行政院所屬各機關因公出國人員出國報告

（出國類別：參加國際會議）

赴日本參加「第六屆人用藥品登記技術性要求一致化國際會議(ICH-6)」

出國報告

服務機關：行政院衛生署中醫藥委員會

出國人　職　　稱：薦任技士

　　姓　　名：張曼釗

出國地區：日本・大阪

出國期間：民國九十二年十一月十一至十一月十六日

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赴日本參加「第六屆人用藥品登記技術性要求一致化國際會議(ICH-6)」

出國計畫主辦機關／聯絡人／電話

中醫藥委員會　江盈盈　02-25872828 ext.267

出國人員姓名／服務機關／單位／職稱／電話

張曼釗　中醫藥委員會　科技政策小組　薦任技士　02-25872828 ext.288

出國類別：□1 考察□2 進修□3 研究□4 實習☑5 其他

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關鍵詞：藥品、法規、一致化、ICH

內容摘要：

「第六屆人用藥品登記技術性要求一致化國際會議〔THE SIXTH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE〕」 簡稱〔ICH-6〕於 2003 年 11 月 12 日至 15 日在日本中部大阪（Osaka, Japan）舉行。行政院衛生署中醫藥委員會為全國中醫及中藥最高主管機關，為積極推動中醫藥法規環境之建置，有必要了解國際法規之趨勢，期能於制定法規時能溶入國際趨勢，爰派員參加，此次參與會議者多達二千五佰餘人，主要參

與國家計有美、日、歐盟、加拿大、澳洲、 APEC 等三十餘國家地區，涵蓋全球 75%以上之藥品商業行為，會中就國際法規及審查藥品有效性、安全性、對病患之保護法規等一致化之工作進度、推行成效、未來展望及方向等議題廣泛討論，交換看法及意見。大會之議程共有 Shared Experience on the Implementation of the Common Technical Document、New Quality System Topic、Safety Pharmacology、Clinical Evaluation、Implementation Issues related to Existing ICH Guidelines 及 Future Challenges facing ICH 等主題，分別在不同的場地同步進行。討論內容包含：藥物安全性、有效性、人體臨床試驗規範、藥品警語標示及其他特別主題等討論會，本會將於爾後制定法規時將國際法規趨勢納入，以與國際同步。

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

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摘　　要

「第六屆人用藥品登記技術性要求一致化國際會議〔THE SIXTH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE〕」簡稱〔ICH-6〕於 2003 年 11 月 12 日至 15 日在日本中部大阪（Osaka, Japan）舉行。行政院衛生署中醫藥委員會為全國中醫及中藥最高主管機關，為積極推動中醫藥法規環境之建置，有必要了解國際法規之趨勢，期能於制定法規時能溶入國際趨勢，爰派員參加，此次參與會議者多達二千五佰餘人，主要參與國家計有美、日、歐盟、加拿大、澳洲、 APEC 等三十餘國家地區，涵蓋全球 75%以上之藥品商業行為，會中就國際法規及審查藥品有效性、安全性、對病患之保護法規等一致化之工作進度、推行成效、未來展望及方向等議題廣泛討論，交換看法及意見。大會之議程共有 Shared Experience on the Implementation of the Common Technical Document、New Quality System Topic 、 Safety Pharmacology 、 Clinical Evaluation 、 Implementation Issues related to Existing ICH Guidelines 及 Future Challenges facing ICH 等主題，分別在不同的場地同步進行。討論內容包含：藥物安全性、有效性、人體臨床試驗規範、藥品警語標示及其他特別主題等討論會，本會將於爾後制定法規時將國際法規趨勢納入，以與國際同步。

關鍵詞：藥品、法規、一致化、ICH

壹、目的：

行政院衛生署中醫藥委員會為全國中醫及中藥最高行政主管機關，為積極推動中醫藥法規及臨床試驗環境等公共政策之建置，極需了解及掌握國際法規之趨勢，期能於制定中醫藥相關法規時能溶入國際趨勢而與國際同步，並能有助於國內中藥品之查驗登記作業，爰派員參加。

貳、過程

一. 行程

本次代表行政院衛生署中醫藥委員會參加，為求全程參與，故於會議開幕前一日，即十一月十一日由桃園中正機場搭長榮航空班機前往，抵達日本中部關西機場時已是下午時分，隨即轉搭尚稱便捷之捷運系統至大阪市區，而後以安步當車之方式，瀏覽市區感受異國風調，抵達位於大會會場隔壁之旅館時已是華燈初上時分，稍事休息之後即參加由 JPMA(日本製藥協會)具名邀請之非正式介紹會。大會正式於十一月十二日早晨開始至十五日中午結束，該日下午臨時由 JPMA 召開有關藥廠 GMP 之 WORK SHOP (大會議程及各組議程詳見附錄一、二)，報告人於研討會完成後即於十六日束裝返國。

二、ICH 簡介

(一)組織：

ICH 成立於 1990 年 4 月由下列七個政府組織及民間機構共同發起

1.美國食品藥物管理局(FDA)

2.美國製藥公會(The Pharmaceutical Manufacturers Association, PMA)

3.歐洲共同體委員會(The Commission of European Communities, CEC)

4.歐洲製藥公會聯盟(The European Federation pf Pharmaceutical Industries Association, EFPIA)

5.日本厚生省(The Ministry of Health and Welfare Japan, MHW)

6.日本製藥公會(The Japan Pharmaceutical Manufacturers Association, JPMA)

7.國際製藥公會聯盟(The International Federation of Pharmaceutical Manufacturers Association, IFPMA)

其組織主要包括五大部門，分別為；

1. 指導委員會(The steering Committee)
   共有 14 位委員，分別來自前述七個組成團體，主要功能為督導 ICH 會議及 ICH 議題。
2. 觀察員(Observers)
   組成成員為來自 WHO、加拿大 Health Protection Branch 及 European Free Trade Area(FETA)的代表。
3. 專家工作小組(Expert Working Groups)
   設有 Quality、 Safety 及 Efficacy 等三個專家小組，分別由三個國家地區所派出之衛生法規主管機關及產業界代表所組成，主要係將技術性議題充分討論之後提交給指導委員會做最後之確認。
4. 秘書處(Secretariat)
5. 非會員組織(Global Cooperation Group)

ICH 之主要發起國家地區，其人口數僅佔全球之 20%，但卻涵蓋 75%之藥品商業行為及 95%之研發投資，另 ICH 前五次大會所陸續完成之 45 個 Guideline (如附錄五所列)，據調查幾乎 100%已被全球主要研發國家政府及業界採用，由此數據可知其影響力及重要性。

(二)ICH 之目的：

在不影響藥物品質、安全性及有效性的原則下，加速全球研發新藥及上市的速度，以；

1. 減少新藥研發及各國上市時重複實驗時之成本。
2. 加速新藥上市，使患者及早得到較新、較佳之治療。

(三)歷次大會：原則上每二年由美、日、歐等三個國家地區輪流主辦。

1. ICH-1：1991 年 11 月於比利時之布魯塞爾舉行，參與人數約 1200 人。
2. ICH-2：1993 年 10 月於美國佛羅里達州之奧蘭多舉行，參與人數約 1500 人。
3. ICH-3：1995 年 11 月於日本橫濱舉行，參與人數約 2400 人。
4. ICH-4：1997 年 7 月於比利時之布魯塞爾舉行，參與人數約 1600 人，本次我國派出 36 人之代表團與會。
5. ICH-5：1999 年 10 月於美國加州聖地牙哥舉行，參與人數約 1700 人。
6. 本次 ICH-6：2003 年 11 月於日本大阪舉行，參與人數約 2500 人。

(四)法規一致化之工作階段：

ICH 之法規一致化過程大致包括下列各階段

1. 階段一：由專家工作小組擬定議題草案，提交指導委員會確認。
2. 階段二：依據指導委員會之建議，提案交與三個地區主管機關正式進行討論、修正完成建議草案。
3. 階段三：各地區建議草案收回後由專家工作小組討論會整後交予指導委員會。
4. 階段四：最後之草案經指導委員會確認後，隨即建議各三個地區

主管機關採行。

5. 階段五：建議案依各不同之行政程序落實為各個國家之規定。

(五)主要關切議題：

ICH 主要關切議題可分四大類(Q、、S、E、M)：

1. *"Quality" Topics*：those relating to chemical and pharmaceutical Quality Assurance.

例如: Q1 Stability Testing, Q3 Impurity Testing

2. *"Safety" Topics*：those relating to in vitro and in vivo pre-clinical studies.

例如: S1 Carcinogenicity Testing, S2 Genotoxicity Testing

3. *"Efficacy" Topics*：those relating to clinical studies in human subject.

例如: E4 Dose Response Studies, Carcinogenicity Testing, E6 Good Clinical Practices. (Note Clinical Safety Data Management is also classified as an "Efficacy" topic - E2)

4. "Multidisciplinary" Topics:cross-cutting Topics which do not fit uniquely into one of the above categories.

M1: Medical Terminology

M2: Electronic Standards for Transmission of Regulatory Information (ESTRI)

M3: Timing of Pre-clinical Studies in Relation to Clinical Trials

M4: The Common Technical Document

三、本次大會主要議題節錄：

今年大會主題訂為『New Horizons and Future Challenges(新視域與未來挑戰)』，本次會議議題眾多，內容豐富而多面，分多個場地同時進行(大會議程及各組議程詳見附錄一、二)，因此若要每場均參加是為不可能之事，只好擇要參與，其餘各場則儘量收集資料，現場演講則忍痛割捨。

現場演講分為十五大項進行：(A) Satellite Session I(Partnership in Harmonisation), II(MedDRA User's Group) and III(Gene Therapy)；(B) Opening Plenary Session(New Horizon For The Pharmaceutical Sector, Shared Perspectives on CTD Implementation)；(C) CTD Breakout Sessions(Sessions I, II, III, IV 分別以 Quality, Safety, Efficacy and eCTD 等四主題展開與對談)；(D) Topic Breakout Session(I, II, III 分別以 Quality, Pharmacovigilance and Regulatory Communication, Safety and Efficacy 等三主題展開深度進階討論與對談)；(E)最後一天排有 Closing Plenary Session, ICH Global Cooperation Groups(GCG), Future Challenges 等三主題。由以上議題安排可看出本次會議議題眾多，內容豐富而多面，充分呈現 ICH 自上次大會後各部門共同研訂法規一致化之成果及大會主辦者之用心。

每個報告時間大致為 20~30 分鐘，之後有 10~20 分鐘之小組討論，以供研討會參與者及小組主持人引言或提問，時有質疑及精采而熱烈的討論。

本次大會係第六次舉行，如有關 Quality, Safety, Efficacy 等較傳統之 Guidelines 已發展制定幾近完成，這次大會較新的主題為 eCTD (技術性文件之電子化)及 Pharmacovigilance (藥品警語之標示)and Regulatory Communication(不同語文法規間之銜接溝通)。

大會日程於十一月十二日晨間開始報到註冊。隨即以三個場地開始分別同時進行報告，議題包含非 ICH(Non-ICH)國家對法規一致化活動之分享、經驗交流等，值得一提的是我國醫藥品查驗中心副執行長—陳恒德博士以ＡＰＥＣ代表身分，以 E5 – Ethnic Factors (E5) in APEC –the Regulatory Science, Evaluation Process and Experience 為題發表報告(報告摘要如附錄三)，暢談及宣導我國經驗，使參與之眾多國家對我國參與國際法規劃之工作有所認識，是為難得之國際發聲。 第一天的活動尚包含 MedDRA User's Group 及有關 Gene Therapy(基因治療)等方面之主題報告。

第二天(十一月十三日)由日本厚生省(MHLW)之 Mr. Shuichi Kishida 及大會主辦單位之日本製藥工會(JPMA)的 Mr. Tohru Uwoi 共同主持正式開幕典禮，之後隨即以 New Horizon For The Pharmaceutical Sector 及 Shared Perspectives on CTD Implementation 為主軸分別展開活動。大致上，十三日下午及十四日整天之研討除圍繞歷屆所關注較基本之議題，如；Quality、Safety、 Efficacy 等大部份均已制定完成相關 Guideline(如附錄五)，且已落實至各國主管機關之政策中之議題，但仍展開深度之報告及討論，以探討可能之後續發展外，這次大會較新的議題如；因應各國網際網路之普及，電子化線上申報及審查(eCTD)之法規及建置、Pharmacovigilance (藥品警語標示)、Regulatory Communication(不同語文間法規之溝通)等議題之討論，研討會以開放議題之型態，安排各地區提出不同看法，點出因文化、語文背景差異而出現之困擾等問題，以尋求共識，並期獲得解決方案。

十五日上午則為大會閉幕式、GCG(ICH 全球合作組織)、未來之挑戰及展望等討論，大會於下午二時正式宣佈結束，之後，由 JPMA 安排 GMP 相

關之 Workshop 以日本為例，交換各國心得，熱烈討論至下午六時方散會。

參、心得

1．中醫藥在我國已經有幾千年使用的歷史，除了在臺灣、大陸、及各國華人聚集的地方甚為普及外，在不使用中文的地方也正方興未艾掀起一片使用及研發熱潮，各國莫不競相投下可觀之人力、物力、財力積極研發尤其是世界衛生組織（WHO）於 91 年 5 月 16 日首次正式對全世界之發表「2002 年至 2005 年世界衛生組織傳統醫學策略」（WHO TRADITIONAL MEDICINE STRAGEDY 2002-2005）中要求各國政府將傳統醫學發展納入現有醫療政策之呼籲後，傳統醫藥之研發更是勢不可檔，中醫藥在這日趨緊密的地球村實在有很多可以著力的地方及無價的幫助，推動中醫藥的國際化可以早日讓這個我們祖先遺傳下來的寶貝早日對世界有所貢獻，我國具有極大之優勢條件以使研發成果更加耀眼，這將是我們責無旁貸的責任。

2、醫藥品有別於其他高科技產品，因其直接影響民眾的生命安全與健康福祉，各國對藥品的品質均有高標準要求外，亦必須於其上市前後，對其有效性及安全性作嚴格的審核與監控，以確保消費民眾之用藥安全。目前國內的中藥臨床試驗環境，經本會多年之積極推動已建立十一家臨床實驗中心，其中有兩家中心已不需本會之挹注而可獨立運作，該等中心經學者專家訪視均合於標準，且一致認為該等中心已具成效，具有符合中醫藥理論及國情之優點，目前急需推展者應為對業者廠商之宣導推廣、臨床環境及周邊法規之補強等，由於中醫基本理論與西醫不同，若完全套用西方的方法及其模式來驗證中藥的療效，無法避免有適用之疑慮及遺珠之憾，惟此次研討內容仍有參考價值之處，吾人可取其精神，作法予以適當修正以符合中醫藥理論及國情則必能達事半功倍之效，例如可適當參考 WHO 於 2000 年發表之「General guidelines for

methodologies on research and evaluation of traditional medicine」，許多中藥都有人類使用經驗，因此對其毒性方面的考量，亦應有別於西藥開發時的要求。因此在用現代科學方法驗證中醫理論或中藥臨床療效時，如何同時保有中醫藥之特色，實為中醫藥現代化亟需解決的問題。

3、臺灣在加入 WTO 後，為避免其他國家以劣質、廉價中藥產品，大舉傾銷臺灣，建構完備之中醫藥產品品質驗證相關法規，透過嚴謹的臨床療效評估，民眾的用藥安全將更有保障！則適當法規之建立實乃刻不容緩之舉。

4、「藥即是毒」，藥是否會使人中毒，與使用之劑量及時間之長短有關，然而，國人普遍存在對中藥是「溫和無毒性、有病治病無病強身、祖傳秘方偏方療效」等觀念應透過教育宣導予以矯正，並明確告知消費者未經合格醫師診治長期服用成藥或使用來路及成分不明之產品會造成無法挽回之傷害，建立正確用藥常識，是為重點工作，亦為本會長期重點推動之工作，除教育宣導外，中醫藥查驗登記法規中亦可考慮適當的以現代之文辭標示產品之作用、服用之注意事項及可能之預期外作用等警語以保護消費者。

5、日本大阪算是一個新舊雜陳的都市，新、舊、現代、傳統文化及建築風貌並列，良好的都市規劃，街道乾淨，留下不錯的印象。這幾天中我經歷了很多事，參與了整場研討會，及了解了日本的歷史文化，使我的眼界又向外開拓了許多。這個會議不啻是一個將所學加以發揮，並感受異國風情的好機會。不論是會議還是日常生活，都是一個令人難忘的經驗。

肆、建議

中藥現代化需以現代化科學的方法來闡明中藥的作用目的和作用機轉，透過嚴格臨床療效的評估證實其療效與安全性，中藥未能進入世

界市場，品管、療效及安全性問題未得到國際的了解應係問題之癥結，中草藥若要為國際與中西醫學界所認定，不僅要在藥品的整個生產及製造過程中作好品管，提供科學化的數據，並應熟悉國內外欲申請上市許可之相關法規的要求與申請流程，減少不必要的試驗，節省經費。臺灣中藥產業的推展，需要人才、資金、技術與市場行銷四大基本要求，臺灣的中草藥產業多屬中小企業，普遍缺乏研發能量與核心技術，並局限在國內市場，政府應扮演著教練及火車頭角色，擁有國際觀，在不同的階段，於行政面、法規面能提供配套措施；中藥業者則應分析國際各國的市場，以選擇於該地區上市的品項，搭配中藥業者本身的強項與雄厚中藥製劑基礎，由點延伸到面及立體發展，以期與歐美日等先進國家並駕齊驅，故有如下之建議：

一、 我國中醫藥產品查驗登記之相關法規釐定時應多參採國際通用規則或了解掌握其趨勢以與國際同步。

二、 科技新知、國際法規不斷推陳出新，透過國際性的研討會多能在此方面獲益。雖然網際網路日益發達，可透過網際網路獲取新知，但關鍵性之研討會，可透過現場與專家學面對面溝通、討論之成效無法由網際網路取代。國內中草藥產品邁向國際化之際，在產品安全性、有效性及品質方面，須符合國際之標準，因此建議能持續派員參與類似會議，不但能汲取經驗，亦能掌握世界趨勢、培養國際觀。

伍、誌謝

首先感謝行政院衛生署中醫藥委員會提供經費之補助，亦誠摯的感謝本會林主任委員宜信以學術研究風格領航、羅主任秘書淑慧、謝組長伯舟及林高級研究員育娟給予機會，並對撰寫心得報告給予指正，謹此致上謝忱！

陸、參考資料

1. ICH 網站；http://www.ich.org./

2. 林宜信等:臺灣中醫藥整合與前瞻，p.p.1 ~492，衛生署中醫藥委員會，台北，2003.12。

3. WHO：「2002-2005 年傳統醫藥全球策略」，http://www.who.org，2002.5。

4. WHO: 「General guidelines for methodologies on research and evaluation of traditional medicine」，2000。

柒、附錄

附錄一 **ICH-6** 大會議程

附錄二 分類主要議題表

附錄三 口頭發表論文摘要

附錄四 **ICH** 常用縮寫對照表

附錄五 **ICH Guideline** 一覽表

附錄一　ICH-6 大會議程

ICH6 THE SIXTH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

WEDNESDAY, 12 NOVEMBER 2003

◆ SATELLITE SESSIONS

09H00 - 17H00	SATELLITE SESSION I : PARTNERSHIPS IN HARMONIZATION (ORGANIZED BY THE ICH GCG)
09H00 - 12H00	SATELLITE SESSION II : MEDDRA USER'S GROUP
13H30 - 17H00	SATELLITE SESSION III : GENE THERAPY

THURSDAY, 13 NOVEMBER 2003

◆ OPENING PLENARY SESSIONS

09H00 - 09H15	WELCOMING REMARKS
09H15 - 10H30	NEW HORIZON FOR THE PHARMACEUTICAL SECTOR
11H00 - 14H30	SHARED PERSPECTIVES ON CTD IMPLEMENTATION
	• THE COMMON TECHNICAL DOCUMENT IN PRACTICE FROM PAPER TO BYTES
	• ICH SURVEY ON CTD / ECTD / GUIDELINES IMPLEMENTATION AND MEDDRA

◆ CTD BREAKOUT SESSIONS

15H00 - 17H00	SESSION 1 : CTD - QUALITY
	SESSION 2 : CTD - SAFETY
	SESSION 3 : CTD - EFFICACY
	SESSION 4 : ELECTRONIC CTD

FRIDAY, 14 NOVEMBER 2003

◆ TOPIC BREAKOUT SESSIONS

09H00 - 17H00	SESSION 1 : QUALITY
09H00 - 12H00	SESSION 2 : PHARMACOVIGILANCE AND REGULATORY COMMUNICATION
13H30 - 17H30	SESSION 3 : SAFETY AND EFFICACY

SATURDAY, 15 NOVEMBER 2003

◆ CLOSING PLENARY SESSIONS

09H00 - 10H10	ICH GLOBAL COOPERATION GROUP (GCG)
10H40 - 13H10	FUTURE CHALLENGES FOR ICH
	• NEW APPROACHES FOR THE DEVELOPMENT / ASSESSMENT OF INNOVATIVE THERAPIES
13H10 - 13H30	CLOSING REMARKS

附錄二　分類主要議題表

SATELLITE SESSION I

09H00 - 17H00 <Main Hall, 5F>　　Wednesday, 12 November 2003

SATELLITE SESSION I
PARTNERSHIPS IN HARMONISATION
(organized by ICH Global Cooperation Group (GCG))

Session Chairs :
Dr. Eric Abadie, EU
Dr. Alexander R. Giaquinto, Schering-Plough Research Institute, PhRMA

9h00	**Introduction on GCG Current Activities and Organization of Symposium** Dr. Alexander R. Giaquinto, Schering-Plough Research Institute, PhRMA
	NON-ICH REGIONAL HARMONISATION INITIATIVES
9h15	**Challenges of Information Sharing** Ms. Precious Matsoso, SADC
9h40	**Mechanisms for Training** Ms. Rosario D'Alessio, PANDRH
10h05	**COFFEE BREAK <Event Hall, 3F>**
10h35	**Maintaining Good Regulatory Practice in a Changing World** Dr. John Lim, APEC
11h00	**A Regional Example of Regulatory Harmonisation** Mr. Dato'Che Mohd Zin Che Awang, ASEAN
11h25	**PANEL DISCUSSION** **Approaches to Harmonisation: Regional Comparisons** Session Speakers and Dr. Lembit Rägo, WHO
12h00	**LUNCH BREAK <Event Hall, 3F>**
	EXPERIENCE OF NON-ICH HARMONISATION INITIATIVES WITH ICH GUIDELINES
13h30	**E5 - Ethnic Factors (E5) in APEC - the Regulatory Science, Evaluation Process and Experience** Dr. Herng-Der Chern, APEC
13h45	**E6 - Good Clinical Practice (GCP)** Dr. Patricia Saidon, PANDRH
14h00	**DISCUSSION** Dr. Robert Temple, FDA
14h20	**Q1 - Stability** ASEAN Stability Working Group Chair or Co-Chair *to be confirmed*
14h35	**DISCUSSION** Dr. Susanne Keitel, EU and Dr. Sabine Kopp, WHO

SATELLITE SESSION I

SATELLITE SESSION I

14h50	**M4 - Common Technical Document (CTD)** Dr. Yuppadee Javroongrit, ASEAN
15h10	DISCUSSION Mr. Yoshikazu Hayashi, MHLW
15h30	COFFEE BREAK **<Event Hall, 3F>**
16h00	**New GCG Activities and Organization** **Introduction** by Dr. Eric Abadie, EU
	PANEL DISCUSSION
17h00	SESSION CLOSED
18h00	COCKTAIL WITH EXHIBITORS **<Foyer, 10F>**

09H00 - 12H00 <Room 1001-1003, 10F> Wednesday, 12 November 2003

SATELLITE SESSION II
MEDDRA USER'S GROUP

Session Chairs :
Mr. Patrick W. Revelle, MSSO
Mr. Yasuo Sakurai, JMO

9h00	Overview of Current Activities at the MedDRA Maintenance and Support Services Organization (MSSO) Mr. Patrick W. Revelle, MSSO
9h20	Overview of Current Activities at the MedDRA Japanese Maintenance Organization (JMO) Mr. Yasuo Sakurai, JMO
9h40	Updates from the FDA regarding Regulatory Requirements Dr. Andrea G. Feight, FDA
10h00	Updates from the EMEA regarding Regulatory Requirements Dr. Sabine Brosch, EU
10h20	Updates from the MHLW regarding Regulatory Requirements Ms. Tomiko Tawaragi, MHLW
10h40	COFFEE BREAK <Foyer, 10F>
11h10	Progress of the MedDRA Term Selection: Points to Consider Dr. Toni Piazza-Hepp, FDA
11h25	Progress of the Council for International Organizations of Medical Sciences (CIOMS) / MSSO Work on MedDRA Data Analysis Mr. Patrick W. Revelle, MSSO
11h40	PANEL DISCUSSION
12h00	SESSION CLOSED
12h00	LUNCH BREAK <Event Hall, 3F>

SATELLITE SESSION II

SATELLITE SESSION II

13H30 - 17H30 <Room 1001-1003, 10F> Wednesday, 12 November 2003

SATELLITE SESSION III
GENE THERAPY

Session Chairs :
Dr. Stephanie Simek, FDA
Dr. Klaus Cichutek, EU

13h30 Update on Gene Therapy Activities since ICH5

Update since ICH5 : Expert Working Group : Activities and Objectives
Dr. Stephanie Simek, FDA

13h40 Current Issues in Gene Therapy
Gene Therapy Issues in Japan
Dr. Teruhide Yamaguchi, MHLW

13h50 Gene Therapy Issues in the EU : Update on x-linked SCID trails
Dr. Klaus Cichutek, EU
Prof. Jean-Hugues Trouvin, EU

14h00 Gene Therapy Issues in Canada
Dr. Anthony Ridgway, Health Canada

14h10 Update since September 2002 Washington DC Meeting
Lentiviral Vectors Safety and Design
Dr. Anthony Meager, EU

Adenoviral Reference Material and other proposed Reference Materials
Characterization and Use
Dr. Beth Hutchins, Canji. Inc., PhRMA

Detection of RCA and AdV by Infectivity PCR
Dr. Teruhide Yamaguchi, MHLW

14h30 Cytoplasmic Gene Therapy: A new Concept using Sendai Virus Vectors
Dr. Mamoru Hasegawa, DNAVEC Research Inc., JPMA

15h05 COFFEE BREAK <Foyer, 10F>

15h30 Current Recommendations regarding Inadvertent Germline Integration and Impact on Gene Therapy Clinical Trials
Dr. Dan Takefman, FDA

16h05 Discussion on Insertional Mutagenesis / Oncogenesis
Vector versus Transgene
Prof. Christoph von Kalle, EU

16h40 PANEL DISCUSSION
Session Chairs, Speakers and Dr. Mette Due Theilade, EU

17h30 SESSION CLOSED

18h00 COCKTAIL WITH EXHIBITORS <Foyer, 10F>

OPENING PLENARY SESSION

9H00 - 10H30 <Main Hall, 5F> Thursday, 13 November 2003

OPENING PLENARY SESSION

WELCOMING REMARKS

9h00 His Excellency The Minister of Health, Labour and Welfare

Session Chairs :
Mr. Shuichi Kishida, MHLW
Mr. Tohru Uwoi, Yamanouchi Pharmaceutical Co., Ltd., JPMA

NEW HORIZON FOR THE PHARMACEUTICAL SECTOR

9h15 **New Era of Drug Discovery and Key Issues for Pharmaceutical Industry**
Mr. Osamu Nagayama, President and CEO, Chugai Pharmaceutical Co., Ltd., and President of JPMA

9h30 **Opportunities and Challenges for Regulatory Harmonisation in the 21st Century**
Dr. Murray M. Lumpkin, Principal Associate Commissioner, Office of the Commissioner, FDA

9h45 **Innovation and Regulatory Harmonisation in a Global Environment**
Dr. Ronald Krall, Senior Vice President, Worldwide Development, GlaxoSmithKline, PhRMA

10h00 **International Approaches to the Challenge of New Technologies in the Area of Pharmaceuticals**
Dr. Paul Weissenberg, Director of Directorate F (Single market: management & legislation for consumer goods), DG Enterprise, European Commission, EU

10h15 **Development of Innovative Medical Products in a Changing Pharmaceutical Environment**
Prof. Paul Herrling, Head of Corporate Research, Novartis International AG, Switzerland, and Member of the Research Directors Committee of EFPIA

10h30 **COFFEE BREAK <Event Hall, 3F>**

OPENING PLENARY SESSION

11H00 - 14H30 <Main Hall, 5F> Thursday, 13 November 2003

OPENING PLENARY SESSION
SHARED PERSPECTIVES ON CTD IMPLEMENTATION

Session Chairs:
Dr. Yves Juillet, LEEM, EFPIA
Dr. Alexander R. Giaquinto, Schering-Plough Research Institute, PhRMA

THE COMMON TECHNICAL DOCUMENT IN PRACTICE
FROM PAPER TO BYTES

11h00 **Awareness of the Impact of the CTD Implementation**
Dr. Christopher Banfield, Amgen Inc., PhRMA

11h30 **Status of the electronic CTD (eCTD) Implementation**
Mr. Timothy M. Mahoney, FDA

12h00 **LUNCH BREAK <Event Hall, 3F>**

ICH SURVEY ON CTD, eCTD, GUIDELINES IMPLEMENTATION AND MEDDRA

13h30 **Presentation of Survey Results**
Mr. Yoshikazu Hayashi, MHLW

13h55 **Views from both Regulators and Industry**
Dr. Christa Wirthumer-Hoche, EU
Dr. Yves Juillet, LEEM, EFPIA

14h10 PANEL DISCUSSION

14h30 SESSION CLOSED

15H00 - 17H00 Thursday, 13 November 2003

CTD BREAKOUT SESSIONS

SESSION 1 : CTD - QUALITY <Main Hall, 5F>

Session Chairs :
Dr. Jean-Louis Robert, EU
Dr. Robert G. Baum, Pfizer Global Research & Development, PhRMA

15h00 **FDA Regulators' Experience with Emphasis on Biotechnology**
Dr. Christopher Joneckis, FDA

15h20 **MHLW Regulators' Experience with Emphasis on Quality Overall Summary**
Dr. Mayumi Shikano, MHLW

15h40 **EU Regulators' Experience with Emphasis on New Chemical Entities**
Dr. Michael Morris, EU

16h00 **Practical Experience in the three Regions**
Dr. John C. Berridge, Pfizer Global Research & Development, EFPIA

16h20 PANEL DISCUSSION
Session Speakers and Ms. Hing Chong, Health Canada

17h00 SESSION CLOSED

18h00 WELCOME RECEPTION **<Rihga Royal Hotel "KORIN", 3F>**

SESSION 2 : CTD - SAFETY <Conference Hall, 12F>

Session Chairs :
Dr. Akira Takanaka, MHLW
Dr. Jennifer Sims, Novartis Pharma AG, EFPIA

15h00 **CTD-Safety as a Single Global Dossier**
Dr. Mutsufumi Kawai, Lilly Research Laboratories Japan, JPMA

15h20 **From Regulatory Experience: Review Comments and Expectation to Applicants**
The Perspective of the FDA on the CTD for Safety
Dr. Martin David Green, FDA

15h40 **What was changed after starting CTD?**
Dr. Hirofumi Kusunoki, MHLW

16h00 **The Usefulness of the Non-Clinical Overview**
Dr. Klaus Olejniczak, EU

16h20 PANEL DISCUSSION

17h00 SESSION CLOSED

18h00 WELCOME RECEPTION **<Rihga Royal Hotel "KORIN", 3F>**

CTD BREAKOUT SESSIONS

15H00 - 17H00 Thursday, 13 November 2003

CTD BREAKOUT SESSIONS

SESSION 3 : CTD - EFFICACY <Room 1003, 10F>

Session Chairs:
Dr. Robert Temple, FDA
Mr. Toshikazu Yoshinaga, Yamanouchi Pharmaceutical Co., Ltd., JPMA

15h00 **Introduction and Summary of Issues**
Dr. Robert Temple, FDA

15h10 **Brief Review of CTD Status in three Regions and Current Usage**
Dr. Justina A. Molzon, FDA
Dr. Spiros Vamvakas, EU
Dr. Shunsuke Ono, MHLW

15h40 **Providing Complete and Accessible Analyses of Efficacy and Safety within the CTD**
Dr. Michael Brennan, Centocor, PhRMA

16h10 **Sponsor Experience in preparing Submission for the three Regions**
Mr. Sumio Kitsugi, Biogen Japan, PhRMA

16h30 PANEL DISCUSSION
Session Chairs, Speakers, Dr. Louis Marzella, FDA and Dr. Charles Boyle, EFTA

17h00 SESSION CLOSED

18h00 WELCOME RECEPTION <Rihga Royal Hotel "KORIN", 3F>

SESSION 4 : eCTD <Room 1001-1002, 10F>

Session Chairs :
Mr. Timothy M. Mahoney, FDA
Dr. Andrew Marr, GlaxoSmithKline, EFPIA

15h00 **eCTD Case Study from Industry**
Mr. Robert E. Hizer, Eli Lilly and Company, PhRMA

15h20 **eCTD Case Study from Regulators**
Dr. C. A. Stan Van Belkum, EU

15h40 **eCTD Lifecycle Management**
Mr. Timothy M. Mahoney, FDA

16h00 **Regional Implementation**
Mr. Tetsunari Kihira, MHLW

16h20 PANEL DISCUSSION

17h00 SESSION CLOSED

18h00 WELCOME RECEPTION <Rihga Royal Hotel "KORIN", 3F>

09H00 - 18H00 <Room 1001-1003, 10F> Friday, 14 November 2003

TOPIC BREAKOUT SESSION 1
QUALITY

Session Chairs :
Dr. Shigeo Kojima, MHLW
Dr. John C. Berridge, Pfizer Global Research & Development, EFPIA

STABILITY TESTING GUIDELINES : Q1D, Q1E, Q1F

9h00 **Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (Q1D)**
Dr. Chi-Wan Chen, FDA

9h15 **Evaluation for Stability Data (Q1E)**
Dr. Sumie Yoshioka, MHLW

9h30 **Stability Data Package for Registration Applications in Climatic Zones III and IV (Q1F)**
Dr. Susanne Keitel, EU

9h45 PANEL DISCUSSION
Session Speakers and Dr. Sabine Kopp, WHO

IMPURITY TESTING GUIDELINES : Q3A(R), Q3B(R), Q3C(M)

10h00 **Revision of the Guideline on Impurities in New Drug Substances (Q3A(R))**
Dr. Jean-Louis Robert, EU

10h15 **Revision of the Guideline on Impurities in New Drug Products (Q3B(R))**
Dr. Norman Schmuff, FDA

10h30 COFFEE BREAK <Foyer, 10F>

11h00 **Maintenance Process of Residual Solvents Guideline (Q3C(M))**
Dr. Ryuichi Hasegawa, MHLW

11h15 PANEL DISCUSSION

12h00 LUNCH BREAK <Event Hall, 3F>

Session Chairs :
Dr. Agnès Artiges, EP
Dr. Takao Kiyohara, Sumitomo Pharmaceuticals Co., Ltd., JPMA

PHARMACOPOEIAL HARMONISATION : Q4/Q6A

13h30 **Pharmacopoeial Discussion Group (PDG) Report: Accomplishments and Difficulties**
Dr. Eric B. Sheinin, USP

13h50 **Industries' Views on Progress and Possibility to contribute to Progress**
Dr. Chris Potter, AstraZeneca, EFPIA

TOPIC BREAKOUT SESSION I

14h10 **Authorities' Views about the Interchangeability of Harmonised Sign-off Texts of the PDG : Contribution to the Harmonisation Program**
Mr. Robert H. King, Sr., FDA

14H40 PANEL DISCUSSION
Session Speakers, Dr. Tsuyoshi Tanimoto, MHLW, Dr. Michael Morris, EU, Ms. Janeen Kincaid, Pfizer Global Manufacturing, PhRMA and Dr. Yasushi Takeda, JP

15h00 COFFEE BREAK <Foyer, 10F>

Session Chairs :
Dr. Takao Hayakawa, MHLW
Dr. Anthony S. Lubiniecki, GlaxoSmithKline Pharmaceuticals, PhRMA

COMPARABILITY OF BIOTECHNOLOGICAL/ BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS (Q5E)

15h30 **Establishing the Need for the Document**
Dr. Alan Morrison, Baxter BioScience AG, EFPIA

15h45 **An Introduction to Q5E**
Mr. Shigeru Matsuki, Kirin Brewery Co., Ltd., JPMA

16h00 **Scope of the Document**
Dr. Anthony Ridgway, Health Canada

16h15 **The Key Role of Characterization and Analytical Results in Comparability**
Dr. Toru Kawanishi, MHLW

16h30 **Planning, Strategy and Impact Analysis for Comparability Studies**
Dr. Barry Cherney, FDA

16h45 **Product and Process Aspects**
Dr. Pierrette Zorzi-Morre, EU

Session Chairs :
Dr. Yukio Hiyama, MHLW
Mr. Neil J. Wilkinson, AstraZeneca, EFPIA

COMPONENTS OF A DESIRED PHARMACEUTICAL QUALITY SYSTEM

17h00 **Vision of Quality Systems for the 21st Century**
Ms. Joyce Ramsbotham, Solvay Pharmaceuticals, EFPIA
Mr. Tetsu Yamada, Otsuka Pharmaceutical Co., Ltd., JPMA

17h20 **Risk Management**
Dr. Gordon Munro, EU

17h35 **Development Pharmaceutics and Manufacturing Science**
Dr. Robert G. Baum, Pfizer Global Research & Development, PhRMA

17h50 PANEL DISCUSSION

18h00 SESSION CLOSED

09H00 - 12H00 <Main Hall, 5F> Friday, 14 November 2003

TOPIC BREAKOUT SESSION 2

PHARMACOVIGILANCE AND REGULATORY COMMUNICATION

Session Chairs :
Dr. Peter Arlett, EU
Dr. Teiki Iwaoka, Sankyo Co., Ltd., JPMA

PHARMACOVIGILANCE GUIDELINES : E2CAdd, E2D, E2E

9h00	**Periodic Safety Update Reports (Addendum to E2C)** Dr. Min Chen, FDA
9h20	**Post-Approval Safety Data Management (E2D)** Dr. Teiki Iwaoka, Sankyo Co., Ltd., JPMA
9h40	**Pharmacovigilance Planning (E2E)** Dr. Yusuke Tanigawara, MHLW
10h00	DISCUSSION
10h30	COFFEE BREAK <Event Hall, 3F>

REGULATORY COMMUNICATION: E2B(M), MEDDRA

11h00	**Electronic Case Reporting: Maintenance of E2B(M)** Dr. Sabine Brosch, EU
11h20	**MedDRA** Mr. Patrick W. Revelle, MSSO
11h40	PANEL DISCUSSION
12h00	SESSION CLOSED
12h00	LUNCH BREAK <Event Hall, 3F>

TOPIC BREAKOUT SESSION 3

13H30 - 18H00 <Main Hall, 5F> Friday, 14 November 2003

TOPIC BREAKOUT SESSION 3
SAFETY AND EFFICACY

Session Chairs :
Dr. Colette Strnad, Health Canada
Dr. Gerd Bode, Altana Pharma AG, EFPIA

SAFETY PHARMACOLOGY STUDIES FOR ASSESSING THE POTENTIAL FOR DELAYED VENTRICULAR REPOLARIZATION (QT INTERVAL PROLONGATION) BY HUMAN PHARMACEUTICALS (S7B)

13h30 **New Requirements to assess the Potential for QT Interval Prolongation**
Dr. Kannosuke Fujimori, MHLW

13h40 **Non-Clinical Testing Strategy and Integrated Risk Assessment**
Dr. Peter K. S. Siegl, Merck & Co., Inc., PhRMA

CLINICAL EVALUATION OF QT/QTC INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS (E14)

14h00 **Evaluation of QT Interval Prolongation Potential in Phase I Trials**
Dr. Robert Temple, FDA

14h20 **Evaluation of QT Interval Prolongation Potential in Phase II and III Trials**
Dr. Maki Ito, Shionogi & Co., Ltd., JPMA

14h40 **Collection and Analysis of ECG Safety Data in Clinical Trials**
Dr. Rashmi Shah, EU

15h00 PANEL DISCUSSION

15h30 COFFEE BREAK <Event Hall, 3F>

Session Chairs :
Dr. Robert O'Neill, FDA
Dr. Chikayuki Naito, MHLW

ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA (E5)

16h00 **Acceptance of Foreign Data with E5 Guideline, Experience from Industry Viewpoint**
Dr. Masuhiro Kato, AstraZeneca KK Japan, EFPIA

16h15 **Japanese Experience of Bridging Studies**
Mr. Kazuhiko Mori, MHLW

16h30 PANEL DISCUSSION

TOPIC BREAKOUT SESSION 3

Session Chairs :
Dr. Jan Willem van der Laan, EU
Dr. Kazuichi Nakamura, Shionogi & Co., Ltd., JPMA

IMMUNOTOXICOLOGY STUDIES

17h00 **Immunotoxicity Testing: European Regulatory Perspective**
Dr. Jan Willem van der Laan, EU

17h15 **Regulatory Considerations for Immunotoxicology Assessment of Pharmaceuticals**
Dr. Kenneth L. Hastings, FDA

17h30 **ICH Survey on Immunotoxicity Data for Development of the Harmonised Guideline**
Dr. Jun-ichi Sawada, MHLW

17h45 PANEL DISCUSSION
18h00 SESSION CLOSED

CLOSING PLENARY SESSION

09H00 - 13H30 <Main Hall, 5F> Saturday, 15 November 2003

CLOSING PLENARY SESSION

Session Chairs :
Mr. Thomas Lönngren, EU
Mr. Kazutaka Ichikawa, JPMA

ICH GLOBAL COOPERATION GROUP (GCG)

9h00 **Background and History of the GCG**
Dr. Harvey E. Bale, Jr., IFPMA

9h10 **Mechanism for Outreach beyond ICH Participants: The Role of WHO**
Dr. Lembit Rägo, WHO

9h20 **Report on the Satellite Session on Partnerships in Harmonisation**
Dr. Robert Yetter, FDA

9h30 **Future Initiatives - The Road Ahead**
Dr. Yves Juillet, LEEM, EFPIA

9h40 PANEL DISCUSSION

10h10 COFFEE BREAK <Event Hall, 3F>

Session Chairs :
Dr. Philippe Brunet, EU
Mr. Brian Ager, EFPIA

FUTURE CHALLENGES : NEW APPROACHES FOR THE DEVELOPMENT - ASSESSMENT OF INNOVATIVE THERAPIES

10h40 **New Technology to enhance Drug Development**
Dr. Toichi Takenaka, President and CEO, Yamanouchi Pharmaceutical Co., Ltd., and Vice President of JPMA

10h55 **New Challenging Areas of Biologicals and Related Issues**
Dr. Takao Hayakawa, Deputy Director General, National Institute of Health Sciences (NIHS), MHLW

11h10 **Pharmacogenetics and Targeted Medicines**
Dr. Kevin Cheeseman, Director, Development Pharmacogenetics, AstraZeneca Research & Development, UK, and Co-Chair of the Pharmacogenetics & Pharmacogenomics Committee of EFPIA

11h25 **Special Pharmacogenetic Considerations for Clinical Trials**
Dr. Robert Peterson, Director General of Therapeutic Products Directorate, Health Canada

11h40 **Risk Management and Patient Safety**
Dr. Murray M. Lumpkin, Principal Associate Commissioner, Office of the Commissioner, FDA

11h55 **Future Challenges for ICH in an Enlarged Europe**
Mr. Thomas Lönngren, Executive Director, EMEA (European Agency for the Evaluation of Medicinal Products), EU

CLOSING PLENARY SESSION

12h10 **Role of International Agreements in Harmonisation with ICH Regions**
Dr. Rolf Spang, Head of International Affairs, Swiss Agency for Therapeutic Products, Swissmedic, and Observer at ICH for the European Free Trade Association (EFTA)

12h25 **New Opportunities for Harmonisation and Implementing Existing Guidelines**
Dr. Peter K. Honig, Vice President, Worldwide Regulatory Affairs and Product Safety Assurance, Merck Research Laboratories, PhRMA

12h40 PANEL DISCUSSION

13h00 SESSION CLOSED

CLOSE OF CONFERENCE

13h10 Mr. Shinji Asonuma, Director General of MHLW

13h30 CONFERENCE CLOSED

ＧＭＰ特別シンポジウム

第30回・平成15年度ＧＭＰ事例研究会

21世紀の品質システム
－日本におけるＧＭＰの将来展望－

JPMA GMP Workshop
－Quality System for the 21st Century－

平成15年11月15日(土)
14時30分～18時
(受付開始14時より)

大阪市北区中之島5丁目3番51号
グランキューブ大阪（大阪国際会議場）
5階メインホール
TEL (06) 4803-5555

Main Hall, 5th Floor
Osaka International Convention Center
November 15th, 2003

JPMA GMP Committee

日本製薬工業協会
ＧＭＰ委員会

JPMA GMP Workshop
Quality System for 21st Century
— Future Evolution of GMP in Japan —

Main Hall, 5th Floor
Osaka International Convention Center, Osaka, Japan
November 15th, 2003

Agenda

14:30 - 14:35 Opening Remarks

Mr. Osamu Goishihara (JPMA)

14:35 - 15:00 Introductory Speech

From GMP to Risk- and Science-based Quality System

Mr. Tetsu YAMADA (JPMA)

15:00 - 15:55 Invited Speech 1

Pharmaceutical cGMPs for the 21st Century
A Risk-Based Approach

Mr. Jon Clark (FDA)

15:55 - 16:15 **Tea Brake**

16:15 - 16:50 Invited Speech 2

Quality System for the 21st Century
Risk-Based Quality Management

Ms. Joyce Ramsbotham (EFPIA)

16:50 - 17:25 Invited Speech 3

Pharmaceutical Manufacturing in the 21st Century
It's About Quality not GMPs

Dr. Tobias Massa (PhRMA)

17:25 - 18:00 Invited Speech 4

The Challenge for Good Manufacturing Practices (GMP) in JAPAN

Dr. Yukio Hiyama (MHLW)

ICH6 THE SIXTH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE
OSAKA, JAPAN
NOVEMBER 12-15, 2003

Wednesday, 12 November 2003

SATELLITE SESSIONS

SATELLITE SESSION I: PARTNERSHIPS IN HARMONISATION (ORGANIZED BY THE ICH GCG)

Introduction on GCG Current Activities and Organization of Symposium

Dr. Alexander R. Giaquinto

NON-ICH REGIONAL HARMONISATION INITIATIVES

Challenges of Information Sharing

Ms. Precious Matsoso

Harmonisation in the SADC Region: Challenges of information exchange, M.P. Matsoso

In 1995, the South Eastern African Medicines Regulatory Authority Conference (SEAMRAC) initiated the first harmonisation process, which was largely driven by the South African Pharmaceutical Manufacturers' Association and Medicines Control Council, as well as the Zimbabwean Pharmaceutical Manufacturers' Association and Medicines Control Authority of Zimbabwe. This was in response to identified problems and lead teams were established specifically to coordinate identified issues.

Four years later, the Southern African Development Community (SADC) Health Ministers resolved that regulators in the region should harmonise their regulatory requirements, with specific emphasis on public health and access to essential medicines. SADC is a regional trade bloc with 14 member states, having a population of 191 million people with significant variability in the level of development, capacities, infrastructure and expertise. Recent transformation and integration in the region has been largely informed by the development agenda, with proposals for structural changes aimed at reduction of all duplications, promotion of intersectoral collaboration and resource mobilisation. Eight of the twenty three objectives of the SADC protocol relate to pharmaceutical issues, including harmonisation.

Several activities involving the control of quality of pharmaceutical products at various stages of drug distribution, have been undertaken by SADC regulatory authorities since the directive by SADC Health Ministers. These were primarily directed at facilitation of access to generic medicines, the strengthening of regulatory capacity, mobilisation of resources, reduction of regulatory burden and duplication of effort as well as facilitation of trade. The process followed included evaluation of legislation, regulations and guidelines. Nine out of fourteen SADC member states submitted their legislation, regulations and guidelines on registration and control of medicines. These laws were in force as far back as 1965 in one country, with the latest laws having been recently passed in 2001. The legislative provisions differ in emphasis but basic elements exist, but are implemented to varying extents. The various regulatory approaches from 6 WHO regions were studied and the approach followed, was adoption of the EU application format, which has since been replaced by the ICH Common Technical Document, a matter that will pose a further to SADC regulators.

Working groups have been established, led by South Africa and Zimbabwe, to develop specific guidelines with technical support from the World Health Organisation. The major constraints have been communication challenges, resource constraints and technical capacity.

The level of development and experience, as well as regulatory infrastructure, differs from one member state to another, with one SADC regulatory agency having a total staff complement of 3 people, mainly pharmacists, and the most developed and well established having a total of 120 people, including medically qualified personnel, pharmacists, biochemists, microbiologists and clinical pharmacologists and support of 190 experts. The pharmaceutical manufacturing operations are almost non-existent in some countries while in others they are fully developed.

Only 3 SADC member states retain fees as a means of revenue generation to fund their activities with the rest funded through fiscus and donor support. The human resources are inadequate in both numbers and technical capacity relative to the regulatory burden and workload. Some of the officials tasked with medicine regulation are also tasked with other non-regulatory functions. There are few countries with the technical capacity to assess pre-clinical and clinical data, and most applications for new chemical entities pose a challenge. Generics medicines form a significant market in SADC countries and harmonisation efforts have been mainly targeted at strengthening evaluation of generic applications and quality assurance, with the aim of centralising evaluation of New Chemical Entities.

Progress thus far includes development of 18 guidelines, some of which have been aligned with WHO technical documents and others ICH guidelines. These guidelines include Stability, Validation, Recalls, Bioequivalence/Bioavailability, Exportation and Importation, Registration, Good Manufacturing Practices, Licensing of various outlets (dispensing sites, retailers, industrial clinics, distributors and wholesalers), Advertising, Post-marketing surveillance and Control of Counterfeits and Spurious Medicines, Donations, Adverse Drug Reactions and Product Defect forms.

The greatest challenge is the practical implementation of these guidelines, including the creation of a sustainable structure that is fully funded for the implementation of the guidelines, formalisation of harmonisation through signing of memoranda of understanding, definition of information flows and exchange of technical reports, confidence building, information exchange in a secured environment that recognises confidentiality, transparency in decision making processes, confidence and consensus building, and strengthening of individual regulatory agencies to meet certain requirements of effective medicine regulation whilst optimising utilisation of resources and development of a model best suited for the SADC region.

Mechanisms for Training

Ms. Rosario D'Alessio

Maintaining Good Regulatory Practice in a Changing World

Dr. John Lim

Effective regulatory practices and systems combined with regulatory policies promoting the growth of life-sciences innovation can facilitate timely access for patients to important and medically needed treatments. These should be guided by principles of good regulatory practice, such as transparency, flexibility, responsiveness and efficiency, that do not comprise on the robustness of the regulatory framework.

Responsiveness to environmental changes is critical for regulators to ensure the relevance and continuing robustness of their regulatory systems in the current climate of fast-changing technical developments and competition, transcending national boundaries. Constant environmental scanning coupled with appropriate organization and system reviews are important for national regulatory agencies.

Experiences will be shared from Singapore's Health Sciences Authority (HSA). HSA engages in ongoing interaction with its stakeholders, including early discussions in reviews of the regulatory framework, and refining systems and guidelines. The approach is outcome-based rather than prescriptive.

HSA seeks to enhance systems efficiency through the use of novel approaches to optimize the use of limited manpower resources, and utilization of information technology to accelerate and streamline communication and regulatory processes. The presentation will discuss HSA's drug evaluation systems, which includes a recently introduced verification route that allows the Authority to expedite verification of the safety, efficacy and quality of new drugs based on assessment reports issued by benchmark regulatory agencies. The new Pharmaceutical Regulatory Information System (PRISM), an electronic system providing on-line submission, approval and regulatory information management functions, will also be discussed.

A Regional Example of Regulatory Harmonisation

Mr. Dato' Che Mohd Zin Che Awang

The Pharmaceutical Product Working Group (PPWG) was formed in September 1999 under the ASEAN Consultative Committee for Standards and Quality (ACCSQ), aimed to develop a harmonization scheme among ASEAN member countries, and to facilitate and complement the objectives of the ASEAN Free Trade Area (AFTA). Nevertheless, safeguarding public health by ensuring quality, efficacy and safety is crucial and cannot be compromised. The PPWG comprises of regulatory and industry representatives from the ten ASEAN member countries namely Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam. Since its inception, Malaysia was appointed the Chair whilst Thailand as the Co-Chair of PPWG.

Over the last 4 years, the PPWG has been involved in several activities including preliminary exchange of information related to existing regulatory requirements, comparative studies of the various ASEAN countries pharmaceutical registration requirements and studies of other regulatory harmonization modalities particularly the International Conference on Harmonization (ICH). The PPWG has developed the ASEAN Common Technical Requirements and ASEAN Common Technical Dossier (ACTR/ACTD), the final adoption of which were made based on wide consultations and consensus agreement of member countries. Similar to the ICH Common Technical Document, the ACTD is a document that incorporates requirements for quality which is coordinated by Indonesia, safety (pre-clinical) by Philippines and efficacy (clinical) by Thailand. Malaysia was tasked to look into requirements for administrative data, product information and also the ASEAN glossary.

Working guidelines specifically for Stability Studies (Indonesia), Analytical Validation (Thailand), Process Validation (Singapore) and Bioavailability and Bioequivalence (BA/BE) Studies (Malaysia) have also been drafted. As of the 7th Meeting held in July 2003, with regards to Stability Studies, specific criteria related to product shelf life studied at proposed storage conditions require further review prior to finalization. As for BA/BE Guidelines, further deliberation on selection of active substances for BE studies, identification of comparator products and accreditation of BE centers needs to be pursued.

The Implementation Working Group (IWG), a committee under the PPWG was formed in September 2002 to oversee the project implementation. Singapore was appointed the Chair and Indonesia the Co-Chair of the IWG. An initial survey on the ASEAN Harmonized Documents conducted by the IWG prior to the 7th PPWG Meeting in July 2003, revealed that there is a need to monitor on-going progress at defined intervals, focusing on implementation status updates, identifying problems encountered by regulators and industry, changes in review timelines and new training requirements.

Up to date, the PPWG has made considerable progress through partnership and consensus building. However, the successful implementation of the harmonized requirements requires commitment and perseverance of member countries. To move forward, there is also the need to bridge the existing gaps in terms of capacity and capability of member countries. Whilst efforts to collaborate and seek possible assistance from potential international dialogue partners continue, the World Health Organization (WHO) has provided technical assistance and financial resources to improve the existing technical infrastructure particularly training needs.

While the framework agreement on Mutual Recognition Arrangements (MRA) has been laid down under AFTA, with mutual understanding and spirit of cooperation, the desired goal of ASEAN pharmaceutical regulatory harmonization will ultimately serve to increase intra-ASEAN pharmaceutical trade through better market access.

EXPERIENCE OF NON-ICH HARMONISATION INITIATIVES WITH ICH GUIDELIENS

E5 - Ethnic Factors (E5) in APEC – the Regulatory Science, Evaluation Process and Experience

Dr. Herng-Der Chern

Ideally the acceptance and exchange of inter-population clinical data between Caucasian and Asian should be bi-directional, but in reality little Asian clinical data has ever been provided in the past. Recently, in compliance with the ICH E5 concept and the regional needs for Asian data, countries including Japan, Korea, and Taiwan

are implementing bridging studies (BS) as part of the requirement for new drug approval.

With the aim of creating a harmonized regulatory environment for the Asian market, Taiwan has been leading annual conferences entitled "APEC (Asia Pacific Economic Cooperation) Network of Pharmaceutical Regulatory Science – APEC Joint Research Project on Bridging Study" since 2000. The first 2 conferences were held in Taipei in 2000 and 2001 while the third one was in Tokyo, 2002. Scientific data and experience related to ethnic factors were reviewed systematically. Taiwan proposed that "ethnic group" should not be defined as "race" or "citizenship" but should emphasize on the patient population taking this particular drug in a new region. All factors should be evaluated in totality for possible clinical impact. In general, Japan and Korea request some local trials in Japanese or Korean while Taiwan accepts all Asian data, without specified Taiwanese, as good references. Other Asian countries have not implemented E5 but kept a high interest on it. On the industrial front, representatives generally accepted the E5 concept, but they also expressed uncertainties concerning future BS and the regulatory approval processes. After all, all parties agreed that the best solution would be involving Asian populations into global trials and suggested that ICH should add an explanatory note or Q & A to clarify E5.

Requirement of possible BS was formally announced in Taiwan in Dec., 2000. Self-evaluation checking list, decision-making tree, consultation procedure, educational workshops, statistic working group, clinical trial review board, web site, monthly meeting with academia and industries were planned by Department of Health with the help from CDE. Parameters, like how many cases of BS evaluated, results of the evaluation, efficiency of the evaluation process and overall impact in investment and time to market, number of pre-NDA trials, IND consultation, will be monitored constantly. In 148 cases evaluated up to Oct. 9, 2003, 71.6% (106) were classified as no BS required.

These new requirements for BS have ushered a new paradigm for regulatory approvals in Asia. This development will gradually phase out previous administrative formality such as the required small-scale local trial for all drugs and free sale certificates. Based on good regulatory sciences and implementation of E5 in the context with the ICH guidelines, this is truly a great opportunity for Asian countries to participate in the global R & D which was confirmed in a industrial survey by CMR. We trust the BS model developed in APEC will be also good reference for all other regions in accepting foreign clinical data, including Asian data.

E6 – Good Clinical Practice (GCP)

Dr. Patricia Saidon

Q1 – Stability

ASEAN Stability Working Group Chair or Co-Chair

M4 – Common Technical Document (CTD)

Dr. Yuppadee Javroongrit

New GCG Activities and Organization

Dr. Eric Abadie

SATELLITE SESSION II: MEDDRA USER'S GROUP

Overview of Current Activities at the MedDRA Maintenance and Support Services Organization (MSSO)

Mr. Patrick W. Revelle

Overview of Current Activities at the MedDRA Japanese Maintenance Organization (JMO)

Mr. Yasuo Sakurai

MedDRA/J is bilingual version of MedDRA in Japanese and English. MedDRA Japanese version and MedDRA English version are exactly compatible.

Most of their aspects are exactly the same, but, in Japanese version, there are several Japanese specific additional information. JMO, Japanese MedDRA Maintenance Organization, was established to maintain MedDRA Japanese version. The activities of JMO are not limited in language translation but including to promote the appropriate implementation of MedDRA in Japan and to overcome the difficulties arising from linguistic or cultural differences between Japanese and English.

Current Japanese situation of MedDRA usage and the activities of JMO are summarized in this presentation.

Almost five years passed since MedDRA version 2.1 was released commercially in March 1999. However, the real usage of MedDRA was started very slowly in limited companies and limited area. In December 1999, MHLW has issued first notice to use MedDRA Japanese version in regulatory reporting. More than 75% companies have started to use MedDRA for their Post-marketing safety reporting by the end of 2002. In December 2002, MHLW has issued a notice concerning E2B/M2 regulatory implementation in which MedDRA/J utilization is one of the essential factors. E2B/M2 regulatory implementation is scheduled in production in 2003 autumn. This will be a big turning point for MedDRA/J utilization in Japan.

Regarding the linguistic or cultural differences between Japanese and English, MedDRA Japanese version has some differences compared with English version. One is the numbers of ASCII files. The structures and the contents of all ASCII files in MedDRA English version are not changed in MedDRA Japanese version, but Japanese specific ASCII files which contain Japanese description are added. So, MedDRA Japanese version has 17 ASCII files while English version has 11 ASCII files. It is very easy to use MedDRA/J as bilingual terminology.

The other is Japanese currency flag. MedDRA English description is controlled as unique, but there are many cases in which multiple MedDRA terms have the exact same meaning, such as British/American spelling or word order differences. It is impossible to keep English uniqueness in translated Japanese terms. Under this circumstance, Kanji description of each MedDRA LLT has own Japanese currency flag. This flag has two functions, one is to reflect llt_currency in English version and the other is to provide uniqueness in Japanese description.

Recently JMO has started to discuss with Japanese users an additional issue. There are many cases multiple Japanese medical descriptions are translated into the same English medical description. In these cases, new Japanese terms are not allowed to add MedDRA terminology. To overcome these linguistic and cultural differences, new common mechanism to control Japanese synonym, of which definition is to have the same English translation as the existing MedDRA term, is proposed from JMO.

Current MedDRA/J utilization in Japan and the activities of JMO will presented with detailed information.

Updates from the FDA regarding Regulatory Requirements

Dr. Andrea G. Feight

The FDA implemented the Medical Dictionary for Regulatory Activities (MedDRA) in the Adverse Event Reporting System (AERS) in November, 1997. At that time, approximately 1.5 million AE reports were converted from the FDA's former terminology, COSTART, to MedDRA. In the 6 years since then, approximately 1.5 million new reports have been entered into the database, all coded using MedDRA.

The FDA signaled their intention to require the use of MedDRA by publishing an advance notice of proposed rulemaking in November, 1998. On March 14, 2003, the FDA published the Proposed Rule: Safety Reporting Requirements for Human Drug and Biological Products. The proposed rule would require that individual case safety reports for postmarket adverse events be coded in MedDRA prior to submission to the FDA. The comment period for the proposed rule closed October 14, 2003. In formulating a final rule, the FDA will consider and respond to all comments submitted by that date.

Despite the current lack of a regulatory requirement, many pharmaceutical companies are submitting postmarket AE reports coded in MedDRA as part of a five-year ongoing effort between the FDA and PhRMA. The FDA hopes to see an 80% rate of electronic submissions by the end of 2004.

The FDA processes electronic and paper-based AERS reports in a similar manner. Currently either MedDRA text or code number are accepting in electronic submissions. Paper reports are coded into MedDRA using the ADR report narrative. Pre-coded reports received electronically are not re-coded unless there is a discrepancy in MedDRA versioning. The report narrative serves as the basis for performing a quality control check on the MedDRA coding. The FDA is establishing a process for evaluating manufacturer-coded electronic submission reports and will communicate their plans with stakeholders

The FDA is involved in several wide reaching MedDRA activities, including active memberships on the MedDRA Management Board, MedDRA Term Selection: Points to Consider Working Group, ICH/CIOMS Standardized MedDRA Queries (SMQ) Working Group, and MedDRA expert on E2BM Implementation Working Group.

Ongoing challenges in the MedDRA arena include: Maintaining internal coding SOPs; FDA expectations on company coding ; Performing QC on coded reports; Autocoder issues; Case retrieval / search strategies; Indications for product use; Training of FDA reviewers; Use in clinical trial AE reporting; Upversioning process; Impact on datamining; Managing change requests - process and content; Level of coding / transmission; Ability to alter E2BM specifications; Medication Error classification. In addition, there are several Department of Health and Human Services (DHHS) initiatives that may impact on the AERS system and related activities.

There are several opportunities related to MedDRA, including: Cost savings from electronic submissions and pre-coded reports; Proposed SADR Rule; MedDRA Term Selection: Points to Consider documents to promote consistency, especially as the mix of received reports shifts from FDA-coded to company-coded; ICH/CIOMS Working Group on Standardized MedDRA Queries (SMQ); E2BM Implementation Working Group; Providing guidance to user community; LLT/PT duality needed in all fields specifying MedDRA.

Updates from the EMEA regarding Regulatory Requirements

Dr. Sabine Brosch

Updates from the MHLW regarding Regulatory Requirements

Ms. Tomiko Tawaragi

MedDRA is an international medical terminology which was developed as an ICH initiative to support standardized communication of regulatory information among regulatory authorities and the industries. MedDRA reached Step4 under the ICH process in July, 1997, and since then MHLW have made efforts to prepare the implementation of using MedDRA under Japanese regulation.

In Japan, the Japanese Maintenance Organization (JMO) operates the Japanese version of MedDRA(MedDRA/J) maintenance activities under the contract with MSSO.

The first MedDRA/J was commercially released in March 1999 at the same time as the release of MedDRA ver.2.1. Responding to the release, MHW issued an official administrative notification in December 1999 encouraging the use of MedDRA for regulatory post-market ADR reporting on and after March 31, 2000. On April 1, 2000, MHLW started to receive ADR reports using both J-ART (the Japanese version of WHO-ART) and MedDRA as ADR terms. In this phase, the use of MedDRA was not mandatory but just recommended.

MHLW conducted several pilot studies for the implementation of the ICH E2B/M2 Guidelines including the use of MedDRA from December 2000 through November 2002. And finally in August 2003, MHLW started to conduct the large pilot study to ensure that the pharmaceutical companies can generate the ICSR (Individual Case Safety Report) SGML data file based on the ICH E2B/M2 Guidelines and to check their EDI tool for electronic transmission of ICSR SGML data file. More than 300 companies joined this pilot study.

Taking into account the results of this pilot study, MHLW issued the final administrative notification about the regulatory implementation of the ADR reporting based on the E2B/M2 Guidelines including the use of MedDRA on August 28, 2003. On and after October 27, 2003, MHLW requires pharmaceutical companies to submit ICSR SGML data file using MedDRA via Internet or by floppy disk for the ADR reporting for both post-market phase and IND phase.

For the regulatory implementation of use of MedDRA, MHLW asked JMO to provide the environment in which small and medium size enterprises(SMEs) can have access to the MedDRA at low cost, and JMO started the new special license service for such SMEs since August 2003.

Progress of the MedDRA Term Selection: Points to Consider

Dr. Toni Piazza-Hepp

The MedDRA Term Selection Points to Consider (PTC) Document became available for use in early 2000. It is an ICH-endorsed guide for MedDRA users which is developed and maintained by a working group charged by the ICH steering committee. The group includes regulatory and industry representation from the United States, Europe and Japan, as well representatives from Canada (regulatory), the MedDRA Maintenance and Support Services organization (MSSO) and the Japanese Maintenance Organization (JMO). The objective of the PTC is to promote consistency in term selection and enhance medical accuracy when retrieving or sharing data within organizations and between organizations premarketing, postmarketing and worldwide. The document is updated as needed by the PTC working group in response to changes in MedDRA versions as well as user experience. Key concepts and relevant examples will be presented to aid in participant understanding of the content and use of the document.

Progress of the Council for International Organizations of Medical Sciences (CIOMS)/MSSO Work on MedDRA Data Analysis

Mr. Patrick W. Revelle

SATELLITE SESSION III: GENE THERAPY

UPDATE ON GENE THERAPY ACTIVITIES SINCE ICH5

Update since ICH5: Expert Working Group - Activities and Objectives

Dr. Stephanie Simek

Update since ICH5: Gene Therapy Expert Working Group - Objectives and Scope

In July 2000 a meeting was held in Brussels to discuss the need for a forum to discuss scientific issues for the rapidly evolving area of gene therapy. There were presentations and discussions on the perspectives of regulatory oversight, scientific endeavors and concerns regarding pre-clinical pharmacotoxicology studies. It was proposed that ICH provide the forum for this high level exchange of information among the regions on emerging technologies such as gene therapy. In May 2001 there was a meeting held in Tokyo on biotechnological and gene therapy products. Participants included the six ICH parties, Canada, EFTA and WHO. The objectives of the meeting were to consider developing a framework for the regulation of biological products in ICH regions and Canada, to exchange scientific information on biological products and to review current developments on product quality and preclinical and clinical issues regarding gene therapy. At the meeting in Tokyo it was concluded that the scientific principles governing the technical requirements on gene therapy products is similar amongst the ICH regions. It was also decided that there was a need to conduct open discussions on scientifically relevant issues and to continue to foster the exchange of information between industry and regulatory authorities within the structure of ICH. The group identified many important scientific area of future discussion, including; dose definition and standardization, virus shedding and germ-line transmission. These discussions lead to the first ICH gene therapy workshop , held in September 2002 in Vienna Virginia. Presentations and panel discussions included topics such as: status of an adenovirus type 5 reference material (ARM), adenovirus vector shedding and the design and safe use of Lentiviral vectors. The recommendation of the Expert Working Group at the end of this meeting was to continue to exchange scientific information on gene therapy, with a priority for future discussions centering around topics such as Germline integration. This years open ICH6 satellite meeting on gene therapy in Osaka, will have presentations on: Sendai Virus vectors, Germline transmission, insertional mutagenesis/oncogenesis and a brief update on gene therapy activities since ICH5. In keeping with the previous objectives of the gene therapy expert working group, this group will continue to exchange scientific information between the ICH partners, Canada and EFTA and identify new emerging issues in gene therapy to be addressed at future workshops under the auspices of ICH. One future objective of this group will be to develop a mechanism for forming consensus across the regions on scientific and safety information obtained from EWG discussions. A draft of proposed topics for discussion in 2004 will be presented.

Current Issues in Gene Therapy

Gene Therapy Issues in Japan

Dr. Teruhide Yamaguchi

In Japan, clinical study on gene therapy has been developed rapidly over the past decade. In response to the marked progress in gene therapy clinical research abroad, "Guideline for gene therapy clinical research" was developed by the Health Science Council (HSC), and was published in 1994. This guideline addresses the requirements and evaluation system of gene therapy clinical research in order to perform the research appropriately while guaranteeing the scientific rationale and ethical properties. In 1995, "Guideline for assuring the quality and safety of gene therapy products" was issued by the Pharmaceutical Affairs Bureau of the MHW (later MHLW) in order to guarantee the quality, efficacy and safety of gene therapy products. Since gene therapy clinical trial is regulated by both guidelines, manufacturers who planed the clinical trial were required to submit the application to both the HSC and the Food Pharmaceutical Affair Council (FPAC). Recently, in 2002, to simplify the reviewing procedure and ensure the rapid reviewing, both guidelines and evaluation system on gene therapy clinical study were amended. The amendment of evaluation of gene therapy is intended to accelerate the procedure of clinical study.

Currently, 18 protocols for clinical studies including clinical researches and clinical trials have been approved in Japan. Viral vector, such as adenovirus vectors or retrovirus vectors have been mainly utilized in these clinical studies, as gene delivery systems. However, recently, the gene therapy protocol without viral vectors has been increased.

Serious adverse events in a clinical trial on the X-SCID trial in France, two children had a developed leukemia as a result of the retroviral gene therapy, have been also marked impact in Japan. Following this report, retroviral gene therapy clinical studies were temporary hold in Japan. The HSC recommended each investigator 1)to follow-up the patients who had been already treated with gene therapy clinical studies using retroviral vectors and also 2) to inform the adverse events or other safety issues arose during a clinical study in French to patients. Until now, the critical adverse effect has not been reported in Japan. On the condition of revision of the informed consent form to explain the potential risk of serious adverse events, the HSC recently approved re-start for some of these hold trials, in which a targeted disease is fatal and/or other choices of therapy are not available.

Gene Therapy Issues in the EU: Update on x-linked SCID trails

Dr. Klaus Cichutek

Prof. Jean-Hugues Trouvin

Gene Therapy Issues in Canada

Dr. Anthony Ridgway

The first Canadian gene therapy trial was approved in 1994 and there have now been over 40 Clinical Trial Applications (CTAs) approved, although rate of growth has slowed in the last few years. Sponsorship has been split approximately equally between institutional investigators and the pharmaceutical industry. The vast majority of CTAs have been for cancer and there has been recent interest in approaches involving the use of oncolytic viruses. There have been no trials addressing monogenic diseases.

In Canada, there are no specific regulations and no special regulatory process for gene therapy, it is regulated like other biological drugs. There is no Canadian equivalent of the NIH Recombinant DNA Advisory Committee, but otherwise, the regulatory approach is very similar to that used in the United States. The scientific issues and safety and ethical considerations are similar in Canada as they are worldwide, however, regulatory and ethical challenges have been few due to the serious and usually terminal nature of the diseases treated. Intentional germ-line gene transfer will be prohibited by law in Canada.

Canada is consistent with the international community in the regulation of gene therapy and strongly endorses a role for the ICH in furthering the discussion of important technical and ethical issues amongst the regions.

Update since September 2002 Washington DC Meeting

Lentiviral Vectors Safety and Design

Dr. Anthony Meager

The safety and design of lentiviral vectors was considered at the 1st ICH Worshop on Gene Therapy (Washington, DC, USA; 9th September 2002). Conclusions reached indicated that safety largely depended on the elimination of pathogenic capabilities of lentiviral vectors, including generation of Replication Competent Lentiviruses (RCL), insertional oncogenesis and potential germline transmission, by suitable vector design and propagation strategies. Since there is currently a strong focus on the develpoment of lentiviral vectors for clinical use in gene therapy protocols, implementation of appropriate in-process and final lot control testing is seen as paramount to the quality and safety assurance of lentiviral vectors. The Biotechnology Working Party (BWP) of the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA) has recently reviewed the current designs of lentiviral vectors and applicable characterisation and lot release testing methods and has drafted its considerations in a CPMP 'Position Statement on the Development and Manufacture of Lentiviral Vectors'. A review of the considerations in this position statement, including the nature of parental lentiviruses and impact on lentiviral vector development, design of lentiviral vectors, manufacturing strategies, and characterisation and control testing of lentiviral vector lots/batches, will be presented.

Adenoviral Reference Material and other proposed Reference Materials

Characterization and Use

Dr. Beth Hutchins

The development of reference testing reagents has been successfully used to standardize measurements among laboratories in the past. This approach was recommended by many parties with a stake in adenovirus vector delivery to address the fact that particle units and infectious units were not standardized in the field. An Adenovirus Reference Material was developed to define the particle unit and infectious unit for adenovirus gene vectors and create a commonality for comparisons especially data related to safety. The Adenovirus Reference Material Working Group (ARMWG), volunteers representing FDA/CBER, ATCC, US Pharmacopeia, NIBSC, The Williamsburg BioProcessing Foundation, 5 academic groups, 15 industry representatives, 5 contract manufacturers, 4 contract testing companies, and 2 suppliers, was formed to oversee the development of an Adenovirus Reference Material and was responsible for identifying the process to evaluate and select appropriate group(s) to manufacture, characterize, and distribute the material. The ARMWG was able to obtain donations of materials and services to produce more than 5000 x 0.5-mL vials of a reference material consisting of Adenovirus 5 WT, a 293 production cell bank, a Adenovirus 5 WT production virus bank, a 293 testing phase cell bank, and repository services for storage and distribution. The Adenovirus Reference Material was characterized by a consortium of more than 24 laboratories around the world including laboratories in the US, UK, Canada, and France. Characterization phase activities included initiation of a 5-year stability study, a short term field use and shipping configuration stability study, determination of the particle concentration, determination of the infectious titer, sequence determination of the full length DNA, and various analyses for impurities. Particle concentration was determined from 60 data points submitted by 15 laboratories using a procedure based on OD260nm absorbance in the presence of 0.1% (w/v) SDS. A small consortium of 5 laboratories also examined a variety of orthogonal methods to measure particle concentration including RP-HPLC, AE-HPLC, EM, quantitative PCR, and PicoGreen DNA assays. Infectious titer was determined in 17 laboratories using a procedure with a 10-day CPE readout from a 96-well 293-cell format. The assigned infectious titer was corrected for the diffusion of the adenovirus particle and reflects data from 34 separate square root of two-fold dilution series.

The Adenovirus Reference Material is now available for a nominal cost through ATCC (www.atcc.org). All information related to the development and characterization is accessible at the Williamsburg BioProcessing Foundation's website, www.wilbio.com. The FDA is requiring sponsors to use the Adenovirus Reference Material to validate their methods for determination of particle concentration for dose and for determination of infectivity in new INDs. The FDA has made recommendations on how to accomplish this. Since August 2002 ATCC has shipped vials of the ARM to countries around the world. The development of the Adenovirus Reference Material was a highly cooperative effort and the process may serve as a model for development of reference materials for other types of gene therapy vectors.

Detection of RCA and AdV by Infectivity PCR

Dr. Teruhide Yamaguchi

Recombinant adenoviral vector is one of the most promising vectors available for human gene therapy. It is important to quantify infectious adenoviral vector (AdV) and replication-competent adenovirus (RCA) precisely with high sensitivity, in order (1) to determine the accurate dosage of AdV, (2) to avoid safety concerns due to the presence of RCA in clinical lots of AdV products, (3) to examine the shedding of AdV and RCA from the patients administrated AdV products, (4) to ensure consistency of manufacturing process of AdV products. As a method to quantify AdV and RCA, the cytopathic effect (CPE) assay has generally been used. In the CPE assay, AdV/RCA is infected into the cells (ex. HEK 293 cells for quantification of AdV and RCA, HeLa cells for quantification of RCA), and then the destruction of cells induced by AdV/RCA-proliferation is observed. By this method, the CPE is judged by microscopic observation, and thus the results may not always be accurate and quantitative. In addition, this method requires large-scale cell culturing and a substantial amount of time. As a sensitive method to detect viral DNA of AdV and RCA, PCR is thought to be useful. However, the infectivity of AdV/RCA can not be measured by PCR.

In these contexts, we developed a more sensitive, quantitative, and rapid method utilizing infectivity PCR to quantify AdV and RCA. Infectivity PCR is a hybrid method that combines the best features of the infectivity assay (the CPE assay) and PCR. By this method, AdV/RCA is allowed to replicate in the cell culture, as in the conventional CPE assay, and the amount of AdV/RCA replicated in the cells can be determined by quantitative PCR rather than by observing CPE. In this method, the cells (HEK 293 cells or HeLa cells) infected with AdV/RCA are cultured for only three or more days, while the CPE method usually takes more than ten days. To assess the assay sensitivity, we utilized Adenoviral Reference Materials, and at least 1 pfu of AdV/RCA can be easily detected by the infectivity PCR assay. On the other hand, the CPE can be observed in the cells that had been infected with at least 102-104 pfu of AdV/RCA. Therefore, for the detection of AdV/RCA, the infectivity PCR was shown to be almost 100-10,000 times more sensitive than the CPE assay. The infectivity PCR method is useful to quantify RCA and AdV, and may be utilized for the evaluation of safety of adenoviral vector for gene therapy. We are now evaluating our method to adapt the quantification of AdV/RCA in the serum of the patients to whom AdV has been administrated in order to test the viral shedding during the clinical study.

Cytoplasmic Gene Therapy: A new Concept using Sendai Virus Vectors

Dr. Mamoru Hasegawa

Contrary to the expectation for gene therapy as the innovative therapy with explosive improvement, investingators have been forced to struggle to prove its efficacy and safety. The safety issue is especially critical since it may limit the chance of application of gene therapy in futuree medical fields. It should be pointed out that the ability and safety of vectors might have not been still fully or continuously given critical evaluation on the pretext that vectors are at the dawn of a new age of the therapy. The death with an adenovirus vector three years ago and the trouble with a retrovirus vector in France last year call our sincere attention to the risk itself and the risk control of the existing vectors.

Active integration of retrovirus vectors and occasional one by adenoassociated virus vectors to chromosomes have been revealed to cause entire chromosomal rearrangement and local deletions at integration sites. Other vectors of DNA backbone are also to be superintended because they might have chance to some degree of random chromosomal integration and cause permanent loss or gain of genetic nature of recipients. Furthermore, this serious drawback of the existing vectors is thought to inhibit the rapid growth of businesss in gene therapy that may be the mother of further innovation and improvement of the therapy.

Based on such consideration, we have been working with a vector system of completely new concept, a cytoplasmic RNA vectors. The technology from the reverse genetics of negative strand RNA viruses has enabled us to develop such new vectors using Sendai virus (SeV). The virus replicates strictly in the cytoplasm and does not have DNA phase in its infection cycle. Thus, the vectors (SeV vectors) are believed to be substantially free from genotoxicity. High copy number of its genome in the cytoplasm realizes high level gene expression far over the existing vectors, and allow us to examine efficacy/toxicity dose range in preclinical studies and thus to establish with confidence rational clinical protocols. Such type of cytoplasmic RNA vectors with high level gene expression will be the standard of gene therapy and gene vaccines in coming age.

Current Recommendations regarding Inadvertent Germline Integration and Impact on Gene Therapy Clinical Trials

Dr. Dan Takefman

Inadvertent germline transmission (IGLT) by gene transfer vectors is a theoretical risk, but real concern of the FDA. From a societal/ethical standpoint, deliberate germline alteration has been deemed unacceptable. Additionally, germline alterations have a potential for adverse biological effects on the progeny. In terms of IGLT, FDA places the greatest concern with integrating viral vectors that are administered by systemic routes to clinical trial subjects. For these types of trials, FDA recommends that pre-clinical animal biodistribution studies be performed to detect potential distribution to gonadal tissue before initiating clinical trials. Detection of vector sequences in tissue should be performed by PCR with an assay sensitivity of less than 100 vector copies per microgram of genomic DNA, sampling at least 3 micrograms of genomic DNA. If during pre-clinical animal studies, vector is detected in gonadal tissue (without evidence of permanent germline alteration), this finding and the potential for germline alterations should be included in informed consent documents. In certain cases, clinical monitoring by collection of semen samples may be warranted. There have been a number of public discussions regarding IGLT. In 1999 the recombinant DNA advisory committee (NIH/OBA) held a meeting to discuss pre-clinical data from animal biodistribution studies in which retroviral gene transfer vectors were transiently detected in gonadal tissues. It was concluded at this meeting that the risk of IGLT is relatively low and that the use of fertile clinical trial subject populations is acceptable. In the USA there has been reported detection of vector sequences in patient semen from different two clinical trials. These trials have been publicly discussed at meetings including FDA's biological response modifiers advisory committee (BRMAC). Following discussions at the May 2002 BRMAC, it was recommended that if vector sequences are only transiently detected in semen samples, a clinical hold would not be warranted. However, if vector sequences are detected in semen

samples for a period of a year or more, a clinical hold would be warranted and that further public discussion would be necessary. Additionally, the committee strongly encouraged that sponsors of gene transfer clinical trials continue to develop pre-clinical animal models to better assess the potential for IGLT by gene transfer vectors.

Discussion on Insertional Mutagenesis / Oncogenesis: Vector versus Transgene

Prof. Christoph von Kalle

Retrovirus gene transfer allows the addition of stable genetic information to the cellular genome. Interestingly, semi-random vector integration establishes stable genetic markers of clonal derivation are established by, because every transduced stem or progenitor cells will pass on its unique insertion site to all its progeny cells. Recently, very sensitive detection and sequencing of insertion sites has enabled us to determine the location of such insertions in the genome, the number and contribution of genetically modified stem cells by minimally invasive analysis of the peripheral blood in animal models and clinical gene transfer trials. By displaying the LAM-PCR amplified restriction length polymorphism of retrovirus insertion sites, an analysis of the current clonal contribution to hematopoiesis could be generated for each sampled individual in different scenarios. The stability of oligoclonal stem cell contributions over time could be confirmed in more oligoclonal transplant recipients both of dog and primate models. Sequencing of the insertion sites and semi-quantitative PCR tracking of single insertion sites has allowed us to reconstruct the contribution of particular clones over different time points. These studies have demonstrated that even at the single clone level, long term contribution of pluripotent stem cells can be stable for the entire duration of the observation period, so far for up to 3 years after transplantation. In all long term clones studied systematically in three different primates, the stable contribution to the peripheral blood did not reach detectable levels until six weeks after transplantation. We have now observed stable progenitor cell contribution in a clinical trial for up to 9 years (Schmidt et al. Nat Med 2003). With increasing efficiency of gene transfer, the first ever serious side effects have been observed as clonal cell proliferations induced by replication incompetent retrovirus vectors, first in a mouse model (in collaboration with C. Baum, Hannover, Germany / Cincinnati) and unfortunately, in two patients of the French clinical X-SCID gene therapy trial (in collaboration with A. Fischer, M. Cavazzana-Calvo, Hopital Necker, Paris). We were able to detect that insertional mutagenesis in all three of these cases had most likely initiated the development to leukemia-like disease by insertional activation of a cellular oncogene. Both X-SCID cases demonstrate a strikingly similar molecular origin, pointing to possibilities of circumventing these problems by vector and trial design for ongoing and future gene therapy. The potential interaction of the transgene function with insertional mutagenesis is currently being studied in detail.

NON-EXHAUSTIVE LIST OF ICH TOPICS AND THEIR CODES

Q1A(R2)	Stability Testing of New Drug Substances and Products (Revised\Guideline)
Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
Q1E	Evaluation for Stability Data
Q1F	Stability Data Package for Registration Applications in Climatic Zones III and IV
Q3A(R)	Impurities in New Drug Substances (Revised Guideline)
Q3B(R)	Impurities in New Drug Products (Revised Guideline)
Q3C(M)	Residual Solvents Impurities (Maintenance)
Q4 / Q6A	Pharmacopoeial Harmonisation / Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
Q5E	Comparability of Biotechnological / Biological Products Subject to Changes in their Manufacturing Process
S7B	Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals
E2B(M)/M2	Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports including the Maintenance of the Electronic Transmission of Individual Case Safety Reports Message Specification
E2CAdd	Addendum to E2C: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
E2D	Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting
E2E	Pharmacovigilance Planning
E5	Ethnic Factors in the Acceptability of Foreign Clinical Data
E6	Guideline for Good Clinical Practice
E14	Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
M1	Medical Terminology: Medical Dictionary for Regulatory Activities Terminology (MedDRA Terminology)
M2	Electronic Standards for the Transfer of Regulatory Information (ESTRI) including eCTD
eCTD	electronic Common Technical Document (see M2)
M4 or CTD	Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use with Annex: Granularity
M4Q or CTD-Q	The Common Technical Document: Quality Section
M4S or CTD-S	The Common Technical Document: Safety Section
M4E or CTD-E	The Common Technical Document: Efficacy Section

ABBREVIATIONS

ADR	Adverse Drug Reaction
APEC	Asia-Pacific Economic Cooperation
API	Active Pharmaceutical Ingredients
ASEAN	Association of Southeast Asian Nations
CBER	Center for Biologics Evaluation and Research (US)
CDER	Center for Drug Evaluation and Research (US)
CIOMS	Council for International Organizations of Medical Sciences
CMC	Chemistry, Manufacturing and Controls
CPMP	Committee for Proprietary Medicinal Products (EU)
CTD	Common Technical Document
CTD-Q	Common Technical Document, Quality data
CTD-S	Common Technical Document, Safety (Nonclinical) data
CTD-E	Common Technical Document, Efficacy (Clinical) data
DTD	Document Type Definition
e-CTD	electronic Common Technical Document
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Association
EMEA	European Agency for the Evaluation of Medicinal Products
EP	European Pharmacopoeia
ESTRI	Electronic Standards for Transmission of Regulatory Information
EU	European Union
EWG	Expert Working Group
FDA	Food & Drug Administration (US)
GCG	Global Cooperation Group (Sub-group of the ICH Steering Committee)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICDRA	International Conference on Drug Regulatory Authorities (WHO)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
IGPA	International Generic Pharmaceutical Alliance
ISE	Integrated Summary of Efficacy (US)
ISS	Integrated Summary of Safety (US)
IWG	Implementation Working Group
JMO	Japanese Maintenance Organization (for MedDRA)
JP	Japanese Pharmacopoeia
JPMA	Japan Pharmaceutical Manufacturers Association
MedDRA	Medical Dictionary for Regulatory Activities (ICH)
MedDRA/J	Japanese version of MedDRA
MHLW	Ministry of Health, Labour and Welfare (Japan)
MSSO	Maintenance and Support Services Organization (for MedDRA)
NCE	New Chemical Entity
NIH	National Institute of Health (US)
NIHS	National Institute of Health Sciences (Japan)
PAHO	Pan American Health Organisation
PANDRH	Pan American Network of Drug Regulatory Harmonization
PDG	Pharmacopoeial Discussion Group
PhRMA	Pharmaceutical Research and Manufacturers of America
PSUR	Periodic Safety Update Report
SADC	Southern African Development Community
SC	Steering Committee
US/USA	United States of America
USP	United States Pharmacopeia
WHO	World Health Organization
WSMI	World Self-Medication Industry

附錄五　ICH Guideline 一覽表

SYNOPSIS OF ICH GUIDELINES AND TOPICS

CONTENTS

SYNOPSIS OF ICH GUIDELINES AND TOPICS

The guidelines approved by ICH are listed under four categories, Quality (Q), Safety (S), Efficacy (E), and Multidisciplinary (M). Full text copies are available from the ICH Secretariat or the web site: www.ich.org

Quality

Q1A(R2) **Stability Testing of New Drugs and Products (Second Revision)**

A revision of an earlier guideline on stability testing.

This guideline provides recommendations on stability testing protocols including temperature, humidity and trial duration. Furthermore, the revised document takes into account the requirements for stability testing in Climatic Zones III and IV in order to minimize the different storage conditions for submission of a global dossier.

Q1B **Photostability Testing of New Drug Substances and Products**

This document provides the basic testing protocol required to evaluate the light sensitivity and stability of new drugs and products.

Q1C **Stability Testing for New Dosage Forms**

This document extends the main stability guideline for new formulations of already approved medicines and defines the circumstances under which reduced stability data can be accepted.

Q1D: **Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products**

This document describes general principles for reduced stability testing and provides examples of bracketing and matrixing designs.

Q1E: **Evaluation of Stability Data**

This document extends the main guideline by explaining possible situations where extrapolation of retest periods/shelf-lives beyond the real-time data may be appropriate. Furthermore, it provides examples of statistical approaches to stability data analysis.

Q1F: **Stability Data Package for Registration in Climatic Zones III and IV**

This new document provides guidance on specific stability testing requirements for Climatic Zones III and IV. Besides proposing acceptable storage conditions for long-term and accelerated studies, it gives guidance on data to cover situations of elevated temperature and/or extremes of humidity. The referenced literature provides information on the classification of countries according to climatic zones.

Q2A **Text on Validation of Analytical Procedures**

This document identifies the validation parameters needed for a variety of analytical methods and discusses the characteristics that must be considered during the validation of the analytical procedures that are included as part of registration applications.

Q2B **Validation of Analytical Procedures: Methodology**

This document extends the guideline Q2A to include the actual experimental data for the validation of analytical procedures.

Q3A(R) **Impurities in New Drug Substances (Revised)**

The guideline addresses the chemistry and safety aspects of impurities, including the listing of impurities in specifications and defines the thresholds for reporting, identification and qualification. The revision of the guideline has allowed to clarify some inconsistencies, to revise the decision tree, to harmonize with Q3B and to address some editorial issues.

Q3B(R) **Impurities in New Drug Products (Revised)**

This guideline complements the guideline on impurities in new drug substances and provides advice in regard to impurities in products containing new, chemically synthesized drug substances. The guideline specifically deals with those impurities which might arise as degradation products of the drug substance or arising from interactions between drug substance and excipients or components of primary packaging materials. The guideline sets out a

rationale for the reporting, identification and qualification of such impurities based on a scientific appraisal of likely and actual impurities observed, and of the safety implications, following the principles elaborated in the parent guideline. Threshold values for reporting and control of impurities are proposed, based on the maximum daily dose of the drug substance administered in the product.

Q3C **Impurities: Guideline for Residual Solvents**

This document recommends the use of less toxic solvents in the manufacture of drug substances and dosage forms, and sets pharmaceutical limits for residual solvents (organic volatile impurities) in drug products.

Q3C(M) **Impurities: Guideline for Residual Solvents (Maintenance)**

Limit values for two residual solvents in drug products were revised on basis of the newly recognized toxicity data; lower PDE (permissible daily exposure) for N-Methylpyrrolidone being kept in Class 2 (limited by health-basis) and for Tetrahydrofuran being placed into Class 2 from Class 3 (no health-based).

Q4 **Pharmacopoeial Harmonization**

Harmonization of drug specifications at ICH [Q6A] requires pharmacopoeial harmonization. Several pharmacopoeial general chapters for parenteral, oral and liquids dosage forms and monographs on excipients have already been harmonized. This work is ongoing and discussions are continuing on the way this work will be implemented in the three regions. No guidance document will be generated from this activity.

Q5A **Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin**

This document is concerned with testing and evaluation of the viral safety of biotechnology products derived from characterized cell lines of human or animal origin. The purpose is to provide a general framework for virus testing experiments for the evaluation of viral clearance and the design of viral tests and clearance evaluation studies.

Q5B **Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for the Production of r-DNA Derived Protein Products**

This document advises on the types of information that are considered valuable in assessing the structure of the expression construct used to produce recombinant DNA derived proteins.

Q5C **Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products**

This document augments the stability guidance (Q1A) and deals with the particular aspects of stability test procedures needed to take account of the special characteristics of products in which the active components are typically proteins and/or polypeptides.

Q5D **Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products**

This document provides broad guidance on appropriate standards for the derivation of human and animal cell lines and microbes used to prepare biotechnological/biological products and for the preparation and characterization of cell banks to be used for production.

Q6A **Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances**

This document addresses the process of selecting tests and methods and setting specifications for the testing of drug substances and dosage forms.

Q6B **Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products**

This document provides guidance on justifying and setting specifications for proteins and polypeptides that are derived from recombinant or non-recombinant cell cultures. The scope of this part of the topic is initially limited to well-characterized biotechnological products, although the concepts may be applicable to other biologicals as appropriate. In view of the nature of the products, the topic of specifications includes in-process controls, bulk drug, final product and stability specifications and give guidance for a harmonized approach to determining appropriate.

Q7A **Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients**

Good Manufacturing Practices impact virtually all areas of the global pharmaceutical industry. Due to the wide-impact of this document, this document incorporates geographic perspectives normally outside the ICH process.

Safety

S1A — **Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals**

This document provides a consistent definition of the circumstances under which it is necessary to undertake carcinogenicity studies on new drugs. These recommendations take into account the known risk factors as well as the intended indications and duration of exposure.

S1B — **Testing for Carcinogenicity of Pharmaceuticals**

This document provides guidance on the need to carry out carcinogenicity studies in *both* mice and rats, and guidance is also given on alternative testing procedures which may be applied without jeopardizing safety.

S1C & S1C(R) — **Dose Selection for Carcinogenicity Studies of Pharmaceuticals and Addendum : Addition of a Limit Dose and Related Notes**

This document addresses the criteria for the selection of the high dose to be used in carcinogenicity studies on new therapeutic agents to harmonize current practices and improve the design of studies. This revised guidance gives updated criteria for the selection of the high dose that is to be used in carcinogenicity studies.

S2A — **Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals**

This document provides specific guidance and recommendations for *in vitro* and *in vivo* tests and on the evaluation of test results. It includes a glossary of terms related to genotoxicity tests to improve consistency in applications.

S2B — **Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals**

This document addresses two fundamental areas of genotoxicity testing: the identification of a standard set of assays to be conducted for registration, and the extent of confirmatory experimentation in any particular genotoxicity assay in the standard battery.

S3A — **Note for Guidance on Toxicokinetics: the Assessment of Systemic Exposure in Toxicity Studies**

This document gives guidance on developing test strategies in toxicokinetics and the need to integrate pharmacokinetics into toxicity testing to aid in the interpretation of the toxicology findings and promote rational study design development.

S3B — **Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies**

This document gives guidance on circumstances when repeated dose tissue distribution studies should be considered (i.e., when appropriate data cannot be derived from other sources). It also gives recommendations on the conduct of such studies.

S4 — **Single Dose Toxicity Tests**

Agreement was reached, at the time of ICH 1, in 1991, that the LD_{50} determination should be abandoned for pharmaceuticals. The recommendation was published in the Proceedings of the First International Conference on Harmonisation, page 184.

S4A — **Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent)**

A tripartite, harmonized ICH guideline was finalized *(Step 4)* in September 1998. The recommendations are unchanged from those in the consultation draft issued in July 1997. The text incorporates the guidance for repeat-dose toxicity tests that was agreed at the time of ICH 1, in 1991 (reduction of the duration of repeat dose toxicity studies in the rat from 12 to 6 months)

S5A — **Detection of Toxicity to Reproduction for Medicinal Products**

This document provides guidance on tests for reproductive toxicity. It defines the periods of treatment to be used in animals to better reflect human exposure to medical products and allow more specific identification of stages at risk.

S5B(M) — **Toxicity to Male Fertility: An Addendum to the Guideline on Detection of Toxicity to Reproduction for Medicinal Products (Maintenance)**

An addendum to the S5A, this document provides guidance on non-clinical male fertility studies. These amendments provide a better description of the testing concept and recommendations, especially those addressing flexibility, pre-mating treatment duration, and observations.

S6 — **Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals**

This guidance document covers the pre-clinical safety testing requirements for biotechnological products. It addresses the use of animal models of disease, determination of when genotoxicity assays and carcinogenicity studies should be performed, and the impact of antibody formation on duration of toxicology studies.

S7A — **Safety Pharmacology Studies for Human Pharmaceuticals**

This document addresses the definition, objectives and scope of safety pharmacology studies. It also addresses which studies are needed before initiation of Phase 1 clinical studies as well as information needed for marketing.

S7B — **Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals**

This document addresses the recommendation of nonclinical testing strategy and integrated risk assessment for predicting the potential of pharmaceuticals for delayed ventricular repolarization (QT interval prolongation) associated with ventricular tachycardia and torsade de pointes. This document is coordinately developed with the document on the clinical evaluation of QT/QTc interval prolongation (E14).

Efficacy

E1 — **The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions**

This document provides recommendations on the numbers of patients and duration of exposure for the safety evaluation of drugs intended for the long-term treatment of non-life-threatening conditions.

E2A — **Clinical Safety Data Management: Definitions and Standards for Expedited Reporting**

This document provides standard definitions and terminology for key aspects of clinical safety reporting. It also gives guidance on mechanisms for handling expedited (rapid) reporting of adverse drug reactions in the investigational phase of drug development.

E2B(M)/ M2 — **Maintenance of the Clinical Safety Data Management including the Maintenance of the Electronic Transmission of Individual Case Safety Reports (Version 4.4.1)**

This document extends E2A to standardize the data elements necessary for the exchange of individual case safety reports electronically. Pilot studies indicated the feasibility of the transactions, but also identified areas that could be improved by further discussion in the EWG. The maintenance of the E2B *Step 4* document will be done without major changes, but modifications would make the document clearer and revolve the issues raised in the three regional pilot studies. The revised document is intended to further advance the electronic exchange of safety information and approach a true EDI (Electronic Data Interchange) standard.

Electronic Transmission of Individual Case Safety Reports Message Specification (ICH ICSR DTD Version 2.1)

Download the M2 : E2B(M) (ICH ICSR M2 Version 2.3 specification document) to get instructions on using the DTDs to prepare structured data sets. The E2BM *Step 4* document provides an updated description of the data elements for the transmission of individual case safety reports and instructions on how to use these data elements. Version 2.1 of the DTD has been developed to correspond to the E2BM *Step 4* Document version 4.4.1.

E2B(M) — **Maintenance of the Clinical Safety Data Management Including: Data Elements for Transmission of Individual Case Safety Reports**

Questions and Answers:

Since reaching *Step 4* and publication within the ICH regions, experiences by all parties with the implementation of the E2B(M) Guideline have resulted in the need for some clarification. This supplementary Questions and Answers document intends to clarify key issues.

E2C — **Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs**

This guidance covers the format and content of safety updates that need to be provided at intervals to regulatory authorities after products have been marketed. The guideline is intended to ensure that the worldwide safety experience is provided to authorities at defined times after marketing with maximum efficiency and avoidance of duplication of effort.

E2C(Add): **Addendum to Periodic Safety Update Reports for Marketed Drugs**

The document intends to provide further clarification and guidance in the preparation of PSURs as specified in E2C. Additionally, the document addresses some new concepts not in E2C but reflecting current pharmacovigilance practice needs, including Proprietary information (Confidentiality), Executive summary, summary bridging report, addendum reports, Risk management program and Benefit-risk analysis.

E2D: **Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting**

This document provides a standardized procedure for post-approval safety data management including expedited reporting to relevant authority. The definitions of the terms and concept specific to post-approval phase are also provided. E2A definitions in clinical safety data management was maintained in this document as post-approval safety data management, such as seriousness definition. The practices of the data management were standardized in such cases obtained from consumers, literatures, internets which are all specific to post-approval data management. Good case management practice was focused and recommended for expedited reporting with clear definitions.

E3 **Structure and Content of Clinical Study Reports**

This document describes the format and content of a study report that will be acceptable in all 3 ICH regions. It consists of a core report suitable for all submissions and appendices that need to be available but will not be submitted in all cases.

E4 **Dose-Response Information to Support Drug Registration**

This document provides recommendations on the design and conduct of studies to assess the relationship between doses and clinical response throughout the clinical development of a new drug.

E5 **Ethnic Factors in the Acceptability of Foreign Clinical Data**

This document addresses the intrinsic characteristics of the drug recipient and extrinsic characteristics associated with environment and culture that could affect the results of clinical studies carried out in regions and describes the concept of the "bridging study" that a new region may request to determine whether data from another region are applicable to its population.

Questions and Answers:

Since reaching *Step 4* and publication within the ICH regions, experiences by all parties with the implementation of the E5 Guideline have resulted in the need for some clarification. This supplementary Questions and Answers document intends to clarify key issues.

E6 **Good Clinical Practice: Consolidated Guideline**

This Good Clinical Practices document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRBs. GCPs cover aspects of monitoring, reporting and archiving of clinical trials and incorporating addenda on the Essential Documents and on the Investigator's Brochure which had been agreed earlier through the ICH process.

E7 **Studies in Support of Special Populations: Geriatrics**

This document provides recommendations on the special considerations that apply in the design and conduct of clinical trials of medicines that are likely to have significant use in the elderly.

E8 **General Considerations for Clinical Trials**

This document sets out the general scientific principles for the conduct, performance and control of clinical trials. The guideline addresses a wide range of subjects in the design and execution of clinical trials.

E9 **Statistical Principles for Clinical Trials**

This biostatistical guideline describes essential considerations on the design and analysis of clinical trials, especially the "confirmatory" (hypothesis-testing) trials that are the basis for demonstrating effectiveness

E10 **Choice of Control Group and Related Issues in Clinical Trials**

This document addresses the choice of control groups in clinical trials considering the ethical and inferential properties and limitations of different kinds of control groups. It points out the assay sensitivity problem in active control equivalence / non-inferiority trials that limit the usefulness of trial design in many circumstances.

E11 **Clinical Investigation of Medicinal Products in the Pediatric Population**

This document addresses the conduct of clinical trials of medicines in pediatric populations. This document will facilitate the development of safe and effective use of medicinal product in pediatrics.

E12A **Principles for Clinical Evaluation of New Antihypertensive Drugs**

This first therapeutic area guideline considers the Clinical Evaluation of New Antihypertensive Drugs. It provides a set of "Principles" on which there is general agreement among all three ICH regions covering endpoints and trial designs. Since there are a few differences in the requirements of the three regions that have not been harmonized, this document should be considered an "ICH Principle Document" rather than an "ICH Guideline". It will not be subject to the usual procedures leading to a fully harmonized document.

Multidisciplinary

M1 **Medical Terminology**

The working group has provided a new *Medical Dictionary for Regulatory Activities Terminology* (MedDRA Terminology) that is intended for international adoption. It is designed to support the classification, retrieval, presentation, and communication of medical information throughout the medical product regulatory/life cycle. Its goal is to provide a comprehensive and specific terminology to help standardize, facilitate and simplify regulatory processes.

M2 **Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI)**

This project includes the verification of procedures for consistent, accurate transfer of information; the evaluation of encryption technologies and key certification procedures for the transfer of regulatory information. The working group has undertaken test projects to define logical electronic communication standards to ensure the integrity of information and data exchange between pharmaceutical companies and authorities. Tests have also been conducted which involve transferring encrypted and non-encrypted files between a limited number of international centers. Recommendations have been made on the Implementation for Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI), the Core Standard Set, the Physical Media (Floppy Disks and CD-ROM), Network Messaging, Secure EDI Transmission over the Internet and Electronic Document and Message Formats.

The Electronic Common Technical Document (eCTD) allows for the electronic submission of the Common Technical Document (CTD) from applicant to regulator. While the table of contents is consistent with the harmonized CTD, the eCTD also provides a harmonized technical solution to implementing the CTD electronically. This group has developed and begun to implement the eCTD across the ICH partner and observer regions. The group has developed a change control process to monitor implementation progress and provide solutions and added flexibility found necessary during implementation. Using the change control process, several topics including study report structure, lifecycle management, and consistency with the CTD are being addressed and resolved. This defined change control process ensures that the future of the eCTD is managed in a clear, harmonized manner within the ICH process.

M3 (M) **Maintenance of the ICH Guideline on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals**

This multidisciplinary document addresses principles for the development of non-clinical strategies on the timing of toxicity studies in relation to the conduct of clinical trials. The guideline represents an important step forward on requirements for the different phases of clinical development but it is recognized that there remain some further important issues yet to be resolved.

M4 **The Common Technical Document (CTD)**

The Common Technical Document will provide a harmonized structure and format for new product applications. These documents were agreed upon in November 2000 in San Diego. The four documents will address the application organization (M4 organize), the quality section (M4Q), the safety section (M4S), and the efficacy section (M4E) of the harmonized application.
The Common Technical Document provides for a harmonized structure and format for new product applications. The Common Technical Document was agreed upon in November 2000, in San Diego, USA. This Common Technical Document is divided into four separate sections. The four sections address the application organization (M4 organize), the quality section (M4Q), the safety section (M4S), and the efficacy section (M4E) of the harmonized application. The agreed upon implementation date for the Common Technical Document, in the three regions, was July, 2003.

An electronic version of the Common Technical Document (eCTD) can be produced using the specifications and other information developed by the eCTD Implementation Working Group.

Annex : Granularity Document

The 'Granularity Document' of the M4 Organisation defines a series of standards for the physical construction of CTD submissions. These are applicable to both the paper CTD and the eCTD. The appendix defines the granularity of the documents, their pagination, the use of section numbers, the use of tab dividers (for the paper CTD) and what to include in the Tables of Content for each module (for the paper CTD). The granularity aspects describe what constitutes a document, i.e., divided by tabs and numbered separately in the paper submission and, in an eCTD, provided as separate files. It also defines at what level in the table of contents documents/files should be placed and where multiple documents/files may be provided for a particular section.

Questions and Answers:

In order to help users deal with issues which may arise during attempts to use the CTD, the ICH has supplied a Questions &Answers section on the ICH Web site to answer most, if not question anyone may have. If issues arise that are not answered on the Web site, additional questions can be submitted for a formal response.

M4Q

The Common Technical Document for the Registration of Pharmaceuticals For Human Use –QUALITY
Module 2 : Quality Overall Summary (QOS)
Module 3 : Quality.

The Quality section of the Common Technical Document provides a harmonized structure and format for presenting CMC (Chemistry, Manufacturing, and Controls) information in a registration dossier. The table of contents includes sections on Drug Substance and Drug Product. There are also sections for regional specific information as well as some appendices. Due to the fact that many CMC topics have not yet been the subject of ICH guidelines (e.g., drug substance synthesis, drug product manufacture, container closure), the content of CTD-Q is not totally harmonized. A new section on Pharmaceutical Development has been included to replace the Development Pharmaceutics Report (currently a part of the EU submission requirements). Also, a new CMC summary document, the Quality Overall Summary, has been developed.

M4S

The Common Technical Document for the Registration of Pharmaceuticals for Human Use – SAFETY
Nonclinical Summaries and Organisation of Module 4

The M4S Guideline will delineate the structure and format of the nonclinical summaries in Module 2 of the Common Technical Document, and will provide the organization of Module 4, the Nonclinical Study Reports. The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical, and generally should not exceed 30 pages. The Nonclinical Written Summaries (100 - 150 pages) are recommended to provide more extensive summaries and discussion of the nonclinical information on pharmacology, pharmacokinetics, and toxicology. Thirty-four templates are provided for the preparation of the Nonclinical Tabulated Summaries, and 31 example tables are provided. Finally, the organization of the Nonclinical Study Reports in Module 4 is described. Preparation of the nonclinical sections of the Common Technical Document according to the M4S Guideline will result in a single harmonized dossier of the nonclinical information that will be acceptable in all three ICH regions.

M4E

The Common Technical Document for the Registration of Pharmaceuticals For Human Use – EFFICACY
Module 2 : Clinical Overview And Clinical Summary
Module 5 : Clinical Study Reports.

CTD-Efficacy (M4E) describes the structure and format of the clinical data in an application, including summaries and detailed study reports. There are two high level clinical summaries in Module 2 of the CTD: the Clinical Overview, a short document that provides a critical assessment of the clinical data; and the Clinical Summary, a longer document that focuses on data summarization and integration. Clinical Study Reports and raw data (where applicable) are included in Module 5 of the CTD.