行政院及所屬各機關出國報告

（出國類別：專題報告）

美國細胞、組織工程及生技產品之管理研習報告

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關鍵詞：細胞組織產品、生物科技、藥政管理、美國食品藥物管理局

內容摘要：
隨著醫藥科技的發展，藥品不再侷限以傳統的合成方式來製造，甚至生物科技、基因工程等也變的大眾化，最新的研究是利用細胞、組織、幹細胞及臍帶血，甚至基因治療技術，來發展個人化的治療藥品。由於這些技術相當的先進，即使在國外也多屬研究階段，因此，為了解美國食品藥物管理局對於這類產品之管理方式，因此提出細胞與組織工程產品之管理的研究計畫。本計畫除前往美國食品藥物管理局實地參訪，另外前往美國默克生物製劑廠，以了解產業界的狀況。但也像前面所說的細胞組織工程產品尚屬新興階段，同時這類產品亦屬廣義的生物製劑產品，因此本報告內容將不僅限於細胞、組織工程產品，亦包括其他的生物製劑產品，此外，亦將報告本人於美國俄亥俄州立大學研修醫學法律及公共政策形成及執行課程及相關參訪內容。

本文電子檔已上傳至出國報告資訊網
(http://report.gsn.gov.tw)

摘要

隨著醫藥科技的發展，藥品不再侷限以傳統的合成方式來製造，甚至生物科技、基因工程等也變的大眾化，最新的研究是利用細胞、組織、幹細胞及臍帶血，甚至基因治療技術，來發展個人化的治療藥品。由於這些技術相當的先進，即使在國外也多屬研究階段，因此，為了解美國食品藥物管理局對於這類產品之管理方式，因此提出細胞與組織工程產品之管理的研究計畫。本計畫除前往美國食品藥物管理局實地參訪，另外前往美國默克生物製劑廠，以了解產業界的狀況。但也像前面所說的細胞組織工程產品尚屬新興階段，同時這類產品亦屬廣義的生物製劑產品，因此本報告內容將不僅限於細胞、組織工程產品，亦包括其他的生物製劑產品，此外，亦將報告本人於美國俄亥俄州立大學研修醫學法律及公共政策形成及執行課程及相關參訪內容。

目　錄

前言與目的

隨著科技的日新月益，無論是在太空、資訊、農業、食品、醫療器材、化妝品等各產業都有長足的進步，甚至醫藥品也從傳統的合成製造方法演進到以基因工程技術製造藥品，現在更進步到以細胞、組織、臍帶血幹細胞或基因治療等最新生物科技，發展個人治療之藥物，其目的乃在將治療的副作用降到最低，並能達到最高的治療效果，然究竟新的生物技術用於治療疾病是否已達到初步的成效？其實目前都尚在動物實驗階段，然而依據進行中之研究結果顯示，運用細胞、組織、臍帶血幹細胞或基因治療等新技術來治療疾病，將是未來醫藥界發展的主要趨勢與方向。

然而運用這類新科技的產品或治療方式，所衍生出來的倫理與法律問題，將突破以往傳統的法律概念，因此，也成為醫藥界與法律界研究的新課題，行政院衛生署為因應此類產品或治療方式的管理，目前除已參酌其他先進國家的管理方式，並配合我國國情規劃相關初步管理規範，然因此類產品之複雜程度與科技演進的速度，超乎一般人的想像，為避免未來出現管理法規無法配合科技進展的窘境，因此提出細胞與組織產品管理的出國研修計畫，希望藉由這個計畫了解美國目前管理法規的最新進展，同時與國外建立一個對話溝通管道，進而規劃我國管理法規的未來走向。這個計畫只是一個開端而不是結束，

因為，科技的發展是持續不斷而非停滯不前，唯有不斷吸收國外新知才能跟得上國際的腳步，也唯有如此才能訂出合乎國情與國際標準的管理法規，進而吸引跨國大藥廠來台投資設立研發中心，希望藉此帶動我國整體醫藥產業的研發水準，同時提昇我國的國際知名度，進而達成推動台灣成為亞太生技製藥研發中心的目標。

現階段分工

生技製藥產業為行政院重點推動之科技產業之一，行政院在多年前即成立跨部會小組推動生技製藥產業的發展，其成員主要包括國科會、經濟部及衛生署，除了以行政院開發基金直接投資產業外，並引進國外相關高科技人才與先進技術，希望創造一個良好的研發環境，使國內的生技製藥業不致落後國外先進國家過多，進而開發新產品，使台灣真的成為亞太生技製藥研發中心。

在國科會方面，負責主導基礎研究計畫，歷年來推動國家型製藥研發計畫與國家型基因體計畫，以整合國內的學術與研究單位資源，並確立相關單位的分工，以避免各機關重複編列預算，使納稅人所繳的每一分錢都能達到最大經濟效益。此外，建立人才資料庫，使有需要的廠商能透過資料庫，覓得所需要的生技製藥人才與相關研發技術。

在經濟部方面，推動成立財團法人工業技術研究院、財團法人生

物技術開發中心、財團法人製藥技術發展中心等，鼓勵國資藥廠與前述財團法人建立研發的合作關係，並將研發成果轉移廠商以達實際產品量產與商品化，這部分推動的重點不僅在於技術的移轉，同時也鼓勵研發人員的交流，唯有如此才能提昇整體台灣製藥產業的人員素質，也唯有如此才能提高產品商品化的成功機會。

在衛生署方面，負責主導醫藥品管理政策的制定、法規的鬆綁與執行，透過修改不合時宜的法規並訂定合理可行的新法規與審查制度，使得產業界、學術界以及研究單位，在具體明確的規定下進行新產品及新技術的開發，以期縮短與其他先進國家的科技水準差距。成立財團法人醫藥品查驗中心，目的在建立一個有效率與獨立的審查機制，並輔導國內生技製藥產業於進行早期新藥研發時，建立有效的溝通對話窗口。透過亞太經合會(APEC)計畫，建立與其他會員國衛生單位的溝通管道，希望藉此尋求各國間的審查標準一致化，進而達成醫藥品審查相互認證的最終目標。補助各醫學中心成立早期臨床試驗病房，配合國內優秀的臨床研究人才，鼓勵跨國性企業來台設置臨床研發中心以提昇我國整體的生技製藥業研發能力。此外，對於目前最新的基因治療等新醫療技術的研究，參考美國國家衛生研究院(NIH)的做法，由財團法人國家衛生研究院(NHRI)負責主導整合研究計畫，以期在國內有限的資源下，能產出最大的成效。

簡單的說明目前國內各部會在生技製藥研發與產品上市所扮演的角色後，將進一步介紹衛生署藥政處對於藥物管理現況，以助於了解本計畫的必要性與重要性。藥物包括藥品與醫療器材，以下分別就藥品與醫療器材作簡單說明。

國內藥政管理現況

藥品可區分為新藥、學名藥與生物製劑，目前所有列屬藥品管理的產品均需辦理藥品查驗登記[1]，經衛生署審核產品的安全性、有效性及品質，符合規定並核發藥品許可證後，方得以在市面上販售。此外，藥品的製造工廠須辦理工廠資料備查且須符合確效規範亦即所謂的 c-GMP (current-GMP)，目前為縮短審查時間加速產品上市，衛生署已將法規鬆綁，同意工廠備查案與查驗登記案可同時提出申請，但須兩部份申請案均審核通過後，方可核發藥品許可證。

醫療器材依產品所具危險性高低可區分為一(低危險性)、二(中危險性)、三(高危險性)等三等級，目前除低危險性及部分中危險性醫療器材品項[2]無須辦理醫療器材查驗登記外，其餘醫療器材均須辦理醫療器材查驗登記，俟衛生署審核產品的安全性、有效性及品質，符合規定並核發醫療器材許可證後，方得以在市面上販售，同時自民國九十四年六月二十一日起須全面符合醫療器材優良製造規範(GMP)。醫

[1] 新藥及學名藥查驗登記應檢附資料及注意事項，請參考行政院衛生署出版之藥品查驗登記審查準則，生物製劑類藥品則請參考衛生署網站刊載之「生物製劑類藥品查驗登記」。
[2] 請參考行政院衛生署 89.6.21 衛署藥字第八九０三四二五一號公告附件三。

療器材產品製造工廠則須符合品質系統文件(QSD)認可登錄。

藥物核准上市繼續追蹤上市後使用情形，如發生副作用時則經由全國藥物不良反應通報中心通報系統，並完成安全性評估後，儘速將副作用相關資訊提供給醫療專業人員及全國民眾知悉，以避免類似副作用繼續發生。此外，為確保產品品質，除加強市售品抽驗作業及GMP 後續查廠外，目前亦積極規劃海外查廠，同時已於九十一年完成首件海外查廠，以確實了解海外製造廠生產現況。

又為使正當使用合法藥物而受害者，獲得及時救濟，衛生署仿效德國及日本藥害救濟制度，研擬藥害救濟法，經立法院三讀通過，於八十九年五月三十一總統令公布實施[3]，使我國成為世界上第三個有藥害救濟制度的國家，惟目前僅適用藥事法第六條規定之製劑，且暫不含中藥，以上簡單說明我國目前藥物管理現況，由於衛生署累積多年的審查經驗，同時採取嚴謹的管理方式，因此，國內並未如國外發生非常嚴重的藥物副作用不幸事件。但對於一些新科技衍生的新產品，如細胞、組織、幹細胞等，因其產品不同於一般化學製劑藥品，且涉及醫療器材及藥品等複合產品，同時牽涉到新醫療技術，因此使得這類產品的管理與審查，有別於目前的藥物審查與管理方式，又因為這類產品目前在國內外都有長足進步，且其潛在的醫療價值，使得

[3]藥害救濟法公布實施前，衛生署在八十七年十月十二日公告「藥害救濟要點」，並於八十八年一月十二日正式實施，其目的乃在藥害救濟法通過前，藉由行政命令來救濟藥害受害者。

身為衛生主管機關的我們必須正視未來即將面臨的課題，也確實讓我們體察到這個計畫的迫切與重要。

美國及國內現階段對細胞組織產品之管理規範

什麼是細胞、組織產品？就以往概念上的認知，包括了血管器官、骨髓、血液製劑(全血、紅血球、血小板及血漿)，或是源自於動物的組織等[4]，此外，像由細胞或組織分泌或抽提物，如：母乳、軟骨組織(collagen)、urokinase、cytokines 及生長激素等也都歸屬於細胞及組織產品。然而，並非所有的細胞或組織產品均納入衛生主管機關管理之範疇，唯有當這些產品涉及醫學研究或臨床上使用時，衛生單位方考慮將其列為管理項目。例如，有關人工生殖之胚胎授精卵等品項，實已有完整之管理規範且行之有年，然因科技進步越來越多新的人體細胞及組織產品被運用在醫療上，因此，基於此類產品之來源及於製造、操作過程中之安全及品質上考量，美國食品藥物管理局生物製劑審查暨研究中心在一九九七年二月二十八日，重新且完整的對這類新產品提出「以細胞和組織為基源之產品管理基準草案」，草案中特別指出「以人體細胞和組織為基源之產品」並未包括前面所提到的血管器官、骨髓、血液製劑、母乳、軟骨組織等產品，因為前面所提到的這些產品目前均有相關之管理規範，或是由其他單位負責管理

[4] 在美國上述產品目前係由 Health Resources and Services Administration 管理。

(見註四)，且已被列入管理多年。然經美國食品藥物管理局生物製劑產品審查暨研究中心在匯集產業界、學術單位及其有關研究單位對於該草案內容所提出之建議修改意見後，已將「以人體細胞和組織為基源之產品」之名稱變更為「人體細胞，組織，及以細胞和組織為基源之產品」，不過據美國食品藥物管理局生物製劑審查暨研究中心在二００三年一月二十一日公告之補充說明中特別強調，此項變更僅在進一步澄清及說明該類產品之品項名稱，至於規範之產品實質內容則與原草案中之定義相同並無任何改變。

上面談了這麼多的「以人體細胞，組織，及以細胞和組織為基源之產品」，似乎仍未提到實質列的產品品項，其實這也是困難之一，因為就像前面所說，隨著科技進步，此類產品之項目究竟有多少，其實也很難給一個明確的定義，不過我們可以了解的是，這個基準草案的誕生，與目前最熱門的臍帶血幹細胞在疾病治療及預防上的運用，有相當程度的關聯，由於以往並無這類產品，因此，並未對這類產品加以列管，即使美國食品藥物管理局到二００四年一月二十一日起才強制要求須依「以人體細胞，組織，及以細胞和組織為基源之產品管理基準」辦理產品查驗登記，且其管理的重點乃在防止傳染性疾病的散佈。至於國內目前則僅公告優良組織操作規範，來管理相關之產品。

研究經過

本人之出國研究計畫申請過程與以往的行政院出國計畫有一點不太一樣，那就是本人獲得行政院人事行政局推薦參加財團法人學術交流基金會的傅爾布萊特交換學者計畫(Fulbright Exchange Scholar Program)，因此除需向學校提出入學申請外，同時得向財團法人學術交流基金會提送出國研究計畫，學術交流基金會的申請部分，除填寫一些個人學經歷及履歷表格外，尚需撰寫研究計畫及檢送三封推薦信函。必需在學校同意入學且學術交流基金會審查通過後，才由美國政府的 CISE 核發交換學者的簽證(J-1)。以下就開始報告本人的出國研究經過。

本人的出國研究計畫包括二部分，一是在俄亥俄州立大學選修課程，另一部份則是前往位於賓州西點默克疫苗廠及至美國食品藥物管理局相關部門參訪。在俄亥俄州立大學研修部分，包括與醫學暨公共衛生衛生學院公共衛生學系流行病學暨生物統計組(College of Medicine and Public Health, School of Public Health, Division of Epidemiology and Biostatistics)的副教授茱蒂許沃絲邦(Judith A. Schwartzbaum)博士選修獨立研究[5]課程，同時，考量本次出國研修主題與法規管理及政策擬定有密切之關聯，且期望對於美國相關醫療法規及新政策的研擬及形成有初步了解，因此，在獲得指導教授建議及

[5] 依俄亥俄 州立大學及公共衛生學系規定，需取得該系教授願意擔任指導教授，方取得該系進修之資格。由於 Dr. Schwartzbaum 爲本人碩士論文指導教授，爲簡化重新申請入學之所需經歷之繁瑣程序，且在徵得與本人同意擔任指導教授後，因此獲准入學同時選修獨立研究課程。

同意下，選修旁聽二門課程。

第一門是同所醫療服務管理政策組(Health Services Management & Policy, HSMP)醫事法律課程(Legal Environment of Health Care)，授課教師為凱薩琳海樂律師(Kathryn Haller)，她本人目前擔任俄亥俄州立大學附設醫院首席法律顧問，同時參與俄亥俄州多項醫療相關法律之制定，是一位醫療相關之州法律與聯邦法律專家。上課所用的課本為貝瑞費洛(Barry R. Furrow)、湯瑪斯葛林尼(Thomas L. Greaney)、珊卓拉強森(Sandra H. Johnson)、提摩西史度佛絲裘斯特(Timothy Stoltzfus Jost)及羅柏特許瓦茲(Robert L. Schwartz)等教授的著作醫療法律第四版(Health Law, Cases, Maerials and Problems, 4th edition)一書，課程內容涵括如何透過法律機制保障醫療照護的品質、美國的醫病關係、醫療服務涉及的法律問題、醫療照護的財務原理、衛生主管機關對於醫療機構的管理以及法律與倫理的關聯。每堂課均從醫療法律一書中，指定閱讀教材與討論問題，而學生則須事前閱讀準備，以便於課堂中就討論問題進行辯論，每堂課原則上海樂老師會先就討論主題略作說明，並指定一至二位同學就討論問題作口頭報告，此外，要接受其他同學問題。海樂老師要求每位主講同學在課堂中的表現，就要像一位執業律師，除了能表達其個人法律觀點外，同時要回答同學問題，海樂老師則在口頭報告結束時，就討論問題作更詳細的解

說。除此之外，海樂老師會就討論主題，提供最新的最高法院判例及相關規定給我們參考，例如：談到安樂死這個主題時，她將俄亥俄州公佈的生存遺囑(Living will)提供給我們做參考，而衍生出的相關問題就是，病人是否有接受或拒絕治療的權利，醫師是否應該尊重病患的個人自主意願等等。這種開放式討論的教學方式對於我這個台灣學生而言，真是大開眼界，但也讓我獲益匪淺，一方面對於同學的上課臨場表現及對資料的準備感到佩服，另一方面，也體悟到台灣如果真的要談教改，除了老師要努力外，學生們要更加努力，這樣才有辦法作到像美國的這種程度。

第二門課程則是由社會暨行為科學學院公共政策管理研究所開授之公共政策形成及執行(Public Policy Formulation and Administration)，授課教師為瑪莉瑪威爾博士(Mary K, Marvel)，瑪威爾博士目前為公共政策管理研究所副教授，她的研究主要與公共政策計畫的形成、執行與評估有關，她曾在史丹福大學胡佛學院(Hoover Institution at Stanford University)擔任訪問學者，在日本大阪大學社會暨經濟研究院(Institute for Social and Economic Research at Osaka University, in Osaka, Japan)擔任訪問研究員，同時也曾在英國牛津大學沃佛申學院社會法學研究中心擔任訪問研究員(Center for Socio-Legal Studies at Wolfson College, Oxford University, Oxford, United Kingdom)。課程內容重點在了解公共政策的制定與執行，進而

使學生能運用於未來的實際工作中，且訓練學生深入且確切的思考能力。由於公共政策的制定與執行涉及社會學、經濟學、管理學、群眾心理學等跨領域的課程，因此，會去選讀這門課的主要是公共政策管理研究所或管理相關研究所的學生，上課形式主要由瑪威爾老師主講，同時輔以小組討論的形式，讓學生將所學理論運用於模擬問題，是一門將理論與現實充分結合的課程。此外，課程要求學生須繳交二篇研究報告，學生必須從一九七0年至一九九八年間聯邦政府通過的國內計畫中選擇一項為其報告主題，該項計畫則須至少與二個公共法案相關，同時該計畫之執行需透過政府部門間的聯繫網路，當然最重要的是學生必須對所選擇的題目具備個人本身或專業上的興趣。第一篇報告須就所選擇的聯邦計畫作立法上的分析，不應僅描述該法案的立法歷程，重點應包括研究動機，整個法案立法的演進與變遷，法案問題起源，推動立法的團體及推動立法的原因，反對立法的團體及反對立法的原因，反對與推動團體於立法過程中的互動及策略運用，其他與該政策有關的次團體，活動過程中代號(symbol)及標誌的運用，適用何種議題模式(model of agenda formulation)，如何運用媒體的影響力，主要的政策決定政府機關，哪一類的政策，該類政策是否隨時間改變，該政策與政治是否與羅伊(Lowi)所提的公式一致，政策決定的運用是採取何種模式，此種模式是否隨時間改變，其他彰顯此議題

重要性的社會經濟因素，政黨如何影響此議題及議題內涵，其他對此議題有助於了解、改變或欠缺的因素。第二篇研究報告則為第一篇報告的延續，其重點為分析研究計畫的執行過程，學生必須自行建構出一個執行模式(implementation model)，進一步必須提供相關證據驗證所提之模式。如果說第一篇報告內容是在解釋某一法案的形成與歷程，第二篇報告內容則是在解釋這個計畫與該法案的相關性以及其實際執行內容，此外，學生必須從其研究過程中決定相關政府部門間對該計畫的執行力與影響力，同時提出證據證明其推論。除此之外，計畫的執行與預算的來源有很大的關係，因此透過預算來了解計畫的內容是一個普遍被接受的方式，所以學生須另外制作一個預算表作為附件，預算表的內容應以過去五年的實際撥款數為基礎，其項目則包括預算年度(Fiscal Year)、實際撥款數(Appropriations, actual)、眾議院通過之預算數(House Recomendation)、參議院通過之預算數(Senate Recomendation)、執行單位原提預算數(Budget Requests, estimate)、相關公共法案數目(Public Law Number)、預算相關之參議院報告數目(Senate Report Number)及預算相關之眾議院報告數目(House Report Number)，相關之預算資料可由圖書館政府部門相關資料中查得。同時，學生必須在剛開學即就所選定的計畫，與州政府、地方政府或非營利計畫執行單位接觸，找出合適且願意接受訪問的計畫實際執行人

進行訪談，經由訪談的過程，更深入了解整個計畫的執行面。最後將訪談所得實際執行經驗資料，結合課堂中所學的理論，即達到第二篇報告的要求。從上面所作的簡介似乎有點摸不著頭緒，簡單的套句瑪威爾老師上課所說的話，計畫執行是一個因變數(dependent variable)，而這些影響計畫執行的因素就是自變數(independent variable)，第二篇報告就是要學生找出這些自變數，最後再將所有自變數串起來並結合因變數，就完成了這個計畫的實際內容。我個人對於這種將理論與實際結合在一起的教學方式，覺得非常實用也充滿著挑戰性。這個課程不僅可以訓練學生獨立研究的能力，同時也考驗學生的溝通能力。又因為這門課研究的主題與社會息息相關，因此，增添本課程的趣味與實際，從這門課讓我充分體會到台美除了教育方式的差異外，學生本身求學態度上也非常不一樣。美國研究生讓人感覺比較積極也會對詢問主題預作準備，台灣的學生則認為我來跟你要資料，你就應該給我所有的資料，最好是有電子檔案，這讓我對台灣未來世界上的競爭力感到憂心。

在俄亥俄州立大學研修期間，除了旁聽這兩門課外，因考量到俄亥俄州立大學附設醫院為一設備完整之醫學中心，必定進行相當多的臨床研究試驗，於是向指導教授許沃絲邦提出參觀俄亥俄州立大學附設醫院的臨床試驗研究中心，在指導教授熱心的引薦下，認識了一位

臨床研究整合護士凱若許奈德(Carol Schneider)，凱若目前服務於俄亥俄州立大學附設醫院的急診醫學部，主要負責急診方面有關的臨床試驗整合工作，由於凱若在俄亥俄州立大學從事臨床試驗研究已有十年經驗，且其以往臨床經驗包括在婦產科、麻醉科及外科，因此可稱得上是一位對執行臨床研究計畫相當有經驗的專業醫療人員，此外凱若因工作上需要，目前也正在修習俄亥俄州立大學醫學暨公共衛生學院公共衛生學系的碩士課程。經由凱若的進一步解說，讓我了解到在俄亥俄州立大學附設醫院，除了臨床試驗研究中心負責進行臨床試驗外，其他各醫療部門也都有其獨立之臨床試驗研究人員，負責進行該部門特殊用藥之臨床試驗，由於凱若與俄亥俄州立大學附設醫院臨床試驗研究中心的護理部主任賈桂林芭克博士(Jacalyn Buck)為多年好友，因此，就在凱若的溝通協調下，前往俄亥俄州立大學附設醫院的臨床試驗研究中心進行參觀訪問。當天芭克博士先給我們一個簡單介紹，該臨床試驗中心設置在俄亥俄州立大學附設醫院的十樓，在四十二年前由美國國家衛生研究院(National Institute of Health)輔導補助成立，該中心同時為美國國家衛生研究院最早補助成立的臨床試驗中心之一，從過去到現在曾於該中心進行之臨床試驗包括有心血管科、新陳代謝科、神經科、泌尿科、婦產科、外科等及其他專科之新藥，另外也進行營養品方面之臨床試驗。以臨床試驗分期而言，該中心進行

之臨床試驗包括第一、二期(Phase I、II)臨床試驗、第三期(Phase III)大型臨床試驗及上市後之臨床試驗(Phase IV Clinical Trial)。該中心成員包括醫師、護士、藥師、營養師、統計師及臨床試驗檢體初步處理技術員等，設備方面則有電腦室、營養品調配分析室、實驗室、病房、病患訪談室及病患休息室及測試室等，設備非常完善，但是因為該中心屬使用者付費制，因此，雖然該中心執行過相當多的臨床試驗，其臨床試驗團隊也相當有經驗，但是就使用率而言並未達到百分之百；另該中心自設立至今已有四十二年的歷史，因此，在硬體設備方面，雖持續在更新中，然因空間之使用已達飽和，故對其業務推展似已產生限制，幸而該中心目前已有遷址計畫，預計在數年內將遷至新的大樓，這對該中心未來長期的發展又展現新的契機。在與凱若及賈桂林的討論中更進一步知悉，在俄亥俄州立大學附設醫院進行臨床試驗，均須依優良臨床試驗規範(Good Clinical Practice)進行，試驗開始前必須先經人體試驗倫理委員會(Institution Review Board)審查通過後，方可進行臨床試驗，至於人體試驗倫理委員會的組織，目前除俄亥俄州立大學附設醫院設有院內人體試驗倫理委員會外，另外有一個私人的人體試驗倫理委員會亦從事臨床試驗計畫案件之審查。俄亥俄州立大學附設醫院人體試驗委員會成員數十名，但每次開會僅需五位(須包括醫療、法律、一般代表)代表出席，每二個月招開一次會議，由於

申請案件眾多且委員會委員均為兼任且為無給職，因此，較無法掌握時效，是故很多講求時效的臨床試驗申請案件，即轉而尋求私人經營之人體試驗倫理委員會之審查，然暨屬私人經營之人體試驗倫理委員會，其收取之審查費用自然較高，據凱若的了解每件案件收取之費用大約二千元美金。所有已核准進行的臨床試驗案件，每年均須取得人體試驗倫理委員會的再同意，同時每年須向人體試驗倫理委員會繳交年度報告，報告執行進度及其他重要事項。如發生不良反應事件時，也應事不良反應的嚴重程度，在規定期限內向人體試驗倫理委員會報告狀況及處理情形。其他如有任何計畫變更等也都須向人體試驗倫理委員會報告。基本上，臨床試驗的運作與規範跟台灣目前狀況大同小異，只是美國的醫療保險與台灣的全民健保差異頗大，特別是如涉及美國的醫療照護系統，也就是常聽到的 Medicare System，與其他私人醫療保險給付時，就增加了很多的文書工作。特別是在今年七月 HIPPA 為配合電子病歷及相關資料的網路傳輸之作業，因此，作了大幅修正與要求，重點就是在事先取得病患的個人病歷資料釋出同意，也因此大大增加了臨床試驗進行時的文書作業與歸檔。此外，由凱若的經驗中讓我了解到，其實他們在進行臨床試驗時，也遭遇到所謂的整合與溝通方面的問題，例如，在急診進行某藥品臨床試驗時，需用到一種新的醫療技術或治療方法，然而這種治療方法在其他專科已屬

常規之治療方法，因此已知清楚要如何處理突發狀況，或是已將原來的方式加以改進，然而對於凱若而言，在她摸索了幾個月而找不到好的方法後，就在一次與其他科研究護士閒聊中，發現原來對她而言是新的挑戰，在別人那裡已早不是問題，因此，她也有感而發的告訴賈桂琳其實俄亥俄州立大學附設醫院臨床試驗相關部門，應定期開個溝通協調會議，就此可以聽取別人的經驗，同時也可以彼此交換臨床試驗的心得。我不知道在台灣是否也曾發生相同的狀況，因此我認為提供臨床試驗研究諮詢，應該也是成立臨床試驗研究中心的目的之一。

如同本人在出國研究計畫中所提到，俄亥俄州立大學研發經費充足且具備各方面的研究人才，又因近年來學校非常鼓勵專任教授們與產業界進行產學合作計畫，因此學校特別成立所謂的研究發展基金中心(Research Foundation)，專門負責協助教授們將研發之成果移轉給產業界，同時也提供申請專利或許可證照等相關法規諮詢服務。由於我在俄亥俄州立大學期間，適逢研究發展基金中心成立十週年，同時新的生物醫學研究中心的也舉行動工破土典禮，因此舉辦了一系列的學術演講活動[6]，同時安排一場由一九八九年諾貝爾化學獎得主湯瑪斯凱齊博士(Thomas Cech, Ph.D.)的專題演講，演講題目是「Catalytic RNA to Howard Hughes」。具催化功能的核糖核酸(Catalytic RNA)是凱

[6] 整個系列的演講題目與主講人如附件所示。我因上課衝堂關係只參加了週一及週五的演講活動。

齊博士的主要研究項目，也因為發現具催化功能的核糖核酸，而使他獲得一九八九年的諾貝爾化學獎。此外凱齊博士目前正擔任 Howard Hughes 醫學研究院(Howard Hughes Medical Institute)的董事長，該研究院主要進行生物醫學相關的研究，同時也提供眾多獎學金(Fellowship)與計畫補助(Grant)，讓學生及世界各國的研究人員申請，因此在這個六十分鐘的演講中，凱齊博士從他過去的研究經歷侃侃而談到目前的工作內容，整個講演非常的有啟發性，也讓在場的聽眾瞻仰到大師的風範。我自己則體會到，成功絕非一蹴可幾，不管是在研究工作或是行政工作，同時，也讓自己感受到仍有很多改進的空間與無限的潛能。

以上即為本人在俄亥俄州立大學所進行的研修課程內容，至於第二部分參訪賓州西點默克疫苗廠及至美國食品藥物管理局相關部門參訪的研修內容，將在**觀摩實習參訪過程心得**章節中詳細說明。

具體成果或心得

在俄亥俄州立大學所選修的課程，其中有關公共政策形成及執行，其實收穫頗豐富，一方面是因為過去並未學習過這門課程，透過這門課程讓我進一步了解美國公共政策運作方式，特別是美國採聯邦、州政府與地方政府之制度，大部分政策的形成與執行多由州政府主導，然涉及一些全國性的共同議題，則主要由聯邦政府編列預算，

然後由州政府提出需求與執行之計畫，進而向聯邦政府申請預算，整個運作方式原則上與台灣現階段頗為類似，最大不同點在於一些與州民切身有關之議題，則完全由州政府甚至地方政府自主，州民透過直接或間接民主[7]方式表達其心中意願。舉個例子，由於全球經濟不景氣，美國也遭遇相同的經濟困境，像我所居住的哥倫布市，就面臨下年度預算嚴重削減，因此，就透過民意的直接表達來重新編列預算的重點，我想這是生在台灣的我們所無法想像的，因為我們一向都是透過代議士政治決定國家未來走向，甚至地方政府也是一樣。我國國民所得每年已超過兩萬元美金，台灣的社會已稱得上高度開發，不過我們的民眾卻一直是弱勢的一群，因此，當我學過這個課程後，深覺得要使台灣真的像美國成為一個不只在經濟，在政治上的先進國家，加強民主教育是一個必須，同時這些代議士們，應放棄政黨成見，發自內心為全民福祉，而不是政黨私利，惘顧民眾權益來做一些決策。

另外從醫學法律這門課，由於美國州政府與聯邦政府管轄事項，區分的非常清楚，例如：我讀到幾個有關安養中心的案例，雖然這是屬於州政府的管轄權限，但是州政府都有相當完整的規範，例如照護人員資格及配置、空間大小及病人數目、儀器設備、負責人資格及權責等，且設立安養中心均需經州政府衛生主管機關核准登記。反觀台

[7] 所謂直接民主即公民投票，間接民主則爲代議士政治。

灣的狀況，屬地方社會福利機關主管事項，目前並無完善法規規範照護人員等事項，因此，常在社會版看到一些安養中心的糾紛事件，台灣已漸步入老人化的社會，這些問題應不能再漠視，中央政府也許不應涉入過多地方管轄事項，但是一些原則性的規定，仍可由中央協助訂定，再由地方視其各地區特性制定單行法規。另外，對於病患接受或拒絕治療的權利，我想在台灣一向以醫師為主體的醫病模式，衛生署應致力推動讓病患了解自身病情，然後才決定究竟要接受治療或拒絕治療，這才是對病人基本權利的尊重。以上是個人對於在俄亥俄州立大學研修的心得。

觀摩實習參訪過程心得

由於本次出國研修主題是「細胞及組織工程產品管理」，因此除了到學校學習相關之管理課程外，到藥廠參觀訪問及至美國食品藥物管理局研修，是絕對不可缺少的行程，特別是美國食品藥物管理局，對於醫藥品的管理在全世界居於領導地位，其原因不外乎其有最優秀的審查人力，同時也有科學家進行檢驗技術的研發與改良，因此從最早的臨床前試驗，到進入人體試驗，新藥申請乃至於上市後藥品使用的監測，都建立一系列完備的申請與審查管理制度，這些制度對於我國在更新審查規定時都具有指標性的意義。

整個參觀訪問的行程早在出國前就開始進行聯繫的工作，原本在

出國前即已初步獲得美商默沙東大藥廠位於賓州西點製造廠(West Point Site, PA)及美商惠氏大藥廠位於紐約州珍珠河製造廠(Pearl River Site, NY)，二大生物製劑藥廠同意前往參觀的回覆，當初之所以計畫參觀二家藥廠的原因，一方面是因為目前世界上數一數二的藥廠多位於美東，同時近年來政府財政困難，出國參訪機會大幅的減少，特別是給基層公務人員的出國研修機會更是少之又少，因此，這次有這麼難得的出國機會，不好好把握且有效的運用，實在對不起行政院人事行政局的美意，也辜負了納稅義務人辛苦繳納的稅款。但是在出國後，得知美商惠氏大藥廠與美國食品藥物管理局間協議，從二００三年十月到十一月初，安排一系列的查廠活動，因此，截至我從俄亥俄州哥倫布市出發前兩天，才收到來自該公司聯絡人楊遵明醫師的回覆，原廠因美國食品藥物食品檢驗局將前往查廠，因此，無法安排在原訂時間參訪該製造廠，但是如果我可以更改參訪時間，該廠則可安排在十一月中進行參訪活動。由於本人因受限於行政院人事行政局參訪活動十五日及不得來回繞道的規定，也只好放棄這個難得參觀美商惠氏大藥廠的機會。好在更改後的行程，仍然讓我獲益匪淺，這是直得感恩之處。以下就針對我的整個觀摩實習參觀訪問行程作詳細報告。

我的整個觀摩參觀訪問行程共計十五日，開始於九十二年十月十

八日到十一月二日劃下完美的句點，每日安排的活動行程請參考附件觀摩實習計畫表。另外需在此一提的是，由於處內高科技小組的黃儀君博士，適逢到美國食品藥物管理局進行為期四週的訓練活動，因此本人此次的觀摩參訪行程，主要是與黃博士一起行動的。九十二年十月十八日抵達了夢寐以求的華盛頓巴爾的摩國際機場(Washington Baltimore International Airport)，在此要謝謝黃博士與目前服務於美國食品藥物管理局的李啟仁博士開了一個多小時的車前往機場接機，隨後即前往位於華盛頓地區的派克威爾(Parkville)旅館將行李安置妥當，並聽黃博士說明她在美國食品藥物管理局研習一週的心得，同時對於第二天到賓州默克藥廠參訪的行程，先預作沙盤推演，不僅將兩人預先收集的資料再整理一遍，同時，也將目前處內所遇到的問題作一番整理，以便請默克藥廠研究人員提供以往經驗，作為我們研擬改革方案之參考。第二天一大早，我和黃博士拖著重重的行李，前往華盛頓特區的聯合車站(Union Station, Washington D.C.)，搭乘火車前往賓州的費城，這是我第一次在美國境內搭乘火車，因此，感到格外興奮。途中還認識的一位天普大學民意調查研究學院(Institute for Survey Research Temple University)的梅爾克爾蘭德(Mel Kollander)教授，克爾蘭德教授同時也是天普大學民意調查研究學院華盛頓特區辦公室的負責人，主要負責天普大學與政府單位間委託研究計畫的聯繫工

作，此外，他們也接受一些亞洲國家政府委託於美國進行一些與該國形象等有關的民意調查計畫，他告訴我們他曾拜訪過亞洲的中國大陸及日本，知道我們是從台灣來的，同時又服務於政府單位，因此表現出高度的興趣，本來還有意邀我們一同便餐，以便多了解更多我國現況，然因我們的行程緊湊因此僅交換了名片，從這個短暫的相遇，也讓我感受到其實台灣在美國，也具相當知名度，因此只要我們全體國民更團結努力，立法機關能以全體國民為福祉，少一些口水戰，努力於民生法案審查，必能振興我國整體經濟發展，同時也較易引進一些外商來台投資。

到了賓州的費城，搭上默克藥廠安排的交通工具前往默克藥廠，大約經過了三十分鐘的車程，就到達位於的默克藥廠藍鐘園區(Blue Bell Campus)，這個園區主要是默克藥廠的行政單位，另外一些早期臨床試驗的計畫書編撰及統計分析部門都位在這個園區內。負責接待我們的是一位夏貝爾哈柏博士，哈柏博士出生於貝魯特，九歲時全家移民到法國，後來到美國完成大學及博士學位，從事目前的工作已有四年，主要負責默克藥廠美國總公司與亞洲各國分公司，辦理疫苗產品查驗登記有關之業務聯繫工作，因此，亞洲各分公司的查驗登記部門人員，在進行疫苗新產品查驗登記或已領有許可證之疫苗產品進行各種變更時，都由哈柏博士負責準備資料，也因為如此哈柏博士必須

對製造廠，產品製程，製程及分析方法確效，安定性試驗，檢驗規格方法，臨床前試驗，臨床試驗，產品上市後不良反應通報等，都要有一定程度的了解，才有辦法提供國外分公司的查驗登記部門人員需要的資料。因此，這次哈柏博士特別針對我們的需要，安排了一天半緊湊同時也是最精華的參訪行程。由於我們到達藍鐘園區時已有一點遲到，所以見到哈柏博士後，只簡單的寒喧交換名片後，隨即由夏貝爾博士開車帶我們前往默克藥廠位於西點的廠區(West Point Campus)，沿途風光明媚，特別是在這葉子轉黃的秋季，顯的格外宜人，也讓我們領略到台灣無法觀賞到的美國鄉野美景，大約二十分鐘的車程終於到了西點廠區。到達默克藥廠西點廠區時，先經警衛核對身份證件並換發臨時通行證後，隨即前往第 53B 建築物二樓的會議室展開第一個行程。

第一個行程的講師是默克研發實驗室訓練發展部門經理傑夫葛利克 (Jeff Garelik, MRL Training ad Development)，題目則是「默克研發實驗室的新藥開發歷程(Merck Research Laboratories--Drug Discovery and Development)」。以下簡單介紹簡報內容，葛利克先生首先介紹他自己，他畢業於紐約州立大學水牛城分校，主修生物學，隨即進入默克工作，服務於研發部門，在工作一段時間後，申請在職進修，進入企業管理研究所攻讀碩士學位，取得企管碩士後回到默克

藥廠工作，後來才轉到現在的部門，負責員工教育訓練的工作。這個簡報主要的目的是讓我們對默克藥廠有一個整體的了解，也讓我們知道一個新藥要經過怎樣的歷程，才可以在市面上販售，另外葛利克先生也表示，這個簡報也是所有默克新人的新生訓練第一課。簡報從默克藥廠創辦人喬治默克(George W. Merck)先生所說的一句話揭開序幕，「藥品的開發是為了全人類福祉，而不是為了創造利潤 (The medicine is for the people... not for the profit)」，同時這句話也是所有默克人的座右銘。默克研發實驗室開發的藥物，包括：心血管疾病(Cardiovascular disease)用藥、骨質疏鬆症治療及預防(Osteoporosis treatment and prevention)用藥、抗感染及抗病毒藥物及疫苗(Bacterial and viral diseases / vaccines)、後天免疫不全症候群治療(AIDS therapy)藥物、止痛藥(Pain relief)、青光眼(Glaucoma)治療用藥、氣喘及潰瘍(Asthma and Ulcers)治療用藥以及河盲症(River Blindness)治療用藥等。默克研發實驗室在全世界均設有研發中心，包括：美國的羅威(Rahway)、西點(West Point)、聖地牙哥(San Diego)以及西雅圖(Seattle – Rosetta Inpharmatics)，此外在加拿大蒙特婁(Montreal)，歐洲的英國、法國、義大利(IRBM)、西班牙(CIBE)，以及日本(Banyu)均設有研發中心。除了這些研發中心外，在世界各地也進行多國多中心的新藥臨床試驗，包括：美國本土、加拿大、墨西哥、歐洲、亞洲、澳洲及紐

西蘭等地區。至於默克研發實驗室的目標則希望經由創新的研究來發展新藥及疫苗以達到拯救及增進人類的生命。除了人用藥品之外，默克研發實驗室也從事動物用藥的研發，此外出版品，也是默克研發實驗室研究人員的一項主要工作，默克出版的一些書籍對於從事醫藥研究的人來說絕不陌生，包括：默克手冊(The Merck Manual)、默克指引(The Merck Index)、老人醫學默克手冊(The Merck Manual of Geriatric Medicine)以及動物用藥默克手冊(The Merck Manual of Veterinary Medicine)等。介紹完默克研發實驗室的背景資料後，接著說明如何開發一個新藥，同時葛立克先生給了我們一個神奇數據，那就是開發一個成功的藥品，大約要花上五百萬到八百萬美金。新藥開發的過程，包括下面三個：

(一) 基礎研究階段(Basic Discovery)：這個階段結合了生物學(Biology)及藥物化學(Medicinal Chemistry)的基本理論。在這個階段首先需要確認治療的目標器官，接著尋找活性成分，先進行體外試驗，確認藥品化學結構與活性間的關係(Structure-Activity Relationship - SAR)後，才進入下一個階段。

(二) 臨床前試驗階段(Preclinical)：這個階段結合了製程化學(Process Chemistry)、安全性評估(Safety Assessment)、藥

物代謝(Drug Metabolism)、藥劑學研發(Pharmaceutical R & D)等學門。除了注意製程放大的問題，還要小心藥品會不會導致畸形兒、有沒有致癌性等問題，是否具生體可用性，另外還要從藥物的基本化學性質，以及治療部位來決定要將它作成口服的錠劑或膠囊，還是打針的注射劑，或者是外用的藥膏或貼布。

(三) 臨床試驗階段(Clinical)：這個階段牽涉到臨床研究及藥政管理法規。臨床試驗又可分為三個階段，也就是臨床試驗的第一期(Phase I)、第二期(Phase II)以及第三期(Phase III)。臨床試驗第一期目的除了確定藥品的吸收及代謝外，另外包括藥品在器官及組織的作用及安全性，這個階段的試驗人數大約為十二至八十人，且須為健康自願者。由於這是藥品首次使用在人的身上，因此須格外的小心。第二期臨床試驗目的則在確定藥品用於治療疾病的有效性、短期使用的副作用、治療劑量範圍。這個階段的受侍者人數可從一百人到三百人之間，同時全部的受試者均為病患，採用的試驗設計為隨機、雙盲、對照組試驗。第三期臨床試驗則是在確認藥品在病人的療效及安全，同時希望觀察到較不常見的副作用及長期使用引起之副作用，進

而作為藥品仿單上的說明事項。這個階段的受試者人數約為一千到一千五百人，有時還會持續數年的後續追蹤病患的狀況。

在首次進行臨床試驗前，必須向美國食品藥物管理局(Food Drug Administration, FDA)提出臨床試驗計畫書(Clinical Trial Protocol)申請，這個過程稱為 IND (Investigational New Drug)，經過食品藥物管理局核准後，才可以正式進入臨床試驗。臨床試驗進行到一定程度後，才可提出新藥查驗登記申請，經美國食品藥物管理局審核產品品質、療效及安全後，即可核准藥品上市(有關藥品的審核過程，將於參訪食品藥物管理局乙節中詳細說明)。聽完了葛利克先生的這個簡報，除了讓我重新複習新藥的開發歷程，也讓我初步學習到美國藥政法規的規定。

在結束第一堂課後，也到了中午用餐時間，我們與默克藥廠處理國際性查驗登記部門的工作人員一起用餐，在此不免一提默克藥廠的餐廳，為了提供一萬多名員工的用餐，您就可以想想這個餐廳有多大，設備新穎且具設計感，此外下午還供應下午茶，提供一個舒適環境，進而使員工在這環境中不斷創新開發出新的產品。中午用餐時間也不得閒，因為趁著短暫的休息時間與哈柏博士唐娜芮考斯哈柏基女士詢問一些國內目前遇到的仿單著作權歸屬問題，以及藥品登記時資

料保護的問題，兩位專家表示在詢問相關部門後，將在第二天給予我們答案。同時，他們也藉此機會，詢問我們國家對於製造廠確效，以及藥品登記的相關問題，黃博士和我也將所知道的規定一一答覆。

用餐完畢即開始下午的課程，首先由默克疫苗廠製造部門(Merck Manufacturing Division)疫苗法規及分析組(Vaccine Regulatory and Analytical Science)的資深科學家唐林柏格(Don Lineberger)博士為我們說明「分析方法的開發與確效(Assay Development and Validation)」。這堂課非常符合我們的需求，尤其正當國內積極推動製造廠全面確效(cGMP)之際，林柏格博士以默克疫苗廠的開發經驗，從產品的開發流程，點出分析方法的開發時程與確效研發切入的時點，接著就分析方法的開發、定量方法確效、以及如何設定檢驗規格作詳細解說。從他的說明中了解到，分析方法的開發是與製程同步進行的，並且需要不斷的改進，因為唯有如此，才可以用最專一(specific)的方法檢測出主成分含量，也才能確認分析方法的再現性(reproducible)與有效性(validate)。基本上，默克研發實驗室以國際法規協合會(International Conference on Harmonization, ICH)的 2QA 及 2QB 及美國藥典(USP)為分析規範的藍本，佐以自行研發的分析方法及流程，最後完成分析方法的書面作業程序(Protocol)草案，必須歷經廠內反覆驗證後，再提公司的審查小組確認，最後才正式成為藥廠的

標準作業程序。聽完這堂課，讓我對平常審查的檢驗規格及確效，有了進一步的認識，也才真正明瞭藥廠全面實施確效的重要性。

下一堂課可說是前一堂課的延續，主講者為默克疫苗廠製造部門無菌製劑產品釋出(Sterile Product Release)小組的彼特麥納茲考(Pete Mlnarczyk)經理，主講題目是「無菌製劑的釋出(Sterile Product Release)」，這堂課麥納茲考經理同時請部門裡一位同仁張鏡燕[8]女士參加，巧的是張女士也是來自台灣。麥納茲考經理首先指出他這個部門成立的緣由，依據美國聯邦法規編號 21 冊的 210 及 211 項(Code of Federal Regulations 21, Part 210 and 211)的規定，藥廠應設立一個品質管制部門，該部門必須確認最終產品的品質，同時對該最終產品負全責，在此所謂的最終產品除了藥品本身外，還包括了直接接觸藥品的容器、容器的蓋子、製程中添加的化學物質、外包裝以及標籤等。接著，麥納茲考經理進一步說明一個疫苗產品上市所必須經歷的檢驗程序，首先產品必須通過品管部門的檢驗，接著是製程中所有下料紀錄、抽驗紀錄及製造紀錄等文件均須符合要求，最後也是最重要的就是通過食品藥物管理局生物技術產品評估及研究中心(Center for Biologics Evaluation and Research)的審查及化驗。以下麥納茲考經理將實際的作業程序更具體的解釋給我們聽，第一步是決定及評估檢驗

[8] 張鏡燕女士畢業於師大生物系，在默克疫苗廠服務時間已超過十五年。

的方法，默克研發實驗室對每一項產品會先定出檢驗規格及檢驗方法，製造部門則在規定時點將檢體送檢驗部門進行測試，無菌製劑產品釋出小組則在所有的測試完成後進行評估，對於無法通過檢驗測試的檢體，則由檢驗及製造部門共同進行原因探討。除此之外，無菌製劑產品釋出小組必須對製程相關文件進行評估，這部分的工作包括：確認製造部門工作人員及製造標準作業程序均已先審核通過、製造部門主管已檢視相關製程文件且確實符合規定、無菌製劑產品釋出小組工作人員，則針對上面所提到的這些書面文件作再確認，同時對於不妥之處提出改進建議事項，必要時，製造部門與無菌製劑產品釋出小組的同仁可一起協商如何改善，最後無菌製劑產品釋出小組的工作人員必須簽名確認。另外對於製程中發生的異常狀況，要求必須填報異常程序報告(Atypical Process Reports)，報告內容需詳細描述這個可能會影響產品品質的異常事件，填報人則為製造技術部門人員，報告須先經製造技術部門主管審查通過後，再送無菌製劑產品釋出小組部門審核，無菌製劑產品釋出小組需決定發生製造異常事件的這批產品是否上市或廢棄，同時決定該採取如何的矯正補救措施。基本上，異常程序報告為默克藥廠的內部評估報告，並不會送食品藥物管理局生物技術產品評估及研究中心。其中值得一提的是對於這些書面作業程序文件及製造批次紀錄，依照默克的檔案保存標準作業程序，其保存年

限為十二年。在報告最後麥納茲考經理特別將向食品藥物管理局生物技術產品評估及研究中心申請產品上市的流程提出說明，首先在向食品藥物管理局生物技術產品評估及研究中心前，無菌製劑產品釋出小組需先確認該批產品已完成所有檢驗的規定，同時檢視所有製程資料，接著無菌製劑產品釋出小組需將檢驗結果及這些資料整理成一份書面作業程序，最後再將上面提到的這些資料以及檢體送食品藥物管理局生物技術產品評估及研究中心審查及檢驗，食品藥物管理局生物技術產品評估及研究中心收到申請後，即開始進行書面審查，必要時會就檢體進行化驗，當食品藥物管理局生物技術產品評估及研究中心審核完成通過後，即會以書面通知默克疫苗廠無菌製劑產品釋出小組審核通過的產品批號，接著該批產品即可在市面上販售。其實目前國內對於生物製劑產品亦有類似的規定，每一批生物製劑產品及血液製劑上市前，必須先經過藥檢局檢驗合格封緘後才可在市面上販賣。結束下午第二堂課，先與張鏡燕女士及哈柏博士到餐廳喝下午茶，同時聊一聊默克疫苗廠的一些小故事，這時我也發現很多默克人都一組一組的一起討論，這讓我很羨慕也領悟到，因為有這樣的工作環境，默克才能吸引這麼多世界各國的精英在默克工作，默克也才能開發出這麼多的新藥，以造福全人類。

接下來的節目是參觀默克研發實驗室的先導工廠，負責接待我們

的是生物製研發部門資深主任喬伊布蘭柏博士及生物製劑先導工廠主任馬歇爾蓋敦先生。由於這是一個先導工廠，因此並不需要經過食品藥物管理局的查廠，但是內部的相關設計都是符合 cGMP(current GMP)的規範。又因為生產的產品是生物製劑，因此很多管制區的空氣清淨度都要求達 100 等級(Class 100)，同時在當初設計時就考慮到避免不必要人員進出，但又需要很近距離的觀察到工廠內部運作情形，因此特別在工廠外圍設置一條通道，讓人不需要進到現場，就可以很清楚的看到工廠內大部分的陳設。布蘭柏博士一一為我們說明，所在位置的功能，同時再次強調這個先導工廠是符合 cGMP，原物料、人員、廢棄物的進出通道都是分開的，整個動線要求的標準絕對不低於真正的製造廠。由於先導工廠是作為生產默克研發實驗室開發的新生物製劑以及既有產品改進配方技術之用，所以這些產品只提供臨床試驗之用。廠內容量最大的反應器可達五千公升，我跟黃博士私下討論，可能只要一個二千公升反應器所生產的生物製劑藥品就足供台灣一年的用量。接著布蘭柏博士還帶著我們去參觀先導工廠製造水、空氣管道、廢水處理等設施，光是管道間的建築材質就都是防火、防震的。另外廢水需處理排放標準也是要求高規格，因為整個西點藥廠廠區內就規定先導工廠必須先將廢水處理到一定清淨程度才可排放到園區的下水道中，這也可以看出該廠對於環境保護的重視。最

後，哈柏博士還告訴我們一個小秘密，那就是哈柏博士之前就曾安排過韓國衛生單位人員及其他國家衛生單位人員參觀這個先導工廠，但是都沒能真正成行，我們則是第一個真正成行的團體，結束了這個參觀行程也結束了我們第一天的活動。

第二天第一節課主要是談目前默克進行中的新藥臨床試驗，共包括二部分，第一階段由默克研發實驗室疫苗及生物製劑產品全球策略研發實驗室助理主任保羅克普蘭(Paul Coplan)博士主講的帶狀泡疹(Herpes Zoster)疫苗臨床試驗及人類免疫不全病毒(HIV)疫苗臨床試驗的開發現況。克普蘭博士來自南非，畢業於哈佛大學公共衛生學院，主修生物統計學，同時也取得企業管理碩士學位。由於克普蘭博士報告的內容，為默克目前最新的研發計畫，因此在默克列為最高機密，故並未提供書面資料，僅能就記憶所及撰寫報告。默克之所以開發帶狀泡疹疫苗的原因，主要是因為美國老年人約有百分之二十二到三十患有帶狀泡疹，其症狀會造成病患難以忍受的疼痛，目前並無有效的治療藥物，發作時通常只能以止痛藥與鎮靜劑來緩解病患的症狀。有鑑於此，默克藥廠以其過去對於A型肝炎及B型肝炎疫苗[9]的研發經驗，因此著手於帶狀泡疹疫苗的研發，根據目前初步臨床試驗結果顯示效果不錯。另外，克普蘭博士簡單的提了一下 HIV 疫苗的

[9] 帶狀泡疹爲病毒所引起之疾病，A型及B型肝炎也是病毒引起的疾病，所以默克以其以往開發病毒性疫苗經驗來開發帶狀泡疹疫苗。

開發狀況，默克之所以開發 HIV 疫苗，乃是因為根據默克公司所作的流行病學調查，很多非洲國家的 HIV 感染率高達百分之七十到八十，甚至有些村莊達到百分之百，很多家庭全家都感染 HIV，父母親因感染 HIV 在三十幾歲就死亡，留下來許多感染 HIV 的孤兒，造成非洲非常嚴重的社會問題，至於世界上其他國家，HIV 感染問題也日益嚴重，因此默克投下大筆研發經費進行 HIV 疫苗的開發，目前的開發仍屬非常早期，至於未來是否能成功的開發出治療 HIV 的疫苗，套句克普蘭博士的說法現在下結論還太早一點。

第二階段是由默克研發實驗室全球疫苗及生物製劑法規事務部門研究員賈姬米勒(Jackie Miller)醫師報告輪狀病毒(Rotavirus)疫苗臨床試驗的執行現況。米勒醫師首先對輪狀病毒作介紹，輪狀病毒是在西元一九七三年由澳洲科學家儒仕拜夏柏(Ruth Bishop)首次發現的，輪狀病毒同時也是最常導致嬰兒胃腸疾病的病毒，每年在第三世界國家約造成一百萬人次的死亡，被輪狀病毒感染的嬰兒，會引起發燒及腹瀉等症狀，同時輪狀病毒引起的免疫反應並無法絕對避免下一次感染，發生過一次自然感染以後，對於以後感染的保護力約為 40%，對於以後發生腹瀉的保護力約為 75%，所以很多兒童會不只得到一次輪狀病毒感染，因此有開發輪狀病毒疫苗的必要，基於這個原因，默克藥廠著手開發這個新疫苗，目前已有多個跨國性的第三期臨

床試驗正在進行中。其中一個臨床試驗台灣的臺大醫院亦為試驗中心之一，由於該試驗目前已接近尾聲，同時已開始進行統計分析等作業，據米勒醫師的了解，根據初步的分析結果顯示，這個新疫苗在臨床上顯示有療效，且有統計學上的意義。由於米勒醫師接下來的時間將與公司高層進行輪狀病毒臨床試驗得報告，因此，並沒有留給我們時間發問，但是表示如果我們隨時有疑問，都可以透過哈柏博士詢問。

接下來是由默克研發實驗室全球產品安全及流行病學部門之副作用通報主管席拉庫克(Sheila B. Cook)女士報告的默克的安全監視制度(Safety Surveillance at Merck)，同時出席的有副作用通報部門副主管唐娜馬龍(Donna Marron)女士，由於藥品不良反應通報系統在國內尚屬啟蒙階段，因此了解默克內部的通報流程，及後續追蹤處理方式，可供我國通報系統未來改善之參考，同時也可了解跨國性的大藥廠是如何看待不良反應通報制度。以下僅就庫克女士的報告作重點式的回顧。

默克對於藥品不良反應通報系統，主要分為二大部門，一為臨床評估及安全監視，另一則為全球安全通報及流行病學分析部門，底下又區分為不良反應通報、通報資料處理以及歐洲辦公室等三個支部門，庫克女士即為不良反應通報支部門的主管。

臨床評估及安全監視部門成員包括醫師、藥師及護理師，總人數

約三十人，主要的任務為：(一)對於通報之不良反應，進行即時評估同時區別該不良反應與藥品是否具關聯性；(二)對於試驗中藥品，藉由通報提供臨床試驗主持人最新的副作用資訊，以避免更多甚至更嚴重之不良反應發生；(三)定期評估已上市藥品仿單內容，提供作為全球仿單修改之依據；(四)從醫學及法律觀點審查作為廣告及促銷之資料；(五)作為公司內部諮詢專家。

全球安全通報及流行病學分析部門，依分支部門主管業務，彼此相互合作以達成產品安全監測最終目標。不良反應通報支部門之任務包括：在各國衛生主管機關規定通報時間內完成不良反應通報，不良反應通報之後續追蹤，通報資料品質控管(正確性、完整性、時效性)，不良反應通報相關之教育訓練等。通報資料處理支部門之任務包括：從不良反應通報資料庫產出有價值之報告；維護及改善通報追蹤系統；更新不良反應通報語彙及通報系統之確效；依 ICH E2 之規定及報告格式產出安全性更新報告。有鑒於歐洲與美國時差及歐洲之不良反應通報有別於美國食品藥物管理局之規定，因此設置歐洲辦公室支部門，該部門之主要任務包括：指定「適當人選(qualified person)」負責歐盟各國之藥品監測業務；代表默克歐洲分公司提報歐盟以外國家發生之不良反應報告；主導歐盟藥品監測相關業務；由所謂「適當人選(qualified person)」與歐盟各分公司進行不良反應資訊之收集。默克

目前對於剛上市未滿三年的藥品，規定每季必須通報一次，之後則延長為每年通報一次，與 ICH E2 規定的六個月略有不同。

至於不良反應通報來源，則可細分為試驗中新藥通報、上市後藥品之自發性通報、及其他須通報事項。試驗中新藥通報，如屬警示性也就是危險超出效益(Alarming Events, risk outweighs benefit)之不良反應，需立即以口頭方式，向全球安全通報及流行病學分析部門總部通報，接著書面報告須在二個工作天完成。如屬嚴重不良反應，須在二個工作天以書面方式向全球安全通報及流行病學分析部門總部通報，不論是發生在試驗進行中或試驗完成後之追蹤期間之不良反應均須通報。如屬輕微之不良反應，僅需向分公司及臨床試驗總部通報即可。上市後藥品之自發性通報，可分為嚴重及輕微二類，屬嚴重不良反應須者，書面報告須在二個工作天內完成；屬輕微者其書面報告則在十個工作天內完成通報即可。其他須通報事項包括：懷孕，接觸到農藥或動物用藥，各國藥政單位所規定須通報之事項，書面報告通知期限為二個工作天。

當全球安全通報及流行病學分析部門收到各地傳回之不良反應報告後，對於嚴重且非預期之不良反應，會採取下列行動，立即通報食品藥物管理局，同時請臨床評估及安全監視部門進行初步評估，必要時進行流行病學之分析評估，接著將衛生機關評估結果及公司內部

臨床評估等資訊彙整後，進行仿單更新，接著將更新後之仿單通知全球分公司，以便向各國衛生機關申請仿單更新。另外對於在預期範圍內發生之不良反應，則採取每季通報(剛上市三年內)或每年通報之(上市超過三年)之原則。

聽完庫克女士的報告，再與國內全國藥物不良反應通報中心處理程序作一比較，似乎大同小異，對於較輕微之不良反應，全國藥物不良反應通報中心會主動通知廠商進行仿單之修改，但受限於人力及經費問題，目前僅限於監視中新藥之品項。對於一些上市多年的藥品，由於以往核准之仿單內容過於簡略，並未將陸續出現之不良反應資料更新於仿單中，故常造成病人及醫師的困擾，特別是國內目前推動之藥害救濟制度，其救濟之基礎係依據核准之仿單內容，因此要如何透過副作用通報制度更有效畫分產品或醫師之責任，將是未來努力的方向。

結束了藥品不良反應通報課程後，就到了中午用餐時間，哈柏博士特別安排我們與輪狀病毒疫苗臨床試驗研發小組工作人員一同用餐，在短短的四十分鐘午餐時間，知道輪狀病毒疫苗臨床試驗就目前已完成的幾個中心臨床試驗結果來看前景看好，在不久的將來就可揭曉完整的報告，屆時也會將完整報告送衛生署審查。

午餐後又來到默克藥廠西點廠區(West Point Campus)，因為下午

哈柏博士替我們安排的最後一個活動是參觀無菌製劑充填設備(Tour of Locally Controlled Environment Filling / Formulation Facility)，負責接待我們的是生物製劑產品釋出部門(Biological Product Release)的貝瑞史塔克門(Barry Starkman)先生，在進入廠區參觀前，史塔克門先生先就充填廠區的設計、規劃、人員及物料動線、抽檢(In process control)等作說明，接著換裝進入廠區，由於目前國內正推動製造廠確效，而無菌充填對於注射劑或疫苗等，為最關鍵的步驟，因此，如何確保產品的無菌性，應屬首要之事。基本上默克無菌充填過程中，採全自動化，因此，除了將藥品原液及包裝容器置入需靠人力，其餘步驟均由機器操控，只需一人監測機器運轉，至於充填後包裝如不合規格，亦立即透過紅外線監測系統篩選排除。為確保成品品質，製造完成藥品還會再經過人工檢選，將一些包裝有瑕疵之藥品剔除，史塔克門先生就拿一個實際例子給我們看，因為瓶蓋的地方凹了一點點，所以不符合品管而被剔除。他又說一些第三世界國家因為貧窮買不起疫苗，如果能將未通過品管之瑕疵品送給他們使用，將能改善這些國家的公共衛生問題，不過反對的聲音則表示對默克商譽將造成影響，因此，即使公司內部有這種建議，也僅止於說說的階段。參觀完廠區後就結束了兩天的參訪活動，由於哈柏博士要到費城上課，所以順路送我們到費城火車站搭車，回到華盛頓聯合車站時已是晚上八點多了，睡了一

個好覺繼續明天的活動。

第二天一大早搭乘地鐵前往位於美國國家衛生研究院(National Institute of Health, NIH Campus)的食品藥物管理局生物製劑產品審查暨研究中心(CBER, FDA)，由於我們此次並非透過官方正式管道進行參訪，而是以李啟仁博士研究室訪問科學家進行短期拜訪。所以與生物製劑產品審查暨研究中心其他單位的聯繫工作，均是透過李博士的幫忙。當天早上李博士先告訴我們一些辦公室注意事項，由於美國自從九一一事件後，政府機關加強對於人員進出管制，因此，即使對我們這些外國政府訪客也不例外，在李博士的協助下，先辦好了生物製劑產品審查暨研究中心所在的二十九號建物(Building 29)臨時通行證，接著李博士帶著我們認識國家衛生研究院的環境，我們先到位於二十九號建物對面的醫學中心(Medical Center)，這是國家衛生研究院最主要的建築物，因為所有國家衛生研究院主導或贊助的臨床試驗都在此進行，每天都有從各州來的受試者到此參與臨床試驗。也因為如此這棟建築物內除了有完善的臨床試驗病房外，同時，國際級的演講廳及國家衛生研究院的圖書館都設在這棟建築物內。國家衛生研究院的圖書館館藏非常豐富，訂有最新的生物醫學的雜誌，同時也收藏各類的圖書，早期的圖書則作成縮影片，開放給大眾查詢，只是圖書館服務對象還是以國家衛生研究院園區任職的研究人員為主，因此，圖

書館內的圖書借閱以及電腦設備並未開放給外界使用。參觀完了圖書館，已到中午用餐時間，我們在醫學中心地下室餐廳簡單用完午餐後，回到李博士的研究室，先閱讀李博士提供的一些生物製劑審查參考資料，接著到國家衛生研究院圖書館找一些相關資料，之後看看還有剩餘時間，就到地下室的書店查看一些新出版的書籍，雖然書店格局不大，不過所販售的書籍卻都是最新的，同時也販售食品藥物管理局研究科學家的著作。例如：李博士就和他的女兒露西亞[10](Lucia Lee)醫師共同編寫了一本美國食品藥物管理局對於生物製劑審查有關的新書，據李博士表示這本書自九十二年上半年出版後，就頗受好評。其實李博士傾三十多年在美國食品藥物管理局的審查經驗，所撰寫的寶典要賣不好我想也很難。晚上由於生物製劑產品審查暨研究中心有一個讀書會，因為機會難得所以特別留下來參加，這個讀書會的主講人主要都是生物製劑產品審查暨研究中心各研究室的科學家，參加的人除了各研究室的研究人員外，也有幾位是來自華盛頓地區附近的大學生，因為這個課程也算是學校的選修課程之一。今天主講的題目是小兒麻痺疫苗，主講者從小兒麻痺的病因、疫苗的發現應用，到最新的發展，非常有層次的介紹，兩個小時的課程一下就過去了，讓我從新溫習小兒麻痺這個疾病，同時也學會兒麻痺疫苗的發展現況，收穫

[10] Dr. Lucia Lee 目前亦服務於美國食品藥物管理局生物製劑產品審查暨研究中心，由於她是小兒科醫師，因此主要負責業務是臨床試驗計畫、報告，以及查驗登記臨床資料的審查工作，她曾在九十一年間應本署邀請回台主講美國生物製劑臨床試驗審查現況，頗受好評。

非常的大。

第二天參加食品藥物管理局生物製劑產品審查暨研究中心主辦的「反恐用藥新藥開發廠商說明會」，之所以會參加這個研討會，也算是機緣巧合，剛到美國時因為沒有繁人的業務纏身，多出很多時間上網搜尋資料，無意間在食品藥物管理局的網站上看到這個研討會正開放報名，看看時間跟我到華盛頓地區參訪的時間差不多，同時又是免費，因此，立刻就寫電子郵件報名，第二天馬上就收到主辦單位的回覆確認。這個研討會為期兩天，主要由食品藥物管理局生物製劑產品審查暨研究中心的人員訓練部門規劃主辦，主講者全部都是食品藥物管理局各類產品的研究科學家以及審查人員，此外還邀請疾病管制中心(Center for Disease Control, CDC)的專家，詳細的議程如附件所列。所以這個研討會不單就反恐新藥的查驗登記或臨床試驗檢送資料作討論，還更深到美國政府對於恐怖份子主導生物戰發生時，解藥、疫苗、血液製品等生物製劑，甚至最新的細胞組織產品的國家儲備計畫都有介紹，但是美中不足的是，因為這涉及到大家常聽到的「國土安全(Homeland Security)」法案尚未通過，因此不論是食品藥物管理局的官員，或是疾病管制中心的代表都語帶保留。雖然如此，我仍覺得因為這個問題的產生，使得美國聯邦政府對反恐這個議題有關的法案，都成了重點，也使疫苗開發這兩年再次成為熱門焦點。整個研討

會讓我感受最深的是生物製劑產品審查暨研究中心，對於有心要開發生物戰解毒藥品廠商非常支持，另為了加速新產品上市，特別建立一套減化臨床前動物試驗的機制，同時生物製劑產品審查暨研究中心一再強調請業者作早期諮詢，並且不要放棄任何諮商的機會。從這個研討會我也發現細胞及組織類產品，目前向生物製劑產品審查暨研究中心申請的項目，仍僅止於臨床試驗研究階段且數目不多，主要的主導者仍是國家衛生研究院，經費也由國家衛生研究院掌控。

結束兩天的研討會，適逢週末假期利用這個難得的機會到華盛頓特區幾個景點參觀，原本想進白宮及國會山莊參觀，但因九一一後對參觀者管制非常嚴格，特別是進白宮必須由各州眾議員寫推薦信，且要在一個月前就提出申請，才可入內參觀，所以很可惜錯失參觀美國總統府的機會，但是，還好是參觀了很多免費博物館，總算不虛此行。

隔週，透過李博士的安排下拜訪了食品藥物管理局生物製劑產品審查暨研究中心細胞及基因治療組代理主管(Acting Director, Division of Cellular and Gene Therapies)普利博士(Raj K. Puri, M.D., Ph.D.)會談的一個多小時，由於生物製劑產品審查暨研究中心在去年七月業務重組，基因工程製劑產品審查業務，已改由一般製劑產品審查暨研究中心(Center for Drug Evaluation and Research)負責審查，但是細胞及組織工程產品以及基因治療產品、血液製劑、疫苗審查工作仍留在生物

製劑產品審查暨研究中心。對此，我感到非常好奇，是否有特殊原因才有此改變，然就普利博士及李博士的了解似乎只是單純的高層考量，並未涉及任何技術層面之問題。和普利博士的會談中，了解到目前在基因治療的研發工作主要由國家衛生研究院(NIH)主導，不過國家衛生研究院與生物製劑產品審查暨研究中心間合作非常密切，彼此間對於此新技術的一些細節都互相商討，只不過目前尚未有商品化之產品，僅限於早期臨床試驗之申請案。由於普利博士時間的關係，他答應我們，未來如有任何問題都可透過 e-mail 方式詢問他。

除了拜會普利博士，我們還拜會了負責血液製劑審查業務的翁美英博士，醫療器材審查相關業務的林秋雄博士，以及藥物動力學審查業務的陳美玲博士，這三位博士都是來自台灣的優秀前輩，在食品藥物管理局服務年資都超過十年以上，審查經驗非常豐富，過去也多次回台在研討會上分享審查經驗，對我們的藥政革新有相當大的幫忙。趁著這次難得參訪研修機會，也非別就教於他們，同時將我們心中一些疑問，就近請教大師們。除了拜會這些專家，我們也參加多場李博士他們研究小組內的討論會，李博士也將他三十多年的案件審查經驗及查廠經驗告訴我們，讓我獲益良多。當然週三晚上再次參加讀書會，本週主題是感冒疫苗，主講人也是服務於生物製劑產品審查暨研究中心的科學家，本身研究主題想當然爾就是感冒疫苗。她從感冒的

分類、命名等最基礎開始介紹，讓我豁然開朗，A、B、C 型感冒差異原來在於病毒的酵素 H 跟 N 的類型不同，而產生不同的感染程度，同時表現出來的感冒症狀略有不同，感染的對象或宿主也略有差異。進而介紹感冒疫苗，除了一般知道的注射劑型感冒疫苗，另外也介紹了去年剛核准的口腔噴霧劑型的疫苗 FluMist。時間總是短暫的，兩週的參訪時間一下子就過去了，這次除了讓我親身學習到藥物食品檢驗局對於生物製劑產品(包含細胞及組織工程產品)的審查態度，同時，也利用短暫研修時間盡全力建立與美方的溝通管道，我想這是此行最大收穫。

對業務改進之建議事項

經過三個月在俄亥俄州立大學的研修與美國食品藥物管理局及默克藥廠的參訪活動後，覺得有下列幾點可作為未來業務改進之建議：

一、 加強英文能力：台灣要國際化語文能力必須要加強，特別是基層公務員，因為唯有具備英文溝通能力，才可以將台灣推上國際舞台，而加強的方向先以生活化、簡單化為主，進而應加強業務相關用語之運用。

二、 應加強網路資源的使用性：特別是在網路發達的今天，人與人之間的距離，因為網路而縮短，如何將藥政處資訊完整上網，

同時讓民眾能很容易的找到所需要的資訊，這是一件非常重要的事，參考美國食品藥物管理局所架設的網站，條理非常分明同時在很短的時間內，就將最新的資訊上網，我想藥政處在這方面仍有很大的改進空間，同時希望藉此達到對民眾衛教的目標。

三、 舉辦讀書會，鼓勵處內同仁參加，使同仁能吸收到醫藥相關最新進展，藥政處因為工作繁忙，常常同仁都已經忙到沒時間思考，但是醫藥科技的發展是日新月異的，而衛生署的同仁需要面對民眾各式各樣的詢問，如何讓同仁能正確回覆民眾的問題，在職持續教育是一件必要的事。此外，國際上對於一些審查法規也持續在更新中，加強產品審查新規定的持續教育，則是另一項不可缺少的事。

四、 仿效美國食品藥物管理局舉辦業界溝通座談會，特別是推動新的法規時，為讓業者充分了解本處推動的政策，協助業者配合辦理，最好是每年都能舉辦溝通座談會或訓練課程，也可藉此機會訓練本處業務相關之新進人員，讓他們對自身業務更加了解。

五、 努力建立與美國食品藥物管理局的溝通管道，如能建立官方管道是最好的，不然也應建立與食品藥物管理局的華人良好聯繫

管道，希望透過他們的協助能取得美國對於藥政管理的最新資訊。

六、 由於本次前往美國食品藥物管理局主要研修題目是「細胞與組織工程產品之管理」，而其負責審查這類產品的單位是生物製劑產品審查暨研究中心(CBER)，目前國內雖尚無此類產品之申請案件，但已有類似基因治療的動物試驗在進行中，同時國內已公告的優良組織操作規範(Good Tissue Practice, GTP)係由醫政處負責，其係以醫療法第七條規範的新醫療技術觀點來審查，但以美國的經驗，這類治療最終目標是商品化，因此屬生物製劑產品審查暨研究中心主管業務，同時這類案件所需注意的，仍著重在細胞或組織的來源，以及如何保證細胞組織的不受感染，因此本質上與生物製劑較相近，故藥政處未來應更積極參與此類產品之規範制定與審查工作。

七、 由於本處近年來因業務量大增，人員的流動率也較以往高了許多，如何讓本處減少人員流失，同時吸引更多人願意來本處服務，僅就此次到默克藥廠與食品藥物管理局觀摩研習，提出個人淺見，先從空間來看，如果有機會希望長官能協助爭取更寬廣的工作空間，一個好的工作環境，將激發員工的工作情緒；簡化業務內容，例如：個人自用藥品業務之簡化，可將較常申

請之藥品列冊，授權海關核發或請藥學系工讀生協助審理。鼓勵員工參加持續教育或在職進修課程，必要時准予留職停薪；人才的培養不易，好的人才更是難尋，如何運用好的人才為機關建立最大利潤，完善的福利制度也是不可欠缺的，特別是對約聘人員，我想這是長官需要思考的；重新塑造本處形象，不要讓業界認為本處為培訓中心，建立約聘人員優先進用成為正式人員制度，讓約聘人員看得到未來，另外對正式人員也應有適度的培訓計畫，如此才不會出現人才中斷的現象。之所以會有上面這些看法實在是這次在美國食品藥物管理局或默克藥廠碰到的人都是資歷很深的人，很少有一、兩年的新手，當然人員的新陳代謝也是很重要，但是一、兩年的轉換率(turnover rate)似乎過於頻繁一點，這對資深同仁而言也是很累人的一件事，因為，一天到晚訓練新人，然後不久就離職，又需要承接新人留下的業務，這讓資深同仁情何以堪。此外，對人的基本尊重要建立，近年來因民意高張，廠商或民眾認為自己是頭家，而公務員就是公僕，所以頭家所說的話，僕人只得照辦，公務員代表國家，確實以服務民眾為目的，常常會發生衝突的狀況，是民眾對於法令不清楚所產生的誤解所造成，因此，如果能依前面建議改進衛生署網站資料，應能減少紛爭的比率。

結語

短暫的三個月研修在九十二年十二月底結束，非常珍惜這三個月的時間，自一九九六年完成學業回到台灣就職於衛生署藥政處，忙碌的工作，讓我沒有多餘的思考時間，獲得這個得來不易的機會，同時，也讓我回到校園，重新享受身為學生的樂趣，首先要感謝許科長蒨文推薦我報名參加考試，同時要謝謝處長的支持，讓我能夠三個月心無旁騖的在國外學習，當然還要謝謝科裏的同事以及代理人陳建維先生，在我不在的這段期間的協助業務順利進行。另外我還要感謝學術交流基金會的小姐，默沙東藥廠蘇建智先生，美國的李啟仁博士，如果沒有你們的幫忙，我的可能就無法成行，最後要謝謝我的指導教授茱蒂許沃絲邦博士，我的媽媽、弟弟以及我家的小皮蛋。當然還要感謝人事行政局的趙小姐幫了很多的忙。這次的研修也許沒有百分之百達成原訂目標，但是整個過程讓我學到很多事情，也體悟到自己要作修正，不管是在工作上或個人生活上，相信對於我未來的發展絕對是正面的影響。

附錄

1. 美國藥物食品檢驗局生物製劑產品審查暨研究中心主辦的「反恐用藥新藥開發廠商說明會」會議資料。
2. 美國食品藥物管理局生物製劑產品審查暨研究中心「以細胞和組織為基源之產品管理基準草案」。
3. 美國默克大藥廠參訪參考資料。

"COUNTER TERRORISM PRODUCTS REGULATED BY THE CENTER FOR BIOLOGICS EVALUATION AND RESEARCH: EFFECTIVE STRATEGIES TO ASSIST IN PRODUCT DEVELOPMENT"
October 23 - 24, 2003

DAY ONE: October 23, 2003

8:30 - 8:45	**Welcome** *Division of Manufacturers Assistance and Training* *Office of Communication, Training and Manufacturers Assistance, CBER*
8:45 - 9:15	**Counter Terrorism Products - An Introduction** *Jesse L. Goodman, M.D., M.P.H.* *Director, CBER*
9:15 - 10:15	**Submitting the IND: An Overview** *CAPT Donna Chandler, Ph.D., Deputy Director, Division of Vaccines and Related Products Applications* *Office of Vaccines Research and Review, CBER*
10:15 - 10:30	**BREAK**
10:30 - 11:15	**The Animal Rule - Efficacy** *Karen Goldenthal, M.D., Director, Division of Vaccines and Related Products Applications* *Office of Vaccines Research and Review, CBER*
11:15 - 12:30	**Pre-Clinical Issues** *Marion Gruber, Ph.D., Microbiologist, Office of Vaccines Research and Review, CBER* *Mercedes Serabian, M.S., DABT, Acting Chief, Pharmacology/ Toxicology Branch, Division of Clinical Evaluation and Pharmacology/Toxicology, Office of Cellular, Tissue and Gene Therapies, CBER*
12:30 - 1:30	**LUNCH**
1:30 - 2:30	**Clinical Development** *Jeff Brady, M.D., M.P.H., Medical Officer, Office of Vaccines Research and Review, CBER* *Steve Rosenthal, M.D., Medical Officer, Office of Vaccines Research and Review, CBER* *L. Ross Pierce, M.D., Medical Officer, Office of Blood Research and Review, CBER*
2:30 - 2:45	**BREAK**

2:45 - 4:00 **Other Regulatory Issues**

Select Agents *- M. Christine Anderson, Chief, Standards and Testing Staff, Office of Vaccines Research and Review, CBER*

Import/Export *- Kimberly Cressotti, Consumer Safety Officer, Office of Compliance and Biologics Quality, CBER*

Select Legal Issues including Informed Consent *- Mark Raza, Associate Chief Counsel, FDA Office of the Chief Counsel*

4:00 - 4:15 **Closing Summary - Adjournment**

Jesse L. Goodman, M.D., M.P.H.
Director, CBER

Counter Terrorism Products Regulated by the Center for Biologics Evaluation and Research: Effective Strategies to Assist in Product Development

October 23-24, 2003

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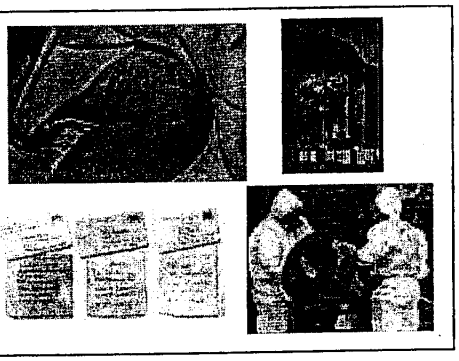
Fast-Tracking Biodefense Vaccines and Therapeutics : An Urgent Challenge We Must Meet

Introduction to CBER Workshop on Development of Counterterrorism Products

Jesse L. Goodman, MD, MPH
Director
Center for Biologics Evaluation and Research (CBER)

Bethesda, MD, October 23, 2003



CT: CBER Roles and Products

- **Roles:**
  - **Facilitate Product Development**
  - **Facilitate Product Availability**
  - **Help assure product integrity**
  - **Related research and regulatory activity**
- **Relevant Products**
  - **Vaccines, Ig, Blood and blood products, gene, cell and tissue therapies**
    - 133 active IND/IDE/MF/ 561 amendments
    - 93 CT research projects for unmet needs

Workshop Goals

- Help provide overview of all phases of CT product development process
- Share experience, lessons learned and help avoid common pitfalls, road bumps
- Stimulate interest, initiate dialogue, address FAQs

Assist in the more efficient development of new & innovative products for biologic, chemical and radiologic defense

Approaches to Speed Product Availability or Licensure

- Early and frequent consultation between sponsor, end user (if different) and FDA
- Availability for emergency use under IND
- Fast track and accelerated approval processes
- Priority review
- Approval under "Animal Rule"
- Careful attention to risk:benefit and risk management issues
- Incentives (existing: orphan, new: push or pull)

Usual Recommended Meetings

Pre-IND Meeting:
- -Manufacturing
- -Lot Release
- -Animal safety & immunogenicity
- -Phase 1 protocol

End-of-Phase 2 Meeting:
- -Phase 3 protocol(s)
- -Phase 1 & Phase 2 data
- -Animal efficacy protocols & data (if "animal rule" used)
- -Update on manufacturing & lot release

Pre-BLA Meeting:
- -Clinical data summary: Safety & Efficacy data
- -Manufacturing, etc.
- -Outline of BLA

Phase 1 → Phase 2 → Phase 3 → License Application

IND = Investigational New Drug Application
BLA = Biologics License Application

Early and Frequent Consultation

- Improves communication process
- Improves quality of laboratory and clinical studies
- Reduces misunderstandings and likelihood of unwelcome "surprises", multiple review cycles
- Improves efficiency of product development
- Very resource intensive for FDA
- Product teams at CBER being used for this purpose for priority BT product development and review (e.g. smallpox, anthrax vaccines)

Availability Under IND

- Can allow rapid access to an unlicensed product if there is an emergency need
- Simplification, flexibility for CT/BT issues
- Work towards licensure, wherever feasible
- Rapid turnaround/active assistance from FDA
  - recent examples in smallpox, anthrax, botulism

critical situation - emergency use : less than 24 hrs review.

Pros and Cons of IND Approach

- Pros
  - Clarity that a treatment is not a standard licensed therapy equivalent to routine prescription drugs
- Cons
  - Potentially Cumbersome
    - Especially in emergency e.g. witnessed, written consent
  - Connotation of "Experimentation"
  - Addressed by Bioshield

CT INDs : Making it Work

- Simplification, flexibility for CT/BT "streamlined" or "emergency use" INDs
- Rapid turnaround/active FDA assistance
  Clarity and language of consent process
  - Why it is "investigational", differentiation from research aimed at product approval, clear risk/benefit
  - Shortened documents, multiple media possible

Priority Review

- Product is a significant advance (drugs)
- For serious or life threatening illness (biologics)
- 6 month complete review of license application
- Recent example: pneumococcal conjugate vaccine
- Most CT products expected to qualify

less than 6 months

Fast Track, Accel. Approval

- Serious/life-threatening: meaningful therapeutic benefit over existing Rx.
- Allows for rolling submission
- Accel. approval:
  - Utilize surrogate endpoints likely to predict clinical benefit (314.510, 601.40)
    - E.g. CD4 cells for HIV, clinical markers (BP)
  - Post-licensure studies required (usually ongoing) to demonstrate effects on disease outcomes
  - Restrictions on use or distribution possible
  - Potential problems obtaining controlled data
- Withdrawal if agreements violated/not S&E
- Can approve through regular mechanisms with validated surrogate (e.g. protective Ab)

? enzyme replacement therapy

Emergency Use Authorization Proposal in *Bioshield*

- EUA – the nuts and bolts
  - An emergency must be declared by the Secretary of Homeland Security (national) or Secretary of Defense (military) or Secretary of HHS (public health)
  - The Secretary of HHS must issue the EUA (likely delegated to FDA)
  - The product must be for an agent that can cause a serious or life-threatening disease or condition; there is no adequate, approved, and sufficiently available product
  - The product's known and potential benefits must outweigh its known and potential risks (a challenge to define standards)
  - The product's use and/or distribution may be limited
  - The authorization will be time limited and can be terminated

Emergency Use Authorization II.

- EUA – the nuts and bolts (continued)
  - Certain information to the user/consumer is required, if feasible
    - product authorized for specific emergency use
    - the significant risks and benefits of the product
    - alternatives
    - option to accept or refuse administration
  - Appropriate information about the emergency use may be collected, if feasible

Animal Rule

- **Drugs & biologicals that reduce or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic chemical, biological, radiological, or nuclear substances**
- **Human efficacy trials *not feasible or ethical***
- **Use of animal efficacy data scientifically appropriate**

Animal Rule II.

- Still need human clinical data:
  - PK/immunogenicity data
  - Safety in population(s) representative of use
    - Civilian use often includes pregnancy, children
- Approval subject to post-marketing studies, any needed restrictions on use
- *Potential limitations:*
  - Where there is no valid animal model of disease
  - How to predictably bridge animal data to humans
  - Confidence may be an issue, even in valid models

Potential Incentive Approaches for Product Development

- Existing:
  - Expedited regulatory pathways
  - Orphan status; < 200k patients; 7 yr exclusivity
- Other possibilities
  - Push: direct financial rewards, tax credits, exclusivity, partnerships, R&D assistance (e.g. basic, proof of principle, pilot lot production, clinical)
  - Pull: known markets, longer term contracts, prices proportional to public health benefit, dual uses (non-BT)
  - Addressing liability issues
- *Bioshield*
  - New indefinite spending authority for critical countermeasures
    - ~$ 1 b FY04; SP, anthrax, bot; $ ~6 b over coming years

Bioshield Procurement

- Procurement Authority – The Basics:
  - The Secretary of Homeland Security has lead in identifying threats
  - The Secretary of HHS assesses availability and appropriateness of countermeasures
  - HHS Secretary identifies countermeasures that should be included in stockpile
  - Presidential approval of procurement recommendations
  - Congressional notice of Presidential decision
  - Contract terms
    - Payment conditioned on delivery of substantial portion of product
    - Can be terminated for non-delivery

Procurement Authority

- The Specifics for Existing Countermeasure Procurement
  - Sufficient amounts can be produced and delivered within 5 years
  - No significant commercial market for the countermeasure

FDA/CBER BT Research: Focus on Critical Pathways to Development

- ***Generally target unmet needs with regulatory implications to facilitate the development of products***
  - Better determine potency
  - Immunogenicity/protection, disease models, correlates
  - Assuring safety (e.g. cell lines, adventitious agents)
  - Make regulation more scientific, less "defensive"
  - Benefit multiple companies across industry
- Maintain staff "cutting edge" expertise needed for dealing with evolving biotechnologies
- Scientific expertise and confidence foster objectivity
  - Reduces risks of reflexive over- or under-protectiveness

CBER Research in BT: II.

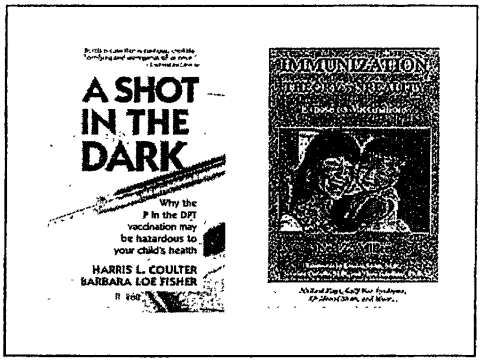
- Examples of current studies on threat pathogens
  - Smallpox: assay for immune response and potency, risk assessment on vaccine strategies and blood safety
  - Anthrax: Improved immunologic assays
  - VIG: Identification of protective isotypes, assays of commercial IGIV for activity, animal efficacy
  - Tularemia: correlates of immunity
  - Botulinum toxin: cellular trafficking of toxin, mechanisms of neutralization
  - General: stimulation of innate immunity/adjuvants
- ***As you develop products, we welcome your input as to unmet scientific needs***

Risk/Benefit for CT Products

- Risk:benefit differs and is assessed by FDA for each product & potential use
  - *Treatment*: For CT related products which have impact on otherwise untreatable serious illness, reasonable to tolerate significant risk & some uncertainty (but desirable to reduce)
  - *Prophylaxis*: If given to well individuals before event or, post-event, to individuals who may not be at risk, balance shifts
- For lethal disease, *lack of efficacy is a safety issue*
  - Ill-placed confidence
  - Something is not always better than nothing
  - Acceptance of an ineffective therapy may inhibit development or use of a more effective one
- All such products:
  - Need for honest and effective/efficient (*vs. legalistic*) risk communication process, *which may be quite challenging in unanticipated emergency settings*

Regulation and BT Products: What is the value added?

- As for other medical products (but perhaps even more important): need for consistent and objective protection of the public's safety *and need for trust*
- BT a moving target, no predictable epidemiology;
  - witness post-anthrax experience, extension of military products to broader or older populations
- The public expects safe (and effective) and products, especially vaccines given to well individuals, and looks to FDA for protection and reassurance.
- Preserving confidence in medical products, and in public health leadership, is critical.
  - When things go "wrong" (or even if someone just thinks they did); few will remember the crisis



What FDA Cannot Do

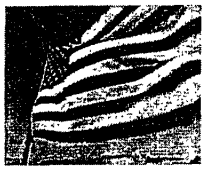
- Provide monetary or tax incentives
- Assure that anyone makes a product
- Advanced product development (conflict of interest)
- Provide indemnification or compensation
- Guarantee absolute safety
- Guarantee efficacy based on non-human data or based on non-BT experience

What FDA Can Do

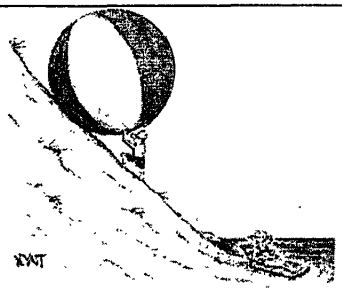
- Work with partners to identify unmet public health needs and coordinate responses
- Encourage sponsors to make needed products and facilitate their development through regulatory process: why we are here today!!!!
- Perform research that facilitates product development, safety and improves regulation
- Provide intensive & early interactions and regulatory priority where appropriate
- Increase confidence in efficacy of products
- Reduce likelihood of serious adverse events
- Partner with other agencies, health systems to improve monitoring of product use

Recent and Ongoing CBER Actions

- Meetings to encourage developing new products
- Early interactions w/ sponsors
- Collaboration and rapid turnaround on INDs
- Proactive trips to examine facilities
- Participation in multiple interagency and interdepartmental teams.
- Expedited approval of key product(s) apps.



- INDs/IDEs/MFs:
  - -2001 New-14, Amend.- 435
  - -2002 New-25, Amend.- 533
- License/License Supplement – 3
- "Site Visits": 18 manufacturing, 4 pre-approval (US/global)

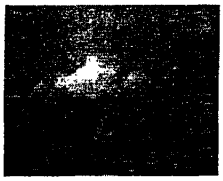


"Can't you ever relax?"

Thanks!

www.fda.gov/cber

- Email
  - Manufacturers: matt@cber.fda.gov
  - Consumers, health care: OCTMA@cber.fda.gov
- *Questions/comments now or later?*
- *As new CBER Director, I ask that you take advantage of your opportunity to help us move forward.*
  jgoodman@cber.fda.gov
- *We are very willing to work closely with investigators and sponsors of important BT products.*
- *We look forward to this meeting and welcome your input.*
- *Tremendous interest and we plan to modify as needed and repeat if successful.*



SUBMITTING THE IND: AN OVERVIEW

COUNTER TERRORISM PRODUCTS REGULATED BY CBER: EFFECTIVE STRATEGIES TO ASSIST IN PRODUCT DEVELOPMENT

October 23-24, 2003

Donna Chandler, Ph.D.
CAPT, US Public Health Service
Division of Vaccines & Related Products Applications
OVRR, CBER, FDA

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SUBMITTING THE IND: AN OVERVIEW

- Introduction & regulatory process
- IND content and format: original submission
- Maintaining the IND
- Common pitfalls
- CT Issues
- FDA guidance

2

INTRODUCTION REGULATORY AUTHORITY

- Food Drug & Cosmetic Act (21 USC 301-392)
  - FDAMA, November 12, 1997
- Public Health Service Act (42 USC 262 Section 351)
- Code of Federal Regulations

3

21 CODE OF FEDERAL REGULATIONS (CFR):

Part 600-680	Biologics
Part 312	INDs
Part 201, 202	Labeling and Advertising
Part 210, 211	cGMPs
Part 800	*In vitro* Diagnostics
Part 25	Environmental Assessments
Part 50	Informed Consent
Part 54	Financial Disclosure
Part 56	Institutional Review Boards
Part 58	GLP-Nonclinical Lab Studies

4

REGULATORY DEFINITIONS (21 CFR 600.3)

- **Safety**
  - ✓ Relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered...
- **Purity**
  - ✓ Relative freedom from extraneous matter in the finished product...
- **Potency**
  - ✓ Specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

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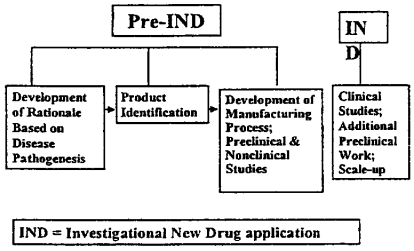
Product Development



IND = Investigational New Drug application

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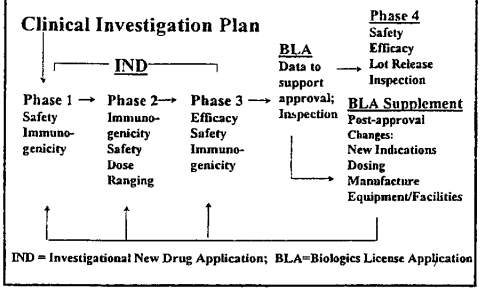
Stages of Vaccine Review and Regulation



IND = Investigational New Drug Application; BLA=Biologics License Application

PRODUCT APPROVAL PROCESS – BIOLOGICS LICENSE APPLICATION (BLA)

- Clinical Safety Data
- Efficacy Data (Clinical, Animal)
- Manufacturing
  - 21 CFR 600 Requirements
  - Process and Quality Control
  - Consistency
  - Lot Release
- Manufacturing Facility(ies)
  - Pre-Approval Inspection
- Product Stability Data – Expiry Dating
- Labeling
- Advisory Committee Discussion

INVESTIGATIONAL NEW DRUG APPLICATION (IND) ROLE IN BIOLOGICS APPROVAL PROCESS

- Mechanism and process to collect clinical data to support the license application
  - Demonstrate safety and efficacy
  - Goal: Information for the package insert
- Chemistry, manufacturing, and controls (CMC)
  - General biological product standards (21 CFR 610)
  - Process validation
- Assay validation
  - Immunogenicity/activity
  - Product quality control, lot release
- Stability data

→ vaccine

PRE-IND INFORMATION

- Manufacturing process
- Product characterization
- Pre-clinical/non-clinical animal toxicity studies for safety
- Data to support the IND clinical studies, e.g., dose selection for initial Phase 1 study
- Focus: initiate first Phase 1 clinical study
- Pre-IND meeting with FDA strongly recommended

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IND GENERAL PRINCIPLES

- Scope (21 CFR 312.1):
  "An investigational new drug for which an IND is in effect...is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug."

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IND GENERAL PRINCIPLES

"FDA's primary objectives in reviewing an IND are, in all phase of the investigation, to assure the safety and rights of subjects, ... FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations..., [21 CFR, 312.22(a)]

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IND GENERAL PRINCIPLES

"...and in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety...."
[21 CFR, 312.22(a)]

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IND CONTENT & FORMAT FOR ORIGINAL SUBMISSION (21 CFR 312.23)

- Cover sheet (Form 1571) *(roadmap)*
- Table of contents *(what's where)*
- Introductory statement & general investigational plan *(where you are headed)*
- Investigator's Brochure *(preliminary package insert)*
- Clinical Protocol *(plan for collecting safety and activity/efficacy data)*

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IND CONTENT & FORMAT (2) (21 CFR 312.23)

- Chemistry, manufacturing, and control information *(how you made the product and the testing you did)*
- Labeling *(investigational use only)*
- Environmental analysis
- Pharmacology & toxicology information *(data to conclude that it is reasonably safe to conduct proposed clinical study)*
- Previous human experience *(same or similar products)*
- Additional information *(e.g, critical references)*

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→ FDA concern live organism

CLINICAL PROTOCOL ELEMENTS
21 CFR 312.23 (a)(6)(iii)

- Objectives & Purpose
- Investigator Info (Form 1572, CVs)
- Inclusion/Exclusion/No. of Subjects
- Study Design (e.g., controls and blinding)
- Dose & Schedule
- Monitoring to Meet Objectives
- Monitoring to Minimize Risks

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MAINTAINING THE IND

- Clinical Hold
- IND Amendments
- Safety Reports
- Annual Reports

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CBER CLINICAL HOLD POLICY

- Regulation: 21 CFR 312.40
  - ✓ IND goes into effect (study may proceed) 30 days after FDA receives the IND, unless sponsor is notified otherwise by FDA
- Clinical Hold: 21 CFR 312.42
  - ✓ Order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation

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CBER CLINICAL HOLD POLICY (2)

- Grounds - Phase 1:
  - Unreasonable & significant risk
  - Clinical investigators not qualified
  - Inadequate investigator's brochure
  - Insufficient information to assess risk

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CBER CLINICAL HOLD POLICY (3)

- Grounds - Phase 2/3:
  - Same Reasons as for Phase 1
  - Protocol design inadequate to meet objectives

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CBER CLINICAL HOLD POLICY (4)

- Notification:
  - ✓By telephone or fax
- Clinical Hold Letter:
  - ✓Within 30 calendar days of hold notification
- Additional Comments (Non-Hold) Letter
- Review of Complete Hold Response
  - ✓Letter within 30 days of receipt of response

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IND AMENDMENTS (21 CFR 312.30 – 312.33)

- Protocol Amendments:
  - ✓Existing Protocol
  - ✓New Protocol
- Information Amendments, e.g.,
  - Product changes
  - Clinical Study Reports
- Safety Reports
- Annual Reports (within 60 days of anniversary day)

TYPICAL REVIEW TEAM

- Regulatory Reviewer
- Clinical/Medical Officer
- Product Reviewer(s)
- Statistician
- Pharm/Tox Reviewer
- Other, as needed (e.g., cell substrate, assay validation, facilities)

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USUAL TIMELINES FOR REVIEW

- IND: original submission reviewed within 30 days of receipt, study may proceed at 30 days unless placed on clinical hold by FDA
- IND amendments:
  - New protocols may proceed immediately, although FDA strongly encourages end-of-phase 2 and pre-BLA meetings
  - Frequently, discussions occur between FDA and sponsors re: new protocols
  - An IND can be placed on hold at any time for safety reasons or for clinical design issues for Phase 2 or 3 studies
- Contact regulatory reviewer

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master file.

IND SUBMISSIONS: COMMON PITFALLS

- Manufacturing
- Lot Information
- Preclinical Issues
- Protocol Issues
- Administrative
- CT Issues

IND SUBMISSIONS - COMMON PITFALLS: MANUFACTURING

- Insufficient information
- Variable conditions
- Lot release test results lacking
- Potentially toxic substances - validation of removal or assay for residual component (ex: organic solvent)

Resolution: Provide specific information for proposed clinical lot

IND SUBMISSIONS - COMMON PITFALLS: MANUFACTURING (2)

- Adventitious agents - inadequate testing or inadequate information on source materials

IND SUBMISSIONS - COMMON PITFALLS: LOT INFORMATION

- Lots not clearly identified
- Test results not submitted
- 21 CFR 312.23(a)(7)(i): assure proper identification, quality, purity and strength
- 21 CFR 610: potency, general safety, sterility, purity, identity (license product)
- Summary table - stage of manufacture, test, acceptance criteria, test result, data attached

Identify lot number and include QC info for lot to be used in clinical study

IND SUBMISSIONS - COMMON PITFALLS: PRECLINICAL ISSUES

- Pyrogenicity
- Attenuation (live organisms)
- Inactivation/reversion
- Potency (e.g., immunogenicity) data lacking
- GLP safety study (Phase 1), for novel product (prior to Phase I & case by case basis)

IND SUBMISSIONS - COMMON PITFALLS PRECLINICAL DATA (2)

- Experimental details lacking
  - Need information on lot, dose, route, assays to evaluate immune response
- Data lacking to support dose proposed for clinical trial
- Pre-IND meeting with FDA not held

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IND SUBMISSIONS - COMMON PITFALLS: PROTOCOL ISSUES

- Include subject diary and case report form(s) to monitor reactogenicity
- Define stopping rules
- Describe assays to evaluate immune response
- Define end point(s) & case definition
- Describe statistical analyses
- Inconsistencies

IND SUBMISSIONS - COMMON PITFALLS: ADMINISTRATIVE

- At least three copies of each original submission and each amendment
- Signed, completed Form 1571 for each submission
- Specific cross-reference: IND/MF, date, volume number, page
- Pages numbered sequentially, including attachments
- Clear images of gels and blots

CT- SPECIFIC ISSUES

- Multiple party involvement
  - FDA/Sponsor, vs. FDA/Sponsor/Other
  - (Other = DHHS, CDC, NIH, DoD) → Defense
- Expectation for accelerated development
- Animal rule vs. clinical efficacy trial
- Strategic National Stockpile (prev. NPS)
- Use under IND

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CT = Counter Terrorism

GUIDANCE AVAILABLE FROM FDA

- Meetings
- Web page
- Telephone/e-mail

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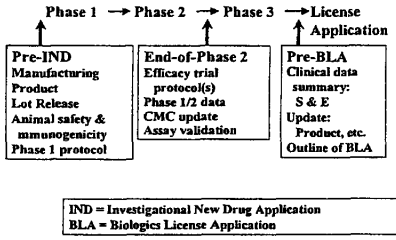
Meetings with FDA

(21 CFR 312.47)



IND = Investigational New Drug Application
BLA = Biologics License Application

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teleconference. call ...

AVAILABLE CBER GUIDANCE

- Code of Federal Regulations
- Guidance for Industry/Reviewers
- Guidelines
- Points to Consider
- CBER SOPPs → on website
- Federal Register (FR) Notices on web
- International Conference on Harmonisation (ICH) Documents (U.S., E.U. and Japan) on web

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Guidance Documents - Examples

- **FDA Guidance for Industry**
  - Content and Format of Chemistry, Manufacturing Controls Information and Establishment Description Information for a Vaccine or Related Product (1999)
- **ICH Guidance Documents**
  - Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (1998)
  - Quality of Biological Products: Derivation and Characterization of Cell Substrates (1998)

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CONTACT INFORMATION

- **FDA documents /Federal Register (FR) notices /FDA regulations**
  - **http://www.fda.gov/cber/publications.htm**
  - **1-800-835-4709 or 301-827-1800**
- **Questions:**
  - **OCTMA@CBER.FDA.GOV (Consumer Questions)**
  - **MATT@CBER.FDA.GOV (Manufacturers Assistance)**
  - **DVRPA: 301-827-3070**

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Division Vaccine related product application

SELECTED REFERENCES

- Baylor N, Midthun K: Regulation & Testing of Vaccines. Vaccines 4th ed, 2004, WB Saunders
- Goldenthal KL, et al: Safety Evaluation of Vaccine Adjuvants. AIDS Res Human Retroviruses 1993; 9:S47-S51
- Chandler D, McVittie L, Novak J: IND Submissions for Vaccines. Vaccines: From Concept to Clinic 1999, CRC Press

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SUMMARY: IND OVERVIEW

- IND process: Collect data to support approval (clinical safety and efficacy)
- Be specific: Lots to be used, manufacturing process, testing results, procedures for monitoring trial, etc.
- Helpful information available on web
- Consult FDA (meetings, teleconferences, questions)

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e-submission
open label protocol

Perspective on the "Animal Rule"

Karen L. Goldenthal, M.D.
OVRR/CBER
FDA

1

Efficacy Issues for Biological Warfare (BW) Defense Products

- In some cases, human efficacy trials may not be feasible nor ethical
  - ☑ Epidemiology precludes "field trials", the usual source of efficacy data, and
  - ☑ Cannot conduct human challenge/protection studies

2

Animal Rule

- New Drug and Biological Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible. Federal Register 67: 37988-37998, May 31, 2002. (Final Rule)
  - ☑ 21 CFR 601.90-95 (biologicals)
  - ☑ 21 CFR 314.600-650 (drugs)

3

Animal Rule

- Drugs & biologicals that reduce or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances

4

Animal Rule

- FDA may approve a product for which
  - ☑ Safety has been established and
  - ☑ Requirements of Sec. 601.90 (314.600) met based on adequate and well-controlled animal trials when results of those animal studies establish that product reasonably likely to provide clinical benefit in humans

5

Animal Rule

- Rely on evidence from animal studies only where
  - ☑ Reasonably well understood
    - Mechanism of toxicity of agent
    - How product prevents the toxicity
  - ☑ Effect independently substantiated in >1 species (some exceptions)
    - Including species expected to react with a response predictive for humans

6

Animal Rule

- Animal study endpoint clearly related to desired benefit in humans
  - ☑ Generally, enhancement of survival or prevention of major morbidity
- Selection of an effective dose in humans
  - ☑ Kinetics & pharmacodynamics and/or other relevant data, in animals & humans
- Still need human clinical data
  - ☑ Safety
  - ☑ PK/immunogenicity data

7

Animal Rule

Continued

Approval subject to three requirements

- Postmarketing studies
  - ☑ To verify and describe the product's clinical benefit when feasible and ethical
  - ☑ May not be feasible until an exigency arises
- Restrictions to assure safe use
  - ☑ Distribution, if needed
- Labeling for users
  - ☑ Explain that product's approval based on efficacy studies conducted in animals alone

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Animal Rule - Scope

Continued

- Rule does <u>not</u> apply if product approval can be based on standards described elsewhere in FDA's regulations
  - ☑ e.g., accelerated approval based on human surrogate markers or clinical endpoints other than survival or irreversible morbidity

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HIV therapy use surrogate endpoint not apply animal rule

Safety Data

Indication: Preventive vaccines for healthy persons

- Target populations
- How much is enough to support licensure?
- Thousands, ideally from randomized studies
- Data quality important
- Risk/benefit

10

Safety Evaluation

- Animal rule does not address safety evaluation of products to which it applies
- Safety discussed briefly in preamble to Rule
  - ☑ Use "preexisting requirements"
- Agency believes that, w/one limitation, safety of most of these products can be studied in volunteers similar to people who would be exposed to the product
- Limitation – may be inability to examine possible adverse interactions between toxic substance and new product

11

"Supplemental Clinical Studies" To Assess Safety (Prelicensure)

- Small efficacy trials or other limitations
  - ☑ E.g., if efficacy assessed by comparative immunogenicity study(s) with several hundred per group (combination vaccines)
  - ☑ "Animal rule"
- Novel vaccine concepts

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Simultaneous Administration (SA)

- FDA's Guidance for Industry for Evaluation of Combination Vaccines (1997)
- Note: No previous FDA policy on this topic
- Licensed vaccines administered simultaneously w/the new vaccine:
  - ☑ Obtain immunogenicity & safety data to support SA if recommended schedule for new vaccine is same, or overlaps, with one or more licensed vaccines
  - ☑ Timing: Prelicensure

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Standards of Licensure

- Safety
- Purity
- Potency
- Efficacy
- Stability
- cGMP Compliance

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Vaccine Production/Quality Control

Common Principles

- Detailed manufacturing procedures: consistency of production
- Defined compatible components
- Product characterization: specifications
- Cell substrate; Adventititous agent testing
- Source (e.g., BSE)
- Examination for extraneous materials
- Stability

Parkman P, Hardegree MC: Regulation & Testing of Vaccines. Vaccines 3rd ed, 1999, WB Saunders Co.

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Implications of Proposed Rule for Drug Development

- Early/multiple discussions with FDA
- Detailed justification concerning why efficacy trials not feasible/ethical
  - ☑ Agency may not concur
  - ☑ Ability to perform "field trials" may change over time, e.g.,
    - Clinical endpoint efficacy trial for anthrax vaccine possible in 1950s/60s (US mill workers)*

*Brachman, et. al., 1962. Field evaluation of a human anthrax vaccine. Am J Public Health. 52:632-645

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Implications - Drug Development

- Pilot efficacy studies in animals
- Pivotal animal efficacy studies
  - ☑ Prospective primary endpoint
  - ☑ Prospective statistical plan
  - ☑ GLP (21 CFR 58)
- Multiple interactions with FDA Advisory Committees
  - ☑ Prior to animal efficacy trials, for concurrence w/concepts, in some cases
  - ☑ Following Agency's BLA review

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→ analogous to human efficacy study.

Assays in Vaccine Trials

Importance of:

- Assays to detect vaccine-elicited response(s)
- Assays to identify/characterize infections (immunologic, virologic)
- Considerable R & D can be necessary to develop and validate assays

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CDC. assay in anthrax

Assays in Vaccine Trials

Importance of:

- Assay performance data
  - ☑Specificity, sensitivity, ruggedness, reproducibility, e.g., procedures to minimize false positive PCR
  - ☑Important for early trials
  - ☑Validation of assays before pivotal study

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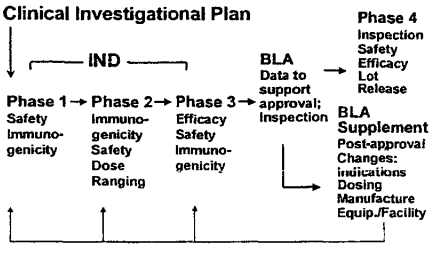
Stages of Review and Regulation



IND =Investigational New Drug Application; BLA=Biologics License Application

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Meetings with FDA (21 CFR 312.47)

Phase 1 → Phase 2 → Phase 3 → BLA

Pre-IND Meeting:	End-of-Phase 2 Meeting:	Pre-BLA Meeting:
Manufacturing Product	Efficacy trial protocol(s)	Clinical data summary:
Lot Release	Phase 1/2 data	S & E
Animal safety & immunogenicity	Update** Product, etc.	Update** Product, etc.
Phase 1 protocol	Rationale	Outline of BLA

BLA = Biologics License Application **Shouldn't be a surprise

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submit animal model assay part.

FDA can't put animal model efficacy protocol on. However, can't get approval for this measure.

P focus on human efficacy CT

Available Resources

Example of an FDA document:

- ☑ Guidance for industry - Content & format of chemistry, manufacturing & controls information & establishment description information for a vaccine or related product (1999)

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Available Resources

- FDA documents/Federal Register notices/regulations
  - ☑ http://www.fda.gov/cber/publications.htm
  - ☑ 1-800-835-4709 or 301-827-1800
- International Conference on Harmonisation (ICH) documents
  - ☑ U.S., E.U. and Japan

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Conclusion - Vaccine Development

- BW vaccines present unique issues for clinical development
- Overall planning and coordination:
  - ☑ Product characterization/manufacturing
  - ☑ Early/frequent interaction with Agency, esp. if approval will be based on animal efficacy data
  - ☑ Anticipate future trials (e.g., critical assays)
  - ☑ Obtain sufficient safety, immunogenicity & efficacy data during development
- Utilize FDA documents & resources

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MVA working group — product specific, based on company not official

Non-Clinical Safety Assessment of Vaccines

Marion F. Gruber, Ph.D., CBER/FDA

CBER Counter Terrorism Workshop
Bethesda, MD
October 23 & 24, 2003

Objectives

- Regulatory requirements
- Key components in non-clinical evaluation
- Potential safety concerns
- Challenges/goals pertaining to toxicity assessments for vaccines
- CBER approach to toxicity assessment of vaccines
- CT products: Special considerations

Definition of Vaccine

- "a heterogeneous class of medicinal products containing antigenic substances capable of inducing specific, active and protective host immunity against an infectious agent or pathogen
  - Preventive vaccines
    - Pre- and post-exposure prophylaxis
  - Therapeutic vaccines against infectious disease

Regulatory Jurisdiction: Vaccines

- OVRR/CBER regulates preventive and therapeutic vaccines for infectious disease indications
  - Toxicology review
    - OVRR/CBER
    - CDER consult review

Vaccine Regulatory Requirements

- 21 CFR 610 – General Biological Product Issues
- Lot release (each lot)
  - Potency
  - General Safety/Abnormal Toxicity
  - Sterility/Bioburden
  - Purity – moisture, pyrogenicity
  - Identity
  - Constituent Materials
    - All ingredients shall meet accepted standards of purity and quality: Certificate of analysis provided to IND
    - Adjuvant may be included if no AE on safety and potency (21 CFR 610.15)

Vaccine Regulatory Requirements

- 21 CFR 312 – IND regulations
  - 312.23 (a)(7) – Chemistry/ Composition, manufacturing and Control Information
    - Assure proper identification, quality, purity and strength of product
    - Stability for the planned duration of trial
  - 312.23(a)(8) – Pharmacologic and Toxicologic studies
    - *In vivo* or in *vitro studies* to conclude that proposed clinical studies are reasonably safe (GLP)

Key Components in Non-clinical Assessment

- Product characterization
- Manufacturing process
  - Starting materials
  - In-process controls for intermediates
  - Validated process procedures
  - Consistency in manufacture
  - Lot release
    - Adequate specifications
    - Purity, potency, identity
  - Stability
- *In vitro* studies
- Animal studies
  - Immunogenicity
  - Pyrogenicity testing
  - General safety testing
  - Neurovirulence testing
  - Reversion to virulence
  - Biodistribution studies
  - Integration studies
- Safety studies
- Efficacy studies
  - CT products

Definition: Preclinical & Nonclinical Safety Assessment

- Pre-clinical safety assessment
  - Includes product characterization, proof of concept studies, animal safety testing
  - Prerequisite to the initiation of clinical trials
- Non-clinical safety assessment
  - Preclinical safety assessment plus further product characterization and safety assessments during various stages of clinical product development
    - Includes studies if changes to the product manufacturing and/or formulation are made
    - Evaluates potential safety concerns that may have arisen from Phase 1 and Phase 2 clinical trials

Vaccine Safety:

- Major Public Concern in Developed Countries
- Majority of vaccines given to healthy individuals
  - Public expects safe (and effective) products, especially vaccines given to healthy individuals (children)
- Perception of risk outweighs perception of benefit
  - For CT products, in emerging event, balance may shift
- Focus on non-clinical safety assessment including toxicity testing

Pre-clinical Safety Evaluation: Goals

- To support entry into clinical trials, where human safety is ultimately evaluated
  - Rare toxicities, or potential effects of sub-populations often only addressable in humans
- Maximize the benefit-to-risk of vaccine development
- Determine a safe dose
- Identify any potential or unknown toxicities, target organs

Broad measures	⇒	unpredictable toxicity
Specific assays	⇒	key theoretical concerns

CBER Precedence for Toxicity Studies for Vaccines

- Immunization of pregnant women
- Route of administration
- Novel adjuvants/novel antigens
- Adverse effects observed in clinical trials
  - Potential toxicity of vaccine assessed in non-clinical trials designed to replicate specific clinical events

Potential Safety Concerns

- Inherent toxicity of the vaccine
- Toxicity of impurities/contaminants
- Toxicity due to interaction of components
- Toxicity linked to the immune response induced

Toxicity Assessments of Vaccines: Challenges

- Vaccines – complex, diverse class of biological products
- Act through complex mechanism whereby the product itself is not the final triggering component; elements of the immune system are the effectors
- Challenges:
  - Applicability of drug toxicity testing programs?
  - Applicability of available documents?
  - Timing of toxicity studies?
  - What products?

Currently Available Guidance for Toxicity Assessments

- CPMP Note for guidance on pre-clinical pharmacological and toxicological testing of vaccines, 6/1998
- ICH S6 Pre-clinical safety evaluation of biotechnology-derived Pharmaceutical, 7/1997
- ICH S5a Detection of Toxicity to Reproduction for Medicinal Products, 1994
- US FDA Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive & Therapeutic Vaccines for Infectious Disease Indications, 2000 (*revised*)

Workshop on Non-clinical Safety Evaluation of Vaccines (December 2&3, 2002)

- Discussions on non-clinical methods for safety assessments of vaccines
  - Animal models
  - Study design (dose, ROA, schedule)
  - Endpoints (parameters evaluated)
  - Alternative methods
- Provided basis for the development of guidance
- http://www.toxicology.org.memberservices/meetings/cct-vaccines.html

General Principles of Non-clinical Evaluation of Vaccines

- Risk/benefit
  - Target population
  - Clinical indication
  - Available clinical data
  - ROA
  - Mechanism of action
  - Product features, e.g., novelty
  - Relevant animal models
- USE SCIENTIFIC JUDGMENT!

ROA : Route of Application

General Principles of Non-clinical Evaluation of Vaccines (cont.)

- Adequate to identify/characterize toxic effects
- Need and design based on scientific judgment and best available science
- No one study design for all product categories!
- May not be needed for all products

General Principles of Non-clinical Evaluation of Vaccines (cont.)

- Need for balance in interpretation of nonclinical data
- Parameters to be considered:
  - Animal species/strain, dosing schedule, dose, ROA, devices, product features
- Evaluation of potential toxic effects:
  - Target organs, dose, routes of exposure, frequency of exposure, reversibility of observed toxic effects

Non-clinical Lot(s) used in Toxicity Study

- Ideally, same lot as used in clinical study and in compliance with GMP
- If this is not feasible, then preclinical should be comparable to the clinical material with respect to physico-chemical data, stability, formulation, etc
  - Lot release protocol

Toxicity Assessment: Study Design

- Dedicated stand alone toxicity studies
  or
- Combination safety/activity study
- Control arms
  - Base line
  - Comparison to test group
  - Reversibility of adverse effects
  - Delayed adverse effects

Toxicity Assessment: ROA/Dosing

- Route of administration (ROA) and dose should corresponded to clinically intended ROA and dose
- Total number of doses equal to or exceed number of clinically administered doses
  - ["N plus 1"]
- Episodic dosing, e.g., weeks between doses

Toxicity Assessment: Dose

- Maximum human dose (1x)
  - In general, no need for dose response
    - Possible Exceptions (e.g., adjuvants)
  - Dose defined by the immune response
  - Volume
    - Same as administered to humans (1x)
    - Scale based on mg/kg, if 1x dose not feasible
    - Don't change formulation

Toxicity assessment: Parameters Monitored

- Local/systemic events
- Immunogenicity
- Clinical observations (general health, body weight and food consumption, injection site, limb use impairment)
- Serum chemistries including liver and renal function tests (ALT, AST, creatine kinase, BUN)
- Hematologic analysis (CBC and differential)
- Injection site histopathology
- Terminal procedures (necropsy, organ description, weights, histopathology on tissue including evaluation of immune organs)
- Good Laboratory Practice (GLP, 21 CFR 58.1)

Toxicity Assessment (cont.) Immune Response

- Characterization of the immune response
  - Changes in immune parameters are expected
  - Parameters to be evaluated include white blood cell count, histopathological examination of bone marrow & lymphoid tissue
- Tiered testing approach
  - In some cases specific immune investigations may be necessary
  - Hypersensitivity reactions

Toxicity Assessment: Animal Model

- "Relevant" animal species
  - An animal species susceptible to respond to the test article activity, e.g., development of an immune response after vaccination
    - Ideally, species should be sensitive to the pathogenic organism or toxin
  - One relevant animal species in general sufficient
    - Exceptions on a case-by-case
    - Non-human primates not generally necessary
  - Group size dependent on the animal model

Toxicity Assessment: Animal Model (cont.)

- Additional considerations
  - Recognize limitations of animal model
  - Judicious use of animals
  - Use of naïve *vs.* partially immune or immune animals
  - Juvenile animal models???
  - Animal validation (e.g., historic control data such as hematological, serum chemistry parameters, pathology, etc.)
- Justify animal model!

Special Considerations for Toxicity Assessments (cont.)

- Adjuvants
  - Demonstrate effect in non-clinical immunogenicity study
  - Evaluate relevant vaccine/adjuvant formulations in preclinical GLP safety studies:
    - Vaccine product with and without adjuvant in preclinical studies
    - Antigen/adjuvant formulation intended for clinical use
  - If novel adjuvant, then safety assessment of adjuvant by itself

Special Considerations for Toxicity Assessments

Developmental Toxicity Studies

- Considered if product includes females of child bearing potential or pregnant women
- Need for developmental toxicity study will depend on the product
- Restricted to pre- and postnatal developmental studies, no fertility and post-weaning assessment for most vaccine products
- Tiered approach
- CBER guidance revised to reflect this approach

reproductive guidance will revise this Dec. (workshop)

Special Considerations for Toxicity Assessments (cont.)

- Genotoxicity studies: In general not needed
  - Exception adjuvant, excipient (case-by case)
- Carcinogenicty studies: In general not needed
- Safety pharmacology (circulatory/respiratory system): In general not needed, (case-by-case)
- Pharmacokinetic studies: In general not needed
  - Case-by case: novel adjuvants, alternate ROA

Timing of Preclinical Toxicity Studies

- Prior to initiating Phase 1 clinical trials
- Discuss with CBER prior to or during pre-IND meeting
  - Provide adequate information on clinical plan
- Submit toxicity protocols for CBER review prior to initiation of animal studies
  - Avoid additional toxicity studies
- Submit toxicity study report to original IND
  - Full tabulation of data, line listings
  - Safety of clinically intended dose/ROA
- Additional toxicity studies may be necessary as product/clinical development continues

CT Products: Special Considerations

- Expeditious development and licensing of products to treat or prevent outbreaks from exposure to the pathogen identified as bioterrorist agents
- CBER guides products through the regulatory process
  - Manufacturing process, pre-clinical testing, clinical trials and approval process

CT Products: Special Considerations

- Early and frequent communication with sponsor essential
- Need for pre-pre-IND CBER consult
  - Insure quality of toxicity studies
  - Reduce misunderstandings
  - Prevent unnecessary use of animals
  - Expedite initiation of Phase 1 clinical trials
  - Expedite product development

pre-pre-IND is not binding (∵ reviewer may different from pre-IND to meeting)

CT Products: Special Considerations

- Significance of pre-clinical assessments:
  - CT product availability under IND
    - Potentially large numbers of healthy individuals
  - Acceptable basic safety data derived from *in vivo* or *in vitro* pre-clinical studies
    - Assure no unreasonable risk
  - "Proof-of-concept" studies provide reasonable scientific basis for activity

CT Products: Special Considerations

- Preclinical safety data help provide confidence that risk:benefit ratio favorable enough for timely product access

Summary

- Non/pre-clinical safety assessment is a key component in vaccine development
  - Of special significance for CT products
- Case-by-case, science based
- Approach to optimal study and/or toxicity assessment for vaccines evolving
- Emphasis on early communications with sponsor
- Vaccine specific guidance for non-clinical safety assessment of vaccines currently being developed
  - WHO guideline on nonclinical evaluation of vaccines

Acknowledgment

- Members of the Expert Panel (colleagues from industry, academia and regulatory agencies) convened at the SOT/CBER/FDA OWH co-sponsored workshop "Nonclinical safety evaluation of vaccines," December 2&3, 2003
- Elizabeth Sutkowski, Ph.D.
- Donna Chandler, Ph.D.
- Karen Goldenthal, M.D.

CBER contact information

- Web:www.fda.gov/cber/reading.htm
- Fax: 1-888-CBER-FAX
- Division of Vaccines and Related Products Applications (OVRR)
  - Phone: 301-827-3070

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Preclinical Evaluation of Cellular and Gene Therapy Products

Mercedes A. Serabian, M.S., DABT
FDA/CBER/OCTGT

Workshop on Counter Terrorism Products Regulated by CBER: Effective Strategies to Assist in Product Development

October 23, 2003
Bethesda, MD
serabian@cber.fda.gov

Requirements for Therapeutic Agent Approval

- Product development/characterization
  - Manufacturing & QC issues
- Toxicology/pharmacology development
  - *in vitro* and/or *in vivo* "proof-of-concept"
  - Acute & long-term testing designed to determine safety for clinical use
- Clinical development
  - Demonstration of safety & effectiveness in controlled clinical trials

Requirements for Therapeutic Agent Approval: Per the Animal Rule*

- Product development/characterization
  - Manufacturing & QC issues
- Toxicology/pharmacology development
  - *in vivo* "proof-of-concept"
  - Acute/long-term testing designed to determine safety for clinical use

*New Drug & Biological Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies are not Ethical or Feasible; FR 67: 37988-37998, 5/31/02

The Bottom Line...

Prior to the availability of human data, preclinical studies provide the sole source of data upon which activity [efficacy] & safety assessments are made

Goals of Preclinical Safety Evaluation

- Preclinical considerations for Phase 1/2 trials
  - To discern the mechanism of action [activity/toxicity] of the agent
  - Recommendation of initial safe dose & dose escalation scheme in humans
  - Identification of potential target organ(s) of toxicity/activity
  - Identification of parameters to monitor clinically
  - Identification of patient eligibility criteria
  - Terminate potentially unsuccessful development programs

Achievement of Goals for **All** Products – CBER/OCTGT/PTB

- "Pre-pre-IND" discussions..which lead to ..
- Pre-IND meetings
  - Establish safety of the product & intended pharmacological action
    - Preclinical safety issues
    - Preclinical "proof-of-concept"
    - Rationale for starting human dose
- Submission of IND

Pre-pre-IND Process

- Non-binding, informal scientific discussions between FDA and sponsor
  - Via telecons
  - Via CBER attendance at scientific meetings/workshops
  - Via outreach presentations (i.e., this workshop)
- Often minimal pre-read materials submitted by sponsor
- Targeted discussion of specific issue of interest
- Allows for information exchange – a "two-way street"

could be many times

summary

ROA, dosing frequency, dose indication ...

Pre-IND Process

- Non-binding, but formal meeting between FDA and sponsor
- Pre-read materials must be submitted by sponsor at least 30 days prior to meeting
- Formal minutes generated by FDA - sent to sponsor within 30 days after meeting
- Meeting emphasis - summary data and sound scientific principles to support use of a specific product in a specific subject population

The IND Review Process - Team Concept

- Regulatory project manager (RPM)
- Product reviewer (CMC)
- Preclinical reviewer (P/T)
- Clinical reviewer
- Biostatistics reviewer (when applicable)
- Consult Reviewer (when applicable)

CDRH, CDER or other agency

How Are Animal Studies Integrated into the Proposed Clinical Plan?

- 21 CFR, part 312.23(a)(8)

Pharmacologic & Toxicologic Studies

- "...adequate information about the pharmacological & toxicological studies...on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, & scope of animal and other tests required varies with the duration & nature of the proposed clinical investigations."

OCTGT-Regulated Products: Application of 21 CFR 312.23

Repair, Replace, Restore, Regenerate

- Somatic cell therapy
  - Gene therapy
- Xenotransplantation/therapy
  - Device + biologic* → delivery device + biologics
- Stem cell selectors*
  - Tumor vaccines

(* in conjunction with CDRH)

Definition of Gene Therapy:

Introduction into the human body of genes or cells containing genes foreign to the body for the purposes of prevention, treatment, diagnosis or curing disease

Definition of Somatic Cell Therapy:

Administration to humans of:

- Autologous, allogeneic, xenogeneic cells
- Manipulated/processed to change their biological characteristics
  - Metabolic
  - Pharmacologic } examples
  - Immunologic
- Not genetically modified

Preclinical Evaluation

- "Traditional" biologics vs. cellular & gene therapy agents
  - Similar general requirements for safety
    - Pharmacologic profiles
    - "Proof-of-concept"
    - Dose-response relationship
    - Toxicology profile

Preclinical Evaluation – Cellular & Gene Therapy Agents

- BUT… the approach by which safety data are obtained will differ

Gene Therapy	.....	Cell Therapy
	Animal models	
Biodistribution of vector		Migratory potential
Kinetics of gene expression		Cellular differentiation
		Cell phenotype expressed
		Anatomic/functional integration into host physiology
		Post-transplant survival
	Long-term toxicity	
	Reproductive toxicity	
Carcinogenicity/mutagenicity		Tumorigenicity (proliferative potential)

And…It's Not that Simple…

- Cellular Therapies
  - Infused*
  - Surgically implanted
    - Solid support (CBER + CDRH)
    - Encapsulated material (CBER + CDRH)
    - Aggregated form
- Gene Therapies*
- Cellular Therapy + Gene Therapy*

* May/may not require the use of an experimental delivery device

Regulatory Expectations for Toxicology Studies

21 CFR 312.23 – IND Content and Format

- Preclinical data should be adequate to support the proposed clinical trial
  - Range of doses, schedule and/or duration of treatment, route of administration should mimic those planned for the clinic
  - Sufficient safety data should be available to determine endpoints for monitoring in the clinic

The First Step… Pharmacology Studies

- What is the ability of a test article to induce the desired pharmacologic/biologic effect?
- Data may come from *in vitro* or *in vivo* studies, or both
  - Randomization/blinding/controls
- Demonstration of pharmacologic activity is the first step in the development of ANY new drug or biologic
- Collect safety data in the animal model of disease

Goals of Preclinical Pharmacology Studies

- Establish basis for conducting clinical trial
  - Feasibility/establishment of rationale
  - Kinetics of gene expression [for genetically modified products]
  - Pharmacodynamic effect - extent of functional correction
- Establish dose-response relationship - MED/OBD
- Optimize ROA/dosing regimen
- Rationale for species/model selection for further tests

→ most are single
some are repeat dosing

Selection of Animal Species/Model

- Use of relevant species/model
  - Traditional
    - Normal animals; rodent & non-rodent
  - Non-traditional
    - Spontaneous disease
    - "Non-spontaneous" disease (induced, challenge)
    - Genetically modified animals
    - "Humanized" animals
  - Understand the limitations of the species/model
    - Availability, size, gender/age, housing needs, cost, ACUC concerns, technical feasibility, historical data, statistical limitations

→ animal care use center

Selection of Animal Species/Model

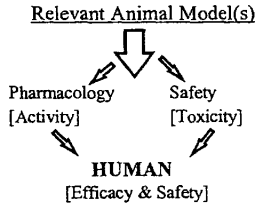
- Identify relevant model
  - Relevance to the specific clinical condition
    - Affect of disease on product
      - Increased sensitivity – good or bad?
  - Relevance to the therapeutic agent
    - Affect of product on disease
      - Exacerbation of current condition
      - Induction of new disease
- Use the data to support clinical use – risk/benefit

Use of Animal Models: Assessing Predictive Value

Animal*	Human**	Predictive?	
		Activity	Toxicity
Finding	Finding	☑	☑
No finding	No finding	☑	☑
No finding	Finding	X	X
Finding	No finding	X	?

* Multiple of human dose
** Human effective dose

Assessment of Safety/Activity - "Disease" Models



Sources of Preclinical Pharmacology Data

- Data in support of clinical trial can come from:
  - Well-controlled studies conducted in house
  - Published data in peer-reviewed journals
  - Cross-reference to similar products in previously submitted MF/INDs

Preclinical Safety Evaluation - Focus

- How can toxicological data derived from preclinical models provide information for the clinical management of potential toxicities?
  - Preclinical ID of specific toxicities = requirement for clinical monitoring
  - Predictiveness of the toxicology data for the human response
  - Impact on clinical development

The Next Step… Toxicology Studies – Gene Therapy

- Evaluate single/repeat exposure to the vector product (V)
  - Toxicities related to the delivery system
- Evaluate the safety of gene expression (T)
  - Persistence, level of expression *in vivo*
  - Identify target tissues/functional endpoints
  - Delayed toxicities/reversibility of toxicities
- Evaluate V + T
  - Characterize general toxicities
  - Identify specific toxicities
  - Characterize dose/exposure – NOAEL, MTD

V: vector (retrovirus, plasmid)
single may simple. in toxicity

The Next Step… Toxicology Studies – Cellular Therapy

- Evaluate the safety of the implanted cells (C)
  - Use cells intended for clinical use
    - May have to use non-human cells in analogous species
  - Influence of local microenvironment
    - Cell differentiation
    - Cell phenotype expression
  - Cell migration *in vivo*
  - Identify target tissues/functional endpoints
  - Delayed toxicities/reversibility of toxicities
  - Characterize general toxicities
  - Identify specific toxicities
  - Characterize dose/exposure – NOAEL, MTD

ex: CD34

CBER Guidance – Endpoints Gene Therapy

- Emphasis on clinically relevant endpoints/ surrogate markers – e.g., angiogenic factor
  - Activity
    - Increased formation of collateral vessels
      - [Cardiac] Improved myocardial function (perfusion, flow, wall thickening)
      - [Peripheral] Increased vascular/capillary density to the ischemic limb
      - Presence of transgene in target tissues
  - Toxicity - local/systemic effects
    - Injection site rxn
    - Hypotension
    - Biodistribution/persistence of vector in nontarget tissues
    - Formation of Abs to vector/transgene
    - Acceleration of atherosclerosis
    - Inflammatory response in target/nontarget tissues

Preclinical Study Design – Vector Biodistribution

- Determination of distribution of the vector to intended therapeutic site/unintended site(s)
  - Presence of vector sequence via PCR analysis:
    - Dissemination of vector to the germline
    - Distribution of vector to non-target tissues PCR
- Performance of biodistribution studies prior to Phase 1 when:
  - A new class of vector; no/little experience
  - A change in formulation
  - A change in the ROA w/ an established vector
  - Known potential of transgene to induce toxicity if aberrantly expressed in non-target tissues

CBER Guidance – Endpoints Cellular Therapy

- Emphasis on clinically relevant endpoints/ surrogate markers – e.g., cells (osteogenic/ dermal) + matrix
  - Activity
    - Contribution of each component
    - Graft performance -morphological/functional aspects
    - Effect of antimicrobial agents on graft performance
    - Time to/extent of engraftment
    - Prevention of morbidity
  - Toxicity - local/systemic effects
    - Contribution of each component
    - Implant site rxn
    - Ectopic bone formation
    - Formation of Abs to any foreign proteins
    - Inflammatory response in target/nontarget tissues

Biodegradation of matrix
Tumorigenicity

↳ B: - degradation
tumorigenicity

Regulatory Expectations for Toxicology Studies

21 CFR 312.23 (a)(8) – Pharmacology & toxicology

- For each toxicology study intended primarily to support safety, a full tabulation of data shold be submitted
- Each study submitted should be performed per GLP, or an explanation provided

complete study

Sources of Toxicology Data

- Toxicity data in support of a clinical trial can come from:
  - GLP-compliant toxicology studies conducted by a contract laboratory
  - Well-controlled studies conducted in house
  - Published data in peer-reviewed journals
  - Cross-reference to similar products in previously submitted MF/INDs

The Bottom Line....

- Study design should answer specific questions regarding product safety/activity, using the relevant animal species/model
  - Determine a bioactive level (MED) & a safe level (NOAEL)
  - Determine margin of safety - toxic effect(s) vs. beneficial effect(s) for the product
  - Determine a safe starting clinical dose/dose escalation scheme

[Some] Limitations of Preclinical Studies

- Lack of information/understanding regarding fundamental biochemical and physiological mechanism of axn
- Target site/receptor absent in test species
- Treatment does not lead to sufficiently sustained protein concentrations at target site
- Lack of available animal model(s) of disease
- Extrapolation to relevant physiological state

Findings Resulting in Possible Modification to Clinical Trial(s)

- Serious life-threatening events
- Unexpected toxicities
- Delayed effects
- Irreversible effects
- Additional findings in long-term studies
- Enhanced toxicity in an animal model of disease
- Similar adverse findings displayed in several models
- Tumor development

CBER Approach to Preclinical Safety Evaluation – for **All** Products

- Data-driven
- Problem-solving, creative
- Should be based on best available science, technology to date
- Careful design of preclinical studies results in judicious use of animals

Take Home Messages

- The most useful approach to preclinical safety evaluation of cellular & gene therapies should:
  - Utilize rational, scientifically-designed, & problem-solving study designs
  - Be based on the best available technology/ methods
  - Follow FDA guidances, ICH, & the CFR
  - Include the judicious use of animals

BRMC

Biological research

Take Home Messages

- Sponsors are encouraged to utilize relevant animal species & animal models of disease in preclinical studies ....

  ...keeping in mind that..

- No one species will be representative or predictive for all humans [including humans]

Take Home Messages

- A better understanding of fundamental & physiological mechanisms will help to provide a scientific basis for safer & faster clinical development
- The goal: To avoid inappropriate use of the product
- The goal: To optimize the predictive value of the product

Take Home Messages

- **Sponsors should contact CBER at an early stage of preclinical development to discuss study designs to answer the necessary questions**
- **Early and frequent interactions with CBER P/T reviewers are encouraged**

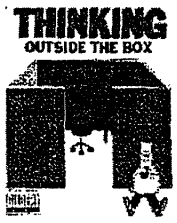
For Additional Information…

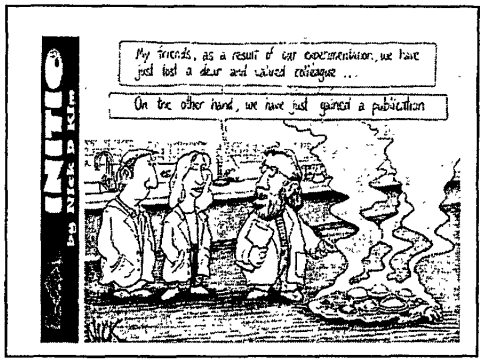
- Guidance for Industry: Providing Evidence of Effectiveness for Human Drug and Biological Products
  http://www.fda.gov/cber/guidelines.htm
- Guidance for Human Somatic Cell Therapy and Gene Therapy
  http://www.fda.gov/cber/gdlns/somgene.pdf
- ICH Documents
  http://www.fda.gov/cber/guidelines.htm

The CBER Connection…

Pharm/Tox Branch
OCTGT/DCEPT

(301) 827-5102 [phone]
(301) 827-0910 [fax]




My friends, as a result of our experimentation, we have just lost a dear and valued colleague ...
On the other hand, we have just gained a publication

Clinical Development - Counter-Terrorism Vaccines

Center for Biologics Evaluation and Research

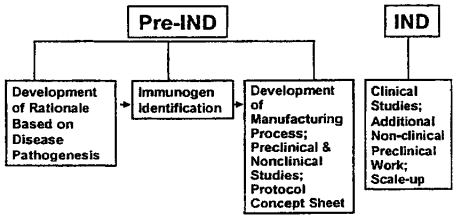
October 23, 2003
Jeff Brady, M.D., M.P.H.
Medical Officer, CBER, DVRPA

U.S. Department of Health and Human Services
Food and Drug Administration

Purpose of Presentation

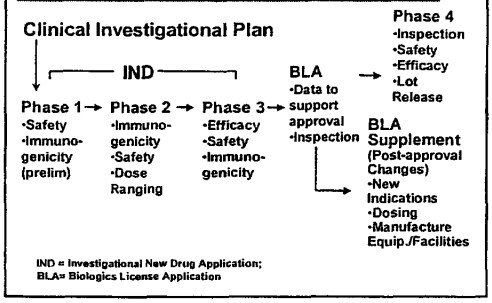
- Overview of clinical development
- Focus on Phase 1 and 2 trials
- Identify special considerations for vaccine development
- Encourage sponsors to identify global development goals early
  - target populations
  - label indications
  - anticipated use

Vaccine Development



IND = Investigational New Drug application

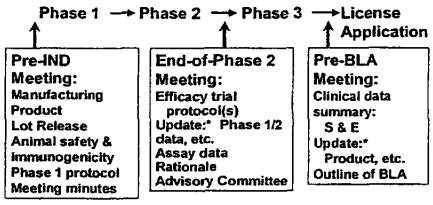
Stages of Review and Regulation



IND = Investigational New Drug Application;
BLA= Biologics License Application

Recommended Meetings with FDA

(21 CFR 312.47)



IND =Investigational New Drug Application
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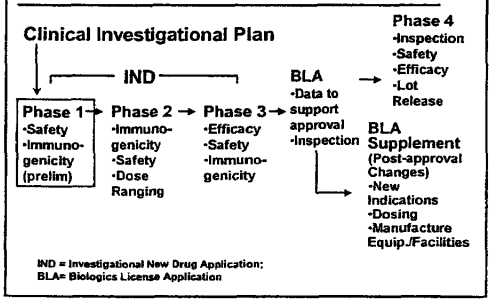
*Shouldn't be a surprise

Stages of Review and Regulation



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Bio-Terrorism Diseases / Agents

Category A
- Smallpox
- Anthrax
- Botulinum toxin
- Plague
- Tularemia
- Viral hemorrhagic fevers (Ebola, Marburg)
- Arenaviruses (Lassa, Junin)

Category B
- Brucellosis
- Glanders
- Q-fever
- Alphaviruses (EEE, WEE, VEE)
- Epsilon toxin (*Cl. perfringens*)
- Ricin toxin
- Staphylococcal enterotoxin B
- Salmonella spp.
- Cholera
- *E. coli* 0157:H7
- Cryptosporidiosis
- Shigellosis

Category C
- Nipah virus
- Hantavirus
- Yellow Fever
- Mulitdrug-resistant tuberculosis
- Tickborne hemorrhagic fever viruses
- Tickborne encephalitis viruses

TAB 7

Phase 1 Study
General Considerations

- Objectives and endpoints
  - Primary: Safety and tolerability
  - Secondary: Preliminary immunogenicity
- Closely monitored (safety)
- Adults, at least for first phase 1 study
- Sample Size
  - Small study: e.g., 20 to 80
- Special instructions for vaccinees, if needed

Phase 1 Study
Features and Components

- Consider vaccine-specific features when planning trial (e.g., live vaccine)
- Develop Inclusion and Exclusion Criteria
  - Healthy adult volunteers
  - Age range: 18-40 years (esp. for first phase 1 study)
  - Special considerations
    - age, serostatus, concomitant medications allowed, etc.
    - where applicable, vaccinee contacts
      - E.g., vaccinia

Safety Monitoring

- Goal:
  - Protect subjects by monitoring local, systemic, and potential end-organ toxicity
- Clinic visits
  - Symptom review, diary cards
  - Clinical exam
- Laboratory studies
  - CBC: hematologic
  - Chemistries: e.g., hepatic, renal (U/A), endocrine
  - Others? Per pre-clinical toxicology study, previous experience with similar vaccines, etc.

Safety Monitoring (cont'd.)

- Safety and activity (e.g., immunogenicity):
  - Items to be assessed/time schedule
    (Well organized summary in a table)
  - Active post-vaccination monitoring
  - Monitoring tools
    - Submit to IND with protocol, regardless of Phase
      - Prototype Case Report Forms (CRFs)
      - Diary cards
      - Scripted interviews
    - Other, e.g., photographs

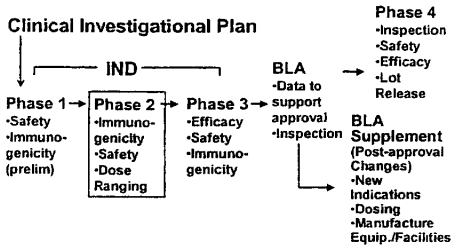
Safety Monitoring (cont'd.)

- Toxicity Grading Scales
  - Defines grades for specifically monitored parameters (clinical and laboratory AEs)
  - Based on healthy volunteers
- Stopping rules
  - Provide specific criteria
  - Address grade 3 (serious) or grade 4 (life-threatening) adverse events
  - If criteria met, stop vaccination and investigate
    - Safety review, if appropriate, resume study +/- changes to protocol/IC

Phase 1 Study Features and Components (cont'd.)

- Dose escalation
  - Even in first Phase 1 study
  - Provide details of dose escalation scheme
    - Clear criteria for dose escalation
    - Safety review of lowest dose cohort

Stages of Review and Regulation



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Phase 2 Study General Considerations

- Goals:
  - Immunogenicity
    - Dose-ranging data
    - Identify preferred dose, schedule, formulation, route of administration for advancement to Phase 3
  - Safety
    - More precise estimates of common adverse events
      - Local reactogenicity
      - Systemic effects

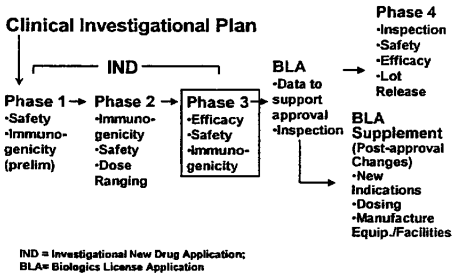
Phase 2 Clinical Trials

- Up to several hundred subjects in a trial
- Persons at high risk for infectious disease of interest (classical vaccine development)
- Often randomized & controlled
- Vaccine-elicited immune responses
  - Qualitative
  - Quantitative
  - Duration
- Safety
- Pilot evaluation of efficacy endpoints (where feasible)

Phase 2 Clinical Trials

- Planning for Phase 3
- Logistics and Protocol:
  - Compliance with protocol
  - Accrual of subjects
  - Target populations for licensure
  - Monitoring tools
  - Sample handling

Stages of Review and Regulation



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Phase 3 Development General Considerations

- Develop adequate safety, immunogenicity, and efficacy data to support
  - Proposed use(s) and indication(s)
  - Target population(s)

Phase 3 Study General Considerations

- Objectives and endpoints:
  - Pivotal efficacy - options
    1) Clinical endpoint, if feasible
    2) Immune response endpoint, if established (e.g., combination vaccines w/previously licensed components)
    3) "Animal Rule", if appropriate
  - Pivotal pre-licensure safety database
    - Sample Size: Thousands for safety in humans, regardless of path to licensure

Phase 3 Vaccine Efficacy Trial Protocol

- Study population/background epidemiology
- Control group
- Randomization scheme/Study masking
- Items assessed/time schedule:
  - Clinical & lab parameters: safety, immunogenicity, microbiology and efficacy
- Prospective 1^0 & 2^0 efficacy endpoints

Efficacy Trial Endpoints

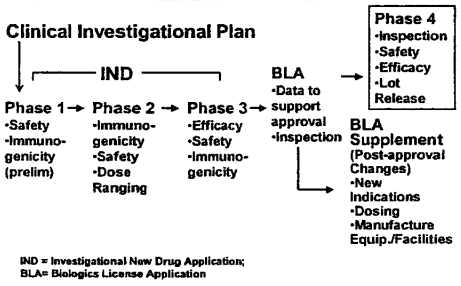
- Clinical relevance of case definition, esp. for primary endpoint
- Specificity of case definition emphasized*
- Validation of assays before efficacy study
  - Performance Parameters

*Lachenbruch PA Sensitivity Specificity & Vaccine Efficacy. Controlled Clin Trials 10:569-574, 1989
*Orenstein WA et al. Assessing Vaccine Efficacy in the Field: Further Observations Epidemiol Rev 10: 212-241, 1988.

Phase 3 Protocols

- Use of animal rule
  - Criteria for dose used in Phase 3 must consider results of animal efficacy studies
    - Correlate immune response in animals and humans
- Develop Phase 3 safety data at appropriate dose
  - Randomized, controlled safety data most interpretable
  - Appropriate control group

Stages of Review and Regulation



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Post-marketing Studies

- Limitations of pre-licensure studies
  - Rare adverse events
  - Delayed onset / long term effects
  - Sub-population
  - Efficacy
- Specific post-marketing commitments at the time of approval
  - Review of recent vaccine approval letters may be instructive

Published Guidance
FDA, ICH

FDA Guidance Documents for Industry
- http://www.fda.gov/cber/guidelines.htm
- http://www.fda.gov/cder/guidance/

International Conference on Harmonisation
- E6: http://www.ich.org/ich5e.html#GCP

Conclusions: Counter-terrorism vaccine development

- Early and frequent regulatory communication
  - Pre-IND Meeting: feedback on phase 1 trial design
  - Early articulation of development goals
    - Target population(s)
    - Indication(s)

Conclusions: Counter-terrorism vaccine development (cont'd.)

- "Animal rule" if applicable
- Develop data on relevant dose in Phase 2 to be investigated in Phase 3
- Adequate safety data

Workshop on Counter-Terrorism Products Regulated by CBER: Effective Strategies to Assist in Product Development

– OBRR Perspective on Clinical Development Phase

L. Ross Pierce, M.D.
Clinical Review Branch, Div. Of Hematology, Office of Blood Research & Review, CBER, FDA

The Problem

- Provide substantial evidence of safety and efficacy when subjects infected/intoxicated with the target agent are not available.

The Solution

- Provide evidence of efficacy in *appropriate* animal models (e.g., "Animal Rule").
- Provide data to support the choice of animal models and to help bridge animal data to the human situation, including:
  - Comparative pathophysiology and natural history of target disease in the respective species
  - Comparative PK of drug in blood; tissue levels
  - Compare concentrations of pathogen/toxin across species.
- Provide human safety and PK data in healthy volunteers.

Overall strategies for development of CBT Biologics

- Decide which indication(s) will be sought and in what order.
  Example: Anthrax Ig + antibiotic
  - Pre-exposure prophylaxis
  - Post-exposure prophylaxis
- - Therapy at early-, middle-, or late-stage disease
- - Monotherapy or combination therapy?

Focus Development Plan

- Early crafting of a draft INDICATIONS AND USAGE section of the eventual package insert can help focus clinical development

The urgency of the perceived threat may drive the timeline of product development

- –Fast Track if providing unmet medical need to treat serious and/or life-threatening aspect of disease.
- –Sequential vs. Parallel Pre-Clinical and Clinical Testing depending on circumstances (e.g., Anthrax Immune Globulin) . *Agency flexibility will be determined case-by-case*.

Timeline of product development

- "Contingency protocol" Treatment IND once human safety, PK, and basis for concluding substantial evidence of efficacy are available may be appropriate.
- Phase 4 Confirmation of Efficacy and Appropriateness of Dosing Regimen *in the event of* bioterrorism event involving the agent being targeted.

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

- Plan developed during 2001 U.S. Anthrax Episode (*Assumed Ongoing New Cases* of Inhalational Anthrax)
- Need: Inhalational anthrax carried historical ~90% mortality rate with antibiotic therapy (5/11 in 1991).
- Rationale for adjunctive use of Ig product to inactivate pre-formed and well-characterized anthrax toxins based on other disease models (tetanus, etc.)
- Anecdotal historical use of crude AIG/AIP products in inhalational anthrax of little value.
- Considered both human and animal Ig products.

no information about titer

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

1. **Prepare product using well-accepted methodologies.**
2. **Conduct proof-of-concept/activity study in animals.**
3. **If #2 successful, consider conducting preclinical efficacy, preclinical PK, clinical safety, and clinical PK simultaneously rather than sequentially (case-by-case basis).**

Clinical Phase *of Anthrax Immune Globulin*
Clinical Product Development Plan

- **1. Single-dose dose-ranging safety/tolerability and PK study in normal volunteers (or in patients with confirmed cutaneous anthrax).**
- **2. Single-dose dose-ranging safety/efficacy phase II multicenter "field" treatment IND study in patients with strongly suspected or confirmed inhalational anthrax.**

Clinical Phase *of Anthrax Immune Globulin*
Clinical Product Development Plan

- **3. Repeat dose dose-ranging safety/efficacy phase II treatment IND multicenter "field" study in patients with strongly suspected or confirmed inhalational anthrax.**
- **4. Phase III safety/efficacy treatment IND study. This might be a continuation phase of #1 or #2 or #3 above.**

Anthrax Immune Globulin – Pharmacokinetic (PK) Considerations

- Single dose tolerability/PK study of an IV product in normals should evaluate the $AUC_{(t)}$, $AUC_{(infinity)}$, C_{max}, Clearance, Vol of Distribution, and half-life. PK model should be pre-specified.
- Single dose tolerability/PK study of an IM or SC product should also evaluate T_{max}.
- Optional PK data in patients with inhalation anthrax in subset of phase II study subjects.

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

- Number of doses studied product-specific.
- Depending on perceived urgency, in the phase I single-dose tolerability and PK study the 2 lowest unstudied dosage groups might be studied in parallel (e.g., 1 cohort dosed at x mg/kg while another cohort receives 3x mg/kg). When safety data deemed satisfactory for those cohorts, the next 2 dosage levels could be studied either sequentially or in parallel.

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

- Stratify Subjects by Stage of Inhalation Anthrax.
- • Early (flu-like syndrome with known inhalation exposure)
- • Middle (dyspnea or chest pain without alternative explanation in conjunction with stated typical symptoms and strongly suspected exposure)
- • Late (hypoxemia, respiratory failure, hypotension, meningitis, widened mediastinum and/or pleural effusion on CXR). Patients with meningitis should also be analyzed as a subgroup.
- Product might prove most effective in early disease where burden of anthrax toxin least.

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

- For subjects with very early suspected but unconfirmed disease and only flu-like syndrome including fever, it can be argued that a placebo-control + antibiotic is ethical and appropriate (low risk, add-on tx)
- For subjects with Middle or Late-stage disease, a randomized dose-ranging design may be most appropriate.
- Dose ranging especially important with large population exposure requiring large quantities of product. Knowledge of the minimum effective dose would be key.

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

- If active-only dose-ranging design employed, the highest and lowest doses should differ substantially (e.g., 10-50 fold) and should include a probably less-than-fully therapeutic dose in combination with antibiotic.

Anthrax Immune Globulin – Efficacy Analyses

- The primary efficacy variable: survival/total mortality either as a proportion or as time to death.
- Secondary efficacy variables include:
  - days in ICU
  - hospitalization duration
  - respiratory failure (requirement for mechanical ventilation)
  - need for vasopressors.
- Additional clinical variables would include time between exposure, onset of illness, initiation of antibiotic therapy, and initiation of Anthrax Ig.

What to include in original IND submission

- - Overall clinical development plan, including
  - Specific Indication(s) to be sought
  - Plans for phase I, II, III, and IV studies, if applicable, including finished (not draft) protocol for initial human trial.

What to include in original IND submission

- -Justification for the starting and maximum doses for the initial human tolerability studies
- -Discuss relevance of chosen animal species for any animal efficacy/proof of concept studies.
- May include comparative animal and anticipated human pharmacokinetic data.
- Complete data including line listings of any prior human use.

Considerations for design of phase 2/3 safety and PK clinical studies

- o The design and analyses of the study should be prospectively defined in the protocol.
  - o The dose and dosing schedule for the proposed studies should be justified.
- o The data analyses presented in the BLA should be consistent with the analytical plan submitted to the IND.
- o Obtain and analyze appropriate secondary endpoints including candidate surrogate efficacy outcome variables.

Considerations for design of phase 3 safety and PK clinical studies

- o Secondary endpoints and their corresponding statistical analyses should be prospectively defined in the study protocol.
- o For studies employing randomization (such as different doses of study drug), the study's power to detect differences in the overall incidence of adverse events (AEs) between study arms should be stated in the protocol.

Considerations for design of phase 3 safety and PK clinical studies

- The protocol should state the minimum true incidence of an adverse effect that the study has 95% power to detect.
- o The size of the PK study should be justified (generally ~ 20 subjects).
- - When fewer subjects needed to characterize PK than are needed to characterize product safety, consider separate or nested PK study design.

Safety analyses

- • number of test product administrations by subject
- • number of adverse experiences (AEs) reported at any time during the study irrespective of opinions concerning relatedness to administration of the investigational agent
- • number of adverse experiences temporally associated with infusions

Safety Analyses (cont.)

- - number of infusions temporally associated with one or more adverse experiences.
- - the proportion of infusions for the trial population for which "infusional" AEs have been reported and
- - the proportion of subjects who experience one or more AEs at any time during the course of the trial.

Adverse Events and Product Infusion Rate

- Begin with a slow infusion rate and titrate upward according to a pre-specified *forced titration* scheme as tolerated.
- Analyze AEs as a function of both dose and infusion rate (for IV products).
- The CRF must provide a space for recording the infusion rate at the time AEs are first noted to permit AE analysis by infusion rate.

Safety Endpoints for Trials of Ig Products

- Serious hypersensitivity reactions
- Renal insufficiency
- Aseptic meningitis
- Thrombosis and other SAEs
- Severe AEs
- All other AEs
- Vital signs, physical exams (repeated) routine chemistry, hematology, UA.
- Monitor for seroconversions and NAT for HIV 1&2, HBV, HCV, Parvovirus B19 in normals.

Considerations for design of phase 3 safety and PK clinical studies

- Use subject diaries kept current in "real time" as essential source documents for the complete collection of AE data.
- Data in subject diaries should support corresponding case report forms (CRF) entries and study database.

CT Clinical Product Development Plan Summary

- Develop both focused initial and long-term clinical development plans
- Be flexible in tailoring your development plan to the specific disease/drug and/or biologic combination, good science, and what is feasible.
- Consult periodically with FDA to keep abreast of CBER Current Thinking regarding evolving data and how they may affect your development plans.
- Have a detailed statistical analysis plan and stick to it.
- Insure adequate study monitoring to help avoid GCP-related product approval delays.

CT Clinical Product Development Plan Summary (cont.)

- Develop Phase III/IV contingency protocols to
  - Provide expanded use
  - Validate efficacy in target disease/population
  - Validate adequacy of dosing regimen
  - Validate safety in patients with target disease.

A Regulatory Perspective on the Development of New Vaccines Against *Bacillus anthracis* and Lessons Learned Thus Far

Julianne C. M. Clifford, PhD
FDA/CBER
OVRR/DVRPA

Anthrax Disease

Bacillus anthracis:
- Gram positive, spore forming bacterium
- Highly resistant spores

Natural Infection:
- Cattle, sheep, goats, wild game

Experimental Infection:
- Nonhuman primates, rabbits, mice, rats, guinea pigs

Human Disease:
- Cutaneous anthrax
- Gastrointestinal anthrax
- Inhalational anthrax

Bacillus anthracis

Virulence
- pX01– toxins
  - PA—protective antigen
  - LF—lethal factor
  - EF—edema factor
- pX02—capsule

Bacillus anthracis

LF + PA = Lethal Toxin

EF + PA = Edema Toxin

A-B toxins

- B domain—target cell binding, internalization & translocation
- A domain—cytotoxic domain

Anti-PA Antibodies: associated with protection against anthrax disease and disruption of cytotoxic pathway

PA = antigen of interest for vaccines

Anthrax Vaccines

US Licensed Vaccines

Human: BioThrax™ (Anthrax Vaccine Adsorbed)

- Protective Antigen (PA) Based Vaccine
- Active immunization against *Bacillus anthracis* of individuals between18 and 65 years of age...

Veterinary: Anthrax Spore Vaccine

- Nonencapsulated Live Culture
- Suspension of Viable Spores

Next Generation Anthrax Vaccines

Highly purified recombinant proteins
- Single or multivalent immunogens

Viral or bacterial vectored vaccines

DNA vaccines

Others ?

Next Generation Anthrax Vaccines

Novel delivery systems
- Proteosomes, microsomes, liposomes

Novel adjuvants
- Inactivated toxins (CT, LT), chemical, lipid based

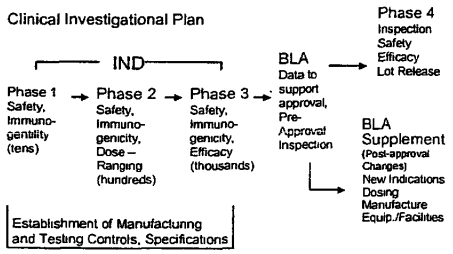
Nontraditional routes of administration
- Oral, intranasal, transdermal

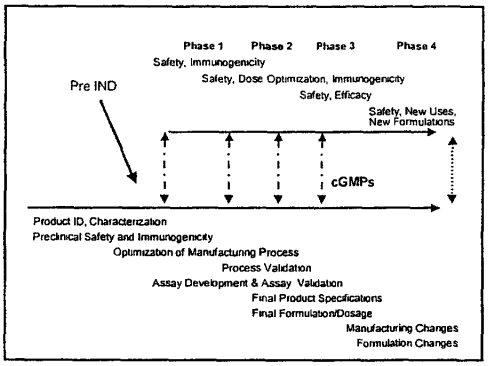
CBER Regulatory Philosophy

Application of Regulatory Standards with consideration for ...

- uniqueness of the product
- target population
- intended use
- evolving scientific knowledge

Stages of Review and Regulation In Vaccine Development:





Biological Agents/Diseases

Category A:

- Anthrax (*Bacillus anthracis*)
- Botulism (*Clostridium botulinum* toxin)
- Plague (*Yersinia pestis*)
- Smallpox (variola major)
- Tularemia (*Francisella tularensis*)
- Viral hemorrhagic fevers (Ebola, Marburg, Lassa, Marchupo...)

Category B:

- Brucellosis (*Brucella species*)
- Epsilon toxin of *Clostridium perfringens*
- Food Safety Threats (*Salmonella* spp, *E. coli* 0157:H7, Shigella)
- Glanders (*Burkholderia mallei*)
- Melioidosis (*Burholderia pseudomallei*)
- Psittacosis (*Chlamydia psittaci*)
- Q fever (*Coxiella burnetii*)
- Ricin toxin from *Ricinus communis*
- Staphylococcal enterotoxin B
- Typhyus fever (*Rickettsia prowazekii*)
- Viral encephalitis (VEE, EEE, WEE)
- Water Safety Threats (*Vibrio cholerae*, *Cryptosporidium parvum*)

Demonstration of efficacy via the Animal Rule...

... means an additional development program (animal efficacy model) to be conducted in parallel with the clinical and manufacturing programs.....

Animal Model Considerations

Identification of appropriate animal species

- Experimental infection
- Pathophysiology of the disease
  - Time to onset of symptoms
  - Nature of symptoms
  - Time to death
  - Effects of agent challenge dose and route of exposure on morbidity and mortality

Animal Model Considerations

Identification of appropriate animal species (cont.)

- Immune response to vaccine
  - Antibody response
  - Cell mediated immune response
  - Kinetics of response

Animal Model Considerations

Identification of appropriate animal species (cont.)

- Proof-of-Concept studies:
  - Dose ranging
  - Schedules of administration
  - Challenge-protection studies
  - Initial demonstration of a protective level of response or protective threshold
  - Insight on selection of human doses and immunization schedules

Animal Model Considerations

Efficacy Study Design Considerations

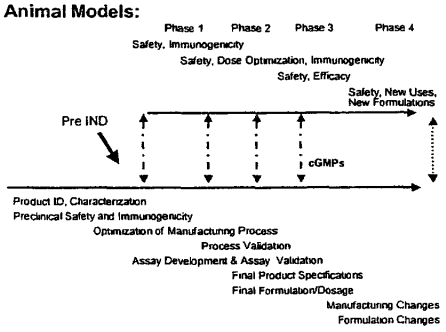
- Dose/schedule optimization to elicit response reflective of human immune response to vaccine
- Immunogenicity endpoints (assays, kinetics, duration, correlates)
- Efficacy endpoints (morbidity, mortality)
- Challenge doses
- Route of exposure
- Concomitant Therapies

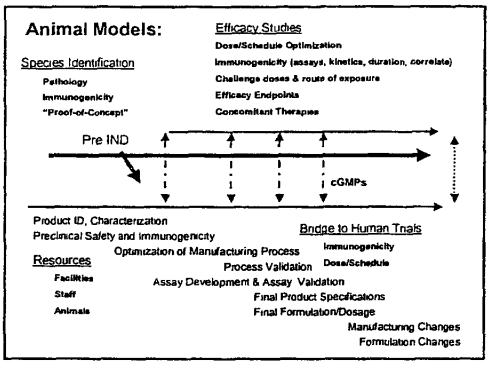
Animal Model Considerations

Bridging Animal Efficacy and Human Trails

- Extrapolation of animal model protective level as a predictor of human protection
  - Bridging/Correlating animal and human clinical immunogenicity assays
  - Passive (human-to-animal) immunization-challenge studies

Animal Models:





Clinical Indication

Vaccines, traditionally, are intended for prophylaxis in a pre-exposure setting.

From a counter-terrorism perspective, however, both pre-exposure and post-exposure prophylaxis clinical indications may be desired.

Clinical Indication

Pre-exposure & Post-exposure prophylaxis

- Presumed differences in optimal vaccination schedules for these scenarios
- Human immunogenicity data
- Human safety data

Clinical Indication

Pre-exposure & Post-exposure prophylaxis

- Animal model efficacy studies to support each indication
  - Post-exposure study considerations
    - Time to treatment after challenge
    - Challenge dose
    - Concomitant therapies
    - Immunogenicity & Efficacy Endpoints

Clinical Indication

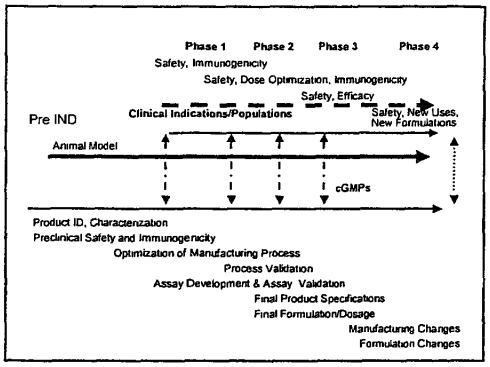
Intended or Target Patient Population

- Healthy adults
- Pediatric populations
- Geriatric populations
- Other considerations
  - Immunosuppressed/Immunocompromised
  - Pregnancy

Clinical Indication

Intended or Target Patient Population(s)

- Safety
- Immunogenicity
- Bridge to Efficacy



Stockpile Considerations

Product stability

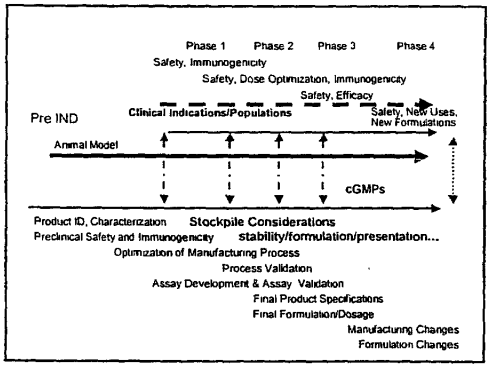
- Shelf-life and supply rotation
- Product Formulation
  - Preservatives
  - Excipients & Stabilizers

Preclinical data
Manufacturing/product testing data
Clinical data

Stockpile Considerations

Product Packaging/Presentation

- Multidose vs Single dose presentation
- Delivery system
  - Injection:
    - solution vs. lyophilized powder w/ diluent
  - Oral
  - Transdermal
  - ??



Potential Availability under IND

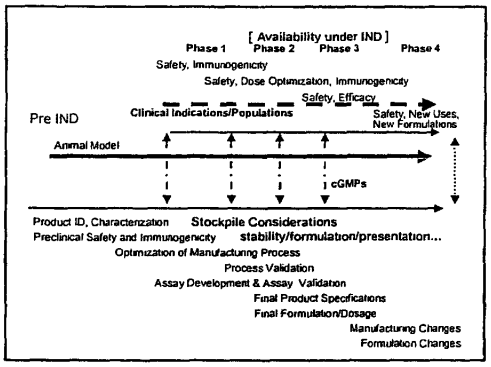
Data to support IND use

- Preclinical Safety
- Human Immunogenicity
  - Dose/Schedule
- Human Safety
  - Dose/Schedule
- Effectiveness/Protection in Animal Model
  - Not necessarily pivotal Animal Rule Study

CBER Regulatory Philosophy

Application of Regulatory Standards with consideration for ...

- uniqueness of the product
- target population
- intended use
- evolving scientific knowledge



Perceived sense of urgency and/or expectation for condensed development timeframes places an even greater importance on...

- Careful attention to detail and application of sound scientific principles at even the earliest points in development.
- Pre-IND activities
  - Antigen identification/characterization
  - Disease pathophysiology in humans and experimental animal models
  - Mechanisms of vaccine protection
- Foundation for product, clinical and animal model development programs

Facilitation of development programs....

- Frequent and early communication
- Open communication channels
  - Early disclosure of complications can promote problem-solving collaborations
- Incorporate CBER advice points or provide alternative approaches and sound scientific rationale

Facilitation of development programs....

- Seek input from experts in academic and medical communities
- CBER Guidance to Industry and Points-to-Consider Documents
- International Committee on Harmonization Guidance Documents
- Workshops: announcements, summaries, slide presentations
  www.fda.gov/cber/reading.htm

Acknowledgments

Karen L. Goldenthal, MD
Director
Division of Vaccines and Related Products Applications
OVRR/CBER

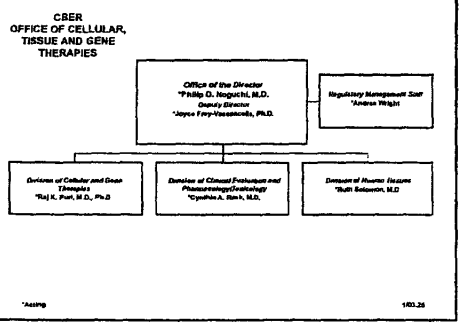
Colleagues in...
Division of Vaccines and Related Products Applications
Division of Bacterial, Parasitic and Allergenic Products
Division of Manufacturing and Product Quality

POTENTIAL USE OF TISSUE GENE, AND CELL THERAPY PRODUCTS: REPAIR, REPLACE, RESTORE, REGENERATE

Steven R. Bauer, PhD
Laboratory of Stem Cell Biology
Division of Cellular and Gene Therapies
Office of Cellular, Tissue, and Gene Therapies

Office of Cellular, Tissue, and Gene Therapies
October 1, 2002

- Regulatory/review responsibility for tissues, cellular, gene therapies, and xenotransplantation products
- Regulatory programs and scientific research to assure the continued safety, identity, purity, and potency of these products
- Collaborative reviews for combination products that consist of cells/tissues combined with a drug or device

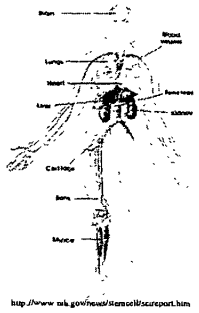


OCTGT Counterterrorism Approach: Potential Uses

- Goals
  - OCTGT perspectives on importance of novel approaches for treating terrorism-related injuries, long-term consequences
  - Stimulate thoughtful consideration of unmet needs in this area

OCTGT Counterterrorism Approach

- Encourage and facilitate development of cellular, tissue, and gene therapy products as medical countermeasures



Repair

Replace

Restore

Regenerate

OCTGT Counterterrorism Approach

Repair, Replace, Restore, Regenerate

- **Biological, radiological, chemical, traumatic injuries**
- **Address with tissue, cell, gene therapy-based products**

Repair, Replace, Restore, Regenerate

- **OCTGT Products**
  - **Tissues**
  - **Cellular Therapy**
  - **Gene Therapy**
  - **Cellular + Gene Therapies**
  - **Tissue Engineering**
    - Combination Cell/Tissue with Device/Gene Therapy/Recombinant Protein

Use of Human Cells, Tissue and Cellular and Tissue-based Products(HCT/Ps)

- **Musculo-skeletal**
- **Ocular**
- **Skin**
- **Hematopoietic stem cells**
  - **peripheral/cord blood derived**
- **Bone marrow stem cells**

Useful and Needed as Countermeasures

- **Adequacy of supply?**
- **Not all conditions amenable**

Human Cell, Tissue Product not regulate under IND

Repair, Replace, Restore, Regenerate

- UNMET NEEDS: sufficient medical counter-measures for acute and long-term consequences
- Acute needs
  - E.g.: live skin replacement for burn victims, bone repair or organ replacement for trauma victim
- Long-term needs
  - E.g.: complete immune reconstitution, cell or gene therapy for cancer subsequent to irradiation

trauma induced

Potential Uses: Address Unmet Needs

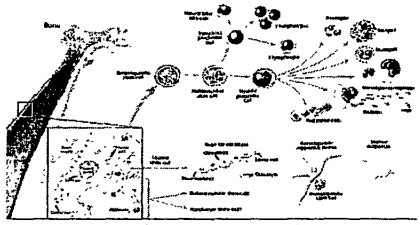
- **Cellular Therapies**
  - **Hematopoietic Reconstitution**
  - **CNS Repair**
  - **Cardiac Repair**
  - **Stem Cells**
- **Tissues and Tissue Engineering**
  - **Skin**
  - **Bone**
  - **Organs**
    - **Xenotransplantation**

Potential Uses

- **Stem Cell-Based Therapies**
  - **Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including, spinal cord injury, burns, heart disease**
  - **In vitro differentiation**
  - **In vivo differentiation**

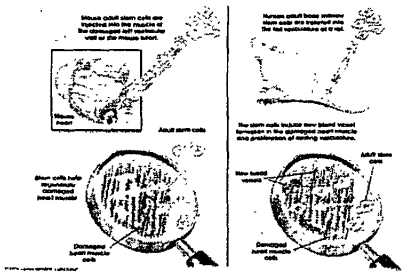
Potential Uses

Bone marrow stroma/Mesenchymal stem cells
Facilitate hematopoietic reconstitution



http://www.nih.gov/news/stemcell/scireport.htm

Potential Uses



http://stemcells.nih.gov/info/Center/stemCellBasics.asp#6

CD34 stem cell Bank. To
(血液 Bank for emergency needs)
Already have priority
*National donor program
donate human stem cell
cord blood Bank.

Potential Uses

Adult Stem Cell

- **Satellite cells = Muscle stem cells**
- **Divide in response to injury**
  - **Self renew and differentiate**
    - **more stem cells, new muscle cells**
- **Wnt signaling pathway stimulates muscle forming processes**
  - **Polesskaya et al., *Cell* 113:841–852, 2003**

Potential: repair damaged muscle

Potential Uses

Human embryonic germ cells
- partially restore paralyzed rat motor activity
- migrate into the spinal cord of paralyzed rats
- prevent existing host neurons from dying
- secrete factors for regrowth of connections between nerves and motor neurons
  - Kerr et al., *J Neurosci* 23:5131–5140) 2003

Potential: repair spinal cord damage

Potential Uses

Dental pulp stem cells
- Origin: baby teeth
- Progeny express molecular markers for dentin, bone, fat, and nerve cells
- Accessible source of stem cells to repair damaged teeth, regenerate bone, and treat nerve injury or disease
  - Miura et al., *PNAS* 100:5807–5812, 2003

Potential: repair bone, dental, and nerve injuries

Potential Uses

Genetic modification of stem cells
- Homologous recombination in human embryonic stem cells
  - OCT4, HPRT1
- Modify hESC-derived tissues for use in treating patients.
  - Zwaka and Thomson, *Nat Bio* 21:319–321, 2003

Potential: alter stem cells to match recipient, enhance performance, etc

Potential Uses

Genetic modification: Gene Transfer
- *Ex vivo* transformation with gene transfer vectors
- *In vitro* transformation with gene transfer vectors
- Enhance function, performance, longevity, other characteristics of cells or tissues

Repair, Replace, Restore, Regenerate

- Tissues available and useful
  - Limited supply, unmet needs remain
- Great potential for cell, gene, or combination products
  - Much product, clinical, pharmtox development needed
  - Consider need in different terrorism scenarios
    - likely numbers, storage, delivery, etc

CBER/OCTGT Contact Information

- PHONE: 800-835-4709 or 301-827-1800
- INTERNET: http://www.fda.gov/cber
- Send e-mail to: OCTMA@CBER.FDA.GOV
- CBER Regulatory and Guidance Documents on the Internet at: http://www.fda.gov/cber/guidelines.htm
- Bauer@CBER.FDA.GOV
- 301-827-0684

Cord Blood Bank. without history or baby parent medical history & grand parent ...

(IND)

Information on HCT/Ps

- Website at www.fda.gov/cber/tiss.htm
  - Form 3356 – Registration/Listing
  - Published documents and letters
  - Meeting minutes/summaries/transcripts/presentations
- E-mail address for registration questions tissueregs@cber.fda.gov
- HCTERS Queries – information on registered establishments http://intranet.fda.gov/cber/tissue/hcters.htm

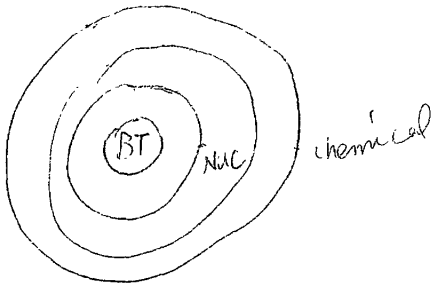
34, 35 IND This year Gene therapy

phase 1/2

NIH. (Genetis) web site.

cell or tissue therapy are more obvious

CT strategy : Concentric circle.
Expendary Tangment



long term follow up

Development of West Nile virus Testing and Donor screening as a Model for Screening Bioterrorist Agents

Hira Nakhasi, Ph.D.
Director, DETTD/OBRR
CBER, FDA

Office of Blood Research and review Counterterrorism strategic plan

- Facilitate the development and availability of safe and effective medical products to prevent and treat the health consequences of terrorist event
- Protect the integrity of the blood supply and other biological products
- Provide accurate and timely information regarding medical products used to prevent or treat consequences of terrorist acts
- Enhance emergency preparedness and response capability

Office of Blood Research and review Counterterrorism strategic plan

- **Protect the integrity of the blood supply and other biological products**
  - Devise and implement donor screening methods and tests to assure that affected individuals do not spread agent
    - Investigate testing methodologies for screening donors
    - Develop policies for screening and standards for lot release and validation assays
    - Assess studies characterizing agent pathogenesis
    - Communicate with manufacturers for development of screening assays
  - Develop a program to evaluate approved and unapproved methods for removal and inactivation of possible bioterrorist infectious agents
    - Pathogen removal and inactivation
    - Develop antiviral compounds

Office of Blood Research and review Counterterrorism strategic plan

- Investigate testing methodologies for screening donors
  - Develop Real Time PCR and hybridization to a microarray of DNA oligonucleotides to detect bioterror agent (BT) nucleic acids in blood and blood products in a multiplex format
    - Accomplishments:
      - Optimized Real time PCR amplification for 3 category A agents
      - Achieved simultaneous detection of cells from the 3 BT agents in blood samples using microarray platform

Development of WNV donor screening test as a model for BT agent screening in blood and blood products

Progress in Donor Screening for West Nile virus

- FDA's actions to date regarding donor testing
- WNV test development including the lot release and validation panel development
- WNV testing of blood donors using investigational tests

West Nile Virus and Blood Safety: FDA's Actions to Date

- Alert notices posted on FDA's website
  - August 17, 2002 Vigilance in excluding symptomatic donors urged prior to any actual report of transmission
  - October 3, 2002 FDA states its interest in facilitating development of donor screening & supplemental tests
- Congressional hearings or briefings on September 10 & 24, October 3, 2002, and June 6, 2003
- FDA is working closely with the test kit manufacturers to expedite test development and implementation (Sept. 2002 industry meeting, Nov 2002 FDA scientific workshop, BPAC update in 12/02, BPAC discussion 3/03)
- FDA issued a guidance on "Recommendation for the assessment of donor suitability and blood and blood product safety in cases of known or suspected West Nile virus infection", Oct. 25, 2002
- FDA issued a revised guidance on "Revised recommendation for the assessment of donor suitability and blood and blood product safety in cases of known or suspected West Nile virus infection" May 1, 2003

West Nile Virus and Blood Safety: FDA's Actions to Date

- FDA has approved:
  - GenProbe (16 samples/pool) phase 1 IND for repository testing on March 21, 2003
    - phase 2 IND for prospective WNV NAT testing on May 27, 2003
  - American Red Cross IND for WNV NAT testing (GenProbe test 16 samples/pool) on May 27, 2003
  - Roche IND for WNV NAT testing (6 samples/pool) on May 22, 2003
- Investigational WNV NAT testing has started since mid June 2003 using pooled or individual samples.
- FDA is participating in weekly meetings with the task force established by blood banking community, which includes CDC and NIH to coordinate the epidemiological data on WNV infection and to monitor the out come of testing.

Background Information

- WNV is an enveloped single stranded RNA virus
- WNV is a mosquito-borne flavivirus
  - Primarily infects birds
  - Occasionally infects humans and other animals
- About 80% of human infection is asymptomatic, and 20% develop mild febrile illness (flu-like illness)
- Approximately 1 in 150 infections results in meningitis or encephalitis
  - Advanced age is by far the most significant risk factor for severe neurologic disease
- Viremic period can occur up to 2 weeks prior to symptoms and last up to a month from the initiation of the infection

Background Information.....

- The 2002 US outbreak of WNV resulted in the identification of other modes of transmission including:
  - Blood transmission (RBCs, plasma and platelets), Transplantation, Breast-feeding, Transplacental and Occupational by percutaneous injury
- The magnitude of the risk of WNV from transfusion is unknown.
- Virus titer in blood is low compared to other transmissible viruses (~1-5x10^3 copies/ml) and the viremia is transient.
  - Viremia in encephalitis patients can be as high as 2 5x10^6 copies/ml
- Viremia resolves rapidly after seroconversion to IgM
- IgM can persist for a long time in some cases up to 2 years
- No chronic stage of WNV infection has been reported

Status of WNV pathogenicity and epidemiology in the US in year 2002

- In year 2002 total number of WNV cases reported were 4156 out of which 284 deaths and 2942 cases of WNME
- 44 states including DC are endemic for WNV
- The average risk of WNV by transfusion in 2002 was 0.4 per 10,000 donations nation wide with a maximum risk 10.46/10,000 donations in Michigan
- During Aug 28, 2002- June, 2003, 61 possible Transfusion-Transmitted cases reported (Retrospective testing of 2002 epidemic)
  - 23 are confirmed from 16 blood donations
  - 19 are not transfusion related,
  - 19 inconclusive due to incomplete donor follow-up
  - 6 deaths- WNV could not be established as the cause in most cases

FDA's Research Activities on WNV

- Panel development
  - To monitor sensitivity of assays to detect viral nucleic acids and antibodies
- Isolation and characterization of WNV strains from human samples obtained during the 2002 and 2003 epidemics
  - Genetic variation of viral strains
  - Detection by currently available WNV assays
- Natural history studies to evaluate infectiousness in blood to better understand risk and define unit/donor management strategies

Analytical sensitivity of WNV assays

- FDA's current standard for licensure WNV NAT assays is 100 copies/ml for the individual donation
- WNV panel designed to monitor this sensitivity limit
- Standard may be revised based on infectivity data or sensitivity improvements

FDA NAT Panels

- FDA NY99 and FDA-Hu2002 isolates characterized by genetic sequencing
- Viral infectivity determination
- RNA concentration measurements
- Final panel specifications are being established through collaborative studies
  - The prototype panel consists of two isolates
  - Viral concentration ranges between 1000-5 copies/ml

Viral Titer Determination Copies/mL

Isolate (dilution)	Average of multiple testing performed by each laboratory*					Final Copies/ml
	Lab 1	Lab 2	Lab 3	Lab 4	Lab 5	
FDA-Hu2002 (10^{-1})	10^9	10^9	10^9	10^9	10^9	10^{10}
FDA-Hu2002 (10^{-4})	10^6	ND	10^6	10^6	ND	10^{10}
FDA-Hu2002 (10^{-7})	10^3	ND	10^3	10^3	10^3	10^{10}
NY99 (10^{-1})	10^9	10^9	10^9	10^9	10^9	10^{10}
NY99 (10^{-4})	10^6	ND	10^6	10^6	ND	10^{10}
NY99 (10^{-7})	10^3	ND	10^3	10^3	10^3	10^{10}

Correlation between Copies/mL and PFU/mL

Sample	Copies/ml average (FDA & NYSDOH)	PFU/ml
FDA-Hu2002	10^{10}	10^{7}
NY99	10^{10}	10^{8}

Correlation between Copy/mL and PFU/mL

Sample	Av. copy	PFU
HuWNV	10^{10}	10^{7}/mL
HuWNV 60°C/2 hr	10^{7}	0
NY99	10^{10}	10^{8}/mL
NY99 60°C/2 hr	$10^{6.5}$	0

Status of WNV pathogenicity and epidemiology in the US in year 2003

- During 2003 total number of WNV human cases reported so far are ~5000 out of which 88 deaths, of the total infections ~29% cases of WNME and ~ 60% cases of WNV fever
- 44 states including Washington D.C. are endemic for WNV
- Putative WNV transfusion related cases are being analyzed
  - Confirmation of NAT and IgM reactivity
  - Donor and recipient F/U
- CDC reported two confirmed cases of WNV transmission through transfusion

West Nile Virus and Blood Safety: Current Status

- Starting July 1, 2003 blood donor screening under IND in place covering all geographic regions of the US
- **Several confirmed asymptomatic infection interdicted**
  - ~ >1000 units of WNV infected blood detected from ~ $3x10^6$ donations screened
  - Units would otherwise have been transfused
- MP-NAT testing has effectively removed >75% of infected blood donations from entering the blood supply for transfusion

West Nile Virus and Blood Safety: ID-NAT study

- Potential for transmission of WNV through minipool (MP) NAT negative blood and blood components. Because of the low level of viremia in some patients and window periods of detection before and after seroconversion.
- A limited retrospective evaluation of MP-NAT negative units from 2003 epidemic from four high incidence regions (~1/250 + rate using MP) and retrospective studies on samples collected during 2002 epidemic were done using ID-NAT GenProbe test.
  - Samples with low level of viremia may be missed in minipool testing
  - Putative WNV transfusion related cases are being analyzed
    - Confirmation of NAT and IgM reactivity
    - Donor and recipient F/U

West Nile Virus and Blood Safety: ID-NAT study

- **Goals of the ongoing ID-NAT study are:**
  - To perform ID-NAT prospective and retrospective testing in high incidence areas, F/U and determine infectivity of such units
  - Compare testing of the ID-NAT positive samples between the two test kit manufacturers
  - Perform an infectivity study in various animal models including non-human primates and using the MP-NAT (-), ID-NAT (+) units

West Nile Virus and Blood Safety: ID-NAT testing

- Pending data on the infectivity of MP NAT-/ID NAT reactive units
  - ID-NAT is being performed prospectively in high incidence areas based on the capacity for additional testing and the frequency of MP-NAT + units collected in the region.
  - Frozen plasma is being withdrawn in areas with high incidence of WNV based on MP-NAT.

West Nile Virus and Blood Safety: Summary

- Blood donor screening for WNV using investigational MP-NAT was achieved in a record time (~9 months) since FDA stated its interest in the development of donor screening test
- Because of the implementation of MP-NAT >75% of infected blood donations have been interdicted
- In addition, in limited setting ID-NAT is being performed in high incidence areas
- Studies are underway to determine the infectivity of low level viremic donations [MP-NAT (-), ID-NAT (+)]
- This has been possible due to close cooperation between public health agencies, blood establishments and the test kit manufacturers

Acknowledgements

- Task force which consists of public health agencies (FDA, CDC. NIH, DOD) and blood establishments for weekly updates and monitoring the progress of WNV epidemic and testing
- Test kit manufacturers for development of investigational tests in a timely manner
- FDA staff for interactive review and formulating policies
- Blood establishments for timely implementation of WNV testing

Product Development and Manufacturing

"Counter Terrorism Products Regulated by CBER: Effective Strategies to Assist in Product Development"

October 24, 2003

John Finkbohner, Ph.D., Deputy Director
Division of Manufacturing and Product Quality
Office of Compliance and Biologics Quality

Presentation Outline

- Overview of challenges
- Survey of some focus areas related to general manufacturing control:
  - Equipment
  - Facility / Manufacturing Environment
  - Raw Materials / Component Controls
  - Validation / Qualification Programs
  - Quality Systems
- *Product specific process development issues to follow in later presentations*

Key Challenge to Manufacturing Unit:

Due to compressed development timelines for counter bioterrorism (CBT) agents, there's a loss of development time to learn how the process behaves in routine manufacturing

Compressed Timelines for:

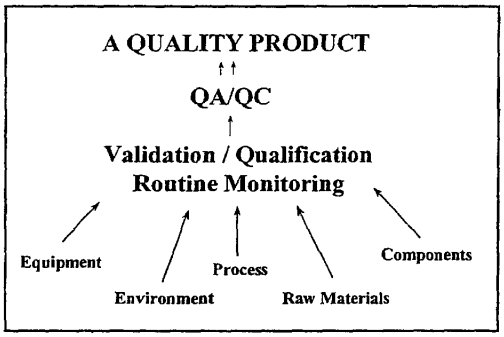
- Defining the process:
  - Process operating parameters and equipment SOPs complete and "road tested"?
  - Equipment supporting various unit operations qualified?
  - Experience with product allow predictability for unit operations?
- Qualification/Validation:
  - Process alteration and optimization
  - Ongoing qualification and validation (concurrent)
  - Sufficient resources?

Key Challenges to Quality Unit:

Due to compressed development timelines for counter bioterrorism (CBT) agents, there's a loss of time to get quality systems in place and to complete supporting operations!

Compressed Timelines for:

- Establishing Quality Systems:
  - Records and documentation,
  - Raw material specifications and testing procedures (sampling, sample size, test methods, etc.),
  - Vendor audit program – level of completion
  - Change control system
  - Deviation/Investigation system
- As you approach licensure....
  - Adverse event reporting system
  - Product complaints and recall systems
  - Regulatory reporting systems (supplements and BDPRs, etc.)



Critical Resources to Facilitate Rapid Availability of CBT Agents

- **Very** careful choice of contract partners and vendors including "track history"

Contract Partners: Quality Agreements

- Do the quality agreements between the applicant and any contract manufacturer include adequate reporting of deviations not directly related to product manufacture?
- Example: If system failure noted covering a period bracketing contract manufacturing operation, does reporting to applicant include notification to allow assessment of impact on their product?

Contract Partners: Quality Agreements

- Does change control system of the contract manufacturer include notification of applicant and/or direct involvement of applicant in implementation decision?
- Example: Does introduction of an investigational product operation into areas utilized for contract manufacturing include applicant notification?

Critical Resources to Facilitate Rapid Availability of CBT Agents

- Experienced and knowledgeable staff – manufacturing AND quality units

Critical Resources to Facilitate Rapid Availability of CBT Agents

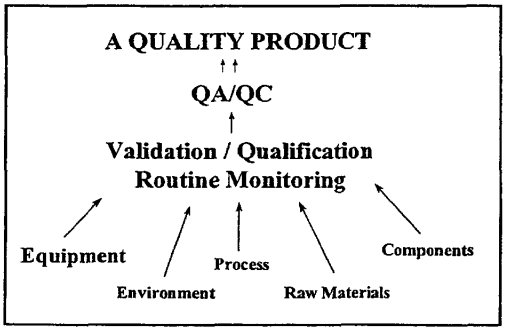
- Open dialog with CBER as early as possible in the planning process
- Emphasis on locking down process as rapidly as possible, *especially if early production lots intended for licensure*

Compressed timelines for addressing:

- Safety related issues:
  - Adventitious agents,
  - Maintaining sterility or bioburden control,
  - Immunogenicity concerns, etc.
- Process consistency:
  - Process alteration and optimization
  - Process scale up impacts
    - Confounded by ongoing qualification and validation activities

Some early priorities include:

- Prioritization of safety related qualification and validation activities
- Performing equipment capability assessments for each unit operation as processing parameters are defined



Equipment: Capability Assessment - 1

- H as each unit operation been assessed for suitability of equipment and process stream contacts? (i.e., under operating conditions)
- H as each unit operation that is critical for safety of the product been validated? (e.g., sterilization of final container closure system components)

Equipment: Capability Assessment - 2

- P erformance testing in place where needed? (performance capability demonstrated via appropriate qualification, validation, and/or routine manufacturing data)

Equipment: Capability Assessment - 3

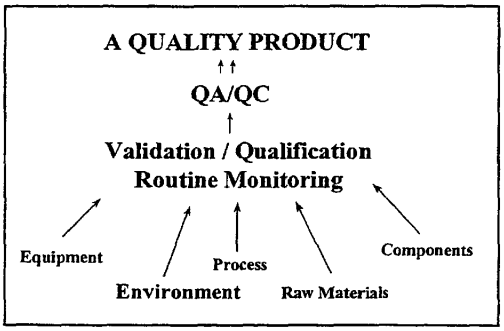
- F iltration/Concentration steps validated ?
- R outine use of purification columns controlled ?
- A ny rework or reprocessing steps in the process due to potential equipment function concerns ? If so, are they validated ?

Equipment: Personnel

- Personnel gowning practices appropriate?
- Personnel adequately trained ?
- Manufacturing supervisors appropriately experienced with the process ?
- Manufacturing supervisors practicing a quality approach to operations ?

Why were personnel listed under "Equipment" ?

- The process depends upon their function as specified.
- The most common cause of deviations for a well controlled process is the personnel.
- Training and qualification programs are critical

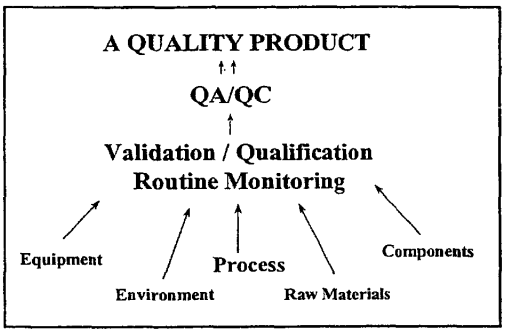


Environment: Monitoring - 1

- Are the controlled production environments appropriately qualified and monitored for HVAC system performance and microbiological quality?
- Are the controlled production environments appropriate to support the manufacturing processes being performed ?

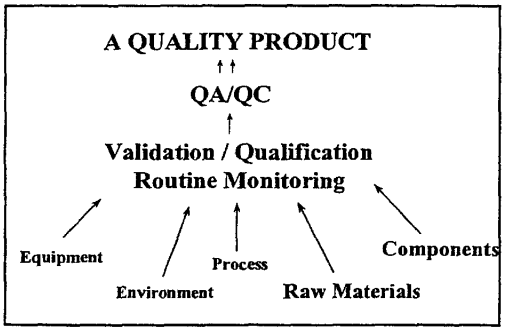
Environment: Monitoring - 2

- Monitoring systems adequate for open product manipulations and aseptic operations ?
- HVAC systems appropriately maintained and qualified / requalified ?
- Preventative maintenance and calibration programs appropriate ?



Process Validation

- Do the unit operations include operating parameters based upon the validation studies?
- Does the documentation (e.g., BPR) capture all relevant operating information?
- *More detailed discussion of this topic from my colleagues speaking later this morning*

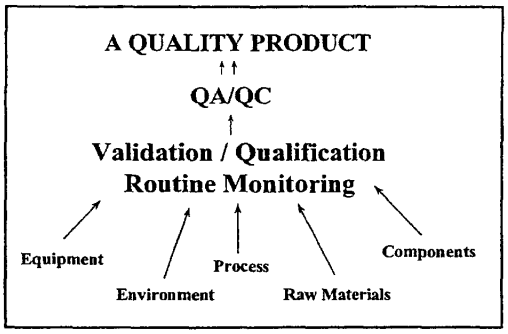


Raw Materials

- Incoming material sampling plans appropriate ?
- Acceptance criteria supported ? (i.e., fitness for use quality attributes understood)
- Vendor audits conducted for critical raw materials ?
- Quarantine / Release procedures for raw materials appropriate ?
- Quality procedures and documentation for release appropriate ?

Components

- Diluent formulation defined ?
- Clinical administration kit components that require qualification ?
- Primary packaging (container closure) system defined ?
- Contract partners for any components evaluated and qualified as a vendor ?
- Sampling programs by vendors implemented (if needed)?
- Documentation for release appropriate ?



Validation

- Sterility assurance validation studies and aseptic processing qualification studies (e.g., media challenges) completed ?
- Are cleaning validation studies appropriate for the context of use for the equipment ? Does validation approach include potential for highly biologically active cross contamination or adventitious agents (as appropriate) ?
- Are computer and PLC controlled systems appropriately controlled (and validated, if necessary) ?
- Are "closed" systems appropriately qualified ?

cleaning validation
cross contamination

press integrity horse
(make sure system is close)

Validation

- How are failures handled during execution of a validation protocol ?
- Are qualification/validation studies for critical equipment systems performed appropriately ?
- Do the SOPs reflect the validated conditions for use of equipment ?

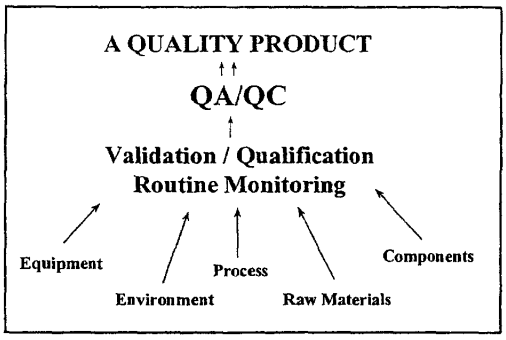
Validation: Legacy Systems

- If "legacy" equipment or facility being utilized, is the approach rigorous based upon known prior uses, or lack of prior use information?
- Have the considerations taken into account during protocol design been *documented* ?

对於無可考究系統所作之
validation (Legacy system)
系統買自破產之公司、or 其他產業
↳ ex: Bio-reactor

Issues to address for lots intended for licensure

- Validation data to support processing parameters and hold times?
- Reprocessing and/or Rework procedures, if allowed?
- Conformance lots produced using the method submitted in the license application?
- Capable of successful manufacture of consecutive lots?



Quality Systems: Documentation

- Manufacturing unit operation data recorded directly in BPR ?
- Does BPR reflect actual production ?
- Documentation for material and intermediate(s) release appropriate ?
- Final release procedures appropriate ?

Batch Product Record.

Quality Systems: Issues

- How are out-of-specification (OOS) investigations handled ?
- Are deviations and investigations handled effectively ?
- Operations segregated appropriately (as appropriate) ?
- Staff adequately trained ?

Quality Systems: Testing - 1

- Method validation efforts on an appropriate timeline ?
- Are in-process and final testing samples being handled appropriately ?
- Are appropriate compendial methods in place and being performed appropriately ?

Quality Systems: Testing - 2

- Are OOS results being handled appropriately ? (i.e., investigation system triggered?)
- Are appropriate system suitability procedures in place ?
- Is testing equipment being appropriately maintained and are the records for these actions adequate ?

Quality Systems: Final Product Visual Inspection

- Does method include major and minor defect categories with alert and action limits?
- If re-inspection allowed, are there limits?
- Do visual inspectors undergo a rigorous qualification program?

Quality Systems: Vigilance for the unexpected and human factors

- Are deviations reported and are appropriate investigations performed ?
- Does the adverse event reporting system perform properly ?
- Are written procedures under change control and do staff follow the SOPs ?

Common Problem Areas for Previously Unlicensed Applicants

- Written procedures for preventative maintenance systems are lacking
- Written documentation of training programs incomplete
- Written documentation of vendor audit program incomplete, or audits not performed

Common Problem Areas for Previously Unlicensed Applicants

- Written documentation for raw materials program incomplete or ill-defined (fitness-for-use criteria not bridged from unit operation validation protocol design or results)
- Quality Operations unit backlog in final approvals of validation reports, etc. (i.e., inadequate resources for the quality operations unit or validation unit)

Common Problem Areas for Previously Unlicensed Applicants

- Does facility have design flaws relative to cGMP compliance capability? If so, can procedural control adequately support consistent manufacturing operations?

What resources are there to avoid potential pitfalls ?

Communicate with CBER and prepare throughout the process

- Guidance documents
- Feedback throughout the IND process
- Pre-submission meetings with specific questions can be very productive
- *Do not neglect manufacturing facility issues during the development process*

During the pre-BLA period....

- Be careful to have comprehensive project timelines allowing resources and time to complete facility and process related validation / qualification studies
- Let me say it again..... *Do not neglect manufacturing facility issues during the development process*

Resources

WWW Guidance Documents:
http://www.fda.gov

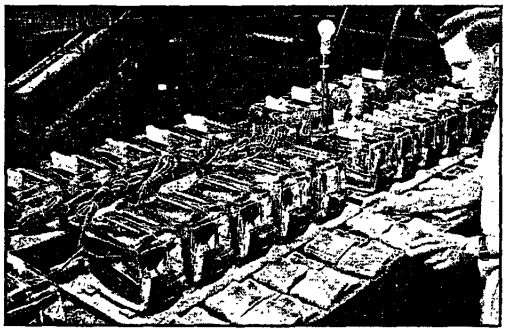
Phone questions for manufacturing facilities to CBER/OCBQ/DMPQ 301-827-3031

Summary

- The challenge relative to manufacturing is to have the appropriate resources to tackle the incredible number of issues that WILL arise.
  - Contract partners that have been fully evaluated
  - Excellent staffing models and expertise to draw upon (in house and external, as needed)
  - Maintain a dialog with CBER on all issues of importance

Summary

- It is critical to have an overall plan with detailed project management oversight to successfully move the product through an expedited development program on ALL fronts (i.e., pre-clinical, clinical, process development, and manufacturing)
- AND.....



Counterterrorism-related Specific Immune Globulins: Problems and Challenges in Development

October 24, 2003
Dorothy Scott, M.D.
Branch Chief, Lab. of Plasma Derivatives
DH/OBRR/CBER

Counterterrorism and Specific Immune Globulins

- Vaccinia immune globulin (VIG): for treatment of life-threatening complications of smallpox vaccine
- Botulism immune globulin (BIG): for treatment of botulism poisoning
- Anthrax immune globulin (AIG): for treatment of subjects not responsive to antibiotics (proposed)
- Other IG's against other agents are/may be considered (proof-of-concept in animal studies)

VIG, BIG already licensed

Challenges (1)

- Product
  - Donor selection/vaccination protocols
    - Live vaccines - ? Viremia
    - Co-vaccination with live vaccines (if enrolled in vaccine programs)
    - Viral validation in manufacturing
  - Potency
    - Bioassays or binding assays?
    - Standards for testing
    - Lot release
    - Dosing

→ can't do in vivo in people.

Challenges (2)

- Clinical
  - Efficacy testing: often product cannot be tested in "real life" scenario, e.g. vaccinia immune globulin for progressive vaccinia
  - Role of the animal rule
  - Limitations animal testing (BSL-4 agents)

Challenges (3)

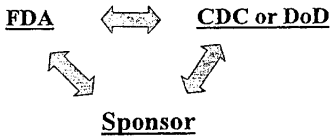
- Provision of material in IND stage
  - IND's for indications (often CDC; industry, other government) ↑ person
  - E-IND's (unexpected events; case-by-case)
- Provision of material long-term (as long as the need exists)
  - Stability monitoring
  - Maintaining supply of product over years; determining when additional lots will be needed

Challenges (4)

- Timing
  - Production timelines (GMP's, and scaleup)
  - Licensure: possible eligibility for Fast Track procedures
    - Priority review
    - Rolling review

case by case based

Coordination/Problem Solving Early



Vaccinia Immune Globulin: Case Study in Development

- Vaccinia immune globulin, intravenous, human (Human plasma)
  - Historically licensed product; very low demand until post 9-11
  - Diminishing potency of old supplies
  - Manufacture of new material indicated

Historical Uses of VIG Products: Complications of Smallpox Vaccination

- **Eczema vaccinatum***
- **Progressive vaccinia (vaccinia necrosum; gangrenosum)***
- **Ocular vaccinia*** (but NOT keratitis)
- Generalized vaccinia* (+/-)
- Prophylaxis against eczema vaccinatum

Smallpox Vaccination Complications – Mortality Without VIG Treatment

Normal Vaccination	**0%**
Eczema Vaccinatum	**30-40%**
Progressive Vaccinia	**100%**

↳ immune compromize

Vaccinia Immune Globulin Products

- **All are under IND**
- **All manufactured from Source Plasma of revaccinated donors**
- **Source Plasma collected 10- approx. 30 days post-vaccination**
- **New VIG's manufactured using S/D treatment and nanofiltration steps for viral clearance**

Challenges in Development and Use of VIGIV

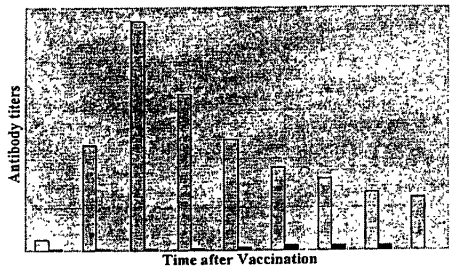
- Plasma donors and live vaccination (vaccinia)
- Potency testing for VIG (lot release)
- Clinical study: real treatment studies not possible in pre-event scenario
- Addressing post-exposure prophylaxis
- Emerging possible indications (the unexpected)
  - Myopericarditis?
  - Monkeypox prophylaxis or treatment?

Smallpox Vaccination and Donor Deferral

- Published January 19, 2003
- Deferral for vaccinees:
  - 21 days after vaccination, OR
  - Until scab falls off
  - WHICHEVER IS LONGER
- Rationale
  - Possibility of viremia
  - Consequences of viral transmission to recipient could be severe

used collecting time 10~20 days after vaccination

DONOR RESPONSE TO DRYVAX VACCINE



Plasma Collection for VIG Products

- VIG products historically made from plasma collected earl y post-vaccination
- In vitro studies (B-gal assay; plaque assays): no plaques observed with VIG alone; no evidence live virus in products
- Need to maximize collection of high-titer material

Evidence-based decision-making

- Historical information about viremia
- Publications on capacity of plasma derivative processing steps to clear vaccinia
- CBER and Industry research on the question of viremia in smallpox vaccinees
- Maximizing product safety

Vaccinia Viremia (?)

- **Herzberg, Kremmer, 1930[1]**
  - **8/17 normal children post vaccine**
  - **titered by bioassay in rabbits**
  - **strains various (cattle lymph)**
  - **viremia days 3-15; mainly day 6-7**
- **Also reported 1953 (journal not available)**

[1]Zentralblatt for Bakteriologie 1930; 115:271-80

Vaccinia Viremia (?)

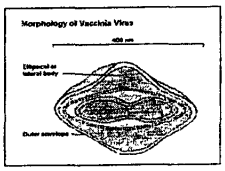
- **Not seen in "over 100" patients studied (no data shown)[1]**

FDA and Industry: plaque assays for Vaccinia in blood from recently vaccinated people

[1] Kempe, CH, Pediatrics 1960; 26:176-89

Vaccinia Virus Clearance Potential of VIGIV Manufacturing Processes

Vaccinia Virus



- **Enveloped**
- **DNA**
- **400 nM size**

Vaccinia Virus and S/D Treatment of FVIII *

	Logs Inactivation					
Virus	Minutes S/D (TNBP 0.3% / Triton X-100 1.0%)					
	0.25	1	10	30	60	120
Vaccinia	1.0	2.5	3.8	4.4	4.7	4.7
HSV-1	>5.1	>5.1	Nd	Nd	Nd	Nd
Sindbis	4.9	5.4	>5.6	Nd	Nd	Nd

*Resistance of Vaccinia Virus to Inactivation by S/D treatment of Blood products. Roberts, P. Biologicals 2000; 28. 29-32

Vaccinia Virus and S/D Treatment of Fraction II Precipitate (0.3% TNBP/1% PS80, 60-180 min.)*

		Recovered		Eliminated	
Virus	Added	Pre-S/D	After S/D	Clearance	Reduction
Vaccinia	7.75	6.88	4.41	3.34	2.47
HIV-1	> 11.5	> 11.5	<1.5	>10	>10
VSV	7.43	7.32	<1.86	>5.57	>5.46

* Inactivation and elimination of viruses during preparation of human intravenous immunoglobulin Uemura et al, Vox Sing 1994, 67.246-54

S/D : Solvent / Detergent treatment (current product

Plasma Fractionation – Viral Clearance Steps for VIGIV

All recently manufactured new IND products have 2 viral inactivation steps that are expected to clear vaccinia:

1. Solvent-detergent treatment

1. Nanofiltration

Vaccinia Viral Validation for VIGIV Products

- **Donor exclusion for 21+ days post-vaccination would result in loss of high-titer plasma**
- **Working Assumption: Viremia likely to be low level, rare and/or intermittent, if present at all, in normal vaccinated donors**
- **Testing for post-vaccination viremia ongoing in several laboratories (no positive reports to date, but studies are not finished, and not prospectively designed for viremia monitoring)**
- **Viral clearance studies suggest vaccinia can be inactivated by S/D treatment, but that vaccinia is relatively resistant compared to other enveloped viruses**
- **Nanofiltration is expected to remove vaccinia due to its large size**
- **Process-specific validation will provide enhanced assurance of safety**

Potency of VIG

- Bioassays vs. solid-phase (e.g. ELISA) for lot release
  POTENCY does not always equal BINDING
  because non-neutralizing (e.g. non-useful) antibodies may bind to antigens on a plate
- CBER has stated preference for bioassay use for VIG products (neutralization)
- CBER in-house assays developed for VIG potency
  - Research-level
  - To enable product characterization
  - To increase bioassay understanding and capabilities

The Old Method: Plaque Reduction Neutralization Test (PRNT)

- **First developed in 1960's**
- **Slow (3-6 days)**
- **Requires large amounts of plasma**
- **Day-to-day and person-to-person variability**
- **Time-consuming (manual counting of plaques); not automated**
- **Difficult to consistently reproduce**
- **Difficult to transfer to new labs**

CBER RESEARCH: Meeting the Needs
H. Golding et al, OVRR, CBER, FDA

- **We developed an improved test using a beta-galactosidase reporter-gene containing virus:**
  - **Faster (24 hr); High throughput; important for large scale evaluation of many samples in clinical trials**
  - **Read-out: automated; Machine reads color-change**
  - **Sensitive, quantitative, reproducible**
  - **Easy to transfer to manufacturers/DOD**

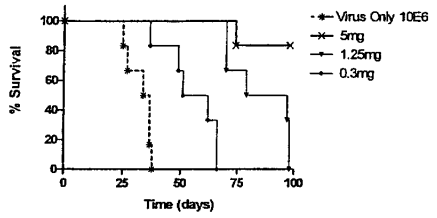
In vivo assays

- CBER developed an in vivo model of potency in severely immunocompromised (SCID) mice

- May reflect neutralization of forms of virus not easily cultured, e g extracellular enveloped form,
- Useful for comparison to in vitro bioassays
- Provides useful early assurance of likelihood of efficacy
- Other animal models also under development

CBER Research: Protective Effect of VIGIV at Different Doses in SCID Mice

immuno-compromized



CBER/Manufacturer Testing and Provision of Interim VIG Standard

- MPHBL* VIGIV, manufactured under GMP conditions
- Aliquotted, frozen; no loss of potency with 2 freeze-thaws
- Tested in 3 different laboratories for plaque neutralizing activity, with good agreement
- Available from CBER (scottd@cber.fda.gov)

* Massachusetts Biologic Laboratories

Clinical Studies for Licensure of CT Products: VIGIV Strategy

- How to perform clinical studies pre-event?
  - Actual studies for the disease states (EV and PG) not possible due to very low rate of these complications. Licensure based upon PK equivalence and safety data PK not inferior (≥ 0.8) to VIG given I.m
  - Studies in animal models (e.g tailpox, SCID mice)
  - Discuss with CBER for product-specific advice
- Post-approval commitments; use of Animal Rule

Current Thinking: Clinical Trials for Licensure of VIGIV, Indications

- (2002) New product indications limited to treatment of VIG-treatable vaccinia vaccine complications; labeling specific to data provided by manufacturer of each product
- (2003) Potential consideration post-exposure prophylaxis possibilities
  - Immunocompromised vaccinees
  - Exfoliative skin conditions
  - Note indication in previously licensed product (Baxter): post-exposure prophylaxis for exfoliative/inflammatory skin conditions, including eczema [not based on controlled studies].

Unexpected Events during IND Phase

- Requests for use of product for post-exposure prophylaxis
- Unanticipated clinical scenarios

Clinical Issues: Recent Use of VIG

- To date, no cases of progressive vaccinia (PG), or confirmed eczema vaccinatum (EV)
  - 0/ 454,856 military vaccinees[1]
  - 0/ 37,478 civilian vaccinees[2]
- VIG requested for[3]:
  - Prophylaxis EV in recently vaccinated burn patient (1)
  - Ocular vaccinia (1)
  - Post-vaccination discovery of pregnancy

[1] Col. J. Grabenstein, Military Vaccines Agency, USAMC, presented to the Advisory Committee for Immunization Practices (ACIP) 6/18/03
[2] G. Mootrey, National Immunization Program, ACIP 6/18/03
[3] Discussed at ACIP 6/18/03

Use of VIG(IV) in Pregnancy

- Estimates of fetal vaccinia risk extremely low[1]
  - NYC 1942: 0/ 170,000 pregnant vaccinees
  - U.S. 1967-7: 1/ 5,600 to 17,000 primary vaccinations
- Inadvertent vaccinations in most cases due to very early (undetectable) pregnancy, or to post-vaccination conception
- CDC advice " Women should contact their healthcare provider regarding use of VIG. Currently, CDC's ACIP does not recommend preventive use of VIG for pregnant women."[2]
- CDC has established a pregnancy registry for follow-up of vaccinated pregnant women

[1] S Goldstein, CDC National Immunization Program
[2] (www.bt.cdc.gov/agent/smallpox/vaccination/preg-factsheet.asp)

CDC do a lot of research

Smallpox Vaccination and Myo/pericarditis

- Newly recognized complication in U.S.
- DOD: 46 cases/ 454, 856 vaccinees
- Civilian: 22/ 37,000 vaccinees
- No fatalities
- Etiology - possibly immune-mediated; VIG use would have to be carefully weighed
- Ongoing follow-up of cases for long-term sequelae

Monkeypox and VIG Use

- VIG use, if any, was discussed
- Note that CDC has recommended smallpox vaccination for people who were likely to have been exposed to monkeypox (http://www.cdc.gov/ncidod/monkeypox/smallpox vaccine_mpox.htm)
  - Contraindicated for certain immunocompromised people

CT Product Development: Common Themes

- Uniqueness of some products
- Need to support supply and supply capability closely in the interests of public health
- Stability of products that may be "on the shelf" for prolonged time – monitoring critical to maintain supply of product
- Evolving recommendations as assays, testing, and product characterization continue
- Frequent discussions among FDA, sponsors, and manufacturers are important !

Product Development for Preventive Vaccines

CT products regulated by CBER: Strategies to assist in product development

October 24, 2003

Preventive Vaccines Against Bio-T Agents

- Disease Prevention
  - –"classical" vaccine role
- Deterrence
  - –Discourage potential use of disease agent

Preventive Vaccines Against Bio-T Agents

- Prevention of disease spread
  - – Ring vaccination
- Pre-immunization against exposure
  - – Immunization of troops, health care workers

Preventive Vaccines Against Bio-T Agents

- Agents pose significant risk
  - –High mortality, highly infectious
- Long term protection
  - –single treatment

Preventive Vaccines Against Bio-T Agents

- Government role in public health response
  - –"Orphan" drugs
  - –Instrument of public policy

在此"orphan"非真的orphan drug definition不同，也就是非指真的orphan drug。
∵不確定是否会用到 or patient之數量

Challenges Associated with Preventive Vaccines

- Manufacturing
- Efficacy measurements
- Stockpile and use

Manufacturing

- New substrate is a new product
  - Tissue culture replacing old methods
  - Modern adventitious agent testing
- New vaccines
  - Limited experience

Manufacturing

- Limited and rapid production
  - Early development of manufacturing process
  - Inspection and GMPs
- Maintaining manufacturing potential
  - Changeover protocols

Cell Culture Smallpox Vaccine

- Manufacturing issues for a new vaccine
  - Tissue culture instead of calf skin means new vaccine
  - Accelerated process development
  - Inspections early and often

Efficacy

- Surrogate assays for vaccine effectiveness in the absence of the disease
  - Potency, immunogenicity
  - Modern assays
  - Animal models

cannot use human subject in surrogate

Efficacy

- Assay validation
  - New assays for old measurements
  - New assays to measure immune response
- Clinical decisions from efficacy measurements
  - Duration of protection

Cell Culture Smallpox Vaccine

- Efficacy issues for a new vaccine
  - Human challenge/protection study, as well as field efficacy trial, not feasible
  - Immune correlate of protection unknown
  - Develop confidence in efficacy, not proof

Cell Culture Smallpox Vaccine

- Efficacy issues for a new vaccine
  - Non-inferiority to product with proven effectiveness
  - Assays for comparison of immune response, potency
  - Humoral and cellular response important

Stockpile

- Store or use
- Instant availability
  - IND then license
- Storage conditions (NPS)

Stockpile

- Long-term stability studies
  - Potency assays
  - Validation of assays
  - Product storage lifetime
- Re-labeling of product
  - Transition from IND to license

Stockpile

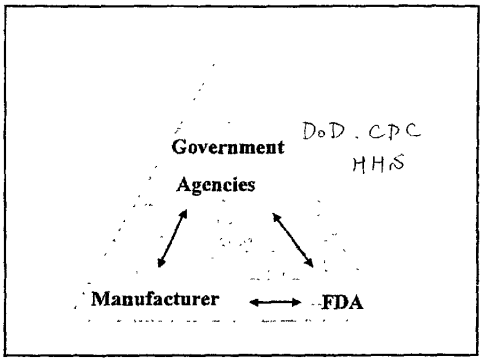
- Transport and Use
  - –Retention of potency through distribution chain
- Product shelf-life
  - –Extension of dating
  - –Replenish stockpile

Smallpox Vaccine

- Storage and potency of remaining calf skin vaccine
- Re-licensure of remaining calf skin vaccine
- Storage and re-labeling of tissue culture smallpox vaccine

Summary

- Preventive vaccines against biological agents of terror provide a critical response to actual and potential acts of bio-terrorism
- The development of preventive vaccines against biological agents of terror pose unique problems in manufacturing, analysis and storage


Government
Agencies
DoD . CDC
HHS
Manufacturer
FDA

CHALLENGES IN CELLULAR, TISSUE, AND GENE THERAPY PRODUCT DEVELOPMENT IN THE CT ARENA

Steven R. Bauer, PhD
Laboratory of Stem Cell Biology
Division of Cellular and Gene Therapies
Office of Cellular, Tissue, and Gene Therapies

Office of Cellular, Tissue, and Gene Therapies

October 1, 2002

- Regulatory/review responsibility for tissues, cellular, gene therapies, and xenotransplantation products
- Regulatory programs and scientific research to assure the continued safety, identity, purity, and potency of these products
- Collaborative reviews for combination products that consist of cells/tissues combined with a drug or device

OCTGT Counterterrorism Strategy

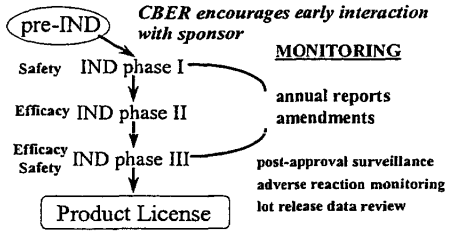
- **Encourage and facilitate development of novel cellular, tissue, and gene therapy products as medical countermeasures**
- **Safeguard integrity of tissue supply**

Regulatory Concerns Common to all Biologicals

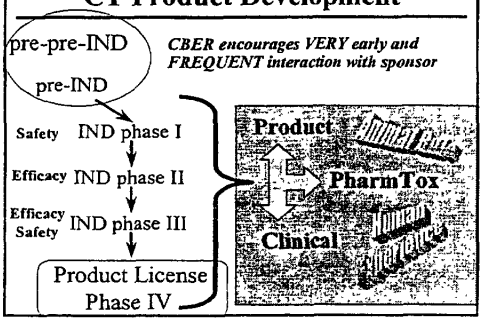
- Safety, efficacy, identity, purity, potency
- Regulation of both product and process
- Quality control of product and intermediates
- Reproducibility of lots

Challenges of Expedited CT Development

Regulatory and Approval Process



CT Product Development



OCTGT Counterterrorism Strategy

- **Biological, radiological, chemical, traumatic injuries**
- **Could be addressed with cell, tissue, gene therapy-based products**

Repair, Replace, Restore, Regenerate

Challenges for Tissues

- **Safeguard integrity of tissue supply**
  - Devise appropriate donor deferral contingencies
    - Infectious agent, radiological, chemical exposure
  - Adapt new donor screening tests
  - Assure that affected individuals do not cause inadvertent spread/exposure

→ new donor screening test

Tissues: cGTPs

- **CGTP requirements govern the methods used in, and the facilities used for, the manufacture of HCT/Ps**
- **Intended to prevent the introduction, transmission and spread of communicable disease, and to preserve function and integrity**

Extra vigilance when urgent need for tissues exists

FDA Measures to Facilitate Potential Use of Human Tissue for CT/BT

- **Communication with industry**
  - **regional shortages; emergency plans**
- **Temporary exceptions to certain FDA requirements, when benefit outweighs risk**
  - **E.g., waiver of requirement to use infectious disease test kits validated for cadaveric blood samples**
- **Stockpiling of tissues**
  - **However, many tissues have short shelf life—e.g., corneas, "fresh"refrigerated skin**

Repair, Replace, Restore, Regenerate

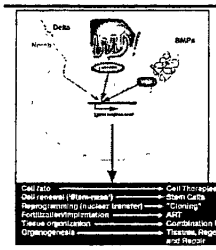
- **Cellular Therapies**
- **Gene Therapies**
- **Cellular Therapies + Gene Therapies**
- **Tissue Engineering**
  - Combination Cell/Tissue with Device/Gene Therapy/Recombinant Protein

Combination Products: Multiple FDA Centers

CBER Research and Regulation

- **CBER Research/Review Model**
  - Scientists / Clinicians: lab based and full-time review staff
- **Challenges for CT use of cellular, tissue, and gene therapies**

CBER research relevant to stem cells: Control pathways in development



Signaling pathways crucial in differentiation and development:

Conserved in all metazoans
(Work in model organisms cheaper, faster)

Affect many stages of development
Cell types, cell fates
Repair and regeneration

Importance of the microenvironment

Cell Therapy Challenges

- **Cell therapies hold great promise but present challenges to CBER**
  - **Measures of safety, quality, potency, efficacy complex**
    - sufficient characterization
    - appropriate differentiation
    - transformation
    - affected by *in vitro, in vivo* conditions

Cellular Product Testing

- Donor
- Incoming cellular or tissue sample
- Components and reagents used in manufacturing
  - Animal product- FBS, BSA, enzymes
  - Cell culture- MAbs
- Manufacturing intermediates
- Final product

Cellular Product Safety

- Sterility (21 CFR 610.12)
- Mycoplasma (21 CFR 610.30)
- Freedom from Adventitious Agents
- Pyrogenicity/Endotoxin (21 CFR 610.13)

Cellular Product Identity/Purity

- Cell Viability
  - Recommend >70%
  - Freedom from Extraneous Material
  - Media Components
  - E.g.: serum, cytokines
- Phenotypic Analysis
  - Cell Types
  - Quantitative assessment of each cell type present

Reproducibility

Cellular Product Biological Activity potency

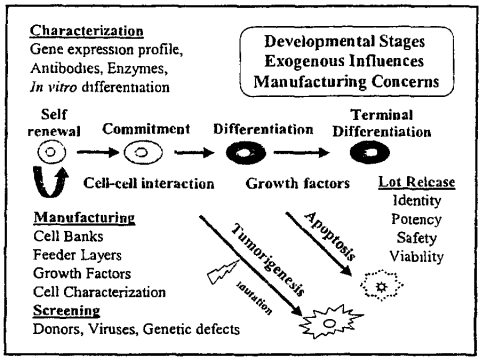
- **Assay that correlates with function of product**
  - **Gene expression pattern**
    - ***In vitro* differentiation correlated with specific gene expression**
  - **Expression of antigen**
    - **Cytokine release assay correlated with expression of protein**

Correlation often challenging

RT-PCR

tumor vaccine.

Bio-assay



stem cell

Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs) - 8/15/2003

http://www.fda.gov/cber/guidelines.htm

Gene Therapy Product Manufacturing

- Vector manufacturing
  - Vector construction, characterization
  - Cell Banks
  - Virus Seed Stocks
  - Plasmid stocks
  - Vector Production/Purification Methods
  - Formulation of Final Product
  - Storage/Stability

Gene Therapy Product Safety

- **Safety Testing**
  - Sterility
  - Mycoplasma
  - Adventitious Virus
    - in vitro and in vivo virus
    - bovine and porcine viruses (or certified reagents)
    - human viruses: EBV, HBV, HCV, CMV, HIV 1&2, HTLV 1 & 2, B19, AAV, (others)
  - Replication Competent Virus

Gene Therapy Product Characterization

- Identity
  - restriction map+southern blot
  - nucleic acid sequence
- Activity
  - transgene specific
- Titer
- Purity
  - cell substrate DNA, RNA, protein, other reagents
- Stability
- Potency
  - Qualified assay required by end of phase II
  - Assay should reflect intended biological effect of product

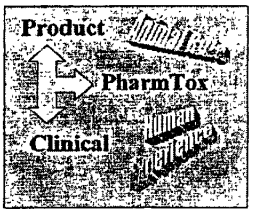
Gene Therapy: Unique Safety Concerns

- Viral Vectors: rescue of replicating virus
- Contamination of product with viruses from cells used in manufacture
- Inadvertent germ-line gene transfer
- Integration into genome
  - Insertional mutagenesis

vector

CT Product Development

- CBER-Sponsor interactions: early and often
- Encourage novel cell, tissue, and gene therapy products
- Repair, replace, restore, regenerate



CBER/OCTGT Contact Information

- **PHONE: 800-835-4709 or 301-827-1800**
- **INTERNET: http://www.fda.gov/cber**
- **Send e-mail to: OCTMA@CBER.FDA.GOV**
- **CBER Regulatory and Guidance Documents on the Internet at: http://www.fda.gov/cber/guidelines.htm**
- **Bauer@CBER.FDA.GOV**
- **301-827-0684**

Information OCTGT Products

- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy, March 1998.
- PTC in the Characterization of Cell Lines to Produce Biologicals, CBER, FDA, 1993.
- Proposed Approach to Regulation of Cellular and Tissue-Based Products, February 1997
- ICH Harmonized Tripartite Guideline: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

Information on HCT/Ps

- Website at www.fda.gov/cber/tiss.htm
  - Form 3356 – Registration/Listing
  - Published documents and letters
  - Meeting minutes/summaries/transcripts/presentations
- E-mail address for registration questions tissueregs@cber.fda.gov
- HCTERS Queries – information on registered establishments http://intranet.fda.gov/cber/tissue/hcters.htm

The Biologics License Application Process

An Overview

10/11/2003

What is a Biologics License Application (BLA)?

A request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce

21 CFR 601.2

CBER Regulatory Authority

- BIOLOGICS
  - Investigational New Drug Exemptions (IND, 21 CFR 312)
  - Biologics License Applications (BLA, 21 CFR 600-680)
- EXAMPLES
  - Vaccines and allergenic products
  - Blood Products (including blood grouping reagents and donor screening tests for bloodborne pathogens)
  - Cellular & gene therapies, xenotransplantation)

Who Submits a BLA ?

MANUFACTURER (Applicant)

- **Any legal person or entity who is engaged in manufacture**

or

- **An applicant for a license who takes responsibility for compliance with product and establishment standards**

→ can contract out.
(inventor can apply.)
可以由个人提出申请.

What is in a BLA?

- **Form FDA 356h (cover sheet)**
- **Applicant Information**
- **Product / Manufacturing information** (for Inspection purpose)
- **Pre-clinical studies**
- **Clinical studies**
- **Labeling**

New product need to do site inspection

BLA – Applicant Information

- **Name, address & phone number**
- **Name & address of facilities**
- **Authorized official**

BLA – Product/Manufacturing Information

- Source material / raw materials
- Manufacturing process and controls
- Formulation
- Facility information
- Contamination/cross-contamination information
- Environmental assessment or categorical exclusion

BLA – Safety, Efficacy and Use Information

- Pre-clinical studies
- Clinical studies
- Labeling

Labeling : not only label but package insert (circular)

International Harmonization

Using the CTD (Common Technical Document)

- An agreed upon common format for the modular presentation of summaries, reports and data
- Content is harmonized to the extent of relevant ICH guidelines
- Guidance for Industry:
  Submitting Marketing Applications According to the ICH-CTD Format - General Considerations
  - http://www.fda.gov/cber/gdlns/mrktapich.pdf

CTD can not replace BLA

CTD only content

Japan. EU July adopt CTD

Electronic Submissions

- Submission of BLA/S may be made on paper or electronically
- Submissions should be made in accordance with published guidance:
  - http://www.fda.gov/cber/esub/esub.htm

→ may be mixture of two

Before the BLA is Submitted

- Pre-BLA meeting
  - CBER SOPP 8101.1 Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants
- Identify potential review committee
- Consider Advisory Committee needs & schedule
- Arrange for BiMo Inspection

↳ Bio research monitoring

CBER urge to ask a BLA meeting

Advisory committee (4 ~7 /yr)

if Novel product ⇒ must go to advisory committee

The Review Committee

CONSTITUTED TO CONTAIN THE NECESSARY EXPERTISE TO REVIEW THE SUBMISSION

CT (medical officier

P/T . Biostatistician

Regulatory manager .

BioMo . . .

Responsibilities – Chairperson/Lead

- CONSTITUTE the committee
- ASSIGN sections for review
- SCHEDULE and CONDUCT meetings
- WRITE "action" letters
- PRESENT at Advisory Committee Meetings
- REQUEST a pre-license inspection (facility) – BIMO responsibility
- PREPARE a Summary of Basis for Approval (SBA)

Responsibilities Regulatory Project Manager

- MANAGE the review of the application
- REVIEW assigned portions of application
- PERFORM quality control check on the review
- ASSURE reviews are documented properly
- ASSURE review of labeling is complete
- COORDINATE compliance status check
- PREPARE approval letter for new products
- PREPARE finding of no significant impact

Responsibilities Discipline Reviewer

- REVIEW assigned sections of the application
- WRITE an annotated review memo
- ATTEND review committee meetings
- COMMUNICATE with the applicant as necessary and document the discussion (as per Staff Manual Guide 2126.2)
- PREPARE for Advisory Committee meetings
- PARTICIPATE in the pre-approval inspection (if necessary)
- CONSIDER if a public health and/or research questions need to be answered relative to product approval

Application Received

- Administrative processing
  - Submission tracking number assigned (STN)
  - data entry
  - user fee verification
- First committee meeting
  - review assignments
  - time frames

STN

SUBMISSION TRACKING NUMBER
aaaaaa.bbbb/cccc

Filing Review

- Review for completeness
  - RTF policy
  - CBER SOPP 8404 Refusal to File Guidance for Product License Applications and Establishment License Applications
- Filing meeting
- Filing letter
- Communicate any significant deficiencies noted up to that time (but not a complete review)

within 45 days after submission

Refuse To File

A refusal to file (RTF) letter is issued when the submission has been deemed not sufficiently complete for a meaningful review

- 21 CFR601.2(a), RTF Policy, SOPP 8404
- The Applicant may request that the submission be Filed Over Protest: SOPP 8404.1

RTF letter will be detail the deficancy

Complete Review

- Substantive review
  - Information requests
  - Review memos
  - Discipline reviews
  - labeling
  - lot release protocols
- Inspections
  - Facility
  - Bioresearch Monitoring — clinical site
- Advisory Committee presentation

Information Requests (IRs)

- Issued while the review is in progress
- Requests information needed to continue the review
- IRs may be made by letter, telephone or FAX
- IRs are documented in the file
- The response to an information request should not be so great as to constitute a major amendment
- Responses to information requests do not necessarily have to be reviewed in the current review cycle
- DOES NOT STOP THE REVIEW CLOCK
- SOPP 8401.1

Discipline Reviews (DRs)

- A DR letter is issued when a particular discipline (clinical, CMC, etc.) has finished its review, but the complete review is not yet done
- A DR letter contains comments and questions that might appear in the action letter
- Responses to DR letters need not necessarily be reviewed prior to issuance of the action letter
- DOES NOT STOP THE REVIEW CLOCK
- SOPP 8401.1

supervisor doesn't see it before it goes out – DR letter

Administrative Record

- Paper trail documenting the decision making process and basis for the decision
- Copies of Telecons, FAXes, Review Memos, Meeting Minutes, etc., become part of the administrative record and are entered into the file and the tracking system

Action Decision

- After a complete review is finished
  - Inspections
  - Advisory Committee
- Review Committee meeting
  - Outstanding issues
  - Agreements & commitments
- License action recommendation
  - Not ready for approval (letter explain why)
  - Approval

ACTION
Not Ready for Approval

- COMPLETE RESPONSE LETTER
  - Itemizes all deficiencies in the application that must be corrected prior to approval
  - Stops the review clock
- RESUBMISSION
  - Class 1 or 2
  - Restarts the clock

PDUFA Resubmissions

- Guidance for Industry: Classifying Resubmissions in Response to Action Letters, May 14, 1998
- SOPP 8405.1 Procedures for the Classification of Resubmissions of an Application for a Product Covered by PDUFA III

Performance Goals (con't)

Resubmitted Applications

- Class 1
  - 90% in 2 months
- Class 2
  - 90% in 6 months
- Clinical Hold Responses
  - 90% in 30 days
- Major Dispute Resolution
  - 90% in 30 days
- Protocol Assessments
  - 90% in 45 days

CT product : security of facility disposal of waste product.

先 CMC ⇒ inspection

先 CT ⇒ BIMO inspection

Dispute Resolution

- Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level
- SOPP 8005 Major Dispute Resolution Process (2/11/99)

review committee → division office

→ dispute resolution (formal)

ACTION Approval

- Compliance check
- Summary of Basis for Approval (SBA)
- Finding of No Significant Impact (FONSI) or confirm categorical exclusion
- Approval letter
  - Grants permission to distribute
  - Itemizes all agreements & commitments
- Issue license

Rules of the Road for Reviewers

- SGRA
  - –SOPPs
  - –Guidances
  - –Regulations
  - –Acts

Select Agents in Product Development

- **Continual updates regarding Terrorism concerns**
  - http://www.bt cdc.gov/agent/index asp
  - Agents, Diseases and Threats
    - Chemical
    - Radiation
    - Biological
  - Select Agents within Biological Category
    - http //www cdc gov/od/sap/general htm
    - http://www cdc gov/od/sap/appen1 htm
    - http://www cdc gov/od/sap/docs/42cfr73 pdf
- **Awareness of these regulations in product development**

visit CDC web site update

Origins of Select Agent Regulations

- **First Biological Select Agent Regulation, 42 CFR 72.6**
  - Proposed June 10, 1996, by CDC and HHS
    - Notice of Proposed Rulemaking to implement Section 511 of Public Law 104-132, "The Antiterrorism and Effective Death Penalty Act of 1996"
    - Requires the Secretary of HHS to regulate the transfer of select agents; delegated responsibility to CDC
  - Effective date April 15, 1997
    - Registration of facilities/supporting documentation
    - List of Select Agents
    - Mechanism for possible exemptions

Anthrax

Current Biological Select Agent Rule

- **Interim Final Rule 42 CFR part 73**
  - Possession, Use and Transfer of Select Agents and Toxins; Interim Final Rule
- **Co-published with 42 CFR part 1003**
  - Established monetary penalties for violations
- **Significant dates**
  - Published Friday December 13, 2002
  - Effective February 7, 2003 (phased in timelines for some aspects)
  - Comment deadline February 11, 2003
  - Full compliance by October 11, 2003

Purpose of the Select Agent Update

- 42 CFR 72.6
  - Transfers/shipping/sending/receiving SA in the USA
- 42 CFR 73 (2001 Anthrax)
  - Possession, use and transfer within USA, receipt from outside US
  - Additional requirements/security risk assessments
  - Bolstered authority to protect against misuses of Select Agents and Toxins whether inadvertent or as a result of terrorist acts against US homeland.

"Reducing the Chance of Accidental or Intentional Release"

- **42 CFR 73 Critical Requirements**
  - Register/determine where select agents and toxins are located
  - Ensure that transfer, storage and use are tracked
  - Screen personnel with access
  - Required entities in possession of Select Agents to:
    - Develop/implement effective bio-safety programs
    - Develop/implement effective physical security programs
- **42 CFR 1003 Civil Penalties for non compliance**
  - Individuals $250,000
  - Others $500,000

Authorities under 42 CFR 73

- HHS (CDC) has authority and responsibility for regulating activities to protect protect public health and safety (HSS Select Agents, 42 CFR 73.4)
- USDA has authority and responsibility for regulating activities to protect animal and plant health and animal and plant products (42 CFR 73.5)
- 'Overlap' Select agents subject to regulation by both groups; control by Interagency coordination

Definition of a Biological Select Agent (Part 1)

- **Microorganisms**
  - including but not limited to bacteria, viruses, fungi, rickettsiae or protozoa
- **Infectious substances**
  - any naturally occurring, bio-engineered or synthesized component of any such microorganism or infectious substance
- **Capable of causing**
  - death, disease or other biological malfunction in a human, an animal, a plant or another living organism
  - deterioration of food, water, equipment, supplies or material of any kind
  - deleterious alteration of the environment

Definition of a Biological Select Agent (Part 2)

- **For which the HHS Secretary is concerned about:**
  - Effect on human health of exposure
  - Degree of contagiousness/method of transmission
  - Availability/Effectiveness of prevention/treatment
  - Any other criteria, e.g. needs of children and vulnerable populations

special populations

Current List of Biological Select Agents

Agent Type	Viral	Bacterial	Fungal	Toxins
HHS Select Agents	▪Crimean-Congo Haemorrhagic Fever Virus ▪Ebola Viruses ▪Cercopithecine Herpesvirus 1 (Herpes B Virus) ▪Lassa Fever Virus ▪Marburg Virus ▪Monkeypox virus ▪South American Haemorrhagic Fever Viruses (Junin, Machupo, Sabie, Flexal Guanarito) ▪Tick-borne Encephalitis complex (Flavi) Viruses ▪Variola Major Virus (Smallpox) and Variola Minor Virus (Alastrim)	▪*Rickettsia prowazekii* ▪*Rickettsia rickettsii* ▪*Yersinia pestis*	▪*Coccidioides posadasii*	▪Abrin ▪Conotoxins ▪Diacetoxyscirpenol ▪Ricin ▪Saxitoxin ▪Tetrodotoxin ▪Shiga-like ribosome inactivating proteins
Overlap Select Agents	▪Eastern and Venezuelan Encephalitis ▪Nipah and Hendra Complex Viruses ▪Rift Valley Fever Virus	▪*Bacillus anthracis* ▪*Brucella abortis, B. melitensis and B. suis* ▪*Burkholderia mallei and B. pseudomallei (Pseudomonas)* ▪Botulism neurotoxin producing strains of *Clostridium* ▪*Coxiella burnetii* ▪*Francisella tularensis*	▪*Coccidioides immitis*	▪Botulism neurotoxins ▪*Clostridium perfrigens* epsilon toxin ▪Shigatoxin ▪Staphylococcal enterotoxins ▪T-2 toxin

42 CFR 73.4 and 73.5

Genetic Elements, Recombinant Nucleic Acids and Recombinant Organisms of Select Agents (SA)

Additional details in Interim Regs

- (e)(1)
  - SA viral nucleic acids that can encode for infectious or replication competent forms of SA viruses
- (e)(2)
  - Nucleic acids (naturally derived or synthetic) that can encode for functional form of any of the SA toxins
- (e)(3)
  - Viruses, bacteria, fungi and toxins listed in 73.5 a-d (overlap SA) that have been genetically modified

Genetic Elements, Recombinant Nucleic Acids and Recombinant Organisms Considered Select Agents

- Expanded (e)(1) viral nucleic acids from SA
  - naturally derived or synthetic
  - contiguous or fragmented
  - in host chromosomes or in expression vectors
  - that can encode for infectious or replication competent forms of SA viruses
- Expanded (e)(2) nucleic acids (naturally derived or synthetic) that can encode for functional form of any of the SA toxins
  - in a vector or host chromosome
  - that can be expressed *in vivo* or *in vitro*
  - are in a vector or host chromosome and can be expressed *in vivo* or *in vitro*

Exclusions Codified in the Interim Rule

- **General Exclusions across sections of 42 CFR**
  - Naturally occurring Toxins and SA; not introduced, cultivated collected or otherwise extracted from natural source
  - Specific Vaccine Strains
    - Junin virus Candid #1, Rift Valley MP12, VEE TC-83
  - Specific toxins when aggregate amount does not exceed certain milligram quantities
    - 0.5 mg Botulism Toxin, 5 mg Staph enterotoxin, 100 mg Shiga toxin
  - Nonviable SA organisms or non functional toxins

What about…

- Investigational New Drugs
  - Subject to the SA regulation
  - Must notify CDC of use
  - Must notify CDC if there is a clinical hold
  - Exemptions on case-by case basis

Exemptions from SA rule 42 CFR 73

- **Exemptions for Agent and Facility**
  - Responsibility of the User/Entity to file
    - **Must apply to CDC or USDA, depending on the agent**
    - **Provide scientific information and justification for requested exemption**
    - **Must have specific procedures for use, transfer and destruction**
  - CBER and other exemptions announced on Website

CDC Select Agent Program

Office of the Director

Select Agent Program

Program Links

Select Agent Regulation, 42 CFR 73.0, Interim Final Rule

- Application Information and Additional Forms
- General Information
- Helpful Resources

Select Agent Regulation, 42 CFR 73.0

- Application Package
- Application Information

Notification of Exclusion

Additional Resources Materials

Contact Us

Search SAP

The Centers for Disease Control and Prevention is required to regulate the possession of biological agents and toxins that have the potential to pose a severe threat to public health and safety. CDC's Select Agent Program oversees these activities. The Select Agent Program currently requires registration of facilities including government agencies, universities, research institutions, and commercial entities.

On this Web site you will be able to download application packages, view current regulations regarding select agents and access additional resource information. If you still have questions or concerns after reviewing the material contained in this website, please contact our program via email at lrsat@cdc.gov, phone at 404-498-2255 or fax at 404-498-2265.

Materials on this site last updated: 07/10/2003 04:48 PM

Attention Dermatologists: Botulinum neurotoxin is only considered a select toxin under the Select Agent regulations when the amount under the control of a physician exceeds 0.5 mg. Additionally, all dermatology clinics using FDA-approved botulinum toxin preparations in accordance with labeling instructions are excluded from the requirements to register under the Select Agent regulations and DO NOT need to submit a letter to CDC or USDA to declare exemption from registration with the Select Agent Program.

Select Agent Regulation, 42 CFR 73.0, Interim Final Rule

- Application Information and Additional Forms
  - Application Package
  - Additional Forms
- General Information
  - Letter of Solicitation
  - Public Comments on the New Regulation
  - Public Meeting, Washington, DC, December 16, 2002
  - Regulatory Impact Analysis and Appendices
- Helpful Resources
  - FAQ for New Regulation (updated 07/08/2003)
  - List of Select Biological Agents and Toxins
  - Notification of Exclusion (updated 06/12/2003)

USDA APHIS Information

Veterinary Services

Safeguarding Animal Health

Import / Export

Agricultural Bioterrorism Protection Act of 2002

Biological Agents and Toxins; Possession

- HHS, USDA Establish New Regulations for Use of Select Biological Agents of 2002 (pdf)
- December 13, 2002, Agricultural Bioterrorism Protection Act of 2002; Possession, Use and Transfer of Biological Agents and Toxins; Interim Final Rule, Department of Agriculture, APHIS (pdf)
- Agent and Toxin List (pdf)
- December 13, 2002, Possession, Use, and Transfer of Select Agents and Toxins, Interim Final Rule, Department of Health and Human Services, Office of the Inspector General (pdf)
- August 12, 2002 Federal Register Notice - Agricultural Bioterrorism Protection Act: Biological agents and toxins; possession
- Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (pdf)
- Citations and Acronyms

Search

FORMS

- APHIS Form 2044/CDC Form 0.1319 - Application for Laboratory Registration
  - Attachment 1, 42 CFR Part 73, Select Biological Agents and Toxins Final Rule, Federal Register, December 13, 2002
  - Attachment 2, 9 CFR Part 121 - Agricultural Bioterrorism Protection Act of 2002; Possession, Use, and Transfer of Biological Agents and Toxins, Federal Register, December 13, 2002.
  - Attachment 3, 7 CFR 331 - Possession of Select Agents, Federal Register, December 13, 2002
  - Attachment 4, APHIS application for permit to import or transport controlled materials or organisms or vectors (VS form 16-3)
  - Attachment 5, Additional Information for cell cultures and their products (VS form 16-7)

In order to fulfill the Department of Justice responsibilities under the Act, the Federal Bureau of Investigation (FBI) is responsible for conducting security risk assessments of individuals seeking access to listed agents and toxins and individuals or entities seeking to register under the Act. .

USDA Select Agent Information

- USDA/HHS Select Agricultural Agents
  - www.aphis.usda.gov/vs/ncie/bta.html
    (APHIS is the Animal & Plant Health Inspection Service)
  - Regulated under Animal Protection Act
  - Use is Regulated under USDA rather than CDC
  - Links to CDC information

Transport or Export of SA

- **42 CFR 73 has a Procedural impact on actual transportation of Biological Select Agents**
- **42 CFR 73 places no restrictions on exportation of SA or toxins**
- **Shipping/Transport in the US**
  - Department of Commerce 15 CFR
  - Department of Transportation 49 CFR 171-178
    - IATA, ICAO, Individual Commercial Carriers
  - CDC revising 42 CFR 72 to harmonize other regs

Stay Tuned for More Info.....

- **Frequent updates on various Websites**
  - Changes in status/ additions/deletions
  - Exemptions (Sterne Strain, FVS)
  - Revisions to 42 CFR 72 (shipping) expected soon
- **Direct Information from CDC/USDA**
  - Reviewed on a case-by case basis
  - Timely Review
- **Institutional Safety Committees/Officers/Scientists**
  - Registration, access/training, security, risk assessments, procedures

BT/CT Import Export for Biological Products Under Development

Kimberly A. Cressotti
Division of Case Management
Office of Compliance and Biologics Quality
(301) 827-6201

How do I import a material under development prior to having an IND?

Samples for testing purposes only

- **In process material**
  - **Permits CDC, USDA**
  - **Labeling**
  - **Get FDA involved early to facilitate Import**

How do I import a material for test development?

- **Samples for Research Use**
  - **Permits CDC, USDA**
  - **Labeling**

↳ for research use

Import permit
not approve by CBER

How can I import an Investigational New Drug (IND)?

Under an Investigational New Drug (IND) Application

- **IND in effect under 21 CFR 312.40**
- **Person receiving the investigational product is a listed investigator in a study submitted to and allowed to proceed under the IND**

How can I export an Investigational New Drug?

Under an Investigational New Drug (IND) Application

- **IND in effect under 21 CFR 312.40**
- **Person receiving the investigational product is a listed investigator in a study submitted to and allowed to proceed under the IND**
- **Study complies with the laws of the importing country**

How can I export an Investigational New Drug?

- **Under the 312 Program – 21 CFR 312.110**
  - **Foreign Government Request**
  - **Firm Request**

Gov: ask FDA to permit export
name of manufactures
IND w/ only 研究者
quantity. 研究项目
Firm: Notification letter.
foreign company import permit
in English

How can I export an Investigational New Drug?

Proposed Changes to 312 Program – Proposed Rule, published 6/19/02

- Describe Drug (i.e., trade name, generic name, dosage form) and identify the countries
- Certification Process

How can I export unapproved New Drugs and Biologics?

"Simple" Notification Process – 802(b)(1)(A)

- Marketing authorization in a listed country (ies) will allow export anywhere
- Process – Section 802(g)
  - Notification to FDA when begin to export
  - Record-keeping
    - Marketing authorization
    - Distribution records
    - Labeling used
  - Meet conditions for export – Section 802(f)

What are the conditions for export?

Conditions for export include – Section 802(f)

- Substantial conformity with GMPs (or FDA-recognized international standards)
- Not otherwise adulterated
- Meets requirements of 801(e)
- Not an imminent hazard
- Labeled with requirements and conditions for use
  - in the country where it received valid marketing authorization, and
  - in the country to which it is to be exported, and
  - in the language and units of measurement to which it would be exported or language designated by such country
- Promoted as labeled

How can I export unapproved New Drugs and Biologics?

Direct Export Process – Section 802(b)(2)

- Drug complies with laws of foreign country
- Has valid marketing authorization
- FDA determines that the Foreign Country has certain statutory and regulatory requirements.
- Record-keeping
  - Marketing authorization
  - Distribution records
  - Labeling used
- Meet conditions for export – Section 802(f)

How can I export unapproved New Drugs and Biologics?

Petition Process – 802(b)(3)

Appropriate health authority in foreign country
- requests export approval
- certifies they understand the drug is not approved under the FD&C Act or by a listed country
- concurs that the scientific evidence provided to FDA is credible that the drug would be reasonably safe and effective in the foreign country

FDA review of credible scientific evidence

Record-keeping - 802(g)

Meet conditions for export – Section 802(f)

Could the import for export provision be used to manufacture a product for export only?

This provision allows for the import of component not meeting the requirements of the FFDC Act if it is to be incorporated or further processed into a product that will be exported under the FFDC Act, or PHS Act – Section 801(d)(3)

Could the import for export provision be used to manufacture a product for export only?

Yes.

As Long as:

- Your firm can meet the Import for Export provisions discussed in the previous slide, AND
- Your firm can meet the requirements of the chosen export mechanism

Examples of Frequently Asked Questions and Common Problems/Issues

- How do I import a material under development prior to having an IND?
  - Permits
  - Labeling
- How can I export an Investigational New Drug?
  - Export Request
- How can I export unapproved New Drugs and Biologics?
  - Export Petition
  - Export Request

Examples of Frequently Asked Questions and Common Problems/Issues

- How do I import a material under development prior to having an IND?
  - Permits
  - Labeling
- How can I export an Investigational New Drug?
  - Export Request
- How can I export unapproved New Drugs and Biologics?
  - Export Petition
  - Export Request

SELECT LEGAL ISSUES, INCLUDING INFORMED CONSENT

Mark Raza
Associate Chief Counsel
Office of the Chief Counsel
Food and Drug Administration

CT Products Regulated by CBER:
Effective Strategies to Assist in Product Development

Drugs and Vaccines for the Common Defense: Refining FDA Regulation to Promote the Availability of Products to Counter Biologic Attacks

Gail Javitt, J.D., M.P.H.

19 Journal of Contemporary Health Law & Policy 37 (2002)

Background information.

ACCELERATED APPROVAL

Drugs: 21 CFR 314.500 – 314.560 "Subpart H"
Biological Products: 21 CFR 601.41 – 601.46

- serious or life-threatening illness
- provide meaningful therapeutic benefit over existing treatments
- surrogate endpoint or clinical endpoint

Bio-shield Bill

FAST TRACK PRODUCTS
Section 506 of the FDC Act

- serious or life-threatening condition
- potential to address unmet medical needs
- clinical endpoint or surrogate endpoint

Public Health Security and Bioterrorism Preparedness and Response Act of 2002

(BT Act)

section 122

ANIMAL RULE

Drugs: 21 CFR 314.600 - 314.650
Biological Products: 21 CFR 601.90 – 601.95

- serious or life-threatening conditions caused by CBRN substances
- unethical or not feasible to study effectiveness
- effectiveness based on animal studies which establish that clinical benefit in humans is reasonably likely

Final Rule (May 2002) 67 Fed. Reg. 37988
Proposed Rule (October 1999) 64 Fed. Reg. 53960
Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (June 2002) Sections 122 and 123

CBRN (Chemical, Biological, Radiological, Nuclear)

INVESTIGATIONAL PRODUCTS

Section 505(i) of FDC Act

21 CFR Part 312 – IND regulations

– Waiver - 21 CFR 312.10

21 CFR Part 50 - Protection of Human Subjects

21 CFR Part 56 – Institutional Review Boards

– Waiver - 21 CFR 56.105

INVESTIGATIONAL PRODUCTS

A. Treatment IND 21 CFR 312.34 – 312.35
   - serious or immediately life-threatening disease condition
   - no comparable or satisfactory alternative available

B. Open-label Protocol amendment to existing IND

C. Streamlined IND or Contingency Protocol

INVESTIGATIONAL PRODUCTS

Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses

21 CFR 312.80 – 312.88

- "especially" where no satisfactory alternative therapy exists
- FDA will "exercise the broadest flexibility in applying the statutory standards" of safety and effectiveness
- risk-benefit analysis in review of marketing applications

INFORMED CONSENT

21 CFR 50.25 - basic elements
- description of risks, benefits, and appropriate alternatives

21 CFR 50.27 – documentation
- written consent document or
- short form written consent document (verbal presentation)

INFORMED CONSENT - exceptions

505(i)(4) FDC Act IND

- except where it is not feasible or contrary to the best interests

21 CFR 50.23 - exception from general requirements

- life threatening situation
- informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent

21 CFR 50.24 – exception for emergency research

- subjects will not be able to give informed consent as a result of their medical condition

BIOSHIELD

H.R. 2122

Section 4 – Authorization for Medical Products for Use in Emergencies

564(b) – Declaration of emergency

564(c) – Criteria for issuance of authorization

564(e) - Conditions of authorization

BIOSHIELD
564(c) – Criteria for issuance of authorization

- CBRN agent can cause a serious or life-threatening disease or condition
- based on totality of evidence, including adequate and well-controlled clinical trials, if available, it is reasonable to believe
  - product may be effective
  - known and potential benefits outweigh known and potential risks
- no adequate, approved, and available alternative

BIOSHIELD
564(a) and 564(l) – 505(i) does not apply

564(e)(1)(A)(ii) – the Secretary, to the extent feasible, given the circumstances of the emergency, shall establish appropriate conditions designed to ensure that individuals to whom the product is administered are informed

- that the Secretary has authorized the emergency use of the product
- of the significant known and potential risks and benefits
- of the option to accept or refuse administration of the product: the consequences, if any of refusing administration, and of alternatives

SPEAKER BIOGRAPHIES

Mark Abdy, DVM, Ph.D. is with the Office of Vaccines Research and Review in the Division of Vaccines and Related Products Applications. Within this office, Dr. Abdy works on bioterrorism vaccine issues that pertain to the "Animal Rule".

M. Christine Anderson is the Chief of the Standards and Testing Section in the Office of Vaccines Research and Review of CBER. This section is responsible for the preparation, testing, acquisition, control and shipment of CBER Standard, Reference and Research preparations.

Steven Bauer, Ph.D., received a Ph.D. in Biochemistry from the University of Maryland in 1986. His thesis work was done in the laboratory of Dr. Michael Potter at the National Cancer Institute and involved an investigation of the mutations responsible for oncogene dysregulation in mouse tumors of B lymphocyte origin. He then became a scientific member of the Basel Institute for Immunology in Basel, Switzerland from 1986 though 1991 where he continued work on B-cell transformation and worked on the role of the surrogate light chains in early B-cell development. In 1991, Dr. Bauer joined the FDA's Center for Biologics Evaluation and Research, Division of Cellular and Gene Therapies. In October, 2002, he became Acting Chief of the Laboratory of Stem Cell Biology and pursues research on stromal cell-hematopoietic cell interactions that influence development of lymphocytes. Dr. Bauer's duties at CBER include review of proposed trials of novel biological therapies, policy development in emerging areas of biological therapeutics, and pursuit of research projects related to the regulatory mission of FDA. Dr. Bauer reviews cellular and gene therapy IND applications and serves with colleagues to develop policy related to use of stem cells.

Paul Jeffrey Brady, M.D., M.P.H., is a medical officer and clinical reviewer in the Division of Vaccines, Food and Drug Administration. He is a graduate of Mercer University, College of Liberal Arts where he received the Bachelor of Arts Degree, graduating in 1991 (Chemistry, Biology). He attended the Medical College of Georgia, from 1991 to 1995, and completed internship training in the Department of Internal Medicine at the Naval Medical Center, San Diego, California. After serving two years as the Medical Officer aboard the USS Coronado, Dr. Brady studied public health at the Uniformed Services University of the Health Sciences (USUHS), in Bethesda, Maryland. In July 2000, he completed the Navy's General Preventive Medicine Residency, also at USUHS. Dr. Brady worked as a medical epidemiologist and the Navy's Liaison to the Army Medical Surveillance Activity which operates the central epidemiological database for the Department of Defense. In July 2002, he transitioned to the U.S. Public Health Service and entered his current position. He is board-certified in Public Health and General Preventive Medicine.

Julianne Clifford, Ph.D., received her Doctorate of Philosophy degree in cell biology from the Department of Biology, Georgetown University, Washington, DC in 1994. She then conducted post-doctoral research applying cell and molecular biology techniques to the study of bacterial and plant derived protein toxins at the Division of Experimental Therapeutics at Walter Reed Army Institute of Research in Washington, DC and continued that research in the Laboratory of Bacterial Toxins, Office of Vaccines Research and Review within the Center for Biologics Evaluation and Research, FDA. She is currently a Biologist/Regulatory Scientist in the Division of Vaccines and Related Products Applications in OVRR where she serves as a scientific and regulatory reviewer of Investigational New Drug applications and Biologics License Applications for toxin- and toxoid-based products including vaccines against biological warfare agents.

Kimberly A. Cressotti is the Import/Export Consumer Safety Officer in the Office of Compliance and Biologics Quality, Division of Case Management with in the Center for Biologics Evaluation and Research at the Food and Drug Administration (CBER/FDA). Her responsibilities include interpretation and implementation of the FDA Export Reform and Enhancement Act of 1996, review and evaluation of Export Certificates, and Compliance Checks. Ms. Cressotti is also responsible for CBER Import Compliance Programs, Import Alerts and Bulletins, and import inquires concerning biological products. Prior to her assignment to the Division of Case Management, Ms. Cressotti was a Consumer Safety Officer for the Division of Surveillance and Policy with CBER/FDA. Her responsibilities included reviewing applications for the export of unapproved biological products subject to the Drug Export Amendments Act of 1986. Ms. Cressotti joined FDA in 1988 and served as a Biologist in the Office of Blood Research and Review in CBER/FDA. Prior to joining FDA, She worked in industry with the production of in vitro diagnostic test kits. Ms. Cressotti received a B.S. in Biology from Frostburg State College.

John Finkbohner, Ph.D. is the Deputy Director of the Division of Manufacturing and Product Quality in the Office of Compliance and Biologics Quality at CBER. This division serves as the Center's focal point for policy regarding pre-licensure issues related to Good Manufacturing Practices (GMPs) for biological drugs and devices, review of biologics license submissions, and is responsible for the CBER lot release program. The staff in this division review the chemistry and manufacturing controls (CMC) and the establishment description (ED) sections of biologics license applications and supplements, lead the inspection team during the conduct of pre-approval inspections for biologics, and participate in various policy groups addressing cGMP issues for biologics. Prior to joining CBER in 1993, he was a Resident Assistant Professor of Chemistry with the University of Maryland, University College. Dr. Finkbohner completed his M.S. and Ph.D. at The Pennsylvania State University working in purification and physicochemical characterization of proteins derived from both microbial and invertebrate model systems.

Karen L. Goldenthal, M.D., is currently Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, CBER/FDA. She received a B.A. degree with highest honors from the University of Texas at Austin, and an M.D. degree with honors from Baylor College of Medicine, Houston, Texas. She completed a residency in clinical and anatomical pathology at St. Luke's Hospital in Houston and is a Diplomate of the American Board of Pathology (AP/CP, 1982). She gained research experience in the field of cell biology as a medical staff fellow at the National Cancer Institute, N.I.H. Dr. Goldenthal joined the Food and Drug Administration in 1985 as a medical reviewer at the Center for Devices and Radiological Health, and transferred to the Center for Biologics Evaluation and Research in 1987.

Jesse L. Goodman, M.D., M.P.H., Director of FDA's Center for Biologics Evaluation and Research (CBER), where he is responsible for overseeing a broad range of medical and public health policy activities concerning the development and assessment of vaccines, blood products and novel therapeutics including cellular and gene therapies. He first came to FDA in late 1998 from the University of Minnesota where he had joined the Faculty in 1985 and most recently served as Professor of Medicine and Director of the Division of Infectious Diseases as well as Director of the Immunology and Infectious Diseases Program. A graduate of Harvard College, he received his M.D. at Albert Einstein, did residency and Fellowship training at the Hospital of the University of Pennsylvania and at UCLA (where he was also Chief Medical Resident), and is Board Certified in Internal Medicine, Oncology and Infectious Diseases. He trained in the virology laboratory of Jack Stevens at UCLA and has had an active laboratory program in the pathogenesis of infectious diseases, in particular tick-borne infections. In 1995, his NIH funded laboratory in Minnesota isolated the etiologic agent of a new disease, human granulocytic ehrlichiosis (HGE) and has since characterized fundamental events involved in infection of leukocytes, including its cellular receptor. He has been an active clinician, investigator, administrator, and educator, and is the author of numerous peer reviewed scientific publications. He is currently Editor of the book "Tick Borne Diseases" to be published by the ASM Press and is a Staff Physician and Infectious Diseases Consultant at the NIH Clinical Center and the National Naval Medical Center/Walter Reed Army Medical Center. Dr. Goodman obtained a MPH at the University of Minnesota and is interested in improving public health through science-based policy and communication. He originated and co-chaired both the FDA Task Force and the U.S. Government Interagency Task Force on Antimicrobial Resistance. At FDA, and representing FDA within the government and to the public, he is active in a wide variety of clinical and public health issues including bioterrorism preparedness and response, emerging infectious disease threats (e.g. West Nile Virus), product development, human subject protection, blood and vaccine safety and risk management. He has received honors and awards including election to the American Society for Clinical Investigation

(ASCI) and has served on a number of committees and review panels for groups such as NIH, CDC, the Minnesota Department of Health and the Institute of Medicine.

Marion F. Gruber, Ph.D., is a Scientific and Regulatory Reviewer (Microbiologist) in the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review in the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration. Dr. Gruber obtained her B.Sc. degree, Microbiology, from the University of Ulm, Germany (1982), and her Ph.D. (Microbiology, 1986) from the Christian Albrecht University of Kiel, Germany. She was a postdoctoral fellow for three years in the Department of Immunology at the Oklahoma Medical Research Foundation, Oklahoma, OK. Dr. Gruber joined CBER in 1989 as a National Research Council Fellow in the Office of Therapeutics Research and Review and was converted to CBER staff fellow in 1992. Her research projects have included the regulation of growth factor and cytokine production by human B cells and monocytes, and the role of macrophage growth factor in regulating HIV-1 replication in these cells.
Dr. Gruber joined the Office of Vaccine Research and Review of CBER in 1995. For the past 11 years, Dr. Gruber has reviewed investigational new drug applications (INDs) and biologics license applications (BLA) for therapeutic proteins and preventive vaccines, initially in the Division of Cytokine Biology in the Office of Therapeutics Research and Review and since 1995 in the Division of Vaccines and Related Products Applications in the Office of Vaccines Research and Review. Dr. Gruber is chairing an inter-agency committee charged with developing policy and guidance for developmental toxicity study for preventive vaccines and serves on a number of national and international committees addressing nonclinical safety assessment of these products.
Dr. Gruber has presented CBER at a number of national and international meetings to discuss CBER policy pertaining to nonclinical safety evaluation of preventive vaccines and biological products.

Bruce Meade, Ph.D., currently serves as Chief of the Laboratory of Methods Development and Quality Control, Division of Bacterial, Parasitic, and Allergenic Products, OVRR, CBER. Dr. Meade has worked within CBER since 1977, except for the period from 1985-87, during which time he was a research microbiologist in the Division of Toxicology, USAMRIID.

Michael Merchlinsky, Ph.D., is a Senior Investigator in the Laboratory of DNA Viruses, Division of Viral Products, CBER. He completed his undergraduate education at the University of Maryland and received his Ph. D. in the Department of Molecular Biophysics and Biochemistry at Yale University. After serving as a post-doctoral and Senior Staff Fellow with Dr. Bernard Moss in the Laboratory of Viral Diseases NIAID Dr. Merchlinsky moved to CBER where he serves as a principal investigator pursuing scientific research and providing expertise in product review for orthopoxviruses.

Hira Nakhasi, Ph.D., is currently Director, Division of Emerging and Transfusion Transmitted Diseases, Office of Blood Research and Review, CBER/FDA. He received his Ph.D. degree in India and postdoctoral training at Columbia University, NY and at the National Cancer Institute at Bethesda, MD. He has been with CBER/FDA for the last 19 years with tour of duty in various offices including OVRR, OTRR and now in OBRR. His research interests include understanding the pathogenesis of parasites such as Leishmania, Chagas and Malaria. His laboratory is also interested in the development of diagnostic methods for the detection of such parasitic agents in blood and blood products. Recently his interests have also extended into the area of detection of bioterrorist agents in blood and blood products using high through put genomics.

L. Ross Pierce, M.D., obtained his B.S. in chemistry from M.I.T, completed graduate course work and research in biochemistry and obtained his M.D. from the University of California, Davis, served in the Endocrine Service as Medecin Resident Etranger at the Pietie-Salpetriere Hospital in Paris, France, where he was a recipient of a grant from the College de Medecine, completed residency training in Internal Medicine at Mercy Hospital and Medical Center, affiliated with the University of California, San Diego, and completed a 3-year fellowship in Endocrinology and Metabolism at the NIADDK, National Institutes of Health. Dr. Pierce is board certified in Internal Medicine, Endocrinology and Metabolism, and Clinical Pharmacology. Dr. Pierce has been a Staff Endocrinologist at the National Naval Medical Center in Bethesda since 1986. Dr. Pierce joined FDA in 1985 as a Medical Officer in the Division of Metabolism and Endocrine Drug Products, Center for Drug Evaluation and Research (CDER), where he served as a Supervisory Medical Officer from 1987 to 1993. From 1993 to 1997, Dr. Pierce worked in the Clinical Investigations Branch of CDER's Division of Scientific Investigations. Here he coordinated, participated in, and reviewed the outcomes of Bioresearch Monitoring clinical investigator and Sponsor/Monitor/Contract Research Organization inspections of clinical trials supporting marketing applications for coagulation, anti-viral, anti-infective, pulmonary/allergy, cardiac, dermatologic, gastrointestinal, and ophthalmological drug products. In mid 1996, Dr. Pierce joined the Center for Biologics Evaluation and Research (CBER) at FDA, serving as a medical reviewer in the Hematologic Products Branch, Division of Blood Applications, Office of Blood Research and Review (OBRR). The Hematologic Products Branch subsequently became part of the Division of Hematology within OBRR and was renamed the Clinical Review Branch. Dr. Pierce has served as Acting Branch Chief, Clinical Review Branch, and as Acting Deputy Director, Office of Blood Research and Review (OBRR).

Dr. Pierce has lectured on clinical trial design and analysis at the School of Public Health of the University of Pittsburgh, PA, at the Medical College of Pennsylvania, at CDER Staff College, and at CBER. Dr. Pierce has published papers on a variety of topics in biochemistry, lipidology, and on adverse effects of cholesterol-lowering drug, and immune globulin intravenous (human). Dr. Pierce

has been involved in the development and regulation of various immunoglobulin products for counter-bioterrorism indications.

Mark Raza is an Associate Chief Counsel in FDA's Office of the Chief Counsel where he focuses primarily on legal issues concerning the regulation of biological products. Over the last couple of years, Mark has worked on a number of bioterrorism preparedness-related issues. He is a graduate of Harvard Law School.

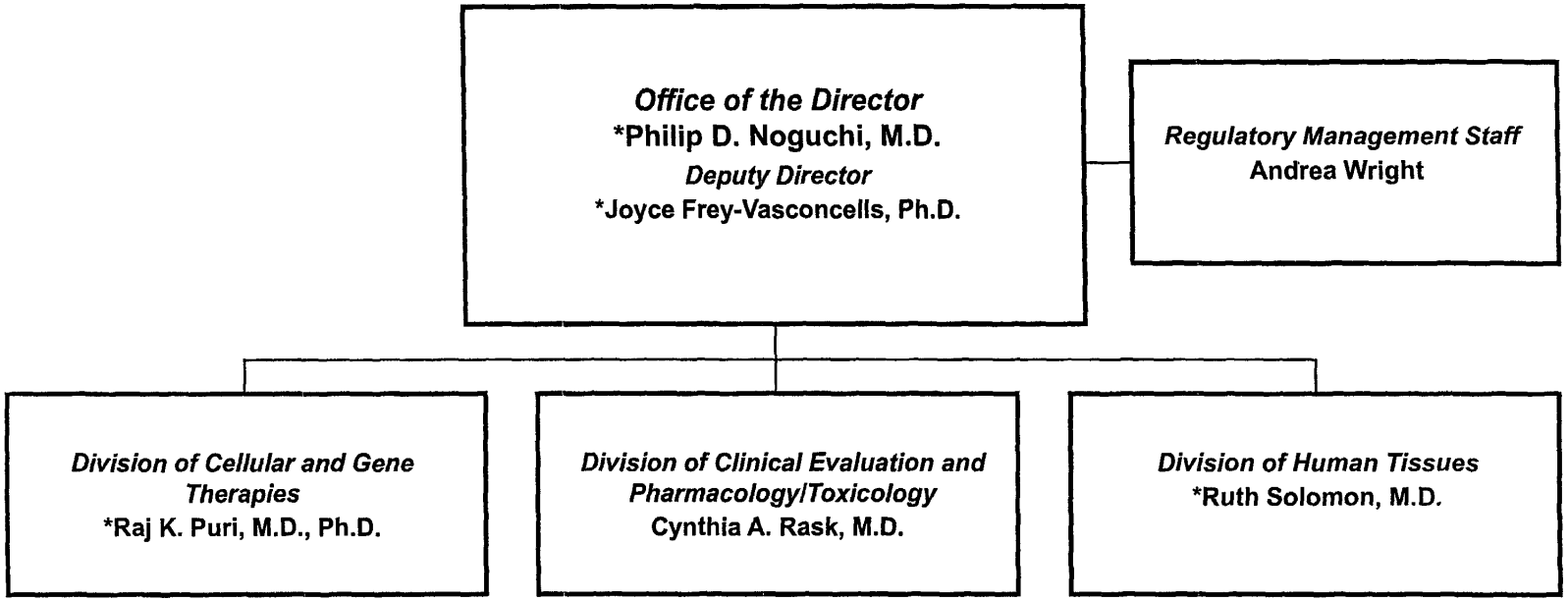
Dorothy Scott, M.D. is a graduate of University of Virginia Medical School. She trained in Internal Medicine at the University of Rochester and University of Maryland, and completed a fellowship in Rheumatology at the National Institute of Health. Dr. Scott has worked as a scientist and regulator at FDA since 1993. Her research topics include licensed immune globulins, and animal models of efficacy for vaccinia immune globulins. She is involved in regulation of safety of plasma derivatives, with particular emphasis on transmissible spongiform encephalopaties, and other transmissible diseases. Dr. Scott is also a product reviewer for specific immune globulins, including vaccinia immune globulin and other counter-terrorism related products.

Mercedes Serabian, M.S., DABT, has an M.S. degree in Toxicology and she is also a diplomat of the American Board of Toxicology (DABT). Prior to joining the Center for Biologics Evaluation and Research, in the Office of Therapeutics Research and Review (OTRR), Division of Clinical Trials Design and Analysis (DCTDA) in 1993, Mercedes worked at Hazleton Washington (now CoVance) as a Senior Study Director, responsible for animal studies designed to specifically test the toxic potentials of the biotechnology-derived products. She has extensive experience in preclinical protocol design for both traditional pharmaceuticals and biologics. While in OTRR, Mercedes was responsible for the critical review of the preclinical data submitted to all offices in CBER (i.e., therapeutics, blood, and vaccines) in the form of INDs, IDEs, BLAs, PMAs, and related documents. She joined the Office of Cellular, Tissue, and Gene Therapies (OCTGT) in October, 2002. Ms. Serabian currently retains the title of Expert Toxicologist and is the Chief, Pharmacology/Toxicology Branch in OCTGT.

Robert A. Yetter, Ph.D., is the Associate Director for Review Management, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA). He previously served as the Special Assistant to the Associate Director for Policy and the Acting Director for Policy, CBER. The Center is responsible for research and regulatory activities for biological products licensed under Section 351 of the Public Health Service Act, including biotechnology-derived products. Dr. Yetter's duties involve development of regulatory review policies and procedures, including recent Reinventing Government initiatives. Prior to taking his present position in the Center, as a member of the Office of Vaccines Research and Review, he was responsible for conducting reviews and inspections leading toward approval of biological

products. Dr. Yetter received his B.S. from Emory University, his M.S. from Georgia State University and his Ph.D. from the University of Florida. He spent six years at the National Institute of Allergy and Infectious Diseases and four years in the Research Service of the Department of Veteran's Affairs.

CBER
OFFICE OF CELLULAR, TISSUE AND GENE THERAPIES



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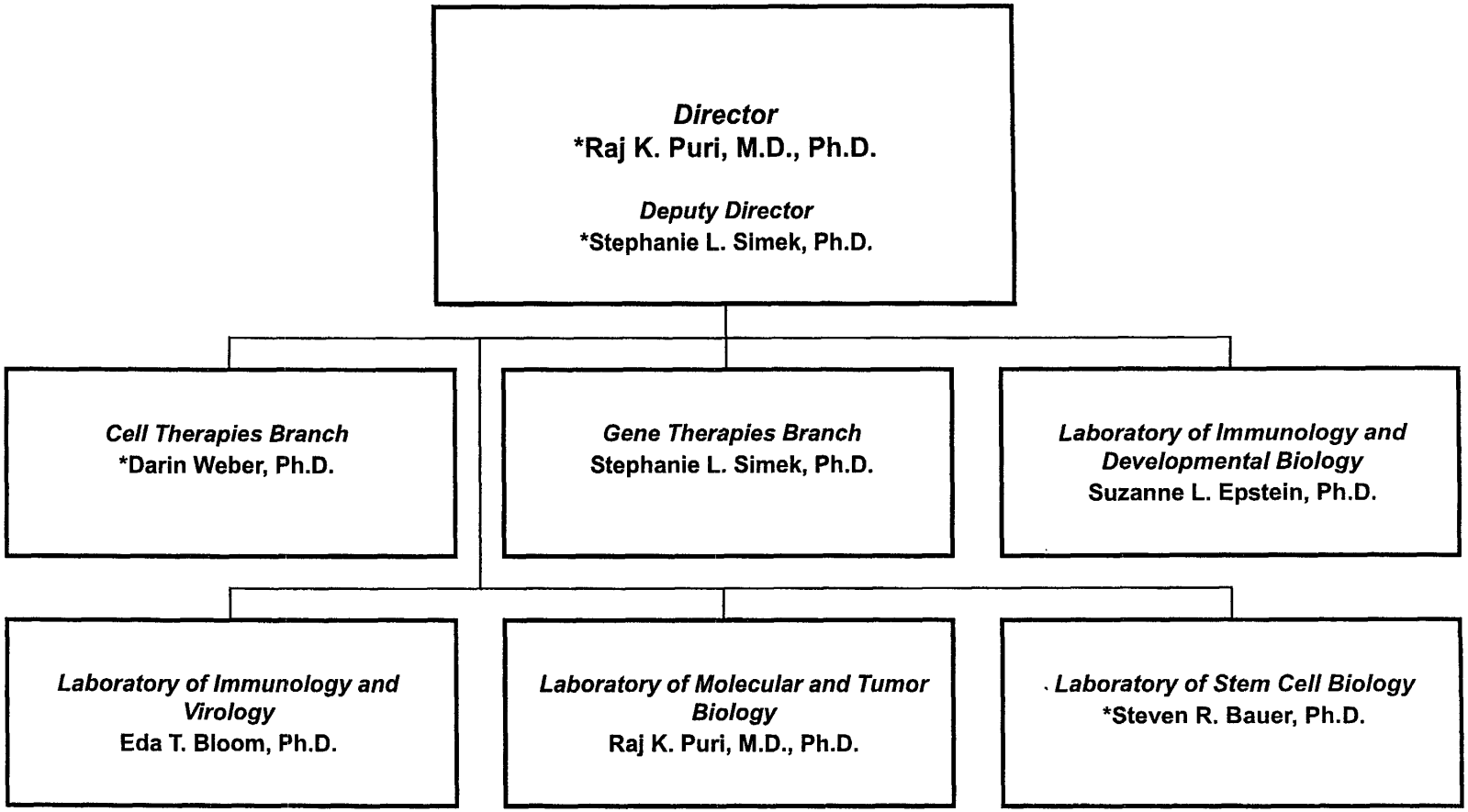

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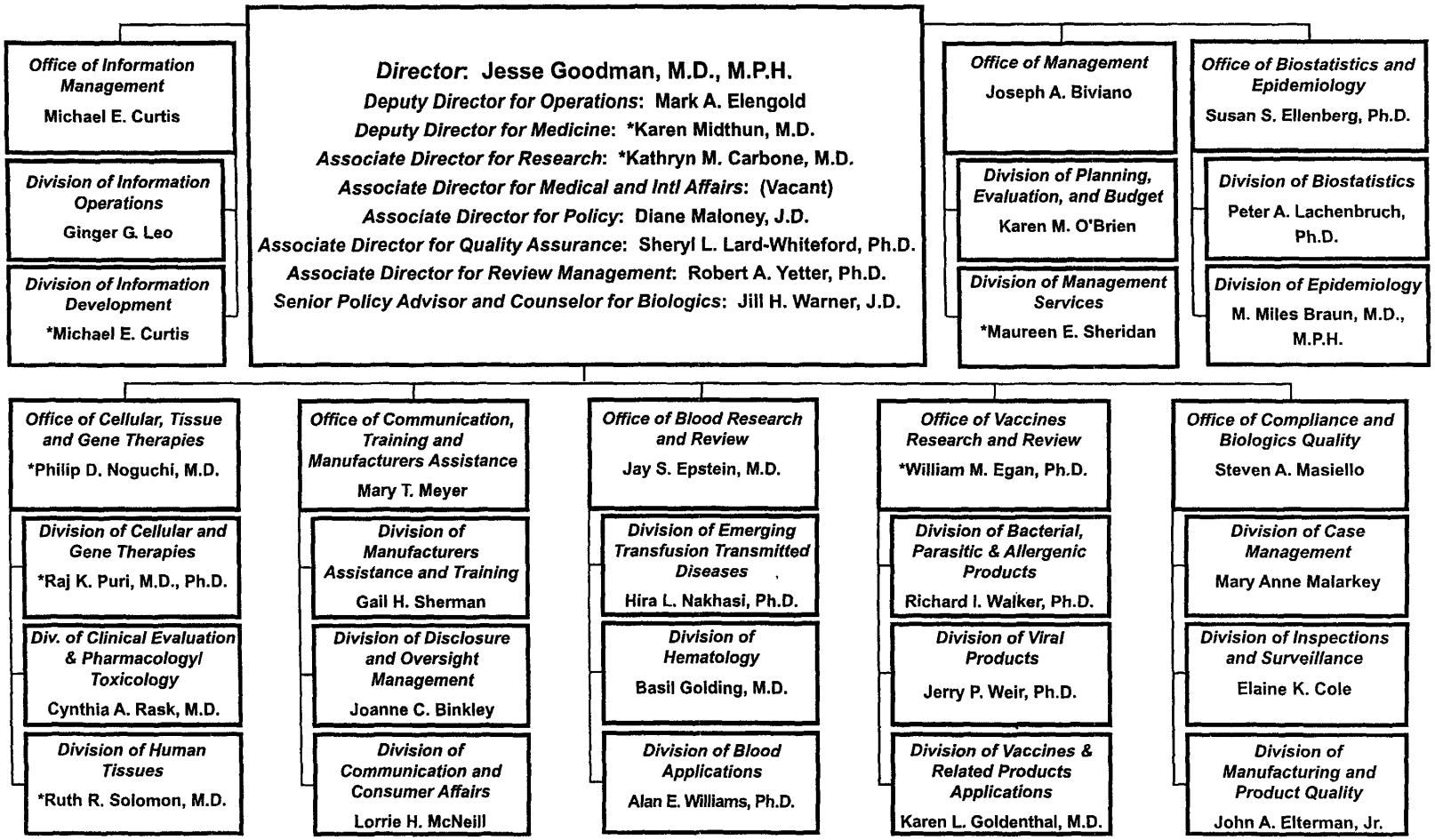

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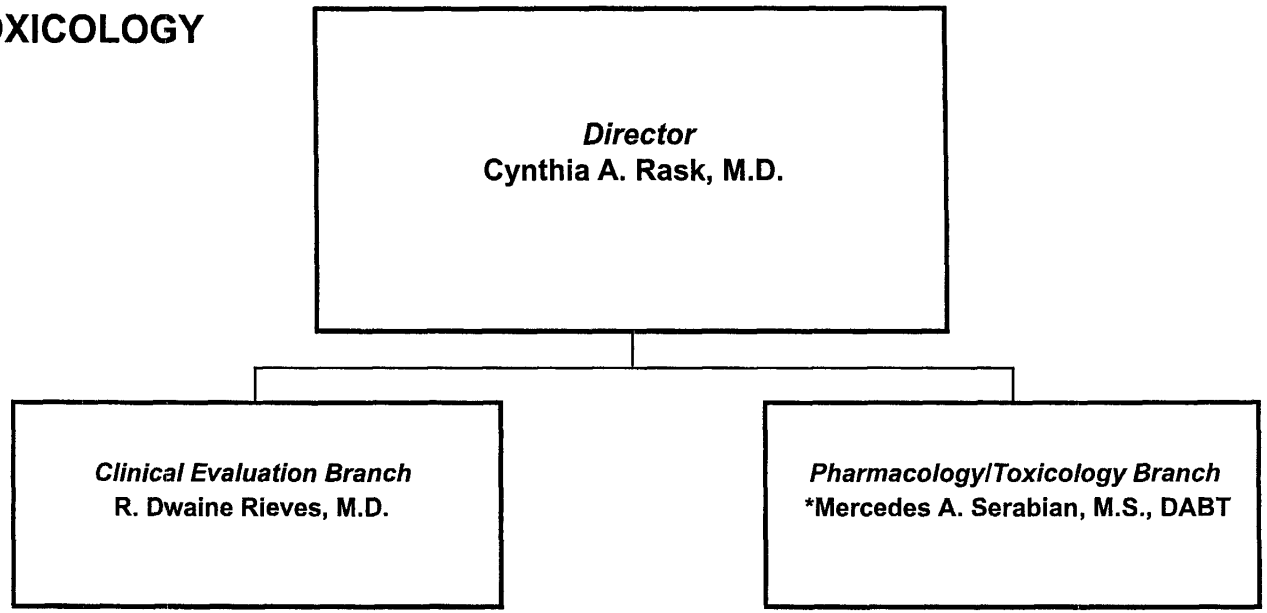

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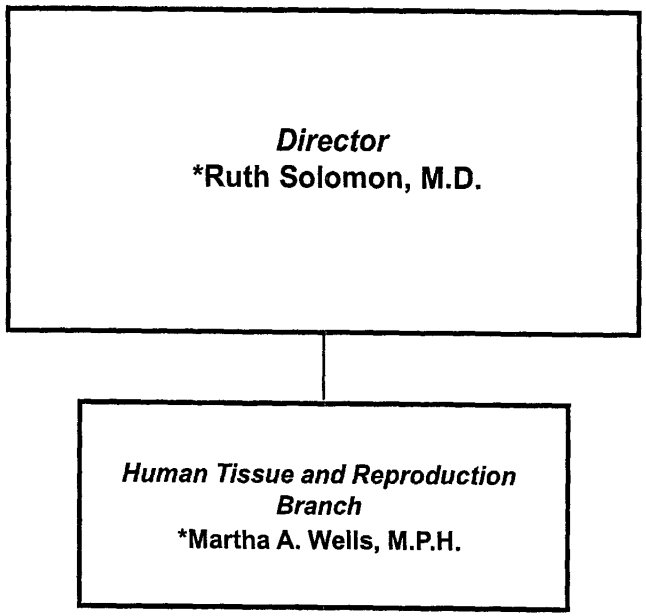

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PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS

The Food and Drug Administration

February 28, 1997

PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS

[Docket Number 97N-0068]

For further information regarding this document, contact:
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1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
301-594-3074

Submit written comments on this document to:

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Food and Drug Administration
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PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS

February 28, 1997

EXECUTIVE SUMMARY

The Food and Drug Administration is proposing a new approach to the regulation of human cellular and tissue-based products. Tissues have long been transplanted in medicine for widespread uses--such as skin replacement after severe burns, tendons and ligaments to repair injuries, heart valves to replace defective ones, corneas to restore eyesight, and the use of human semen and implantation of eggs to help infertile couples start a family. In recent years, scientists have developed new techniques, many derived from biotechnology, that enhance and expand the use of human cells and tissues as therapeutic products. These new techniques hold the promise of some day providing therapies for cancer, AIDS, Parkinson s Disease, hemophilia, anemia, diabetes, and other serious conditions.

The existing FDA approach to the regulation of human cellular and tissue-based products is highly fragmented. The agency has not previously clearly defined criteria for product characterization, sometimes resulting in confusion on the part of both industry and FDA reviewers. The new regulatory framework, as articulated in this document, would provide a unified approach to the regulation of both traditional and new products. The framework clearly specifies criteria for regulation, and would provide for harmonized review of applications by different Centers within the agency. Additionally, the framework would provide only the degree of government oversight necessary to protect the public health. For products with limited public health concerns, the new framework would allow flexibility and innovation without an application review process.

This new framework would provide a tiered approach to cell and tissue regulation. Regulation would focus on three general areas: 1) preventing unwitting use of contaminated tissues with the potential for transmitting infectious diseases such as AIDS and hepatitis; 2) preventing improper handling or processing that might contaminate or damage tissues; 3) ensuring that clinical safety and effectiveness is demonstrated for tissues that are highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes.

The agency would recommend, but not require, that screening and testing procedures be followed when reproductive tissues are used between sexually intimate partners, and when tissues are transplanted back into the person from whom they were obtained. The agency would require infectious disease screening and testing for cells and tissues transplanted from one person to another (except for reproductive tissues used between sexually intimate partners). The agency would also require that cells and tissues be handled according to procedures designed to prevent contamination and to preserve

tissue function and integrity. In general, there would be no agency submissions required regarding infectious disease controls and handling requirements. Thus, most conventional and reproductive tissues would not be subject to premarket approval requirements. (The agency would impose no requirements on cells and tissues transplanted within a patient s body in a single surgical procedure.)

Cells and tissues that were manipulated extensively, combined with non-tissue components, or were to be used for other than their normal functions would be regulated as biologics or devices requiring premarket approval by FDA. Metabolic cells and tissues, unless minimally manipulated and used for their normal function in the person from whom they were obtained or in close blood relatives of that person, also would be regulated as biologics requiring premarket approval by FDA.

The agency would require that all tissue processing facilities register with the agency, and list their products, via a simple electronic system. And the agency would require that all labeling and promotion be clear, accurate, balanced, and non-misleading.

This new system would provide a rational, comprehensive and comprehensible framework under which tissue processors could develop and market their products. It would ensure that innovation and product development in this rapidly growing medical field could proceed unhindered by unnecessary regulation. At the same time, it would provide physicians and patients with the assurance of safety that the public has come to expect from drugs, biologics, medical devices and other medical products overseen by the FDA.

I. INTRODUCTION

The FDA has formulated a comprehensive approach to the regulation of human cellular and tissue-based products. This approach would provide more appropriate oversight for the wide spectrum of cellular and tissue-based products that are now marketed or envisioned for the future. It would maintain or improve protection of the public and increase public confidence in these new technologies, while permitting significant innovation to go forward unfettered by unnecessary regulatory requirements.

The approach does not encompass vascularized organs or minimally-manipulated bone marrow (both of which are regulated by the Health Resources and Services Administration), transfusable blood products (e.g., whole blood, red blood cells, platelets, and plasma), which the agency already comprehensively regulates,[1] or tissues derived from animals.[2] It also does not encompass other tissue-related products, such as products used in the propagation of cells or tissues, or that are secreted by or extracted from cells or tissues (e.g. human milk, collagen, urokinase, cytokines, and growth factors.) Such products often raise different manufacturing, safety, and effectiveness issues, and generally are covered by other rules, regulations, and/or standards.

II. BACKGROUND

The term 'tissues' covers a wide range of products used for many medical purposes. In the past, most human tissue used in medicine was comprised of such body components as skin, bone, corneas, and heart valves that were transplanted for replacement purposes, and semen and ova implanted for reproductive purposes. Except for a small number of tissues previously regulated as devices since 1993, FDA's regulation of the conventional tissues used for replacement purposes has focused on preventing the transmission of communicable disease, as authorized by the Public Health Service Act (PHS Act). Three years ago, FDA promulgated interim requirements that such conventional non-

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[1] The agency recognizes that it may be desirable to regulate traditional blood products in a manner more like the regulation of other cellular and tissue-based products (to the extent that they present similar issues), and will examine this issue in a future initiative.

[2] Transplantation of animal tissues into humans (xenograft transplantation) is not addressed in this document, as it raises different public health issues from those raised by transplantation of human tissue into humans. Among other things, the spectrum of infectious agents potentially transmitted via xenograft transplantation is not known, and infectious agents that produce minimal symptoms in animals may cause severe morbidity and mortality in humans. The Public Health Service published a draft Guideline on Infectious Disease Issues in Xenotransplantation in September 1996. (September 23, 1996 Federal Register, 61 FR 49919).

reproductive tissues be tested for HIV and hepatitis and that their donors be screened for risk of infection. FDA has not previously regulated reproductive tissues.

In recent years, scientists have developed innovative methods of manipulating and using human cells and tissues for therapeutic uses. For example, in what is known as somatic cell therapy, scientists are studying the use of human cells that have been manipulated in the laboratory to treat viral infections (including HIV infection), Parkinson s Disease, diabetes, and other diseases and conditions. Other tissue research includes the use of blood from the placental/umbilical cord, to treat diseases or conditions. In general, these forms of cellular and tissue therapy are regulated by FDA as biologics under both the PHS Act and the Federal Food, Drug, and Cosmetic Act (FDCA) , with premarketing approval requirements.

III. PUBLIC HEALTH AND REGULATORY CONCERNS ASSOCIATED WITH CELLULAR AND TISSUE-BASED PRODUCTS.

Cellular and tissue-based products and their potential uses are too diverse for a single set of regulatory requirements to be appropriate for all. In an effort to develop a comprehensive scheme that would treat like products alike, but that would establish appropriate regulatory distinctions among cellular and tissue-based products in areas where there were differences, the agency identified the principal public health concerns and attendant regulatory issues associated with the use of these products. Stated as questions, these five overarching public health and regulatory concerns are:

A) How can the transmission of communicable disease be prevented?

B) What processing controls are necessary, e.g., to prevent contamination that could result in an unsafe or ineffective product, and to preserve integrity and function so that products will work as they are intended?

C) How can clinical safety and effectiveness be assured?

D) What labeling is necessary, and what kind of promotion is permissible, for proper use of the product?

E) How can the FDA best monitor and communicate with the cell and tissue industry?

With these concerns in mind, the FDA differentiated cells and tissues and their uses by their risk relative to each concern, so as to enable the agency to provide only that level of oversight relevant to each of the individual areas of concern. Thus, under the plan, tissues would be regulated with a tiered approach based on risk and the necessity for FDA review.

IV. PRODUCT FACTORS (TISSUE CHARACTERISTICS AND USES) AFFECTING EACH AREA OF CONCERN - AN OVERVIEW

The agency has identified the following key product factors relating to the above concerns.

A) Direct transmission of communicable disease. The level of public health concern about communicable disease varies depending in substantial part on the following factors: whether the cells or tissues are used in the same person from whom they were obtained (autologous use); whether the cells or tissues are used in a person different from whom they were obtained (allogeneic use); whether they are banked (stored), shipped, or processed in a facility that handles cells and tissues from multiple donors; whether the cells or tissues are minimally, or more-than-minimally, manipulated; whether the tissue is viable or nonviable; and for reproductive cells or tissue, whether they are obtained from a sexually-intimate partner of the transplant/insemination recipient.

B) Processing concerns. The level of concern relating to processing is dependent on the following factors: whether or not the cells or tissues are more-than-minimally manipulated; whether or not they are used for their normal (homologous) function; whether or not they are combined with non-cell/non-tissue components; and whether or not they are used for metabolic function. As will be discussed below in VI B, Control of Processing, products that are more-than-minimally manipulated, or are used for purposes other than their normal function, or are combined with non-cell/non-tissue components, or are used for metabolic function, generally will be subject to more comprehensive regulation of processing than products not characterized by any of these factors, although some exceptions may apply. (For example, use for metabolic function would not in and of itself lead to more comprehensive processing regulation when the product was used in the person from whom it was obtained, or in a close blood relative of that person;[3] use of minimally manipulated tissue for other than its normal function may lead to only limited additional regulation of processing, as appropriate to help

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[3] As a policy matter, the agency would not require investigational use exemptions and premarketing submissions for metabolic cells or tissues that were only minimally manipulated, were to be used for their normal function and were not combined with non-cell/non-tissue components, when those cells or tissues were to be used in the person from whom they were obtained or in a close blood relative of that person. Therefore, FDA would require no agency submissions other than registration, listing, and reporting of adverse events for such products used between close blood relatives. The products would still be subject to appropriate labeling and processing controls.

A close blood relative (also referred to in this document as a family relative) is defined in this document as a first degree blood relative (i.e., parent, child, or sibling). "Unrelated" is used in this document to refer to someone other than a close blood relative of the donor.

ensure intended function). Products not characterized by any of these factors would be regulated under section 361 of the PHS Act, and would not be subject to premarketing requirements. Products characterized by one or more of these factors would be regulated under section 351 of the PHS Act and/or under the FDCA, and generally would be subject to some level of premarketing requirements.

C) Clinical safety and effectiveness concerns. Clinical safety and effectiveness concerns depend on the same factors as do processing concerns (i.e., extent of manipulation; homologous or non-homologous function (that is, whether or not tissue is used for its normal function); combination with non-cell/non-tissue components; and metabolic function). The kinds of information the agency will need to address these concerns may differ depending on whether the cellular or tissue-based product is to be used for a local structural purpose (i.e., reconstruction or repair), a reproductive purpose, or a metabolic purpose. As noted above for processing concerns, and as will be discussed below in section VI C, Clinical Safety and Effectiveness, products that are more-than-minimally manipulated, or are used for non-homologous function, or are combined with non-cell/non-tissue components, or are used for metabolic function, will generally be subject to more comprehensive regulatory controls than products without any of these factors. However, for some products subject to regulation under section 351 and/or the FDCA (see section VI, A, Stem Cells) the agency anticipates establishing product-class-specific processing controls and product standards based on data demonstrating that such controls or standards ensure safety and effectiveness. For these products, applicants would be eligible to certify that these controls and standards have been met in lieu of submitting the underlying data to support such controls and standards.

D) and E) Promotion and labeling and the agency's **baseline knowledge of industry** are cross-cutting issues that apply to all cellular and tissue-based products, with the exception of cells and tissues obtained from and transplanted back into the same person during a single surgical procedure.

V. THE REGULATORY SCHEME: PRODUCT CONCERNS, PRODUCT CHARACTERISTICS AND USES, REQUIRED INDUSTRY ACTIONS, AND REQUIRED REGULATORY SUBMISSIONS.

The agency has developed a chart (Table 1) that outlines the five principal areas of public health or regulatory concern (rows A through E, as described below), the product factors that affect those concerns (and that are the basis for the subdivisions within rows A, B, and C), the industry actions that would be required to address each set of concerns, and the types of required notifications or submissions to the agency. Thus, to determine all the regulatory mechanisms that would apply to any particular product or use, one must look at all the items in the table. The table is provided only as a very short summary of the regulatory approach. As such, it is not intended to stand alone, but to be referred to in conjunction with this document. The following text elaborates on the issues as presented by row in Table 1.

A) Direct transmission of communicable disease - donor screening, donor/product testing.

1) Overview.

Transmission of communicable disease is a concern for all uses of all cellular or tissue-based products. However, the degree of risk, and the appropriate measures to control risk, vary with the source and use of the product. FDA intends to adjust its regulatory approach accordingly.

Row A of Table 1 broadly distinguishes between cellular and tissue-based products for which the agency would not require communicable-disease controls (A1), and products for which it would require communicable-disease controls (A2). A2 is further subdivided according to the kinds of requirements and tests the agency would consider appropriate, based on the source, use, and characteristics of the tissue. Proposals for specific screening, testing, and related requirements for products in these categories are provided in Table 2.

2) Regulatory requirements.

a) Row A1. The agency would not assert any regulatory control over cells or tissues that are removed from a patient and transplanted back into that patient during a single surgical procedure. The communicable disease risks, as well as safety and effectiveness risks, would generally be no different from those typically associated with surgery. Regulated products used in such procedures would continue to be regulated.

b) Row A2. The use of allogeneic rather than autologous cellular or tissue-based products increases the risk of transmission of communicable disease, because the donor from whom the cells or tissue was obtained could carry an infectious agent to which the recipient is susceptible. Also, for both autologous and allogeneic settings, the use of cellular or tissue-based products that are banked, transported, or processed in facilities with other cellular or tissue-based products increases the risk of transmission of communicable disease, because the products are susceptible to contamination or mix-up at each step of such procedures. For example, an infected product could cross-contaminate other cellular or tissue-based products stored in the same liquid nitrogen freezer, or could contaminate processing equipment, which, if not properly treated, could contaminate other tissue processed with that equipment. If contaminated tissue is not properly tested or labeled, health care workers as well as patients may be put at risk.

Therefore, as shown in rows A2b and A2c of Table 1 and in Table 2, the agency intends to require establishments and persons that bank, ship, or process cells or tissues for allogeneic use (except reproductive tissues from sexually intimate partners of the intended recipient of the tissue) to follow specific donor screening and/or donor or product testing and/or product quarantine procedures. Test requirements will differ depending on whether the cells or tissues are nonviable (A2b) or viable (A2c). Viable cells and tissues that are rich in leukocytes (such as stem cells) can harbor human T-cell lymphotropic virus (HTLV) and cytomegalovirus (CMV), and thus would be required to be tested for

those viruses. Viable tissues that are not rich in leukocytes (such as corneas and skin), and nonviable tissues (which do not contain viable leukocytes) would not be subject to HTLV and CMV testing requirements.

In general, the screening and testing would be required to be completed prior to final release of the cells or tissue for transplantation. The establishment or person responsible for determining suitability of release of cells or tissues would be responsible for ensuring that required screening and testing had been performed prior to final release of the material.[4] For cells or tissue to be obtained from a living donor for allogeneic use, screening and testing would be required prior to collection of the cells or tissue (except in extenuating circumstances).

Additionally, as shown in row A2a of Table 1 and in Table 2, the agency intends to recommend (but not require) that establishments and persons that bank, ship or process cells or tissues from multiple donors for autologous use, or reproductive cells or tissues for reproductive use obtained from sexually intimate partners of the intended recipients of the cells or tissues, also follow the screening and testing procedures prior to collecting the cells or tissue. The agency intends to require that such establishments and persons keep records and label their products as to whether or not recommended donor screening and testing was performed, and if performed, the results obtained. Untested products would be labeled as "untested for BIOHAZARDS."

The screening and testing procedures would be recommended rather than required for such autologous or reproductive uses because 1) autologous use of cells and tissues raises lesser communicable-disease concerns than does allogeneic use; and 2) use of reproductive tissues from sexually intimate partners of intended recipients raises lesser communicable-disease concerns than other allogeneic uses of tissues because the recipient generally will have had prior exposure to the potential risk of receiving communicable disease from that partner. (In contrast, cells or tissue from family-related donors raise the same communicable-disease risks as do cells or tissue from unrelated donors, and consequently family-related donors would be subject to the same testing and screening procedures as are unrelated donors. However, the agency believes that it is appropriate to leave it up to the family and their physician to decide whether to use such tissue, and would not prohibit use even of contaminated material from closely-related donors.)

Cells or tissue from donors who test positive for an infectious disease agent or who have positive risk

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[4] Cells and tissues processed or shipped to a consignee prior to determination of donor suitability would have to be under quarantine, accompanied by records assuring identification of the donor, and indicating that the material had not yet been determined to be suitable for transplantation, insemination, fertilization, further shipment or release. The consignee would be responsible for keeping such material in quarantine, and not shipping it further until donor screening tests had been completed.

factors (that is, whose behavior or experiences could have exposed them to infection) would be required to be labeled 'BIOHAZARD' or "UNTESTED FOR BIOHAZARD" as applicable, and could only be used for transplantation with the documented advance informed consent of the recipient. Autologous tissue from such donors would be required to be labeled 'FOR AUTOLOGOUS USE ONLY.' In those situations in which cells or tissues from such donors are not destroyed, the material could be released from a bank or quarantine only upon documented concurrence of the recipient s physician. Such situations would include cells or tissue to be used in the person from whom it was obtained or in a close blood relative (e.g., autologous stem cells); and reproductive tissue for reproductive use (e.g., semen) from a sexually intimate partner of the intended recipient or from a directed donor; medically necessary and otherwise unavailable cells or tissue (e.g., the tissue is a rare histocompatibility match in a setting where matching is critical).

The agency would engage in rulemaking[5] under section 361 of the PHS Act to establish procedures and standards for cellular and tissue-based products not subject to premarket requirements under the PHS Act or the FDCA. While under the section 361 rule there would be no required premarketing submissions to the agency concerning communicable-disease testing, the agency would have authority to inspect facilities subject to the requirements, and to take actions to prevent transmission of communicable disease (e.g., orders of retention, recall, and destruction of cellular and tissue-based products).

Cellular and tissue-based products subject to premarket requirements because of processing or clinical attributes (see sections V B and V C below) would still be subject, unless the requirements were unnecessary in a particular situation, to the same core communicable-disease standards and procedures as are cellular and tissue-based products regulated under section 361, and would generally be subject to no additional submission requirements regarding these communicable-disease issues. To the extent that a product requiring premarketing approval were to raise additional communicable-disease concerns as a result of its source, processing, or use, additional standards or procedures could be required in the marketing application[6] to address these concerns.

B) Control of Processing.

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[5] FDA published an interim rule (21 CFR Part 1270) that contains requirements for communicable disease controls for a subset of cellular and tissue-based products discussed in this document. FDA plans to finalize those requirements, and then engage in further rule making as is necessary, to achieve the purposes of this proposed regulatory scheme.

[6] For example, manipulation of cells or tissue can affect the infectivity, virulence, or other biological characteristics of adventitious agents in the tissue, thereby increasing communicable-disease risks, and potentially requiring new standards or procedures.

1) Overview.

Row B of Table 1 differentiates products based on whether their characteristics and uses warrant handling and processing controls aimed only at preventing transmission of communicable disease (B2); or warrant processing controls aimed at providing assurance of clinical safety and effectiveness, including but not restricted to preventing transmission of communicable disease (B3). Autologous use of cells and tissues harvested and transplanted in a single surgical procedure would be subject to no FDA oversight (B1). Regulated products used with the cells or tissues or to process the cells or tissues would continue to be regulated.

Improper handling can alter or destroy the integrity or function of cells or tissues. Improper handling also can allow cells or tissues to become contaminated (e.g, bacterial contamination during collection, processing, storage, or transplantation, or cross contamination from other contaminated tissues). Similarly, inadequately-controlled processing can alter or destroy the integrity or function of cells or tissues. Use of cells or tissues contaminated with an infectious agent obviously increases the risk of transmission of communicable disease. Use of cells or tissue with impaired integrity or function also increases the risk of transmission of communicable disease: tissue with impaired integrity or function can lead to transplantation failure, with attendant communicable disease risks (e.g., by increasing the patient s susceptibility to communicable disease, or requiring additional transplantation procedures, with their attendant communicable-disease risks.)

2) Factors Affecting Processing Concerns and Clinical Safety and Effectiveness Concerns.

As previously discussed above, the factors affecting the level of concern regarding processing controls and product safety and effectiveness are: manipulation (i.e., whether the product is minimally or more-than-minimally manipulated); homologous or non-homologous function; whether or not the cells or tissue are combined with non-cell/non-tissue components; and whether or not the product is used for metabolic function as opposed to reproductive or structural function. The agency describes these factors and their regulatory implications below.

(a) Non-cell/non-tissue components. Cellular and tissue-based products may be combinations of cells or tissues with mechanical or synthetic components, with drugs, or with non-cell/non-tissue biologics. The largest and fastest growing class of such combination products are those containing synthetic or mechanical components. These components raise concerns about function, compatibility, and durability. Examples of such combination products would include epithelial cells on a biomatrix to cover burns; allogeneic pancreas cells in a capsule that allows exit of insulin but not entry of antibodies; and bone when combined with collagen or growth factors.

The agency does not anticipate that its planned regulatory approach for cellular and tissue-based products would alter existing agency regulatory policies concerning cellular and tissue-based products containing non-cell/non-tissue components. These combination products are generally subject to

premarketing requirements. The decision as to which part of the agency has primary regulatory responsibility for such combination products will depend on the primary mode of action of the product.

Combination products whose primary mode of action is that of a device are regulated by the Center for Devices and Radiological Health (CDRH). Combination products whose primary mode of action is that of a biologic are regulated by the Center for Biologics Evaluation and Research (CBER). Combination products whose primary mode of action is that of a drug are regulated by the Center for Drug Evaluation and Research (CDER). The agency intends to assure that its reviews of these products are consistently performed, regardless of which Center is responsible for the review.

For combination products with synthetic or mechanical components (which comprise the largest class of combination products), clinical trials and marketing applications must address the clinical safety and effectiveness of the overall product, as well as the function and compatibility of the synthetic or mechanical components. The agency s principal concerns with the use of these materials are that they function correctly, that they last a predictable and adequate length of time, and that they are compatible with surrounding tissue. Clinical trials would thus be required under IND or IDE, as appropriate.[7]

The agency is setting up a Tissue Reference Group to assist in making jurisdictional decisions and applying consistent policy to these products. The agency hopes thereby to resolve expeditiously any scientific or regulatory questions that arise as to where and how such products should be reviewed. The Tissue Reference Group will consist of three CBER and three CDRH employees. It will provide a single reference point for all tissue-related questions received by the Centers or the Office of the Chief Mediator and Ombudsman.

b) Manipulation. The agency would consider processing of structural tissue to be "minimal manipulation" when the processing does not alter the original relevant characteristics of the tissue. The relevant characteristics of structural tissue are those relating to the tissue's ability to carry out the function of reconstruction and/or repair. Thus, separation of structural tissue into components whose characteristics relating to reconstruction and/or repair are not altered would be minimal manipulation. Similarly, extraction or separation of cells from structural tissue, in which the remaining structural tissue's characteristics relating to carrying out reconstruction and/or repair were unaltered, would be considered minimal manipulation. Other examples of procedures that would be considered to constitute only minimal manipulation include cutting, grinding, and shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or gamma irradiation; cell separation; lyophilization;

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[7] Tissue-based products that are intended for diagnosis or therapeutic effect by physical action (including reconstruction or repair), and that contain synthetic or mechanical components, and achieve their primary mode of action by means other than metabolic or systemic action, are regulated as devices by CDRH.

cryopreservation; and freezing.

In contrast, extraction of endogenous substances such as minerals or proteins from structural tissue would be considered more-than-minimal manipulation, because such modifications would ordinarily alter the tissue's relevant characteristics.

The agency would consider processing of cells (both structural and non-structural) and non-structural tissues to be "minimal manipulation" when the processing does not alter the biological characteristics of the cells or tissue. The agency would consider processing of cells and non-structural tissues to be "more-than-minimal manipulation" when the processing alters the biological characteristics (and thus potentially the function or integrity) of the cells or tissue, or when adequate information does not exist to determine whether the processing will alter the biological characteristics of the cell or tissue. Examples of more-than-minimal manipulation of cells and tissues include cell expansion, encapsulation, activation, or genetic modification.

Cells or tissues that are more-than-minimally manipulated would be subject to processing controls that generally would cover chemistry, manufacturing, and controls (CMCs), and to premarket requirements for determination of safety and effectiveness because manipulation has the potential, or is intended, to change the cell or tissue's biological characteristics or function. The agency has previously used the concept of manipulation to identify those cellular therapies for which premarket approval would be required. In the somatic cell and gene therapy statement published in October, 1993 (58 FR 53248), the agency stated:

> Cells subject to licensure as final biological products when intended for use as cell therapy include cells manipulated in a way that changes the biological characteristics of the cell population...

As described for row B3 in section V B2c below, these products would continue to be subject to CMCs, including process controls and product specifications designed to ensure safety, purity, and potency, and to IND or IDE and marketing application procedures. The agency has prepared CMC guidances for some of these products.

As additional information is generated about procedures in the "more-than-minimal-manipulation" category, the agency intends to consider them to be in the "minimal-manipulation" category when clinical data and experience show that the procedure does not alter the biological characteristics of the cells or non-structural tissue, or the relevant structure-related characteristics of structural tissue. This flexibility will permit product processing that has been found not to affect the pertinent characteristics of the product to be subjected to a lower level of regulation.

In the somatic cell and gene therapy statement, the agency stated that it considered cell selection to

constitute more-than-minimal manipulation. After additional experience and deliberation, the agency now considers cell selection (e.g., selection of stem cells from amongst lymphocytes and mature cells of other lineages) to be minimal manipulation.

In cases where the agency has not made known whether it considers a particular kind of processing to be minimal or more-than-minimal manipulation, individuals may request an opinion from the agency s Tissue Reference Group. Individuals who believe that a particular kind of processing is only minimal manipulation and choose to proceed without seeking clarification assume the risk that they may be out of compliance with premarketing and labeling requirements if the agency determines that the processing is more-than-minimal manipulation.

c) Homologous and non-homologous function. The distinction between homologous and non-homologous function will differ depending on whether or not the product is a structural tissue. The agency considers structural tissue to be used for a homologous function when used to replace an analogous structural tissue that has been damaged or otherwise does not function adequately. Conversely, the agency would consider structural tissue to be performing a non-homologous function when used for a purpose different from that which it fulfills in its native state, or in a location of the body where such structural function does not normally occur.

Examples of homologous uses of structural tissues include bone allograft obtained from a long bone but used in a vertebra; skin allograft obtained from the arm but used as a skin graft on the face; pericardium, a structural covering of the heart, used as a structural covering for the brain; human heart valves; and human dura mater, a fibrous covering of the brain, used as a covering. (Thus, the agency would redesignate human heart valves and human dura mater from devices to tissues subject to section 361 oversight.)

Examples of non-homologous use of structural tissue include amniotic membrane used for wound healing on the cornea, and cartilage placed under the sub-mucosal layer of the urinary bladder to change the angle of the ureter and thereby prevent backflow of urine from the bladder into the ureter. The amniotic membrane, which covers the amniotic sac in utero, would be intended to heal a damaged corneal epithelium by growing new corneal epithelial cells, a function it does not normally perform in utero. The cartilage would be acting as a structural support (its normal function), but in a location where such structural support does not normally exist.

The agency considers cellular products to be used for a homologous function when they are used to perform their native function, and for a non-homologous function when they are used to perform other functions. An example of homologous use would be hematopoietic stem cells used for hematopoietic reconstitution of individuals with marrow aplasia, chemotherapy-induced marrow ablation, Fanconi's anemia, or severe combined immunodeficiency disease. An example of non-homologous use of the same cellular product would be treatment of some adrenal leukodystrophies (which are congenital

metabolic deficiencies), because the sponsor would be intending for the stem cells to perform a metabolic function other than hematopoietic reconstitution.

As for manipulation, the agency would have increased safety and effectiveness concerns for cellular and tissue-based products that are used for non-homologous function, because there is less basis on which to predict the product s behavior. Thus, a tendon used to replace a tendon, even one elsewhere in the body, is still being used for a homologous function and can reasonably be expected to function appropriately. However, without clinical trials, one cannot predict with any certainty how a tendon would act when used for a non-homologous function, such as to constrict a blood vessel to prevent pulmonary embolism.

As described above for manipulation, in cases where the agency has not made known whether it considers a particular use to be homologous or non-homologous, investigators may request an opinion from the agency s Tissue Reference Group. Individuals who believe that a use is homologous and choose to proceed without seeking clarification assume the risk that they may be out of compliance with premarketing and labeling requirements if the agency determines that the use is non-homologous.

d) Metabolic function. Products with a metabolic mode of action usually rely on viable, functioning cells (e.g., pancreatic islet cells, pituitary cells, stem cells) for function. They therefore are sensitive to perturbations and may not retain normal function after the transplantation process. Failure or improper functioning of such products often can have a broad variety of systemic adverse effects, and can be life-threatening (e.g., hematopoietic stem cell replacement after marrow ablation by chemotherapy, pancreatic islet cell therapy for diabetes). Relatively few such products have an established history of safe use. (The agency believes that some autologous and family-related-allogeneic uses of hematopoietic stem cells may have such an established history.)

As noted above, minimally manipulated cellular and tissue-based products with metabolic function raise greater clinical safety and effectiveness concerns than do products with structural or reproductive function. The agency intends to assert premarketing requirements over these products (except when the cells or tissues are used in the person from whom they were obtained or in a close blood relative of the donor, in which case as a policy matter the agency would not require premarket submissions). Thus, for example, the agency would not call for clinical safety and effectiveness information for autologous or family-related allogeneic use of minimally manipulated hematopoietic stem cells (for which no non-homologous use promotional claims were made), but would require clinical safety and effectiveness information for non-family-related allogeneic use of the same cells. As noted in B3 above and section IV below, the agency believes that, for minimally manipulated stem cells used allogeneically to reconstitute the cellular components of blood, sufficient clinical safety and effectiveness data may exist in the near future to enable the development of processing and product standards for certain uses that would obviate the need for applicants to submit CMC and clinical safety and effectiveness information prior to marketing.

e) Reproductive function. In contrast to other metabolic tissues, reproductive tissues raise less substantial issues of rejection, graft versus host disease, or compatibility. Indeed, unlike other tissue, they perform their normal biological functions in an allogeneic setting. Failure of reproductive tissue generally does not have life-threatening or systemic adverse effects except for fertility per se. Reproductive tissues have a long history of use in the medical community. (Assessments of pregnancy success rates for live births in clinics is currently being addressed by the Centers for Disease Control and Prevention, under the Fertility Clinics Success Rate and Certification Act of 1992.)

f) Structural function. Cells and tissues used for structural purposes generally raise different clinical safety and effectiveness concerns than do metabolic cells and tissues. Many structural cellular and tissue-based products raise limited safety concerns beyond adverse local effects. Depending on location, failure of most structural cellular and tissue-based products is unlikely to lead to life-threatening consequences. In many cases, determination of effectiveness of structural therapies is more straightforward than is determination of effectiveness of metabolic therapies.

Additionally, many structural tissue-based products rely predominantly on non-living tissues (e.g., tendons) for function. They therefore usually are relatively insensitive to external factors and are more likely to retain normal function after the transplantation process. Also, many structural tissue-based products are conventional tissues having a long and established history of safe use in the medical community.

3) Regulatory requirements.

a) Row B1. Autologous cells and tissues collected and transplanted in a single surgical procedure (e.g., skin or vein grafts) would not be subjected to any regulatory requirements.

b) Row B2. Cells and tissues not collected from and transplanted into the same person in a single surgical procedure, and not having any of the factors that lead FDA to require section 351 and/or FDCA regulation (i.e., they are minimally manipulated, for homologous use, without non-cell/non-tissue components, and not for metabolic use when from an unrelated donor), would be subject only to handling and processing requirements under section 361 of the PHS Act. The agency intends to promulgate, under section 361, good tissue practice requirements (GTPs) that would be aimed at preventing contamination and preserving product integrity and function through proper handling and processing practices. Apart from registration, listing, and reporting requirements, there would be no required FDA submissions; for example, there would be no premarketing approvals. All establishments or persons that recover, screen, test, procure, bank, process, transport or distribute cells or tissues for allogeneic use or from multiple donors would be subject to some or all of these requirements as appropriate.

Examples of B2 products would include banked tissues, such as semen, human heart valves, powdered

lyophilized non-demineralized bone and other conventional tissues, as well as banked autologous and banked or unbanked family-related allogeneic peripheral and placental/umbilical cord blood stem cells.

c) Row B3. Inadequately controlled or otherwise improper processing can result in products that are ineffective, and in products that are unsafe for reasons other than increasing the risk of transmission of communicable disease. For example, products may be unsafe because they are ineffective (e.g., nonviable stem cells used for hematopoietic reconstitution after chemotherapy) or because they function improperly (e.g., cells or tissue that inappropriately secrete a hormone may cause unwanted metabolic effects). Thus, processing controls for products that raise such clinical concerns often must be more comprehensive than those needed to address risks of transmission of communicable disease.

As discussed in sections IV and V, cellular and tissue-based products that are more-than-minimally manipulated, or are used for non-homologous function, or in combination with non-tissue components, or for a metabolic purpose raise a higher level of processing concerns pertinent to assurance of clinical safety and effectiveness. The agency would subject such products/uses to processing-controls under section 351 of the PHS Act and/or under relevant sections of the FDCA.[8]

Such processing controls generally would cover product chemistry, manufacturing, and controls (CMCs) and be subject to premarket submissions. However, if FDA determines that class-wide standards can be developed such that products in a specified product class are known to be clinically safe and effective when manufactured in accordance with certain defined product specifications and process controls, FDA could establish such standards through rulemaking and require premarketing submission of certification by the applicant that the products met the published standards, rather than a more detailed submission of the clinical data.

For non-family-related allogeneic cord or peripheral blood stem cells for hematopoietic reconstitution, which in some cases have been studied without an investigational new drug exemption (IND), the agency intends to call for a phase in of IND and licensure submissions (see section VI, Implementation of Regulatory Procedures). If, prior to the end of the phase-in period, the agency has received adequate data and information to enable the agency to promulgate standards designed to ensure safety and effectiveness for particular uses of these products, FDA anticipates making a class-specific finding of safety and effectiveness for products meeting those standards (see section V C, Clinical Safety and

[8] However, as a policy matter, the agency would not subject cells or tissues used for metabolic purposes to such regulation if the cells or tissues were used in the person from which they were obtained or in a close blood relative of the donor, and were minimally manipulated, without non-cell/non-tissue components, and for a homologous function.

Effectiveness, and section VI, Implementation of Regulatory Procedures). Individuals pursuing licensure subsequent to the adoption of such standards would not have to submit clinical safety and effectiveness data to the agency in their premarketing applications, but would merely have to certify that they meet the standards.

Examples of B3 products used for metabolic function would include hematopoietic stem cells intended for use in recipients who are not close blood relatives of the cell donor or for uses other than to reconstitute the cellular components of the blood; cloned and/or activated lymphocyte therapies for cancer or infectious diseases; and hematopoietic stem cells that have been expanded or modified as part of gene therapy.

Examples of B3 products used for structural function would include demineralized bone (which the agency plans to propose to classify as a class I device and to exempt from premarket submissions), and bone combined with collagen or growth factors.

C) Clinical Safety and Effectiveness - Use-specific Concerns.

1) Overview.

Row C of Table 1 distinguishes products based on whether they have none of the factors relating to clinical safety or effectiveness that would lead FDA to require section 351 or FDCA premarketing submissions requirements (C1); whether they have one or more of such factors and are used to achieve a local structural function (i.e., reconstruction or repair) (C2); and whether they have one or more of such factors and are used to achieve a reproductive or metabolic function (C3).

Products described under C1 would be subject to no section 351 or FDCA requirements for clinical trials demonstrating safety and effectiveness. Products under C2 and C3 would be subject to section 351 and/or FDCA requirements. Requirements for premarket clinical data submissions for C2 and C3 cellular and tissue-based products would generally be as for other regulated products, tailored as appropriate to the characteristics of the product and the concerns raised by the specific indication and product. For serious and life-threatening illnesses, all other applicable policies (e.g., expedited review, treatment IND, accelerated approval) would be available to help speed product availability.

C2 products are separated from C3 products to indicate that in general they would be subject to different safety and effectiveness endpoints to fulfill clinical trial requirements. Clinical trial requirements for C2 products (whether regulated as biologics or devices) would generally be consistent with those for devices for the same indication, whether regulated under INDs or IDEs (investigational device exemptions). Clinical trial requirements for C3 products would generally be consistent with those for new drugs or biologics for the same indication.

2) Regulatory Requirements.

a) Row C1. FDA would not require premarket review and approval for

cellular and tissue-based products that are minimally manipulated, are used for homologous function, do not contain non-cell/non-tissue components, and are for structural or reproductive use. Such products raise relatively limited clinical safety and effectiveness concerns, and thus would not be subject to premarket submission of clinical data. Additionally, as a policy matter the agency would not require premarket submission of clinical data for cellular or tissue-based products that are minimally manipulated, are used for homologous function, do not contain non-cell/non-tissue components, and are for metabolic use, when they are to be used autologously or in a close blood relative of the donor. Communicable-disease risks would be addressed under section 361 as discussed above in sections VI, A, 2, and VI, B, 2.

Examples of such products would include heart valve and dura mater transplants, vein grafts, tendons to repair or replace tendons, autologous or family use of peripheral or cord blood stem cells for hematopoietic reconstitution, and human gametes (sperm and eggs), zygotes, and embryos intended for insemination, fertilization, or transfer.

b) Row C2. The agency recognizes that cellular and tissue-based products for structural use raise different safety and effectiveness issues than do products for metabolic or reproductive use, and that they can be evaluated in a manner generally consistent with that of devices for the same indication, modified as appropriate for the nature of the product. (They may also be classified as devices). The agency outlined its approach for evaluating a major subset of such products in the May, 1996 Guidance on Applications for Products Composed of Living Autologous Cells Manipulated Ex Vivo and Intended for Structural Repair or Reconstruction (MAS Cells) and the CMC Guidance for Autologous Cell Therapy (1997).

The agency recognizes that many of the highly manipulated cellular and tissue-based products intended for structural purposes often will be used for the same indication as are some devices, or will be classified as devices. It is the intent of CBER and CDRH to ensure consistent review of such products, whether regulated as devices or biologics, and to establish clinical effectiveness standards for structural cells regulated as biologics that would be consistent with those existing for comparable devices. However, different products may raise different safety, effectiveness, or durability concerns, and may be amenable to different methods for measuring outcomes.

Some examples of C2 cellular and tissue-based products include manipulated cells for autologous structural use (MAS cells) such as expanded chondrocytes to repair damaged knee cartilage, and devices such as demineralized bone. (The agency does not intend for demineralized bone used alone to be subject to premarket submission requirements. The agency plans to propose to classify demineralized bone as a class I device and to exempt it from premarket submissions, as described in section VI.)

c) Row C3. Some examples of C3 cellular products include autologous

genetically-manipulated cellular therapies involving correction of genetic defects, non-family-related allogeneic cord or peripheral blood stem cells, stem cell therapies involving growth factors such as interleukin-3 and stem cell factor or gene therapy, activated lymphocytes for treatment of cancer, and cloned lymphocytes for the treatment of HIV infection or other infection. (See section VI A below regarding phase-in of licensure requirements for non-family-related allogeneic cord and blood stem cells.)

D) Promotion and Labeling. Row D of table 1 addresses the issue of potentially false or misleading claims. For cellular and tissue-based products regulated under section 361, labeling would need to be clear, accurate, balanced, and non-misleading. Such labeling could include what the tissue is and how it has been processed; the homologous uses of the tissue; and the communicable-disease screening, testing and quarantine procedures that were followed and results obtained. FDA intends to propose regulations to address labeling requirements under section 361 of the PHS Act.

Products that are intended or promoted for use for a non-homologous function would fall outside the scope of the section 361 regulation the agency intends to promulgate, and would be subject to regulation as biological drugs or devices under section 351 of the PHS Act and/or the FDCA. For cellular and tissue-based products regulated under FDCA and/or section 351 of the PHS Act, the agency intends to regulate labeling under existing authorities therein.

E) Monitoring and Education. At present, FDA does not know the full size and scope of the cell and tissue industry and its potential products. The agency believes that, in order for it to understand the issues raised by these new products and be able to educate the industry and keep it up to date regarding FDA policies, guidances, and requirements, as well as to enable the agency to inspect establishments for compliance with applicable laws and regulations, all establishments that recover, screen, test, procure, bank, process, transport or distribute cells or tissues from multiple or allogeneic donors, should register and list their products with FDA. Therefore, the agency would require registration and listing for all such establishments and products over which FDA is asserting its jurisdiction under section 361 of the PHS Act, section 351 of the PHS Act, or the FDCA. The agency is developing a simple electronic filing system that it will use for establishment registration and product listing. Registration and listing for products subject to section 361 oversight would not be required until the electronic system is in place.

FDA does not intend to require that it be sent reports of errors and accidents that occur during processing and distribution of cellular and tissue-based products subject to section 361 controls. However, as part of the GTP requirements, establishments and persons will be required to identify and investigate errors and accidents, take appropriate corrective action, and maintain records of such failure assessments. The agency does intend to propose post-market adverse event reporting requirements relating to transmission of communicable disease.

The agency intends to apply registration and listing requirements in section 510 of the FDCA as well as existing post-market reporting requirements to those cellular and tissue-based products subject to regulation under section 351 of the PHS Act and/or the FDCA. The agency intends to propose regulations for registration, listing, GTPs, and post-market adverse event reporting of those cellular and tissue-based products regulated under section 361 of the PHS Act.

VI. IMPLEMENTATION OF REGULATORY PROCEDURES

The agency intends to implement this regulatory plan in a step-by-step fashion. The agency intends to promulgate through notice and comment rule-making new regulatory requirements, and to allow for phase-in as appropriate. Some examples of how FDA intends to implement this regulatory plan for selected products are as follows.

A) Stem cells. The agency intends to phase in its regulatory oversight of minimally manipulated hematopoietic stem cells derived from cord or peripheral blood and used for hematopoietic reconstitution in patients who are not close blood relatives of the donors from whom the cells were obtained. (Minimally manipulated hematopoietic stem cells to be used for their normal function in the person from whom they were obtained or in a close blood relative would be regulated under section 361, and would not be subject to premarket application requirements.) The agency intends to phase in regulation of allogeneic use of these products as follows.

1) Registration and Listing. FDA intends that all facilities that recover, screen, test, procure, bank, process, transport or distribute stem cells, derived from umbilical cord blood or peripheral blood, to treat, cure, diagnosis, or mitigate diseases in humans, be required to register with the FDA and list the products at their facility. Registration and listing would be accomplished through an electronic system that the agency is developing.

2) Communicable-Disease Screening and Testing. The agency intends to require testing of blood samples from allogeneic donors of hematopoietic stem cells in order to prevent the transmission of communicable diseases. For peripheral blood stem cell donors, the donor's blood, and for umbilical cord blood donors, the mother's blood, would be required to be tested for HIV, cytomegalovirus, HTLV, syphilis and hepatitis infection (i.e., HBsAg, anti-HIV-1, anti-HIV-2, HIV-1-Ag, anti-HTLV-I/II, anti-HCV, a serologic test for syphilis, and anti-CMV). The medical history and physical examination of prospective donors would include screening for high risk for HIV and hepatitis, Creutzfeldt Jacob Disease (CJD), and tuberculosis.

The agency intends to recommend, but not require, that testing be performed when the stem cells will be used in the person from whom they were obtained. In such case, the agency would recommend only the following tests: HBsAg, anti-HCV, anti-HIV-1, anti-HIV-2, HIV-1-Ag, and anti-HTLV-I/II. The agency also would recommend that the history and physical examination of the donor include screening

for high risk for HIV and hepatitis. The agency would require that record-keeping and labeling reveal which of the recommended tests were performed, and the results obtained from those tests, as well as which of the recommended tests were not performed. Appropriate labeling would be as follows: 'tested and negative', 'tested and positive', or 'not tested for biohazards.'

Ordinarily, cells or tissue would not be collected from a donor testing positive for any of these viruses, and if collected would be required to be destroyed. However, the agency recognizes that there may be circumstances justifying storing or using such cells or tissues. For example, in cases where a stem cell donor tests positive for a virus or has been found to be at risk of infection (even if testing negative), and the stem cells are intended for autologous use, for use in a close blood relative, or for use in a transplant recipient with a rare histocompatibility match, the agency intends to require that 1) the cells be labeled "BIOHAZARD", 2) autologous products also be labeled "FOR AUTOLOGOUS USE ONLY", 3) written advanced informed consent of the recipient be documented, and 4) there be documented concurrence of the recipient's physician before the cells could be released from a cell bank.

3) Processing Standards. The agency intends to promulgate establishment controls, processing controls, and product standards under section 351 of the PHS Act. For minimally manipulated stem cells used for hematopoietic reconstitution, the agency believes that it may be possible to develop product standards (including manufacturing controls and product specifications aimed at ensuring product safety and efficacy) from existent published clinical trial data or data developed in the near future. FDA intends to invite professional groups and individuals to submit to the agency data and standards that they believe would ensure safety and effectiveness. If sufficient data are not available to develop processing and product standards after a specified period of time, the stem cell products would be subject to IND and marketing application requirements.

FDA intends to list in the Federal Register relevant questions for developing the data and standards, and the deadline for submission of responses. Examples of the kind of information that the agency believes will be necessary to have in standards include criteria for acceptance of a unit (such as volume, storage temperature limits, limits on microbial or other contamination, viable cell number, and functionality), and procedures for handling, transporting, storing, and thawing materials, and for when and how contamination and viability testing should be carried out.

Upon development and promulgation of standards designed to ensure safety, purity, and potency, FDA would issue licenses based on a certification by the applicant that the standards are met. The certification could be made in the same submission as the registration and listing. FDA would issue a license based on the certification submission.

During the interim period, FDA would not call for licensure of such products for unrelated allogeneic use, but would require establishment registration and product listing. The agency also could perform inspections for applicable GMP compliance, and could take enforcement action against facilities as

needed (for example, because of lack of appropriate communicable disease-testing).

B) Demineralized bone. FDA would consider demineralized bone (decalcified freeze dried bone allograft) to be an unclassified pre-Amendments device rather than a tissue under section 361 because the bone is more-than minimally manipulated.[9] FDA would seek a classification recommendation from the Orthopedic/Dental Advisory Panels. The device to be classified would be defined as including allograft bone that is processed ONLY to demineralize and preserve the bone, and ONLY intended to be used as a bone filler in orthopedic and/or dental procedures.

Based on current information, FDA expects to propose that demineralized allograft bone be regulated as a Class I medical device exempted from premarket notification. In addition, FDA expects that it would also propose to exempt demineralized allograft bone from the GMP requirements except for certain requirements consistent with those proposed for human tissues regulated under section 361.

To ensure that the GMP requirements applicable to demineralized bone are ultimately consistent with the requirements for human cellular and tissue-based products regulated under section 361, the Federal Register documents regarding the requirements for each would be published as companion documents.

VII. CONCLUSION

The agency believes that the above-described proposed approach to the comprehensive regulation of cellular and tissue-based products would provide adequate protection of public health, both from the risks of transmission of communicable disease and from the risks of therapies that may be dangerous, while enabling investigators to develop new therapies and products with as little regulatory burden as possible. The agency intends for this regulatory scheme to encourage research and innovation, while at the same time set boundaries between the kinds of experimentation with human products that warrant only minimal FDA oversight and the kinds of experimentation with human products that warrant greater FDA oversight.

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[9] In contrast to how it would regulate demineralized bone, FDA would regulate powdered bone (freeze dried bone allograft) under section 361 (falling in rows B2a and C1 of Table 1), because the bone is only minimally manipulated - the processing does not change the integral structure of the bone.

GLOSSARY OF TERMS AS USED IN THIS DOCUMENT

ablation	Removal or destruction
allogeneic use	Cells or tissue transplanted from one person to another.
autologous use	Cells or tissue removed from and transplanted back into the same person.
close blood relative	A first degree blood relative (i.e., parent, child, or sibling).
cord blood	Blood in the placenta and umbilical cord, e.g., blood taken at the time of birth
family relative	A first degree blood relative (i.e., parent, child, or sibling).
hematopoietic	Giving rise to the cellular elements of the blood (e.g., white blood cells, red blood cells, platelets).
hematopoietic Stem cells	Cells capable of generating white blood cells, red blood cells, and platelets. For the purposes of this document, these would include progenitor cells that are committed to develop into a particular cellular lineage. Hematopoietic stem cells presently can be collected (as a very small fraction of the cells) from peripheral blood, placental/umbilical cord blood, and bone marrow, often for transplantation into patients whose own hematopoietic stem cells have been destroyed by anticancer treatment or disease
homologous function	Use for the normal function of the cell or tissue, and, for structural tissue, use for a structural purpose in a location of the body where such functional purpose normally occurs (see P. 15).
MAS cells	Manipulated Autologous cells for Structural use
metabolic use	For systemic effect.

minimal manipulation	Processing that does not alter the biological or relevant functional characteristics of cells or tissue (see P. 13).
more-than-minimal manipulation	Processing that alters the biological or relevant functional characteristics of cells or tissue (see P. 13).
non-homologous function	Use for other than the normal function of the cell or tissue, or for structural tissue, use for a structural purpose in a location of the body where such functional purpose does not normally occur (see P. 15).
peripheral blood	Circulating blood (in contrast to, for example, blood in bone marrow)
reproductive tissue	Semen, ova, embryos.
reproductive use	To treat infertility.
stem cells	Cells capable of replicating themselves and of generating more-differentiated daughter cells.
structural use	For anatomic reconstruction or repair.
unrelated	Someone other than a close blood relative.

RELATED PRODUCTS

PROPOSAL FOR SPECIFIC COMMUNICABLE DISEASE CONTROLS[1]

	Testing[2]									Screening				Quarantine[3]
	HIV	HCV	HBV	HTLV	CMV	Treponema pallidum	Chlamydia trachomatis	Neisseria gonorrhea		High risk for HIV & Hepatitis	CJD screen[5]	TB screen		
2a Autologous Banked Tissue														
Stem Cells	R	R	R	R						R				
Other Autologous Tissue	R	R	R							R				
2b Allogeneic, Nonviable Tissue	X	X	X			X				X	X	X		R
2c Allogeneic, Viable Tissue														
Stem cells from Family-related donors	X	X	X	X	X	X				X	X	X		
Reproductive Tissue from Sexually Intimate Partners	R	R	R	R	R	R	R	R		R	R	R		
Other Reproductive Tissue (including directed donors)	X	X	X	X	X	X	X	X		X	X	X		X
Other allogeneic Viable Tissue[4]	X	X	X	X	X	X				X	X	X		R

Legend:
X-required
R-recommended, for tests; labeling as: 'tested/negative', or 'not tested for biohazards' will be required.

notes:

[1]Banked tissue for autologous use, from allogeneic family-related donors, from directed reproductive tissue donors, from sexually intimate partners, or in cases where there is a documented urgent medical need from a donor who has a positive risk factor and/or tested positive for an infectious disease agent, will not be required to be destroyed if:

a) the product is labeled 'BIOHAZARD' or 'untested for BIOHAZARDS', as applicable
b) autologous tissue is labeled 'FOR AUTOLOGOUS USE ONLY'
c) written advance informed consent of the recipient is documented
d) there is documented knowledge and authorization of the recipient s physician

Tissue unsuitable for transplantation may be used for non-clinical research purposes if labeled 'BIOHAZARD' or 'untested for BIOHAZARDS', and 'FOR RESEARCH USE ONLY'

[2]For autologous or allogeneic cord blood donors, a mother's sample may be used for screening and testing.

[3]For allogeneic tissue that can be stored, quarantine for six months pending retesting of the donor will be required for all reproductive tissue, excluding sexually intimate partners. For other banked tissue and cells from living donors, quarantine for six months pending retest of the donor, or of the mother will be recommended, where appropriate and feasible, not required.

[4]Requirements for HTLV and CMV testing only apply to leukocyte rich tissue (e.g. stem cells); they will not apply to cornea or skin donors.

[5]For dura mater donors, in addition to history for risk factors, a gross and histological examination of brain tissue will also be required.

Table 1

Relationships among product concerns, product characteristics, regulatory approaches

Product Concern	Product Characteristic (Product Factors)	Industry Action Required	Regulatory Submission
A. Direct transmission of communicable disease (e.g., donor screening and testing)	1. SURGERY (Cells or tissue are removed from and transplanted back into the same person in a single surgical procedure)	1. None.	1. None
	2a. AUTOLOGOUS banked/processed/shipped; REPRODUCTIVE from sexually intimate partner	2a. Screening, testing recommended; other GTPs would be required, e.g., recordkeeping, labeling, product tracking, recalls, notification of communicable disease transmission.	2a 2b 2c. No FDA submission. Requirements would be set in new final rule for allogeneic tissue-related products under section 361 (finalization of the interim final rule), and in rulemaking under sections 361 and 351 which would add more products and more specific testing requirements.
	2b. ALLOGENEIC, nonviable tissue 2c. ALLOGENEIC, viable tissue	2b, 2c. GTPs would be required e.g., screening, testing, recordkeeping, labeling, product tracking, recalls, notification of communicable disease transmission.	
B. Control of Processing Improper handling or inadequately controlled processing may result in product contamination and consequent communicable disease transmission;	1. SURGERY (Cells or tissue are removed from and transplanted back into the same person in a single surgical procedure.)	1. None	1. None
or in failure to preserve product integrity and function, and consequent enhanced susceptibility to communicable disease;	2. MINIMALLY MANIPULATED & homologous function & no non-tissue components, and structural, reproductive, or autologous/related-allogeneic metabolic	2. GTPs relating to contamination, integrity and function.	2. No FDA submission regarding processing. Requirements would be set in rulemaking under section 361.
or in failure to preserve product integrity and function with resulting unsafe or ineffective products.	3. MORE-THAN-MINIMALLY MANIPULATED or non-homologous function or non-tissue components or unrelated metabolic	3. Would have to follow GMPs and have stricter processing controls encompassing clinical safety and effectiveness concerns.	3. A marketing application would ordinarily be required to contain a CMC section. If determinations are made that the safety and effectiveness of a product category can be assured by meeting product specifications and processing controls, then applicants would need only to submit a certification that they meet the product specifications and processing controls.

Table 1 (continued)

C. Clinical safety (not restricted to communicable-disease risks); clinical effectiveness (including use-specific concerns). Attributes of importance are: **a) more than minimal manipulation;** **b) non-homologous use;** **c) combination with non-cell/non-tissue components;** **d) metabolic use (other than reproductive) except when used autologously or in a close family member.**	1. Product is without any of factors a, b, c, or d. 2. Product is for local, structural reconstruction or repair and has factors a, b, or c. 3. Product is for reproductive or metabolic use with factors a, b, c, or d.	1. None. 2. Would have to gather clinical safety and effectiveness data. 3. Would have to gather clinical safety and effectiveness data.	1. No FDA submission. 2. Studies would have to be done under IND or IDE; Marketing application would have to be submitted (BLA, 510(k) or PMA); standard for determination of effectiveness would be consistent with that for devices. Standards for manipulated autologous structural cells would be as described in MAS cell policy guidance. 3. Studies would have to be done under IND; marketing application would have to be submitted (BLA); standard for determination of effectiveness would be consistent with that for biologics.
D. Promotion and labeling	All cellular and tissue-based products (excluding cells and tissues that are removed from and transplanted back into the same person in a single surgical procedure).	Clear, accurate, balanced and non-misleading labeling	No FDA submission concerning labeling for products regulated only under section 361 (providing claims are limited to those within homologous use). For products regulated under section 351 or as a device, the usual rules would apply concerning labeling.
E. Baseline Knowledge of Industry	All cellular and tissue-based products (excluding cells and tissues that are removed from and transplanted back into the same person in a single surgical procedure).	Notification of FDA	Registration and listing under new regulation under 361 or under sec. 510 of the FDC Act.

ITINERARY
October 20-21, 2000

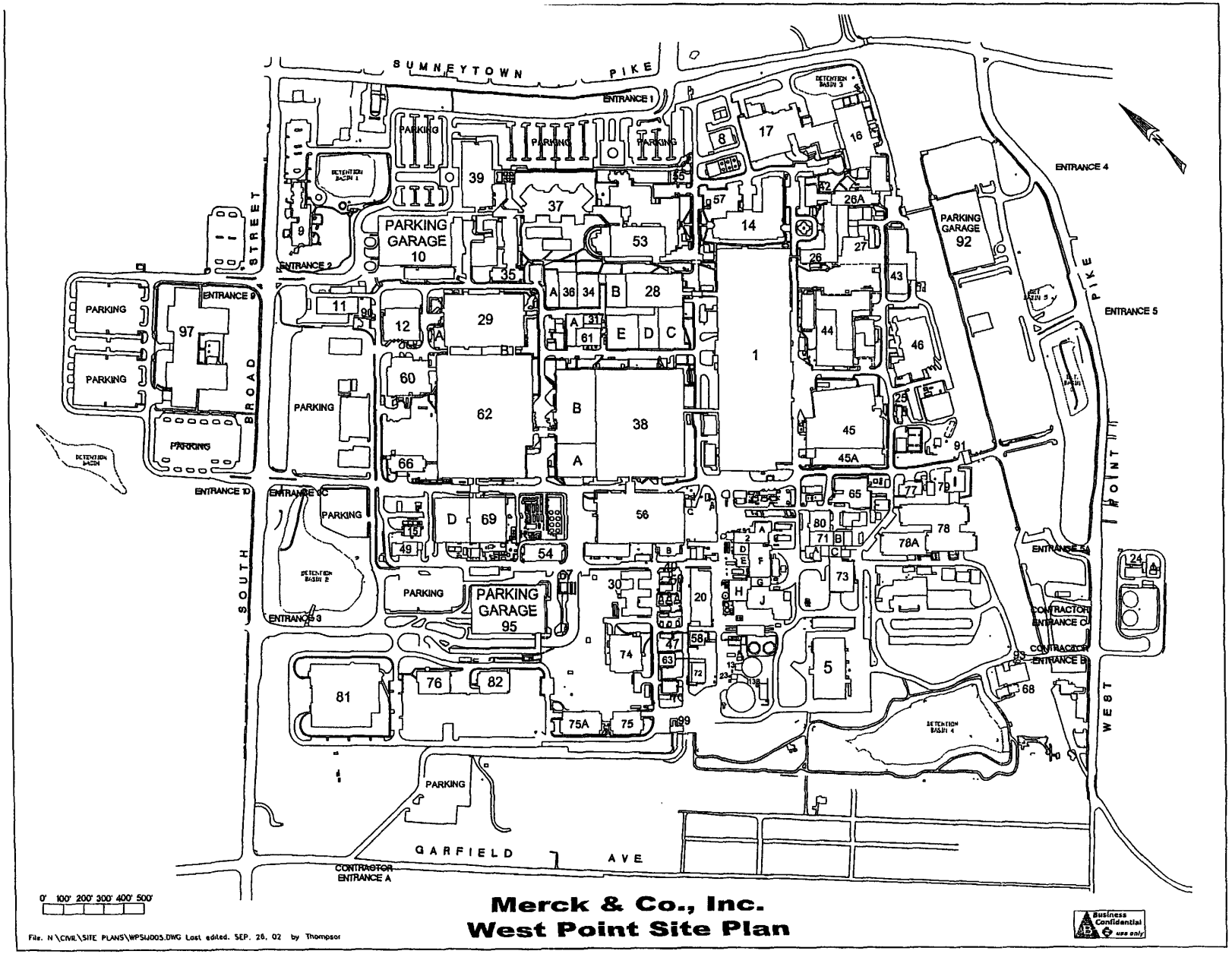
Ms. Chao-Yi Wang, Staff Officer and Dr. Yi-Jiun Huang, Senior Researcher
Bureau of Pharmaceutical Affairs
Taiwan Department of Health

October 20, 2003 (Monday)

9:45	Pick-up from the 30th Street Station	
11:00-12:00	**MRL Drug Discovery** *Mr. Jeff Garelik, MRL Training and Development*	WP53B, 2nd floor, Polo C
12:00-1:00	**Lunch** *International Registration Team*	WP 53B, NY Room
1:00 -2:00	**Assay Development and Validation** *Dr. Don Lineberger, Vaccine Regulatory and Analytical Sciences*	WP37A-1002
2:00- 3:00	**Sterile Product Release** *Mr. Pete Mlynarczyk, Biological Product Release*	WP35-2060
4:00-5:00	**Tour of the Biologics Pilot Plant** *Dr. Joye Bramble and Mr. Marshall Gayton, Bioprocess R&D*	WP17
5:00	**Depart for Hotel**	
6:30	**Dinner** *Ms. Kimberly Bradely, Dr. Paul Coplan, Dr. Elaine Esber.*	

October 21, 2003 (Tuesday)

8:45	Pick-up from the Marriott Courtyard	
9:00-10:45	**Clinical/Regulatory programs presentations** - **Zoster and HIV programs** *Dr. Paul Coplan* - **Rotavirus Program** *Dr. Mark Bagarazzi, Dr. Jackie Miller*	BL10-234
10:45-11:45	**Safety Surveillance** *Ms. Sheila Cook, Worldwide Product Safety and Epidemiology*	BL10-234
11:45-1:00	**Lunch** *Dr. Mark Bagarazzi, Dr. Ron Moss.*	
1:00- 2:00	**Tour of Locally Controlled Environment Filling/Formulation Facility** *Mr. Barry Starkman, Biological Product Release*	WP38-Main Entrance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ENTRANCE 9
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BROAD STREET
SOUTH BROAD STREET
WEST POINT PIKE
GARFIELD AVE
CONTRACTOR ENTRANCE A
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Merck & Co., Inc.
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&
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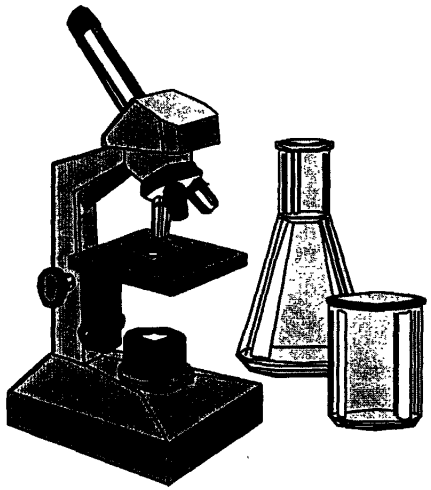
Jeff Garelik
MRL Training & Development



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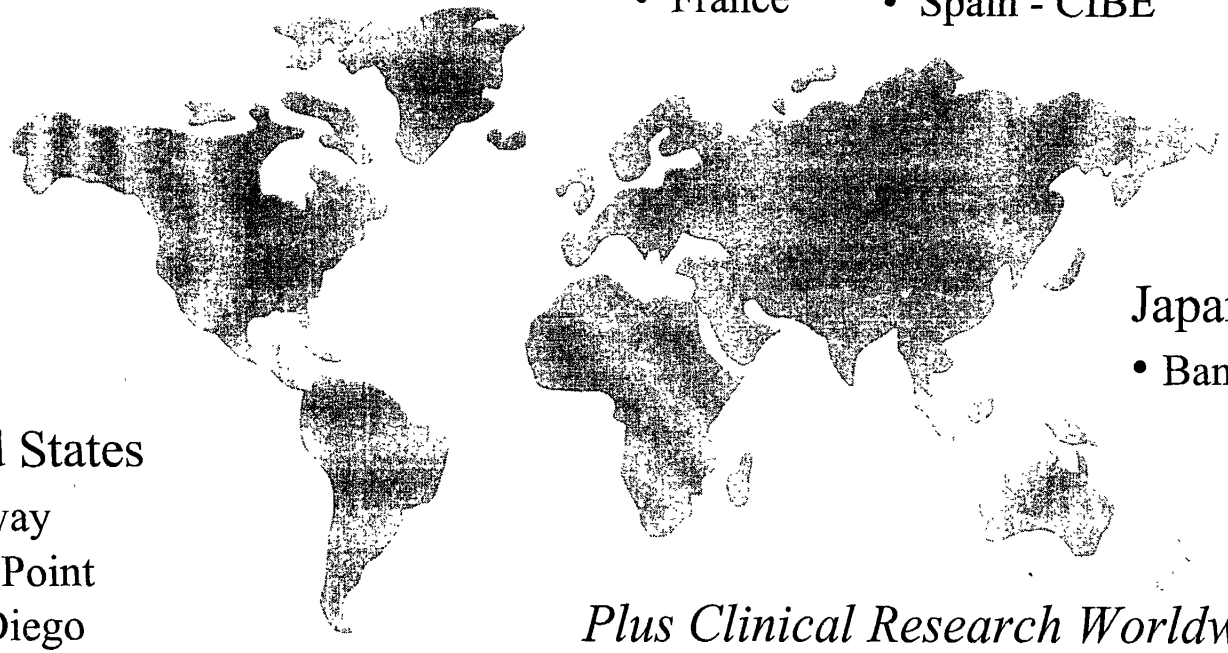

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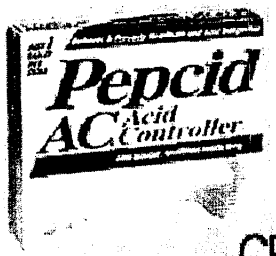

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Cardiovascular disease	*Aldomet, Blocadren,* **Vasotec**, *Prinivil, Plendil, Aggrastat, Cozaar / Hyzaar*
Cholesterol-lowering	**Mevacor**, *Zocor, Zetia*
Endocrine & Metabolic diseases	**Pepcid**, *Proscar, Fosamax, Propecia, Emend*
Allergy & Inflammatory diseases	*Indocin, Clinoril, Dolobid, Vioxx, Singulair*
Infectious diseases	*Mefoxin, Primaxin, Noroxin, Mectizan, Crixivan, Stocrin, Cancidas, Invanz* > river blind.
Neurologic disorders	*Sinemet, Maxalt*
OTC programs	*Pepcid AC, Mylanta*
Vaccines	*MMR II, Varivax, Vaqta, Recombivax HB, Pneumovax 23, Meningovax, PedvaxHIB*
Ophthalmics	*Timoptic, Trusopt, Cosopt*
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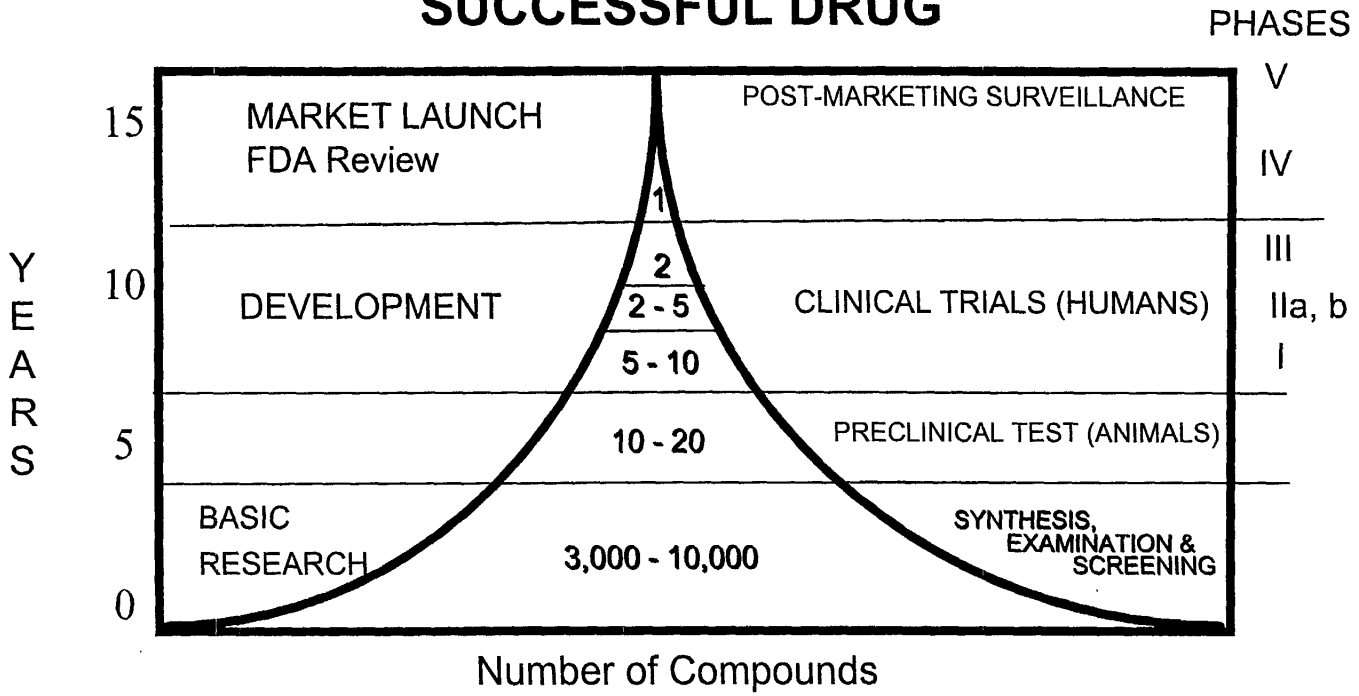
- Cancer
- Arthritis
- AIDS
- Asthma

R&D: SCIENTIFIC RISK

Est. cost: $500 - 800 million

DISCOVERY AND DEVELOPMENT OF A SUCCESSFUL DRUG



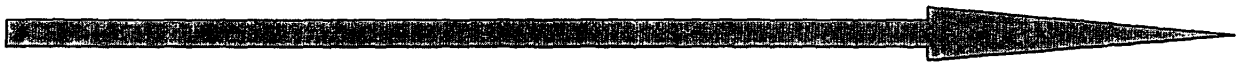
Source: Based on PhRMA analysis, updated for data per Tufts Center for the Study of Drug Development (CSDD) database.

Highly regulated industry
People's lives and quality of life depend on our success
Shareholders demand a return on their investment

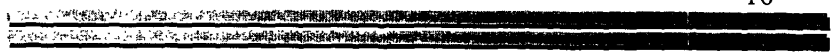
Need to invest $ billions every year
Need to motivate & attract talented people
Need to innovate
Need a lot of luck!!

The Process

Basic Discovery	*Preclinical*	*Clinical*
Biology	Process Chemistry	Clinical Research
Medicinal Chemistry	Safety Assessment	Regulatory
	Drug Metabolism	BARDS, etc.
	Pharmaceutical R &D	

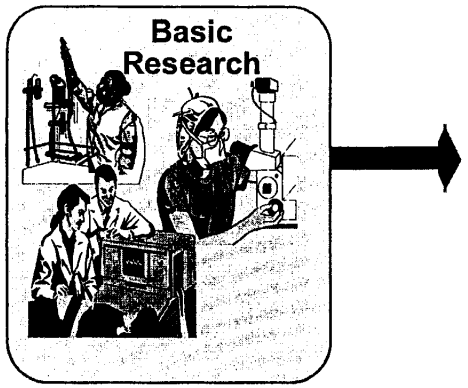


Identify target	Scale up?	Bioavailable in humans?
Find actives --> leads	Safe?	Dose? Safe? Effective?
In-vitro binding	Bioavailable?	
Structure-Activity	Dosage form?	
Relationship (SAR)		

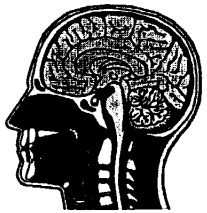


Strategy For Drug Discovery

- Understand the molecular basis of the disease
- Select & validate a therapeutic target
- Link the therapeutic target to a defined mechanism
- Discover a chemical lead (drug compound) that is novel & works in-vitro



A + B ---> C



Identify & validate a TARGET

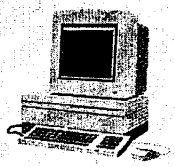
Screening

A + B ---> C

x ?

Chemical compounds

Computer Models



+ license in

Basic Laboratory Research

SAR & Combinatorial Chemistry
High Throughput Screening
Data Analysis
=> actives

Genomics:
- Bioinformatics
- Proteomics
- Genes on a chip

Synthesis / modification to optimize the compound

Issues in Drug Discovery & Development

Basic Research

- Assemble high quality compound collections with a high proportion of actives
- Maximize our use of robotics & HTS
- Efficiently evaluate all of the data

- Understand disease mechanisms
- Identify targets / receptors that matter
- Collaborate efficiently with others
  - *for example: material transfers*
- Understand the impact of genetic variability in disease processes

Basic Research

Biology

- Animal Health
- Animal Pharmacology
- Antiviral Research
- Atherosclerosis & Endocrinology
- Automated Biotechnology
- Biochemistry & Enzymology
- Bioinformatics
- Bone Biology
- Cancer Research
- Endocrinology & Cell Biology
- Genetic & Cellular Toxicology
- Immunology & Rheumatology
- Metabolic Disorders
- Virus & Cell Biology
- Neuro Bio & Pharmacology
- Genomics, Molecular Profiling

Chemistry

- Medicinal Chemistry
- Molecular Modeling, Design & Diversity
- Analytic Research

PCC

WW Licensing &
External Research

PreClinical

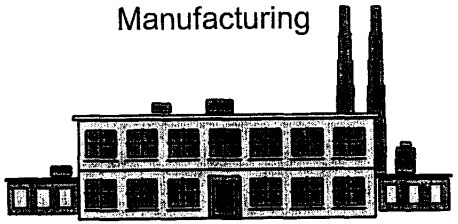
Drug Metabolism
(ADME)

Pharmacology

Comparative Medicine
Lab Animal Resources

Process R&D
Chem Eng. R&D
Manufacturing

Safety Assessment
Toxicology



IND

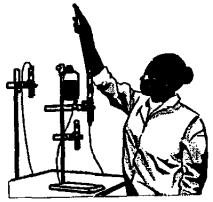
Bio Process R&D

Clinical Investigator
& patient (Hospital)

Pharmaceutical R&D
Formulation

Development

Clinical
- Resp. & Allergy
- Metabolism
- Endocrinology
- Clinical Oncology
- Immun. & Analgesia
- Clinical Pharmacology
- Infectious Diseases
- Biologics
- HIV Vaccines
- Cardiovascular
- Clinical Neuroscience &
  Opthalmology
- GI



CROPS
Clin. Res. Ops.

WRAPS (WW Regulatory &
Product Safety
- Global Stategic Reg. Devel.
- Global Regulatory Affairs
- WW Product Safety & QA

BCD (BARDS, CROPS, Data)
- Statistics & Epidemiology
- Data Coordination (BARDS)
- WW Clinical Data Mgmt Op (WCDMO)

Project Planning & Development
WW Strategic & Capital Planning

Research Information Systems (RIS)
Information Services (IS)

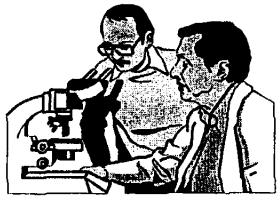
Marketing

Merck Research Laboratories

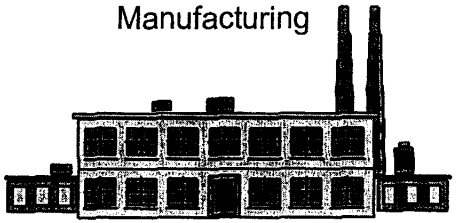
Preclinical

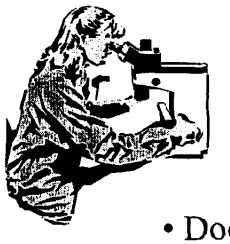
Pharmacology

- Does the compound bind to the target in-vivo?



Process R&D
Chem Eng. R&D
Manufacturing





Drug Metabolism
(ADME)

- Does the compound get into the circulation?
- Is it destroyed by the liver?
- How long does the compound remain in the body before it is excreted?

Pharmaceutical R&D
Formulation

- How will the compound be delivered?
- Will it be stable?
- Can it be stored? How? For how long?
- Should the compound be protected from stomach acid?

Bio Process R&D

- Can the compound be made efficiently, safely in large amounts with reasonable yields?

Safety Assessment
Toxicology

- Is the compound toxic?
- Is it a teratogen?

Early
Development
Teams (EDT)

Investigational New Drug application

IND →

Clinical Trials

Project Development Teams (PDT)

Project Teams

Phase I

Product Profile ⟹ Marketing SOI

12 - 80 normal, healthy volunteers

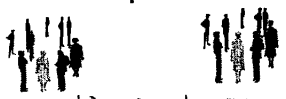
1. Absorption and metabolism
2. Effects on organs and tissue
3. Safety

Phase II

100 - 300 patients

Treatment Group Control Group

Gold standard



dB. Randomize.

1. Effectiveness in treating disease
2. Short-term side effects in patients
3. Dose ranging

IIa - proof of concept

IIb - dose ranging

Phase III

1,000 - 15,000 patients

1. Safety & efficacy in patients
2. Less common and longer term side effects
3. Labeling information

Compassionate Use

Clinical Trials
Continued

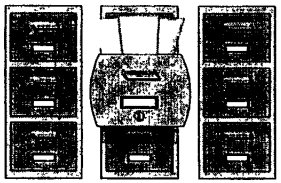
Advisory Committee

Regulatory Review Team

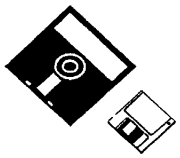
APPROVAL PROCESS
(Ex. FDA)

Reviews, comments, and discussions

Submit to Regulatory Agencies



New Drug Application (NDA)



Merck/Regulatory liaison activities

APPROVAL
- package circular

Worldwide Marketing Authorization (WMA) in other countries

Development

- *Can we speed up drug development overall?*
  - Can we identify the genetic phenotypes of our lab animals?
    - *Does that effect their susceptibility to drug toxicity?*
    - *Is it different from humans?*
    - *Can we link genetics to outcomes?*
  - Can we continue to identify realistic animal models?
  - Can we identify & license compounds, tools, etc. that complement our internal research activities?
  - Can we continue to coordinate the massive personnel & logistics to efficiently complete multi-center clinical trials worldwide?
  - Can the industry sustain the economic ratios that makes investment in drug discovery & development possible?

Future of the Labs

- Truly global research system
- Rational drug design
- Reach maximum efficiency

- Incorporate pharmacogenomics into discovery
- Genetic profiles (proteomics) will influence the complex decisions that drive research direction

"We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear…

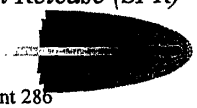
How can we bring the best of medicine to each and every person? We cannot rest till the way has been found, with our help, to bring our finest achievement to everyone."

- - -George W. Merck

Thank you very much

MERCK
Research Laboratories

Sterile Product Release (SPR)



Department 286

Why do we need a release department?

- The Code of Federal Regulations (CFR) 21 CFR Part 210 and 211 [written by the FDA states]:
  - "There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, ..."

Release Requirements

- Satisfactory testing by the Quality Control Laboratories: CFR 211.165
- Satisfactory documentation of the manufacturing process: CFR 211.192
- CBER (Center for Biologics Evaluation and Research) Release

Determining and Evaluating the Testing

- Every product has a Quality Standard that lists all test requirements with the pass/fail specifications
- The manufacturing unit takes samples at required time points and submits them to the laboratories for testing.
- The release group evaluates the testing as it is completed.
- All lots with failing test results are quarantined for laboratory and manufacturing investigations.

Evaluating the Manufacturing Document

- Production personnel document all manufacturing steps in an approved document.
- Production supervisor reviews the document to make sure everything is satisfactory. Stages document for release.
- Sterile Product Release (SPR) Associates reviews and return with comments.
- SPR and Production work together to settle comments, if required.
- SPR associate signs the end of the document.

APRs

(Atypical Process Reports)

- Written to address unplanned events that may affect the quality of the product
- Authored by Production/Technology
- Approval required by Production and Technology management
- SPR performs final report approval
  - establishes final product disposition
  - approves corrective/additional actions (CAFU)

Contextual Review

- What is it?
  - Composite Review of Quality Issues
    - Testing - Release & Environmental
    - Accountability
    - Investigations
    - Quarantine closure evidence
    - Previous Contextual Review on Inputs
- Purpose is to ensure combination of issues do not impact product quality

CBER Release

- All testing and document review is complete
- SPR puts together a protocol with all of the test results.
- SPR sends the protocol with samples to CBER.
- CBER reviews the protocol and may or may not test the samples.
- CBER sends SPR a release memo for the lot.

Recapping the Release Process

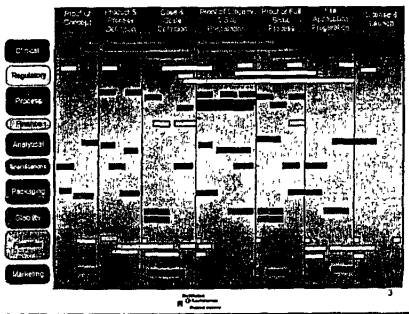
- Document Review
- Evaluate Testing vs. Quality Standard
- Ensure Quarantines Resolved
- Investigation Review & Approval (APR)
- Contextual Review
- Protocol Assembly, Review, & Approval
- CBER Review and Approval
- System Release

Analytical Development in Biologics

Donald Lineberger
Vaccine Regulatory and Analytical Sciences

Analytical Development in Biologics

- Outline of Presentation
  - Overview of Product Development
  - Analytical Development
  - Assay Validation
  - Setting Specifications



Analytical Development in Biologics

- Analytical Development
  - Commensurate with development of manufacturing process
  - Determine the characteristics of the product that are critical to defining its identity, purity, potency and stability
  - Develop, validate and implement quality control testing
  - Establish appropriate specifications

Analytical Development in Biologics

- Analytical Development Plan
  - Entire scope of analytical development
  - Provides direction and tracking of analytical activities
  - Refined throughout the process of product development

Analytical Development in Biologics

- Validation of Analytical Procedures
  - ICH Guidelines
    - Topic 2QA, Text on Validation of Analytical Procedures
    - Topic 2QB, Validation of Analytical Procedures: Methodology
  - USP 26, <1225> Validation of Compendial Methods

Analytical Development in Biologics

- Validation of Analytical Procedures
  - Types of Procedures to be Validated
    - Identification Tests
    - Quantitative Tests for Impurities
    - Limit Tests for the Control of Impurities
    - Quantitative Tests of the Active Moiety

7

Analytical Development in Biologics

- Validation of Analytical Procedures

"The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which will need to be evaluated."

8

Analytical Development in Biologics

- Validation of Analytical Procedures
  - Typical Validation Characteristics
    - Accuracy
    - Precision
      - intra-assay precision (repeatability)
      - intermediate precision (within laboratory variations)
      - reproducibility (between laboratory variations)
    - Specificity
    - Detection Limit

9

Analytical Development in Biologics

- Validation of Analytical Procedures
  - Typical Validation Characteristics (cont.)
    - Quantitation Limit
    - Linearity
    - Range
    - Robustness
    - Ruggedness

10

Analytical Development in Biologics

- Validation of Analytical Procedures
  - Who Performs Validation?
    - New assays/products - typically Merck Research Laboratories
    - Revalidation - Merck Manufacturing Division or Merck Research Laboratories
      - change in manufacturing process
      - composition of finished product
      - changes in analytical procedure

11

Analytical Development in Biologics

- Setting Specifications
  - ICH Guideline
    "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products"
  - Merck Biological Specifications Guideline

12

Analytical Development in Biologics

- Setting Specifications
  - Establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.
  - Part of a total control strategy to ensure quality and consistency.

13

Analytical Development in Biologics

- Setting Specifications
  - Origin of Specifications
    - Scientific literature
    - Clinical
    - Regulatory requirements
    - Research and manufacturing data

14

Analytical Development in Biologics

- Setting Specifications
  - Developing or Revising Specifications
    - Classification of method
    - Correlation to current method
    - Type of specification required
    - Requirements for the specification
    - Relationship to the current specification
    - Required or available data

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Analytical Development in Biologics

- Setting Specifications
  - Specification Development Planning
    - Rationale must be defined
    - Purpose of the specification
    - Representative data from typical manufacturing used to set specification (unless other requirements exist)
    - Manufacturing risk
    - Owner of periodic review of the specification

16

Analytical Development in Biologics

- Setting Specifications
  - Biological Specification Subcommittees
    - Ensure uniform, prospective, systematic approach to setting/re-evaluating specifications across product lines
    - Ensure proper documentation to track origin and evolution of product specifications
    - Establish partnership between Merck Research Laboratories and Merck Manufacturing Division

17

92.10.20

Safety Surveillance at Merck

Sheila B Cook
Director, Adverse Experience Reporting
Worldwide Product Safety & Epidemiology

Safety Surveillance at Merck

I Worldwide Product Safety and Epidemiology (WPS&E)

- Who are we?
- What is our role as a department?
- What are our specific responsibilities?

II Adverse Experience Collection

- Worldwide Sources
- Worldwide Procedures

A Clinical Trials
B Spontaneous (Voluntary)
C Other Reportable Events

- Worldwide Systems

A WAES
B WAES*Net
C New WAES

Safety Surveillance at Merck

III Adverse Experience Processing (including Medical Review)

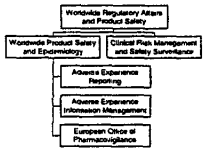
IV Adverse Experience Reporting to Regulatory Agencies

- Expedited (Prompt) Report (Single Case)
- Periodic Report (Summary of aggregate data)

V Communication of Safety-Related Information to Regulatory Authorities

VI Summary

Safety Surveillance at Merck



→ 20~30 人.

Role of Worldwide Product Safety and Epidemiology (WPS&E)

- Ensure the timeliness and appropriateness of reporting to Regulatory Agencies worldwide

Role of Clinical Risk Management and Safety Surveillance (CRMSS)

- Apply the highest quality clinical expertise and judgment in promptly evaluating, identifying, and describing the safety profiles of Merck marketed products.
- Review and provide expert advice on specific safety issues for investigational products and plans for post-marketing pharmacovigilance

What Do We Do?

Adverse Experience Reporting

1 Regulatory Compliance

- Domestic → FDA
- Worldwide → Merck Subsidiary → Local Agency

2 Follow-up of Reports

- Domestic - Direct contact
- Worldwide - Via subsidiaries

3 Business Partner Agreements

4 Quality Control of Data

- Accuracy
- Completeness
- Timeliness

What Do We Do?

Adverse Experience Reporting

5 Education and Training

- Domestic - Local FDA requirements
- Worldwide - Company standards

What Do We Do?

Clinical Risk Management and Safety Surveillance (CRMSS)

1 Clinical Review of Adverse Experience (AE) Information

2 Medical Evaluation of AE Information

3. Review of Product Label
   - Domestic Label (marketed products)
   - Worldwide Core Safety Data Sheet

4 Medical/Legal Review of Promotional/ Advertising Material

5 Provide answers to ad-hoc safety questions
   - Internal customers
   - External customers

Clinical Risk Management and Safety Surveillance (CRMSS)

- **CRMSS Physicians**
  - Responsible for specific products
  - Internal specialists
- **CRMSS Associates**
  - Advanced practice nurses/pharmacist
  - Assist MDs
    - Especially with follow-up of SAEs

Ensuring completeness and accuracy medical data

- Telephone follow-up of 15-day AEs and all AEs of concern in USA
- Review of serious AE reports for medical content, AE coding, etc

Ensuring completeness and accuracy medical data

- Monitor AE reports for signals of possible unrecognized adverse effects
  - continuous
  - regular periodic (Adverse Experience Review Team)
- Review signals in context of clinical and pre-clinical data
- Follow-up signals
  - confirm
  - characterize
  - label
- Respond to safety inquiries and labeling requests from regulatory authorities
- Periodic Safety Update Reports (E2C)

What Do We Do?

Adverse Experience Information Management

1 Maintain and develop output reports from worldwide safety database

2 Maintain and develop output reports from Optical Imaging System

3 Maintain and provide enhancements for follow-up correspondence system

4 Maintain dictionaries and validation files needed for worldwide reporting

5 Generate Safety Update Reports

- ICH E2C content and format

What Do We Do?

European Office of Pharmacovigilance - UK

1 Appointment of "qualified person" responsible for Pharmacovigilance in the European Union (EU)

2 Submits reports originating outside the EU on behalf of EU Merck subsidiaries

3 Coordinates EU pharmacovigilance activities

4 Works with each EU subsidiary designated "qualified person"

Adverse Experience Collection

Worldwide Procedures

- Investigational Studies (Pre-marketing)
- Spontaneous (voluntary) Reports on Marketed Products

  → detect early warning "signals" of safety concerns not recognized in pre-marketing clinical trials

  - involves ADR monitoring to detect signals
  - involves epidemiology to generate hypotheses and assess signals

- Post-marketing Safety Surveillance Studies (PMS)
- Literature
- Agency Reports

Adverse Experience Collection

Worldwide Procedures

A. Clinical Trials

- Unexpected Fatal or Life-Threatening Experience
  - Verbal report to WPS&E (Headquarters) immediately
  - Written report to WPS&E within two (2) working days from date of first Company notification

Adverse Experience Collection

Worldwide Procedures

A. Clinical Trials

- Alarming Events (risk outweighs benefit)
  - Verbal report to WPS&E (Headquarters) immediately
  - Written report to WPS&E within two (2) working days from date of first Company notification

Adverse Experience Collection

Worldwide Procedures

A. Clinical Trials

- Serious
  - To WPS&E (Headquarters)
  - Within two (2) working days from date of first Company notification
  - Pertains to initial and follow-up
  - Regardless of relationship to study drug or vaccine

Adverse Experience Collection

Worldwide Procedures

A Clinical Trials

- Non-Serious
  - To subsidiary and Clinical Group (Headquarters) according to time frames defined per protocol

Adverse Experience Collection

Worldwide Procedures

B Spontaneous → voluntarily

- Serious
  - To WPS&E
  - Within two (2) working days from date of first Company notification
  - Pertains to initial and follow-up

Adverse Experience Collection

Worldwide Procedures

B Spontaneous → voluntarily

- Non-Serious
  - To WPS&E
  - Within ten (10) working days from date of first Company notification
  - Pertains to initial and follow-up

Adverse Experience Collection

Worldwide Procedures

C Other Reportable Events

- Pregnancies
- Human exposure to agricultural/ veterinary products
- Serious adverse experiences from regulator databases

2 working days to WPS&E

Adverse Experience Collection

Worldwide Systems

A WAES (Worldwide Adverse Experience System)*

WAES is a central source of safety information for

- reporting to regulatory agencies
- monitoring safety profile of Merck products
- reviewing package circular labeling
- answering ad-hoc safety questions

*NewWAES = 20 October 1997

Adverse Experience Collection

Worldwide Systems

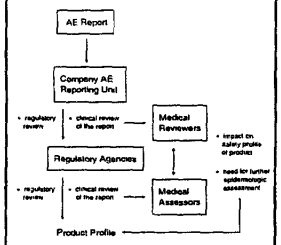
B WAES*New/NWAES

- A network system for remote data collection and electronic transmission
- Provides a local database for subsidiaries to meet local regulatory requirements

C NewWAES Rollout to Subsidiaries

- EU Office of Pharmacovigilance and UK Subsidiary - June 15, 1998
- 15 sites -- 1999
- 13 sites -- 2000
- 10 sites -- 2001

Adverse Experience Information Flow



Adverse Experience Review

Document Worklow

AE Document(s)
- WAES*Net
- Non-WAES Net (optical imaging system)

AER Coordinators
- Quality Control WAES*Net elements
- Determine local (FDA) reportability
- Determine worldwide reportability
- Abstract and data enter AE information
- Determine local (FDA) reportability
- Determine worldwide reportability

CRMSS Physician
- Medical review
- Follow-up (indirectly via subsidiary)
- Medical review
- Follow-up (directly with reporter)

AER Managers
- Regulatory review
- Regulatory review

AER Coordinators

FDA — Worldwide Merck subsidiaries

Adverse Experience Reporting to Worldwide Regulatory Agencies

What to Report on an Expedited (Prompt) Basis?

- Single cases that are both serious and unexpected
  - Causality assessment needed for clinical trial reports
  - Implied causality for spontaneous cases

Adverse Experience Reporting to Worldwide Regulatory Agencies

When should expedited (Prompt) Reports be made?

- Unexpected fatal or life-threatening adverse drug reactions (ADRs from clinical trials)
  - FAX/Verbal
    - no later than seven (7) calendar days - ICH E2A
  - Written follow-up
    - within eight (8) additional calendar days - ICH E2A

Adverse Experience Reporting to Worldwide Regulatory Agencies

When should expedited (Prompt) Reports be made?

- All other serious, unexpected ADRs
  - No later than 15 calendar days - ICH E2A

Adverse Experience Reporting to Worldwide Regulatory Agencies

What to Report in Periodic Safety Update Reports (SUR)?

- ICH E2C Guideline (CIOMS II) - General Principles
  - one report for one active substance
  - relevant clinical and non-clinical safety data
  - main focus on adverse drug reactions (ADRs)
  - arrangements for multiple-manufacturer sourced products
  - international birthdate (IBD) determines the data lock point (cut-off date for data inclusion in SUR)
  - data sets of six months or multiples thereof
  - submission of SUR within 60 days of data lock point
  - Company Core Safety Information (CCSI) = reference document for determinaton of "listed" or "unlisted" AE terms

剛上市 1~3年 Quarterly
Yearly.

Adverse Experience Reporting to Worldwide Regulatory Agencies

What to Report in Periodic Safety Update Reports (SUR)?

- Format and Content
  - Introduction
  - Worldwide Market Authorization status (cumulative)
  - Update to reference Product Information
  - Patient Exposure
  - Individual Case Histories (line listing, tabulation, or both)
  - Studies
  - Other Information (eg Special Populations)
  - Overall Safety Evaluation
  - Conclusion

Adverse Experience Reporting to Worldwide Regulatory Agencies

When should Periodic Reports be made for marketed products?

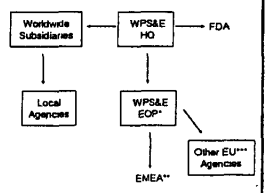
- ICH E2C Guidelines
  Per local requirements - based on six (6) month data sets

Communication of Safety-Related Information to Regulatory Authorities

Routine

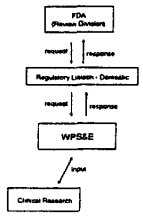
1. Adverse Experience Reporting to meet national and international reporting requirements
   eg
   - Expedited (CIOMS I) reports
   - Periodic Safety Update (ICH E2C) reports
2. Responses to Individual National Authorities' requests for information related to an adverse experience report
   eg
   - BfArM "step plans"
   - Scientific assessment of specific report
3. Labeling Changes

Routine - "Adverse Experience Reporting"



* EOP = European Office of Pharmacovigilance (UK)
** EMEA = European Medicines Evaluation Agency
*** EU = European Union

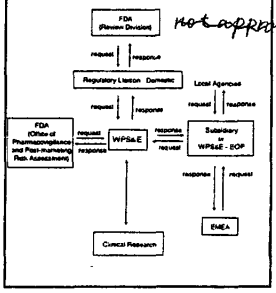
Routine - "Response to Safety Questions"



Liaison

clinical trial

Routine - "Response to Safety Questions"



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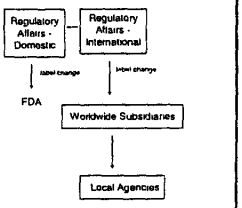
Routine - "Labeling Changes"



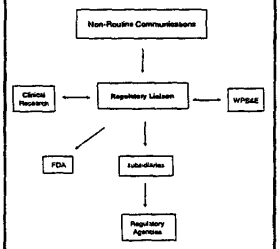
Communication of Safety-Related Information to Regulatory Authorities

Non-Routine

1 Urgent Safety Issue likely to lead to regulatory action
   eg
   - Urgent labeling change
   - Dear Doctor letter
   - New warning

2 Coordinated communication to multiple authorities

Non-Routine - "Communications"



Summary

Timely collection of adverse experience information

Timely medical review and evaluation

Timely identification of safety issues

Timely notification of health authorities, medical community, public