INTERNATIONAL CONFERENCE ON HARMONIZATION OF TECHNICAL REQUIRMENTS FOR REGISTRATION OF PHRMACEUTICALS FOR HUMAN USE

ICH

Proceedings of ICH Public Meeting: ICH Japan Symposium 2009

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ICH Japan Symposium 2009

June 12, 2009

Tower Hall Funabori, Edogawa-ku, Tokyo, Japan

ICH Public Conference

Organized by the
Society of Japanese Pharmacopoeia &
Japan Pharmaceutical Manufacturers Association

Sponsored by the
Ministry of Health, Labour and Welfare
Federation of Pharmaceutical Manufacturers` Association of JAPAN
Pharmaceutical Manufacturers` Association of Tokyo
Osaka Pharmaceutical Manufacturers Association
Japan Pharmaceutical Association

Proceedings of
ICH Public Meeting:
ICH Japan Symposium 2009

Editors:

Shinobu Uzu, International Planning Director, Minister's Secretariat, Ministry of Health, Labour and Welfare

Kohei Wada, Chair, ICH Committee, Japan Pharmaceutical Manufacturers Association, VP/General Manager, Asia Development, R&D Division, Daiichi Sankyo Co., Ltd

Takayuki Okubo, Deputy Director, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

Kurajiro Kishi, DVM, PhD, Director, Medical & Scientific Department, Japan Pharmaceutical Manufacturers Association

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Scientific Program Committee

Mr. Shinobu Uzu	International Planning Director, Ministry of Health, Labour and Welfare
Mr. Takayuki Okubo	Deputy Director, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Mr. Kazutaka Ichikawa	Director General, Japan Pharmaceutical Manufacturers Association
Mr. Kohei Wada	Chair, ICH Committee, Japan Pharmaceutical Manufacturers Association (VP/General Manager, Asia Development, R&D Division, Daiichi Sankyo Co., Ltd)
Dr. Kurajiro Kishi	Director, Medical & Scientific Department, Japan Pharmaceutical Manufacturers Association

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Mr. Kohei Wada	Chair, ICH Committee, Japan Pharmaceutical Manufacturers Association (VP/General Manager, Asia Development, R&D Division, Daiichi Sankyo Co., Ltd)
Dr. Kurajiro Kishi	Director, Medical & Scientific Department, Japan Pharmaceutical Manufacturers Association
Ms. Aya Kuramoto	ICH Secretariat, Japan Pharmaceutical Manufacturers Association

For further information, please contact JPMA ICH Coordinator:
Dr. Kurajiro Kishi, Tel.: +81-3-3241-0326, Fax: +81-3-3242-1767
E-mail:kishi@jpma.or.jp
JPMA postal address: Japan Pharmaceutical Manufacturers Association, Torii Nihonbashi Bldg., 3-4-1, Nihonbashi Honcho, Chuo-ku, Tokyo 103-0023, Japan

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Center for Product Evaluation,
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Background to the Second Regional ICH Public Meeting in Japan

Since the ICH Steering Committee agreed to the organization of meetings focused on a regional basis at the Brussels Meeting in May 2007, regional ICH public meetings have been held in each ICH region; first in Tokyo on November 2, 2007, then the following year in the US and Europe. The meeting entitled “ICH Japan Symposium 2009” is the second regional ICH public meeting held in Japan which took place at the Tower Hall Funabori in Tokyo on June 12, 2009, the following day of the ICH Yokohama Meeting (June 6 - 11, 2009).

The Symposium aimed to provide an opportunity to update to the public on the progress made during the ICH meeting in Yokohama and on the status of the various ICH guidelines under development. It also aimed to provide an opportunity for participants and the ICH experts/rapporteurs to have a Q&A on a face-to-face basis on all the topics discussed at the Yokohama Meeting. In addition, the Symposium also had a special session on the implementation of ICH guidelines in Asian countries, with regulatory speakers mainly from Asian countries of the ICH Global Cooperation Group presenting on the use of ICH guidelines and on the value of training in helping to facilitate implementation.

The Symposium was well attended with approximately 600 participants of the pharmaceutical industry, the regulatory authorities, etc. from the following 18 countries in Africa, Asia, Europe and North America; Botswana, Mozambique, China, Chinese Taipei, India, Korea, Singapore, Thailand, Austria, Belgium, France, Germany, Sweden, Switzerland, UK, Canada, USA and Japan. The participants had the opportunity to receive an update on the progress, to enhance the mutual understanding and to meet with regulators and industry experts from both ICH and non-ICH regions.

The Symposium was jointly organized by Japan Pharmaceutical Manufacturers Association (JPMA) and the Society of Japanese Pharmacopoeia (SJP, non-profit organization), and supported by the Ministry of Health, Labour and Welfare (MHLW), the Federation of Pharmaceutical Manufacturers’ Association of Japan, the Pharmaceutical Manufacturers’ Association of Tokyo, the Osaka Pharmaceutical Manufacturers Association and the Japan Pharmaceutical Association.

August 24, 2009

WELCOMING ADDRESS

Kohei Wada, *JPMA*
Member of the Steering Committee

Welcome to the ICH Japan Symposium. I am Kohei Wada from Daiichi Sankyo Company.
As the chair of JPMA ICH Project Committee, I would like to thank you all for coming to the ICH Japan symposium 2009. I am so happy to see so many faces today. On behalf of the organizer, I would like to say a few words of welcome.

Up until yesterday, we had been having the ICH meetings in Yokohama with the participation of more than 350 people. Among the meetings during the week, on Sunday and Monday we had the Regulators Meeting and the Regulators Forum. On Monday, there was the Industry Coordination Group meeting and on Tuesday, we had the GCG meeting. Wednesday and Thursday, we had the Steering Committee meeting. In parallel, there were many expert meetings, more than 70 meetings in 16 topics. We had major progress and achievements in most of the topics. Today, we would like to take a day to share about what was achieved during the meetings.

Every time, I feel that ICH meeting is existing on the hard work of the experts all over the world and I am always impressed by their efforts and commitment. With their dedication, we had been able to make major progress of ICH activities. Until recently, we had a major ICH event once in a while. However, we decided to have more frequent ICH meetings to include the general public for the sharing of ICH information on regional basis. This is the second Japan symposium following the first one in November of 2007.

This slide shows today's aim of the symposium. We have three aims. Up until yesterday, we had very intensive meetings, so we would like to share the hot topics discussed during the meetings. In other words, the presentations today will be the latest information. Also, we would like to share with you, information on topics not only from the Yokohama meeting, but covering the other ICH topics, so that you can understand the situation of ICH. We also have a special session focused on the Asian region in the afternoon.

As I mentioned earlier, the organizer and the speakers had to rush into this venue from the Yokohama meeting. Therefore, we may have some short comings in the meeting, but I hope you would understand.

Furthermore, in realizing today's symposium, we had support from many people. They are the ones who are working outside of this venue as well as those who are sitting inside of this venue today. With their support, this symposium was made possible. So taking this opportunity, I would like to extend my gratitude to all those who had been working behind the scenes.

Finally, I hope this symposium will be a fruitful one for all of you. Thank you very much.

Welcome to

ICH Japan Symposium

Kohei Wada
Chair, JPMA ICH Project Committee

v1

The Yokohama ICH >350 people

6/6 Sat	6/7 Sun	6/8 Mon	6/9 Tue	6/10 Wed	6/11 Thurs
	Coordin. -mtg	Steering com Industry mtg	GCG meeting	Steering com	
	Regulators forum				
Various Working Groups (EWGs, IWGs, etc) met throughout the week: 16 topics; >70 meetings					

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ICH Japan Symposium: Aim

- Share the "Hot Topics" discussed until yesterday => Latest Info
- Cover all the ICH topics, including those did not meet in Yokohama => Full coverage
- Special session in the end => Asian Regional taste

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PLENARY SESSION

Overview of ICH Activities

Shinobu Uzu, *MHLW*
Member of the Steering Committee

Abstract
Mr. Shinobu Uzu will present the overview of the history and structure of ICH.

Mr. Uzu is the International Planning Director at the Ministry of Health, Labor and Welfare as well as the current member of the Steering Committee at the ICH meetings.

Questions and Answers

There were no questions.

Overview of ICH activities

Shinobu UZU
International Planning Director
MHLW

ICH Objectives

- To improve the efficiency of the process for developing and registering new medicinal products in Europe, Japan and the United States through harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, in order to make these products available to patients with a minimum of delay

ICH Structure

JAPAN
MHLW/PMDA・JPMA

EU
EC/EMEA・EFPIA

USA
FDA・PhRMA

Observer: WHO, Health Canada, EFTA
Secretariat: IFPMA

ICH Structure

Steering Committee (SC)

Expert Working Group (EWG)

Quality | Safety | Efficacy | Multidisciplinary

Implementation Working Group:Q&A for Guidelines

Steps of ICH Harmonization

1. Formal Procedure

Step 1: Consensus Building

Step 2: Confirmation of six-party consensus

Step 3: Regional Regulatory Consultation & Discussion
a) Regional Regulatory Consultation
b) Discussion of Regional Consultation Comments

Step 4: Adoption of Confirmation of six-party consensus

Step 5: Implementation

2. Other Procedures

Q&A Procedure

Revision Procedure

Maintenance Procedure

Outcome of ICH
- Over 50 ICH Guidelines -

	Topics / guidelines
Quality	10 topics / 24 guidelines
Safety	8 topics / 13 guidelines
Efficacy	14 topics / 19 guidelines
Multidisciplinary	MedDRA, eCTD, ESTRI, E2B, CTD, M3

Beyond ICH

1. Global Cooperation Group (GCG: 1999-)

   Mission: To promote a mutual understanding of regional harmonization initiatives in order to facilitate the harmonization process related to ICH guidelines regionally and globally, and to facilitate the capacity of drug regulatory authorities and industry to utilize them.

2. Regulators Forum (2008. 6 -)

   Forum for discussion and sharing information of best practices between regulatory authorities on issues related to the implementation of ICH guidelines and impact on regulatory systems

Thank you

http://www.ich.org

http://www.pmda.go.jp/ich/ich_index.html (日本語)

Overview of ICH Topics

Kurajiro Kishi, *JPMA*
ICH Coordinator

Abstract

Date of Meeting, Venue

June 6-11, 2009
Yokohama Royal Park Hotel, Yokohama, Japan

Steering Committee Main Participants (members and observers)

Japan: Mr. Shinobu Uzu (Chair, MHLW), Dr. Satoshi Toyoshima (PMDA),
Mr. Kazutaka Ichikawa, Mr. Kohei Wada (JPMA)

USA: Dr. Robert Yetter, Dr. Justina Molzon (FDA),
Dr. Alice Till, Dr. Peter Honig (PhRMA)

EU: Ms. Lenita Lindström-Rossi, Dr. Tomas Salmonson (EU),
Dr. Christine-Lise Julou, Dr. André Broekmans (EFPIA)

Observers: Mr. Mike Ward (Health Canada), Dr. Lembit Rägo (WHO),
Dr. Petra Doerr (EFTA)

ICH Secretariat: Dr. Odette Morin (IFPMA)

EWGs/IWGs/Discussion Groups (1): Face-to-Face Meeting in Yokohama

Multidisciplinary/e-Groups:

- M2(SDOs)/eCTD : Electronic Standards for the Transfer of Regulatory Information and the Electronic CTD
- E2B(R3) : Revision of the Electronic Submission in Individual Case Safety Reports
- M5 : Data Elements and Standards for Drug Dictionaries

Safety Groups:

- S2(R1) : Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
- S6(R1) : Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- S9 : Nonclinical Evaluation for Anticancer Pharmaceuticals
- M3(R2) : Revision of Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- Safety Interface Meeting

Quality Groups:

- Q4B : Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

Annex 5 : Disintegration Test
Annex 8 : Sterility Test
Annex 9 : Tablet Friability
Annex 10 : Polyacrylamide Gel Electrophoresis

- Q11 : Development and Manufacture of the Drug Substance
- Quality IWG : Quality Implementation Working Group

ICH Efficacy Groups:

- E2F : Development Safety Update Report
- E7(R1) : Revision of Studies in Support of Special Populations: Geriatrics
- E16 : Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions

Other Groups:

- Gene Therapy Discussion Group (GTDG)

EWGs/IWGs/Discussion Groups (2): No Face-to-Face Meeting in Yokohama

- M1 PtC : MedDRA Points to Consider
- Terminology : Maintenance of ICH Controlled Terminology Lists
- E14 IWG (Q&A) : Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: Q&A
- CTD-Q : CTD-Quality Implementation Working Group

Other Meetings in Yokohama

- ICH Global Cooperation Group (GCG)
- MedDRA Management Board (MB)
- Communication About ICH: Regional ICH Public Meeting: ICH Japan Symposium 2009 (June 12, 2009, Tokyo)

Dates of Next Meeting

- Oct 24-29 2009, St. Louis, Missouri, USA
- Jun 5-10 2010, Brussels, Belgium
- Nov 6-11, 2010, Yokohama Japan

Main Outcomes of Steering Committee Meeting:

Multidisciplinary/e-Groups:

- M2:
  SDO Process : ICSR and IDMP Projects
  eCTD : Next new major version
  (identification of issues, harmonization of user requirement)
- M5
  IDMP Project : Committee Draft (CD)
  Reconfirmation of the scope for M5 Step 2 Guideline
- E2B(R3):
  ICSR Project : Draft International Standards (DIS)
  ICSR Step 2 for Testing Package
  Public Awareness

Safety Groups:

- S2(R1):
  Step: Before Yokohama Meeting : 3
  At Yokohama Meeting : 3
- S6(R1):
  Step: Before Yokohama Meeting : 1
  At Yokohama Meeting : 1
- S9:
  Step: Before Yokohama Meeting : 3
  At Yokohama Meeting : 3
- M3(R2):
  Step: Before Yokohama Meeting : 3
  At Yokohama Meeting : 4
- Safety Interface Meeting:
  Discussion between the Safety topics (S2(R1), M3(R2), S9 and S6(R1)) in order to synchronize the work of each topic.

Quality Groups:

- Q3C(R4):
  Re-establishment of maintenance EWG was endorsed for the revision of the Q3C(R4) guideline.
- Q4B
  Annex 5, 8:
  Step: Before Yokohama Meeting : 3
  At Yokohama Meeting : 4
  Annex 9, 10:
  Step: Before Yokohama Meeting : 1
  At Yokohama Meeting : 2
- Q11:
  Step: Before Yokohama Meeting : 1
  At Yokohama Meeting : 1
- Quality Informal IWG:
  Second set of Q&As to help facilitate the implementation of the

Q8/Q9/Q10 guidelines was finalized

Efficacy Groups:

- E2F:

  Step: Before Yokohama Meeting : 3
  At Yokohama Meeting : 3

- E7(R1):

  Step: Before Yokohama Meeting : 1
  At Yokohama Meeting : 1

- E16:

  Step: Before Yokohama Meeting : 1
  At Yokohama Meeting : 2

Other Groups:

- GTDG:

  ICH Considerations document on “Viral/Vector Shedding” was finalized

Others:

ICH Global Cooperation Group:

Participants include SC members, Regional Harmonization Initiatives (RHIs) and Drug Regulatory Authorities (DRAs).
Strategy on training and capacity-building related to the use of ICH guidelines was discussed.

ICH Japan Symposium 2009:

The regional ICH public meeting was held on June 12, 2009 in Tokyo.
Approximately 600 participants from 18 countries attended the meeting. The symposium provided an opportunity to update to the public on the progress and the status of the ICH topics during the Yokohama meeting. It also provided a special session on the implementation of ICH guidelines in Asian countries

Questions and Answers

There were no questions.

ICHの最新動向
Overview of ICH Topics:
General Update on ICH

2009年6月12日 June 12, 2009

日本製薬工業協会 JPMA
ICH コーディネーター ICH Coordinator
岸 倉次郎 Kurajiro Kishi, DVM, PhD

本日の発表内容 Contents

- 全般 general:
  1. ICH横浜会議(運営委員会、専門家/実施作業部会)ICH Yokohama Meeting (SC, EWG/IWG meetings)
- 主要ポイント main points:
  1. 新たなトピック new topics
  2. ステップアップしたトピック topics stepped-up
- 主な検討結果 main outcomes:
  1. 各領域 areas: 複合 multidisciplinary、有効性 efficacy、安全性 safety、品質 quality
  2. その他 others(対面会議非開催、no face-to-face meeting)
  3. ICH 国際協力委員会 ICH global cooperation group
  4. ICH地域会議 ICH regional meetings:
- 今後の予定 future of ICH meetings
  1. 運営委員会・各作業部会 SC, EWG/IWG meetings

全般 general

- 会議日程・場所 meeting dates, venue
  - 2009年6月6～11日、横浜ロイヤルパークホテル
    June 6-11, 2009, Yokohama Royal Park Hotel
- 参加者 attendees
  - 登録総数:351名 total no. of registrants: **351** (as of June 11)
  - EU(42)、EFPIA(32)、FDA(40)、PhRMA(31)、MHLW(68)、JPMA(67)、オブザーバーObservers(EFTA 8、H. Canada 10、WHO 6)、ICH 事務局Secretariat、RHIs、DRAs、関連団体 interested parties, 他 others
- 専門家等作業部会(除合同会議) : EWG/IWG meetings (except joint mtg)
  - S(4)、Q(3)、e(3)、E(3)、MedDRA(1)、others (GTDG 1)
- 運営委員会 Steering Committee (SC):
  - 委員members: EU(EC) L. リンドストリームーロッシ Ms. L Lindstrom-Rossi
  - ステップアップしたトピック topics stepped-up:6 (含付属書including annexes)
  - 新規作業部会の結成 new EWG/IWGs: なし

主要ポイント main points:

1. 新たなトピック new topics
   - なし:
   - 再開トピック: Q3C(R4)残留溶媒ガイドライン(見直し)
     Impurities: Guideline for residual solvents (rev)
2. ステップアップしたトピック topics stepped-up
   - Q4B: 局方テキストのICH地域相互利用
     付属書 annex 5(崩壊試験法 disintegration test)、8(無菌試験法 sterility test) →ステップStep 4
     付属書 annex 9(摩損度試験法 tablet friability), 10 (ポリアクリルアミドゲル電気泳動法 polyacrylamide gel electrophoresis) →ステップStep 2
   - M3(R2):非臨床試験の実施時期(見直し)timing of nonclinical studies →ステップStep 4
   - E16:ゲノムバイオマーカーの記載法 genomic biomarker: →ステップStep 2

主な検討結果 main outcomes:
1. 各領域 areas(1.1 複合/電子 Multi./e)

- M2 (SDOs):医薬品規制情報の伝達に関する電子的標準化electronic standards for transfer of regulatory information
  - 標準作成団体との共同作業SDO (standards develop. org.) process
  - プロジェクトpilot project: ICSR (individual case safety reports)、IDMP (identification of medicinal products)
- E2B(R3): 安全性データの報告様式(見直し)electronic submission in individual case safety reports (rev)
  - ISO/HL7 ICSR 標準 (draft international standard, DIS)
  - ICSR Step 2 for Testing Package (含:ICH使用説明書(ガイド)ICH Implementation guide、test plan、E2B(R3) v3.96等)の承認。テストはPublic Awarenessの名のもので実施
- M5: 医薬品辞書のためのデータ項目及び基準data elements and standards for drug dictionaries
  - IDMPプロジェクト: Committee Draft (CD)、対象範囲scope(M5 Step 2 Guideline)、ICSRではM5 termを使用use of M5 terms in the ICSR
- M2 (eCTD):医薬品規制情報の伝達に関する電子的標準化electronic standards for transfer of eCTD
  - eCTD次期大型改定 next new major version of eCTD
  - 検討事項の明確化identification of issues、ユーザーの要望の調和 harmonization of user requirement:ICH eCTD NMW Requirements v1.0承認、SDO processで開発

主な検討結果 main outcomes:
1. 各領域 areas (1.2 有効性 efficacy)

- E2F:開発時定期的安全性最新報告 development safety update report
  - ステップ4 ならず didn't reach Step 4
  - 論点 points.:PSURとの重複overlap w/ PSUR、複数成分combination products、地域規制local requirements、用語定義definition、盲検情報clarification of safety info.
- E7(R1): 高齢者に使用する医薬品の臨床評価(見直し、Q&A)studies on support of special populations (rev): geriatrics
  - ステップ1のまま Step 1
  - Q&A(1～6): 含旧版との関係等rationale for Q&A, 被験者数sufficient no.,年齢・男女分布 age & gender distribution, etc
  - 論点points:患者数と年齢分布no. and age distribution (target disease, "very elderly")、アプローチdevelopment approach (marketing application, in case postmarketing)、評価項目 specific elements (specific age adequate endpoints, specific consideration on PK study)
- E16: ゲノムバイオマーカーの記載方法 genomic biomarkers related to drug response
  - ステップ2に到達 reached Step 2
  - 目的objectives:ゲノムバイオマーカーの的確性確認用統一資料harmonized submission for g-BM qualification、規制当局、その間の議論の促進 facilitation of joint discussion w/ and among regulatory regions
  - 内容contents:I. Introduction, II. Structure of g-GB qualification submission (organizational analogy to CTD Modules 1, 2 and 3 → Sections 1, 2, 3 and 4)

主な検討結果 main outcomes:
1. 各領域 areas（1.3 安全性 safety）(1)

- S2(R1): 遺伝毒性試験（見直し）genotoxicity testing (rev)
  - ステップ4到達ならず still Step 3
  - 目的objective: S2AとS2Bガイドラインの統合merging S2A and S2B into S2(R1)、3R's の実施consideration of 3R's
  - 内容:1ガイドラインS2（R1）、試験系への2選択肢2 options for test battery, in vivo試験の反復投与毒性試験への組み込みintegration of genotox studies into repeated dose tox.
  - EWGレベルでは最終化済（FDA当局内のissue）agreed within EWG
- S6(R1):バイオ医薬品の安全性試験（見直し） preclinical safety evaluation of biotechnology-derived pharmaceuticals (rev)
  - ステップ1のまま Step 1
  - 検討項目items: 動物種選択species selection、試験デザインstudy design、生殖毒性reprotox、がん原性carcinogenicity、免疫原性immunogenicity

主な検討結果 main outcomes:
1. 各領域 areas（1.3 安全性 safety）続きcontinue (2)

- S9: 抗がん剤の非臨床安全性試験 nonclinical evaluation for anticancer pharmaceuticals
  - ステップ4到達ならず still Step 3
  - 目的objective: 非臨床試験のデザイン及び実施design & conduct of nonclinical studies、開発促進と患者の保護acceleration of development, protection of patients from unnecessary AEs、3R's の実施consideration of 3R's
  - 内容content: 緒言introduction、非臨床評価studies to support nonclinical evaluation、臨床試験デザイン・承認に必要な非臨床データ nonclinical data to support clinical trial design and marketing、他others

主な検討結果 main outcomes:
1. 各領域 areas（1.3 安全性 safety）続きcontinue (3)

- M3(R2):非臨床試験の実施時期（見直し） timing of nonclinical studies (rev)
  - ステップ4到達 reached Step 4
  - 目的objective: 臨床試験実施に必要な非臨床試験の実施時期の見直しnonclinical studies to support clinical trials (revision)
  - 改定範囲scope:
    - 急性毒性 acute toxicity studies
    - ヒト初回臨床投与量の算出 estimation of the first dose in human
    - 一般毒性試験の用量設定 limit dose in toxicity studies
    - 非げっ歯類反復投与試験での投与期間duration of repeat tox for non-rodents
    - 探索臨床試験 exploratory clinical studies
    - 遺伝毒性試験 genotoxicity studies
    - 生殖毒性試験 reproductive toxicity studies
    - 特殊毒性試験の実施時期 timing for special studies:
      小児臨床試験をサポートする非臨床試験studies to support pediatric clinical trials、免疫毒性immunotox、光毒性phototox、依存性abuse liability、配合剤の非試験 fixed combination drug

主な検討結果 main outcomes:
1. 各領域 areas（1.3 安全性 safety）続きcontinue(4)

- GTDG: 遺伝子治療医薬品ディスカッショングループ gene therapy discussion group
  - ICH見解書の作成 development of "ICH Considerations" documents
  - ICH見解書 ICH Considerations document :
    - ✓ 腫瘍溶解性ウイルス oncolytic viruses: 最終化途上progress toward finalization
    - ✓ ウイルス/ベクターの排出 viral/vector shedding: 最終化 finalized
  - ICHガイドライン:
    - ✓ ウイルス/ベクターの排出に関するガイドライン（案）:コンセプトペーパー、ビジネスプランの作成開始 initiation of development of a Concept Paper and Business Plan on this topic

主な検討結果 main outcomes:
1. 各領域 areas（1.4 品質 quality）

- Q3C（R4）: 残留溶媒（見直し）impurities: guideline for residual solvents
  - EWG再開承認 nomination of experts 、見直しは「改定」revision、作業は電子メール・電話会議等で実施 by TC or email
- Q4B: 局方テキストのICH地域相互利用:付属書 regulatory acceptance of analytical procedures and/or acceptance criteria: annex
  - ステップ4到達 Step 4:annex 5（崩壊試験法disintegration test）、8（無菌試験法 sterility test）
  - ステップ2到達 Step 2:付属書 annex 9（摩損度試験法 tablet friability）, 10（ポリアクリルアミドゲル電気泳動法 polyacrylamide gel electrophoresis）
- Q11: 原薬の製造と開発 development and manufacture of drug substance
  - ステップ1. 依然ガイドライン案を検討中。ステップ2は来春を予定
- Q IWG:品質実施作業部会 quality implementation working group
  - 追加Q&A（10項目）到達Step 4 、事例提示 case studies、トレーニング・ワークショップ training/workshops

主な検討結果 main outcomes:
2. その他 others（対面会議非開催 no face-to-face meeting）

対面会議非開催トピック topics w/o face-to-face meeting in Yokohama

- M1 PtC: MedDRA Point to Consider
- Terminology: ICH管理用語リストのメインテナンスプロセス maintenance of ICH controlled terminology list
- E14 : QT延長及び重篤な不整脈の臨床評価 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs:
  - Step 5: 本体E14: EU, US, 2005 、Q&A: EU, US, 2008. Japan: 通知予定 not yet impl.
  - 維持maintenance: メールによる質問箱 Questions in ICH E14 mailbox
  - 今後①: 実施作業部会解散 disbanded IWG、質問箱閉鎖 mail box to be closed、
  - 今後②: 次回に向けて検討グループを結成し、集積データの検討とガイドライン改定の必要性を検討 organization of discussion group to review data and discuss need for guideline update
- CTD-Q: CTDの品質に関する実施作業部会CTD-quality implementation working group
  - eCTDに寄せられた質問への対応 questions for CTD-Q based on change requests
  - Q&A: 原薬、製剤のヘッダ情報（2.3.S/3.2.S）、（2.3.P/3.2.P）: 品名name, 製造業者 manufacturer、品名name、剤形dosage form→eCTD Q&A Doc v1.18, v1.19

主な検討結果 main outcomes:
3. ICH国際協力委員会
ICH Global Cooperation Group (GCG)

方策strategy、GCGの役割GCG' role 、ミッションステートメントMission Statement
- ICHガイドラインの使用に関連する教育・能力向上に対する方策 strategy on training and capacity-building related to the use of ICH guidelines
- 医薬品業界、規制当局の両者によるガイドラインの正しい解釈、効率的な利用促進ensuring their proper interpretation and effective utilization by industry and regulators
- ミッションステートメント:ICHガイドラインの調和プロセス促進するため、非ICH地域の相互理解の増進、能力向上支援 to promote a mutual understanding of RHIs in order to facilitate the harmonization process related to ICH guidelines regionally and globally, and to facilitate the capacity of drug regulatory authorities and industry to utilize them

構成 membership
- 運営委員会メンバー、非ICH地域において医薬品規制調和活動を実施している地域代表(5)、規制当局(4) SC member, Regional Harmonization Initiatives (RHIs), Drug Regulatory Authorities (DRAs)

活動 activities
- 情報の提供・共有real-time information provision/information sharing
- ガイドライン案に対するコメント募集Invitations to submit comments to ICH draft guidelines
- 研修会開催の支援 supporting training program based on requests(専門家派遣など)
- 規制当局者会議への参加 invitation to the Regulators Forum

主な検討結果 main outcomes:
4. ICH地域会議
ICH regional meeting

- ICH地域会議ICH regional meeting:
  - ICH 6 以降3極でそれぞれ地域ごとに実施 in each ICH region following ICH 6
  - 第1回会議を日本地区で開催1st regional ICH public meeting in Tokyo, 2007
  - ICH成果の共有、討論の場 communication about ICH
- ICH日本シンポジウム2009 ICH Japan Symposium 2009
  - ICHの正式な公開シンポジウムICH Public Meeting
  - 内容program: トピックでは、品質、安全性、有効性、複合領域の横浜会議の成果を発表。また、アジア地域におけるICHガイドラインの取り組み等を報告 outcomes of Yokohama meeting on topics: quality, safety, efficacy and multidisciplinary. panel discussion: implementation of ICH guidelines in Asian countries
  - 演者speakers:ICH 6団体 ICH 6 parties、オブザーバーobservers、RHIs、DRAs
  - 参加者participants:18ヵ国から約600名弱about 600 over 18 countries

今後の予定
future of ICH meetings:

- 運営委員会、専門家/実施作業部会
  SC, EWG/IWG meetings

2009年会議予定 2009 meeting dates
- 10月24-29日 Oct 24-29 セントルイス、米国 St. Louis, Missouri, USA

2010年会議予定 2010 meeting dates
- 6月5-10日 Jun 5-10 ベルギー、ブリュッセル Brussels, Belgium
- 11月6-11日 Nov 6-11 横浜、日本 Yokohama, Japan

Topics for the Electronic Exchange of Information

M2 (SDOs): Electronic Standards for the Transfer of Regulatory Information

Yasuhiro Araki, *MHLW (PMDA)*
Topic Leader

Abstract
Mr. Yasuhiro Araki will present the overview summary of the series of M2 (SDOs) meetings held in Yokohama.

Mr. Araki is the Senior Reviewer of Office of New Drug I at the Pharmaceuticals and Medical Devices Agency as well as the current MHLW Topic Leader of the M2 topic at the ICH meetings.

Questions and Answers

There were no questions.

Electronic Standards for Transmission of Regulatory Information : ICH M2

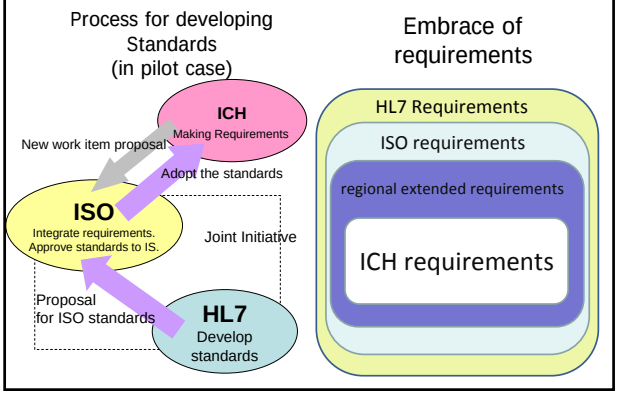
SDO management

Yasuhiro Araki
Pharmaceuticals and Medical Devices Agency (PMDA)

Background

- What's "SDO process?"
  - SDO = Standards Development Organization
  - "SDO process" is something like partnership with SDOs to develop electronic standards which ICH needs.
  - SDOs (ISO/CEN/HL7/CDISC) which concern HealthCare Information form Joint Initiative (JI).
  - To start SDO process, ICH submits proposal to one of Joint Initiative member to develop electronic standards.
  - For pilot cases, two projects (ICSR & IDMP) is running on SDO process.

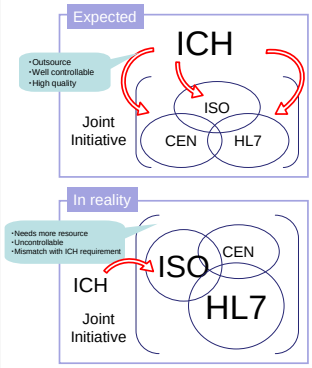
Image for SDO process



Objective of SDO process

- Resource and expertise constraints inside ICH
- Desire for more open, robust process for development of standards
- Needs for authorized Electric Standards by SDO

Practical Issues of SDO process



- SDO doesn't always accept proposals from ICH.
- SDO may accept opinions from any participants, and merge or change the requests for standards.
- ICH has no veto or no voice for ISO draft standards.
- ICH needs to follow schedule of SDOs.

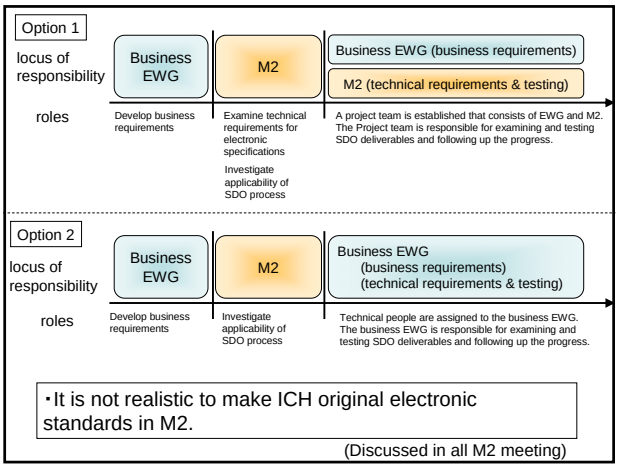
Issues to be discussed at the Yokohama meeting

- Review of relationship management with ISO and HL7
- Lessons learned and corrective actions
- Consideration of requesting Liaison A status with ISO TC 215
- ICH involvement in the HL7 Common Product Model(CPM)

Outcome of Yokohama meeting (1)

- ICH involvement in the HL7 Common Product Model
  - M2/M5 subgroup consider whether ICH undertakes a element-by-element gap analysis of ICH requirements versus the CPM
  - Submit ICH comments to CPM DSTU ballot (September)

(Discussed in M5/M2 meeting)



・It is not realistic to make ICH original electronic standards in M2.

(Discussed in all M2 meeting)

Outcome of Yokohama meeting (3)

- Consideration of requesting change to ISO Liaison A status
  - No objection to change to Liaison A.
  - Prepare recommendation for St. Louis meeting
- Corrective Actions – ICH Process
  - Need to have agreed ICH Lead Representative with ISO (and an alternate) and mechanisms to support the lead

Outcome of Yokohama meeting (4)

- eCTD NMV Path Forward
  - ISO and HL7 recommend completing Joint Initiative Proposal form
  - Submit NMV requirements from Yokohama to RPS team for consideration at Atlanta HL7

Outcome of Yokohama meeting (5)

- Other Business
  - HL7 Copyright
    - E2B(M3) IG contains HL7 and ISO documents.
    - Contact HL7 before posting IG on ICH site.
  - HL7 MoU
    - FDA lawyer concerns due to existing relationship
    - SDO group to review key points from existing MoU draft to ensure how to best ensure ICH interests are met.
  - JIC Membership Expansion Impact
    - Current: ISO, HL7, CEN, CDISC, IHTSDO
    - Likely: LOINC, IEEE, DICOM

Topics for the Electronic Exchange of Information

E2B (R3): Revision of the Electronic Submission in Individual Case Safety Reports

Ayumi Endo, *MHLW (PMDA)*
Rapporteur

Abstract
Ms. Ayumi Endo will present the overview summary of the series of E2B (R3) meetings held in Yokohama.

Ms. Endo is the Professional Officer of the Surveillance and Analysis Division of Office of Safety at the Pharmaceuticals and Medical Devices Agency as well as the current Rapporteur of the E2B (R3) topic at the ICH meetings.

Questions and Answers

There were no questions.

E2B (R3) : Data Elements for Transmission of Individual Case Safety Reports

Ayumi Endo
Pharmaceuticals and Medical Devices Agency (PMDA)

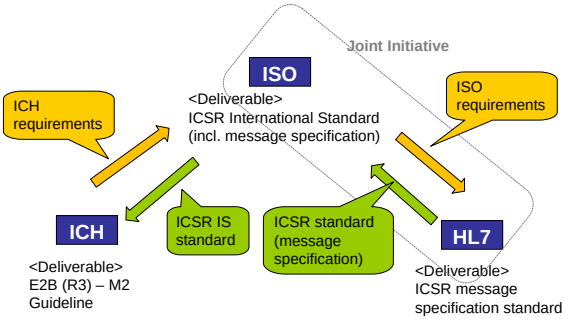
Objectives and Scope

- **E2B (R3)** : Data Elements for Transmission of Individual Case Safety Reports (ICSRs)
  - Standardize the data elements for transmission of ICSRs
  - The data elements cover Adverse Drug Reaction and Adverse Event reports
  - The data elements also cover pre and post authorized products
- **M2** : Electronic Transmission of Individual Case Safety Reports Message Specification
  - Assist reporters and recipients in implementing systems and constructing transmittable messages
  - Enable the electronic exchange of ICSRs between reporter and recipient (e.g. regulatory authority and pharmaceutical company, within companies etc)
  - Enable data to be extracted from safety database

Past key steps in E2B (R3)

- November 2003 E2B (R3) EWG established
- May 2005 Step2
- July 2005 Step3
  - **Moved to SDO Process**
- March 2007 ISO New Work Item Proposal
- August 2007 NWIP approved
- November 2008 HL7 ICSR R2 review
- August 2008 HL7 ICSR R3 initiated

SDO Process for ICH E2B-M2



Adopt / Adapt ISO ICSR standard to ICH E2B-M2

ISO : Standard developer

International Standard
Scope : Broader than ICH requirements
(medical devices, veterinary drugs, cosmetics, foods etc)
Data elements : Much more elements than ICH requirements

Constrain the standard for ICH use

ICH : Implementer

E2B (R3) - M2 guideline
Scope : Focused on pharmaceutical products for human use
Data elements : Limited to E2B (R3) data elements and technical requirements

ISO ICSR standard

- **Current stage of ISO standard**
  - **Draft International Standard (DIS) Ballot**
  - **Ballot Period April 30, 2009 – September 30, 2009**
- **Part 1**
  - Broad scope
  - ICSR specifications
    - Story boards
    - Models etc
  - HL7 materials
- **Part 2**
  - Narrow scope
  - Human Pharmaceuticals Message Specification
    - Models
    - Schemas
    - Reference of HL7 materials (Informative)
    - E2B (R3) guideline (Informative)

E2B – M2 activities

Implementation Guide

- Constrain ISO ICSR message for the purpose of ICH E2B use (constrained message specification and rules for implementation)
  - Provide business rules and indications to create safety reportings
  - Provide constrained message specification to develop a new reporting system

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E2B – M2 activities

ICH Testing

- Test against ISO ICSR DIS during the ballot period
  - Validate the message
  - Confirm the message whether it meets ICH requirements
  - Evaluate usability of ICH Implementation Guide
- Testing is planned to proceed by two steps; Alpha testing and Beta testing
- Testing is on going in three regions
- Issues and problems uncovered will be submitted to ISO through National Member Bodies as ballot comments

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E2B – M2 activities

Step 2 for Testing = Public Awareness

- Public awareness is needed
  - Comments will be accepted
- Step 3, formal ICH consultation on improved version of IG and associated ICH documents will be conducted at a later stage
- The document set will be available on ICH web site
- One month duration otherwise comments cannot be taken into account by ICH

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E2B – M2 activities

Public Awareness Document Set

- Implementation Guide v1.2)
- Annotated superset instance) Merge into IG v1.3 for publication
- Testing Plan
- E2B(R3) guidance v3.96
- Schemas
- Backwards and forwards compatibility mapping spreadsheet

- Provide link to ISO DIS documents on ISO website for any person who feels they need to access. ICH considers that there is sufficient information in the ICH documents to assess the merits of the proposed standard

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E2B – M2 activities

Backwards-Forwards Compatibility

- The conversion rules are required when ICSR is transmitted among the countries through E2B (R2) systems and E2B (R3) systems
- Set business rules for conversion of E2B (R2) and E2B (R3)
- Test the conversion rules whether they are logically applicable

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E2B (R3) guideline

- E2B (R3) guideline version 3.96 13Nov2008 produced in Brussels meeting will not be updated any longer. Additional decisions made by E2B (R3) EWG will be added into Implementation Guide.

- E2B (R3) guideline version 3.96 13Nov2008 will exist for a while as a core business requirements and will be included into Implementation Guide at the end of project process (before Step 4).

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Usage of M5 in E2B (R3)

- Until M5 is implemented, E2B (R3) will use free text or existing code lists in E2B (R2) for data elements supported by M5.
- When M5 is implemented, E2B (R3) will use all IDMP available terms and identifiers (codes) described in the M5 guideline
  - where no IDMP terms and identifiers are available the information will be provided in the corresponding free text fields.

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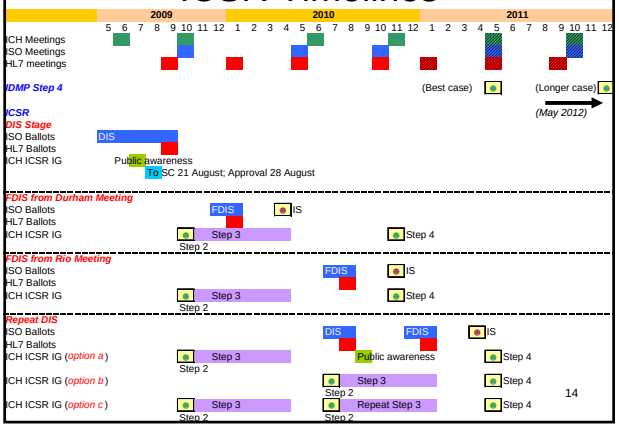
ICSR Timelines



Topics for the Electronic Exchange of Information

M5: Data Elements and Standards for Drug Dictionaries

Toshikazu Yoshinaga, *JPMA*
Topic Leader

Abstract
Mr. Toshikazu Yoshinaga will present the overview summary of the series of M5 meetings held in Yokohama.

Mr. Yoshinaga is the Manager of Regulatory Affairs Department 2 in the Development & Medical Affairs Division at GlaxoSmithKline K.K. as well as the current Topic Leader of the M5 topic at the ICH meetings.

Questions and Answers

There were no questions.

ICH M5

JPMA M5 Topic Leader
GlaxoSmithKline
Toshi. Yoshinaga

History of M5

- 2003 Nov. : Adoption of Topic
  - Scope
    - To develop a new tripartite guideline that defines the ICH Drug Coding Dictionary Data Elements and Standards (ICH DCD) supporting all aspects of pre- and post-authorization pharmacovigilance activities and communication of regulatory information.
- 2005 May : Step 2 reached
- Public Consultation (2005 Jul-Sept.)
- 2006 June : New Proposal of SDO
  - long-term maintenance of the M5 using SDO process
- 2006 Oct. : Get into SDO Process

History of M5 (2)

- SDO (Standards Development organizations)
  - Electronic Standards for the Transfer of Regulatory Information and the Electronic CTD (Topic M2 / eCTD)
  - The SC agreed that the M2 EWG should begin discussions to work collaboratively with Standards Development Organizations (SDOs) through the establishment of a Consortium in which ICH would participate to ensure that the development of electronic standards meets ICH standards.
  - The SC approved that E2B(R) and M5 messages enter the SDO process for development by a Consortium that would be composed of ICH, the International Organization for Standardization (ISO), Health Level 7 (HL7) and the European Committee for Standardization (CEN).

History of M5 (3)

- 2007 Feb. : NWIP (New Work Item Proposal) given to ISO
  - M5 Guideline, version 5.1
- 2009 Mar. : London ad hoc meeting
  - Status of the ISO IDMP project
    - WHO raised a 'red flag' as regards the progressing of the ISO IDMP CDs on Dec. 2008.
    - CPM development was proposed. CPM need to be evaluated in accordance with ICH's business requirements.
  - IDMP Work Plan in ICH M2/M5
    - Conceptual test
    - Gap Analysis
  - ICH core requirements
    - To propose wider scope from current M5 V5.1 Guidance Document.

Meeting Summary at Kyoto (HL7)

- JIC consists of ISO, CEN, HL7, CDISC and IHTSDO. Rrequests made from further organizations such as WHO, IEEE and DICOM to join.
- The IDMP New Work Item Proposals (NWIPs) and Committee Draft ballots are continuing.
- The intended scope will go beyond that of the ISO NWIPs and include 'Clinical' as well as 'Regulatory'.
- HL7 will draft a single scope statement, covering all 5 IDMP projects as to establish the project within HL7.
- HL7 will take over the modeling and messaging (as has been the case with ICSR). The Pharmacy Working Group has discussed as summarized:

NWIPs and CD ballots （ISO）

- NWIPs still cover all ICH requirements
- CD ballot documents have not been updated to include wider scopes of new NWIPs

M5 Scope at Yokohama

- Applicable to a product that has received authorisation in at least one jurisdiction worldwide (not restricted to ICH regions)
- Confirmed as applicable to the list of product types within the original M5 scope namely;
  - Chemicals, Radio-Pharmaceuticals and Precursors, Vaccines, Immunoglobulins and Immunosera, Crude Drugs Plant origin, Crude Drugs Animal origin, Crude Drugs Mineral origin, Crude Drugs Mixtures
- ICH informally tested other classes than those for which the standards were developed and they could be used for other product classes if one so desired. Anything outside of the ICH scope could be handled regionally.

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M5 guidance

- M5 should maintain the M5 Business Requirements as developed at the Face-to-Face meeting in London (March 9-11, 2009) and should add an explanation of how these were derived from the M5 guideline v5.1
- The ICH M5 Implementation Guide Step 2 for public consultation will include as an annex the M5 guideline v5.1 and the M5 Step 2 document
- The ICH M5 Implementation Guide will be released as a joint M5/M2 Step 4 documents and it should not include the M5 guideline v5.1
  - Same process as for E2B(R3)

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ICH & ISO/CEN/HL7 Relationships

- ICH critical conditions:
  - FDA requires HL7 compliant standards
  - EU requires CEN and/or ISO standards
- IDMP is comprised of 5 work items in ISO
  - NWIPs re-submitted to ballot) Close on
  - CD ballot in parallel) 12 Aug 2009
- IDMP is under consideration to become JI project
  - Critical question is whether current scope satisfactory to JIC (meeting 10 June 2009)
- In order to start consideration in HL7 pending adoption as JI, project in approval process to accompany ISO drafts through to standard.
  - Short term intention is to ballot the ISO documents "for information" within HL7 in parallel to ISO/CEN CD ballot

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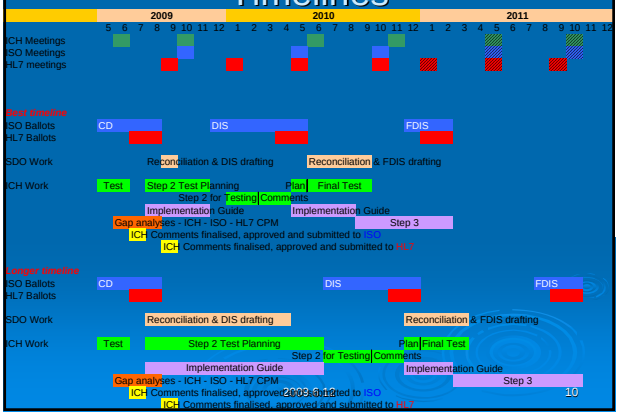
Timelines



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HL7 Common Product Model (1)

- HL7 has an overarching Common Product Model (CPM) which is moving towards a Draft Standard for Trial Use (DSTU)
  - FDA already uses the current CPM to support its identification of medicinal products
- JIC would intend to use CPM as the basis for meeting the requirements of the ISO IDMP standards
  - The CPM may need to be modified to fully meet the ISO requirements for the MPID
  - Decisions need to be taken within HL7 regarding the inclusion of the other 4 IDMP standards within the CPM
  - IDMP requirements are being fed into the CPM by individuals from ICH parties but not as ICH

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CPM (2)

- M2/M5 subgroup has considered whether ICH undertakes a element-by-element gap analysis of ICH requirements versus the CPM
  - Gaps to be identified to HL7 before moving to DSTU
  - We have consensus to recommend to SC that this is done

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Topics for the Electronic Exchange of Information

M2 (eCTD): Electronic Common Technical Document

Takeshi Adachi, *JPMA*
Topic Leader

Abstract
Mr. Takeshi Adachi will present the overview summary of the series of M2 (eCTD) meetings held in Yokohama.

Mr. Adachi is the Director of the Regulatory Affairs Department in the Regulatory Affairs and Pricing Division at Janssen Pharmaceutical K.K. as well as the current Topic Leader of the M2 topic at the ICH meetings.

Questions and Answers

There were no questions.

M2 (eCTD New Major Version)

M2: Takeshi Adachi (JPMA)

Objective

- Identify the issues of eCTD submission in each Regions
- Harmonize the User requirements for next Next Major Version of eCTD
- Based on CTD guideline

Background

- STF
- Many Change Requests
- Vague attributes
  - New, Replace, Append, Delete
- SDO (HL7 Message)
- Etc.

Issues to be discussed at the Yokohama meeting

- Envelope / Module 1 Metadata
- File Life Cycle
- Submission Security, Integrity and Usability
- Regional and ICH Validation
- Compatibility Between Versions
- Two-Way Communication

User Requirements for eCTD NMV

- Total 128 requirements for eCTD NMV
  - Preserves many current requirements
  - Adds some improvements
    - Two-way communication
    - M1 Meta-data
    - etc.
- Requirements will be forwarded into SDO (HL7-RPS2)

Time Line for eCTD NMV

- Under consideration
- Now that requirements are agreed, evaluation and consultation with SDO will determine full details

Change Requests and Q&As

- 7 Change requests
- 1 modification of an existing Q&A (#36, 2 item)
- 1 new Q&A (Web link)
- Q&A document v1.17 has been issued
- Q&As related to CTD-Q will be issued as v1.18 (maybe before St. Louis meeting)

SENTRI

Standards Everyone Needs for the Transfer of Regulatory Information

- PDF File Size (>100MB)
  - No Change
- PDF Version recommendation
  - PDF v1.4- 1.7 (at the next St. Louis meeting)
- MD5
  - MD6 or SHA2 etc. (at the next St. Louis meeting)
- XML for content
  - White paper (at the next St. Louis meeting)
- ESTRI Recommendations
  - Review of the purpose, value and currency of all recommendations (at the next St. Louis meeting)

Efficacy Topics

E2F: Development Safety Update Report

Noriko Akagi, *JPMA*
Topic Leader

Abstract
Ms. Noriko Akagi will present the overview summary of the series of E2F meetings held in Yokohama.

Ms. Akagi is the Group Manager of the Safety Information Department at Novartis Pharma K.K. as well as the current Topic Leader of the E2F topic at the ICH meetings.

Questions and Answers

Question: Concerning the DSUR, how can we utilize the past data?

Akagi: Data following the Development International Birth Date (DIBD) should be listed in the DSUR.

Question: For example, during the clinical development, there are different data coming from different time points. How can we come up with this?

Akagi: All the data should be listed in accordance to the guideline. At Step 5, detail instruction may be released at the time of implementation in each region.
If the DIBD is very old, the data may not be available. In the guideline there is no description with respect to data missing, but the detail will be clarified at the time of implementation in each region.

The Development Safety Update Report (DSUR)

Noriko Akagi

E2F, JPMA

Safety Information Dept., Novartis Pharma K.K.

Outline

1. **Background and Objectives of the DSUR Guideline**
2. **Schedule**
3. **Outcomes of the Yokohama meeting**
4. **Major topics discussed at the meeting**
   - Relationship of DSUR to PSUR
   - Combination products
   - Example DSURs
   - Differences in local requirements
   - Summary of Important Risks
5. **Remaining points to be discussed**

1. Background and Objectives of the DSUR Guideline

Background:

Current regulations on periodic reporting for investigational products vary by region, which leads to duplication of effort for sponsors, and inconsistency in the information each regulatory authority receives.

Objectives:

To standardize the format, content and timing of a periodic report for drugs in development so that sponsor can avoid duplicative work and focus on assessment of risk. Regulatory authorities can receive the same information at the same time, and eventually subjects in clinical trials can be protected from adverse reactions more effectively.

2. Schedule

Step 2	**June 2008:**
Step 3	**Until Dec. 2008**
Yokohama meeting	**Completion; 80% through Guideline**
Step 4	**Sign-off was not achieved in June 2009, but aim to complete prior to St. Louis meeting in Oct. 2009.**

3. Outcome of Yokohama meeting

- **Topics addressed:**
  - **Integration of a number of sections**
  - **Table for combination products**
  - **Clearer definitions of DIBD, DLP**
  - **Relationship to eCTD (Discussion with M2)**
  - **Greater use of graphics**
- **Extensive revisions to improve clarity and reduce redundancy, taking comments into account**
- **Many enhancements**
- **Presently, ~80% through the Guideline**
- **Major Problems/Issues: None foreseen**

4. Major topics discussed at the meeting
Relation of the DSUR to the PSUR

Why DSUR and PSUR should be prepared in parallel?

- **Current regulations do not provide consistent content and format for periodic reports for investigational and approved drugs**
- **Period covered by PSUR and DSUR may be different**
- **DSUR and PSUR may be reviewed by different department**

Why is overlap necessary?

- **Information from marketing experience may be relevant to clinical development and vice versa**

4. Major topics discussed at the meeting
Combination products

- **Fixed Combination Drug**
  - **Single DSUR**
- **Multi drug regimen**

Example	Combination	DSUR
Investigational drug (A) + marketed* drug(s) (X, Y, Z)	A + marketed drugs X, Y, Z	A single DSUR focusing on A
Two investigational drugs (A) + (B)	(A) + (B)	Either a single DSUR focusing on (A + B) **or** Two separate DSURs (A) + (B), each including data on the combination
Two (or more) marketed drugs as an investigational drug combination* (X, Y, Z)	(X) + (Y) + (Z)	A single DSUR focusing on the combination (X + Y + Z)

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4. Major topics discussed at the meeting
Example DSURs

- **2 types of example of DSUR(s);**
  - **Ph-III product for multi-national company**
  - **Single trial by academic sponsor-investigator**
- **Will be posted on ICH-Web site when E2F finalized**

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4. Major topics discussed at the meeting
Differences in local requirements

- **Lists of Deaths and Drop-outs in the reporting period (section 7.4 and 7.5)**
  - **Only applicable for U.S. submission**
- **Summary tabulations of SADRs**
  - **Only applicable for EU submission**

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4. Major topics discussed at the meeting
Summary of Important Risks (Section 15)

- **Examples to be added as an Appendix within E2F guideline**

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5. Remaining points to be discussed

- Dealing with differences in local requirements
  - Phase I protocol amendments, manufacturing changes
- Clarification of "safety information" to be included in the DSUR
  - Section 8 through 12
- Additional definitions to add to the Glossary to clarify the wording used in the Guideline
- Finalization of example DSURs

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Efficacy Topics

E7 (R1): Revision of Studies in Support of Special Populations: Geriatrics

Kazuishi Sekino, *MHLW (PMDA)*
Topic Leader

Abstract
Dr. Kazuishi Sekino will present the overview summary of the series of E7 (R1) meetings held in Yokohama.

Dr. Sekino is the Reviewer of Office of New Drug III at the Pharmaceuticals and Medical Devices Agency as well as the current Topic Leader of the E7 (R1) topic at the ICH meetings.

Questions and Answers

There were no questions.

Session Chair's Comments

Uyama: Since this is a valuable opportunity, I would like to make a comment about the E7 topic.

As Dr. Sekino mentioned, although the details were not possibly explained due to time limitations, the discussion was that it is no longer about simply securing 100 elderly patients that are over 65 years old.

The most important factor is the age-distribution in a disease. For example, with Alzheimer's disease, we have a larger percentage of elderly population compared to those of asthma. Therefore, the study in Alzheimer's disease should include larger numbers of geriatric patients.

We also discussed about how much data should be collected before and after drug approval. In general, data should be collected as much as possible before approval. However, in some situations, geriatric data cannot be collected before approval due to co-morbidity and concomitant medication which refrains the inclusion of geriatric patients from particular studies. In this case, reasons and justifications must be submitted to the regulatory authorities and if those are acceptable, we will identify what would be the data to be collected during the post-marketing period. The benefit risk assessment will be continued after the launch of the products.

Also, we have made progress with PK methods since the original guideline and several guidelines such as drug interaction and PPK methods have been released in different regions. So, we will look at the up-to-date information and recent techniques which could be utilized. That was a part of the discussion that we had at the Yokohama meeting.

E7 (R1): Revision of Studies in Support of Special Populations: Geriatrics

高齢者に使用される医薬品の臨床評価（見直し）

Kazuishi Sekino
Reviewer
Office of New Drug III
Pharmaceuticals & Medical Devices Agency (PMDA), Japan

Outline of Presentation

1. Members of E7(R1) Implementation Working Group
2. Background
3. Objective
4. Issues to be discussed at the Yokohama meeting
5. Outcomes of the Yokohama meeting

Members of E7(R1) Implementation Working Group

Rapporteur (EU):
Kristina Dunder (Medical Products Agency, Sweden)

ICH Parties:
- EU/EMEA (4 persons), EFPIA (2 person)
- FDA (2 persons), PhRMA (1 person)
- MHLW/PMDA (3 persons), JPMA (6 persons)

Observer:
EFTA (1 person), Canada (1 person)

Interested Party:
WSMI (1 person)

MHLW/PMDA
- Topic Leader : Yoshiaki Uyama (PMDA, Japan)
- Deputy Topic Leader : Kaori Shinagawa (PMDA, Japan)
- Expert : Kazuishi Sekino (PMDA, Japan)

JPMA
- Topic Leader : Yasuhiko Imai (Bristol-Myers KK, Japan)
- Deputy Topic Leader : Toshinobu Iwasaki (Shionogi & Co Ltd, Japan)
- Expert : Maki Ito (Shionogi & Co Ltd, Japan)
- Expert : Akiyuki Suzuki (Pfizer Japan Inc, Japan)
- Expert : Noriko Adachi (Bristol-Myers KK, Japan)
- Expert : Kazuhiro Kanmuri (Pfizer Japan Inc, Japan)

EFTA: European Free Trade Association
WSMI: World Self-Medication Industry

Background

- The essential elements for inclusion of elderly patients in clinical studies are outlined in the current ICH E7 guidance document (June 1993).
- ICH E7 notes that for drugs with significant use in the elderly, the inclusion in clinical trials of a minimum of 100 patients aged 65 years or older "would usually allow detection of clinically important differences" in drug responses compared with younger patients.

Background

- With the increasing prevalence of elderly and very elderly in the society and in view of the recent advances in clinical science and clinical trials experience build over the last 15 years, we need to review the current ICH E7 guidance document for better assessment of the risks and benefits of the drug in geriatrics.

Objective

- A Questions & Answers document will be developed to provide further guidance on the E7 Guideline.

ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Final Concept Paper
E7(R1): Studies in Support of Special Populations: Geriatrics
(Revision of the ICH E7 Guideline)
23 October 2008
Endorsed by the Steering Committee on 24 September 2008*

Type of Harmonisation Action Proposed
Establishment of Implementation Working Group to create new questions and answers (Q&A document).

http://www.ich.org/LOB/media/MEDIA4930.pdf

ICH E7(R1)

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Issues to be discussed at the Yokohama meeting

- To discuss the number and age distribution of expected elderly participants in a given indication development and the criteria on which these figures are based. *(Priority 1)*
  - Age distribution should generally reflect that of the target disease (e.g. in Parkinson's disease meaningful strata over 75 and over 85 years should be enrolled).
  - Efforts to include the "very elderly" should be specifically addressed. For issues regarding gender in clinical trials (e.g. possible gender imbalance secondary to late onset of cardiovascular diseases in women, and osteoporosis in men) see Gender Considerations in the Conduct of Clinical Trials)

Pmda Pharmaceuticals and Medical Devices Agency, Japan 7

ICH E7(R1)

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Issues to be discussed at the Yokohama meeting

- To plan a development approach that will ensure exposure of a sufficient number of elderly and very elderly patients, with appropriate testing to adequately characterise the safety and efficacy in that population. These information would ordinarily be expected in a marketing application, but whether in some circumstances these information could be obtained postmarketing should be discussed. *(Priority 1)*

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ICH E7(R1)

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Issues to be discussed at the Yokohama meeting

- To describe specific elements in clinical studies that will be evaluated in the assessment of the risks and benefits of the drug in the elderly, including in the context of co-morbidities and concomitant therapies.
  - The following two points may be included or discussed, if necessary:
    - Use of specific age adequate endpoints (elderly-relevant outcomes to be pre-defined and assessed in the planned subsets).
    - Specific considerations on pharmacokinetics studies, including population pharmacokinetics analysis.

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ICH E7(R1)

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Outcomes of the Yokohama meeting

The following **6 Questions & Answers** were discussed in Yokohama.

- **Q1;** Why do we need an adequate representation of geriatric patients?
- **Q2;** Considerations on estimating an adequate representation of geriatric patients (The geriatric population in the clinical trial program is representative of the target patient population)
- **Q3;** Special patient populations or characteristics in the planning of the clinical development program (Co-morbidities and concomitant therapies)
- **Q4;** Considerations on the clinical development program (Studies for geriatric patients in the marketing application or post-marketing)
- **Q5;** Considerations on the data specific to the geriatric population (Specific adverse events e.g. effects on cognitive function, effects on balance and falls)
- **Q6;** Considerations on pharmacokinetics studies in geriatric patients

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ICH E7(R1)

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Outcomes of the Yokohama meeting

- This topic, ICH E7 (R1), could not reach the Step2 in Yokohama, however, major issues to be discussed were resolved.
- In the near future, we will reach the Step2 and prepare the public consultation of this Q&A document on the E7 guideline, in the three regions.

Pmda Pharmaceuticals and Medical Devices Agency, Japan 11

ICH E7(R1)

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Thank you for your attention.

For the welfare of patients!

Pmda Pharmaceuticals and Medical Devices Agency, Japan 12

Efficacy Topics

E14: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: Q&A

Maki Ito, *JPMA*
Topic Leader

Abstract
Dr. Maki Ito will present the overview of the question and answer of the E14 guideline.

Dr. Ito is the Head of Medical Affairs of Medical Affairs Office in the Drug Safety Management Department at Shionogi & Co., Ltd. as well as the current Topic Leader of the E14 topic at the ICH meetings.

Questions and Answers

Question: As you mentioned, I understand that from a non-clinical point of view, S7B is closely related to the E14 guideline. Is it possible that S7B`s experimental approach would be utilized so that we can reduce testing or studies required for E14? Have you discussed about that within the expert working group?

Ito: We know that non-clinical data under the control of S7B is very important for our group. In the future, we would like to scrutinize what kind of S7B data is available and what we are looking at, and then have further discussions in an informal discussion group that has been proposed.

Uyama: That was one of the major issues at the Yokohama meeting. That is, how we can predict the QT risk for human from non-clinical study results. At the time of Step 4 agreement, E14 group concluded that the predictability of non-clinical study results is currently very low. But, now, the US and EU have four to five years of implementation experience of E14 and more than 100 thorough QT studies have been conducted in those regions. Safety pharmacology studies under the S7B guideline could be looked at so that we can identify the issues of current activities at E14 EWG. More accurate QT risk assessment could be identified within E14 EWG by doing so. In Yokohama, the steering committee decided to establish a discussion group which consists of non-clinical members of S7B and clinical members of E14. Within this discussion group, along with S7B members, we will figure that out.

Comment from the floor: I hope fruitful results will come out from your discussion.

ICH Japan Symposium E14 guideline Q & A

June 12th , 2009
ICH E14 JPMA Topic leader
Maki Ito, MD, PhD

E14 milestones

- Guideline "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs" reached step 4 in May 2005
  - FDA: Implemented in October 2005
  - EU: Implemented in November 2005
  - Japan: To be notified
- Questions and Answers were approved in June 2008
  - EU: Implemented in June 2008
  - FDA: Implemented in November 2008
  - Japan: To be notified

Questions and Answers

1. Adequacy of a positive control
2. Who should read ECGs? Number and training of readers and the need for blindness
3. Categorical analyses regardless of gender
4. A: ECG reading methods: fully manual, fully automated, manual adjudication
   B: Validation of an automated reading method
5. Metric for a parallel design study
6. Baseline measurements
7. Need for blinding the positive control in the TQT study

Mechanism to maintain E14 document

- Questions were received by the ICH E14 mailbox (e14@ich.org)
- The ICH E14 mailbox will be closed
- Rapporteur will be changed MHLW to PhRMA

Efficacy Topics

E16: Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions

Lois Hinman, *PhRMA*
Rapporteur

Abstract
Dr. Lois Hinman will present the overview summary of the series of E16 meetings held in Yokohama.

Dr. Hinman is the Executive Director of the Global Regulatory Affairs at Novartis Pharmaceuticals Corporation as well as the current Rapporteur of the E16 topic at the ICH meetings.

Questions and Answers

There were no questions.

Overview and Update on ICH Genomic Biomarker Guidelines E15 and E16

Lois Hinman, E16 Rapporteur, PhRMA

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Today's Talk

- Why harmonize guidance in this field?
  - Need for harmonized terms/process
- Goals and accomplishments of E15
  - Genomic Terminology –Step 4 final '07
- Objectives and Progress with E16:

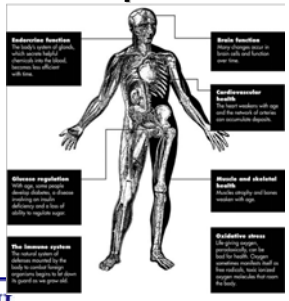
  "Genomics Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions"

2

Biomarkers: Increasingly Important in Drug Development

Biomarker: A characteristic that is objectively measured as an indicator of normal biological processes, pathogenic processes, or a pharmacological response to a therapeutic intervention*

- Used in clinical practice to:
  - identify risk for disease
  - make a diagnosis
  - assess severity
  - identify the organs involved
  - guide treatment



*J Clin Pharmacol Therapeut 2001; 69:89-95

3

Scientific advances being made globally in drug and disease specific biomarkers with genomic biomarkers leading the way

- **A Genomic Biomarker** is a measurable DNA or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes and/or response to therapeutic intervention.
- Progress with techniques to measure **specificity**, **sensitivity**, and **reproducibility** of genomic biomarkers to qualify them for regulatory purposes is being made in all regions.
- Personalized medicine approaches based on genomic biomarkers are generally applicable to other "omics" as well.
  - Metabolomics, Proteomics, etc.

4

Why Harmonize Guidance?

- Academia, industry and regulators see biomarkers as playing an important role in drug development in the future.
  - Many studies are being carried out with results that have global implications.
- Pathways for regulatory decision making are developed independently in different regions.
  - To support the evaluation of biomarkers in each region, a submission standard is important.
  - A submission standard will facilitate harmonization of biomarker qualification applications and use of these data in formal regulatory procedures.

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First ICH Guideline on Genomic Biomarkers: E15

- E15– reached Step 4 final sign-off Yokohama, 2007
  - "Definitions of genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories"
- Objective of E15
  - Timely harmonization of terminology, definitions and review process to create a common foundation upon which future guidance can be built.

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E15 – Contents:

- **Definitions for Sample and Data Coding for PGx Studies**
  - Define benefits and limitations of specific coding procedures
- **Agreed upon categories**
  1. Identified
  2. Coded
     1. Single coded
     2. Double coded
     3. Anonymized
  3. Anonymous

ICH 7

Why are Coding Procedures Important?

- Link between subject identity and genomic data
- Extent of privacy protection
- Actions possible
  - Sample withdrawal
  - Return of individual results
  - Clinical monitoring and follow-up
  - Data verification from GCP perspective

ICH 8

Draft Coding Summary Table

Category		Link Between Subject Identity and Genomic Data	Actions Possible if subject withdraws Consent	Return of Individual Results	Extent of Subject's Privacy protection	Patient's clinical monitoring and follow-up	Data verification from GCP perspective
Identified		Yes	Sample can be withdrawn	Possible	General healthcare confidentiality	Possible	Yes
Coded	***Single Coded***	Yes	Sample can be withdrawn	Possible	General healthcare confidentiality + GCP requirements for clinical research	Possible	Yes
	Double Coded	Yes	Sample can be withdrawn	Possible	General healthcare confidentiality + GCP requirements for clinical research	Possible	Yes
	Anonymzed[1]	None	None	Not possible	No potential to link genomic data to subject through key code(s)	Not possible	*Yes [with caveats to be checked with GCP inspectors]*
Anonymous		None	None	Not possible	No potential for links to genomic data	Not possible	No

ICH [1] **Prior to anonymisation the handling of the samples and data is the same as for coded**

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E16 – Second Genomic Biomarker Topic, Adopted by ICH SC April, 2008

- Recent cases with global implications show a need to harmonize data to be reviewed – format and structure.
  - Examples in both safety and efficacy markers
    - Herceptin active in Her-2 positive patients
    - CYP29 variants and implications for COX-2 inhibitor safety and warfarin dosing
    - HLA-B*1502 is a clear genetic marker for carbamazepine induced SJS.
- Not necessarily to make the same conclusion across regions, but important to look at the same data, presented in the same way.
- Currently, there are no global standards or guidance on what and when to submit genomic biomarker data and what is expected in terms of the structure and format of the submissions.

ICH 10

First Meeting of E16 Expert Working - Portland (June 2008)

- Agreements from first meeting:
  - Key Elements of Guideline
    - Context
    - Structure
    - Format
- Guideline will elaborate on the concept of context and intended use, which will drive specifics of structural elements and formats.

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E16 – General Principles

- The guideline will describe the context, structure and format of regulatory submissions for genomic biomarker qualification.
- The aim of guideline is to facilitate submission and review of biomarker qualification data among regions.
  - Not to establish global *evidentiary standards* or global *regulatory process* for biomarker qualification
- E16 focus is on genomic biomarkers but principles are applicable to other biomarker categories.
- Overall structure of the guideline will facilitate incorporation of biomarker data into product-related regulatory filings.
  - General principles of CTD structure can be applied, noting appropriate CTD sections when applicable

ICH 12

Overall Elements of Guideline: Part I. Introduction

- Objective of Guideline
- Background
- Scope of the Guideline
- General Principles
  - Context of use: Why context needs to be clear
  - Structure: Consistent regardless of the proposed context, facilitate easy review, expand to other contexts
  - Format for data will vary according to context.

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Part II: Structure of Biomarker Qualification Submissions: Organizational Analogy to CTD

- Section 1: Regional Administrative Information
- Section 2: Overview
  - Introduction
  - Context
  - Methodology and Results
    - Integrated Summary
    - Individual Study Report Synopses
- Section 3: Quality (drug product information)
  - not generally needed for qualification submission
- Section 4 (nonclinical) and Section 5 (clinical)
  - Study reports
  - General principles
  - Specific recommendations for reports containing genomic data
  - Other Supportive Documents and References

ICH 14

Context can be defined by the following areas and sub-areas:

- General Area of Proposed Biomarker Use
  - Including, but not limited to
    - Non-Clinical
      - Pharmacology
      - Safety and Toxicology
    - Clinical
      - Pharmacology
      - Safety
      - Efficacy

ICH 15

Defining Context: Specific Applications for Biomarkers including, but not limited to

- Patient selection
  - inclusion/exclusion
- Response prediction
  - stratification
  - enrichment
- Mechanism of effect
- Dose optimization
- Response monitoring
- Toxicity/Adverse reactions/Risk minimization
  - early indicator/predictor of toxicity/adverse reactions
  - management or monitoring of toxicity/adverse reactions
  - minimization of risk(s) associated with treatment

ICH 16

Critical Factors for Context Description Including, but not limited to

- Drug-specific application/Non-drug specific application
- Disease diagnosis, prognosis or staging
- Description of the assay specifications required for consistent biomarker determination or reference to a specific suitable assay or assay protocol.
- Tissue or physiological process
- Species
- Demographics include ancestry and/or geography
- Environmental factors including lifestyle
- Use in clinical trials or clinical practice

ICH 17

Progress with E16: to Yokohama

- Draft Guideline – Brussels 08
  - Collected comments on Draft Guideline - by March 2009
  - Frequent EWG meetings by Webcast
  - Consult on CTD compatibility
- Finalized Step 2 Guideline in Yokohama, June 10, 2009
- Plan to collect comments from extended network of interested groups through end 2009.
- Plan for Step 4 in June 2010

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Next Steps

- Finalize Step 4 Guideline, incorporating all comments by Spring 2010.
- Expert Group to support the drafting of a concept paper and business plan for the next biomarker guideline
  - Progress Report to SC by TC, Fall 2009

ICH

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Thank You

Happy to Answer Questions

ICH

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Safety Topics

S2 (R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use

Makoto Hayashi, *MHLW*
Rapporteur

Abstract
Dr. Makoto Hayashi will present the overview summary of the series of S2 (R1) meetings held in Yokohama.

Dr. Hayashi is the Director General at the Biosafety Research Center as well as the current Rapporteur of the S2 (R1) topic at the ICH meetings.

Questions and Answers

Question: I suppose that, within the FDA, there was not enough level of consultation and so the opposition came from the departments other than the CDER. I assume that department is the Food Section… Do you have any information that the FDA has appropriate authorities other than the CDER to make comments on pharmaceutical related matters?

Hayashi: I do not know. Please ask the FDA people. We have not received any information about who objected to this idea.

Uyama: Regarding the same issue, let me tell you what was discussed at the Steering Committee. So, the department is not the CDER, but another department. The FDA feels that the S2 guideline itself is very important, so they truly wish to implement it. However, they want to discuss it more thoroughly among different centers within the FDA before the implementation. Because S2 is so important, they want to have more discussion within the FDA before going to Step 4. After Yokohama, the FDA will have active discussion so that hopefully it will go in a more positive direction.

ICH Japan Symposium 2009
Tower Hall Funabori, Edogawa-ku, Tokyo
June 12, 2009

S2 (R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use

Rapporteur S2 (R1),
MHLW Dr. Makoto Hayashi
Biosafety Research Center
Director General
Iwata, Shizuoka, Japan

1

Objective

To revise the ICH S2A and A2B guidances taking accounts of followings:

- Merge into one guidance S2(R1),
- Reduction of positives in the *in vitro* mammalian cells assay systems that may NOT be relevant to human risk, and
- Taking into consideration of 3R's for genotoxicity assays whenever possible "without impacting" the scientific value of the tests and the evaluation of the human risk.

2

Background

- EWG of S2 started to revise on October, 2006
- We signed off for the step 2 in January, 2008
- Based on the public comments, validation and familiarization of integration in vivo genotoxicity assay into general toxicological study has been done

3

Summary of major revisions–1

- S2A and S2B guidances merged into one
- *In vitro* mammalian cell assay
  - Reduction in top concentration from 10 mM to 1 mM
  - Tightened acceptable cytotoxicity limits
  - No longer require testing of precipitating concentrations
- Provided advice on weight of evidence and data evaluation to determine relevance of positive findings
- Options provided for the test battery—*Two options considered equally acceptable*
  - Battery with *in vitro* mammalian cell assay
  - Battery without *in vitro* mammalian cell assay but two in vivo endpoints

4

Summary of major revisions–2

- *In vitro* bacterial mutation assay no longer requires duplicate assay
- Potential for integration of genotoxicity endpoints into routine toxicology studies
  - Stringent criteria defined for acceptability of top dose
- Advice on choice of second *in vivo* genotoxicity endpoint
- No longer require concurrent positive controls in every *in vivo* assay

5

Benefits of revisions in the 3 R's

- Reduction in "non-relevant" *in vitro* results will reduce number of follow-up *in vivo* assays
- No longer require concurrent positive controls in every *in vivo* assay
- Potential for integration of genotoxicity into toxicology assays

6

Issues to be discussed at the Yokohama meting–1

- Outcomes of EFPIA, PhRMA, and JPMA initiative collaborative trials on the comet (and MN) assay into 28-day repeat-dose study
- Reliability of integration of *in vivo* assays, *e.g.,* MN and comet, into the repeat-dose toxicological studies
- Combination of *in vivo* assays as a stand-alone study

7

Progress in Yokohama

- Final draft of the step 4 guidance reflecting public comments from three regions was prepared.
- Main changes:
  - Acute and repeat dose (integrated) in vivo tests could be equally acceptable for both options.
- Liver Comet assay in acute as well as repeat dose (integrated) could be acceptable as a second in vivo test according to collaborative studies.
- The step 4 draft guidance was edited by FDA attorney.

8

- The step 4 process will not be finalized in Yokohama.
- A group of genetic toxicology experts in several FDA centers strongly object to the current version of the guideline. In this group, there is concern that the new testing paradigms will weaken safety testing standards for pharmaceuticals.
- The EWG reconsidered these concerns and concluded that these concerns are not justified.
- To resolve the controversy a formal scientific dispute resolution will be conducted at the FDA.
- Depending on the results of this dispute resolution we will continue the ICH process or finalize the existing draft step 4 document.

9

Safety Topics

M3 (R2): Revision of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Abigail Jacobs, *FDA*
Rapporteur

Abstract
Dr. Abigail Jacobs will present the overview summary of the series of M3 (R2) meetings held in Yokohama.

Dr. Jacobs is the ODE Associate Director for Pharmacology and Toxicology Center for Drug Evaluation and Research at the Food and Drug Administration as well as the current Rapporteur of the M3 (R2) topic at the ICH meetings.

Questions and Answers

Question: You mentioned about the limit dose of animal studies, 1000mg/kg/day. If human dose does not exceed 1000mg, in that case, 1000mg/kg/day are allowable. This is not a clinical effective dose, but sometimes doses of higher than 1000mg are loaded to human. If that is the case, are 1000mg/kg/day for animal studies allowable?

Jacobs: The human upper dose limit for use of the limit dose in animals is 1000mg per day. Animal exposure has to be ten-fold the human exposure. So, 1000mg/kg/day would not be a limit dose if the exposure in the animals had not reached ten times the human exposure. It is not an absolute limit. It depends on the human exposure.

Question: So, the human exposure is the basis. That is understandable. If that is the case, is the administration at high doses in Phase 1 also the subject to this limitation?

Jacobs: It applies to all animal studies. This limit dose for animal studies is actually in the OECD guidelines. We added to it that it was not sufficient if the human exposure was not exceeded by ten-fold. It applies to all studies.

Question: In your presentation, non-human primate reproductive study was mentioned. I would like to confirm whether this study should be performed before the submission for the

drug approval.

Jacobs: It says that this applies to monoclonal anti-bodies that do not cross the placenta in the first two trimesters of pregnancy. It does say that the study does not have to be submitted until the marketing application. This is brand new, so we will see how it works out.

ICH M3 (R2) —Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH

Background

- Major revisions to ICHM3(R1) were begun in 2006
- ICHM3(R1) had only a few minor editorial changes to the original ICHM3
- ICHM3(R1) had a number of areas for which harmonization had not been fully achieved in original guidance (ICHM3) more than 10 years ago
- Consideration of recent regulatory documents was desirable
- Step 2 reached in June 2008

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Objectives of ICHM3

- To recommend international standards for, and promote harmonisation of, the nonclinical safety studies to support human clinical trials of a given scope and duration, and for the marketing authorization of drug products

ICH

Scope of Revisions to ICHM3(R1) (a)

- Acute toxicity studies
- Limit dose in toxicity studies
- Duration of repeat dose studies for non-rodents
- Estimation of the first dose in human
- *Exploratory clinical studies: limited clinical studies with nonclinical testing program directed only to support those early exploratory approaches
- Genotoxicity studies

ICH

Scope of Revisions to ICHM3(R1) (b)

- Reproduction toxicity studies
- Timing for special studies
  - Toxicity studies to support clinical trials in Pediatric population
  - Immunotoxicity studies
  - Phototoxicity studies
  - Nonclinical Abuse liability studies
  - Fixed Combination drug non-clinical studies

ICH

Acute Toxicity Studies

- Stand alone studies rarely needed
- Short-term, dose-limiting toxicity can be learned from repeat-dose studies
- Information on the short-term dose-limiting toxicity of pharmaceuticals should be available prior to Phase 3

ICH

Limit Dose for General Toxicity Studies

- Dose limit- 1000 mg/kg/day for rodents and non-rodents if the human dose does not exceed 1 g per day and there are 10x margins to clinical exposure

OR

- Exposure margin limit- Only need to go to 50x the maximum human exposure at the anticipated max recommended human dose
- In U.S. if dose-limiting toxicity has not been identified, 1 study of at least 1 month recommended before phase 3 study at MFD or MTD, whichever is lower

Duration of Repeated Dose Toxicity Studies in Non-rodents

- Reviewed data for all accumulated data sets (dogs, primarily) for about 150 compounds developed for diverse indications from EU countries, the U.S., and Japan--1999-2006
- Re-evaluated 6 vs 9 vs 12 months for opportunity to minimize exceptions to 9 month's duration

Duration of Repeated Dose Studies in Non-rodents

- Criterion: Would clinical decisions have changed based on new toxicity uncovered in longer term studies?
- 6 months in non-rodents (primarily dogs) is usually but not always sufficient
- No data that show that 9 months is not sufficient
- 9 month non-rodent chronic studies should be adequate to support chronic use in human (small molecules) without exception

Exploratory Clinical Studies (a)

- 5 exploratory clinical studies approaches (no therapeutic or diagnostic intent, MTD not examined) are described as examples.
- Supportive non-clinical programs are focused on direct support of those early clinical studies with limited clinical objectives, not on further development

Five Exploratory Clinical Studies (b)

- Two microdose approaches
  - Total dose of 100 µg
  - Up to 5 administration of a maximum of 100 µg/administration
- Single dose subtherapeutic studies
- Two Repeated dose exploratory studies:
  - Exposure based (overage approach)
  - Duration of clinical trial up to duration of dosing in non rodent toxicity studies; an alternate path

Microdose Approach- 1

- Total dose of 100 µg, max of 5 administrations and 1/100th NOAEL and 1/100th Pharmacologically active dose, scaled
- Extended single dose tox study in 1 species by intended route and PK; max dose of 1000x clinical dose, scaled
- PD profile in vitro and in relevant model; genetox not needed

Microdose Approach- 2

- Total dose of 500 µg, 100 µg per dose, max of 5 administrations, with washout between and 1/100th NOAEL and 1/100th Pharmacologically active dose, scaled
- 7-d repeat dose tox study in 1 species by intended route and PK; max dose of 1000x clinical dose, scaled
- PD profile in vitro and in relevant model; genetox not needed

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3. Single Dose Subtherapeutic Clinical Studies

- Starting clinical dose depends on toxicity in extended single dose toxicity studies in rodents and nonrodents in which top dose was MTD, MFD, or limit dose
- Max clinical dose: ½ the NOAEL exposure in the more sensitive species, if tox is monitorable and reversible
- nonclin safety pharm; Ames assay

ICH

4. Single or Repeated Dose Clinical Studies into Therapeutic Range but Not to Evaluate MTD, Exposure Based (a)

- Starting Dose: If tox in both species: follow regional guidance for the starting dose
- Without any tox in either species or tox in one species, starting clinical dose should not exceed 1/50 the NOAEL in the more sensitive species (mg/m^2); for other considerations, follow regional guidance

ICH

4. Single or Repeated Dose Clinical Studies into Therapeutic Range but Not to Evaluate MTD, Exposure Based (b)

- Max Clin dose:
- With tox in both species, max clin dose based on std risk assessment but typically would not exceed the lowest NOAEL AUC
- Without tox in both species, clin dosing up to 1/10 the lower exposure (AUC) in either species at highest dose tested
- If tox in one species, max clin dose would be whatever gave the lower exposure of the above 2 options

ICH

4. Single or Repeated Dose Clinical Studies into Therapeutic Range but Not to Evaluate MTD, Exposure Based (c)

- Std 2-wk repeat dose toxicity studies in rodent and nonrodents, with dose selection in animals based on multiples of the anticipated clinical AUC at the max dose
- Nonclin safety pharm; Ames assay

ICH

5. Single or Repeated Dose Clinical Studies into Therapeutic Range but Not to Evaluate MTD (linked to duration) (a)

- Starting clinical dose should not exceed 1/50 the NOAEL in the more sensitive species(mg/m^2)
- Max clinical dose: not higher than the AUC at the NOAEL exposure in the nonrodents or 1/2 AUC at the NOAEL in the rodent species, whatever is lower (up to 14 days)

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5. Single or Repeated Dose Clinical Studies into Therapeutic Range but Not to Evaluate MTD (linked to duration) (b)

- Std 2-wk repeat dose toxicity studies in rodent (with justification for rodent) and, confirmatory study in nonrodent with duration of a minimum of 3 days and up to clinical study duration
- Nonclin safety pharm

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Genotoxicity Studies

- A gene mutation assay is sufficient to support all single dose clinical development trials
- For multiple dose clinical development trials, referred to S2B

ICH

Reproduction Toxicity Studies (a)

- Nature and timing of reproductive toxicity studies to support the conduct of different phases of clinical trials
- Reviewed data sets from dose ranging and definitive studies in rats and rabbits (several hundred drugs developed for diverse indications from EU countries, the U.S., and Japan--1999-2006
- Criterion: How well do dose-ranging studies predict those results of definitive studies that would changed clinical decisions or have an impact on labeling.

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Reproduction Toxicity Studies (b)

- When dose-ranging studies are available and visceral/external examinations are conducted—good predictivity
- WOCBP (up to 150) with control of pregnancy risk could receive investigational treatment for up to 3 months before completion of definitive reproductive toxicity studies
- WOCBP= women of child-bearing potential

ICH

Reproduction Toxicity Studies (c)

- FDA allows such clinical trials without dose-ranging studies
- In the EU and Japan, although definitive studies are generally required to support inclusion of WOCBP in clinical studies, some situations are defined where early clinical studies could be conducted in WOCBP before completing embryo-fetal developmental studies in animals. These include short duration clinical trials (such as 2 weeks) with intensive control of pregnancy risk.

ICH

Timing for Special Studies

- Toxicity studies to support clinical trials in Pediatric population
- Immunotoxicity studies
- Phototoxicity studies
- Nonclinical Abuse liability studies
- Fixed Combination drug non-clinical studies

ICH

3Rs Achievements (a)

Overall harmonization will result in reduction and refinement of animal use:

- Separate acute toxicity studies were eliminated. (reduction)
- Repeated dose toxicity studies now have exposure and dose limits to establish valid study designs. (refinement and reduction of the need to repeat studies)

3Rs Achievements (b)

- **New exploratory clinical studies section will reduce use of animals needed to support clinical studies and offer refinement of toxicology study design. (reduction and refinement)
- Local tolerance toxicity: recommended against stand alone designs. (reduction)
- Reproductive toxicity studies are deferred until later in development and this will result in elimination of studies for failed compounds. (reduction)

3Rs Achievements (c)

- Recommended that photocarcinogenicity studies generally are not of value for pharmaceutical development. (reduction)
- Studies of combination drugs recommended to be limited to 1 species, usually rodent (reduction, refinement)

ICH M3 (R2) Current Status

- Signed off on step 2 in July 2008
- Started discussing public and 6-party comments on a number of the revisions in November 2008 in Brussels
- Had 3 webex meetings in January 2009
- Had an interim Meeting in MD in the U.S. in March 2009 and finished addressing all comments received on the step 2 document

Outcomes of the Yokohama Meeting

- Reviewed data on the need for skeletal evaluations in dose-ranging embryo fetal developmental studies
- *Concurrence that skeletal evaluations not necessary but data from both rat and rabbit should be collected*
- Agreed on wording with S6 for when combined embryofetal dev./pre/postnatal studies in non human primates can be submitted for marketing rather than before phase 3 clinical studies

Outcomes of the Yokohama Meeting

- Got agreement on areas of overlap with S2 and S9
- Signoff

Conclusions

- This revision R2 of ICH M3 which includes further harmonisation for non-clinical safety studies will help to define current recommendations and reduce the likelihood that substantial differences will exist between regions
- ICHM3(R2) should facilitate timely conduct of clinical trials and reduce the unnecessary use of animals and other resources
- This should promote safe and ethical development and availability of new pharmaceuticals

ICH

Safety Topics

S6 (R1): Revision of Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

Takahiro Nakazawa, *JPMA*
Topic Leader

Abstract
Dr. Takahiro Nakazawa will present the overview summary of the series of S6 (R1) meetings held in Yokohama.

Dr. Nakazawa is the Manager of the Preclinical Japan Regulatory Affairs in Lilly Research Laboratories Japan at Eli Lilly as well as the current Topic Leader of the S6 (R1) topic at the ICH meetings.

Questions and Answers

Question: The S6 guideline is intended to recommend the preclinical studies for biopharmaceuticals. In the main body, it is written that the principles outlined in this guidance may be applicable to plasma-derived products. Some preclinical studies could be omitted for plasma-derived proteins. Does not the addendum deal with the "points-to-consider" on preclinical studies with plasma-derived proteins?

Nakazawa: No, as the scope is not revised.

Question: There may be slightly different opinions even for proteins among the three regions. Were there any different opinions in the EWG meeting?

Nakazawa: No, I learned that experts of EWG have very similar interpretation of the S6 guideline although there may be slightly different implementation in some practical cases.

ICH S6(R1)

Takahiro Nakazawa, Ph.D.

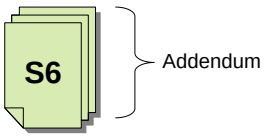
S6(R1) Topic Leader, JPMA

Agenda for This Presentation

- Objective
- Background
  - Five topics to be addressed by S6(R1)
- Issues to be discussed at the Yokohama meeting
- Outcomes of the Yokohama meeting
- Potential conclusion

Objective

- Add clarification and amplification to the original S6 document for effective and efficient development of biopharmaceuticals and improvement of 3R's
  - "Case-by-case" concept of S6 will not be changed
  - Format of revision: Addendum



Background

- 1997 July (Brussels)
  - S6 step 4
- 2006-2008 Regional discussions on revision
- 2008 June (Portland)
  - SC Approval for EWG formation for revision (S6(R1))
  - Identification of 5 topics to be updated
- 2008 Nov (Brussels)
  - Kick-off of EWG
  - Brainstorming
  - Draft of immunogenicity addendum
- 2009 Feb to May
  - Teleconferences or e-mail discussions

Species Selection

- How to justify the choice of a species
  - Receptor binding, functional study, tissue cross reactivity
- When to use a second species
  - Two species, where 2 relevant species, rodent and non-rodent, exist (S6 default position)
    - Does not mean NHP with clinical candidate AND rodent studies with surrogate product
  - When only one relevant species be considered sufficient?
- Use of alternative models, such as transgenics and homologues
  - When to use
    - No relevant species exist for clinical candidate
    - To avoid use of NHP e.g. for reprotox?
  - Clarify critical factors to qualify a surrogate/homologue for use in toxicity testing?

Study Design

- High dose selection
  - PK/PD approaches
    - Maximum pharmacological dose and a 10-fold multiple above the highest anticipated clinical dose?
- Scientific justification of duration
  - Six months duration based on continuous maximum pharmacological effect as intended in clinical use
    - Rationale for shorter or longer duration?
- Utility and length of recovery
  - Not required for all dose groups
  - Rationale for reasonable length of recovery?

Reproductive/Developmental Toxicity Studies

- Justification of species selection
  - Rodents/non-rodents
  - When and how to use transgenics/homologues?
    - Further discussion is needed on the value of surrogate data in rodents in place of NHP with clinical candidate
- Considerations when using NHP
  - Use of combined study designs
    - Enhanced pre- and post-natal developmental (ePPND) study
      - Impact of placental transfer
      - Consider duration of dosing period
      - How to get data from the F1 generation?
      - This ePPND study design has an impact on timing of these studies in clinical development and submission (cross-talk with M3)
  - How to assess a risk on fertility in chronic tox studies?

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Carcinogenicity

- Justification for the approach to address carcinogenic risk
  - Life time rodent bioassay for therapeutic proteins does not provide useful information
- Application of alternative models
  - Inclusion of the carcinogenic risk evaluation in chronic tox study
    - Length of the studies
    - Use of proliferation indices
  - *In vitro* tumor cell lines
  - Tumor explant models
  - Use of homologues and transgenic animals?

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Immunogenicity

- Clarification of purposes of immunogenicity assessment in nonclinical studies that may help better understanding of:
  - Extent of characterization
  - Impact of neutralizing vs. non-neutralizing
  - Role of PD markers
  - Assessment in recovery groups
- Interpretation of tox findings but not prediction of potential immunogenicity in humans

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Issues To Be Discussed at The Yokohama Meeting

- Species selection
  - When only one relevant species is sufficient
  - Tissue cross reactivity assay
  - When and how to use homologues
- Study design
  - Scientific basis for high dose selection, duration and recovery
- Repro/dev tox studies
  - Design and timing of EFD study
  - Value of surrogate data in rodents in place of NHP with clinical candidate
- Carcinogenicity
  - Justification for the approach to address carcinogenic risk
- Immunogenicity
  - Final draft addendum

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Outcomes of Yokohama Meeting

- Species selection: First draft completed
  - When only one relevant species is sufficient
  - Tissue cross reactivity assay
  - When and how to use homologues
- Study design: Agreed on the principle
  - Scientific basis for high dose selection, duration and recovery
- Repro/dev tox studies: Agreed on the principle
  - Design and timing of EFD study: Agreed with M3 and S9
  - Value of surrogate data in rodents in place of NHP with clinical candidate
- Carcinogenicity: Consnsus in EWG
  - Justification for the approach to address carcinogenic risk
- Immunogenicity: First draft completed
  - Final draft addendum

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Conclusion

- S6(R1) will reach step 2 in the St. Louis meeting this fall
  - Remaining issues are:
    - Draft addendums for remaining sections
    - Address concerns about carcinogenicity studies of experts outside EWG

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Safety Topics

S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

Dai Nakae, *MHLW*
Topic Expert

Abstract
Dr. Dai Nakae will present the overview summary of the series of S9 meetings held in Yokohama.

Dr. Nakae is the Senior Principal Research Scientist at the Tokyo Metropolitan Institute of Public Health as well as the current Topic Expert of the S9 topic at the ICH meetings.

Questions and Answers

There were no questions.

S9
Nonclinical Evaluation for Anticancer Pharmaceuticals

Dai Nakae
Senior Principle Research Scientist of
the Tokyo Metropolitan Institute of Public Health
(Representing MHLW in S9 EWG as an Expert)
Japan

Objectives are to

- Provide recommendations on the design and conduct of nonclinical studies to support the development of anticancer pharmaceuticals in patients with advanced disease and limited therapeutic options, and
- Facilitate and accelerate the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse effects, while avoiding unnecessary use of animals and other resources.

Background

Nonclinical evaluations are intended to

- identify the pharmacologic properties,
- establish a safe initial dose level for the first human exposure, and
- understand the toxicological profile (e.g., identification of target organs and reversibility).

Anticancer pharmaceuticals are special, because

- malignant tumors are life-threatening,
- existing therapies have limited effectiveness,
- new effective pharmaceuticals should be provided as expeditiously as possible, and
- the clinical dose level is often close to or at an adverse effect level.

For these reasons,
a separate guideline with flexibility is needed
for nonclinical studies for anticancer pharmaceuticals.

Timeline

- The business plan and concept paper were proposed by PhRMA during year 2006.
- They were endorsed by the ICH Steering Committee in Brussels in May, 2007.
- The S9 Expert Working Group (EWG) started its actions in Yokohama in October, 2007. At that moment, a relatively old specific guideline was present in EU, while such guidelines were still being developed in the US and Japan.
- Development of the S9 guideline reached the step 2 agreement in Brussels in November, 2008, and public comments for the draft guideline were collected in early 2009.
- The ICH Steering Committee and the S9 EWG expect that the development of the S9 guideline will reach the step 4 agreement hopefully in late 2009, not later than the original deadline of early 2010.

Scope

- Pharmaceuticals that are intended to treat cancer in patients with late stage or advanced disease, including both small molecule and biotechnology-derived pharmaceuticals, are to be covered.
- Excluded pharmaceuticals are those for
  - patient with long life expectancy,
  - cancer prevention,
  - treatment of symptoms or side effects of chemotherapeutics,
  - vaccines, and
  - cellular or gene therapy
- Radiopharmaceuticals are not covered, but some of the principles could be adapted.

Assumption

- Recommendations on type and timing of nonclinical studies are to be provided.
- Descriptions are to be restricted for issues specific to anticancer pharmaceuticals. For this, and in order to reduce future maintenance, references to other guidelines are to be encouraged as appropriate.
- In any case, the 3 R's are to be kept in mind.

Accomplishments before Yokohama, 2009

- No need for NOAEL/NOEL to support clinical trials
- No need for 6/9 month studies
- Recovery only to a single species prior to phase I
- Inclusion of safety pharmacology and immunotoxicology assessments within general toxicology studies
- No need for fertility or pre/postnatal studies
- Embryofetal study only to a single species, if positive
- No need for non-rodent studies for the initiation of clinical trials with cytotoxic drugs
- Genotoxicity studies by a marketing application
- No need for carcinogenicity studies or metabolite assessments
- Generally no need for combination or juvenile assessments

Issues to be discussed in Yokohama, 2009

- Examination of public comments for the step 2 document of the S9 guideline obtained in each region
- Improving the guideline, including appropriate reaction to and reflection of the public comments
- Search for other problems in order to prepare the step 4 document, and if possible their resolution
- Start of the preparation of the step 4 document
- Setting of a future plan
- Harmonization with other safety EWGs for potential conflicts, overlaps and *etc*

Accomplishments in Yokohama, 2009

- Resolution of all public comments, a total of 219, and other problems raised by experts
- Interaction with S6 and M3 EWGs for the consistency with their guidance documents; such as scope, reproductive assessment and reversibility
- Use of S6 for biopharmaceuticals testing
- Reference to M3 for healthy volunteers and patient populations other than advanced cancer as appropriate
- Improving the guideline to become ready for the preparation of step 4 document

Accomplishments in Yokohama, 2009

<u>Concrete accomplishments that also lead to a reduction of animal use</u>

- 3 month studies sufficient for registration
- Eliminated the need for fertility and pre- and postnatal development studies
- Required only 1 embryofetal development study if a positive is observed
- Safety pharmacology assessments could be conducted within the general toxicology studies
- Eliminated the need for the non-rodent for initiation of clinical trials with cytotoxic drugs
- Reduced to 1 rodent study
- Reduced recovery requirement to a single species prior to phase I
- Need for recovery period based on scientific justification
- No need for photosafety testing

Issues to be discussed up to St. Louis, 2009

- Examination of the Yokohama-version document of the S9 guideline among colleagues/parties of each region
- Improving the guideline, including appropriate reaction to and reflection of regional concerns/comments
- Start of the preparation of the step 4 document

Safety Topics

GTDG: Gene Therapy Discussion Group

Klaus Cichutek, *EU*
Co-Rapporteur

Abstract
Professor Klaus Cichutek will present the overview summary of the series of GTDG meetings held in Yokohama.

Professor Cichutek is the Vice President at Paul Ehrlich-Institute as well as the current Co-Rapporteur of the GTDG topic at the ICH meetings.

Questions and Answers

There were no questions.

Activities of the ICH Gene Therapy Discussion Group (GTDG)

Klaus Cichutek
Paul-Ehrlich-Institut,
63225 Langen, Germany

Chair, EMEA/CHMP GTWP
Co-Chair ICH GTDG

E-mail: **cickl@pei.de**

Disclaimer

The views expressed in this presentation are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the EMEA or one of its committees or working parties.

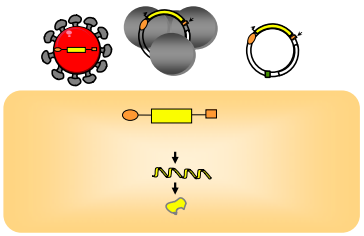
Agenda

1. Overview of GTDG activities in ICH
2. Exchange of information between ICH regions (Japan, US FDA, EU, Health Canada, EFTA)

ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Website: www.ich.org (-> GTDG)

Gene therapy: gene correction (future) or gene addition to restore cell function or provide new cell function



Genes are added to cells by gene delivery vehicles.
- replication-incompetent viral vector particles
- non-viral vector complexes
- naked DNA (naked nucleic acid) in bacterial plasmids
- related: oncolytic bacteria and viruses, DANN and live vector vaccines

ICH Gene Therapy Discussion Group

- ✓ Medicines Agency and pharmaceutical industry representatives from the 3 ICH regions (Japan, USA, EU) and experts from the European Free Trade Association (EFTA), Health Canada and the WHO meet as the ICH Gene Therapy Discussion Group since 2001.
- ✓ An observer from the Chinese SFDA attended meetings and has contributed a regional update.
- ✓ Objectives:
  - Monitor emerging scientific issues
  - Proactively set out principles that may have a beneficial impact on harmonizing regulations of gene therapy products
  - Develop new ways of communication to ensure that the outcomes of ICH are well understood and widely disseminated such as
    - public ICH gene therapy workshops
    - public gene therapy press statements from the ICH SC
    - establish a publicly available ICH gene therapy web page

ICH Gene Therapy Discussion Group

- ✓ Four public workshops held on topics such as
  - Workshop on Viral / Vector Shedding, Rotterdam October 30, 2007
  - ICH Workshop on Oncolytic Viruses, Chicago, November 7, 2005
  - Presentations at ICH6, Satellite Session III on Gene Therapy, Osaka, November 15, 2003
  - Second Workshop on Gene Therapy - Satellite Session, Osaka, November 12, 2003
  - First Workshop on Gene Therapy, Washington, September 9, 2002

ICH Gene Therapy Discussion Group

✓ GTDG Considerations documents:

- General Principles to Address Viral / Vector Shedding (will be released in 2009 for comments)
- Oncolytic Viruses (released in 2008 for comments, revised in 2009)
- General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (2006)
- General Considerations (2004) (SCID GT, long-term follow-up, HIV vaccination in healthy volunteers, replication-competent adenovirus in repl,-incomp. adv. vector preparations, germline transmission studies)

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ICH Gene Therapy Discussion Group Report from Yokohama meeting 8-11 June 09

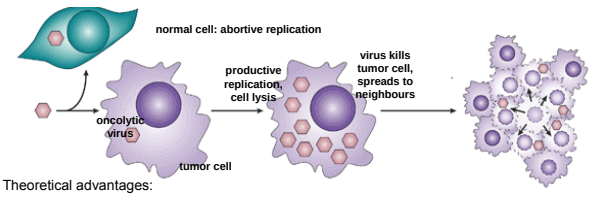
The scope of the ICH Gene Therapy Discussion Group (GTDG) meeting included:

- sharing regional updates,
- discussing the ICH Considerations on Viral / Vector Shedding,
- revising the ICH Considerations on Oncolytic Viruses,
- discussing and making plans for future activities (discussions on writing an ICH Guideline on Viral/Vector Shedding).

12 June 2009 Open Workshop on Gene Therapy 8

Conditionally replicating oncolytic virus

Virus engineered to direct their cytotoxicity towards cancer cells



Theoretical advantages:

- viral replication within tumor mass allows infection of many cells
- lack of cross-resistance with standard therapies
- ability to cause tumor destruction by a variety of mechanisms

Theoretical risks:

- chronic infection, introduction of new pathogens into the human population and adaptation

ICH Gene Therapy Discussion Group Interesting topics from regional updates

✓ GTDG regional updates:

- Gamma-retro- and lentiviral trials in EU leading to clonal cell dominance, sometimes oncogenesis (tumour development due to insertional mutagenesis; see next slide)
- Autologous T bodies are potent mediators of effects, severe adverse reactions in cancer patients observed
- State of MAA applications in the EU: 3x applications under review
- China: 2x gene therapy medicinal products on Chinese market, in vivo vectors in clinical trial, others in medical use

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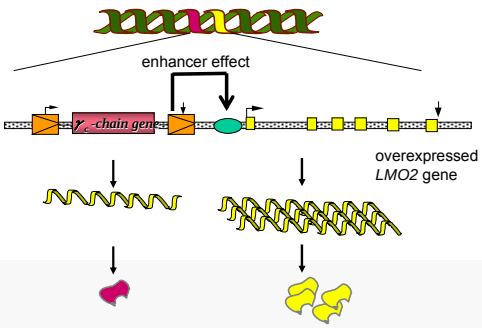
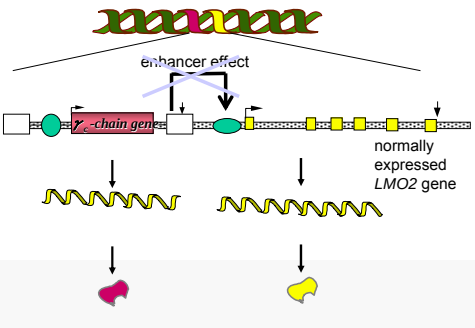
Insertional mutagenesis of integrating retroviral vectors: *p-onc* overexpression



SIN (self inactivating) vectors may reduce neighbouring *p-onc* overexpression



ICH Gene Therapy Discussion Group Interesting topics from regional updates

- ✓ Insertional mutagenesis/oncogenesis and clonal cell dominance:
  - Insertional oncogenesis previously observed in X-SCID trials using early generation retroviral vectors
  - From data analyses and field investigations next generation vectors developed to decrease oncogenic effect
    - Scientific data supported safety features
  - Next generation lentiviral vector was then used in β-Thalassemia *ex vivo* clinical trial
    - Clonal cell dominance as a possible precursor of oncogenesis observed
  - Clinical benefit seen
    - Defining appropriate benefit:risk balance
    - Discussion of inclusion criteria

ICH Considerations on Viral/Vector Shedding

- ✓ Shedding and possible transmission, potential consequences for public health
  - Following administration of viral and plasmid vectors and of oncolytic viruses or bacteria to patients, they may be shed through secreta (saliva) and excreta (urine, faeces)
  - If infectious, the virus particle and bacteria may be transmitted
    - to other human contacts (third party transmission) and/or
    - to the environment.
  - If transmitted to third parties, they may stay at entry site (tissue, organ, cells) or they may be biodistributed (e.g., by replication)
  - The transmitted genes/viruses/bacteria may have pathological consequences for the person to which the virus/bacteria is transmitted to.

ICH Considerations on Viral/Vector Shedding

- ✓ Issues discussed
  - Definition of viral/vector shedding
  - Sampling and assays (qPCR vs. infectivity)
  - Non-clinical testing (to help design clinical shedding studies)
  - Clinical testing (in early clinical studies)
- ✓ Not discussed: shedding into the environment and consequences
  - Transmission of plasmid DNA to bacteria in the environment
  - Persistence of viruses/vectors in the environment and possibilities of transmission to live organisms (animals, plants, humans)

ICH Gene Therapy Discussion Group Conclusions

- As gene therapy development is global, products travel between Asia, America and Europe.
- Sharing of information on benefits and risks observed with administered gene therapy medicinal products allows for measures to reduce risks for patients.
- ICH Considerations and ICH Guidelines mediate harmonized approaches for product regulations and development.
- Development of an ICH Guideline on Viral/Vector Shedding is being discussed.
- Comments to ICH Considerations on Viral/Vector Shedding are welcome (www.ich.org).

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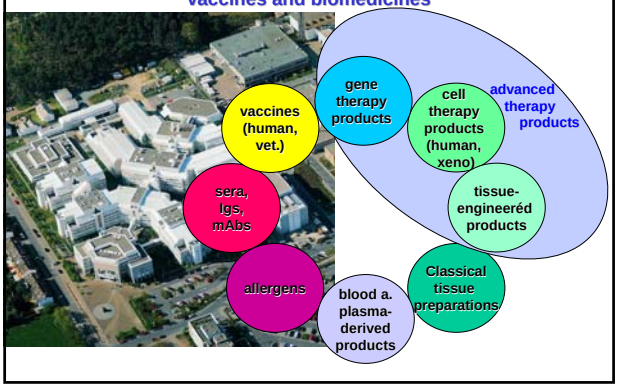
Paul-Ehrlich-Institut: research on and regulation of vaccines and biomedicines



Quality Topics

Q4B: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

Nobukazu Igoshi, *JPMA*
Topic Leader

Abstract
Mr. Nobukazu Igoshi will present the overview summary of the series of Q4B meetings held in Yokohama.

Mr. Igoshi is the Manager of the Quality Assurance Group in the Quality Assurance Department at Daiichi Sankyo Co., Ltd. as well as the current Topic Leader of the Q4B topic at the ICH meetings.

Questions and Answers

Question: The last page of your presentation mentioned that the Q&A and training slides are going to be created. What are the objectives of creating those slides? Would you elaborate on that?

Igoshi: The Q4B guideline as for the structure is somewhat different from other quality guidelines. Especially structure is different. The reference of pharmacopeia is there. How to use pharmacopeia as a reference is mentioned. What kind of format is used for the submission of dossier and how to corporate this into the dossier, are mentioned. Dr. Hiyama mentioned about the field inspection. So far, we have not identified what kind of questions will be raised in the field. So, the support will be provided. That is the agreement we have reached so far. Further activities will come to an agreement at the next St. Louis meeting.

Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

ICH Q4B Expert Working Group

NOBUKAZU IGOSHI
JPMA Topic Leader

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Presentation Outline

- Short History and Overview of ICH Q4B
- The Pharmacopoeias and the Regulators
- The Q4B Process and Annex
- Interaction: Q4B Expert Working Group (EWG) and PDG
- Q4B EWG meeting outcomes (successes) and current work in progress

2

History of ICH Q4B EWG

- The harmonisation of specific compendial test chapters has been considered as critical by the ICH Steering Committee to attaining full utility of the ICH Q6A guideline (1998)
- Industry requested ICH SC to create an EWG to address how the regulatory authorities (3 regions) will recognise the interchangeability of harmonised pharmacopoeial chapters from Ph. Eur./JP/USP (PDG) – July 2003
- ICH SC established Q4 EWG with a scope to address 11 General Test Chapters discussed during development of ICH Q6A Guideline - November 2003
- SC approves Q4B Work Plan – April 2004

3

History of ICH Q4B EWG (2)

- SC approves development of an ICH Guideline with topic specific annexes – June 2004
- Q4B EWG begins evaluating PDG harmonised text – November 2004
- Step 2 ICH Q4B Core Guideline approved by SC – June 2006
- 1st Annex (Residue on Ignition/Sulphated Ash) approved (ICH Step 2) – June 2006
- Regulatory consultation (ICH Step 3) on Core Guideline completed by each regulatory region (60-day comment period) – October 2006

4

History of ICH Q4B EWG (3)

- Core Q4B Guideline reworked based on constituent comments; ICH Step 4 documents finalised for ICH signoff – November 2007
- Consist of "parent guideline" Step 4 Q4B – ERPTUIR (new title)
- "Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH regions"
- First Annex No. 1 approved at Step 4 – ROI/Sulphated Ash – November 2007
- SC approves limited expansion of scope – November 2008

5

ICH Q6A-related General Chapters

Dissolution	**Disintegration**
Uniformity of Content *	**Uniformity of Mass ***
Extractable Volume	**Particulate Matter**
Sterility	**Microbiological Quality**
Bacterial Endotoxins	**ROI/Sulphated Ash**

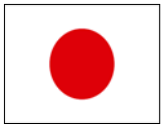
Colour and Clarity
(per ICH SC, work will just be on "*Colour*")

Above chapters identified as the basis of Q4B activity

* Combined to ***Uniformity of Dosage Units***

6

The Pharmacopoeias and the Regulators
Different Approaches for Moving Forward



JP (PMDA)

Governmental

Ph. Eur. (EDQM)

Governmental Partnership

USP

Independent of Government

Not for profit organisation

ICH

7

The Q4B Process
Value of the Q4B Activity

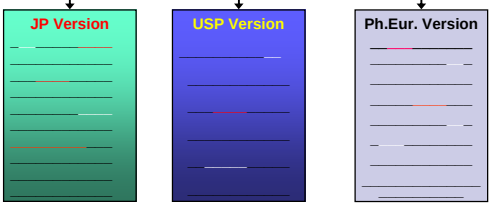
- A component of international harmonisation efforts to assist in common specifications
- A savings in time, effort and cost
  - Industry: to globally unify testing strategies [for applications and other regulatory (compliance) needs] – one test rather than three
  - Regulators: to reduce or eliminate the need to go through a justification procedure as to the use of other compendial methods (done one time to eliminate repetitive justifications)

ICH

8

PDG Process Results in Harmonised Text

Individual Pharmacopoeial Approval & Official Publication Process



Challenge to regulators: Do differences impact on the ability to achieve a result with the same accept and reject capability? Are they interchangeable?

ICH

9

Q4B Process Steps

FOR EACH TOPIC:

- PDG provides to Q4B Expert Working Group:
  - PDG-harmonised text
  - JP/Ph.Eur./USP draft versions of how harmonised text will be implemented in their compendia
  - Briefing note to delineate any local differences or potential issues
  - Printing timelines to move approved pharmacopoeial text to official status
- Q4B member parties bring the documents back to their constituents for independent evaluation

ICH

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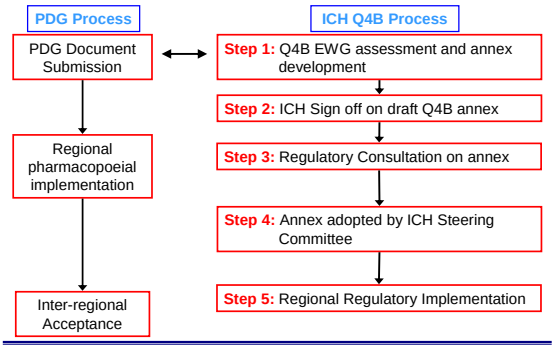
Q4B Process Steps (continued)

- Q4B EWG reviews the evaluations
- Issues discussed within Q4B EWG for possible resolution
- Evaluation results and possible resolution mechanisms conveyed back to and/or discussed with PDG
- Once issues are resolved, Q4B EWG recommends approval (ICH Step 2) to the ICH SC
- Start of Annex process – Moving the Q4B evaluation outcome into the regulatory mechanisms for each region

ICH

11

Topic Specific Annex Process



ICH

12

Q4B EWG and PDG Interaction

- Dedicated time (set aside) at each formal ICH EWG meeting venue to discuss issues
- Stakeholder partnering – all parties focused to achieve interchangeability
- Direct feedback mechanisms to resolve issues
- Clear delineation of what steps are necessary for problem resolution
- Success more likely versus single, independent efforts

ICH 13

Q4B Successes – November 2007, Yokohama

Primary objectives achieved:

- Core Q4B Guideline (establishing Q4B Process)

Completed and signed off at ICH Step 4 -- Step 5 Regional Implementation

- Title for the Q4B Core Q4B Guideline finalised

The Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

- First Annex (1) – ROI/Sulphated Ash

Completed and signed off at ICH Step 4 -- Step 5 Regional Implementation

ICH 14

Q4B Successes – November 2008, Brussels

Limited Scope Expansion:

Steering Committee approved addition of 5 new PDG-harmonised general chapters to the Q4B process:

- Tablet Friability
- Bulk density and tapped density
- Analytical Sieving
- Capillary Electrophoresis
- Polyacrylamide Gel Electrophoresis [PAGE]

ICH 15

Q4B Successes – June 2009, Yokohama

- Step 2 documents moved to Step 4 sign-off:
  - Annex 5 Disintegration Test
  - Annex 8 Sterility Test
- Additional annexes moved to Step 2 sign-off:
  - Annex 9 Tablet Friability
  - Annex 10 Polyacrylamide Gel Electrophoresis [PAGE]
- Complete preparation of draft Step 4:
  - Annex 7 Dissolution Test

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Current Status – Q4B EWG

ICH June 2009 Meeting, Yokohama, Japan

Completed Annexes to the Core Q4B Guideline

#1 Residue on Ignition	*Step 5*
#2 Extractable Volume	*Step 5*
#3 Particulate Matter	*Step 5*
#4A, 4B, 4C Microbiological Tests	*Step 5*
#5 Disintegration Tests	*Step 4*
#8 Sterility Test	*Step 4*

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Yokohama 2009 Update (1)

Work in Progress

- #6 Uniformity of Dosage Units
- #7 Dissolution
- #9 Tablet Friability
- #10 PAGE
- Bacterial Endotoxins
- Colour
- Analytical Sieving
- Bulk Density and Tapped Density
- Capillary Electrophoresis

→ **Drafting Step 4 document**

→ **Signed at Step 2 – Regulatory Consultation (ICH Step 3)**

→ **Submissions awaited from PDG**

ICH 18

Yokohama 2009 Update (2)

Industry-suggested Prioritisation for PDG Harmonisation

1. Chromatography General Chapter(s)
2. Infrared absorption spectroscopy (including Near IR)
3. pH
4. Water Determination (volumetric)
5. Water Determination (coulometric)

ICH 19

Yokohama 2009 Update (3)

Training Items – Will discuss

- Training Slide Presentation
  - Education on implementation of annexes (general and specific guidance)
- Q & A
  - Assist in the interpretation and use of Q4B guideline and Annexes

ICH 20

Members of the ICH Q4B EWG

Cindy Buhse (FDA)
Nick Cappuccino (IGPA)
Jon Clerk (FDA)
Gérard Damien (EFPIA)
Martine Draguet (EFPIA)
Nobukazu Igoshi (JPMA)
Tomoko Jingo (MHLW)
Robert King (FDA)
Sabine Kopp (WHO)
Yoshiaki Maruyama (MHLW)
Carmen de la Morena-Criado (EU)
Osamu Morita (MHLW)
Tsuneo Okubo (JPMA)
Stéphanie Parra (Health Canada)
Janos Pogany (WHO)
Hideki Sasaki (JPMA)
Janeen Skutnik (PhRMA)
Toyashige Tanabe (JPMA)
Yumi Tanaka (MHLW)
Petar Vojvodic (WSMI)
Kiyoshi Washida (MHLW)
Jonathan Mark Wiggins (PhRMA)

Robert H. King, Sr. (FDA) – 1st Rapporteur
J.M. Morris (EU) – Current Rapporteur

ICH 21

Quality Topics

Q11: Development and Manufacture of Drug Substances

Brian Withers, *EFPIA*
Rapporteur

Abstract
Mr. Brian Withers will present the overview summary of the series of Q11 meetings held in Yokohama.

Mr. Withers is the Director CMC of GPRA at Abbott Laboratories as well as the current Rapporteur of the Q11 topic at the ICH meetings.

Questions and Answers

Question: I think the speed of the harmonization process is very slow. Of course, I know it is very difficult. But, if we could divide the guideline into chemical compounds and biotechnological products, it is easier to develop such a guideline. What is the merit of combining the biotech products and chemicals?

Withers: I think that is a very good question. The question that you asked is one that impacted on the time it took to get agreement to prepare the guideline in the first place. However, within the expert working group, we have members who have an interest in biotechnological products and others with an interest in chemical compounds. What we discovered in our discussion is that we have more in common than there are differences. We found that the principals apply to all molecules and there are some things where there is more emphasis on one molecular type than another molecular type. We are finding more agreements than differences.

Question: You showed us the Priority Harmonization Subject List in which five items from the starting material to the process validation are listed. Among the five items on the list, which one do you think is the easiest to harmonize, or has the least gap within the three regions?

Withers: I can probably tell you which one is the hardest. Currently, the hardest one might be starting materials because at the moment it is a difficult subject since there are different views

between the regions, so I think that might be the hardest. The easiest one might be guidance for process validation. Principals are already generally accepted across the three regions.

Question: Two years ago, I attended the Quality of Biotech Products meeting. At that time, the SC asked us to incorporate the idea the “Quality by Design” into the guidance. I am surprised with your lecture because the word of the Quality by Design is no where. So, I would like to know what has happened.

Withers: For Q11, there is definite interest in expressing the principals outlined in Q8R and to give examples of how different approaches to the development could be followed and that will include the Quality by Design. One of the challenges is that we must make a balance so that the guideline can be applicable to a company whichever approach they choose for the development. So, it has to cover a wide spectrum of approaches to the development. Certainly, a lot of the discussion within the expert working group has been done about the principals of the Quality by Design and how they apply to the development of the molecule irrespective of the complexity. So, it is certainly vey much on our agenda.

Okuda: In my opinion, the idea of the Quality by Design is reflected in drafting the Q11 guideline, but there are also different approaches. Therefore, although it is adequately discussed, it is one of the approaches and thus had not been mentioned in Mr. Wither’s presentation.

Q11 Update

Brian Withers,
Abbott Laboratories

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

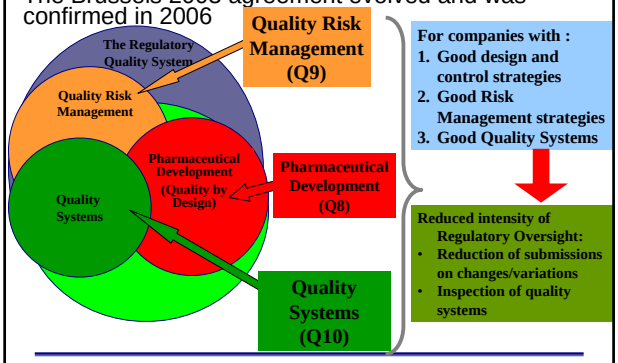
ICH

Content

- History of Concept Paper Development
- Review Concept Paper and Business Case
- EWG Activities Latest status

ICH

The Brussels 2003 agreement evolved and was confirmed in 2006



ICH

Topics to be considered

ICH-Q Strategy
Report to Steering Committee
October 2006

- ***Drug substance guidance addressing chemical and biotech (similarities & differences), traditional and 'best scientific practices' for S2 of CTD***
- Clarity on terms and concepts (implementation of Q8, Q9, Q10)
- Q8 and Q10 EWGs to work together on high priority terms
- Guidance on content of an 'improved' QOS placing key information into QOS backed up by Mod 3.
- Updating of existing guidelines to accommodate technical advances

ICH

ICH-Q Strategy
Report to Steering Committee
October 2007

ICH Quality Roundtable, September 2007

Drug Substance Agreements and Understandings

- Principles of Q8, Q9, Q10 are applicable to chemical and biotech drug substances and drug products
- Broad spectrum of process and molecular complexity could impact implementation
- Principles provide significant opportunities (and challenges) for more complex molecules and processes
- Fundamentals of good product development need to be addressed regardless of 'traditional' or 'new' development paradigms
- Focus should be on enhancing the process for ensuring quality rather than specific terminology
- Lack of guidance on drug substance still a remaining gap

ICH

ICH-Q Strategy
Report to Steering Committee
October 2007

ICH Quality Roundtable,September 2007

Recommendations

Development of an ICH guideline on Development and Manufacture of the Drug Substance (Section 'S2' of CTD-Q)

- Follow process used by CTD-Q EWG where biotech & chemical experts work together and in parallel (if necessary)
- Core group (1-2/party + 1/observer) to develop concept paper and business case

ICH

ICH-Q11
Proposal to Steering Committee
March 2008

Concept Paper Q11
Key Points

- Promote harmonisation of requirements
- …..High level technical guidance relevant to design, development and manufacture of drug substance as part of a total control strategy……
- Intended to provide guidance for drug substances as defined in Q6A and B
- Should identify similarities and differences for biologics and chemical entities

ICH-Q11
Proposal to Steering Committee
March 2008

Concept Paper Q11
Issues to be resolved

- Selection of materials for manufacture of DS
- Control strategy
- Impurities and product related substances
- Process Robustness
- Scale Down models
- Critical Intermediates

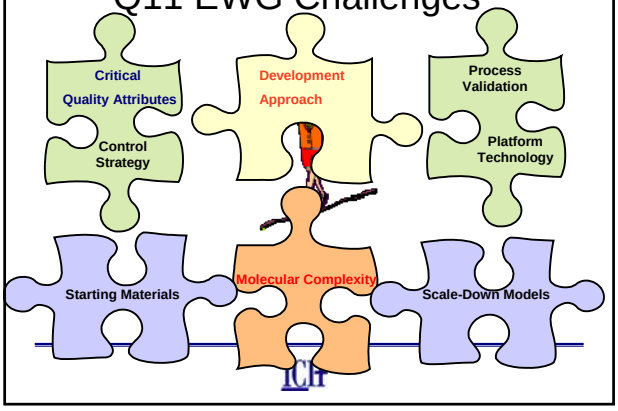
ICH-Q11
Proposal to Steering Committee
March 2008

Concept Paper Q11
Goals of Guideline

- Harmonise submissions
- Outline science based concepts
- Recommend approaches to demonstrating process and product understanding
- Address complexity of processes/products
- Accommodate different development approaches
- Address enhanced and systematic approaches to drug development.

Expert Working Group Progress

Q11 EWG Challenges



EWG Activities

- Three Working Sessions
  - Portland – June 2008
    - Defined Initial Draft
    - Requested observers be invited
  - Brussels – November 2008
    - Revised structure
    - Defined workplan
  - Yokohama
    - Reviewed Draft
    - Discussed “Priority” Issues

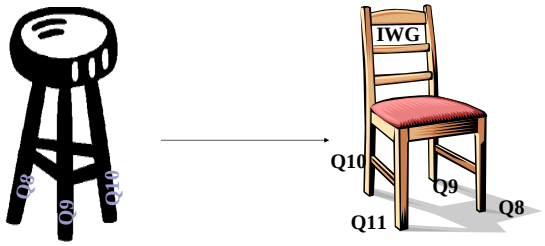
Working Structure

- Introduction
- Manufacturing Process Development
- Process Validation/Evaluation
- Controls
  - Materials
  - Critical Steps and Intermediates
- Manufacturing Description

Priority Harmonisation Subjects

- Starting Materials
- Process Validation
- Control Strategy
- Development Section
- Manufacturing Description

Value of Q11



Thank You

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Quality Topics

Q-IWG: Quality Implementation Working Group

Yukio Hiyama, *MHLW (NIHS)*
Deputy Topic Leader

Abstract
Dr. Yukio Hiyama will present the overview summary of the series of Q-IWG meetings held in Yokohama.

Dr. Hiyama is the Section Chief of the 3rd Section in the Division of Drugs at the National Institute of Health Sciences as well as the current Deputy Topic Leader of the Q-IWG topic at the ICH meetings.

Questions and Answers

Question: When the idea of the Quality by Design is implemented, we will have more flexibility than before in changing methods of manufacturing. Inspectors or reviewers will be able to reduce the resource for inspection, and they will be able to put more resources in the areas that are necessary. The FDA announced a Quality by Design pilot program last year. Regarding the Quality by Design, the industry side will have an opportunity to have discussions with the regulatory authorities. But, in EU and Japan, how are the regulatory authorities trying to communicate with the industries? In EU and Japan we have no information on that.

Hiyama: First, we have issues about the Quality by Design. You also mentioned about how to write the submission dossier. I would like you to read the ICH Q&A that is already published. A Quality by Design approach is a development method, and the Q8R explains about the method. It does not say whether you have to set up the design space or the real time release testing. Whether it applies to design space or not and how extensively the design space is used are based on the decision of the company. In my understanding, in ICH regions, there is no expectation that submission should have a label of the Quality by Design. In the US, the regulatory authority has conducted a pilot program to communicate with the companies directly. In EU, the PAT group was designed for the same purpose. In Japan, Dr. Okuda led the MHLW-sponsored group on the Quality by Design. The points studied were the changes expected and the impact of real time release testing when the Quality by Design approach is

applied. What extent is in the description in the CTD, if the real time release testing is applied, has already been published as was mentioned elsewhere in our presentations. Before submission, if the sponsor would like to utilize the design space or real time release testing, the company has an opportunity to have preapproval consultation with the PMDA, Japan. I had been involved as the regulatory side.

Okuda: I think Dr. Hiyama covered them all. The industry and government joint study has already been published on the website of NIHS.

Withers: European regulators have an EMEA PAT team which will discuss elements of the Quality by Design and approaches you have. You can contact them, and ask to go and discuss your Quality by Design development particularly if it includes elements of PAT, or you can go to a formal scientific advice process. From an industry point of view, the biggest advantage in discussing with companies who have started to use the Quality by Design is that they have a better assurance of the quality of the product. The regulatory flexibility or the ability to make changes is proving to be a secondary effect. It is not the prime benefit of following the Quality by Design approach.

Implementation Working Group on ICH Q8, Q9 and Q10

ICH Tokyo Symposium 2009
Yukio Hiyama
National Institute of Health Sciences

Objectives

- Globally consistent implementation of Q8, Q9 and Q10
- Maximum benefit from the interaction between the guidelines

Final Concept Paper , ICH IWG on Q8, Q9 and Q10, November1, 2007
http://www.ich.org/LOB/media/MEDIA4457.pdf

Background

- In Brussels 2003 a new quality vision was agreed on. emphasising a risk and science-based approaches to pharmaceuticals in an adequately implemented quality system.
- As a consequence, Pharmaceutical Development (Q8),Quality Risk Management(Q9)and Pharmaceutical Quality System(Q10) were drafted.
- Because concepts and principles are rather new, it is important to provide clarity/further explanation and to remove ambiguities and uncertainties.

History

- Quality Strategy Meeting, Fall 2006 Chicago
- Quality Strategy Meeting, Spring 2007 Brussels
- Quality Satellite Roundtable, Fall 2007 Rockville
- Informal Q-IWG, October 2007 Yokohama

  Final Concept Paper endorsed by Steering Committee
- First Q-IWG Meeting, June 2008 Portland

  Three breakout sessions on Knowledge Management, Quality by Design, Pharmaceutical Quality System/Inspection.
- Second Q-IWG Meeting, November 2008 Brussels

  More than 40 Q&A's agreed by IWG. Feedback collected.
- Teleconference on March 11, 2009

  30 Q&A's adopted
- Third Q-IWG Meeting, June 2009 Yokohama

Issues to be resolved

- Technical issues & related documentation:

  Common understanding of terminology; address inter-relationship between Q8, Q9 and Q10applicability to both review and inspection; final status after partial implementation is established (e.g. level of details in the dossier);
- Additional implementation issues:

  Influence on existing ICH guidelines;
- Communication and training:

  e.g. Q&A, briefing packs from ICH; external Collaborations; workshops

Final Concept Paper , ICH IWG on Q8, Q9 and Q10, November1, 2007

Q IWG operation

- Areas of Topics

Quality by Design, Knowledge Management, Pharmaceutical Quality System/Inspection

- Outcome/Product from IWG

Q&As
White papers
Examples and Case studies
Training, Workshops

- Work processes/Collaborations

Within IWG
Proposals to IWG at the following ICH Q-IWG web site
(http://www.ich.org/cache/html/5050-272-1.html)
Collaborations with non-profit organizations

Progress in Portland meeting

- Three Brain-storm Breakout Sessions on Topics

Knowledge management
Quality by Design/Criticality
Pharmaceutical Quality System/Inspection

- Home work on the three areas to the three regions assigned
- Discussion on external collaborations for examples/case studies and for training

Progress in and after Brussels meeting

- More than 40 draft QA's were agreed
- Regional review of draft QA's
- 30 QA's were adopted at telecon on March 11,2009
  http://www.ich.org/LOB/media/MEDIA5290.pdf

Examples: Q-IWG on ICH Q8/Q9/Q10 Questions and Answers adopted by Q-IWG at telecon March 11 2009

2. Quality by Design

2.2 Real Time Release Testing

Q01: How is batch release affected by employing real time release testing?

Batch release is the final decision to release the product to the market regardless whether RTR testing or end product testing is employed. End product testing involves performance of specific analytical procedures on a defined sample size of the final product after completion of all processing for a given batch of that product. Results of real time release testing are handled in the same manner as end product testing results in the batch release decision. Batch release involves an independent review of batch conformance to predefined criteria through review of testing results and manufacturing records together with appropriate GMP compliance and quality system, regardless of which approach is used.

Examples Q-IWG on ICH Q8/Q9/Q10 Questions and Answers adopted by Q-IWG at telecon March 11 2009 (2)

3 Pharmaceutical Quality System

Q01: What are the benefits of implementing a Pharmaceutical Quality System (in accordance with ICH Q10)?

The benefits are:

- **Facilitated robustness of the manufacturing process, through facilitation of continual improvement through science and risk-based post approval change processes.**
- **Consistency in the global pharmaceutical environment across regions**
- **Enable transparency of systems, processes, organisational and management responsibility.**
- **Clearer understanding of the application of a Quality System throughout product lifecycle.**
- **Further reducing risk of product failure and incidence of complaints and recalls thereby providing greater assurance of pharmaceutical product consistency and availability (supply) to the patient.**
- **Better process performance.**
- **Opportunity to increase understanding between industry and regulators and more optimal use of industry and regulatory resources. Enhance manufacturer's and regulators' confidence in product quality.**
- **Increased compliance with GMPs, which builds confidence in the regulators and may result in shorter inspections.**

Examples: Q-IWG on ICH Q8/Q9/Q10 Questions and Answers adopted by Q-IWG at telecon March 11 2009 (3)

4 ICH new quality guidelines' impact on GMP inspection practices

Q01: How will <u>product-related</u> inspections differ in an ICH Q8, Q9 and Q10 environment?

In the case of product-related inspection (in particular pre-authorisation) depending on the complexity of the product and/or process, there could be a need for greater collaboration between inspectors and assessors for example for the assessment of development data. The inspection would normally occur at the proposed commercial manufacturing site and there is likely to be greater focus on enhanced process understanding and understanding relationships e.g. Critical Quality Attribute (CQAs), Critical Process Parameters (CPPs). It will also extend into the application and implementation of quality risk management principles, as supported by the Pharmaceutical Quality System (PQS).

Examples: Q-IWG on ICH Q8/Q9/Q10 Questions and Answers adopted by Q-IWG at telecon March 11 2009 (4)

5 Knowledge Management

Q01: How has the implementation of ICH Q8, Q9, and Q10 changed the significance and use of knowledge management?

Q10 defines knowledge management as: 'Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components'.

Knowledge management is not a system; it enables the implementation of the concepts described in ICH Q8, Q9 and Q10.

Knowledge Management is not a new concept. It is always important regardless of the development approach. <u>Q10 highlights knowledge management because it is expected that more complex information generated by appropriate approaches (e.g. QbD, PAT, real-time data generation and control monitoring systems) will need to be better captured, managed and shared during product life-cycle.</u> In conjunction with Quality Risk Management, Knowledge Management can facilitate the use of concepts such as prior knowledge (including from other similar products), development of design space, control strategy, technology transfer, and continual improvement across the product life cycle.

Agenda for Yokohama

- **Additional Q&As**
  ***10 additional Q&As adopted**
- **Collaboration with external association on scientific articles**
- **Training issues / workshops**
- **Next steps**

Example: **Q-IWG on ICH Q8/Q9/Q10 Questions and Answers adopted by Q-IWG in Yokohama, June 10, 2009**

2. Pharmaceutical Quality System

Qxx: What information and documentation of the development studies should be available at a manufacturing site?

- Pharmaceutical development information (e.g. supporting information on design space, chemometric model, risk management,…) is available at the development site. Pharmaceutical development information which is useful to ensure the understanding of the basis for the manufacturing process and control strategy, including the rationale for selection of critical process parameters and critical quality attributes should be available at the manufacturing site.

  Scientific collaboration and knowledge sharing between pharmaceutical development and manufacturing is essential to ensure the successful transfer to production.

Case Studies
(Articles / Position Papers)

- **Q-IWG findings**
  - Many publications, workshops etc. available
  - Q-IWG will not endorse existing articles
    - Resource intensive: reviewing, decision, maintenance etc.
    - Potential regulatory concerns
  - Q-IWG will initiate, encourage and collaborate on paper development consistent with Q8, Q9, Q10 guidelines and Q&A

Case Studies
(Articles / Position Papers)

- **How can this be achieved?**
  - Task force within Q-IWG
    - Identification of topics and potential collaborators
    - Establish process for outside contribution
    - Recommend the topic and potential collaborators to Q-IWG
  - Q-IWG to assign topic cordinator(s) among its members
  - Final review and approval by entire Q-IWG (e.g. by telecon)

Training / Workshops
Goals and objectives

- **Enhanced harmonised implementation training to industry and regulators at the three ICH regions**
- **Conducted by ICH experts, who developed the guidelines and members of the ICH Quality Implementation Working Group (Q-IWG)**
- **The only workshops endorsed by the ICH Q-IWG and conducted by the same faculty in all three ICH regions.**
- **The training will cover the integrated use of the ICH Q8, Q9 and Q10 guidelines and Q&A across the product life cycle, from development to manufacturing and commercialisation**

Training / Workshops
Outline of the training

- **Outline**
  - **Presentations (lecture)**
  - **Break outs / Small discussion groups**
  - **Panel Discussion Session**
- **2 days workshop before the ICH meeting**
  - **Europe: Spring 2010**
  - **US: In between in Washington D.C.**
  - **Japan: Autumn 2010**

Proposed additional activities

- Identifying the need of revision / update of existing ICH Quality guidelines in the context of ICH Q8, Q9, Q10 and pending Q11
- Other evolving topics impacted and stimulated in the light of the new paradigm to be identified for avoiding potential dis-harmonisation
- Proposal to revise the Q-IWG mandate will be presented in ICH St. Louis

SPECIAL SESSION

Implementation of ICH Guidelines in Asian Countries

ICH Global Cooperation Group (GCG): History & Framework

Kohei Wada, *JPMA*
Member of the Steering Committee and Co-Chair of the Global Cooperation Group

Abstract
Mr. Kohei Wada will present the overview of the history and framework of the ICH Global Cooperation Group (GCG).

Mr. Wada is the Vice President and General Manager of Asia Development, R&D Division at Daiichi Sankyo Co. Ltd. as well as the current member of the Steering Committee and the Co-Chair of the Global Cooperation Group at the ICH meetings.

Questions and Answers

There were no questions.

Special Session:

Implementation of ICH guidelines in Asian countries

Kohei Wada
VP/General Manager, Asia Development Dept, Daiichi Sankyo, Japan
JPMA representative, ICH Steering Committee
& Co-chair, ICH Global Cooperation Group (GCG)

Version June 6

ICH Japan Symposium, June 12, 2009

Non-ICH regions are playing major role in drug Development

- Arena of clinical trials:
- API / Drug product supplier
- Many of the countries adopted or adapted ICH guidelines.

Adopt=そのまま採用

Adapt=修正して採用

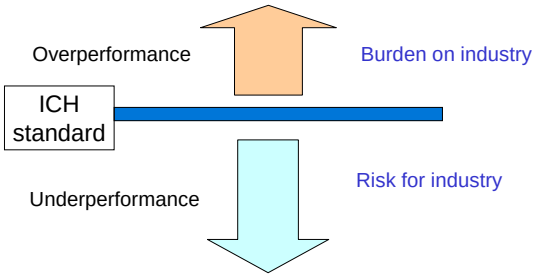
page 2

Issue Statement

- Even if guidelines look the same, sometimes actual implementation is different.
- On the other hand, even there seems to be difference in guidelines, sometimes the actual implementation is very similar.

page 3

Slight difference requires additional efforts



page 4

ICH-GCG is

promoting better understanding of ICH and its guidelines to non-ICH regions.

The ideal situation is:

- ICH guidelines are adopted
- and implemented as written.

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Today's Presenters

ICH-GCG: History & Framework
Mr. Kohei Wada, JPMA (GCG Co-chair)

ICH training in non-ICH regions: Concept & Procedure
Mr. Mike Ward, Health Canada (former GCG Co-chair)

Current Status of ICH GL implementation in Singapore
Dr. Christina Lim, Health Sciences Agency, Singapore

Current Status of ICH GL implementation in Chinese Taipei
Dr. Chao-Yi Wang, BoPA, Dept. of Health, Chinese Taipei

Training of ICH GLs in Thailand (Clinical Workshop)
Dr. Yuppadee Javroongrit, Thai FDA (ASEAN representative)

Training of ICH GLs in Korea (Quality Workshop)
Dr. Dong Sup Kim, National Institute of Tox Res, Korea
(former APEC representative)

Special Session:
Implementation of ICH guidelines in Asian countries

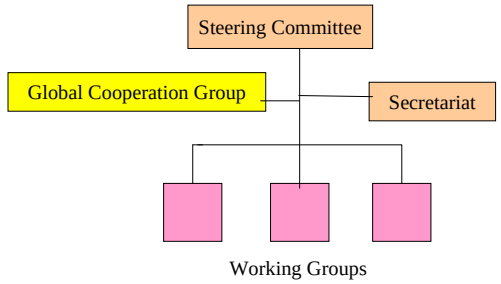
ICH Global Cooperation Group (GCG): History & Framework

Kohei Wada
VP/General Manager, Asia Development Dept,
Daiichi Sankyo, Japan
JPMA representative, ICH Steering Committee
& Co-chair, ICH Global Cooperation Group (GCG)

Version April 24

ICH Japan Symposium,
June 12, 2009

GCG was established in March 1999 as sub-committee of ICH SC



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GCG's Mandate

- Role: Promote better understanding of ICH and guidelines to non-ICH regions
- Mission Statement (May 2005, Brussels)

  "To promote a mutual understanding of regional harmonization initiatives in order to facilitate the harmonization process related to ICH guidelines regionally and globally, and to facilitate the capacity of drug regulatory authorities and industry to utilize them"
- Not a technical body!

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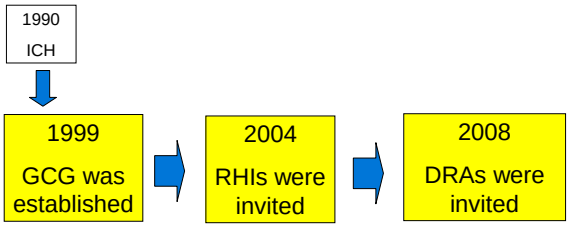
Evolution of GCG



RHI: Regional Harmonization Initiatives
DRA: Drug Regulatory Agencies

page 10

List of RHIs (Regional Harmonization Initiatives) 2004-

APEC (LSIF)
Asia-Pacific Economic Cooperation

ASEAN (PPWG – Observer**)**
Association of the Southeast Asian Nations

GCC
Gulf Cooperation Council

PANDRH
Pan American Network for Drug Regulatory Harmonization

SADC
Southern African Development Community

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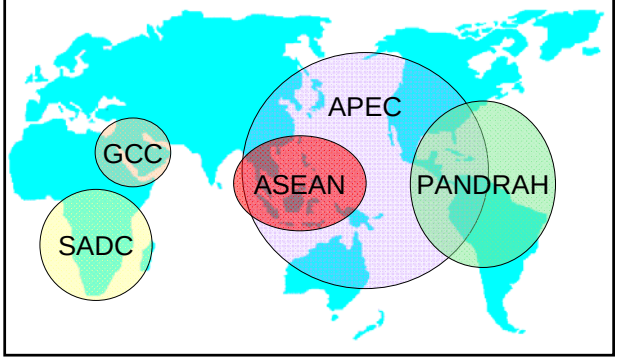
Location of RHIs (Regional Harmonization Initiatives)



DRAs were invited (=Expanded GCG) 2008-

Countries with advanced understanding of ICH concepts

Countries been the arena of multinational clinical trials

Countries functioning as global API/drug product supplier

Countries/Economies so far invited

Australia	Brazil
China	Chinese Taipei
India	Korea
Russia	Singapore

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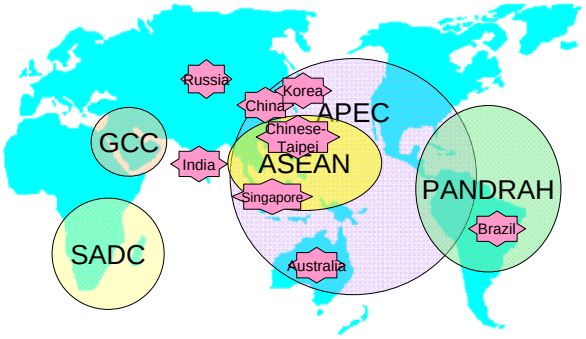
DRAs & RHIs



also endorsed was ICH Regulators Forum

- For discussion and sharing of best practices among regulatory authorities on issues related to the implementation of ICH guidelines and impact on regulatory systems
- The Regulators Forum will complement activities and objectives of GCG

GCG:

Capacity building & training

Regulators Forum:

Share best practices on regulatory challenges

page 15

The ICH Week

Sun	Mon	Tue	Wed	Thurs
Regulators Forum	Industry meeting (ICG)	Expanded GCG meeting	Steering Committee	

Working Groups

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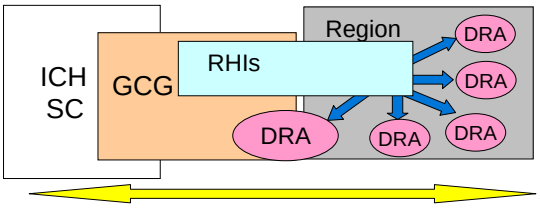
RHIs/DRAs Role: Influence on regions



Establish two-way dialogue, collaboration

- Non-ICH **to better understand ICH guidelines**
- Non-ICH to better understand ICH process
- To spread the ICH message for harmonization
- ICH can reach non-ICH much easier
- ICH to better understand the needs of non-ICH

page 17

Specific measures to understand ICH GLs

Participate in ICH meetings

- GCG, Regulators Forum,
- Technical working group meetings

Have chance to review Step 2 guidelines

- Webinars, Mini-symposium

Training events

page 18

Important Guiding Principles of GCG

- ICH will not impose its views on any country/region – rather, to facilitate understanding and use of ICH GLs
- GCG will work with the WHO and other international organizations to achieve its goals
- GCG recognizes that some non-ICH countries may not be in a position to utilize ICH guidelines

page 19

Summary

- ICH is committed to responding to needs of regions and countries interested in implementing ICH guidelines
- The GCG is aiming at facilitation of global drug development through training, focusing on clinical studies, API/drug product quality and CTD.

Added

Thank you!!

page 20

Implementation of ICH Guidelines in Asian Countries

ICH Training in Non-ICH Regions: Concept & Procedure

Mike Ward, *Health Canada*
The Steering Committee and the Global Cooperation Group

Abstract
Mr. Mike Ward will present the overview of the concept and procedure of ICH training in non-ICH regions.

Mr. Ward is the Manager of International Policy Division in the Bureau of Policy and Coordination, Therapeutic Products Directorate at the Health Products and Food Branch, Health Canada as well as the current member of the Steering Committee and the Global Cooperation Group at the ICH meetings.

Questions and Answers

There were no questions.

ICH Public Meeting:
ICH Japan Symposium 2009

ICH Training in non-ICH Regions: Concepts and Procedures

Mike Ward
Health Canada

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Presentation Objectives

- Address the following points:
  - Why this topic is important
  - Steps taken to improve the effectiveness of ICH's approach to training
  - Lessons learned
  - Future improvements

2

Why is ICH Training in non-ICH Regions Important?

- Growing interest in ICH guidelines:
  - ICH guidelines serve as reference documents – define science-based principles and approaches
  - Relevance of certain guidelines not limited to new drugs
  - Globalization of industry (innovative and generic) – desire for common standards
  - Trend towards global drug development strategies and desire of countries to be reflected in these strategies

Why is ICH training in non-ICH Regions important? (2)

- In order to derive full benefit from the use of ICH guidelines it is necessary to understand the **intent and thinking** behind the guidelines
- Training involving ICH experts long recognized by the GCG as key to promoting a better understanding of ICH guidelines beyond the ICH regions – a view shared by the more recent GCG representatives from RHIs and individual DRAs

Framework and mechanisms established to effectively respond to training requests

- Strategy document lays out principles for effective, strategic use of training resources
- Clearing house of training events created to identify opportunities
- Procedures and templates developed to improve efficiency and effectiveness of process – including 2 year planning cycle
- Public access: training materials now posted to ICH website – a wealth of information!

Strategy outlines ICH's philosophy and overall approach to training

- Whenever possible, training activities directed through the GCG should:
  - Optimally, be regionally-based, with flexibility to consider nationally-based training, if deemed appropriate
  - Be coordinated amongst ICH parties and RHIs/DRAs and leverage existing regional training activities and events
  - Leverage the experience and resources of non-profit training organizations
  - Be planned and reviewed on a periodic basis;
  - Take full advantage of appropriate training modalities/technologies

Formalized Process Established

- Procedures and template adopted in 2008 to aid in the prioritization, selection and response to training requests
- Procedures:
  - Establish nature of request (incl. sponsors, scope, target audience, funding, etc.)
  - Provide standardized review criteria (which consider mandate of ICH/GCG and training strategy principles)
  - Establish roles/responsibilities and process for actioning endorsed training
  - Call for the evaluation of training outcomes

ICH

Together the strategy, procedures and planning cycle are meant to ensure most effective use of ICH resources in promoting better understanding of ICH guidelines while at the same time addressing the priority needs of RHIs and DRAs

Also reflects evolution of GCG role from information dissemination to active dialogue to results oriented actions

ICH

Training to Date

- To date, GCG has endorsed and contributed to growing number of successful workshops:
  - ICH/APEC Q8,Q9,Q10 Workshop: September 2008, Seoul, Korea
  - ICH/APEC workshops on clinical trial assessment (March 2008, February 2009, Bangkok)
  - ICH/APEC workshops on GCP inspection (June 2008, March 2009, Bangkok)
  - ICH/APEC/JCCT Quality by Design workshop December 2008, Beijing
- Recently endorsed requests:
  - Quality, MedDRA (ASEAN); Q5 series (GCC).

ICH

Good Model

- Multi-party effort: leveraging of resources; same message – same time
- Shared responsibility
- Delivered to group of countries, including some outside given: a desired approach
- Materials made available on ICH (and APEC) websites – promotes transparency, understanding and use
- Workshops on CTA assessment and inspection have moved training *beyond understanding of ICH guidelines* to *their application* from a regulatory perspective – consistent with GCG mission statement

ICH

Lessons Learned

- Important to be clear on objectives and message
- Training shouldn't be didactic presentation of ICH guidelines: need to convey underlying thinking/objectives
- Set context for topics
- Interactive sessions key to facilitating better understanding of guidelines and challenges associated with their use
- Shared responsibility: all parties need to be clear on roles/responsibilities, process and objectives

ICH

Lessons Learned (2)

- Delivery of well structured, successful training sessions requires much work, dedication and coordination! Importance of core planning committee and effective project management cannot be overemphasized!
- Workshop not only means of promoting better understanding of ICH guidelines: e.g., ICH webinars also proving to be a valuable tool
- Leverage off existing material and work whenever possible
- Feedback important in improving training approach and promoting best practices
- Much more could be done:
  - Stand alone workshops not sufficient
  - Need to move from reactive to more proactive approach

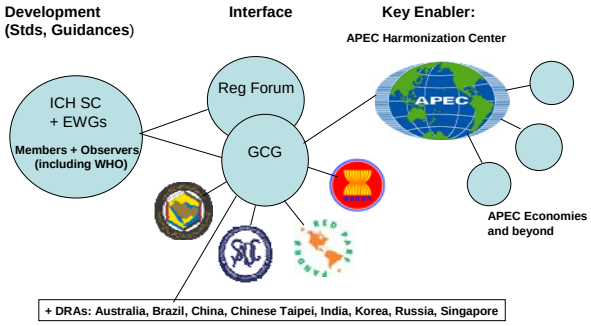
ICH

Future Improvements

- Adopt a more strategic, effective and sustainable approach:
  - Training curriculum based on collective assessment of priority needs
  - Take advantage of training institutions/organizations
  - Make better use of existing training events, modules and technology

ICH

Building a Better Harmonization Model



Thank you for your attention
Arigato!

ICH

15

Implementation of ICH Guidelines in Asian Countries

Current Status of ICH Guideline Implementation in Singapore

Christina Lim, *DRA of Singapore*
The Global Cooperation Group

Abstract
Dr. Christina Lim will present the current status of ICH guideline implementation in Singapore.

Dr. Lim is the Deputy Group Director of the Health Products Regulation Group, and Senior Advisor for International Collaboration at the Health Sciences Authority, Singapore as well as the current member of the Global Cooperation Group at the ICH meetings.

Questions and Answers

There were no questions.

Current Status of ICH Guidelines Implementation in Singapore

Dr Christina Lim
Deputy Group Director (Operations)
Health Products Regulation Group
Health Sciences Authority
Singapore

12 June 2009

Singapore

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"Uniquely Singapore"

- Total land area: 697.1 sq km
- Population
  - 4.5 million
- Ethnic diversity:
  - Chinese : 75.2%
  - Malay : 13.6%
  - Indians : 8.8%
  - Others : 2.4%

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Health Sciences Authority

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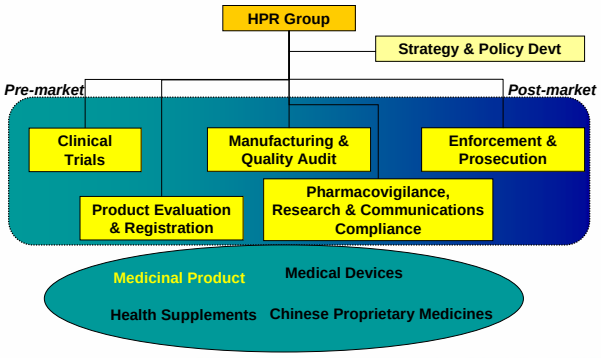
Health Products Regulation Group

To safeguard public health
To wisely regulate health products

Key Functional Areas of Health Products Regulation Group



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Drug Regulation In Singapore

- Drug Registration System was first implemented in 1987
- Legal requirement under Medicines Act (Chapter 176)
  - ▶ To ensure that medicinal products marketed in Singapore meet appropriate standards of safety, efficacy and quality

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Drug Regulation in Singapore

- Singapore does not follow a specific set of guidelines in the regulation of medicinal products.
- Singapore accepts internationally agreed guidelines, including ASEAN guidelines and ICH guidelines.

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Regulatory Approaches

- Judicious adapting of good international regulatory principles & practices to meet Singapore's unique situation, *without*:
  - ▶ Over-regulating
  - ▶ Simplistically adopting systems of reference agencies
  - ▶ Blindly approving products already approved elsewhere
- Wise use of regulatory tools & risk-based regulation
- Tap on expertise of external experts and researchers
- Foster strategic partnerships internationally and regionally
  - ▶ Information sharing and collaborations through MOU & MRA
  - ▶ Leverage on expertise of more advanced agencies
  - ▶ Work-sharing with like-minded agencies

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Pre-Market Benefit-Risk Assessment

3 "confidence-based" pathways allow companies to opt for route potentially offering shortest time to market for products

- **Abridged (from 1987)**
  - Original pathway based on 'don't re-invent the wheel' principle
- **Full (from 1998)**
  - First-in-world evaluation of innovative products, with focus on innovative therapies for diseases predominant in region and those originating from Singapore
- **Verification (from 2003)**
  - 'Safest' applications (based on reference agencies approvals) →quick review and regulatory outcome

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Pre-market Evaluation

Since the mid1990s, relevant ICH guidelines have been used in the evaluation of the Quality, Safety and Efficacy of a new medicinal product.

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Dossier Submission

- ICH CTD format was first implemented at end 2003
- Encourage industry to submit dossier in ASEAN CTD format
- Presently
  - Approximately half of the dossiers are submitted in ICH format
  - Multinational companies are the major users of ICH format

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Clinical Trial

- All clinical trials on medicinal products conducted in Singapore requires Clinical Trial Certificates (CTC)
- Singapore's guidelines for Good Clinical Practice were adapted from ICH E6 : Good Clinical Practice: Consolidated Guideline in 1998
- Singapore's GCP guidelines include Singapore's specific administrative requirement
  - Submission to Medical Clinical Research Committee

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Post Market Monitoring

- Post licensing updates including changes in the manufacturing and safety update of Product Insert
- ADR reporting- compulsory for drug companies and voluntary by healthcare professionals
- Safety review
- Product recall

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ICH and Singapore

ICH and Singapore

- ICH guidelines have been used in drug evaluation and registration since their launch in the mid 1990's
- Singapore's guidelines for Good Clinical Practice were adapted from ICH E6 : Good Clinical Practice: Consolidated Guideline in 1998
- Singapore was first invited to participate in ICH meeting, Global Cooperation Group and Regulator Forum in May 2008

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Why does Singapore follow ICH guidelines?

- To keep abreast with international best practices in regulatory science
- To enable Singapore to be an international player in multi-center pharmaceutical research and development
- To facilitate timely access to medicine

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Experiences till date….

- Some generic drug companies have problems fulfilling the requirement of ICH
  - Inability to obtain complete information on API
  - Financial issues leading to
    - Inability to provide all the milestones in accordance with ICH recommendation for stability study
    - Limited resources and knowledge in performing the full range of test requirements to ensure reproducibility and reliability
    - Minimal checking for identity and impurities
    - Fewer specification conducted test procedure

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Experiences till date….

- Multinational companies do not have any issues to fulfill the Singapore GCP guidelines
- However, we need to work with local investigators to understand and follow the Singapore GCP guidelines

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Understanding of ICH Guidelines

Before May 2008

- Understanding of guidelines from reading the guidelines and attending the relevant meetings/trainings

After May 2008

- Have chance to review Step 2 guidelines and participate in Webinars
- Training events organised by ICH

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Understanding of ICH guidelines by Industries and Investigators

- Pre-submission meeting / consultant for the regulators to discuss with the industries and investigators on their questions

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Moving Ahead

Increased participation in ICH activities (ICH meetings, Webinars, Trainings) to better understand the guidelines

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Implementation of ICH Guidelines in Asian Countries

Current Status of ICH Guideline Implementation in Chinese Taipei

Chao-Yi Wang (representing Chi-Chou Liao), *DRA of Chinese Taipei*
The Global Cooperation Group

Abstract
Dr. Chao-Yi Wang will present the current status of ICH guideline implementation in Chinese Taipei on behalf of Dr. Chi-Chou Liao.

Dr. Wang is the Section Chief of Bureau of Pharmaceutical Affairs at the Department of Health, Chinese Taipei. Dr. Liao is the Director General of Bureau of Pharmaceutical Affairs at the Department of Health, Chinese Taipei as well as the current member of the Global Cooperation Group at the ICH meetings.

Questions and Answers

There were no questions.

Current Status of ICH Guideline Implementation in Taiwan

Chao-Yi Wang
Bureau of Pharmaceutical Affairs,
Department of Health, Taiwan

June 12, 2009

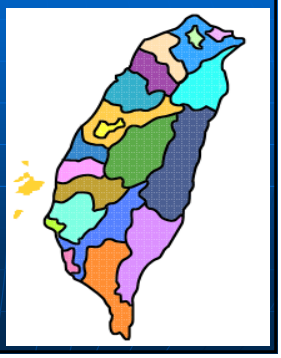
ICH Public Meeting: ICH Japan Symposium 2009

Outline

- General Information
- Review Process
  - Investigational New Drug (IND)
  - CT Report (including GCP Inspection)
  - New Drug Application (NDA)
- ICH Guidelines Implementation - Current Status
- Hot Issues

Taiwan - Geographic features

- Geographic features
  - South-eastern coast of Asia
  - Total area of 36,179 sq. km
  - Population of 23 millions



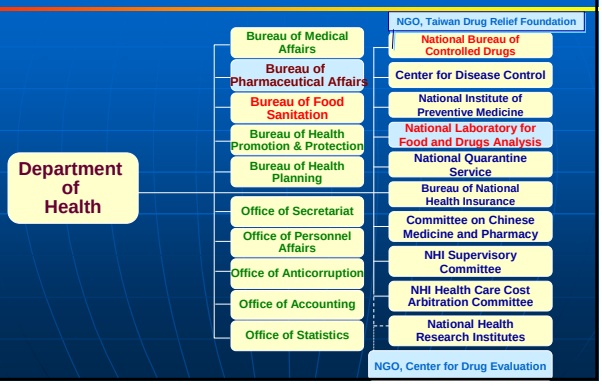
Missions

- Advocator of Health for All
- Educator of Healthy Lifestyle
- Promoter of Healthcare Industries
- Contributor of International Health Activities

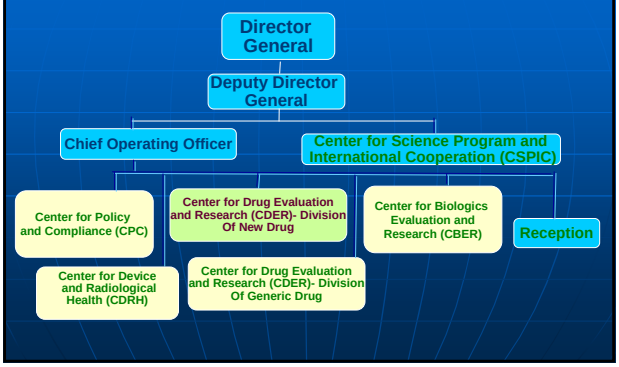
Roles of Regulatory Authorities

- Balance between Public Health Protection & Promotion
- Gate-keeper
  - Prudent evaluation based on Good Review Practice
  - Drug quality, safety and efficacy
- Health-promoter
  - Consultation program
  - Efficient and transparent review process
  - International harmonization

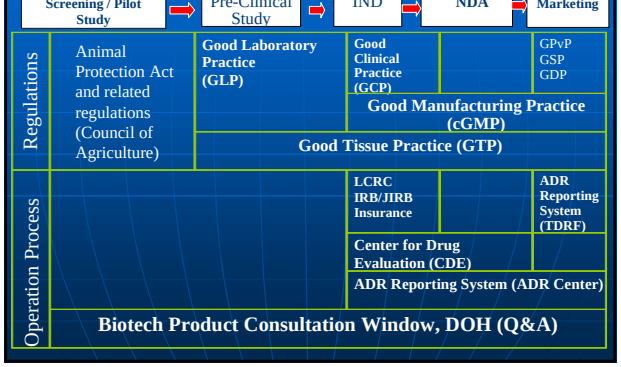
Current Organization of the Department of Health (DOH)



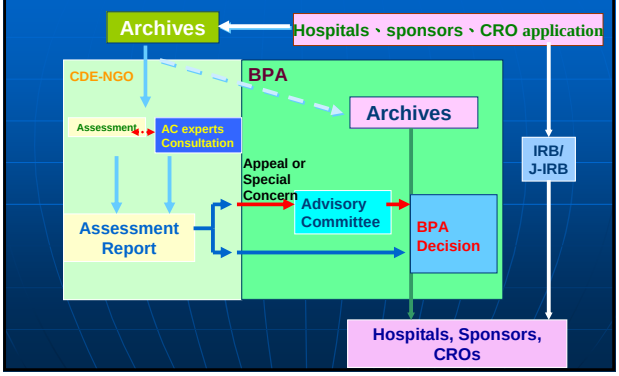
Organization Chart of the Bureau of Pharmaceutical Affairs (BPA)



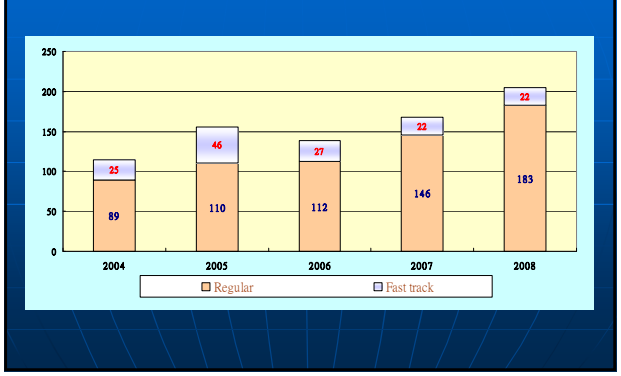
Regulations of New Drug R&D



Review Process for IND



IND Application (2004-2008)



Distribution of CT Phases (2004-2008)

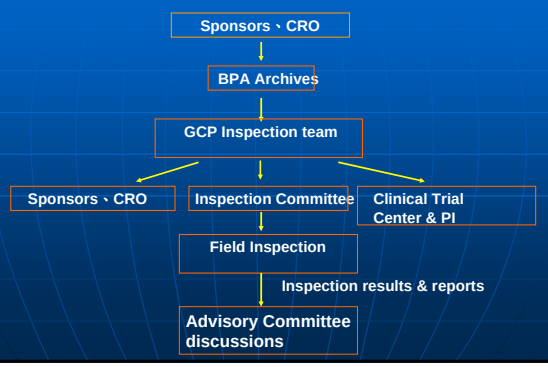
	2004		2005		2006		2007		2008	
	P	S	P	S	P	S	P	S	P	S
Phase I	8	12	14	26	12	20	10	18	11	14
Phase II	22	57	33	78	32	98	46	158	46	120
Phase III	85	237	69	242	86	300	106	391	132	527
Phase IV	4	10	4	5	3	4	6	14	16	21
Total	119	316	120	351	133	422	168	581	205	682

P: protocol S: site

Measures to Improve Clinical Trial Quality

- Conform to international regulations on protection of human subjects
- Improve IRB review quality
- Training programs for Health Professionals
- Establish clinical trial research centers
- Serious Adverse Event Reporting during Clinical Trial
- GCP Inspection

Review process for Clinical Trial Report



Statistics for Clinical Trial Reports (2002-2008)

Year	2002	2003	2004	2005	2006	2007	2008
Inspection cases	37	47	36	34	38	23	23
Disapproval Reports	4	4	5	2	2	0	4
Disapproval rate	11%	9%	14%	6%	5.2%	0%	17.4%

Clinical Trials Network in Taiwan

http://www.cde.org.tw/ct_taiwan/index.htm

Guidelines for Drug Review and Approval

(藥品查驗登記審查準則)

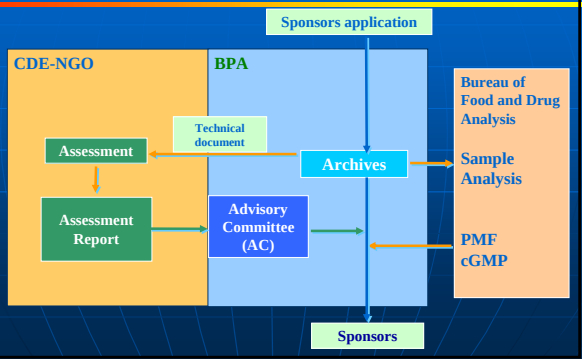
Effected since 01.07.2005, the administration order issued by DOH No. 0930339211

Website:
http://www.doh.gov.tw/CHT2006/DM/DM2_p01.aspx?class_no=2&now_fod_list_no=8109&level_no=3&doc_no=40202

Application Fee

Type	US $ (rounded)
New Molecular Entity	18,000
New Indication, New Administration Route, New Combination	1,500
New Dosage Form, New Dose	1,050
Generic (non-proprietary) product	1,050
Investigational New Drug	450

Review Process for NDA



NME of NDA Therapeutic Category Analysis

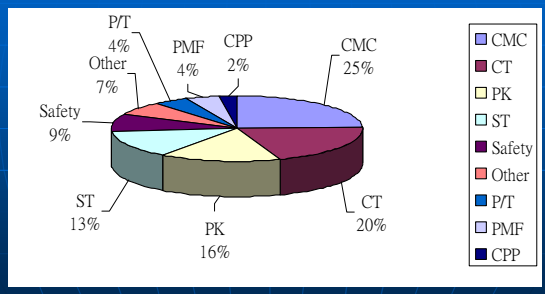
TC	2006	2007	2008	Total
Oncology	3	3	2	8
Cardiovascular	4	4	1	9
Infection*	9	6	4	19
CNS	6	6	1	13
Metabolic	3	8	2	13
Immunology	3	3	2	8
Analgesics	2	1	1	4
Hematology	4	4	4	12
Respiratory	1	1	0	2
GI	2	1	0	3
OB/GYN	2	1	0	3
Others **	6	2	0	8
Total	45	40	17	102

* Include Vaccines
** Include Dermatologic, ophthalmologic, radio-pharm etc.

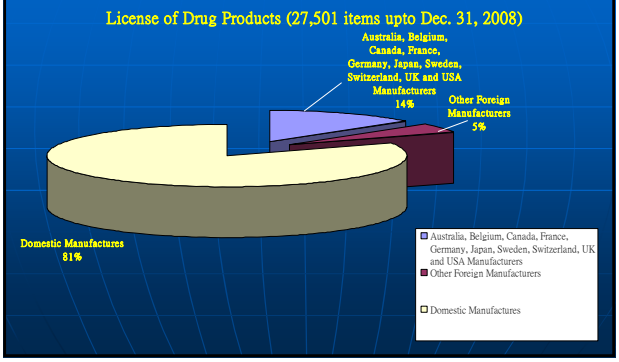
NDA (2008)

	Case No	Timeline	Approval rate
NME	26	7.1 months	59%
Other New Drug	112	5.4 months	73%

Major Deficiency of NME



Distribution of Drug Products



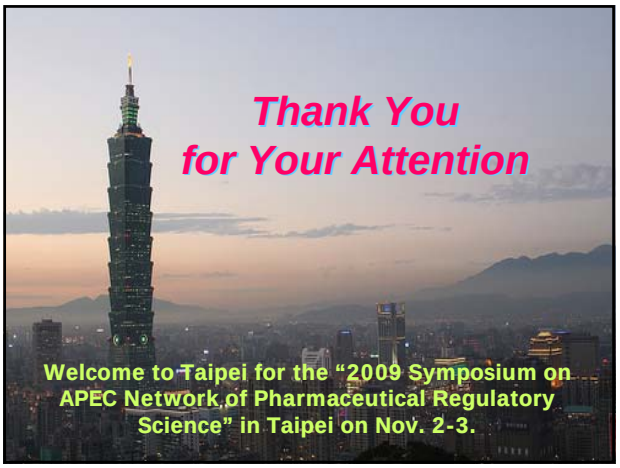
ICH Guidelines Implementation - Current Status

- 27 Quality Guidelines are already announced as regulations
  - Fully follow 7 (Q1A, Q2, Q5A-D, Q6B)
  - Partial follow 20
- 5 Efficacy Guidelines are already announced as regulations
  - Fully follow E3、E5
  - Partial follow E2C、E2E、E6
- All Multidisciplinary Guidelines are fully complied with ICH standard
- Safety Guidelines are not formally announced as regulations yet but follow ICH spirit during review

Hot Issues

- New Organization
- CPP Relaxation
- IP related issue

…… Still Ongoing


Thank You
for Your Attention
Welcome to Taipei for the "2009 Symposium on APEC Network of Pharmaceutical Regulatory Science" in Taipei on Nov. 2-3.

Implementation of ICH Guidelines in Asian Countries

Training of ICH Guidelines in Thailand (Clinical Workshop)

Yuppadee Javroongrit, *RHI* (*ASEAN)*
The Global Cooperation Group

Abstract
Dr. Yuppadee Javroongrit will present the overview of the clinical workshop training of ICH guidelines in Thailand.

Dr. Javroongrit is the representative of ASEAN as a RHI (Regional Harmonization Initiative) as well as the Assistant Director & Head of International Affairs & IND Section of the Drug Control Division at the Food and Drug Administration Ministry of Public Health, Thailand. She is also the current member of the Global Cooperation Group at the ICH meetings.

Questions and Answers

There were no questions.

Training of ICH guidelines in Thailand (Clinical Workshop)

Special Session: *Implementation of ICH guidelines in Asian Countries*

by

Yuppadee JAVROONGRIT, Ph.D.

Drug Control Division, FDA, Thailand

The ICH Public Meeting : ICH Japan Symposium 2009
Tower Hall Funabori, Edogawa-ku, Tokyo, JAPAN
12 June 2009

Yuppadee_JpSymp Tokyo-12 Jun.09

Topics

- Introduction
- Acknowledgement
- The Actions
- The Project
- The Trainings
- Lesson Learnt & Recommendation

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Introduction

- Current & Trend
  - Increasing participation in…
    - Multinational Clinical Trials
    - Phase I trials
    - Pharmacogenetic study
    - big/major Public Clinical Trials
  - Increasing number of the Clinical Trials
- Actively Involving in International Forum :-
  – ICH/ICH-GCG, APEC-LSIF, ASEAN-PPWG, etc….
- Greater Needs on Consumer protection
- WHO's Pre-qualification Programme

The Drives → *for Building & Strengthening Capacity on Clinical Trial Monitoring System*

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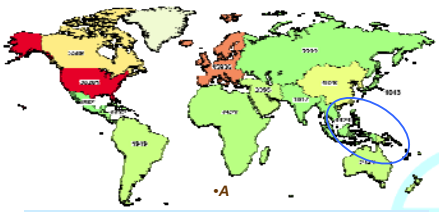
Global Clinical Trials

Ref.→ Feb.09 (www.ClinicalTrials.gov)



All 69,091 Clinical Studies = 1,121 Studies in ASEAN

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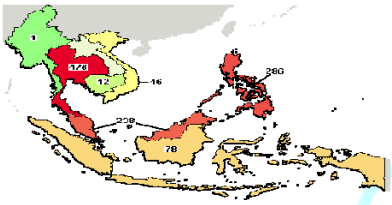
Clinical Trials in ASEAN/Thailand

Ref.→ Feb.09 (www.ClinicalTrials.gov)



from 1,121 Clinical Studies in ASEAN
→ 476 Studies are in Thailand

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The Acknowledgement

- The Brain & Developer :- Mr.Mike WARD
- The Trainers :-
  - Health Canada
  - PMDA
  - US FDA
  - PhRMA
- The Supportive Organizations :-
  - APEC/APEC-LSIF for funding support
  - ICH/ICH-GCG for the Trainers
- The Host & Organizer :-
  - DSG Weerawan Tangkaew – *ThaiFDA*
  - Ms.Akanid Wapeewuttikorn– *ThaiFDA*

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TFDA

The Actions

1. Development of the Projects	by *ThaiFDA*
2. Submission for APEC-funding	→ *APEC-LSIF & -CTI*
3. Seeking support on the Trainers	→ *ICH-GCG*
4. Development of the Training Programme/Module	by- *Mr.Mike WARD (H.C.)* - *Dr.David LEPAY (US FDA)* - *relevant ICH Parties (PMDA, US FDA, PhRMA, H.C.)*
5. Logistic arrangement	by *ThaiFDA*
6. Preparation for the Training	by *ThaiFDA*
7. Conduct of the Trainings	by *Trainers & ThaiFDA*
8. Post-Training Wrap-up	*Public Document, Rpt., Budget*

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TFDA

The Project (1)

Title	Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice			
Major Plan	Set 1 Review of Drug Development in Clinical Trial		Set 2 GCP/Clinical Research Inspection	
	Preliminary WS (17-21 Mar.08)	Advance WS (02-06 Feb.09)	Basic WS (27-30 May 08)	Advance WS (02-06 Mar.09)
Trainer	-Dr.Celia LOURENCO (HC) -Dr.Junko SATO (PMDA) -Ms.Susan D'AMICO (PhRMA*) -Dr.NamrataBAHADUR(PhRMA*) -Dr.Odett MORIN (ICH) (Note: -HC = Health Canada - PhRMA* = Novartis)	-Dr.Norman VINER (HC) -Dr.Willem STEVENS (HC) -Dr.Junko SATO (PMDA) -Dr.Sudhichai CHOKEKIJCHAI (PhRMA-Novartis Thailand)	-Dr.David LEPAY (US FDA) -Dr.Jean TOTH-ALLEN (US FDA)	-Dr.David LEPAY (US FDA) -Dr.Martin K.YAU (US FDA) Mentors -Mr.Gerald N.McGIRL (US FDA) -Ms.Alicja KASINA (HC) -Dr.Beat WIDLER (Roche) -Ms.Joanne NORTH(GSK-R&D) -Ms.Larvan AMORNWICHET (Merck &Co)
Trainee	= 20 regulators (APEC: Chile, Id, My, Sg, Th, Vn RHIs:-GCC, ASEAN)	= 26 regulators (APEC:-Chile, Id, My, Peru, Ph, Sg, Th, Tw RHIs:-GCC, ASEAN)	= 22 regulators (APEC:-Chile, Id, My, Sg, Th, Vn RHIs:-GCC, ASEAN)	= 30 regulators (APEC:-Chile, Id, My, Peru, Ph, Sg, Th, Vn RHIs:-GCC, ASEAN)
Course	-Lectures -Case Studies+Gr. Exercises	-Lectures -Case Studies+Gr. Exercises	-Lectures -CaseStudies+Gr. Exercises	-Lectures -Mock Inspection

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TFDA

The Training (1)

Major Plan: Set 1 : Review of Drug Development in Clinical Trial → Preliminary WS (17-21 Mar.08)

Day 1
- Opening Ceremony *(Senior Expert ThaiFDA-Mrs.Wilai Bunditanukula)*
- Special Session –Overview of ICH & GCG *(Dr.Morin)*
- General Information *(A.Wapewuttikorn)*

Session 1: Status of CT Environment in Respective Countries
- Country report *(Trainees)*
- Status of CT+ Application procedures
  - Canada *(Dr.Lourenco)*
  - Japan *(Dr.Sato)*
  - EU & USA *(Ms.D'Amico)*
  - Large Pharma Perspective *(Dr.Bahadur)*

Session 2: Overview of Clinical Trial Oversight
- Origin of CT regulation, subject right, GCP,… *(Dr.Lourenco)*
- Roles and responsibilities of Various players involved in conduct/ assessment of CTs *(Dr.Lourenco)*
- Good Regulatory Practices-Canadian &Japanese experience *(Dr.Sato & Dr.Lourenco)*
- Regulations / guidelines (ICH, WHO, etc) *(Dr.Lourenco)*
- Inspection (GCP, GMP) *(Dr.Sato)*

Session 3: Overview of Drug Development
- Clinical Development plans, phases, post-market assessment *(Dr.Sato, Dr.Lourenco, and Dr.Bahadur)*

Session 4: Clinical Trial Assessment : Overview *(Dr.Lourenco)*

Day 2

Session 5: Quality (CMC) considerations *(Dr.Lourenco)*

Session 6: Clinical Trial Assessment-Phase I *(Dr.Lourenco-Lead)* *(Dr.Bahadur-Industry perspective), (Dr.Sato&Ms.D'Amico-support)*

Day 3

Session 7: Clinical Trial Assessment-BE Studies *(Dr.Sato/Dr.Lourenco)*

Session 8: Clinical Trial Assessment-Phase II *(Dr.Sato-Lead)* *(Dr.Lourenco& Ms.D'Amico-support)*

Day 4

Session 9: Clinical Trial Assessment-Phase III *(Ms.D'Amico-Lead)* *(Dr.Lourenco& Dr.Sato-support)*

Day 5

Session 10: Concept of product life-cycle, DSURs and Safety Monitoring Boards *(Dr.Sato)*

Session 11: Industry Perspective on Safety Monitoring Boards , and Product Life Cycle *(Ms.D'Amico)*

Session 12: Pharmacogenomics *(Dr.Lourenco)*

Session 13: Essential Elements of CT Assessment *(Dr.Lourenco)*

Session 14: Panel Discussion,Q&A*(Dr.Sato/Dr.Lourenco/Ms.D'Amico/ All)*
- Conclusion, Closing & Certification *(ICH, Trainers, & ThaiFDA)*

Yu

TFDA

The Training (2)

Major Plan: Set 1 : Review of Drug Development in Clinical Trial → Advanced WS (02-06 Feb.09)

Day 1
- Opening Ceremony *(DSG. ThaiFDA-Mrs.Tangkaew)*
- Introduction of Faculty&WS logistics *(A.Wapewuttikorn)*
- Overview of the Advanced WS *(Dr.Viner)*
- Country Report *(Trainees)*
- Follow-up from the Preliminary WS *(Dr.Sato/Dr.Viner)*
  - Regulatory Infrastructure/Authority
  - Best Practice Sharing -strategies for Review & requirement for Ethics
- Refresher of preliminary course topics *(Dr.Viner/Dr.Stevens/Dr.Sato)*
- What is required for setting up the business of a review operation? *(Dr.Viner-on CT/Dr.Stevens-on CMC)*

Day 2
- Chemistry and Manufacturing(Quality) Review *(Dr.Stevens-Lead)*
  –Examples and exercises

Day 3
- Dose Selection: Review principles of dose selection *(Dr.Sato)*
  - Is the dose planned appropriate?
  - Exercise and examples !
- Critiquing Higher Risk Trial-Practical Approaches with Exercise *(Dr.Chokekijchai & Dr.Viner)*

Day 4
- Novel Designs in Clinical Trials *(Dr.Chokekijchai-Lead)*
  - Adaptive designs
  - Protocol exercise
- Ethics in Clinical Trials + Exercises *(Dr.Viner-Lead)*
  - Ethics Article for review
  - Role of Regulator vs.that of REB
  - Setting REB standards
- Pharmacovigilance: the concept of continuous Safety through the lifecycle of a product + Exercises *(Dr.Sato)*
  - Risk management plan *(Dr.Chokekijchai)*
  - Challenges *(Dr.Viner)*

Day 5
- Clinical Trial Review Practicum *(Dr.Viner/Dr.Chokekijchai)*
  - small group exercises
  - Protocol exercise
- Panel Discussions *(Everyone)*
  - Gaps,
  - Challenges for implementation,
  - Suggestion for future cooperation to APEC-LSIF
- Closing & Certification *(Trainers + ThaiFDA)*

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The Training (3)

Major Plan: Set 2 : GCP/Clinical Research Inspections →Basic WS (27-30 May 08)

Day 1
- Opening Ceremony *(DSG. ThaiFDA-Mrs.Tangkaew)*
- Introduction of Faculty&WS logistics *(A.Wapewuttikorn)*
- Introduction of Participants & Country Report *(Trainees)*
- Review of GCP Goals, Principles, Roles, and Responsibility (The Process Approach to Clinical Research, International GCP Standards, Roles/Responsibilities for Investigators, Sponsors/CROs, and ECs, Regulator's Role in GCP, Q & A)
- Informed Consent (Review of Required and Additional Elements of Consent, Informed Consent Process, Interactive Exercise: Evaluating Informed Consent)
- The Interface Between Regulatory Review and CT Inspection
  - Introduction to FDA's Clinical Research Review Process
  - Identifying Issues for Inspection (Case Examples)
- Q & A

Day 2
- Review of Day 1 + Q&A
- Anatomy of a GCP Inspection
- Inspector's Preparation for a Clinical Investigator Inspection
- Interactive Exercise / Case Study (Developing an Inspection Plan)
- The Opening Interview
- Mock Interview Exercise
- Auditing Clinical Data
- Q&A

Day 3
- Review of Day 2 + Q&A
- Common GCP Deficiencies Encountered at Clinical Investigator Sites
- Misconduct in Research (Fraud)
- Documenting an Inspection
- Assessing Sponsor and EC Compliance from the Clinical Investigator Inspection
- Prepare for the Site Visit
- Visit the Clinical Research Site

Day 4
- Discussion of Clinical Site Visit and Accomplishment of Obj.
- The Close-out Discussion
- Summary of Clinical Investigator Inspecting
- Inspecting Sponsors and CRO (+ Case Study & Exercise)
- Inspection of Ethics Committee (+ Case Study & Exercise)
- Enforcement Strategies to address Identified Serious Deficiencies
- Wrap-up Q & A
- Round Table Discussions (Identifying Specialized Topics and Defining Obj. and Approaches for the Advanced WS)
- Closing Remarks, and Certification *(US FDA + ThaiFDA)*

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The Training (4)

Major Plan: Set 2 : GCP/Clinical Research Inspections →Advanced WS (02-06 Mar.09)

Day 1
- Opening Ceremony *(DSG. ThaiFDA-Mrs.Tangkaew)*
- Introduction of Faculty&WS logistics *(A.Wapewuttikorn)*
- Overview of the WS *(Dr.Lepay)*
- Introduction of Participants & Country Report *(Trainees)*
- Review of the Basic GCP Inspection WS *(Dr.Lepay)* (Preparation, and Conduct)
- Basic Concepts of BE that Underlie the science of the Inspection *(Dr.Yau)*
- Special Meeting *(Trainers & Mentors)*

Day 2
- Clinical Component of BE Inspecting *(Dr.Yau)*
- Review of the Basic GCP Inspection WS-Reporting *(Dr.Lepay)*
- Small Group Meeting *(Trainers, Mentors + Small Groups)*

Day 3 & 4
- Mock Inspection *(Mentor + Small Group)* (6 Small groups, in 6 different Clinical Sites)

Day 5
- Analytical/Analytical Facilities component of BE Inspection *(Dr.Yau)*
- Report out of Group 1-6
- Wrap-up Q & A *(Dr.Lepay)*
- Round Table Discussions
  - Evaluation
  - Gaps and Challenges for implementation
  - Suggestion for future cooperation to APEC-LSIF
- Closing Remarks, and Certification *(US FDA, Mentors, ThaiFDA)*

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The Trainers & ThaiFDA
Preliminary WS- Review of DD in CT

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The Trainers & Trainees
Preliminary WS- Review of DD in CT

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The Trainers, Trainees, and ThaiFDA
Basic WS- GCP/Clinical Research Inspection

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Lesson Learnt/Recommendation (1)

- **The Programme**
  - Lectures → *gave "Great Information"*
  - Case Studies, Exercise & Mock Exercises → *provided "Know-how"*
  - Ref.Link/Info. → *support "further Understanding"*
- **Trainers**
  - Regulators
    - → *provided Understanding to the issue, at the same ground*
    - → *also could share "Regulatory approach & interpretation"*
    - → ICH's Regulator know the ICH Technical guideline very well
  - Industry –R&D
    - → *gave details on "Drug Development", in depth*
    - → *sharing and help complete the loop of understanding & best practice*

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Lesson Learnt/Recommendation (2)

- **Optimization the Trainings' Outcome**
  - post the "Training Materials" *in the Website(s)*
  - exercising and implementing all Trainings' Knowledge/Experiences
  - follow-up & support "Consultation/Advice" further
    for the successful & sustainable Implementation after the Trainings

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The Recommendation

- **very useful Trainings programme**
  - essential Knowledge & know-how Experiences for DRAs
  - networking between ICH & Non-ICH, and among DRAs
  - one of the powerful tools of Harmonization
- **the Training Module :-**
  - well thought and well developed
  - could be benefit in Training, the DRAs
  - recommend as a Training Module, for other RHIs/DRAs
- **final recommendation**

- follow-up programme, of Trainers & Trainees, annually
- Continuation support from ICH-Regulators, for further Trainings

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TFDA
Thank You
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Implementation of ICH Guidelines in Asian Countries

Training of ICH Guidelines in Korea (Quality Workshop)

Dong Sup Kim (representing Daibyung Kim), *DRA of Korea*
The Global Cooperation Group

Abstract
Dr. Dong Sup Kim will present the overview of the quality workshop training of ICH guidelines in Korea on behalf of Dr. Daibyung Kim.

Dr. Dong Sup Kim is the Director General of the Toxicological Research Department at the National Institute of Toxicological Research, Korea. (Dr. Daibyung Kim is the former Director of the Drug Evaluation Department at the Korea Food and Drug Administration, Korea as well as the former member of the Global Cooperation Group at the ICH meetings.)

Questions and Answers

There were no questions.

Traning of ICH Guidelines in Korea (Quality Workshop)

Dong Sup Kim, Ph.D.
DRA, KOREA

Director
Department of Pharmaceutical & Medical Devices Research
Korea Food & Drug Administration

Highlights

- History of recent training on ICH guidelines
- KGMP for 21st century
- Recent regulatory progress in quality management system in Korea
- 2009 plan of training on ICH guidelines (including Quality)

History of recent training on ICH guidelines in Korea

- APEC LSIF ICH Quality Guidelines Workshop held in September 13~14, COEX Seoul, Korea (2007)
- APEC Harmonization Center Workshop held in June 15~18, Grand Hilton, Seoul, Korea (2009)-Multi-regional clinical trials

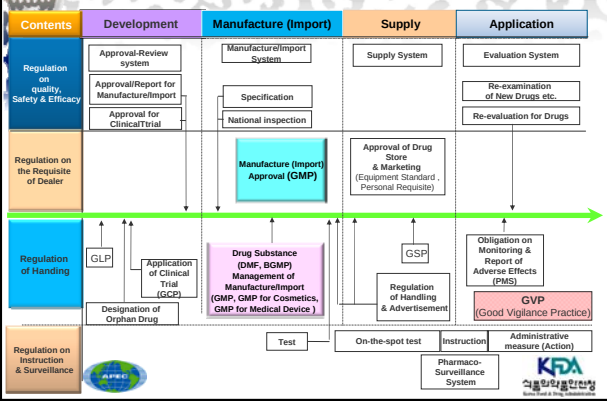
KGMP for 21st century

- The concept of quality system approaches are incorporated into the manufacture of pharmaceuticals while maintaining product quality
- New KGMP includes
  - ✓ Adoption of product based pre-approval GMP
  - ✓ Mandatory validation by law
  - ✓ Adoption of change control, annual product review
  - ✓ Control on out of specification / deviation
- Revision of Pharmaceutical Affairs Law (effective January 2008)

KGMP for 21st century

- KFDA GMP inspector training
  - ✓ GMP professional training in SNU through MOU with KFDA
- User fee policy for pre-approval inspection
  - ✓ Hire special inspector with career of manufacturer using User fee
- Publication of New GMP guide, Validation protocols for utilities, GMP Q&A book

Approval & Risk Management System of Drug



Milestone of Post-Approval Management

Introduction of System		No Graded GMP control system	Introduction of Graded GMP control system	Graded control for Low-graded industry	Product-based graded GMP control	Graded GMP control of industry based on GMP assessment results
Year		Before 2005	2005	2006	2007	2008
Supervision		Regional KFDA	Combination of headquarter & regional KFDA	Combination of headquarter & regional KFDA	Headquarter, Support of regional KFDA	Headquarter, Support of regional KFDA
Selection of object		Regional KFDA	Headquarter	Headquarter	Headquarter	Headquarter
Evaluation	Type	Facility based	Formulation-based	Formulation-based	Product-based	Quality system of industry
	Assessment	No grade	5-grade	5-grade	5-grade	5-grade
	Object	Periodic (2-year), all	1-year (all)	Low-grade (C,D,E)	Frequently-consumed products	Not done last year
	Key point	Documents	Facilities	Facilities	Facilities & environment management	Validation
	keynote	Administrative Measure	Administrative Measure	Administrative Measure	Guidance of new GMP	Establishment of new GMP
	Inspection period	0.5~1 day	1~3 day	1~3 day	3~5 day	1~2 day
	Assessment form	Same form	Form by formulation	Form by formulations	Form by ingredients	Same form

Evaluation of the GMP grade

◆ Category of 5-graded GMP

A	B	C	D	E
Over 90	80~89	70~79	60~69	Below 60

It should not be the administrative disposition related to GMP in A-grade

◆ Scoring Standard by Item

Total	Scoring Standard	
	Facilities & Management	Administrative Measure (Self-Audit)
100	00	00

Outcome of Graded GMP control system (1)

◆ Withdrawal Status of Approval

	Total	2003	2004	2005	2006	2007	2008 (the first half of the year)
Number of Product	27,693	1,657	1,971	9,456	6,289	4,363	3,957

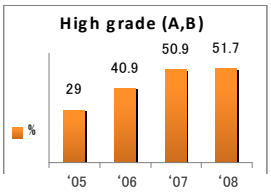
※ **Annual mean withdrawal of approval:**
Before the graded GMP control (1,814 products/year)
→ After the graded GMP control (6,702 products/year) (3.7-fold increase)

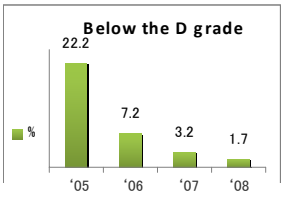
Outcome of Graded GMP control system (2)

◆ Return status of GMP certificate for vulnerable industry

	Total	2006	2007	2008 (the first half of the year)
Number of Industry	50	40	8	2
Number of Formulation	61	48	10	3

Outcome of Graded GMP control system (3)



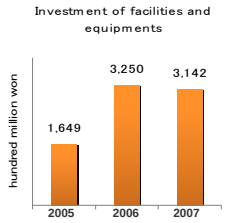


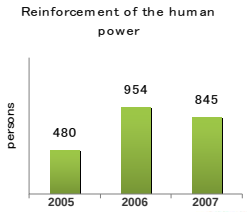
Outcome of Graded GMP control system (4)

Year	total	A	B	C	D	E
2005 (%)	560 (number of formulation)	43(7.7)	119(21.3)	274(48.9)	94(16.8)	30(5.4)
2006 (%)	362 (number of formulation)	5(1.4)	143(39.5)	188(51.9)	26(7.2)	0(0.0)
2007 (%)	1,194 (number of drug company)	60(5.0)	548(45.9)	548(45.9)	38(3.2)	0(0.0)
2008 (%)	60 (number of drug company)	4(6.7)	27(45.0)	28(46.7)	1(1.7)	0(0.0)

Outcome of Graded GMP control system (5)

- **Improvement of the pharmaceutical environment :**
  - ✓ Investment of facilities and equipment
  - ✓ Continued reinforcement of the human power

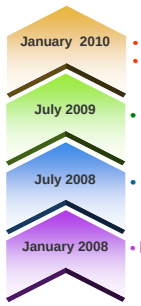




Additional policy for Post-approval Management

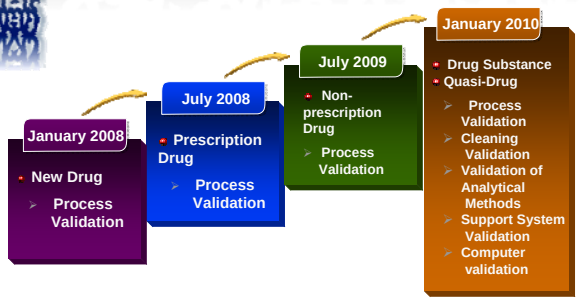
section	2007	2008	2009	2010
Graded Control	O	O	X (self-audit)	X
Pre-approval GMP (product base)	X	New drug ETC	New drug ·ETC ·OTC	New drug ·ETC ·OTC Quasi drug (oral solid &Liquid preparation) Drug Substance
Introduction of validation	X	New drug ETC	New drug ·ETC ·OTC	New drug ·ETC ·OTC Quasi drug (internal solid formulation·liquid formulation) material medicines
Object for validation	X	Process	Process	Process, Cleaning, Test method, Manufacture Support, Computer System
On the job Practice of Validation	X	O	O	Not determined
Site Audit of Validation	X	Desired industry	Not-done industry	Not determined
Coaching method for Validation	X	Focusing on the guidance	Focusing on the guidance & audit (mainly Not-done industry)	Not determined
GMP investigator	X	Introduction the second half of the year	O	O

Pre-approval KGMP

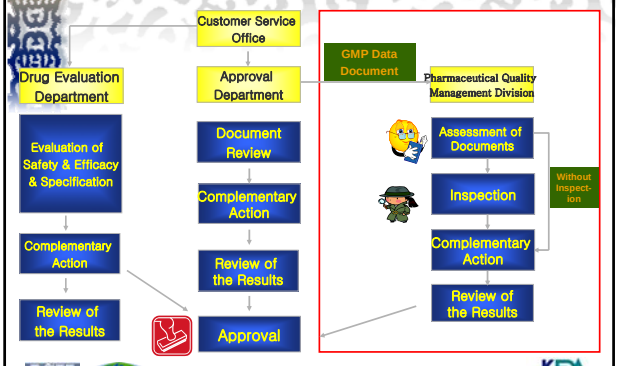


- Drug Substance
- Quasi-Drug (Oral Soild & Liquid Preparation)
- Non-prescription Drug
- Prescription Drug
- New Drug

Validation (Product-based)



Flow Chart of Pre-approval GMP



Approval Status of Pre-approval GMP

2009.3.31

		Application	Approval			On going
			Approval	Approval with Supplement	Non-Approval	
New drug		33	16	9	–	8
ETC drug	Approval	73	18	5	–	50
	Notification	108	29	37	2	40
Total		214	63	51	2	98

KGMP for IND

- **IND Dossier : Documents on manufacture facilities**

➡ GMP Certificate:

: Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

KGMP education for Industry

Recipient	Mandatory (draft)	Exception
All who first desired to become an authorized manufacturer for KFDA's approval or declaration (including any change of the manufacturer)	• Should complete the education designated by KFDA • More than 16 hrs biennially	Anyone who have completed the same education designated by KFDA within 2 years

2009 plan of training on ICH guidelines (including Quality) in Korea

- APEC Harmonization Center Workshop held in September 16~18, Seoul; coincides with BIO Korea 2009
- APEC Harmonization Center Workshop held in November 11~13, Seoul

Thank You !

CLOSING REMARKS

Satoshi Toyoshima, *MHLW (PMDA)*
Member of the Steering Committee

Participants, ladies and gentleman, thank you for your participation today.
I am Toyoshima from PMDA. ICH Japan symposium 2009 is coming to a close. At the occasion of the closing of this symposium, I would like to say a few words on behalf of the organizer.

ICH has been working in three areas, so that we can secure the Safety, Quality and Efficacy of the pharmaceutical products. At each ICH meeting, we held a symposium to report the current status of ICH harmonization. Today, there are more than 18 countries participating in the meeting, and the number of participants exceeds 600. We are very grateful that we could have this successful meeting today. With your enthusiasm and interests, importance in ICH activity is recognized once again.

At the ICH Yokohama meeting, the experts of each topic as well as the participants from non-ICH regions came together and had a very enthusiastic discussion for four days. Good results had been brought about. For example, M3 guideline was revised and agreed as Step 4. We could revise the timing of nonclinical studies. We also have revision of the pharmacopoeia. E16 guideline on biomarkers reached Step 2. There are many other topics which are still on going. Topic leaders and Rapporteurs made their presentations today and through the discussion, I believe that you have obtained the most recent and current information in the implementation of ICH guidelines.

I believe that you would bring the ICH harmonization efforts back to your places so that you can work out and have very good activities. With this, I would like to conclude my short speech. Thank you very much once again, for a long day today.