission on the prevention of pandemic flu. CDE has set-up the priority review on clinical trials and products of mock-up/pandemic vaccines and established an accelerated approval mechanism. Through the pandemic task force working group (PTFWG) and the advisory committee, the draft guideline on evaluation of mock-up/pandemic vaccine in Chinese language has been completed. CDE will work to compose the guideline on clinical evaluation of new vaccines in Taiwan, to play key roles in critical path and R&D consultation of vaccines, to set priority review and to established accelerated approval mechanism for mock-up/ pandemic vaccine, and to create post-licensure surveillance system, and finally, to fully participate in WHO's vaccine and pandemic influenza prevention.

The Experiences of Vaccine Products Review in Taiwan

Center for Drug Evaluation, Taiwan
Jung-Chun Wang, M.D., M.P.H.
November 3, 2006

Vaccine Approvals in 2005-6

- CBER, U.S. FDA
- Vaccine Working Party, EU EMEA
- CDE, Taiwan

U.S. Food and Drug Administration

2005-6 FDA Vaccine Approvals

Tradename	Proper Name	Approval
FluLaval	Influenza Virus Vaccine	Oct 5, 2006
Gardasil **	Quadrivalent Human Papillomavirus (Type 6, 11, 16, 18) Recombinant Vaccine	Jun 8, 2006
Zostavax **	Zoster Vaccine, Live, (OKA/MERCK)	May 25, 2006
RotaTeq **	Rotavirus Vasccine, Live, Oral, Pentavalent (Prevention of serotypes G1, G2, G3, and G4)	Feb 3, 2006
ProQuad **	Measles, Mumps, Rubella and Varicella Virus Vaccine Live	Sep 6, 2005
Fluarix	Influenza Virus Vaccine	Aug 31, 2005
Adacel	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed	Jun 10, 2005
Boostrix	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed	May 3, 2005
Menactra	Meningococcal Polysaccharide (serogroups A, C, Y and W-135) Diphtheria Toxoid Conjugate Vaccine	Jan 14, 2005

U.S. Food and Drug Administration

2005-6 FDA Vaccine Supplement Approvals

Tradename

- Boostrix
- Menactra
- Havrix
- Dryvax
- Tetanus toxoid adsorbed
- Fluvirin
- FluMist
- VAQTA
- Fluzone
- Biothrax
- Varivax

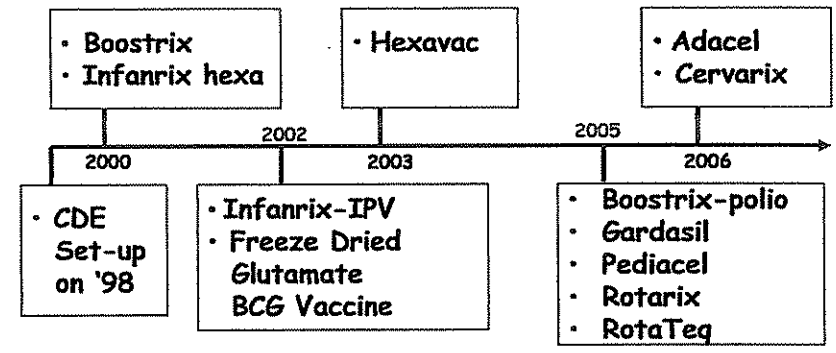
Tradename

- Menactra
- Daptacel
- Fluarix
- Fluvirin
- FluMist
- Varivax
- Fluzone
- Pediarix
- Havrix
- Adacel

2005-6 EMEA Vaccine Approvals

Tradename	Proper Name	Approval
Silgard	Quadrivalent Human Papillomavirus (Type 6, 11, 16, 18) Recombinant Vaccine	Sep 20, 2006
Gardasil **	Quadrivalent Human Papillomavirus (Type 6, 11, 16, 18) Recombinant Vaccine	Sep 20, 2006
RotaTeq **	Rotavirus Vasccine, Live, Oral, Pentavalent (Prevention of serotypes G1, G2, G3, and G4)	Jun 27, 2006
Zostavax **	Zoster Vaccine, Live, (OKA/MERCK)	May 19, 2006
MMRVaxpro	Measles, Mumps, Rubella Vaccine, live	May 5, 2006
ProQuad **	Measles, Mumps, Rubella and Varicella Virus Vaccine Live	April 6, 2006
Rotarix	Human Rotavirus, live attenuated	Feb 21, 2006
Quintanrix	Tetanus Toxoid, Diphtheria Toxoid and adsorbed inactivated Pertussis Vaccine, Hepatitis B, H imfluenza b conjugate Vaccine	Feb 17, 2005
Fendrix	Hepatitis B (rDNA) Vaccine (adjuvanted, adsorbed)	Feb 2, 2005

Vaccine Products Review in CDE, Taiwan



Vaccine R&D Consultations in CDE, Taiwan

- BCG Vaccine
- LT Mucosal adjuvant for nasal influenza vaccine
- Adenovirus-vectored influenza vaccine
- Adjuvant for H5N1 mock-up vaccine
- Cell substrate for H5N1 mock-up vaccine

2000 — 2004 — 2005 — 2006

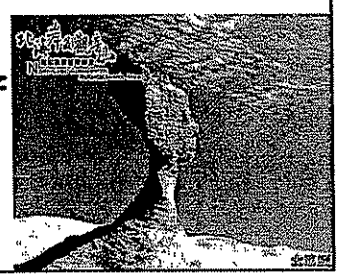
- CDE Set-up on '98
- BCG Vaccine

2005-06 non-R&D Consultation:
- ProQuad
- Zostavax
- UBITh AD immunotherapeutic vaccine

Guidelines for Vaccine Product Review

- 行政院衛生署【藥品非臨床試驗安全性規範】第三版，2000年6月8日公告。
- 行政院衛生署【藥品查驗登記審查準則－疫苗類藥品之查驗登記】，2002年1月31日公告。

➢Unavailability of Guidelines on the Clinical Evaluation of New Vaccine in Taiwan



疫苗類藥品之查驗登記 2002.1.31

第二條　疫苗類藥品應檢附之資料：

1. 疫苗類原料藥的定義及化學、製造與管制的要求
2. 疫苗類原料藥之製造方法
3. 疫苗類原料藥之製程管制資料
4. 疫苗類原料藥製程一致性資料
5. 疫苗類原料藥之規格
6. 疫苗類原料藥之再製
7. 疫苗類藥品之組成與特性
8. 疫苗類藥品之製造業者與設備
9. 疫苗類藥品之製造方法
10. 疫苗類藥品之規格
11. 容器與封蓋
12. 微生物之管制
13. 安定性
14. 藥理及毒性試驗資料
15. 藥物動力學資料
16. 臨床使用文獻
17. 生物藥品之藥品優良製造規範及確效資料
18. 檢驗封緘

FDA Guidance: CBER

U.S. Food and Drug Administration
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

- Draft Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases (9/28/2006)
- Guidance for Industry: Development of Preventive HIV Vaccines for Use in Pediatric Populations (5/4/2006)
- Draft Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines (3/2/2006)
- Draft Guidance for Industry: Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines (3/2/2006)
  - FDA Initiative Helps Expedite Development of Seasonal and Pandemic Flu Vaccines (3/2/2006)
- Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications (2/13/2006)
- FEDERAL REGISTER Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Final Rule and Final Order - 12/15/2005 - *(PDF), (Text)*
- FEDERAL REGISTER Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed; Final Order (12/15/2005) *(PDF), (Text)*
- Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (4/29/2005)
- Draft Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications (2/17/2005)
  - Points to Consider on Plasmid DNA Vaccines for Preventive Infectious Disease Indications (12/27/1996) *(PDF), (Text)*

FDA Guidance: CBER

U.S. Food and Drug Administration

- Guidance for Industry: FDA Review of Vaccine Labeling Requirements for Warnings, Use Instructions, and Precautionary Information (10/1/2004) *(PDF)*, *(Text)*
- Federal Register Notice; Biological Products; Bacterial Vaccines and Related Biological Products; Revocation of Biologics Licenses (5/29/2001) *(PDF)*, *(Text)*
- Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines (3/12/2001)*(PDF)*, *(Text)*
- Guidance for Reviewers: Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol (11/20/2000) *(PDF)*, *(Text)*
- Draft Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications(9/8/2000) *(PDF)*, *(Text)*
- FEDERAL REGISTER Biological Products; Bacterial Vaccines and Related Biological Products; Implementation of Efficacy Review; Proposed Order (5/15/2000) *(PDF)*, *(Text)*
- Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (1/5/1999) *(PDF)*, *(Text)*
- Guidance for Industry: How to Complete the Vaccine Adverse Reporting System Form (VAERS-1) (9/8/1998) *(PDF)*, *(Text)*
- Guidance for Industry for the Evaluation of Combination Vaccines for Preventable Diseases: Production, Testing and Clinical Studies (4/10/1997) *(PDF)*, *(Text)*

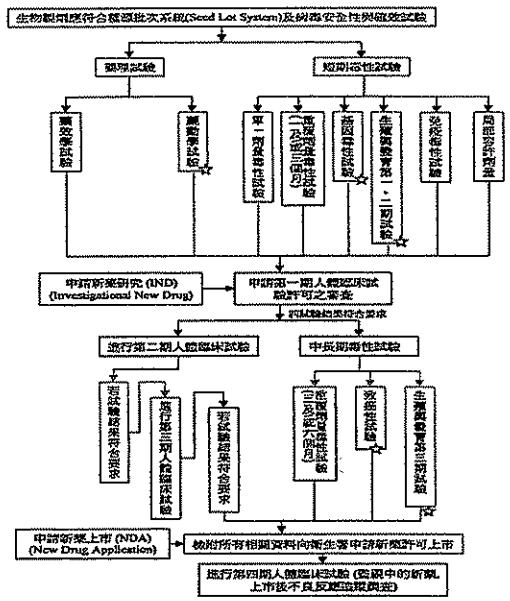
EMEA Guidance: Vaccine Working Party

- EMEA/CHMP/VWP/263499/06 Guideline on dossier structure and content of Marketing Authorisation applications for Influenza vaccines with avian strains with a pandemic potential for use outside of the core dossier context (Released for consultation July 2006)
- EMEA/CHMP/VWP/73919/2004 Mandate, Objectives and Rules of Procedure for the CHMP Vaccine Working Party
- EMEA/397403/05 EMEA Pandemic Influenza crisis management plan for the evaluation and maintenance of Pandemic Influenza vaccines and antivirals (Released for consultation November 2005); Annex I - EU influenza pandemic process map
- EMEA/CHMP/VEG/193031/04 Core SPC for Pandemic Influenza Vaccines (CHMP Adopted June 2005)
  EMEA/CHMP/5579/04 Rev. 1 Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization (WHO) for the evaluation of medicinal products intended exclusively for markets outside the Community (CHMP Adopted May 2005)
- EMEA/CHMP/VEG/164653/05 Note for Guidance on the Clinical Evaluation of Vaccines (Released for consultation May 2005) NEW!
- EMEA/CHMP/134716/04 Guideline on Adjuvants in Vaccines for Human Use (CHMP Adopted January 2005)
- EMEA/CPMP/1820/04 Concept Paper on the Development of a CHMP revised Guideline on Clinical Evaluation of New Vaccines
- EMEA/CPMP/4986/03 Guideline on Submission of Marketing Authorisation Applications for Pandemic Influenza Vaccines through the Centralised Procedure (CPMP Adopted March 2004)
- EMEA/CPMP/4717/03 Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application (CPMP Adopted March 2004)
- EMEA/CPMP/VEG/17/03/2004v5 /Consultation Guideline on Adjuvants in Vaccines (CPMP released for consultation March 2004)
- EMEA/CPMP/1100/02 Note for Guidance on the Development of Vaccinia Virus Based Vaccines against Smallpox

EMEA Guidance : Biologics Working Party

- CPMP/BWP/2758/02 Guideline on Pharmaceutical Aspects of the Product Information for Human Vaccines (Adopted by CPMP December 2003)
- CPMP/BWP/2490/00 Note for Guidance on Cell Culture Inactivated Influenza Vaccines (Adopted by CPMP January 2002) - Annex to Note for Guidance on Harmonisation of requirements for Influenza Vaccines CPMP/BWP/214/96;
  See also EMEA/CPMP/BWP/498/01 - Explanatory Note for Medicinal products for Human use on the Scope of the Guideline.
- CPMP/BWP/477/97 Note for guidance on Pharmaceutical and Biological Aspects of Combined Vaccines, (CPMP adopted Jul. 98).
- CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP adopted March 97)

Flow Chart of New Vaccine Approval in Taiwan



☆：疫苗類藥品原則上不需執行，但需視各案而定。

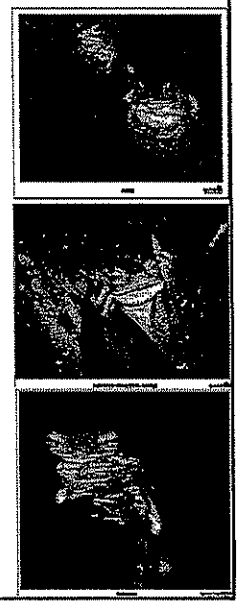
圖一：生物製劑/疫苗類藥品之上市流程

The Consideration on the Evaluation of New Vaccine

- Chemical Manufacturing & Control
- Pre-clinical safety
- Immunogenicity
- The consideration of clinical studies
- Post-licensure planning
  - Post-marketing surveillance
- Special consideration
  - Adjuvant
  - Cell substrate
  - New administration route

Chemical Manufacturing & Control

- 審查重點：
  1. 抗原來源的建立及管控
  2. 生物安全管制及能預防外來因子（病毒、細菌、真菌、及黴漿菌）可能造成的污染
  3. 相關標準操作過程資料
  4. 製程管制與製程確效報告
  5. 製程一致性資料
  6. 疫苗抗原活性之敘述與效價測試
  7. 規格與檢驗應包括鑑別、純度、效價（生物活性）及與效價有關之物理化學測定
  8. 安定性試驗



Chemical Manufacturing & Control

- 常見缺失：
  1. 安定性試驗資料
  2. 製程管制與製程確效
  3. 製程改變前後不同疫苗批次的比較

Pre-Clinical Safety

- 審查重點：
  1. 臨床前安全性試驗：異常毒性試驗、單一劑量毒性、重複劑量毒性、局部刺激性、免疫性(免疫活性與過敏性評估)試驗等
  2. 疫苗佐劑：未具有人類使用經驗之疫苗佐劑
     - 單獨執行試驗; 以及
     - 疫苗佐劑合併抗原後執行試驗
  3. 藥物動力學試驗：一般不需要執行
  4. 基因毒性試驗與致癌性試驗：一般不需執行
  5. 生殖毒性與生物發育毒性試驗：視各案而定

Pre-Clinical Safety

- 常見缺失：
  1. 重複劑量毒性試驗時程
  2. 重複劑量毒性試驗的用法用量
  3. 生殖毒性與生物發育毒性試驗是否執行

Immunogenicity

- 審查重點：
  1. 動物(preclinical)免疫生成反應試驗：進入人體臨床試驗前，必需先執行小型動物（例如雞、小鼠）的免疫性試驗
  2. 人體臨床試驗：
     - 探討劑量的選擇以及劑量投與時程
     - 免疫生成反應的持續性程度與臨床上保護效益之關連
     - 是否需要追加接種疫苗
     - 高危險族群之免疫生成反應
  3. 免疫生成反應結果：
     - 抗體的種類(antibody class/subclass)
     - 抗體生成的多寡(antibody level)
     - 短/長期的抗體反應(short/long-term antibody response)
     - 抗體反應之持續性(persistence of antibody response)
     - 血清陽轉率比例(seroconversion rate)
     - 抗體交互保護力(cross-reactive antibody)
     - 細胞性免疫反應生成(cell-mediated immunity)
  4. 疫苗生產批次一致性：以欲上市之疫苗批次執行三批次的免疫生成反應，做為一致性(lot-to-lot consistency)的佐證
  5. 族群銜接性試驗

Immunogenicity

- 常見缺失：
  1. 免疫生成反應與臨床上保護效益之關連資訊缺失
  2. 是否需要追加接種資訊不足
  3. 接種後詳細免疫反應資訊缺失
     - 長期的抗體反應
     - 抗體反應之持續性
     - 抗體交互保護力
     - 細胞性免疫反應生成
  4. 缺乏免疫生成反應之族群銜接性試驗報告

The Consideration of Clinical Studies

- 審查重點：
  1. 臨床試驗設計
     - 隨機、對照組、多個試驗中心、目標族群為受試者
  2. 主要效益指標
     - 臨床上預防疾病的保護力(clinical protection endpoint)
     - 經過確效後的血清學替代指標(validated serological surrogate endpoint)
  3. 統計樣本數：針對試驗設計及主要效益指標等事先計算之
  4. 疾病的診斷(definition) 及偵測方式(detection)
  5. 臨床試驗期間：視疾病而定， 一般為1～ 5年
  6. 安全性評估
     - 標準化之毒性評估等級(standardized toxicity grading scale)
     - 局部/全身反應性(local/systemic reactogenicity)

The Consideration of Clinical Studies

- 常見缺失：
  1. 抗體持續性與臨床效益關係未清楚呈現
  2. 不同血清亞型 (serotype)之免疫生成反應是否產生交叉性的保護效果(cross-protection)
  3. 替代性效益指標指標是否經過確效
  4. 特定安全性資訊提供不足 (e.g. 腸套疊)
  5. 缺乏族群銜接性試驗之臨床效益分析
  6. 與其他疫苗同時接種時之疫苗間交互作用

Post-Licensure Planning

- 審查重點：
  1. 免疫生成反應研究：
     - 瞭解疫苗免疫生成反應持續性及保護性，追加接種之需求
     - 是否產生群體免疫反應(herd immunity)之效果
  2. 預防之疾病：
     - 是否產生疾病年齡層之變化(shift of age)
     - 是否產生血清亞型或菌種之變化現象 (serotype/strain replacement phenomena)
  3. 長期的疫苗安全性議題：
     - 疫苗接種失敗視同為安全性議題，需經由上市後的疫苗監測 (post-marketing surveillance) 計畫加以評估之
     - 罕見的副作用

Post-Licensure Planning

- 常見缺失：
  1. 未曾提供上市後應執行之監測計畫

CDE's Mission on the Prevention of Pandemic Flu

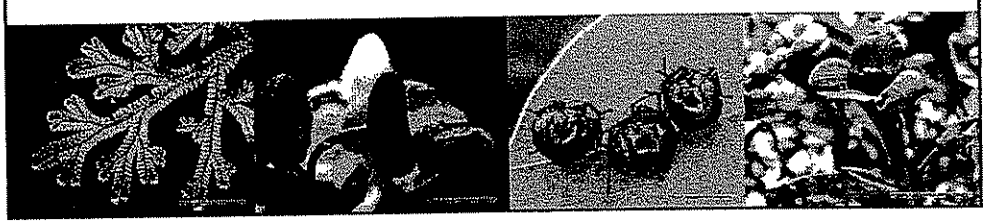
目標：建立我國新型流感疫苗製劑
(Pandemic Influenza Vaccine)
之臨床試驗管理機制及規範

CDE's Mission on the Prevention of Pandemic Flu

1. 設立新型流感專案工作小組「Pandemic Task Force Working Group (PTFWG)」
2. 建立問題導向之專家諮詢委員會議「Issue-Oriented Advisory Committee Meeting (IOACM)」制度
3. 提供疫苗相關產品研發的法規諮詢輔導
4. 協助衛生署建立疫苗相關產品研發過程的法規管理結構及框架
5. 協助衛生署建立緊急情況下之疫苗相關產品查驗登記審查流程

CDE's Mission on the Prevention of Pandemic Flu

- 新型流感專案工作小組：2005年12月成立
- 草擬【新型流感疫苗查驗登記之審查注意要點(草案)】：2006年8月28日
  - 協助衛生署藥政處法條化公告作業中

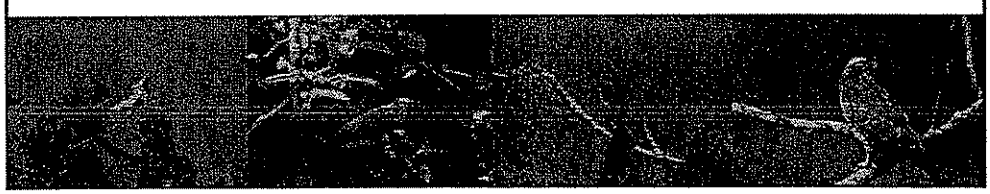


CDE's Mission on the Prevention of Pandemic Flu

- 專家諮詢委員會議
  - Issue-Oriented Advisory Committee Meeting (IOACM)
    - 2006年6月30日：法規草案內容
    - 2006年10月26日：研發過程之法規要求

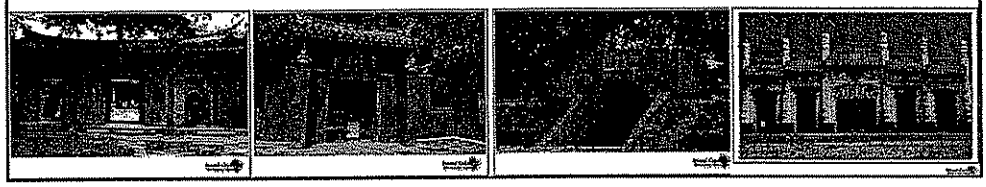
CDE's Mission on the Prevention of Pandemic Flu

- 疫苗相關產品研發的法規諮詢輔導
  - LT Mucosal adjuvant for nasal influenza vaccine
  - Adenovirus-vectored influenza vaccine
  - Adjuvant for H5N1 mock-up vaccine
  - Cell substrate for H5N1 mock-up vaccine



CDE's Mission on the Prevention of Pandemic Flu

- 協助衛生署建立緊急情況下之疫苗相關產品查驗登記審查流程
  - 提供新型流感疫苗臨床試驗計畫書之快速審查流程
  - 建立新型流感疫苗 accelerated approval 之查驗登記審查流程

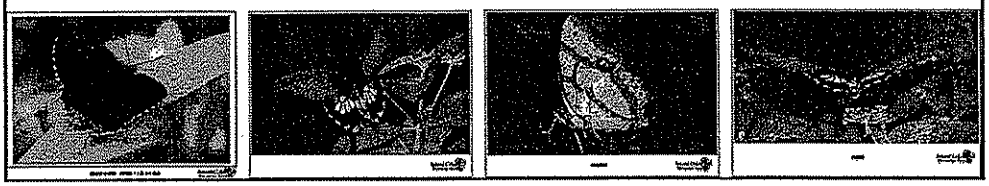


CDE's Achievements in Vaccine Regulatory Science in 2005-6

- Completion: 6 Vaccine NDAs Review; 8 Consultations
- 新型流感疫苗查驗登記之審查注意要點(草案), 2006年8月28日. 協助衛生署藥政處法條化公告作業中.
- 王蓉君, 陳恆德, 朱夢麟. 醫藥品查驗中心於禽流感防疫中所扮演之角色. 台灣醫界雜誌 2006, Vol.49, No.3 p.40-42.
- 王蓉君, 李明亮, 莊再成. 新型流感疫苗之臨床試驗. Acta Paediatrica Taiwanica. 2006; Vol. 47 Suppl. p.18-22 (in print).
- 王蓉君, 朱夢麟, 陳恆德. 新疫苗法規科學現況之簡介. (submitted).

CDE's Progress on Vaccine Product Review

- **IND**
  - From Phase III to Phase I clinical trials
  - e.g. Therapeutic DNA Plasmid pdpSC18 Vaccine
- **NDA**
  - Concurrent review of new vaccine product with FDA or EMEA
  - e.g. Rotateq & Rotarix; Gardasil & Cervarix
- **R & D Consultation**
  - New vaccine R&D manufacturing technology
  - e.g. adjuvant/cell substrate for H5N1 mock-up vaccine



Taiwan CDE's Future Perspectives

- Guidelines on the clinical evaluation of new vaccines in Taiwan
- Key roles in critical path and R&D consultation
- Mechanism for accelerated approval in mock-up/pandemic vaccines
- Post-marketing surveillance
- Participation in WHO for vaccines and pandemic influenza prevention

Acknowledgements

Mong-Ling Chu
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Ywan-Feng Li
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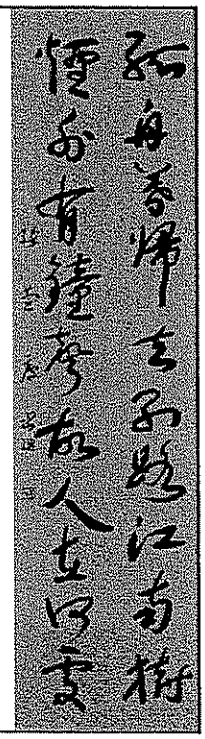
Yi-Chi Lee
Tzu-Hsin Liao
and
All CDE's Colleagues
Participating in Vaccine Review !



TAIWAN
Partner for Global Health

World Health Organization

U.S. Food and Drug Administration
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

EMEA new website address: emea.europa.eu

Merci Beaucoup!

INVITED SPEAKERS

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Supervisory Research Chemist
Center for Biologics Evaluation and Research
Food and Drug Administration
U.S.A.

Chi-Jen Lee, Sc.D., is Supervisory Research Chemist, Center for Biologics Evaluation and Research, Food and Drug Administration (FDA), Bethesda, MD. (1974-present, Chief, Polysaccharide and Conjugate Vaccine QC Section).

Dr. Lee graduated in 1957 from National Taiwan University, College of Medicine, School of Pharmacy, with B.S. in Pharmacy. He obtained his Sc.D. in Biochemistry from the Johns Hopkins University, Bloomberg School of Public Health, Department of Biochemistry. He served as an Assistant Professor at the Rockefeller University, New York city, from 1968 to 1973. He was a Visiting Professor, National Cheng Kung University, College of Medicine, Taiwan in 1984. He was awarded The Honorary Professor (8/4/00), by Inner Mongolia Medical College, China. He has received several FDA Awards of Merit (FDA's highest award, in 1986, 1991, and 2001), FDA Commendable Service Awards (1978, 1988), and Reward & Recognition Award Certificate and Cash Award (3/30/01).

Dr. Lee is the author of books, Development and Evaluation of Drugs: From Laboratory Through Licensure to Market, (1993, CRC Press, Inc.; 2nd edition, 2003), Managing Biotechnology in Drug Development (1996, CRC Press, Inc.), a co-author of Polysaccharides in Medicine and Biotechnology (1996, Marcel Dekker, Inc.), the editor of Professional Frontiers in 21st Century (2002, Chinese-American Professionals Asso. in Greater Washington) and the chief editor of Clinical Trials of Drugs and Biopharmaceuticals (2006, CRC Press, Taylor & Francis Group, 500 pages). He has published more than 160 research papers and abstracts. He served as a thesis director for Ph.D. candidate in Department of Microbiology, The George Washington University Medical Center, Washington D.C., 1988-1991, and President of Chinese-American Professionals Association of Greater Washington, 2001-02.

Lucia H. Lee, M.D.

Medical Officer
Center for Biologics Evaluation and Research
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Lucia Lee, M.D. is currently a medical officer at the Center for Biologics Evaluation and Research in Food and Drug Administration (FDA).

Dr. Lee received her medical degree and the University of Rochester School of Medicine. She completed her pediatric training at the Johns Hopkins Hospital and then returned to Rochester, NY for pediatric infectious diseases fellowship. There, she worked to clone and characterize the cDNA encoding a kexin-like protease in mouse Pneumocystis carinii, and which was also found to be cross-reactive with human Pneumocystis carinii. Dr. Lee's research has been recognized by awards from the Pediatric Infectious Diseases Society and Eli Lilly and Company.

Dr. Lee has extensive training and experience in clinical trial design. Prior to coming to the FDA, Dr. Lee served in several capacities as a co-investigator and research coordinator for studies conducted in collaboration with the NICHD Pediatric AIDS Clinical Trials Unit and Vaccine Trial Evaluation Unit at the University of Rochester. At the FDA, she is involved in the design of vaccine clinical trials conducted in the United States, Europe, Africa, South America and Australia. She serves on committees on both a national and international level. Dr. Lee is also a fellow of the American Academy of Pediatrics and a member of the Pediatric Infectious Disease Society.

Dr. Lee is the co-author of the book, Development and Evaluation of Drugs: From Laboratory Through Licensure to Market (2003, 2nd edition, CRC Press, 241 pages) and the co-editor of the book Clinical Trials of Drugs and Biopharmaceuticals (2006, CRC Press, Taylor & Francis Group, 500 pages).

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Present Position

Director
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Selected Experience

- Acting Secretary, Taiwan Influenza Vaccine Strain Advisory Team
- Project Manager, Taiwan Influenza Vaccine R&D Project
- Acting Director, Division of Emerging Infectious Disease, CDC, Taiwan
- Deputy Director, Division of Planning; Division of Immunization; Division of AIDS & EID, CDC, Taiwan
- Taiwan CDC Liaison for international influenza research and pandemic preparedness.
- Taiwan CDC Liaison for SARS research projects of European Commission

Education

M.S. Graduate School of Microbiology, Institute of Medicine
National Taiwan University

B.S. Department of Medical Technology
National Yang-Ming Medical College, Taiwan

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Vaccine R&D Center of National Health Research Institute, Taiwan

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EDUCATION

1974-78	B.Sc. (Honors) Biochemistry, University of Alberta, Edmonton, Canada.
1978-83	Ph.D. Biochemistry, University of Alberta
1983-85	MRC Post-doctoral Fellow, University of British Columbia, Vancouver, Canada.

ACADEMIC AWARDS AND DISTINCTIONS

1974	Alberta Matriculation Scholarship
1980-83	Alberta Heritage Foundation for Medical Research Studentship
1983-85	MRC Post-doctoral Fellowship
1983-85	Alberta Heritage Foundation for Medical Research Independence Research Allowance
1990	Connaught H.G. Macmorine Publication Prize
1992	Connaught H.G. Macmorine Publication Prize
1993	Connaught H.G. Macmorine Publication Prize

PROFESSIONAL EXPERIENCES

1978-82	Ph.D. Student, University of Alberta Biochemistry, Dr. R. S. Hodges (Supervisor). Design, synthesis and application of a new heterobifunctional photoaffinity probe for the studies of protein-protein interactions involved in the actin-linked calcium-regulated system of muscle contraction.
1978-81	Teaching Assistant, Biochemistry, University of Alberta
1983-85	MRC Post-doctoral Fellow, University of British Columbia Pathology, Dr. S. Gillam (Supervisor). Development of rubella virus vaccine using recombinant DNA.
1985-87	Associate Research Scientist, Connaught Laboratories Limited Immunobiology Department. Supervised 4 technologists to develop an acellular pertussis vaccine.
1988-1991	Research Scientist, Connaught Laboratories Limited Department of Protein Engineering Group Leader in Bioorganic Synthesis Supervised 10 research staff (3 Ph.D.)
1989-1993	Research Project Leader Supervised a project team of 20 staff to develop a H.influenzae Outer Membrane Protein-Based Conjugate Vaccines
1993-1997	Project Manager Managed a project team of 15 staff to produce GMP-grade HIV-1 Synthetic Peptides for human clinical trials
1992-1997	Research Project Leader Supervise a project team of 12 staff to develop Synthetic Adjuvants and Novel Biodegradable Polymer for Vaccine Delivery Systems
1991-1994	Senior Research Scientist Section Head, Department of Bioorganic Synthesis Connaught Centre for Biotechnology Research
1994-2000	Director (supervise 23 research staff, 12 Ph.D.) Department of Biochemistry Research Centre, Aventis Pasteur Canada
1998-2000	Corporate Platform Leader of Biochemistry (supervise ~75 staff) Aventis Pasteur
2000-2003	Vice President of Vaccine Development, United Biomedical Inc. (UBI)
2000-2003	Chief Scientific Officer, UBI-Asia Taiwan
2003-Present	Director and Distinguished Investigator National Health Research Institute Taiwan

PUBLICATIONS

Related to Ph.D. thesis:

1. R.S. Hodges, A. Saund, P.C.S. Chong, S. St. Pirre, and R. Reid (1981). "Synthetic Model for Two-Stranded a- Helical Coiled-coils: Design, Synthesis, and Characterization of an 86-residue Analog of Tropomyosin". J. Biol. Chem. 256:1214-1224.
2. P.C.S. Chong, and R.S. Hodges (1981). " A New Heterobifunctional Cross-Linking reagent for the Study of Biological Interaction between proteins: I. Design, Synthesis, and Characterization". J. Biol. Chem. 256:5064-5070.
3. P.C.S. Chong, and R.S. Hodges (1981). " A New Heterobifunctional Cross-Linking Reagent for the Study of Biological Interaction Between Proteins: II. Application to the Troponin C- Troponin I Interaction". J. Biol. Chem. 256:5071-5076.
4. P.C.S. Chong, and R.S. Hodges (1982). "Proximity of Sulfhydryl Groups to Site of Interaction Between Components of the Troponin Complex from Rabbit Skeletal Muscle". J. Biol. Chem. 257:2549-2555.
5. P.C.S. Chong, and R.S. Hodges (1982). "Photochemical Cross-Linking between Rabbit Skeletal Troponin T and a-Tropomyosin: Attachment of the Photoaffinity Probe, AGTC, to Cysteine 190 of a-Tropomyosin". J. Biol. Chem. 257:9152-9160.
6. P.C.S. Chong, and R. S. Hodges (1982). "Photochemical Cross- Linking between Rabbit Skeletal Troponin Subunits: Troponin I- Tropnin T Interaction". J. Biol. Chem. 257:11667-11672.
7. P.J. Cachia, J. Van Eyk, P.C.S. Chong, A. Taneja, and R. S. Hodges (1983). "Separation of Basic Peptides by Cation-Exchange HPLC". J. of Chromatography 266:651-659.
8. P.C.S. Chong, P.J. Assebbergs, and R.S. Hodges (1983). " Interaction of rabbit Skeletal Muscle Acto-S1 ATPase by Troponin T". FEBS Letters 153:732-736.
9. P.C.S. Chong (1983). " Design, Synthesis and application of New Heterobifunctional Photoaffinity Probe for the Studies of Protein-Protein Interactions Involved in the Actin-Linked Calcium-Regulated System of Muscle Contraction". Ph.D. Thesis, University of Alberta.

Related to Vaccine Development

10. P.C.S. Chong, and S. Gillam (1985). "Purification of Biologically Active Rubella Virus Antigens by Immunoaffinity Chromatography". J. of Virological Methods 10:261-268.
11. P. Chong, I. Hui, T. Loo, and S. Gillam (1985). "Structural analysis of the GC specific Insertion Element IS186". FEBS Letters 192:47-52.
12. D. Clark, I. Hui, T. Loo, P. Chong, and S. Gillam (1987). " Nucleotide Sequence and In Vitro Expression of Rubella Virus 24S Subgenomic mRNA Coding the structural Proteins E1, E2, and C". Nucleic Acids Research 15:3041-3057.
13. D.Y. Sia, P. Chong, B. Rovinski, J. Haynes, and M. Klein. "Identification of a Potent HIV-1 p24 T-cell Epitope which Mediates Antibody Response to Both Autologous and Heterologous B-cell Epitopes". Miami Biotechnology Winter Symposium. Advance in Gene Technology: The Molecular Biology of Immune Diseases and the Immuneresponse.
14. D. Ou, P. Chong, B. Tripet and S. Gillam. (1992) " Analysis of T- and B-cell Epitopes of Capsid Protein of Rubella Virus using Synthetic Peptides". J. of Virology. 66:1674-1681.
15. D.Y. Sia, P. Chong, B. Caplan, T. Matthews, R. Oomen, J. Caterini, D. Bolognesid and M. Klein. (1992) " Structure and Immunogenicity of Synthetic HIV Tandem Epitopes". The 6th Colloque Des Cent Gardes. p105-110.
16. H. Chaye, P. Chong, B. Tripet, B. Brush and S. Gillam. (1992) "Localization of the virus neutralizing and hemagglutinin epitopes of E1 glycoprotein of rubella virus". Virology. 189:483-492.
17. D. Ou, P. Chong, P. McVeigh, W.A. Jefferies and S. Gillam. (1992). "Characterization of the specificity and Genetic Restriction of Human CD4+ Cytotoxic T Cell Clones Reactive to Capsid Antigen of Rubella Virus" Virology. 191:680-686.
18. D. Ou, P. Chong, Y. Choi, P. McVeigh, W.A. Jefferies, G. Koloitis, A.J. Tingle and S. Gillam. (1992) "Identification of an immunodominant epitope on E2 protein of rubella virus reconized by human CD4+ cyctotoxic T-cell clones." J. Virology. 66:6788-6793.
19. D. Ou, P. Chong, B. Tripet, A.J. Tingle and S. Gillam (1993). " Mapping T-cell epitopes of rubella virus structural proteins E1, E2 and C recognized by T-cell lines and clones derived from infected and immunized population. J. of Med. Virology 40:175-183.
20. P. Chong, C. Sia, E. Tam, A. Kandil and M. Klein (1993). "Synthesis and Characterization of a 134-Mer Synthetic peptide Corresponding to the N-terminal

Half of the HIV-1 Nucleoprotein p24". Inter. J. Pept. Prot. Res. 41:21-27.

21. M. Klein, P. Chong, T. Matthews, S.Zolla-Pazner, O. James, G. Cates and D.Y. Sia (1993). "Immunogenicity of Synthetic HIV-1 T-B Tandem Epitopes". The 7th Colloque Des Cent Gardes. p169-174.
22. H. Chaye, D. Ou, P. Chong and S. Gillam. (1993) Human T- and B-cell epitopes of E1 glycoprotein of rubella virus. J. Clinical Immun. 13:93-100.
23. D. Ou, P. Chong, and S. Gillam. (1994) "Immunogenicity study of a synthetic T-cell epitope of rubella virus capsid protein recognized by human T-cells in different strains of mice". Viral Immun. 7:41-45.
24. A.G. Abimiku, G. Franchini, J. Tartaglia, K. Aldrich, M. Myagkihh, P.D. Markham, P. Chong, M. Klein, M.P. Kieny, E. Paoletti, R.C. Gallo, and M. Robert-Guroff. (1995) "HIV-1 recombinant poxvirus vaccine induces cross-protection against HIV-2 challenge in rhesus macaques". Nature Medicine, 1:321-329.
25. M. Klein, X.S. Cao, G. Cates, P. Chong, C. Sia, O. James, T. Matthews and B. Rovinski (1995). "Immunogenicity of Synthetic HIV-1 T-B Tandem Epitopes". The 9th Colloque Des Cent Gardes. p191-195.
26. Z. Liu, D. Yang, Z. Qiu, K-T. Lim, P. Chong and S. Gillam (1996). " Identification of domains in rubella virus genomic RNA and capsid protein necessary for specific interaction. J. Virology 70:2184-2190.
27. P. Chong, S-P. Shi, C. Sia, O. James, B. Tripet, T. Matthews and M. Klein (1996). "Comparative immunogenicity studies of different HIV-1 V3 peptides". In proceeding of the 14th American Peptide Symposium. Peptides: Chemistry, structure and biology. Eds. by P.T.P. Kaumaya and R.S. Hodges. Escom Leiden. pp790-791.
28. P. Chong, S. Gillam, S-P. Shi, A. Olivier and M. Klein (1996). "A synthetic peptide-based candidate vaccine against rubella virus". In proceeding of the 14th American Peptide Symposium. Peptides: Chemistry, structure and biology. Eds. by P.T.P. Kaumaya and R.S. Hodges. Escom Leiden. pp788-789.
29. J. Yao, D. Yang. P. Chong, D. Hwang, Y. Liang and S. Gillam. (1998) "Proteolytic processing of rubella virus nonstructural proteins" Virology 246:74-83.
30. A. Pedyczak, D. McLeod, O. James, M. Klein and P. Chong (1999). "Comparative immunological properties of lipidated HIV-1 gp41 fragments on various structural templates". In proceeding of the 15th American Peptide Symposium. Peptides: Chemistry, structure and biology. Eds. by J. Tamd and P.T.P. Kaumaya. Escom Leiden. pp777-778.

Artur Pedyczak, Dwo Y. Sia, Dave McLeod, Michel Klein and Pele Chong. Lipidated HIV-1 Rev Peptide as a potential AIDS Vaccine Candidate in Peptides 1998, Sandor

Bajusz and Ferenc Hudacz (Eds.), Akademiai Kiado, Budapest 1999, pp. 534-535.

D. Burt, S. Woods, R. Arpino, S. Sambhara, D. Mcleod, P. Chong, S. Sanherza, M. Ewasyshyn, and M. Klein. "Synthetic peptides from RSV M2, F, and N proteins define H-2Kd restricted epitopes recognized by CD8+ CTL from RSV-infected BALB/C mice". J. Virol. (In press).

Bacterial Vaccines

31. G. Zealey, S. Loosmore, S. Cockle, H. Boux, K. Radika, R. Yacoob, P. Chong, R-Y, Yao, and M. Klein (1988). "Construction of B. pertussis Strains that Secret Inactive Pertussis Toxin Analogs ". Ed. R. Lerner et al. Modern Approach to Vaccine Including AIDS. Cold Spring Harbor. p259-263.
32. P. Chong, and M. Klein (1989). " Single-Step Purification of Pertussis Toxin and its Subunits by Heat-treated Fetuin-Sepharose Affinity Chromatography". Biochem. and Cell Biology 67:387-391.
33. S. Cockle, S. Loosmore, K. Radika, G. Zealey, H. Boux, P. Chong, And M. Klein (1989). "Detoxification of Pertussis Toxin by Site-Directed Mutagenesis" in Immunobiology of Proteins and Peptides V. Ed. M.Z. Atassi. Plenum Publishing Co. p209-214.
34. G. Tyrrell, M. Peppler, R. Bonnah, P. Chong, and G.D. Armstrong (1989). "Examination of the Wheat Germ Agglutinin-like Properties of Pertussis Toxin" Infec. Immun. 57:1854-1857.
35. P. Chong, M. Sydor, G. Zobrist, H. Boux, and M. Klein (1990). "Mapping the Neutralization Epitope of the S1 Subunit of Pertussis Toxin using Synthetic Peptides". In proceeding of the 11th American Peptide Symposium. Peptides: Chemistry, structure and biology. p751-754. Eds. by J.E. Rivier and G.R. Marshall. Escom Leiden.
36. P. Chong, G. Jackson, W. Cywk, and M. Klein (1990). "Simultaneous Determination of Pertussis Toxin and Filamentous Hemagglutinin Concentrations by Hydroxylapatite-HPLC". J. of Chromatography. 512:227-236.
37. P. Chong, D. Sia, M. Sydor, and M. Klein. (1990) " Identification of a Potent synthetic HIV-1 Immunogen Compromising of gag-p24 Tandem T and B-cell Epitopes. FEBS Letters 264:231-234.
38. S. Loosmore, G. Zealey, H. Boux, S. Cockle, K. Radika, R. Fahim. G. Zobrist, F-Y. Yao, P. Chong, and M. Klein. (1990) " Engineering of genetically detoxified pertussis toxin analogous for the development of a recombinant whooping cough vaccine". Infection and Immunity 58:3653-3662.

39. P. Chong, S. Cockle, H. Boux, and M. Klein. (1991) " Purification and Characterization of HPLC-Purified pertussis Toxin Subunits". Biochem. and Cell Biology 69:336-340.
40. P. Chong, M. Sydor, G. Zobrist, H. Boux, and M. Klein (1991). " Structural and Functional Analysis of the S1 subunit of Pertussis Toxin Using Synthetic Peptides". Molecular Immunology 28:239-245.
41. L. Tan, R. Fahim, G. Jackson, K. Philips, P. Wah, D. Alkema, G. Zobrist, P. Chong, M. Klein, and J. Vose (1991). " A Novel Process For Preparing An Acellular Pertussis Toxin and Filamentous Hemagglutinin". Molecular Immunology 28:251-255.
42. D. Martin, R. Munson, S. Grass, P. Chong, G. Zobrist, J. Hamel, B. Brodeur, and M. Klein. (1991) "Mapping of B-cell Epitopes on the OMP P2 Porin protein of H. influenzae by using Recombinant Proteins and Synthetic Peptides". Infect. Immun. 59:1417-1422.
43. R. Munson, Jr., B. Brodeur, P. Chong, S. Grass, D. Martin, and C. Proulx. (1992) "Outer Membrane Proteins P1 and P2 of H. influenzae Type b: Structure and Identification of Surface-Exposed Epitopes". J. Infect. Dise. 165:S86-89.
44. J. Hamel, D. Dugourd, D. Martin, C. Proule, P. Chong and B. Brodeur. (1992) " Localization of Conserved Antigenic Structure among Encapsulated and Non-encapsulated H. influenzae P2 Porin Protein Using Synthetic Peptides". J. of Gen. Microbiol. 138:161-168.
45. B.R. Brodeur, J. Hamel, D. Martin and P. Chong. (1992) "Synthetic peptides and anti-idiotypic antibodies as immunogens for the induction of an antibody response to Haemophilus influenzae serotype b". J. of Infectious Diseases. 185(S1):162-164.
46. P. Chong, G. Zobrist, Y-P. Yang, R. Fahim, C. Sia, B. Tripet, Y. Choi and M. Klein. (1992) "Mapping of the Immunodominant B- and T-cell Epitopes of the Outer Membrane Protein P1 of H. influenzae tpye b Using Overlapping Synthetic Peptides". In proceeding of the 12th American Peptide Symposium. Peptides: Chemistry, structure and biology. pp697-698. Eds. by J. Smith and J.E. Rivier. Escom Leiden.
47. P. Chong, G. Zobrist, C. Sia, S. Loosmore and M. Klein (1992). "Identification of T- and B-cell Epitopes of S2 and S3 Subunits of Pertussis Toxin by Use of Synthetic Peptides". Infection and Immunity. 60:4640-4647.
48. R. E. Harkness, P. Chong and M. Klein. (1992) " Identification of two iron-response Periplasmic Proteins in H. influenzae. J. Gen. Microbiol. 174:2425-2430.
49. A.A. Kandil, N. Chan, P. Chong and M. Klein. (1992) "Synthesis of fragment of the capsular polysaccharide of Hib on soluble polymer support". SynLetter. 9:555-557.

50. C. Proulx, J. Hamel, P. Chong, D. Martin, and B.R. Brodeur. (1992) "Epitope analysis of an immunodominant domain of the P1 of H. influenzae type b using synthetic peptides and anti-idiotypic antibodies. Microbiol. Pathogenesis. 12:433-442.
51. L.D. Heerze, P.C.S. Chong and G.D. Armstrong (1992). "Investigation of the Lectin-like Binding Domains in Pertussis Toxin Using synthetic Peptides Sequences. Identification of a Sialic Acid Binding site in the S2 Subunit of the Toxin. J. Biol. Chem. 267:25810-25815.
52. P. Chong, G. Zobrist, B. Tripet, Y. Choi, M. Sydor, D. Sia, R. Fahim, and M. Klein (1993). "Mapping of the immunodominant linear B-cell epitope of the outer membrane protein P2 of H. influenzae type b Using Overlapping Synthetic Peptides". Infection and Immunity. 61:2652-2661.
53. H. Panezutti, O. James, R. Harkness, E. Hansen, Y. Choi, M. Klein and P. Chong (1993). " Identification of the surface-exposed B-cell epitopes recognized by a Hib P1-specific monoclonal antibodies". Infection and Immunity. 61:1867-1872.
54. S.Loosmore, G. Zealey, S. Cockle, H. Boux, P. Chong, R. Yacoob and M. Klein (1993). "Characterization of Pertussis Toxin Analogs Containing Mutations in the B Oligomer Subunits". Infection and Immunity. 61:2316-2324.
55. P. Chong, G. Zobrist, Y-P. Yang, C. Sia, B. Tripet, Y. Choi and M. Klein. (1994) "Mapping of the Immunodominant B- and T-cell Epitopes of the Outer Membrane Protein P6 of H. influenzae tpye b Using Overlapping Synthetic Peptides". In proceeding of the 13th American Peptide Symposium. Peptides: Chemistry, structure and biology. pp730-731. Eds. by R.S. Hodges and J. Smith. Escom Leiden.
56. F.S. Flack, S. Loosmore, P. Chong and W.R. Thomas. (1995) "Sequence of the Mr 80K D15 protective surface antigen of H. influenzae". Genes. 156:97-99.
57. P. Chong, Y-P, Yang, D. Persand, M. Haer, B. Tripet, E. Tam, D. Sia, and M. Klein. (1995) "Idendification of the immunodominant T- and B-cell epitope of the outer membrane protein P1 of H. influenzae type b". Infection and Immunity. 63:3751-3758.
58. S. Loosmore, R.K. Yacoob, G.R. Zealey, G. Jackson, Y-P. Yang, P. Chong, J.M. Shortned, D.C. Coleman, J.D. Cunningham and M.H. Klein. (1995) "Hybrid genes overexpress pretactin from Bordetella pertussis" Vaccine. 13:571-580.
59. S.M. Loosmore, D.C. Sauer, J.M. Shortreed, D.X. England, R.E. Harkness, P. Chong and M. Klien (1996). "Cloning and expression of the H. influenzae transferrin receptor genes". Mole. Microbiol. 19:575-586.
60. A.A. Kandil, N. Chan, M. Klein and P. Chong (1997). "Chemical synthesis of Haemophilus influenzae glycopeptide conjugates." Glycoconjugate Journal.

14:13-17.

61. Y-P. Yang, L.E. Myers, U. McGuinness, P. Chong, Y. Kwok, M.H. Klein and R.E. Harkness (1997). "The major outer membrane protein, CD, extracted from Moraxella catarrhalis is a potential vaccine antigen that induces bactericidal antibodies". FEBS Immunol. Med. Microbiol. 17:187-199.
62. Y-P. Yang, R.S. Munson, S. Grass, P. Chong, R.E. Harkness, L. Gisonni, O. James and M.H. Klein. (1997) " Purification of a recombinant non-fatty acylated form of the P6 protein from H. influenzae and comparsion with its native counter part". Vaccine 15:976-987.
63. Y-P. Yang, W.R. Thomas, P. Chong, S. Loosmore and M.H. Klein. (1998) "A 20kDa N-terminal fragment of D15 protein contains protective epitope(s) agaisnt Haemophilus influenzae type b" Infection and Immunity 66:3349-3354.
64. R.-P. Du, Q.Wang, Y-P. Yang, A.B. Schryvers, P. Chong, M.H. Klein and S. Loosmore (1998). "Cloning and expression of the Moraxella catarrhalis lactoferrin receptor genes". Infection and Immunity 66:3656-3665.
65. P. Chong, O. James, Y-P. Yang, C. Sia, S. Loosmore, D. McLeod and M. Klein (1999). "Mapping of the immunodominant B- and T-cell epitopes of the outer membrane protein D15 of H. influenzae type b using overlapping synthetic peptides". In proceeding of the 15th American Peptide Symposium. Peptides: Chemistry, structure and biology. Eds. by J. Tam and P.T.P. Kaumaya. Escom Leiden. pp787-788.

P. Chong, N. Chan, O. Jasmes and M. Klein. "A novel glycoconjugate containing four S. pneumococcal oligosaccharides covalently linked to tetanus toxoid". Submitted to J. Glycoconjugates.

Vaccine Technology

66. P. Chong, M. Sydor, E. Wu, and M. Klein. (1992) "Resin-Bound Synthetic Peptides: Use as Antigens and Immunogens". Molecular Immunology. 29:443-446.
67. H-S. Gao, B. Tripet, Y. Choi, M. Klein and P. Chong. (1992) "Enhancement of the Immune Response to Synthetic Viral Peptides Using the Multiple Antigenic peptide System". In proceeding of the 12th American Peptide Symposium. Peptides: Chemistry, structure and biology. pp699-700. Eds. by J. Smith and J.E. Rivier. Escom Leiden.
68. X. Li, F. Rock, L. Aarden, P. Chong, S. Cockle, A. Keating, H. Ziltener and M. Klein. (1993) " Structure-function analysis of the C-terminal segment of human IL-6". J. Biol. Chem. 288:22377-22384.

69. F.L. Rock, X. Li, P. Chong, N. Ida and M. Klein. (1994) "Roles of disulfide bonds in recombinant huamn IL-6 conformation". Biochemistry 33:5146-5154.
70. P. Chong, C. Sia, B. Tripet, O. James and M. Klein (1996). "Comparative immunological properties of enantiomeric peptides". Letters in Peptide Sci. 3:99-106
71. P. Chong, A. Kandil, B. Tripet, N. Chan and M. Klein. (1997) " A strategy for rational design of fully synthetic glycopeptide conjugate vaccine". Infection and Immunity 65:4918-4925.

K. Sokoll, H. Pszczolko, M. Klein and P. Chong. " An expeditious synthesis of a novel copolymer derived from alpha-hydroxy acid and amino acid precursors". Submitted to Marcomolecules.

K. Sokoll, H. Pszczolko, P. Frank, Y-P. Yang, B. Underdown, M. Klein and P. Chong. "Encapsulation and release of vaccine candidates from novel targetable polymeric microparticles". Submitted to Infection and Immunity.

K. Sokoll, H. Pszczolko, P. Frank, Y-P. Yang, B. Underdown, M. Klein and P. Chong. " Encapsulation and release of vaccine candidates from novel targetable polymeric nanoparticles".
Submitted to Vaccine.

K. Sokoll, H. Pszczolko, P. Frank, Y-P. Yang, M. Klein and P. Chong. " Influence of copolymer properties on the formation and morphology of polymeric microspheres containing proteins". Submitted to J. Controlled Release.

With Outside Collaborators

72. P. Ala, P. Chong, V.S. Anaanthanarayanan, N. Chan and D.S.C. Yang. (1993) "Synthesis and characterization of a fragment of an ice nucleation protein". Biochem. Cell Biol. 71:236-240.
73. W-C. Hon, M. Griffith, P. Chong, D.S.C. Yang. (1994) "Extraction and isolation of antifreeze proteins from winter rye leaves". Plant Physiol. 104:971-980.
74. R. Bischoff, Y. Cordier, U.B. Rasmussen, Y. Schlesinger, C. Gachet, M. Jaquinod, B. Tripet, P. Chong and A. Pavirani. (1994) "Synthesis and characterization of photoactivatable peptide agonists of the human thrombin receptor". FEBS Letters 349:301-306.
75. P. Chong, L.D. Heerze, G.D. Armstrong and M. Klein. (1994) "Synthetic peptides

for the development of pertussis toxin receptor-targeted drugs". In proceeding of the 13th American Peptide Symposium. Peptides: Chemistry, structure and biology. pp652-653. Eds. by R.S. Hodges and J. Smith. Escom Leiden.

76. L. Zhang, M. Yang, P. Chong and S.S. Mohapatra (1996). "Multiple B- and T-cell epitopes on a major allergen of Kentucky Blue grass pollen". Immunology 87:283-290.

77. M. Yang, Y.Y. Wang, L. Zhang, P. Chong and S.S. Mohapatra (1996). "Host genetic and adjuvant factors influence epitope specificity to a major recombinant grass allergen". Int. Arch. Allergy Immunol. 111:173-181.

78. Parronchi, P., Mohapatra, S., Sampognaro, S., Giannarini, L., Wahn, U., Chong, P., Maggi, E., Renz, H., and Romagnani, S. (1996): Effects of interferon-alpha on cytokine profile, T cell receptor repertoire and peptide reactivity of human allergen-specific T cells. Eur J Immunol, 26:697-703.

Publications Since Joining NHRI in June /2003

1. Szu-Chia Lai, Pele Choi-Sing Chong, Chia-Tsui Yeh, Levent Shih-Jen Liu, Hsiang-Yun Chi, Jia-Tsrong Jan, Hwan-Wun Liu, Ann Chen, Yeau-Ching Wang. Characterization of Neutralizing Monoclonal Antibodies Recognizing a 15-residues Epitope on the Spike Protein HR2 Region of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)", (2005) Journal of Biomedical Sciences. 12(5):711-727.
2. Chia-Ya Chang, Willy W.L. Hong, Pele Chong, and Suh-Chin Wu. "Influence of Intron and Exon splicing Enhancers on Mammalian Cell Expression of a Truncated Spike Protein of SARS-CoV and Its Implication for Subunit vaccine Development". Vaccine 24(2006))1132-1141.
3. Desmond Persad*, Souheil-Antoine Younes*,Cheryl M. Cameron, Alibdolai Danesh, Mark J. Cameron, Alyson A. Kelvin, Wayne Gold, Margaret Herridge, 1Elizabeth Phillips, Marie Louie, Barbara D. Mederski, Linda Dresser, Barbara M. Willey, Mary Latchford, Mona R. Loutfy, Donna I. McRitchie, Gregory P. Downey, Matthew P. Muller, Shaf H. Keshavjee, JoAnne E. de Jager, Susan Richardsn, Tony Mazzulli, Donald E. Low, Anita R. Rachlis, Andrew E. Simor, Mark Loeb, Allison J. McGeer, James Mahoney, James Brunton, Janna S. Chamberlin, Camille Johnson, Lori R. Lofaro, Pele Chong, Kurtis R. Bray, Rafick-Pierre Sekaly, and David J. Kelvin "Identification of immunodominant human T cell epitopes of the SARS-CoV Nucleocapsid Protein" Accepted for publication in Journal for Experimental Medicine
4. Shih-Jen Liu, Chih-Hsiang Leng, Shu-pei Lien, Hsiang-Yun Chi, Chung-Yi Huang,

Chang-Ling Lin, Wei-Cheng Lian, Chi-Ju Chen, Shie-Liang Hsieh, and Pele Chong "Immunological Characterizations of the Nucleocapsid Protein Based SARS Vaccine Candidates". Vaccine 24 (2006)3100-3108.

5. Hui-Wen Hsiao, Pele C-S, Chong, Chi-Ju Chen, Yi-Rong Chen, Vanessa B-Y, Chuang, Shu-Pei Lian, Lucy C-L Lin, Eve Ho, Wei-Cheng Lian, Yi-Ping Shih, Yi-Ming Arthur Chen, and Shie-Liang Hsieh. Identification of the Receptors and their Respective Binding-Domains of SARS Coronavirus Spike Protein. Submitted to Journal of General Virology

MANUSCRIPTS IN PREPARATION (Aventis Pasteur has no publication policy since 1998)

1. H.Boux, M. Makinen, L. Gucciardi, S. Loosmore, P. Chong, S. Cockle, and M. Klein. " Structure-Function Relationship of Pertussis Toxin As Delineated Through The Use of Monoclonal Antibodies".
2. P. Chong, C. Sia and M. Klein. "Construction of Synthetic Immunogens using Define T and B-cell Epitopes of Human Immunodeficiency Virus Type 1 (HIV-1): 1. Structure-Function Characterization of a p24 T-cell Epitope."
3. B. Caplan, J. Caterini, H. Boux, P. Chong, G. Zobrist, B. Barber, and M. Klein. " Enhancement of Immunity and Immunotargetting by IgG2a Monoclonal Antibodies".
4. P. Chong, E. Wu, and M. Klein. "Studies on the Sites of Interaction Between HIV-1 gp120 and CD4 Using Synthetic Peptides".
5. R.A. Bonnah, P.C.S. Chong, and G.D. Armstrong. "Examination of Pertussis toxin Binding to ceruloplasmin".
6. G. Jackson, P. Chong, L.Tan, R. Fahim, S. Cockle, H. Boux, and M. Klein. "Chemical detoxification studies of pertussis toxin".
7. P. Chong, Y. Choi, N. Chan, M. Sydor, G. Zobrist, and M. Klein. "Structural and Functional Analysis of S4 and S5 subunits of Pertussis Toxin Using Synthetic Peptides".
8. P. Chong, E. Wu, M. Sydor, and M. Klein. "Synthesis and Characterization of IgG Binding Domain of Protein G".
9. D. Sia, P. Chong, Y-P. Yang and M. Klein. " Identification of T-cell Epitope of the Outer Membrane Protein P2 of H. influenzae tpye b.
10. G. Jackson, R. Fahim, L. Tan, P. Chong, J. Vose, and M. Klein. "Purification of a pertussis outer membrane protein (OMP69)".
11. S. Loosmore, P. Chong, W. Thomas, and M. Klein. "Molecular cloning, expression, and primary sequence of outer membrane protein D15 of Haemophilus

influenzae".

12. Y-P. Yang, P. Chong, O. James, S. Loosmore and M. Klein. " Purification, Biochemical and Immunological Characterization of Recombinant D15".
13. R.S. Hodges, J. Pearlstone, P.C.S. Chong, and L.B. Smillie. " Periodicity of Hydrophobicity Parameters and a a-Helical Potential in the Tromyosin Sequence".
14. S. Loosmore, Y-P. Yang, P. Chong, R. Oomen, and M. Klein. "Analog of Haemophilus Hin47 with reduced protease activity".
15. S. Loosmore, P. Chong, Y-P. Yang, R. Harkness and M. Klein. "Use of Transferrin receptor and Its Peptides as Vaccine against Haemophilus influenzae".
16. Y. Kwok, S.P. Shi, A. Oliver and P. Chong. " Analyses of GMP-grade synthetic peptides by HPLC and HPCE".

PATENTS

1. L. Tan, R. Fahim, G. Jackson, K. Philips, P. Wah, D. Alkema, G. Zobrist, P. Chong, and M. Klein " A Novel Process For Preparing An Acellular Pertussis Toxin and Filamentous Hemagglutinin". US Patent #4,997,915 (1993).
2. C. Sia, P. Chong, and M. Klein. "Synthetic Peptides for an HIV-1 Vaccine". U.K. Patent No. 0470980 (1994).
3. G. Jackson, R. Fahim, L. Tan, P. Chong, J. Vose, and M. Klein. "Purification of a pertussis outer membrane protein (OMP69)". US Patent #5,444,159 (1996). European patent #EP0527753 (1997). US Patent#5,667,787 (1997). Canadian Patent#2,079,887 (1998).
4. R. Munson, S. Grass, P. Chong, R. Fahim, Y-P. Yang, P. McVerry, and M. Klein. "Synthetic Peptides of Outer membrane Protein P1 as vaccine component against Haemophilus influenzae". U.K. Patent 500576 (1996).
5. P. Chong, A. Kandil, and M. Klein. "A Fully Synthetic Glycopeptide H. influenzae conjugate Vaccine". US patent#5679352 (1997).
6. P. Chong, A. Tingle and S. Gillam. " Synthetic Peptides for an Rubella Vaccine". UK patent application WO9314206-A2, Australian patent #662954. US patent3 6037448.
7. P. Chong, S. Loosmore, W. Thomas, Y-P. Yang and M. Klein. "Use of Outer Membrane Protein D15 and Its Peptides as Vaccine against Haemophilus influenzae". US Patent# 6083743..
8. S. Loosmore, Y-P. Yang, P. Chong, R. Oomen, and M. Klein. "Analog of Haemophilus Hin47 with reduced protease activity". US patent #5506139 (1996), #5656436 (1997), #5869302 (1999), #5939297 (1999).
9. S. Loosmore, P. Chong, Y-P. Yang, R. Harkness and M. Klein. "Use of Transferrin

receptor and Its Peptides as Vaccine against Haemophilus influenzae". US patent #5708149 (1997)..

10. P. Chong, A. Kandil, O. James and M. Klein. "Potent Immunomodulators Formulation". US patent #5837250 (1998).
11. C. Sia, P. Chong and M. Klein. "Tandem Synthetic HIV-1 peptides" US patent#5639854 (1997). US patent #5759769 (1998). US patent #5795955 (1998). US Patent #5800822 (1998). US patent #5817318 (1998), US patent #5876731 (1999).
12. A.A. Kandil, P. Chong, and M. Klein. " A Neisseria meningitidis capsular polysaccharide conjugate." US patent #5780606 (1998); # 6,080,589 (2000)
13. S. Loosmore, R. Harkness, A. Schryvers, P, Chong, S. Gray-Owen, Y-P. Yang, A. Murdin and M.H. Klein. H. infleunzae transferrin binding protein. US patent#5922562, #5922841 and 5922323(1999), .
14. P. Chong, and M. Klein. " A novel process for preparation of multivalent glycoconjugates against cancer." US Patent is filed.
15. A.A. Kandil, P. Chong, and M. Klein. " New glycosamides useful as immunomodulators." US Patent #6,290,971..
16. K. Sokoll, P. Chong, and M. Klein. " The preparation of sub-micron targetable polymeric particles and application to the delivery of vaccines." US Patent#6,228,423.; 6,312,732.
17. K. Sokoll, D. Gravett, P. Chong, and M. Klein. " Targetable biodegradable polymeric particles for vaccines delivery." US Patent #6,471,996.
18. P. Chong, Alf Lindberg and Michel Klein. "Novel multi-oligosaccharides glycoconjugate bacterial meningitis vaccines." Patent application is filed to US PTO.
19. L.W. Riley and P. Chong. " Isolated DNA molecules from Mycobacterium tuberculosis - useful as a method of vaccinatin, for passive immunization, for the detection of M. tuberculosis and as a method of drug delivery". US PTO # 689411 and WO9805784-A1.
20. K. Sasaki, R. Harkness, S. Loosmore, P. Chong and M. Klein. "New outer membrane protein of a Moraxella catarrhalis strain-useful as an immunogenic composition for treatment and prevention of otitis media". US Patent #5808024.
21. P. Chong, D. Burt, M. Ewasyshyn and M. Klein. "Synthetic peptides for Respiratory Syncytical Virus vaccine that induce cytotoxic T-lymphocytes in vivo". Patent application is filed to US PTO.
22. C. Sia, P. Chong, A. Pedyczak and M. Klein. "HLA-A0201 binding and immunogenic peptides of prostatic specific membrane antigen (PSMA) and prostate specific antigen (PSA)". Patent application is filed to USPTO.

23. P. Chong, F-L. Yao, C. Sia, A. Pedyczak, B. Rovinski and M. Klein. " A plasmid expressing multiple MHC class I restricted epitopes of HIV. Patent application is filed to USPTO
24. C. Sia, P. Chong, A. Pedyczak and M. Klein. "HIV-specific cytotoxic T-cell responses against rev protein". ". PCT/CA99/00287.
25. E. Pai, P. Chong, A. Pedyczak and M. Klein. "Fab'-epitope complex from HIV-1 cross-neutralizing monoclonal antibdoy 2F5". US Patent #6,482,928
26. R. S. Munson, Jr. R. Tolan, P. Chong, R. Fahim, P.McVerry and M. Klein. " Membrane proteins and ppetides of H. influenzae type b. US patent #5916562.
27. P. Chong and E. Hsieh. "Identification of the High affinity Binding domain of S protein and its utilities of vaccines and immunotherapeutic against SARS CoV infections, and diagnostic kits for detecting SARS CoV in a sample". Submitted to US PTC Jan/2004. #60/535641
28. P. Chong, D. Kelvin, and M Klein. "SARS N Protein Epitopes Mapping and their utility thereof." April/2004. #86363-6
29. 王有欽, Yeau-Ching Wang (NDMC). 賴思佳, Szu-Chia Lai (NDMC), 萊嘉翠, Chia-Tsui Yeh (NDMC)' Pele Choi-Sing Chong (NHRI) and Levent Shih-Jen Liu (NHRI). "Synthetic Peptides for Severe Acute Respiratory Syndrome (SARS) Vaccine and Diagnostic kits Development" . Submitted to US PTC July/2004

MEMBERSHIP

1. American Peptide Society
2. American Microbiology Society
3. Society of Chinese Bioscientists in America
4. Canadian Biochemical Society
5. Controlled Release Society, Inc.
6. American Association of Pharmaceutical Scientists

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Education

BS. School of Pharmacy, College of Medicine, National Taiwan University, Taiwan,1985
M.D. Medical College of National Yang-Ming University,Taiwan, 1991
M.P.H. Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taiwan, 1998

Certifications

Certified Pharmacist, National Certification, Taiwan, 1985
Certified Medical Doctor, National Certification, Taiwan, 1991
Board Certified Pediatric Specialist, Taiwan Pediatric Association, Taiwan, 1994

Professional experience

Since July 2002	Medical reviewer, Division of Clinical Sciences in CDE
Oct. 1996-July 2002	Attending Physician, Pediatric Department of Taipei City Hospital
Oct. 1994-Sep. 1996	Division Head, Zhongzheng District Health Center, Taipei City
July 1993-Oct. 1994	Chief Resident, Pediatric Department, National Taipei College of Nursing Hospital
July 1991-June 1993	Resident, Pediatric Department of Taipei Veterans General Hospital

Research

Jan. 1995-Dec. 2000	Principal Investigator, Physical heights of children with prolonged low dose-rate γ-radiation exposure in radiocontaminated buildings in Taiwan. National Health Research Institutes Grant Project
Dec. 1998-Jan. 2000	Research Fellow in Endocrinological Division of Pediatric Department, National Taiwan University Hospital
Jan. 2006- present	Co-principal Investigator, The establishment of regulatory guidelines for clinical trials on new-strain influenza vaccine in Taiwan. Grant Project of Center for Disease Control, Taiwan.

Publications

1. Wang JC, et al. Systemic adenovirus infection. Acta Paediatrica Taiwanica 1992; Vol. 33, Suppl. C.
2. Wang JC, et al. Frequencies of basal physical status assessment in elementary schools in Taipei County. Acta Paediatrica Taiwanica 1995; Vol. 36, Suppl. B.
3. Wang JC, Wang LA, Lin BM, Hou SW, Chang WP. Evaluation of health effects on the children with prenatal overexposure in radioactive buildings in Taiwan. In the International Congress of Radiation Research (ICRR10) meeting, Wurzburg, Germany, 1995.
4. Wang JC, Chang SH, Chien YC, Dong CH, Laio YB, Teng RJ, Chang WP. Evaluation on body height in children grown up in buildings with elevated Radioactivity in Taiwan. Epidemiology. 1997; 8 (4) Suppl: S81.
5. Wang JC, Chang WP, Wang JD, Chang SH, Chen KC, Hwang JS. Evaluation of physical growth in children with chronic excessive γ-radiation exposure. Acta Paediatrica Sinica. 1998; 39 Suppl A: 133-134.
6. Jung-Chun Wang, Wushou P. Chang, Jung-Der Wang. The effects of excessive radiation exposure on the growth of children. Chinese Journal of Public Health. 1999; Vol.18 (1): 3-12.
7. Wang JC, Chang WP, Wang D, Guo HR. The Feasibility of using photographs to estimate historical heights of children. Acta Paediatrica Taiwanica. 2000; Vol. 41, No.3:136-139.
8. Wang JC, Lin YP, Hwang JS, Hsieh WH, Tsai YJ, Chang WP. Physical heights of children with prolonged low dose-rate γ-radiation exposure in radiocontaminated buildings. Int. J. Radiat. Biol. 2001; Vol. 77 (1):117-125.
9. JC Wang, Y-P Lin, S Hwang, WA Hsieh, J-C Chen, et al. Late haematological

changes in a population exposed to chronic low dose rate radiation during childhood. Chronic Irradiation: Tolerance and Failure in Complex Biological Systems. The British Institute of Radiology. 2002; p.44-49.

10. 王蓉君, 陳恆德, 朱夢麟. 醫藥品查驗中心於禽流感防疫中所扮演之角色. 台灣醫界雜誌 2006, Vol.49, No.3 p.40-42.
11. 王蓉君, 李明亮, 莊再成. 新型流感疫苗之臨床試驗. Acta Paediatrica Taiwanica. 2006; Vol. 47 Suppl. p.18-22 (in print).
12. 王蓉君, 朱夢麟, 陳恆德. 新疫苗法規科學現況之簡介. (submitted).

Development of Pandemic Influenza Vaccine

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Center for Biologics Evaluation and Research, FDA
Bethesda, MD U.S.A.

Pandemic and Seasonal Flu Vaccines

"Preparing for influenza pandemic is a top priority for U.S."
– said FDA Commissioner, Dr. Andrew von Eschenbach.
3/2/06

Two guidances; one for seasonal and the other for pandemic influenza vaccines.

- -- submitting clinical data to show safety and effectiveness.
- -- describe pathways for both traditional and accelerated approval approaches.
- -- using new technologies in adjuvants and different vaccine delivery method.

Influenza Viruses

1. Influenza viruses are enveloped RNA viruses, and are divided into 3 types.
   - -- Two types, Type A and B – cause yearly epidemic outbreaks of respiratory illness; further classified based on major external glycoproteins, HA and NA.
   - -- Type B viruses have a single HA and NA subtypes. In contrast, there are 15 HA and 9 NA Type A subtypes.
   - -- Since 1977, Type A viruses (H1N1, H3N2) and type B viruses have been in global circulation. Trivalent vaccines are formulated to prevent influenza illness caused the these viruses.

Pandemic Influenza Outbreaks

1. During 20th century, 3 pandemic influenza outbreaks occurred:
   - -- 1957 H2N2 and 1968 H3N2 subtype pandemic strains. genetic reassortant of 2 co-circulating viruses, from animal reservoir and human origin.
   - -- 1918-1919 subtype strain
     likely resulted form a series of genetic mutations in multiple genes in avian origin.
     the most lethal of 20th century, resulted in about 50 million deaths worldwide.

Avian Influenza Virus

1. Influenza H7N7, H9N2, an H5N1 subtype strains have been recovered from humans with influenza illness.
2. H5N1 strains are highly virulent with mortality of about 50% among clinical cases – Hong Kong in 1997.
3. Between 2003-05, H5N1 strains have mutated.
   Recent strains are more lethal in animal models and the host range has expanded into mammalian species.

Types of Pandemic Influenza Vaccines

1. "Split virus" and whole virus inactivated pandemic influenza vaccines propagated in embryonated chicken eggs.
2. Cell culture derived, recombinant hemagglutinin-based and adjuvanted pandemic influenza vaccines.
   - -- More antigen per dose and more than one dose are needed to elicit immune responses, compared to trivalent inactivated flu vaccine.
   - -- All influenza vaccines formulated with an adjuvant should be submitted as new products.

Dose and Formulation of Adjuvanted Vaccines

1. Immune response elicited by the adjuvanted antigen should be better than the same antigen alone.
   – HI Ab titer and seroconversion should be significantly higher, e.g. two-fold difference in GMT ratio ,
   HI Ab titer >= 1:40 (0.3 $\log_{10}$ mean difference).
2. Selection of dose and formulation should be guided by the safety profile of the formulation and regimen being studied.

Clinical Data to Support the Licensure

A. Pandemic influenza vaccine as a supplement to the trivalent influenza vaccine.
   1. Imunogenicity
   2. Safety

B. Accelerated approval of BLA for Pandemic influ vaccine.

C. Post-marketing studies
   1. Effectiveness
   2. Safety

Recently Licensed Influenza Vaccines

Vaccine	Tradename	Manufacturer	Approval date
Influenzae Virus	Fluarix	GSK	7/25/06
	Fluvirin	Chiron	7/21/06
	Fluzone	Sanofi Pasteur	7/10/06
(Intranasal)	FluMist	MedImmune	7/21/06

Influenza Virus Vaccine – Fluarix, GSK

1. Contains 45 mcg HA per 0.5 ml dose
   – Ratio of 15 mcg HA of each of following 3 strains:
   Type A H1N1, H3N2 and type B strains.
   – Formulated without preservatives.
2. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and B viruses have been in global circulation.
3. HI antibody titers of >= 1:40 have been associated with protection. Indicated for active immunization of adults. Annual vaccination is necessary.

Fluvirin – Chiron Vaccine Ltd

1. The virus is inactivated with betapropiolactone. Each 0.5 ml contains 15 ug each of HA of strains two type A and one type B (inactivated).
2. It is indicated for immunization against the influenza virus strains for persons of 4 yrs of age and older.
   – prevents influenza illness in 70-90% of adults aged, <65 yrs.

Fluzone – Sanofi Pasteur Inc

1. The virus is inactivated with formaldehyde, and then disrupted using nonionic surfactant, Triton X-100 producing a "split virus".
2. It contains 15 ug HA each of three strains: A (H1N1), A (H3N2), and B per 0.5 ml. Gelatin 0.05% is added as a stabilizer.
3. It is indicated for active immunization in subjects from 6 months of age and older. ACIP recommends for persons aged >= 65 yrs, and other high risk population.

FluMist – MedImmune; Live, Intranasal

1. Each 0.5 ml dose contains $10^{6.5-7.5}$ $TCID_{50}$ A (H1N1), A (H3N2) and B stains. These strains are:
   - -- cold-adapted; they replicate efficiently at 25° C.
   - -- temperature sensitive; restricted at 37-39° C.
   - -- attenuated
2. It is a genetic reassortant of a Master Donor Virus (MDV) and a wild-type influenza virus. It does not contain any preservative.
3. Serum Abs, mucosal Abs, and influenza-specific T cells may play a role in prevention and recovery from infection.
4. It is indicated for immunization of 5-17 yrs children, and 18-49 yrs of age.

Clinical evaluation of vaccines for pandemic influenza

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U.S. Food and Drug Administration
Center of Biologics Evaluation and Research
Office of Vaccine Research and Review

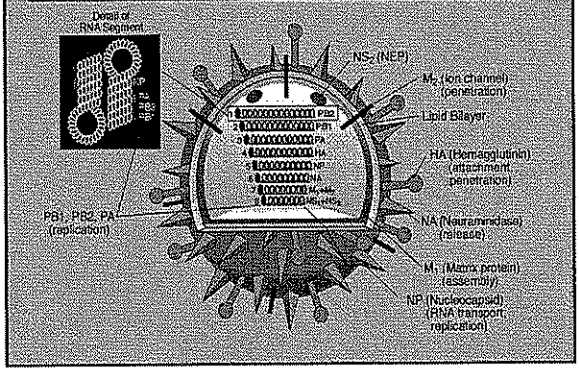
1

Outline

- Introduction
  - Influenza A + B virus
- Background
  - 1918 Pandemic
  - Pandemic Threat of Avian Influenza Virus
- Pandemic Preparedness
- Guidance for Industry

2

Proteins and RNA's of Influenza A Virus



3

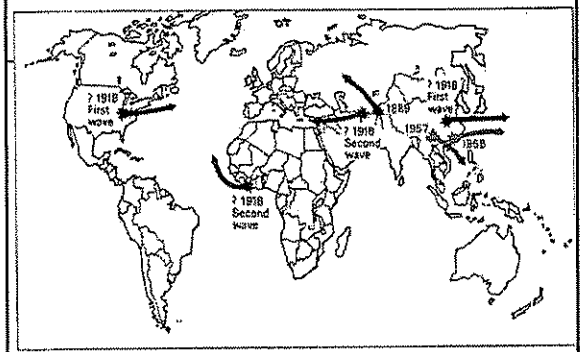
Introduction

- Type A and B influenza variant strains
  - Point mutation in viral genome that result in small changes in HA and NA glycoprotein structure
  - Reassortment between two co-circulating strains

4

1918 Influenza pandemic

5



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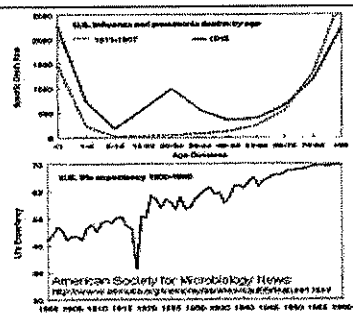
1918 Influenza pandemic



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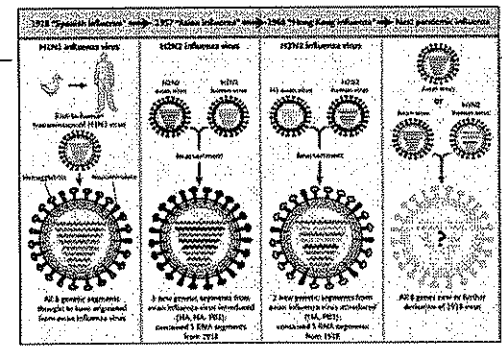


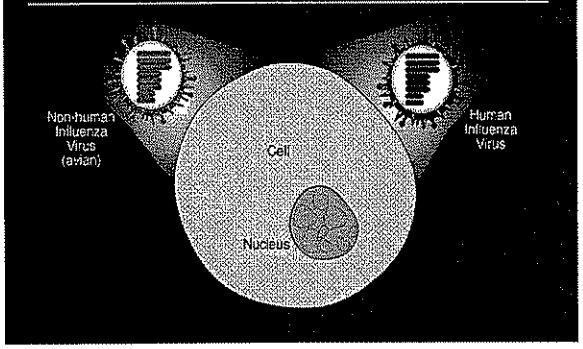
NEJM 2005;353:2209-2211

8

- Pandemic Threat of Avian Influenza Viruses

9

Generation of New Pandemic Virus by Gene Exchange: Antigenic Shift



Examples of Transmission of Avian Influenza Viruses to Humans*

Year and Country	Virus	Designation
1997, Hong Kong	H5N1	A/HK/156/97
		A/HK/483/97
2003, Hong Kong	H5N1	A/HK/213/03
2003, Hong Kong	H9N2	A/HK/2018/03
2004, Thailand	H5N1	A/Thai/16/04
2004, Egypt	H10N7	NA

* H5 and H9 viruses have generally been associated with respiratory disease, whereas H7 has generally been associated with conjunctivitis. NA denotes not available.

NEJM 2005;353:2209-2211

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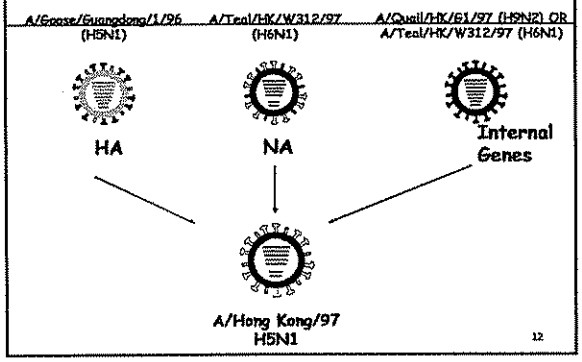
ORIGIN OF THE HONG KONG H5N1 VIRUSES



12

H5, H7 and H9 infections

- Concomitant outbreaks of H5N1 and H7N7 disease occurred in poultry and viruses isolated from humans and birds were genetically identical.
- Avian influenza viruses can infect humans directly without reassortment or passage through an intermediate host.
- Avian influenza virus infections can be similar to those caused by human influenza viruses; virologic surveillance is necessary to identify such infections.
- Viruses with different genotypes and antigenicity will appear in nature as the viruses circulate in aquatic birds.

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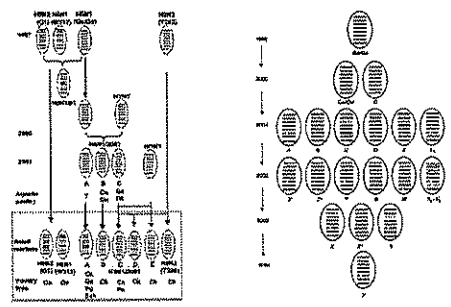
Emergence of Multiple Genotypes of H5N1 Avian Influenza Viruses in China



PNAS 99: 8950-8955, 2002

Nature 430: 209-213, 2004

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Changes in H5N1 viruses 1997-2004

- Reassortment leading to new genotypes
- Evidence of antigenic drift
  - due to selection pressure of vaccine or naturally acquired immunity OR
  - HA derived from variants in the community
- Resistance to adamantanes
- Virulence for wild birds, first seen in 2003
- Virulence for ducks and ferrets
- Virulence for cats, leopards and tigers
- Longer survival in the environment
- Now endemic in poultry

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Prerequisites for the Start of a Pandemic

- Isolation from humans of a novel subtype of influenza, to which the general population has little or no immunity.
- Demonstrated ability of the virus to replicate and cause disease in humans.
- Efficient spread from person-to-person, expressed as sustained chains of transmission causing community-wide outbreaks.

Potential Social and Economic Impact of an Influenza Pandemic

- Mathematical model* estimates for first year of a pandemic in absence of effective interventions:
  - 89,000 - 207,000 deaths in the U.S.
  - 314,000 - 734,000 hospitalizations
  - 18 - 42 million outpatient visits
  - additional 20 - 47 million illnesses
  - economic impact: $71- $166 billion
- Modeling based on 1968 pandemic** project excess deaths worldwide 2-7.4 million

*Meltzer et al. Emer Infect Dis 1999; 5:659-71
** WHO Report on Avian Influenza: assessing the pandemic threat, 2005

17

Elements of Pandemic Preparedness

- Virologic and disease surveillance in humans and animals
  - WHO global network for human influenza
  - WHO animal influenza network
- Plan for stockpiling and rational use of antiviral agents
  - Antineuraminidase drugs (Oseltamivir, Zanamivir)
  - Adamantanes (Rimantadine, Amantadine)
- Vaccines: library of reassortant viruses, improve production methods, allocation and distribution, alternative substrates
- Emergency plans to deal with community disruption and increased demand for medical services
- Guidance document: facilitate and expedite the licensure of influenza vaccines for the prevention of disease caused by pandemic influenza viruses.

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Guidance for Industry:

Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines

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Guidance for Industry: **Clinical Data Needed for Licensure of Pandemic Influenza Vaccines**

- Types of pandemic influenza vaccines
  - "split virus" and whole virus inactivated vaccine propagated in embryonated chicken eggs
  - cell-culture derived, recombinant hemagglutinin-based protein
  - adjuvanted vaccines
  - live attenuated vaccine
- Does not apply to influenza vaccines that do not contain a hemagglutinin component

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Pandemic Influenza

- Use existing mechanisms for current licensed influenza vaccines
  - Existing U.S. inactivated TIV vaccine + same manuf process
  - Existing U.S. live, attenuated seasonal vaccine + same manuf. Pr.
  - New pandemic influenza vaccine
    [no existing license for seasonal vaccine and/or new manuf. Pr.]

21

Accelerated Approval of Licensure

22

Influenza vaccine [Fluarix®]

Split Virus Inactivated Vaccine, Trivalent

- Composition
  - 15 µg of each H1N1, H3N2, B antigens
  - Contains "trace" amounts of thimerosal
    - <2.5 µg/0.5ml dose
  - Adjuvant free
- Dose
  - 0.5 ml for adults and children >36 months of age
  - 0.25 ml for children 6-36 months of age
- Marketed for use in over 78 countries

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Influenza vaccine [Fluarix®]: Regulatory Timeline

Sept. 17, 2004	pre-IND request
Oct. 5, 2004	US shortage
Nov. 19, 2004	pre-IND meeting
Dec. 1, 2004	IND submitted: Fluarix US-001
Dec. 2, 2004	FDA review comments provided
Dec. 8, 2004	final protocol submitted
Dec. 20, 2004	enrollment completed
May 27, 2005	BLA filed
Aug 31, 2005	BLA approved

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Influenza vaccine [Fluarix®]

- European clinical data: previous human experience
  - **1992 European registrational study**
  - **European study in geriatric population**
    Fluarix™ in one study group (age > 60y)
  - Young adults: supportive safety data, SAEs
  - Geriatric indication (≥65y): safety and immunogenicity
- U.S data
  Study FluarixUS-001: Controlled trial using immune response endpoint in adults 18-64 years old
- **Safety database accelerated approval: N~1400**
- Post-marketing study: Clinical endpoint efficacy trial in U.S.

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Licensure Approach:
Existing seasonal TIV vaccine, same manufacturing process

If existing U.S. Licensed TIV vaccine + same manufacturing process used for devmt of pandemic influenza vaccine
- Clinical trials to support dose and dosing regimen, immunogenicity and safety
- Protocol proposal for post-licensure field trial [in the event of pandemic influenza situation]
- Indication: adults, including geriatric population
- BLA w/ cross-reference to manufacturing process
- Change in subtype submitted as manufacturing supplement (clinical data not necessary)

26

Cont. Licensure of Inactivated Pandemic Influenza Vaccine

- Rationale for BLA (vs. BLA supplement to TIV licensed vaccine)
  - Trade name and package insert for pandemic influenza vaccine that is separate from seasonal influenza vaccine
  - Categorical VAERS adverse event reporting and collection in the event of parallel distribution of pandemic and seasonal influenza vaccines
  - Change in subtype submitted as manufacturing supplement to the license for pandemic influenza vaccine
  - Change in subtype for seasonal vaccine submitted as manufacturing supplement to the license for seasonal influenza vaccine

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Cont. Licensure of Inactivated Pandemic Influenza Vaccine

Licensure approach
- Demonstration of immunogenicity
  - Hemagglutination inhibition (HI) antibody
- Primary endpoint: seroconversion rate
  - Pre-vaccination HI titer <1:10 and post-vaccination titer ≥ 1:40
  - Pre-vaccination HI titer ≥1:10 and a ≥4-fold increase in HI antibody titer post-vaccination

  Other endpoints: geometric mean titer (GMT)
- Hemagglutination inhibition (HI) antibody assay
  - Validation
  - Use of suitable assay control

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Cont. Licensure Approach:
Existing seasonal TIV vaccine, same manufacturing process

- Demonstration of safety
  - Sequential approach: adults, then pediatric population
  - Detailed safety data
    - Solicited local and systemic reactions
    - Unsolicited adverse events
    - Serious adverse events (SAE)
    - Visit / telephone call 6m following last vaccination
      - Additional SAEs
      - Occurrence of new onset chronic illness

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Licensure Approach for Live, Attenuated Pandemic Influenza Vaccine

If existing U.S. licensed live attenuated seasonal Influenza vaccine + same manufacturing process
- Same requirements for demonstration of safety and immunogenicity as for existing TIV vaccine + same manuf process

Additional safety considerations:
- Inpatient location
- Evaluation for amount and duration of shedding
- Instructions for contact precautions for patients and study personnel
- Instructions for evaluation by study personnel in the event of influenza illness symptoms thought to be due to the vaccine strain. Empiric treatment with antiviral agent pending culture results.

Indication: only for use after the onset of a pandemic influenza outbreak

30

Licensure Approach:
No existing license for seasonal vaccine/ new manuf process

- Accelerated approval for licensure
  - Improvement, compared to existing available treatments, for serious / life-threatening illness
  - Clinical trial based on surrogate endpoint
  - Post-licensure trial to verify surrogate and clinical benefit

31

Licensure Approach:
No existing license for seasonal vaccine/ new manuf process

- New inactivated pandemic influenza vaccine
  - Manufacturing methods and product testing
  - Rationale for dose and dosing regimen (adjuvant)
  - Clinical trial based on immune criteria: HI antibody response
- If no U.S. licensed pandemic influenza vaccine exists
  - Co-primary endpoints:
    - Upper limit of the 2-sided 95% confidence interval on the GMT ratio ($GMT_{\text{U.S. licensed vaccine}}$/ $GMT_{\text{new vaccine}}$) >1.5
    - Upper limit of the 2-sided 95% confidence interval for the difference in seroconversion rate <10%

32

Licensure Approach:
No existing license for seasonal vaccine/ new manuf process

- New inactivated pandemic influenza vaccine
  - Manufacturing methods and product testing
  - Clinical trial based on immune criteria: HI antibody response
    - Control group: placebo
    - Endpoints: lower limit of the confidence interval for seroconversion rate >30-40% and seroresponse (%≥1:40) rate ≥60-70%
    - Control group: U.S. licensed pandemic inf vaccine
    - Non-inferiority comparison
    - Co-primary endpoints:
    - Upper limit of the 2-sided 95% confidence interval on the GMT ratio ($GMT_{\text{U.S. licensed vaccine}}$/ $GMT_{\text{new vaccine}}$) >1.5
    - Upper limit of the 2-sided 95% confidence interval for the difference in seroconversion rate (% licensed-% new) <10%

33

Licensure Approach:
No existing license for seasonal vaccine/ new manuf process

- Cont. new inactivated pandemic influenza vaccine

Safety database
- Rule out serious adverse event occurring at 1/300
- Novel process or adjuvanted pandemic vaccines: dependent on nature of manuf process and available clinical data, respectively

Lot consistency
- Primary endpoint: GMT
- Secondary endpoint: seroconversion rate

Post-marketing commitment
- Confirmatory study to confirm clinical benefit

34

Licensure Approach:
No existing license for seasonal vaccine/ new manuf process

- New live attenuated pandemic influenza vaccine
  - Manufacturing methods and product testing
  - Dependent on identification of an immune correlate
  - Safety database
  - Lot consistency
  - (Post-marketing clinical efficacy trial [if correlate identified])

35

Licensure Approach:
No existing license for seasonal vaccine/ new manuf process

- Other considerations
  - ✓ Adjuvanted formulation
  - Pre-clinical/ previous human experience data supporting benefit of an adjuvant
  - Clinical effectiveness data with unadjuvanted formulation not necessary
  - ✓ Pediatric indication- required under Pediatric Research Equity Act (PREA)

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Questions/Discussion points

- Vaccine R & D Consultations in CDE, Tw

  Pandemic influenza
  - Adjuvant for H5N1 mock-up vaccine
  - Cell substrate for H5N1 mock-up vaccine

  Seasonal influenza
  - LT Mucosal adjuvant for nasal influenza vaccine
  - Adenovirus-vectored influenza vaccine

37

新型流感疫苗查驗登記之審查注意要點

(草稿)

財團法人醫藥品查驗中心，台灣

民國 95 年 8 月 28 日

全球大流行性感冒(Pandemic influenza) 可能發生於任何季節，疫苗將是最主要之預防措施，而疫苗之發展及應用速度乃是防疫措施之關鍵步驟。爲了加速疫苗之研發及查驗登記，吾人參考歐盟(EMEA)針對新型流感疫苗（Pandemic influenza vaccine）快速查驗登記之原則【**CPMP/VEG/4717/03 Guideline on dossier structure and content for pandemic influenza vaccine marketing authorization application**】，並以行政院衛生署於 91 年 1 月 31 日公告之【藥品查驗登記審查準則－疫苗類藥品之查驗登記】爲基礎，擬訂本審查考量重點，以提供【去活化新型流感疫苗】廠商宜檢附資料之參考。

化學、製造與管制部分

一、　前言

行政院衛生署於 91 年 1 月 31 日公告【藥品查驗登記審查準則－疫苗類藥品之查驗登記】含蓋之疫苗種類包括「經減毒處理的活菌、病毒或寄生蟲；去活化的生物有機體；經處理的活細胞，或天然/純化的免疫原（包括於宿主細胞中製造之基因重組成份、共價結合物、合成抗原、聚核苷酸(如質體、去氧核醣核酸疫苗)；表現特定異種免疫原之載體細胞，或帶有免疫原之細胞。亦可包括上述多種疫苗的組合。」，公告的疫苗種類範圍實已包含不同各種生物來源及製造方法之疫苗。

公告內容中對於疫苗「化學製造與管制」部分所應檢附資料已有詳細列舉及說明，所以本文只針對去活化新型流感疫苗(inactivated pandemic influenza vaccine)與其他疫苗不同之處提出重點考量，至於「化學製造與管制」部分應檢附資料的詳細內容則請參考 91 年公告【藥品查驗登記審查準則－疫苗類藥品之查驗登記】內文。歐盟【**CPMP/VEG/4717/03 Guideline on dossier structure and content for pandemic influenza vaccine marketing authorization application**】之考量包含歐

洲藥典及歐盟已公告之細胞培養生產疫苗相關法規，所以本文於適當處亦建議參考相關法規。本文只針對去活化新型流感疫苗（inactivated pandemic influenza vaccine），並不包括減毒之新型流感疫苗 (live attenuated pandemic influenza vaccine)。

新型流感疫苗（Pandemic influenza vaccine）之送審資料及審查可以分爲新型流感核心資料（core pandemic dossier）及新型流感疫苗（pandemic variation）資料兩階段進行。以新型流感模擬疫苗 (mock-up vaccine) 爲藍本之新型流感核心資料（core pandemic dossier）應於非流行期 (interpandemic period) 建立及審核；一旦新型流感發生大流行時，即以新型流感疫苗（pandemic variation；新型流感模擬疫苗之病毒變異株）之資料審核，以達快速審查及即時上市之目的。

1.1 新型流感核心資料（core pandemic dossier）

1.1.1 以新型流感模擬疫苗（mock-up vaccine）爲藍本之新型流感核心資料，內容應包括疫苗研發策略、製造與管控、相關的臨床前試驗、及臨床試驗；以做爲日後流感大流行發生時，新型流感疫苗（intended pandemic vaccine）資料的基礎。

1.1.2 新型流感模擬疫苗（mock-up vaccine）的製造與管控應盡量與新型流感疫苗（intended pandemic vaccine）相同，抗原含量、佐劑（adjuvant）、及給予途徑也應與欲研發之新型流感疫苗（intended pandemic vaccine）相同。

1.1.3 爲了模擬新病毒感染之新免疫生成反應，新型流感模擬疫苗（mock-up vaccine）所選擇的抗原應來自不同於目前已流行之流感病毒。

1.2 新型流感疫苗（**pandemic variation**；新型流感模擬疫苗之病毒株變異）

1.2.1 檢附內容只須包含新型流感病毒株相關修改或更新之製造與管控資料送審，以達快速審查及即時上市之目的。

1.2.2 相關臨床資料則於新型流感發生期間，使用新型流感疫苗同時收集之。

二、新型流感模擬疫苗與新型流感核心資料（**core pandemic dossier**）

2.1 新型流感模擬疫苗參考病毒株 **(Vaccine reference virus)**

2.1.1 新型流感模擬疫苗（mock-up vaccine）所用之疫苗參考病毒株之特性與選擇應由 WHO Collaborative Center 或核可之 reference laboratory 執行與發佈；必要時，由衛生主管機關訂定。選用之參考病毒種批系統及生產方式，則由疫苗廠商自行建立。

2.1.2 建立疫苗參考病毒株

2.1.2.1 疫苗參考病毒株可能源自鳥類、豬、或人類；由下列方法之一沿生而得：

a. 重新組合病毒（reassortant virus）包含已除去鳥類高致病性基因片段之血球凝集素抗原（HA, haemagglutinin）之基因，神經氨酸酶抗原（neuraminidase, NA）基因，及減毒後人類流感病毒（例如 A/PR/8/34 (PR8)）之其餘 6 個片段。重新組合病毒可以以 reverse genetics 方法在哺乳類細胞建立，並於雞蛋或細胞內生產。

b. 重新組合病毒包含非致病性的血球凝集素抗原及神經氨酸酶抗原基因，加上 PR8 的其餘 6 個片段。重新組合病毒可以以傳統方式在雞蛋裡生產，

或是以 reverse genetics 在哺乳類細胞生產。

c. 不論是具有致病性或非致病性的非重新組合（non-reassortant）新的野生型流感病毒。其操作生產需要在適當的生物安全等級實驗室內進行，如 2.1.4 所述。

2.1.3 疫苗參考病毒株的品質

2.1.3.1 利用哺乳類細胞培養，並以 reverse genetics 建立之疫苗參考病毒株時，疫苗產品的品質及安全性，須符合下列條件：

a. 細胞受質（Cell substrate）已被核准作爲人類疫苗生產，參考歐洲藥典 5.2.3「用來生產人用疫苗的細胞」[1]；或已經被用於其他相關臨床試驗中。

b. 參考病毒株建立所用之動物性來源試劑(materials) ，須證明其不含外來物，如 BSE (Spongiform Encephalopathy)，牛製品須註明其地區來源及地點。

c. 保持詳細的實驗室紀錄，紀錄內容應記載同一時段內只處理一種病毒或其 DNA 的程序，以防止交叉汙染。

d. 由壹個 WHO 合作實驗室（WHO collaborating laboratory）評估所建立之參考病毒株，證明其抗原性、遺傳、及表現性適合一般生產用。原則上，病毒致病性的除去可以 WHO 核准之動物試驗（例如雞及雪貂的致病性試驗）證實。

e. 提供病毒株建立之方法步驟、測試規格及結果，如【藥品查驗登記審查準則－疫苗類藥品之查驗登記】第四條三項二款所述。

2.1.4 疫苗參考病毒株的安全性

2.1.4.1 當新型流感模擬疫苗（mock-up vaccine）是由高致病性病毒以 reverse genetics 方法衍生而得時，操作應在生物安全等級 3+或 4 實驗室內進行，所得病毒並以動物實驗證明其非致病性。安全性證實無慮後，病毒生產可以在生物安全等級 2+內進行。

2.1.4.2 由傳統方法衍生之重新組合病毒及野生株病毒生產，可以在生物安全等級 2 內進行。

2.2 疫苗種批系統的建立及外來病源微生物（**extraneous agent**）測試

2.2.1 疫苗生產用之病毒種批系統可以在 embryonated hens eggs 或是細胞株建立。

2.2.2 病毒種批系統應執行外來病源微生物測試，如【藥品查驗登記審查準則－疫苗類藥品之查驗登記】第四條三項所述，測試有無外來病毒、細菌、真菌、及黴漿菌，並可參考歐洲藥典流感疫苗種批系統之測試[2]。

2.2.3 對於由細胞培養生產之流感疫苗，可參考CPMP/BWP/2490/00 Guidance on Cell Culture Inactivated Influenza vaccines[3]，種細胞庫或工作細胞庫應測試有無外來病源微生物（extraneous agent），測試的病毒種類，應與細胞來源相關及細胞對病毒感受性（susceptibility）相關。

2.2.4 對於有時間性限制之疫苗生產，生產業者可以發展較快速之測試方法，例如多標的陣列 PCR 等，但是需要證明其適當性。

2.3 新型流感模擬疫苗之生產

2.3.1 生產製程與管控

2.3.1.1 疫苗生產的製程檢附資料，參考【藥品查驗登記審查準則－疫苗類藥品之

查驗登記】第四至九條。異常毒性試驗是只需用來作爲製程確效用。

2.3.1.2 亦參考【中華藥點第五版－流行性感冒疫苗－異常毒性試驗】,「若其製造方法經確效可證實生產之產品符合異常毒性試驗之規範,則本項試驗得予免做」。

2.3.2 疫苗效價分析

2.3.2.1 新型流感疫苗之血球凝集素抗原(HA)含量可能不同於一般流感疫苗(inter-pandemic vaccine) 使用之 15μg 含量。

2.3.2.2 一般之流感疫苗血球凝集素抗原含量以 immunochemical single radial immunodiffusion (SRD)測定，但 SRD 可能不適用在新型流感疫苗(pandemic vaccine)上。

2.3.2.3 替代之效價分析可以採用其他試驗，如蛋白質含量、小動物免疫生成反應等，但所採用方法的需經確效支持其適用性。

2.3.3 賦形劑及佐劑

2.3.3.1 參考【藥品查驗登記審查準則－疫苗類藥品之查驗登記】第九條說明，如無人類使用經驗，則須提供相關資料支持其安全性及有效性。

2.3.3.2 多劑量劑型（multidose preparations）所添加之防腐劑，於使用期間及儲存期限內應評估其效能。

2.3.4 安定性

2.3.4.1 相關規定參考【藥品查驗登記審查準則－疫苗類藥品之查驗登記】第十三條。

2.3.4.2 以新型流感模擬疫苗資料爲基礎,測試新型流感疫苗安定性之試驗計劃書宜先準備之。

三、新型流感疫苗(新型流感模擬疫苗之病毒株變異)

3.1 新型流感疫苗參考病毒株（Vaccine reference virus）

3.1.1 新型流感疫苗參考病毒株須由 WHO Collaborative Center 或核可之 reference laboratory 發佈，評估證明其抗原性、基因及表現性；必要時，由衛生主管機關訂定。參考病毒株的種批系統及生產方式則由疫苗製造業者自行建立。

3.1.2 建立流感疫苗參考病毒株

3.1.2.1 新型流感疫苗參考病毒株可能源自鳥類、豬、或人類，以 2.1.2 建議之三種方法之一建立。

3.1.2.2 如果新型流感病毒株具有高度致病性者，將以 reverse genetics 方法改變使其不具致病性。

3.1.2.3 亦可以利用一抗原性與流感病毒相等之非致病性病毒來發展疫苗。

3.1.3 疫苗參考病毒株的品質

3.1.3.1 新型流感疫苗參考病毒株需要經過歐盟醫藥品評審局(CPMP)核准，由 WHO Collaborating Centres 提供。

3.1.3.2 其品質要求相同於 2.1.3 疫苗參考病毒株品質。

3.1.4 安全性考量（生物封鎖）

3.1.4.1 新型流感疫苗操作過程之安全等級相同 2.1.4 疫苗參考病毒株安全性之考量，動物實驗證實病毒沒有致病性後，才可以進行疫苗生產。

3.1.4.2 流感發生後疫苗生產的風險考量及生物安全等級將會由 WHO 檢閱，國家及地區性之安全管理亦應一併考慮。

3.2 疫苗種批系統建立及外來病源微生物測試

3.2.1 同新型流感核心資料（core pandemic dossier），建立種批系統並執行安全性測試，如【藥品查驗登記審查準則－疫苗類藥品之查驗登記】第四條三項所示及 2.2，測試有無外來病毒、細菌、真菌、及黴漿菌[2,3]。

3.2.2 非流行期間，測試結果無慮後才可用來生產疫苗。

3.2.3 流行期間爲了爭取時效，可以使用較快之測試法(例如 PCR 測試病毒及黴漿菌，縮短無菌測試培養時間等)來篩選生產用病毒；但藥典之方法宜同時進行，以確實無外來微生物污染。

3.3 新型流感疫苗之生產

3.3.1 生產製程與管控

3.3.1.1 同新型流感核心資料（core pandemic dossier）。疫苗生產的製程參考【藥品查驗登記審查準則－疫苗類藥品之查驗登記】第四至九條。

3.3.1.2 申請查驗登記時，至少須提供一批成品之動物免疫反應試驗。

3.3.1.3 於繼續生產期間，應執行連續至少三批成品之動物免疫反應試驗，以證明製程一致性。

3.3.2 疫苗效價分析

3.3.2.1 依據新型流感模擬疫苗（mock-up vaccine）臨床試驗結果，新型流感疫苗（pandemic variation）含有之 HA 含量可能不同於一般流感疫苗之 15μg。

3.3.2.2 如果 SRD 試劑當時無法取得，可以使用於新型流感模擬疫苗（mock-up vaccine）確效過之其他方法取代測試疫苗效價。但當得到 SRD 試劑時，則應以其作爲效價測試方法。

3.3.3 賦形劑及佐劑

3.3.3.1 參考【藥品查驗登記審查準則－疫苗類藥品之查驗登記】賦形劑及佐劑第九條三項，如 2.3.3 之說明。

3.3.4 架儲期

3.3.4.1 應依據新型流感核心資料之試驗計劃書，執行新型流感疫苗安定性測試。

3.3.4.2 參考【藥品查驗登記審查準則－疫苗類藥品之查驗登記】第十三條，如使用期間，發現規格測試結果異常，應通知有關單位。

臨床前安全性試驗及免疫生成反應

一、一般考量

1.1 從安全性之角度來說，流感疫苗之反應作用狀況（reactogenicity profile）決定於疫苗純度、抗原種類 (完整的病毒體、分裂或次單位病毒疫苗)、及抗原含量。現今已上市之流感疫苗皆爲高度純化之產品，抗原最高總劑量爲 45μg 血球凝集素抗原（HA, haemagglutinin），在此劑量下，接受者的耐受性良好。

1.2 經由已上市流感疫苗的長久臨床經驗所得之免疫力及安全性資料做爲利益風險評估的基本部分。過去及現在的使用經驗所得到的免疫力、安全性、及耐受性，經審慎評估後，可以用來支持新型流感疫苗（pandemic variation）

相關評估。

1.3 如果新型流感疫苗（pandemic variation）之製造依循一已建立完成之流感疫苗製程，則可以考慮減少臨床前安全性試驗之部分。

1.4 臨床前試驗結果只需於新型流感核心資料（core pandemic dossier）檢附。原則上，新型流感疫苗（pandemic variation）只需檢附免疫生成反應之數據。

二、新型流感核心資料（**core pandemic dossier**）

2.1 臨床前免疫生成反應

2.1.1 進入臨床試驗前，需要小型動物（例如雞、小鼠、雪貂等）的免疫性試驗數據。

2.1.2 免疫性試驗內容包含探討劑量的選擇，以及投與第一劑之後多一劑(或以上)之作用。

2.1.3 動物免疫性試驗亦可支持生產製程的一致性，尤其是在製程確效方面。

2.1.4 免疫力試驗數據將是疫苗實際生產時品質管控的參考。

2.2 臨床前安全性考量

2.2.1 如裂解（split）或次單元（subunit）疫苗的製程與一般流感疫苗（inter-pandemic vaccines）相似，則不需再執行臨床前安全性試驗。

2.2.2 疫苗同 2.2.1，但人體使用劑量改變，而單一劑量不超過 45μg 血球凝集素抗原（Haemagglutinin Ag）時，也不需再執行臨床前安全性試驗。如人體使用單一劑量超過 45μg 血球凝集素抗原（HA, haemagglutinin），則需進行單一及重複劑量局部作用試驗。

2.2.3 若疫苗接種需要多劑量，且其血球凝集素抗原（HA, haemagglutinin）總量大於 45μg 時，需要執行重複劑量局部作用試驗。

2.2.4 經由與已上市疫苗相似之製程製造的完整病毒體（whole virions）流感疫苗亦適用以上情形。

2.2.5 如一熟知(well-established)之疫苗佐劑系統（adjuvanting system）與以上任一情況之疫苗合併時，則僅需執行單一及重複劑量局部作用試驗。

2.2.6 如疫苗是由一全新製程生產時，則須執行完整之臨床前安全性試驗。研發階段之數據及/或文獻亦可接受，但其相關性需要說明。不足之臨床前安全試驗，亦須提供適當理由，並諮詢法規單位。

2.2.7 沒有人類使用經驗之疫苗佐劑系統，應以佐劑單獨以及與疫苗抗原合併之兩種方式，評估安全性。

2.3 攻擊性試驗（Challenge experiment）

2.3.1 若可行，亦應執行動物（例如小鼠、雪貂等）攻擊性試驗證實其有效性。

2.3.2 當攻擊性試驗使用的病毒爲減毒或可能具有毒性時，參考 2.1.4，應在適當之生物安全設備內進行。

三、新型流感疫苗（pandemic variation）

3.1 唯一需要之臨床前試驗資料爲前三批疫苗免疫生成反應試驗數據，以證明產品製程一致性。

3.2 如果從 WHO 得到的減毒病毒株的基因被改變（需要評估基因改變的理由正當性），則應於適當動物模式試驗證明其減毒狀況，例如雞或雪貂的致病性試驗。

臨床試驗應提供之研究結果資訊

一、 臨床試驗計畫之考量

1.1 臨床試驗資料的審查，將依據前言所描述，分爲研發新型流感模擬疫苗以及新型流感疫苗二個階段進行。

1.2 新型流感模擬疫苗的新型流感核心資料中，應該包括臨床效益和安全性資料。在大流行期前(interpandemic phase)取得之資料爲新型流感模擬疫苗接種於未具有抗體(immunologically naïve)的人身上之臨床試驗資料。

1.3 於大流行期(pandemic)實際使用的新型流感疫苗，則應提供額外新增之臨床試驗資料，用來證實其臨床效益和安全性。

1.4 若新型流感疫苗與新型流感模擬疫苗具有相似的本質和相同的生產製造方式，則新型流感模擬疫苗之核心資料中的結果，用來外推(extrapolate)至新型流感疫苗上，將可接受。

1.5 由於預期不同年齡層的人，對於大流行期的新型流感病毒具有不同程度的部份免疫力，因此目前用於評估【去活化流感疫苗之年度變異株】申請時之評估免疫反應的標準，用來評估大流行期的新型流感疫苗，並不清楚是否合適。因此仍然應該努力取得任何與臨床預防效益相關的新資訊，並呈現於後續的研究設計中。

於非流行期間，研究新型流感疫苗的免疫反應(尤其是在孩童身上)之臨床試驗計劃書，以及研究新型流感疫苗之預防接種後產生免疫反應和臨床效益之相關性的臨床試驗計劃書，應事先準備齊全。

二、 研發新型流感模擬疫苗以及建立新型流感核心資料

於實際發生大流行之前，評估新型流感模擬疫苗於臨床上保護效益的臨床試驗，實際上無法執行。所以提供一個關於描述新型流感模擬疫苗的免疫反應之詳細的核心資料，對於未來新型流感疫苗的研發是必需的。

2.1 試驗族群

2.1.1 於核心資料中所提供的資訊，可能只有各種年齡層健康成人的研究結果。在獲得健康成人的資訊用以支持核心資料的同時，建議最好同時具有關於健康孩童安全性方面的初步資料。

2.1.2 當流感大流行發生之際，應該優先考慮孩童族群對於新型流感疫苗所產生免疫反應之評估。

2.1.3 傳統去活化流感疫苗效益評估之臨床試驗，一般受試者區分爲 18～60 歲以及 60 歲以上兩個年齡層。在六個月內曾接受流感疫苗的健康志願者不得參加臨床試驗，以免疫苗的免疫反應結果評估受到干擾[4]。

2.2 臨床試驗設計

2.2.1 臨床試驗設計，應直接的比較不同劑量的抗原、佐劑、以及各種不同的疫苗接種時程表。

2.2.2 各個臨床試驗的受試者人數，提出試驗計畫申請者應該要能證實其樣本數在統計上是具有意義的 (可參考CPMP/EWP/463/97 Note for guidance on the clinical evaluation of new vaccine [5])。

2.2.3 在任何可能的情況下，應該執行年齡、族群之分層分析。

2.3 免疫生成反應之評估標準

2.3.1 對於免疫生成反應之評估標準，目前要求至少大於 40 IU HI (hemagglutination inhibition) titer 以上。但是此壹評估標準，對於新型流感疫苗不一定正確。

2.3.2 在目前沒有其它評估標準可遵循的前提之下，建議接種雛型流感疫苗所產生的免疫生成反應，應該要能符合目前對於流感疫苗要求的三個免疫反應之評估標準(參考CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines [4])。

2.3.2.1 於年齡層 18～60 歲之成年人，應執行下列的免疫反應血清學評估，並達到標準：

a. 血清陽轉率(seroconversion)或者顯著之抗體(antihaemagglutinin antibody titer)增加之數目應＞40%；

b. 幾何平均值增加＞2.5；

c. 受試者達到HI titer≧40 或SRH titer＞25 mm^2之比率(proportion)應＞70%。

2.3.2.2 於年齡層大於 60 歲之老年人，應執行下列的血清學評估，並達到標準：

a. 血清陽轉率(seroconversion) 或者顯著之抗體(antihaemagglutinin antibody titer)增加之數目應＞30%；

b. 幾何平均值增加＞2.0；

c. 受試者達到HI titer≧40 或SRH titer＞25 mm^2之比率(proportion)應＞60%。

2.3.3 宜選擇壹個或數個臨床試驗中心，進行中和性抗體的測量。

2.3.4 在臨床研發過程期間，由於持續積累資訊的匯整，對於現行之疫苗免疫反應評估標準與臨床保護效益之間的相關性之假設，有可能需要重新定義之。

2.3.5 研發新型流感模擬疫苗的廠商應該與法規主管單位在適當的時間進行諮詢。

2.3.6 應持續追蹤完成初步接種的受試者族群六個月以及十二個月後的免疫生成反應。

2.4 預防接種時程表

2.4.1 考量到人類對於新型流感均不具備抗體(naivety)免疫力，且使用的是去活化疫苗，因此在新型流感流行期間只接受壹劑的疫苗接種並不恰當。

2.4.2 必需評估初次預防接種即接受兩劑量(或更多)、並且輔以佐劑之可能性。

2.4.3 最佳劑量以及接種時程表之選擇應該依據下列幾點加以評估：

a. 疫苗特殊具體因素：譬如抗原類型和劑量，任何佐劑含量。

b. 人口具體因素：譬如年齡，對 pandemic strain(s)之免疫力 naivety 狀況。

c. 疫苗需求使用的客觀環境情況：例如在已經有病毒傳播、迫切必需達到免疫保護效益的地方，不同於在較不迫切的情況下(譬如前線醫療保健工作)者。

2.4.4 所有使用於大流行期的流感疫苗，宜具有相似的預防接種時程表。

2.5 安全性評估

2.5.1. 疫苗安全性資料庫應該要能充分反映出頻率大約 1%左右之副作用。

2.5.2. 後續安全性的評估至少應該持續追蹤 6 個月。

2.5.3. 於臨床試驗發展期間任何有關安全性的新問題出現時，必須具體地陳述在後續的研究中。

2.5.4. 去活化新型流感疫苗中可能包含有 thiomersal 或其他佐劑 (adjuvant)存在，根據法規的要求，thiomersal 的使用應侷限在極小含量。而有關佐劑之安全性問題亦應在臨床試驗中仔細研究。

2.6 核准上市後之承諾

2.6.1 在新型流感模擬疫苗核准的同時，申請者應該提供完整之臨床試驗計畫書用以評估新型流感疫苗的免疫生成反應、預防疾病保護效益、以及安全性，以做爲核准上市後之承諾的一部分。

三、新型流感模擬疫苗之病毒株變異以及新型流感疫苗

3.1 初期核准使用

3.1.1 若最後研發之新型流感疫苗和新型流感模擬疫苗相似，僅病毒株內容(strain content)不同但接種時程表並無變更時，則新型流感疫苗將以新型流感模擬疫苗的病毒株變異方式申請核准使用，並且只著重在品管議題上（quality issue）審核，而無需臨床試驗的資料。

3.2 核准使用後之臨床評估

3.2.1. 若在緊急情況下使用新型流感疫苗，則取得新型流感疫苗之免疫生成反應、預防疾病保護效益、以及安全性資訊將顯得非常重要。

3.2.2. 新型流感疫苗之免疫生成反應、預防疾病保護效益、以及安全性累積的資訊應該是跨國、跨公司之公共衛生議題，快速的分享資訊所得將有助於提供新型流感疫苗後續的研發、研究預防接種時程表變更等。

3.3 免疫生成反應評估標準

3.3.1 當新型流感疫苗的供應足夠所需時，申請者應執行各個年齡層以及高危險族群之免疫生成反應研究。

3.3.2 應優先考量研究孩童之免疫生成反應。

3.3.3 適當的臨床試驗計畫書應事先準備妥當。若新型流感模擬疫苗適合使用於大流行期間，則之前於研發新型流感模擬疫苗的核心資料應依據新有的資訊加以補充。

3.3.4 初期的新型流感疫苗接種後免疫生成反應資訊，應該盡速送達法規單位，提供做爲劑量調整建議的再次評估。

3.3.5 在臨床試驗納入的受試者應該小心追蹤其流感症狀的發生。由這群受試者所獲得的資訊，應該用來研究提供足夠保護效益所可能需要的免疫學評估標準(serological criteria for protection)。

3.4 臨床保護效益

3.4.1 於新型流感大流行期間，將會有不同廠商提供的新型流感疫苗，同時在不同的地區接種注射，因此最後只能評估施與預防接種後整體的預防疾病效益(overall effectiveness)。

3.4.2 有關疾病的診斷(case definition)，以及偵測疾病的方式(case detection definitions)，宜事先(ad hoc basis)定義清楚並且一致性使用。

3.4.3 在疾病大流行期間，有可能需要重新思考其疾病的診斷以及偵測疾病的方式是否適當而加以重新定義之。

3.4.4 臨床試驗的計畫書宜清楚描述受試者族群、以及使用疫苗之效益的評估方法。

3.4.5 臨床上的指標(clinical outcome) 宜包括針對不同年齡所分析之罹病率及死亡率，以及住院的比率。

3.5 安全性評估

3.5.1 因爲流感疫苗在臨床試驗中受試者的人數有限，因此其於實際使用後的安全性資訊顯得非常的重要，尤其是對於高危險族群以及孩童族群的安全性資訊更需特別注意。

3.5.2 除了評估接種疫苗之後立即產生的局部和全身性副作用以外，對於非常罕見的副作用例如 Guillain-Barré syndrome，亦需要長期追蹤評估。

3.5.3 對於新型流感疫苗而言，大規模的安全性資料將來自於大流行爆發期間疫苗實際使用的經驗。

3.5.4 定期之上市後安全性資料更新報告(PSUR)應該定期提供給法規單位。

Reference:

[1]Ph. Eur. 5.2.3. Cell substrates for the production of vaccines for human use

[2]Ph. Eur. 01/2002:0158"Infulenza vaccine (split virion, inactivated), 01/2002:0159 Influenza vaccine (whole virion, inactivated), 01/2002:0869 Influenza vaccine (surface antigen, inactivated), CPMP/BWP/2490/00 Note for guidance on Cell culture inactivated influenza vaccine

[3]CPMP/BWP/2490/00 Guidance on Cell Culture Inactivated Influenza vaccines

[4]CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines

[5]CPMP/EWP/463/97 Note for guidance on the clinical evaluation of new vaccine

[6]衛生署 91 年 1 月 31 日公告：藥品查驗登記審查準則－疫苗類藥品之查驗登記。

財團法人醫藥品查驗中心

新型流感疫苗專家諮詢委員會暨第一次專家會議

會議紀錄

一、時　　間：民國 95 年 6 月 30 日（星期五）10:00-12:30

二、地　　點：財團法人醫藥品查驗中心第一會議室

三、主　　席：朱夢麟特聘研究員（請假；陳恆德執行長代）

四、出席人員：

諮詢專家：何美鄉研究員、李慶雲教授、林文理總經理、施信如教授、黃立民教授、黃昭蓮研究員、熊昭主任（依姓名筆劃序）

藥政處：許蒨文科長、黃淑萍技士

藥檢局：陳作琳科長、楊若英技正

疾管局：劉定萍主任、江正榮科長、連偉成科長、李正道科長

國衛院：莊再成主任、周文祥副主任、李敏西副研究員、李慧敏法規經理、包中怡法規助理、蔡浩鵬助技術師、許惠鈞品保經理、郭恩澤品管經理

醫藥品查驗中心：陳恆德執行長、王蓉君審查員、蔡承恩審查員、李元鳳審查員、李逸琦專案經理、廖紫歆專案經理、詹美華企劃經理

五、記　　錄：廖紫歆、李逸琦

六、會議討論事項：

1. 關於國衛院研發流感疫苗之進度與詳細內容將另會討論。
2. 疾管局報告進度：
   2.1. 短期：將採購目前已進入臨床試驗階段之試驗疫苗，以因應緊急所需。
   2.2. 中／長期：將輔導國內自行研發流感疫苗。
3. 法規研議--新型流感疫苗查驗登記之審查注意要點（草案）之雛型流感疫苗與新型流感核心資料。
   3.1. 化學、製造與管制部分：

3.1.1. 雛型流感疫苗參考病毒：

（1）特性與選擇：WHO Collaborative Center / Reference Laboratory 執行與發佈，必要時，由衛生主管機關訂定。

（2）疫苗參考病毒株的品質：細胞受質（Cell substrate）已被核准作為人類疫苗生產，或已經被用於其他相關試驗中。

（3）疫苗種批系統的建立及外來病源微生物（extraneous agent）測試：生產業者可以發展較快速之測試方法，例如多標的陣列 polymerase chain reaction（PCR）等，但是需要證明其適當性。

3.1.2. 雛型流感疫苗之生產：

（1）3.2 疫苗效價分析：

i. 抗原含量以 immunochemical single radial immunodiffusion（SRD）測定，但 SRD 可能不適用在新型流感疫苗（pandemic vaccine）上。

ii. 替代之效價分析可以採用其他試驗，如蛋白質含量、小動物免疫生成反應等，但所採用方法的需經確效支持其適用性。

（2）3.4 安定性：

i. 安定性之試驗計畫書宜先準備。

3.2. 非臨床安全性試驗及免疫生成反應部分：

3.2.1. 因給予劑量依疫苗處方不同而異（e.g., 有無 adjvant...），故法規無訂定，所以可接受用 HA 含量來分析疫苗效價的方法之一。

3.2.2. 非臨床安全性考量：

（1）使用單一劑量超過 45μg 血球凝集素抗原（HA, haemagglutinin），則需進行單一及重複劑量局部作用試驗。

（2）如疫苗是由一全新製程生產時，則須執行完整之非臨床安全性試驗。

（3）沒有人類使用經驗之疫苗佐劑系統，應以佐劑單獨以及與疫苗抗原合併之兩種方式，評估安全性。

3.2.3. 激發性試驗：若可行，小鼠、貂等激發試驗證實其有效性。

3.3. 臨床試驗應提供之研究結果資訊：

3.3.1. 試驗族群：

（1）獲得健康成人的資訊用以支持核心資料的同時，建議最好同時具有關於健康孩童安全性方面的初步資料。

（2）同意受試者區分為 18～60 歲以及 60 歲以上兩個年齡層。

3.3.2. 免疫生成反應之評估標準：宜選擇壹個或數個臨床試驗中心，進行中和性抗體的測量。

3.3.3. 安全性評估：

（1）充分反映出頻率大約 1%左右之副作用

（2）持續追蹤 6 個月

3.3.4. 核准上市後之承諾：申請者應該提供完整之臨床試驗計畫書用以評估新型流感疫苗的免疫生成反應、預防疾病保護效益、以及安全性，以做為核准上市後之承諾的一部分。

3.4. 臨床試驗免疫生成反應之評估標準：

3.4.1. 免疫反應血清學評估應至少達到其中一個標準或 co-primary endpoints：委員建議至少應達到其中一個標準。

3.4.2. 幾何平均值：依目前草案中擬定之即可。

4. 討論議題：

4.1. 因根據國衛院 95 年 5 月 26 日之進度報告，細胞株（MDCK）係購自食品工業發展研究所。擬將 MDCK 細胞株及種批系統送至國外實驗室進行 QC 檢測。

4.1.1. 然而國外實驗室是否亦接受 pandemic virus seed lot 委託尚需進一步詢問；若否，則國內如何進行此 QC 檢測？

結論：在經過確效後之實驗室，其數據才可被接受，擬建議輔導國內成立相關實驗室，以因應將來之緊急情況。

4.1.2. 將來新型 pandemic variation 出現時，因為國內尚無單位或實驗室經過認證可以執行此類 QC 檢測，尤其如於緊急狀況下是否應執行完整之 virus seed lot QC 檢測及如何執行？

結論：同意醫藥品查驗中心建議，於緊急情況下 Virus seed lot 仍應進行與安全性相關之 QC 檢測。QC 檢測項目可參考法規（virus tests 包括 adventitious, species-specific and retroviruses），可請教國外受委託單位是否有特別建議。E.g., PCR test。

4.2. 目前國衛院所取得的是越南株（NIBRG-14）量產製造 for clinical trial use。目前並已向 WHO 索取新的病毒株（印尼株），將來更希望可以建立平台，以在緊急情況下自行建立國內病毒株。

4.2.1. 在緊急情況下，如果國內自行建立病毒株以供疫苗生產時，其 CMC 及 safety 標準為何？

結論：仍然依照法規，但是安定性試驗可與臨床試驗同時進行。

4.3. 相關的 CMC 檢測，國衛院會照法規要求執行，於 safety test 方面，計畫請 CRO 或生技中心協助執行。

4.3.1. 於台灣，是否有 CRO 公司可執行 safety test，並且試驗數據是可被接受的？

結論：

（1）在 safety 部分：中華民國實驗室認證體系（Chinese National Laboratory Accreditation, CNLA）每年認證乙次，例如：DCB 等的機構，其一般毒性試驗如符合 CNLA 則可以被接受。

（2）在 Bio-safety 部分：國內尚無機構可受委託。

4.4. 以 SDS-PAGE 檢測出相對濃度後，建議仍應測試 MDCK 之 residual protein，可放入 in-process control 中。

4.4.1. 國外法規建議以 SRD（analyze the potency of the protein）檢測效價，若緊急情況 SRD reagent 無法取得，可否以 SDS-PAGE（analyze the purity of the protein）檢測取代？其方法是否需經 standardized？

醫藥品查驗中心意見：

（1）Mock vaccine：protein content 可以取代效價測試，但方法需確效過以符合疫苗使用，並佐以不純物之管控。

（2）Pandemic vaccine：緊急情況時，確效後的 protein content 可以先用來做效價測試，但得到 SRD 試劑時，則應使用 SRD 方法。

結論：以上建議尚待進一步討論。

4.5. 此類新型流感疫苗是否應執行生殖毒性試驗，擬提專家會議討論（註：如國衛院來不及於臨床試驗前完成 Reproduction toxicity，則會先於臨床試驗時先排除有相關疑慮之受試者，例如：懷孕／授乳之婦女）。

結論：Hungary：pregnant women were excluded in clinical trial 在一般毒性試驗中加入生殖器官之 histopathology，通常於 rodent 中試驗。

4.6. 臨床試驗之試驗族群：我國於臨床試驗之試驗族群，以往傾向 FDA 之年齡分層；現今年齡分層？

結論：若試驗結果會參閱 immunogenicity study data 則年齡上限不一定須限制於 65 歲，但考量因大多數研發疫苗單及廠商多位於歐洲國家，為方便配合國際現況，建議可比照歐盟之規範一般受試者區分為 18～60 歲以及 60 歲以上兩個年齡層。

4.7. 免疫生成反應之評估標準：

4.7.1. 於年齡層 18～60 歲之成年人，應執行下列的免疫反應血清學評估，並至少達到其中一個標準（or co-primary endpoints）：

（1）血清陽轉率（seroconversion）或者顯著之抗體（antihaemagglutininantibody titer）增加之數目應＞40%；

（2）幾何平均值增加＞2.5；

（3）受試者達到 HI titer≧40 或 SRH titer＞25 mm^2 之比率（proportion）應＞70%。

4.7.2. 於年齡層大於 60 歲之老年人，應執行下列的血清學評估，並至少達到其中一個標準（or co-primary endpoints）：

（1）血清陽轉率（seroconversion）或者顯著之抗體（antihaemagglutininantibody titer）增加之數目應＞30%；

（2）幾何平均值增加＞2.0；

（3）受試者達到 HI titer≧40 或 SRH titer＞25 mm^2 之比率（proportion）應＞60%。

結論：建議應上述 3 項 endpoint 皆應列入，若其中一項達到標準則可認定試驗成功。以上建議尚待進一步討論。

4.8. 宜選擇壹個或數個臨床試驗中心，進行中和性抗體的測量。可行否？

結論：同意醫藥品查驗中心之建議，應可行。

4.9. 臨床試驗中心：

結論：

4.9.1. 無需限定臨床試驗中心。

4.9.2. 無需區分為北、中、南、東四區同步進行。

4.9.3. 試驗計畫主持人資格應依照現行法規。

5. 其他：

5.1. 建議將雛型流感疫苗（mock-up vaccine）之名稱修改為「模擬疫苗」。

（以下空白）

財團法人醫藥品查驗中心

新型流感疫苗專家諮詢委員會暨第二次專家會議

會議記錄

一、時　　間：民國 95 年 10 月 26 日（星期四）15：00～17：00

二、地　　點：財團法人醫藥品查驗中心

三、主　　席：朱夢麟特聘研究員

四、出席人員：

諮詢專家：何美鄉研究員、李慶雲教授、林文理總經理、
張上淳主任、熊昭主任

藥政處：黃淑萍技士

藥檢局：陳作琳科長、楊若英技正

疾管局：劉定萍主任、江正榮科長、連偉成科長、李正道科長

國衛院：莊再成主任、周文祥副主任、李敏西副研究員、
李慧敏法規經理、包中怡法規助理、蔡浩鵬助技術師、
許惠鈞品保經理、郭恩澤品管經理

醫藥品查驗中心：王蓉君審查員、蔡承恩審查員、李元鳳審查員、
李逸琦專案經理、廖紫歆專案經理、
詹美華企劃經理

五、記　　錄：李逸琦、廖紫歆

六、報告事項：

（一）CDC 國內防疫策略現況報告。

1. 國外情況：

- 國際間疫苗策略
- 增加各國季節性流感疫苗之需求
- 疫苗製造技術與研發

2. 國內情況：
   - 短期：購買可取得之最佳市售疫苗（Best available H5N1 vaccine），預計年底達 19 萬劑（GSK：9 萬劑、H5N1 越南株；Baxter：10 萬劑、clade2 印尼株）。
   - 中期：國衛院與疾管局對緊急疫苗之研發。
   - 長期：BOO 案之簽約已屆完成、與疫苗之 cGMP 建廠工程。
3. CDC 目前進度：
   - 已建立雪貂動物模式，並分離 3 株病毒株。
   - 建立疫苗基礎技術: 合成 1st H5 DNA 疫苗與 α-Galcer 醣脂佐劑之研發。
   - 國際合作與國際接軌。
   - 追蹤計畫時程與國內需求量。

（二）NHRI 新型流感疫苗研發現況報告。

1. Cell-Based H5N1 Vaccine Bulk 研發及初步製程說明
2. Cell and virus banks 生物安全品管測試項目說明
3. 預計執行之毒理試驗內容：擬委由 DCB 執行。

（三）CDE 法規考量說明及「新型流感疫苗查驗登記之審查注意要點草案」進度現況說明：

1. 說明 Quality control of the cell substrate 與 Tumorigenicity。
2. 對 Mock-up/Pandemic Influenza vaccine 之臨床試驗設計說明。
3. 因應已於 95/9/6 呈報衛生署之 Draft guidance（彙整專家建議修正完成之 95/8/28 版本），處內回覆應就草案內容召開審查委員會並逐條討論，故查驗中心預計 11 月中開籌備會議。

七、討論事項：

1. 對於毒性試驗動物種類，目前 NHRI 只有執行於大鼠一種，是否應再多選擇一種動物來執行毒性試驗，以更確認 vaccine 之安全性？
   - 目前國內法規針對疫苗沒有相關建議，然參考 ICH 的規範，動物毒性試驗至少要使用一種動物，惟考慮 NHRI 的流感疫苗為國內自行研發之新疫苗，因此建議仍應進行 two species 毒性試驗（Rodent and Non-rodent），以確認其安全性。
   - 該疫苗之毒理試驗擬由 DCB 進行。
2. 目前國內是否可自行建立參考病毒株？
   - 目前國內購入印度及越南種之病毒株，是參考 WHO 核可發佈之病毒株，較能符合國際規範，由於一般病毒約 15 代以後就易開始變異，目前較不考慮國內自行建立 reference virus。
   - 另外建議若已有中國大陸之參考病毒株於 WHO 核可發佈時，應可選擇該種，較易符合未來國內流病狀況。
3. 目前 NHRI 研發中之 vaccine，採用 split virus 及 whole virus 兩種，是否有評估何者較恰當？
   - 目前國外以 whole-virion vaccine 執行臨床試驗較多，以日本現況而言，因其 whole virus vaccine 之製程已建立多年，再加上 split virus 製作時的去 ester 步驟容易發生爆炸反應，因此日本仍多以 whole virus 為主要方式。
4. Adjuvant 的添加要如何考量？目前 NHRI 考慮 Aluminum Phosphate 及 CpG 兩種。
   - 先考量添加 adjuvant 後，相關 side effect 是否會增加。
   - 應先行確認選用之 adjuvant 來源是否為 cGMP 藥廠製造，就 Alum Phosphate 而言，為國內常使用之佐劑，國內亦已有 Alum Phosphate 之原料藥，因此於國內有相當的使用經驗，已減少安全性之考量。
5. 應及早確立 MDCK cell line 之基本特性試驗（Cell biology test），例如：chromosome 是否改變、是否致癌等…。

（以下空白）

衛生署疾病管制局流感疫苗研發計畫
95年度期末報告書面審查意見回覆

計畫名稱：建立我國新型流感疫苗製劑臨床試驗管理機制及規範

計畫編號：DOH95-DC-1415

執行單位：財團法人醫藥品查驗中心

主 持 人：朱夢麟特聘研究員

1. 有關提出新型流感疫苗適用之「藥品查驗登記審查準則—疫苗類藥品之查驗登記」修改建議版本，後續辦理情形請於成果報告中明敘。

回覆意見如下：

1.1 現況：

a. 有關「藥品查驗登記審查準則—疫苗類藥品之查驗登記」修改建議版本，工作小組透過讀書討論會以及專家諮詢委員會會議，初步草擬完成**「新型流感疫苗查驗登記之審查注意要點（草案；95年8月28日版）」**，呈報衛生署藥政處（藥查企字第950671號函文）。

b. 衛生署藥政處函文（衛署藥字第 0950340179 號）指示，惠請查驗中心就95.8.28版本之「新型流感疫苗查驗登記之審查注意要點」草案內容，**再次召開審查委員會（委員成員應包含衛生署藥物審議委員會委員），就草案內容逐條討論**，俟討論完竣，送署憑核。

1.2 未來：

a. 因應衛署藥字第 0950340179 號函文指示，查驗中心擬召開第三次專家會議，就草案內容進行逐條討論。目前籌備會議已研擬好專家委員名單，將於近期內發函邀請。

b. 擬於第三次專家會議與會之專家委員名單：

（1）「新型流感疫苗專家諮詢委員會」核心委員：

李慶雲教授、張上淳主任、黃立民教授**、
何美鄉研究員、黃昭蓮研究員**、施信如教授、
熊昭主任**、林文理總經理

（2）外部專家委員：

楊崑德、林奏延、劉清泉、林敏雄**、張鑾英**、
蘇銘嘉**、劉仁沛**
藥檢局：陳作琳科長、楊若英技正
藥政處五科：許蒨文科長、黃淑萍技正

**：藥物審議委員會委員

2. 計畫任務與中心本身任務應予區分。

回覆意見如下：

2.1 感謝委員建議。**計畫任務**本身之成果報告詳列於研究報告之第肆項、結論與建議中第一點至第四點（25 頁至 27 頁）。

2.2 研究報告第肆項、結論與建議中第五點與第六點（27 頁至 28 頁）中，雖非直接與計畫任務相關，但多數為達成良好執行計畫任務所必需。如：95 年 11 月 6 日舉辦「新型流感疫苗」議題之圓桌討論會議；派員參加「2006 DIA Vaccine Workshop, May 16-17, 2006; Vienna, Austria」研討會；其有助於法規人員對於國內／國際上疫苗之研發進展的現況與未來之瞭解，充實相關人員於法規科學工作上的內涵。

3. 計畫書中要成立 20-25 人之專家諮詢委員會，目前只有 8 位國內核心委員及一位國外法規顧問，但以目前委員會成員所涵蓋之領域及國內現況，8 位委員應已足夠，不要再擴大，有問題需要諮詢再邀請專家針對個案提供意見。

回覆意見如下：

感謝委員建議。然因應衛署藥字第 0950340179 號函文指示，查驗中心擬召開之第三次專家會議中，將會有較多的委員專家參與。但日後之運作，將仍維持 8 位國內核心委員及一位國外法規顧問為主。

4. 在編制經費方面，96 年度之經費個人意見如下：a. 人事費中有一項是（7 等 10）x20 個人月，在 95 年是（7 等 9）x12 人月。工作內容沒有增加，為何由 12 人月變成 20 人月，應是編列錯誤應予修正。b. 辦公室租金分

攤35坪之空間已經相當大，95年度編制一百萬、96年度編了150萬，應解釋為何突然增加50萬。c. 辦公室文具紙張由95年10萬元變為20萬元，不合理。d. 配合業務需要購置之電腦軟體30萬元，前一年度已編制30萬元，在同一計畫內容下的第二年不應該有重覆編制之需要。e. 調查訪問費20萬元前一年度已編列，在計畫書中完全看不到有調查訪問之工作項目，其實也不預期在本計畫案中有調查訪問之需要，應予刪除。f. 旅運費編列過高，因為絕大多數之會議都在台北進行，專家諮詢委員會之委員也都是位居台北縣市，沒有太多旅運費之需求。g. 國外顧問專家學者來台工作之費用編列5位共50萬元，請國外專家學者來訪有其需要但應事先規劃，目前沒有看到規劃內容，建議其中一部份移給CDE兩位專案工作小組成員出國參加疫苗相關研討會之用（計畫書中有提到出國會議但有沒有預算）。

回覆意見如下：

a. 本計畫96年將加強相關法規研擬工作，除原預計進行的工作內容（完成「新型流感疫苗查驗登記之審查注意要點（草案）」法條化公告作業，並建立「新型流感疫苗緊急情況下之快速查驗登記審查流程」機制。）外，配合國內的發展狀況，並擬進行DNA vaccine相關審查注意要點草案建議的草擬工作。因工作負荷加重並增加內容，非增編人力無法完成，故懇請委員支持所增列之人事費用（由95年之12人月變成96年的20人月）。
b. 租金除包含辦公室分攤約35坪外、辦公設備如影印機租金分攤及舉辦研討會場地及設備租金等，95年度編列100萬元稍有不足，故96年度增列50萬元。
c. 文具紙張費用係配合業務量增列10萬元。
d. 本中心各項軟體購置，需於年度更新授權合約版本，故編列30萬元。
e. 有關調查訪問費乙節，將運用在研擬法規草案時，瞭解國內研發單位、學者專家、廠商等對國內法規或研發現況所遭遇之困難及對未來發展方向之看法等，故編列之。
f. 本中心旅運費用科目，除旅費支出尚包含運送文件之運費。另，參加在中南部舉辦之研討會、邀訪中南部學者及赴竹南國家衛生研究院疫苗研發中心討論或開會等，均需要旅費支應。故旅費之編列實有需要。

g. 邀請國外專家學者來訪乙事，將陸續根據國內疫苗研發進程及法規研擬現況所需進行邀請。感謝委員建議將國外專家學者來訪之部分經費，移給 CDE 兩位專案工作小組成員出國參加疫苗相關研討會之用；惟依申請作業手冊有關經費編列之規定，不能於計畫申請時編列出國所需費用，故委員之建議，尚需請疾病管制局長官斟酌裁示。相關工作小組成員如果無法出國參加疫苗相關研討會，則邀請及安排國外專家學者來訪，實在有保留的必要。

5. 期末報告之中文摘要發現與原先計畫書之摘要一模一樣內容，兩者應有不同，前者應包括執行情形、執行成果、執行檢討、哪些未達到或列入明年度執行之部分等作 summary 簡要說明，請修正報告之摘要。

回覆意見如下：

5.1 謝謝委員意見；將按建議修改。

5.2 **修改內容如下：**

醫藥品查驗中心接受委託執行「建立我國新型流感疫苗製劑臨床試驗管理機制及規範」計畫，計畫全程二年；九十五年計畫執行目標及工作重點包括：(1) 設立新型流感專案工作小組「Pandemic Task Force Working Group (PTFWG)」；(2) 建立問題導向之專家諮詢委員會議「Issue-Oriented Advisory Committee Meeting (IOACM)」制度；(3) 提供疫苗相關產品研發的法規諮詢輔導；(4) 提出「新型流感疫苗查驗登記之審查注意要點」之草案。本計畫九十五年一月至十一月上旬重要成果摘錄如下：

(1) 成立新型流感專案工作小組；由三位臨床醫師、一位生醫博士、二位專案經理、一位企劃經理，共同負責規劃、推動業務及計畫之執行。

(2) 成立專家諮詢委員會並成立專家諮詢委員會（IOAC），並已召開二次專家會議。二次會議分別針對「新型流感疫苗查驗登記之審查注意要點草案（95 年 6 月 8 日版）」及「國家衛生研究院新型流感疫苗研發過程臨床前試驗」應符合之法規要求等議題進行討論。

(3) 受理 6 件新型流感疫苗研發相關之法規諮詢輔導案。除 1 件仍

進行輔導外，其餘均依據現行法規科學之要求，函文完成答覆諮詢。

（4）已提出「新型流感疫苗查驗登記之審查注意要點」建議草案（8月28日）；現正協助衛生署藥政處進行草案法條化公告作業。

本計畫95年度執行現況良好；原列年度工作目標及預期績效均已如期完成。96年將依計畫原訂內容，持續運作新型流感專案工作小組以及專家諮詢委員會，並進行法規研擬、法規諮詢輔導等工作，以協助新型流感疫苗臨床試驗之進行。

6. 所擬新型流感疫苗查驗登記之審查注意要點，對於臨床試驗部分較完整，針對CMC部分引用參考中華藥典之內容，建議仍應摘錄重點後,再說明詳細內容見中華藥典哪一部分；或將該詳細內容之文字全都敘述出。

回覆如下：

6.1 同意委員意見。將於第三次專家會議提出修正如下。

6.2 審查注意要點2.3.1.2亦參考【中華藥典第五版】－流行性感冒疫苗部分－異常毒性試驗，「疫苗產品應符合血清疫苗異常毒性試驗法之規定。若其製造方法經確效可證實生產之產品符合異常毒性試驗之規範，則本項試驗得予免做」。

7. 由於流感疫苗生產技術主要以胚胎蛋培養與細胞培養二種製程；原先計畫書亦說明了細胞培養製程法規訂定之重要性；然於新型流感疫苗查驗登記之審查注意要點，對於細胞培養製程CMC部分之管理法規卻僅以參考其他國家法規（例如歐洲藥典、CPMP）字眼帶過，建議仍應將細胞培養製程所需之法規予以中文文字化之擬訂。

回覆如下：

同意委員意見。審查注意要點2.2.2中提及的【藥品查驗登記審查準則－疫苗類藥品之查驗登記】第四條三項已敘述細胞種批系統細胞之管控，除此之外，國內沒有細胞受質（cell substrate）相關的法規。本中心疫苗工作小組是否將此等法規(FDA及EMEA已公佈經由細胞培養產生之疫苗所用的cell substrate相關法規或草案）納入將來之工作項目，尚待討論。

8. 新型流感疫苗查驗登記之審查注意要點 2.3.1.生產製程與管控，認為“毒性試驗只需用來作為製程確效用”是錯誤的認知。

回覆如下：

8.1 審查注意要點 2.3.1.1 生產製程與管控，內文之“毒性試驗只需用來作為製程確效用”乃是直接翻譯自歐盟法規（Guideline on dossier structure and content for pandemic influenza vaccine marketing authorization applicaiton ） 3.1.3 (p.6). 原文為” The European Pharmacopoeia test for abnormal toxicity of the finished product is only required for the validation of the manufacturing process” ，【中華藥典第五版－流行性感冒疫苗－異常毒性試驗】中指出「若其製造方法經確效可證實生產之產品符合異常毒性試驗之規範，則本項試驗得予免做」。

8.2 藥檢局楊若英技正於第一次專家會議後已指出「目前進口及國產流感疫苗仍進行異常毒性試驗」，因此，於第三次專家會議將會提出此項修正討論。

9. 同該要點 3.2.3 流行期間為爭取時效，先以 PCR 針對外來病毒微生物進行測試。由於 PCR 涉及方法之靈敏度與特異性，應強調註明該以經確效之 PCR 方法來進行檢測。

回覆如下：

審查注意要點 2.2.3 及 2.2.4 內文乃引用自歐盟法規(CPMP/BWP/2490/00 Cell culture inactivated influenza vaccines）3.3 第一段。同意委員意見，測試方法，例如 PCR，” 需要經過確效證明” 。將於第三次專家會議提出此項修正討論。

6 至 9 意見一併回覆如下：

（1）非常謝謝委員針對**審查注意要點草案**提供寶貴意見。

（2）針對審查注意要點草案，查驗中心將再召開第三次專家會議，就草案內容進行逐條討論。目前已研擬好專家名單，將於近期內發函邀請。委員所提建議將一併提供專家參考。

10.附件十六，討論議題 4.1，有關使用購自食工所 MDCK 細胞株來製造疫苗，應先釐清食工所供應之細胞株之來源與製備之種批次紀錄資料是否完備，及是否可用於疫苗生產等資訊。

回覆如下：

於與國衛院之數次溝通會議中，已提醒此部份之重要性。未來如果廠商正式提出申請，將會仔細審查此部分資料。

11.附件十七，對於為確認疫苗之安全性而進行毒性試驗動物之選用,建議仍應依中華藥典毒性試驗規定進行為宜。

回覆如下：

【中華藥典第五版】附錄六「生物製品相關測定法」(一) 血清疫苗異常毒性試驗法 為疫苗產品 CMC 規格測試項目之一（與安全性相關），而疫苗的動物毒性試驗為非臨床安全性評估的根據。歐美皆有針對疫苗的動物毒性試驗提出法規，本中心疫苗工作小組是否應此類法規納入將來之工作項目，尚待討論。

10 至 11 意見一併回覆如下：

委員所提內容，係查驗中心召開之第一次及第二次專家諮詢委員會議之紀錄。故委員的意見，將適時於第三次專家會議中提出討論，以供國家衛生研究院疫苗研發之參考。