

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

ICH

**Proceedings of
ICH Tokyo Symposium:
Hot Topics and Influence on Asia
Tokyo 2007**

Proceedings of ICH Tokyo Symposium: Hot Topics and Influence on Asia Tokyo 2007

November 2, 2007

Keidanren Hall, 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 Tokyo Symposium:
Hot Topics and Influence on Asia
Tokyo 2007**

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Implementation of ICH Guidelines in Asian Countries

Co-Chaired by Mr. Mike Ward and Mr. Kohei Wada

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Background to the First Regional ICH Public Meeting

Since the first International Conference on Harmonization (ICH 1) was held in Brussels, November 1991, following International Conferences have taken place to date; ICH 2 in Orland, USA, October 1993, ICH 3 in Yokohama, Japan, November 1995, ICH 4 in Brussels, Belgium, July 1997, ICH 5 in San Diego, USA, November 2000 and ICH 6 in Osaka, Japan, November 2003.

In stead of continuing this practice, the Steering Committee (SC) re-considered the need to organize a large scale public conference and it was recommended that other educational models should be explored for the communication about ICH. An Options Paper on the need for a large scale public conference was drafted by three industry associations. Out of the several options raised, the one to hold smaller, more frequent and more focused ICH meetings, was supported by the SC in Chicago Meeting 2006; hence ICH 6 became the last conference of the traditional large scale. Further to refine this option, the ICH Industry Party Implementation Paper for the ICH public conferences was presented at the Brussels SC Meeting 2007. Here, principles such as size, organization, frequency, format, financial aspects of the meeting and evaluation process were clarified. It was judged appropriate that the conference should be held every eighteen months in each ICH region, either as a one-day additional communication meeting at the end of ICH SC and EWG/IWG meetings, or as an ICH-branded regional meeting in collaboration with other non-profit organizations.

Based on the SC decision, the ICH Tokyo Symposium titled “Hot Topics and Influence on Asia” was held in Tokyo on November 2, 2007, the following day of the ICH Yokohama Meeting (October 27 to November 1, 2007), as the first regional ICH public meeting. The Symposium was jointly organized by the Society of Japanese Pharmacopoeia (SJP, non-profit organization) and Japan Pharmaceutical Manufacturers Association (JPMA) and supported by the Ministry of Health, Labour and Welfare (MHLW), Federation of Pharmaceutical Manufacturers’ Association of Japan, Pharmaceutical Manufacturers’ Association of Tokyo, Osaka Pharmaceutical Manufacturers Association and Japan Pharmaceutical Association. Over 460 participants from the pharmaceutical industry and the regulatory authorities of Europe, Asia and North America (13 countries; France, Luxembourg, Netherlands, Switzerland, UK, Turkey, Thailand, China, Korea, Singapore, Japan, Canada and USA) attended the Symposium.

WELCOMING ADDRESS

Kohei Wada, JPMA
Member of the Steering Committee

Ladies and gentlemen, it is a great pleasure to see so many of you on this occasion. Let me introduce myself. My name is Kohei Wada, of Daiichi Sankyo. On behalf of the organizers, I would like to say a few words.

Originally, the 7th International Conference on Harmonization, namely ICH7, was scheduled to have taken place this spring. However, it was discussed in Chicago last year that, rather than meeting once every 2 to 3 years in such a large gathering, we would do better to meet more frequently on a regional basis. This concept was finally decided in Brussels this May.

This is a very commemorative landmark event – the first of this kind in the regional gathering. Up until yesterday for about a week, the Steering Committee and experts met to discuss various topics in Yokohama, which concluded with great success.

This latest development/outcomes will be reported today by the Rapporteurs as well as the topic leaders representing various countries. In the afternoon we will be discussing the ICH GCP guidelines and their implementation in Asian countries. This is, therefore, somewhat different from the regular reporting meetings we usually had.

It has only been six months since I joined the ICH activities, and it always strikes me that the experts are dedicating their all-out efforts to work on the ICH topics. This truly impresses me. It is because of their daily efforts and contributions that the ICH is where it is right now. I would like to express my hearty appreciation to their dedication.

Furthermore, in realizing today's Tokyo Symposium, there are many people whose time and efforts have made an important contribution. I would like to express my extra gratitude to all those helping us behind the scenes.

I sincerely hope that this ICH symposium will be informative to all of you. Once again, thank you very much for coming.

HOT TOPICS I: MORNING SESSION

General Update on ICH

Kurajiro Kishi, JPMA
ICH Coordinator

Abstract

Date of Meeting, Venue

October 27-November 1, 2007

Yokohama Royal Park Hotel, Yokohama, Japan

Steering Committee Main Participants (members and observers)

Japan: Dr. Toshiyoshi Tominaga (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: Dr. Peter Arlett, Dr. Tomas Salmonson (EU), Dr. James Richie, Dr. Christine-Lise
Julou (EFPIA)

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

ICH Secretariat: Dr. Odette Morin (IFPMA)

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

ICH Multidisciplinary/e-Groups:

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

ICH Safety Groups:

- S2(R1): Guidance on Genotoxicity Testing and Data Interpretation
- M3(R2): Revision of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials
- S9: Oncology Therapeutics
- Safety Joint Meeting: Update on S6 Regional Meetings

ICH Quality Groups:

- Q4B: Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria
- Q4B(Annex 1): Residue on Ignition/Sulphated Ash
- Q8(R1): Pharmaceutical Development (Addendum)
- Quality Informal IWG

ICH Efficacy Groups:

- E2F: Development Safety Update Report

Other Groups:

- M1 PtC: MedDRA Point to Consider

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

- Terminology: Maintenance of ICH Controlled Terminology Lists
- Q10: Pharmaceutical Quality System
- E14: Clinical Evaluation of QT/QTc interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
- E15: Pharmacogenomics
- Gene Therapy Discussion Group (GTDG)
- S1C(R2): Revision of Dose Selection for Carcinogenicity Studies of Pharmaceuticals and Limit Dose

Other Meetings in Yokohama

- ICH GCG: ICH Global Cooperation Group
- MedDRA Management Board (MB)
- Communication About ICH: Regional ICH Meeting: ICH Tokyo Symposium; Hot Topics and Influence on Asia (November 2, 2007, Tokyo)

Dates of Next Meeting

- May 31-June 5 2008, Portland, Oregon, USA
- November 15-20 2008, Brussels, Belgium
- June 6-11, 2009, Japan (Proposal)

Main Outcomes of Steering Committee Meeting: (To be Presented On Site)

ICH Multidisciplinary/e-Groups:

- M2, M5, E2B(R3):

ICH Safety Groups:

- S2(R1):
Step: Before Yokohama Meeting: 1
At Yokohama Meeting:
- M3(R2):
Step: Before Yokohama Meeting: 1
At Yokohama Meeting:
- S9:
Step: Before Yokohama Meeting: 1
At Yokohama Meeting:
First face-to-face meeting
- Safety Joint Meeting on S6:
An update on S6 regional meetings in the three ICH regions

ICH Quality Groups:

- Q4B, Q4B(Annex 1):
Step: Before Yokohama Meeting: 3
At Yokohama Meeting:
- Q8(R1):
Step: Before Yokohama Meeting: 1
At Yokohama Meeting:

- Quality Informal IWG:

ICH Efficacy Groups:

- E2F:

Step: Before Yokohama Meeting: 1

At Yokohama Meeting:

Other Groups:

- M1 PtC:

Others:

Questions and Answers

There were no questions.

General Update on ICH

November 2, 2007

JPMA
ICH Coordinator
Kurajiro Kishi, DVM, PhD

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Overview

- General:**
ICH Yokohama Meeting (SC/EWG/IWG)
- Main Points**
1. New topics
 2. Topics stepped up
 3. Proposals for new topics, revision/maintenance of guidelines and other business
- Main Outcomes**
1. Topics: **face-to-face** meetings in Yokohama
 2. Topics: **no face-to-face** meetings in Yokohama
 3. **Proposals** for new topics and revisions/ maintenance of guidelines and other business
 4. Global Cooperation Group (**GCG**)
- Future of ICH Meetings**
1. ICH public conference: Future, **ICH Tokyo Symposium**
 2. SC/EWG/IWG meetings

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General: ICH Yokohama Meeting

- Date of Meeting, Venue:**
October 27 – November 1, 2007
Yokohama Royal Park Hotel, Yokohama, Japan
- Attendees:**
Total number of attendees: **approximately 250 experts**
Japan (86), USA (46), EU (54), Observer, ICH Secretariat, RHIs, Others
- SC members: **one member replacement as EU**
EWG/IWG Meetings (formal/informal): 18
Safety(4), Quality (5), electronics (6), Efficacy (1), MedDRA (2)
- Topics (including proposals)**
- | | | |
|-----------------------------|----|---------------------|
| Topics discussed at SC Mtg: | 25 | (F2F:15, No F2F:10) |
| Topics stepped up: | 6 | (including Annex) |
| IWG endorsed at SC Mtg: | 2 | |

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Main Points

- 1. New Topics**
- | | |
|----------|-------------------------------|
| New EWG: | None |
| New IWG: | Quality IWG, eCTD-Quality IWG |
- 2. Topics Stepped Up**
- 1) **Q4B:** Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions **Step 4**
 - Q4B(Annex 1): Residue on Ignition/Sulphated Ash **Step 4**
 - Q4B(Annex 2): Extractable Volume **Step 2**
 - Q4B(Annex 3): Particulate Contamination **Step 2**
 - 2) **Q8(R1):** Pharmaceutical Development (Addendum) **Step 2**
 - 3) **E15:** Pharmacogenomics **Step 4**

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Main Points (continued)

- 3. Proposals for New Topics and Revision/Maintenance of Guidelines and Other Business**
- 1) **Drug Substance**
 - 2) **Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (S6, Revision)**
 - 3) **Studies in Support of Special Populations: Geriatrics (E7, Revision)**
 - 4) **Genomic Biomarker Qualification, Format and Content of a Submission**
 - 5) **CHMP Guideline:**
Strategies to Identify and mitigate Risks for First in Man Clinical Trials with Investigational Medicinal Products
 - 6) **CTD Review:**

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Main Outcomes

- 1. Topics: Face-to-Face Meeting in Yokohama**
- 1.1 Q4B:** Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions
- **Core Guideline:** **Step 4**
 - **Annex 1** Residue on Ignition/Sulphated Ash: **Step 4**
 - **Annex 2** Extractable Volume: **Step 2**
 - **Annex 3** Particulate Contamination: **Step 2**

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Main Outcomes (continued)

1. Topics: Face-to-Face Meeting in Yokohama (Continued)

1.2 Q8(R1): Pharmaceutical Development (Addendum)

- **Step 2**
 - ✓ An addendum to Q8 on specific dosage forms (solid, oral and parenterals)
 - ✓ Format supports parent guideline
 - ✓ Exemplifying Quality by Design concepts to enhance product and process understanding and to encourage Industry's sharing with Regulators
 - ✓ Reference tools described in Q9, cross reference Q10
 - ✓ Public consultation: over next 6-9 months

1.3 Quality Informal IWG

- **Formation of a Formal IWG:** Assuring globally consistent implementation and sharing of best practices
- Implementation issues: technical issues and related documentation, communication, training, scope of implementation and influence on existing ICH guidelines
 - ✓ Collaboration within ICH/with external organization
 - ✓ Briefing packages be available through ICH website
 - ✓ Organizing workshops for facilitating globally consistent implementation of Q8, Q9 and Q10

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Main Outcomes (continued)

1. Topics: Face-to-Face Meeting in Yokohama (continued)

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

- Still Step 1, but expected to reach **Step 2 by the end of 2007**
- Guidance S2A and S2B merged into one
- Major points of revision
 - ✓ Options for test battery (Option 1, 2), *in vitro* mammalian cell assay
 - ✓ No positive control, integration into routine general toxicity studies
- Step 4 possibly November 2008

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

- Still Step 1, but expected to reach **Step 2 at Portland Meeting in 2008**
- Revision of single dose, repeated dose, genotox, reprotox, nonclinical study duration, non-rodent toxicity studies, etc
- New studies: exploratory studies (single/ repeated), first dose in human
- New additional studies: immunotox, phototox, abuse liability, etc

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Main Outcomes (continued)

1. Topics: Face-to-Face Meeting in Yokohama (continued)

1.6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (S6, Revision)

- Safety Joint meeting: **feedback from S6 regional meetings**
- As preliminary discussion: need and form of update, section
- Draft Concept Paper (intended paper): Jun/Nov, 2008
- Work plan: establishment of EWG on Nov, 2008

1.7 S9 Oncology Therapeutics

- **1st EWG face-to-face meeting**
- Preclinical evaluation for the development and marketing of cancer therapeutic agents for the treatment of primary cancer
- Future: work plan (Step 2 in Brussels, 2008), starting dose, toxicological studies needed

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Main Outcomes (continued)

1. Topics: Face-to-Face Meeting in Yokohama (continued)

1.8 E2F: Development Safety Update Report (DSUR)

- **Work plan:** reaching Step 2 by June, 2008
- **Issues resolved previously:** annual reporting in three ICH regions, revision once or more a year, scope (pharmaceuticals, vaccines, biologicals)
- **Issues agreed:** reference safety info, identifying unexpected AE terms in tabulations, inclusion of proprietary/unblinded info, study drop-outs, drug combinations, synchronization of DSURs and PSURs, dealing with interruptions, etc
- **Format of the DSUR:** example DSURs as an appendix/Q&A, etc
- **Timelines:** proposal for interim meeting on Feb 25-29, 2008, USA

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Main Outcomes (continued)

1. Topics: Face-to-Face Meeting in Yokohama (continued)

1.9 M2, eCTD:

- **eCTD-Q:**
 - ✓ Establishment of eCTD-Q IWG addressing the quality eCTD Change Requests
 - ✓ Management of Module 3 data in the eCTD
- **eCTD:**
 - ✓ v3.3.3: **termination of development**
 - ✓ v3.2.1: be releases as new version with the improvement of narrative portions
 - ✓ A new version of Change Request/Q&A document (v 1.14); Step 4
- **SDO Process:** E2B(R3), M5 with the input from ISO TC215/WG6 TF Mtg
 - ✓ SDO pilot project: definition of deliverables, international standard & schema, ICH implementation guide, project plan, timeline, etc
 - ✓ Review of the process: development of the "Evaluation Criteria"

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Main Outcomes (continued)

1. Topics: Face-to-Face Meeting in Yokohama (continued)

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

M5: Data Elements and Standards for Drug Dictionaries

- **E2B(R3):**
 - ✓ Formation of and participation to ISO ICSR WG6 TF
 - ✓ **Gap analysis** between HL7-ICSR and ICH E2B(R3)-ICSR
 - ✓ **Proposal for new ISO-ICSR:** a multipart standard with Part 0 (an overview structure of ICSR), Part 1 (human medicinal product), Part 2 (medical device) and other parts
 - ✓ ISO ICSR WG6 TF Mtg (Oct 27-28): limiting the project to human medicinal products initially, then expanding the scope to other parts
 - ✓ **Timeline** to advance ICH pilot projects for the ICSR: working draft (Dec 2007), committee draft, draft Int 1 std, final draft Int 1 standard, int 1 std (Dec 2009)
- **M5:**
 - ✓ Formation of ISO ICSR WG6 TF: June 7-8 at London meeting
 - ✓ Next meeting: Jan, 2008 in Texas

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Main Outcomes (continued)

2. Topics: No Face-to-Face Meeting in Yokohama

2.1 Quality Roundtable for Small/Large Molecule Discussion: Drug Substance

- Formation of an informal WG
- Drug substance guidance addressing chemical and biotech (similarity & differences), traditional and "best scientific practices" for Section S.2 of CTD-Q
 - ✓ Development of an ICH guideline on development and manufacture of the drug substance (Chemical and Biotech) (Section S.2 of CTD-Q)
 - ✓ Developing draft Concept Paper, draft Business Plan

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Main Outcomes (continued)

2. Topics: No Face-to-Face Meeting in Yokohama (continued)

2.2 Q10: Pharmaceutical Quality System

- Reached Step 2 in Brussels Mtg, 2007
- Maintaining public consultation for comments by Oct 2007
- Facilitating innovation and continual improvement throughout the product lifecycle
- Complementing Q8 and Q9 guidelines

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

- Q&A: no consensus is reached yet (Answer 1 to Question 1, falling into a critical situations)
- Development of the work plan to complete Q&A task by the Portland meeting, 2008
- Change in rapporteurship from FDA to MHLW

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Main Outcomes (continued)

2. Topics: No Face-to-Face Meeting in Yokohama (continued)

2.4 E15: Pharmacogenomics

- Step 4 (postal sign off)
- Definitions of key terms in the discipline of pharmacogenomics and pharmacogenetics (genomic biomarkers, pharmacogenomics and pharmacogenetics), data and sample coding categories

2.5 GTDG: Gene Therapy Discussion Group

- Development of ICH Considerations Documents
- Oncolytic viruses: 2nd draft ICH Considerations in progress
- Viral/vector shedding:
 - ✓ ICH GTDG public workshop on viral/vector shedding held on Oct 30, 2007 in conjunction with European Society for Gene and Cell Therapy annual conference
 - ✓ Posting the meeting report and Communications Paper on the ICH public website following SC approval

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Main Outcomes (continued)

3. Proposals for New Topics and Revisions/Maintenance of Guidelines

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

- Formation of informal WG

3.2 Genomic Biomarker Qualification, Format and Content of a Submission

- Continue to revise the draft Concept Paper and Business Plan

3.3 CHMP guideline: strategies to identify and mitigate risks for first in man clinical trials with investigational medicinal products

- Considerations be given to whether the guideline has a potential impact on existing guidelines (S6, M3 and others)

3.4 CTD Review

- Formation of a working group to define and implement a process for periodic review and re-publication of the CTD

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Main Outcomes (continued)

4. GCG: Global Cooperation Group

Promotion of mutual understanding of regional harmonization initiatives (RHIs) in non-ICH regions, and facilitation of the capacity of drug regulatory authorities and industry to utilize them

- Discussions about implementation of ICH guidelines in non-ICH regions: RHI survey update, reports in non-ICH regions, etc
- Training and capacity building
 - ✓ Seoul APEC LSIF Workshop: Reported
 - ✓ ICH GCG endorsed event-APEC LSIF sponsored workshops for regulators: "Review of drug development in clinical trials for DRAs", "Good clinical practices inspections", hosted by Thailand
 - ✓ PANDRH training request: a quality training (risk approach to GMP inspections) in Brazil
- Update on the future of GCG
 - ✓ Considerations in expansion of GCG: Invitation of individual drug regulatory authorities (DRAs) in addition to the RHIs

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Future of ICH Meetings

1. ICH Public Conferences

1) ICH 7

- A large ICH Conference was questioned, not taken place

2) Regional Meetings

- Smaller, more frequent, more focused ICH meetings
- ✓ Options: either one-day additional meeting at the end of EWG and SC meeting or ICH-branded regional meetings in collaboration with other non-profit organization
- ✓ Frequency: one regional meeting every 18 months
- ✓ Japan: ICH Tokyo Symposium
 - One-day additional meeting of Yokohama Meeting at 10:00 - 17:00 on Nov 2, 2007 in Tokyo
 - Attendees: a total of more than 460 including 21 from overseas
- ✓ USA: scheduled in 2008
- ✓ EU: not scheduled

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ICH Tokyo Symposium
Hot Topics and Influence on Asia

Welcome Address: Mr. K. Wada/JPMA

Hot Topics: Chairperson (Dr. K. Kishi/JPMA, Dr. T. Tominaga/MHLW)

1) General Update on ICH:	ICH Coordinator	Dr. K. Kishi	JPMA	
2) S2(R1):	Rapporteur	Dr. M. Hayashi	NIHS/MHLW	
3) E2F :	Topic Leader	Dr. J. Sato	PMDA	
4) Steering Committee:	SC Member	Dr. J. Molzon	FDA	
5) Quality Q8(R1):	Topic Leader	Dr. H. Okuda	NIHS/MHLW	
	New Paradigm :	Rapporteur	Dr. J. Robert	EU
6) M2 :	Rapporteur	Dr. A. Marr	EFPIA	
7) M3(R2) :	Rapporteur	Dr. J. DeGeorge	PhRMA	

Panel Discussion: Chairperson (Mr. Ward/Health Canada, Mr. Wada/JPMA)

Clinical Development in Asia and ICH:

Implementation of ICH Guidelines in Asian Countries

1) GCG/Industry:	Mr. K. Wada	JPMA
2) GCG/Regulator:	Mr. M. Ward	Health Canada
3) APEC China:	Dr. J. Ding	SFDA, China
4) APEC Korea:	Dr. D. Kim	KFDA, Korea
5) ASEAN Thailand:	Dr. Y. Javroongrit	FDA, Thailand

Closing Address: Dr. S. Toyoshima/PMDA

2007.11.2
ICH Tokyo Symposium

Future of ICH Meetings

2. Date of Next Meeting: SC, EWG/IWG Meeting

2008 June 2 - 5:	Portland, USA
2008 November 17 - 20:	Brussels, Belgium
2009 June 6 - 11 (scheduled):	Yokohama, Japan

2007.11.2
ICH Tokyo Symposium

S2 (R1)

Makoto Hayashi, MHLW (NIHS)
Rapporteur

Abstract

The S2A (1995) and S2B (1997) guidelines describe a basic test battery of *in vitro* and *in vivo* genotoxicity tests to support the safety of drugs for human use. This three-test battery is a bacterial mutagenicity assay, a mammalian cell assay (either *tk* mutations in mouse lymphoma cells, or *in vitro* assay for metaphase chromosome aberrations) and an *in vivo* assay for cytogenetic damage, typically a test for micronuclei in erythrocytes of rodents. The major issues prompting revisions to the guidelines are the high frequency with which positive results are found in the *in vitro* mammalian cell assays, and are considered not relevant under *in vivo* conditions because they include many that are weakly positive, associated with considerable toxicity, and/or only seen at high concentrations, and the other tests in the battery are negative. This leads to a great deal of follow-up testing including additional animal testing to assess whether there is any genotoxic risk. We also take account the 3Rs concept into the revision of the guidance.

The group considered options such as: developing a better guidance on weight-of-evidence and interpretation of results. Based on the discussion at the last Chicago meeting in October 2006, we decided to merge two S2 guidances (A and B) into one guidance (S2 (R1)). After the Chicago meeting, we made a survey for JPMA, EFPIA, and PhRMA to ask for examples of the lowest effective concentration for the *in vitro* mammalian assays that were considered relevant positive results. Also we asked the dose and C_{max} values for the single and repeat dose toxicological studies to evaluate the suitability of genotoxicity studies incorporated into the general toxicological studies. Based on the outcomes of the survey, we revised the standard battery to detect genotoxicity to the new standard methods. At the moment, we have not yet well achieved consensus on the new strategy of battery and/or tier system, I would like to discuss this point.

Issues that we agreed at the Chicago and Brussels meetings are as follows: Use of flow cytometry for micronucleus assessment was also discussed and approved, in line with OECD guidance. For *in vivo* MN assay, it is not necessary to include treatments with positive controls in every study. Validation of scoring can be done periodically and quality control samples included for automated scoring. There was consensus that the top dose could be reduced from the existing 10 mM (5 mg/ml) to 1 mM (0.5 mg/ml), and this would reduce the number of irrelevant positive results. The current guideline requires testing several doses above the solubility limit (with visible precipitate in cultures) if necessary to meet the toxicity limits for the assays. We have agreed that the top dose can now be the lowest dose with visible precipitate.

Questions and Answers

Question: This time, a couple of options were presented at the Yokohama Meeting. In the genotoxicity test, we have to consider the test for the compound which contains impurities. Is

there any plan to conduct that kind of discussion?

Hayashi: As to impurities, we received many questions, but did not discuss about it at this meeting. Although we had a different EWG in the past to discuss this, we, as the S2 group, do not have any plans to include a discussion about impurities. Thank you.

Question: When you incorporate the genotoxic evaluation (genotoxicity endpoints) into the routine general toxicity study, it is recommended that the dose should be set to 50 percent of the top dose used for acute or single dose toxicity studies. I think this dose is too high in the repeated dose toxicity study. What do you think?

Hayashi: At the EWG, we had extensive discussion about this point, but in the end we came to the conclusion that we would like to reduce the false negatives as much as possible. We also would like to achieve the sensitivity that is secured by the current guidance. That is the reason why we have included that condition. This acceptance criterion does not mean to satisfy all the criteria. But if you can satisfy one of those acceptance criteria, it is OK. So maybe you can clear that point with other conditions. Then the data can be accepted and can be evaluable.

Question: One more point: Will the genotoxicity endpoints be incorporated into the single dose toxicity study?

Hayashi: It is OK to incorporate that into the single dose toxicity study.

Kishi: If I may have a question or a comment to make about the guideline that is in question, it was designed to resolve many questions or difficulties that we had with the present guideline based upon the accumulated data. Especially for the regulatory authorities as well as for the industry, this is more realistic, and this is more readily acceptable. Therefore, I think the revised new guideline appears to be splendid, especially with the addition of options which are to be considered and concluded scientifically by the industry. From the view point of the 3Rs (Reduce, Refine and Replace) principle, rather than using the animal models independently in both studies, if the routine general toxicity study could be evaluated by integrating the genotoxicity endpoints provided that the requirements are fulfilled, I believe the new guideline would be a great achievement.

Hayashi: Thank you very much. By incorporating into the routine general toxicity study, comprehensive evaluation is possible. That is the direction that we should consider in the future. In the S2 group, from a global point of view, maybe it has been performed by a small number of people. Therefore all of them are familiar with each other. That may have led to a very extensive and detailed discussion.

Kishi: Yes, you are right. To incorporate a genotoxicity test into the general toxicity study allows us to give a very comprehensive evaluation. So that is another benefit of this new guideline. If we do not have further questions, we would like to move on. Thank you very much, Dr. Hayashi.

Tokyo ICH Symposium:
Hot Topics and Influence on Asia
November 2, 2007
Tokyo, Japan

Update on the Maintenance of the ICH S2 Genetic Toxicology

Makoto Hayashi
Division of Genetics and Mutagenesis,
National Institute of Health Sciences
Tokyo, Japan

The current standard battery

- i) A test for gene mutation in bacteria.
- ii) An *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells or an *in vitro* mouse lymphoma tk assay.
-if positive then additional in vivo test
- iii) An *in vivo* test for chromosomal damage using rodent hematopoietic cells.

Motivations of revision

- *Too many positives in the in vitro mammalian cells assay systems that may not be relevant to human risk*
- *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*

Revision of S2A and S2B and make a merged revised guidance

S2(R1)
GUIDANCE ON GENOTOXICITY
TESTING AND DATA
INTERPRETATION FOR
PHARMACEUTICALS INTENDED FOR
HUMAN USE

Summary of major points of the revisions

- S2A and S2B guidances merged into one
- Options provided for the test battery
 - O-1 Battery **with** *in vitro* mammalian cell assay
 - O-2 Battery **without** *in vitro* mammalian cell assay but two *in vivo* assays
- *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
- *In vitro* bacterial mutation assay no longer requires duplicate assay

Cytotoxicity

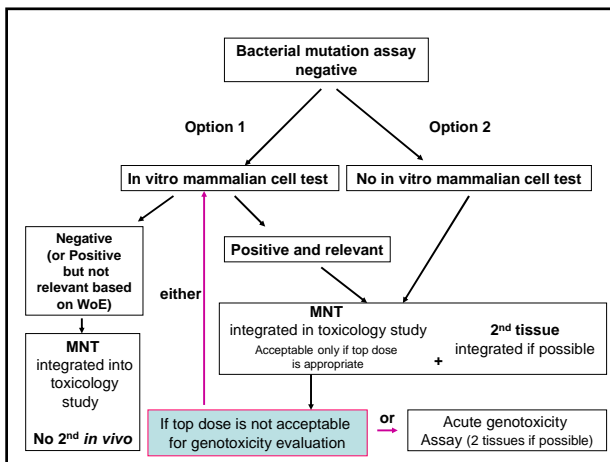
- ***In vitro* metaphase chromosome aberrations or micronuclei**
should approach but not exceed a 50% reduction in cell population growth
- **Mouse lymphoma tk mutation assay**
should approach a reduction of about 80% in RTG (relative total growth)

Summary of major points of the revisions -continued-

- 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
includes Comet assay, decreases emphasis on UDS assay
- Provided advice on weight of evidence and data evaluation to determine relevance of positive findings

Criteria for acceptable dose/exposure in (sub)chronic study

- Maximum feasible dose (MFD) based on physico-chemical properties of the drug in the vehicle
- Limit dose of 1000 mg/kg for studies of 14 days or longer, if this is tolerated
- Exposure:
 - a. plateau/saturation in exposure
 - b. accumulation
- Reduced exposure with time would usually disqualify study
- Top dose is $\geq 50\%$ of the top dose that would be used for acute administration if such acute data are available for other reasons



Benefits of revisions: The 3 R's

- No longer require concurrent positive controls in every *in vivo* assay
- Integration of genotoxicity into toxicology assays
- Reduction in “non-relevant” *in vitro* results will reduce number of follow-up *in vivo* assays

Benefits of revisions:

- Incorporates accumulated knowledge specific to testing of pharmaceuticals
- Takes advantage of new technologies
- More options in the test battery
- Reduction in delays caused by dealing with “non-relevant” *in vitro* positive genotoxicity results
- More efficient use of resources

Expected targets

- Finalization of text of draft guideline
- Ensure ultimate acceptance by groups represented by EWG
- Postal sign off for step 2
end of December 2007
- Publication in the regions and regional consultation period
- Step 4 in June 2008 in Portland pending speed of Federal Register publication and comment period

E2F

Development Safety Update Report (DSUR)

Junko Sato, MHLW (PMDA)
Topic Leader

Abstract

Development Safety Update Report (DSUR) guideline is a report that presents a periodic review and analysis of safety information during the clinical development of an investigational drug. The concept is recommended by CIOMS VI and VII.

The collection, monitoring and regulatory reporting of safety information on trial subjects is an essential part of conducting clinical trials. Regulations and guidance specify the responsibilities and reporting requirements for sponsors, investigators and their institutions. Most focus on the expedited reporting of Individual Case Safety Reports (ICSRs), with ICH Guideline E2A generally considered as the standard for defining what information must be sent to various stakeholders, and when. However, the periodic analysis of involving safety information is crucial to the ongoing assessment of risk during the clinical development of an investigational drug. Regular communication of such information to regulatory authorities and other stakeholders provides an information base critical for protecting the rights and welfare of subjects participating in clinical trials. This is true not only when an investigational drug is being evaluated in an ambitious clinical development program encompassing dozens of trials, but also when a drug is being investigated in a single clinical trial, by a commercial or non-commercial (academic) sponsor. This guidance provides an outline of issues to be considered in preparing a DSUR as well as guidance on its content and format.

The purpose of a drug development program is to characterize the benefit-risk profile of a drug. This includes developing adequate instructions for use, as well as a sound program for risk management. During early drug development, a drug's benefits and risks are purely theoretical. As experience is gained and data accumulate, benefits and risks come into clearer focus. Thus, the development of the benefit-risk assessment is a dynamic process. The balance must be evaluated on an ongoing basis and placed into proper perspective. Therefore data regarding drug safety needs to be available for ongoing regulatory review and evaluation, not only to protect the welfare of trial subjects, but also to ensure that the appropriate data are collected, especially as new safety issues are identified.

Together with other regular and periodic safety monitoring procedures, DSUR provides an opportunity for a broad, overall safety re-evaluation and to ensure that the risks to trial participants are recognized, assessed, and communicated.

This guideline is currently on Step 1. We EWG aim this guideline to be Step 2 at the Yokohama Meeting.

Questions and Answers

Kishi: Thank you very much, Dr. Sato, for your wonderful presentation. It was detailed and yet quite specific about key points. You also shared with us the overall frame work. So first I would like to invite questions or comments from the floor. Since this will be the guideline for the first time, I am sure that the audience is quite eager to ask questions.

Considering that this guideline is not in existence in Japan, three regions have been continuing their discussions on this particular subject matter. By the regions there could be differences. Could you make a comment on such differences and issues for harmonization? Perhaps that would ease the understanding of the audience.

Sato: Yes. As for the differences concerned, a major one would be the fact that the EU and the U.S. each have their own annual reporting system. In Japan, at least at the moment, such a system does not exist. The EU and the U.S. annual reporting systems, although similar by nature, nevertheless have differences. At the Yokohama Meeting we discussed this at length. For example, there is a manufacturing change. When you handle that in the U.S., any manufacturing change would have to be incorporated in the annual report. However, in the EU, not all manufacturing changes have to be incorporated in such a report. At a glance their systems look similar, but they are different in detail. Since that is the practice in the U.S. and the EU, they have difficulty in negotiating which one should precede the other. It is a difficult negotiation. Considering that it is a vacuum in Japan, we would observe and see which one is easier or more beneficial for us to adopt. Listening to the discussion so far, I think the EU approach is closer to our mindset. That is the current situation.

Kishi: At this point, we have not yet reached Step 2. So what would be the major issues or the most important issue?

Sato: Well, as for the “most important issue”, in fact there could be multiple; for instance, how to deal with the combination therapy. The “combination therapy” refers to the situation where there is a two-in-one type of drug – for example, one tablet containing two effective ingredients, or the cancer drug combination therapy that uses two different drug products. Also, the way to formulate line listing would be another issue. For those countries or regions that already have reporting systems, how to align with the existing regulations can also be an issue. For instance, in the EU and the U.S., if different regulations were to be introduced, would they really be acceptable and able to coordinate? Those will be the major issues that we have to consider.

Kishi: Any other questions? No further questions from the floor? Oh, yes. Please use the microphone. Could you repeat that?

Molzon: Thank you, Junko, for your very nice presentation. Will the group be discussing a common format for the information, once it is determined what should be included in these reports?

Sato: Thank you. Where the format is concerned, it is currently being discussed. As for the future, when it is approved, the product would become subject to the PSUR. So transition has to be smooth and we have to secure that. That is the idea for approaching the DSUR. In this regard, as I mentioned yesterday at the Steering Committee, we must consider whether this

should be part of the guideline, or should be part of the Q&A. Or whether this particular process should be applicable not only to the commercial sponsors but also to the non-commercial sponsors. Since they have to be knowledgeable about this, perhaps the format portion should be published in scientific journals and et cetera, to create better knowledge for the people concerned. As far as the methodology is concerned, we have not reached a consensus. Nevertheless, these are the factors discussed so far, and we would like to have a format which will be accepted by a wider audience in an easier manner.

Question: About the DSUR, you mentioned that annual reports that already exist in the EU and the U.S. will be replaced with the DSUR. What about the case for the PSUR? It is considered that the PSUR comes as an additional report required. That is how it is currently used in operation. Therefore, we are very concerned about what the ideas are behind the replacement of the annual report with the DSUR.

Sato: Ideas? Well, in principle, in the EU and the U.S. there already exists a similar system. Therefore, if it results in an increased burden and work, that would be unfortunate – for the industry as well as for the regulatory authorities, because they would be flooded with a lot of documents. Therefore, we want to improve what exists today, by taking advantage of the benefits of the existing system and trying to improve it. But as to the replacement with the DSUR, the EWG members only stated that they would work hard to try to replace it. So it does not mean that the U.S. FDA, for instance, has already accepted the replacement, but at least our EWG members state that they will work so that the replacement will be realized.

Kishi: I hope you are satisfied with the response. Are there any other questions? Any questions on the matter will be fine. This is entirely new to you, I understand. Therefore, it could be a basic question or a detailed question... Yes, please; and please approach the microphone.

Question: As a sponsor I am hesitant to ask this question, but let us say that in Europe and the U.S. a similar system is in place. Still, this is not the case in Japan. They do it because it has some merit, I understand. This is going to be a global scheme, and I am basically in support of such an approach. However, as for Japan, we have to have a clear-cut idea that such a system should not be for the sake of formality. The reports should not be sitting on the desk. It just means extra cost but not much benefit. In such a reporting system, as long as you receive it, you have to be responsible to review it because it is clinical-trial-related information. You can not say, “Oh, we did not take a look at it.” In the case of western countries, the investigation of new drugs is in a true sense and these investigations are conducted on drugs that appear for the first time globally. But you see, in the case of Japan, many of the trials or investigations are for drugs that have been approved already in western countries or elsewhere. So when the system is introduced in Japan, it should not be for the sake of formality. I hope you will be cautious about that.

Sato: Dr. Doi, I understand. You made a very good point, because the benefit or the merit for Japan is that, speaking from the administrators or the agencies side, although individual safety reports had been submitted from time to time, as far as the summary information is concerned, we only had a response when we asked for it taking note of the signals. So the summary information was only in our minds. However, with such a system, the signals become easier to


identify. Yet, what you said is right: sitting on the desk does not mean that we read them. We should make sure that we go through them. As far as the DSUR is concerned, executive summaries would be provided to the investigators and IRBs. That is the basic concept. In the case of Japanese medical institutions, individual case reports had been submitted discretely and so they were not fully utilized in the best way in the past. So upon introducing the DSUR, perhaps medical institutions may benefit – for example, by utilizing the executive summary reports as their latest safety information available for the respective trial drugs. As you had mentioned, the development status is different. Not many drugs would come in Japan for first approval. It would be approved elsewhere. So maybe the data volume would be significantly different. We have to be aware of that difference and by clearly reflecting the EWG discussions, we will discuss with JPMA, PMDA and MHLW on how to manage this.



**ICH-E2F
Development Safety Update Report
(DSUR)**

Junko Sato
Office of New Drug I
Pharmaceuticals and Medical Devices Agency

ICH-E2F Development Safety Update Report



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

Final Concept Paper
E2F: Development Safety Update Report
26 September 2008

Type of Harmonization Action Proposed

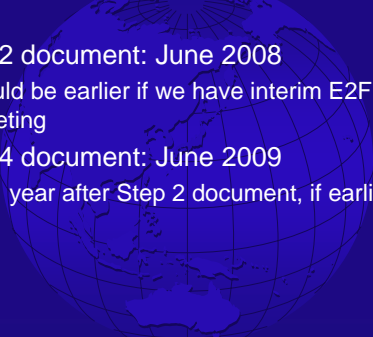
It is proposed that ICH develop a guideline on periodic reporting of safety information from clinical trials. This guideline would define the preferred content, format, and timing of such reports. The CDMP6 VI Working Group referred to this type of report as a Development Safety Update Report (DSUR). The DSUR would be used by industry to regularly inform appropriate stakeholders of new safety data and the evolving safety profile of drugs, vaccines, and therapeutic biologic products before they are marketed, and also when new indications, formulations, etc. are being studied for marketed products. The objective of the proposed DSUR for clinical trials would be similar to that of the Periodic Safety Update Report (PSUR) that is commonly used for marketed pharmaceutical products.

Statement of the Proposed Problem

<http://www.ich.org/LOB/media/MEDIA3302.pdf>

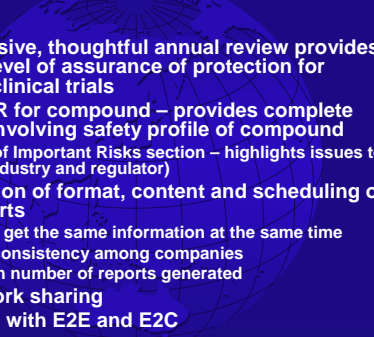
Timelines

- Step 2 document: June 2008
 - Could be earlier if we have interim E2F meeting
- Step 4 document: June 2009
 - or 1 year after Step 2 document, if earlier



Benefits of DSUR


- **Comprehensive, thoughtful annual review provides additional level of assurance of protection for patients in clinical trials**
- **Single DSUR for compound – provides complete picture of evolving safety profile of compound**
 - Summary of Important Risks section – highlights issues to monitor (industry and regulator)
- **Harmonisation of format, content and scheduling of annual reports**
 - Regulators get the same information at the same time
 - Improved consistency among companies
 - Decrease in number of reports generated
- **Facilities work sharing**
- **Harmonises with E2E and E2C**



DSUR Guideline

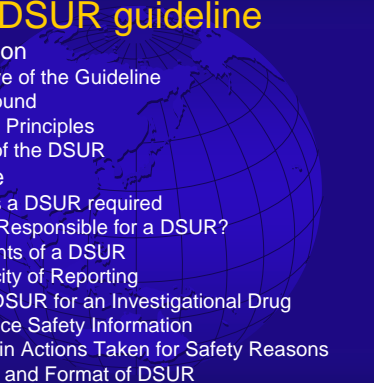
Draft

(2007.11)



DSUR guideline

1. Introduction
 1. Objective of the Guideline
 2. Background
 3. General Principles
 4. Scope of the DSUR
2. Guidance
 1. When is a DSUR required
 2. Who is Responsible for a DSUR?
 3. Recipients of a DSUR
 4. Periodicity of Reporting
 5. Single DSUR for an Investigational Drug
 6. Reference Safety Information
 7. Update in Actions Taken for Safety Reasons
 8. Content and Format of DSUR



General principles

- To present a periodic review and analysis of safety information in order to;
 - Examine whether the information reported during the review period is in accord with previous knowledge of the product's safety
 - Describe new safety issues that could have an impact on the development programme or on an individual trials
 - Summarize the current understanding and management of known and potential risks

Objective of DSUR

- Periodic analysis during the clinical development of an investigational drug
 - evolving safety information
 - be crucial to ongoing assessment of risk
- Outline of points to be considered in preparing a DSUR
 - Its content
 - format

Background

- Necessity of data regarding drug safety
 - To protect the welfare of trial subjects
 - To ensure that the appropriate data are collected, especially as new safety issues are identified.
 - To be available for ongoing regulatory review and evaluation
- CIOMS Working Groups recommended the introduction of DSUR

Scope of the DSUR

- Concise and informative and company safety documents
- Focus on the information that assures regulators that sponsors are adequately monitoring and evaluating the safety of the drug
- Replace existing US and EU annual clinical trial reports
- Include drugs, vaccines, biologics
 - Exclude devices
 - Include entire clinical program
 - Include both commercial and non-commercial clinical trials

What should be summarized ?

- all completed and ongoing interventional studies, conducted by the sponsor,
- data received by the sponsor from other parties conducting clinical trials on the drug including studies conducted by co-development partners in a licensing agreement (if the scope of the licensing agreement allows for this);
- other clinical studies conducted in accordance with INDs/CTAs, e.g., pre-approval access programmes
- safety data from spontaneous reports, Phase IV studies, active surveillance programmes and registries;
- observational and epidemiological studies;
- literature reports and
- late breaking information.

Guideline

When is a DSUR required

- Submit throughout the lifecycle of the investigational drug
- Annual report

Who's Responsible for Preparing it?

- Whether representing a commercial or non-commercial organisation, the sponsor is responsible for the preparation.
- Non-commercial sponsor may delegate individual sponsor activities such as preparation and submission of a DSUR by making a contractual agreement in writing with another party who will prepare or submit it on his behalf.

Recipients of DSUR

- Primarily, regulatory authorities
- Ethics Committee/IRB or investigators, if national legislation requires.
 - Only Executive Summary

Periodicity of Reporting

- Submit on annual basis no later than 60 days from data lock point
- Prior to the first marketing approval of an investigational drug the data lock point should be based on the date of the first approval or authorisation to conduct an interventional clinical trial in any country.
- DIBD is analogous to the IBD for PSUR

*DIBD : Development International Birth Date

Restart of development

- Development stopped or
- Never started in one region but continues in another region and then restarts in the region where it stopped
 - the next DSUR would be the one from the region where trials continued
- A sponsor has discontinued development of a drug but at a later date restarts development
 - provide a summary of the cumulative safety information from the previous development in the application for authorisation and provide an IB based on the available safety data

Single DSUR for an Investigational Drug

- Single DSUR include all safety data from all investigational clinical trials conducted with same investigational drug
 - All indication
 - All dosage forms
 - Intended populations
- Combination therapy
 - To be incorporated into separate section of one of the DSURs of the individual components of the combination.
 - a single DSUR to be submitted for all drugs in the study

Reference Safety Information

- **Prior to approval in any country**
 - Safety Section of Investigators Brochure
- **Authorised product**
 - Summary of Product Characteristics

Update on Actions Taken for Safety Reasons

- Refusal of authorisation of a clinical trial for safety reasons;
- Partial or complete clinical trial suspension;
- Hold or early termination of a clinical trial due to lack of efficacy or safety issues;
- Removal of a clinical hold;
- Changes to the reference safety information;
- Protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in study entrance criteria, intensification of monitoring);
- Changes in target population or indications;
- Changes to the informed consent document relating to safety issues;
- Formulation changes;
- Failure to obtain marketing authorisation for a tested indication;
- Significant changes to the Development Risk Management Plan (e.g. addition of a special reporting requirement, issuance of a Dear Investigator or Dear Doctor letter, plans for new safety studies).

DSUR and PSUR

- Once a drug is approved in any country the DIBD should be changed to coincide with the IBD, to facilitate simultaneous preparation and alignment of the DSUR with the PSUR, and simultaneous submission of the two documents to those regulators requiring both.

DSUR include all sources relevant to investigational drug

- all completed and ongoing interventional studies
- other parties conducting clinical trials on the drug including studies conducted by co-development partners in a licensing agreement
- other clinical studies conducted in accordance with INDs/CTAs
- safety data from spontaneous reports, Phase IV studies, active surveillance programmes and registries
- observational and epidemiological studies
- literature reports and so on

Progress this Week

- **Revised draft Guideline sections:**
 - Introduction
 - Background
 - Periodicity of Reporting
 - Single DSUR for an Investigational Drug
 - Multi-drug regimens, fixed drug combinations and drug-device combinations
 - Reference Safety Information
 - Drop-outs



Challenges:

- FDA agreement on shifting dates for IND Annual Reports(DSURs) to DIBD
- FDA agreement re: combining reports on multiple INDs on a single compound into a single DSUR

Agreements - 1

- Reference Safety Information
- Identifying unexpected events in tabulations
- Issues related to inclusion of proprietary information in DSURs
- Issues related to inclusion of unblinded information in DSURs
- Study withdrawals

Agreements -2

- Combination therapy/combination drugs
- Issues related to including information on all significant manufacturing changes in DSUR

HOT TOPICS II: AFTERNOON SESSION

Steering Committee

Justina A. Molzon, FDA
Member of the Steering Committee

Abstract

Justina A. Molzon, M.S. Pharm., J.D., will present the overview summary of the series of Steering Committee meetings held in Yokohama.

Justina is the Associate Director for International Programs, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration and a member of CDER's senior management team. One of her primary responsibilities is coordination of CDER's efforts related to ICH.

Questions and Answers

There were no questions.

ICH Tokyo Symposium
November 2, 2007

ICH Steering Committee Hot Topics

Justina A. Molzon, M.S. Pharm., J.D.
Associate Director for International Programs
Center for Drug Evaluation and Research/USFDA
CDER ICH Steering Committee Representative

Objectives

- To provide a brief overview of ICH
- Explain the role of the Steering Committee
 - Responsibilities
 - Membership
 - Function
- Report on current "HOT" topics
 - Operating procedures
 - Expert working group (EWG) topics
 - Transparency and communication

ICH

INTERNATIONAL CONFERENCE ON
HARMONIS/ZATION
of
Technical Requirements
for the Registration of
Pharmaceuticals for Human Use

<http://www.ich.org>

Hosted by ICH Secretariat
IFPMA - Geneva, Switzerland

ICH Background

- Unique harmonization project involving the regulators and research-based industries of US, EU and Japan—started in 1990
 - WHO, Canada, and EFTA are observers
- Well-defined objective: to improve efficiency of new drug development and registration process
- Accomplished through the development and implementation of harmonized guidelines and standards

Expert Working Groups

SAFETY

EFFICACY

QUALITY

MULTIDISCIPLINARY

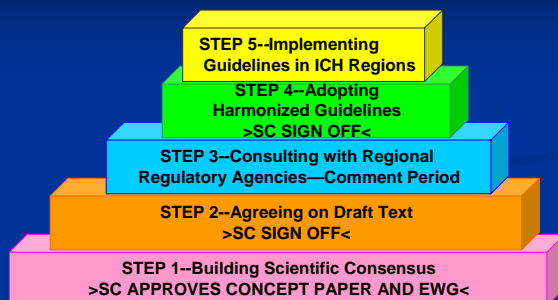
STEERING COMMITTEE

Monitors and Facilitates EWGs

ICH Steering Committee Responsibilities

- The body that governs ICH
- Determines ICH policies and procedures
- Decides on the adoption of ICH projects
 - Selects topics for harmonization
 - Endorses the creation of Expert Working Groups
- Monitors and facilitates the progress of Expert Working Groups
- Signs off ICH documents

Steps of ICH Harmonization



Steering Committee Membership Regulators/Industry

- Japan
 - MHLW/PMDA and JPMA
- Europe
 - EC/EMA and EFPIA
- United States of America
 - CDER/CBER FDA and PhRMA
- Secretariat
 - IFPMA
- Observers
 - WHO
 - Health Canada
 - EFTA

ICH Steering Committee Current Members

- Japan
 - Dr. Toshiyoshi Tominaga—MHLW and Dr. Satoshi Toyoshima – PMDA
 - Mr. Kazutaka Ichikawa and Mr. Kohei Wada--JPMA
- Europe
 - Dr. Peter Arlett—EC and Dr. Tomas Salmonson—EMA
 - Dr. Christine-Lise Julou and Dr. James Ritchie—EFPIA
- United States of America
 - Dr. Justina Molzon—CDER/FDA and Dr. Robert Yetter—CBER/FDA
 - Dr. Alice Till and Dr. Peter Honig-PhRMA
- Secretariate
 - Dr. Harvey Bale, Jr and Dr. Odette Morin—IFPMA
- Observers
 - Dr. Lembit Rago—WHO
 - Mr. Mike Ward—Canada
 - Dr. Petra Doerr-EFTA

Function

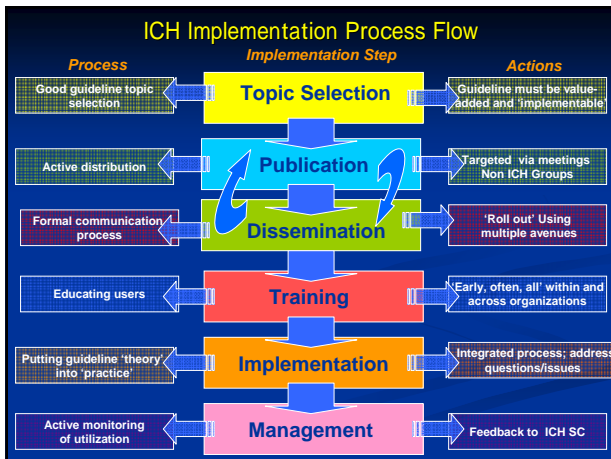
- Steering Committee meetings Wednesday and Thursday of “ICH week”
- Meetings as needed prior to “ICH week” to discuss urgent topics to provide guidance to EWGs
- Subcommittees
 - Global Cooperation Group
 - CTD Implementation Working Group
- Telecons between face to face meetings to deal with urgent issues and to facilitate work between meetings

Results Over 50 ICH Guidelines

- **Efficacy** - 14 topics/18 guidelines
- **Safety** - 8 topics/16 guidelines
- **Quality** - 9 topics/24 guidelines
- **Medical Dictionary** - MedDRA
- **Electronic Standards** - ESTRI, E2B
- **Common Technical Document** - CTD

ICH: Keys to Success

- Effective management and administration
 - Through Secretariat and Steering Committee
- Limited number of members with common focus and objectives
- Comparable regulatory, technical and financial capacity of participants
- Commitment of all parties to implement harmonized guidelines
- Well-defined process



Operating Procedures

Operating Procedures

- The work product of ICH has grown more complex over time - not simply "new topics"
- ICH Steering Committee adopted a Procedures document that outlines and defines the variations of work "categories"
- Defines roles and responsibilities
- Updated every fall to reflect current harmonization activities

- ## Categories ICH Harmonization Activities
- **New** guideline topics under **development**
 - **Existing** topics under **revision**
 - **Existing** topics under **maintenance**
 - Very specific meaning in ICH - adding an identified list of standards, e.g., categories of residual solvents in Q3C
 - **Existing** topics needing **clarification** for **implementation** (Questions and Answers)

Expert Working Group Topics

- ## Topics to be Presented at Symposium
- **S2 (R1)**: Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use
 - **E2F**: Development safety update report
 - **Q8 (R1)**: Pharmaceutical Development
 - **M2**: Electronic standards for the transfer of regulatory information and the electronic CTD
 - **M3(R2)**: Revision of non-clinical safety studies for the conduct of human trials for pharmaceuticals

TYPICAL EWG Pharmacogenomics Expert Working Group

- Reached Step 4 in Yokohama
- Focus is on terminology and definitions with goal of common, harmonized terminology to facilitate consistency in regulatory processes and remove obstacles in advancing drug development
- Next topic under discussion

Q & A E14: The Clinical Evaluation of QT/QTc Interval Prolongation and ProArrhythmic Drugs

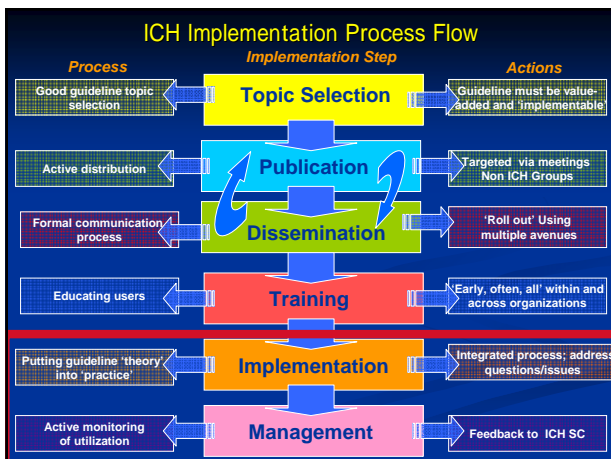
- Questions and Answers being developed to assist in implementation
- Choice of positive control main topic of discussion
- Face-to-face meeting in 6/2008 if needed

IMPLEMENTATION Quality Informal Working Group

- Increased focus and emphasis on implementation and maintenance of ICH Guidelines
- Quality Topic—Q8, Q9, Q10
 - Implementation issues identified
 - Approaches to address discussed
 - Formal Implementation Working Group formed

REVISION E7-Studies in Support of Special Populations: Geriatrics

- Proposal for revision by EU
- Concern about adequacy of guideline for drugs used in elderly
- Request to nominate an Informal EWG
 - To discuss EU Draft Concept Paper
 - To develop a final proposal for consideration by the ICH Steering Committee



Transparency and Communication

Goals of Transparency

- Greater relevance of ICH guidelines and standards to countries
- High quality scientific documents available to non-ICH parties
- ICH Guidelines serve as educational/reference material

Communication ICH Global Cooperation Group (GCG)

- Created in 1999 to address increasing interest by non-ICH parties in ICH guidelines and operations
- Facilitates dissemination of information on ICH activities, guidelines and their use
- Four brochures published on ICH and GCG, available at ICH website www.ich.org

Shift in GCG Focus

- Initial focus on **information-sharing**
- Soon became clear that more active **engagement** was necessary to respond to increasing interest in ICH and ICH guidelines
- Osaka, November 2003 Endorsement by ICH SC of new Mandate and Terms of Reference
 - The **ongoing participation** of Regional Harmonization Initiatives (RHI)
 - Greater **transparency**

Regional Harmonization Initiatives

- **APEC**
 - Asia-Pacific Economic Cooperation
- **ASEAN**
 - Association of the Southeast Asian Nations
- **GCC**
 - Gulf Cooperation Council
- **PANDRH**
 - Pan American Network for Drug Regulatory Harmonization
- **SADC**
 - Southern African Development Community

Thank you for your
attention

Quality: Q8 (R1)

Haruhiro Okuda, MHLW (NIHS)
Topic Leader

Abstract

Preliminary presentation slides submitted as abstracts are omitted.
On-site presentation slides are attached below.

Questions and Answers


Tominaga: We have a presentation by Dr. Jean-Louis Robert, and I see that there is a major trend that is progressing there. What is the ultimate goal that you are trying to reach? Can you comment on that?

Okuda: Well, not only the overall goal but also what the quality is designed to achieve, I think will be presented by the next speaker, Dr. Robert. Therefore, I would like to say here that pharmaceutical products have to be products which can be taken by the patients safely and securely, and we have to always ensure their quality and also have to endeavor to enhance the quality. The ultimate goal is to build up the system to assure it. The production activity of drugs is maintained for many years and new technologies are being invented constantly for the period. If such new technologies would be properly incorporated into their production, more appropriate quality products could constantly be produced so as to realize safety and efficacy of products. If you would be successful, and then you might be able to reduce the cost as well. In order to accomplish that, continual improvement is a key concept that would enable us to reach such a goal. So through such activities, it is essential to supply safe and secure products, and that is the main target which is included in guidelines from Q8 to Q10.



ICH Tokyo Symposium:
Hot Topics and
Influence on Asia

Quality: Q8 (R1)
Q8(R1): 製剤開発 補遺

Haruhiro Okuda, Ph. D
National Institute of Health Sciences
MHLW
November 2, 2007




**Q8(R):
Reached Step 2
at YOKOHAMA
ICH Meeting**



**New vision and ICH Quality
Guidelines Q8~Q10**


A harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to risk management and science

➔ Q8: Pharmaceutical Development
Q9: Quality Risk Management
Q10: Pharmaceutical Quality System




Objective of Q8

- To describe contents for the 3.2.P.2 (Pharmaceutical Development) section in the ICH M4 Common Technical Document (CTD)
- To provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management to the development of a product and its manufacturing process.



**Pharmaceutical development
study: Baseline approach**

- At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified.
- Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.



**Pharmaceutical development:
Enhanced approach**

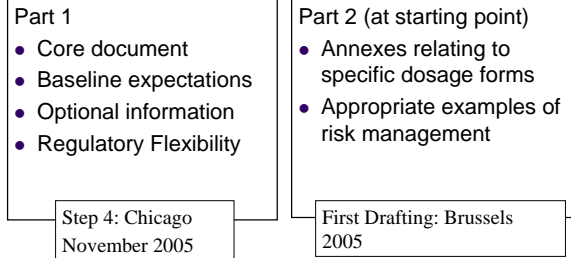
- In addition, applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters.
- This scientific understanding facilitates establishment of an expanded design space.
- Opportunities exist to develop more flexible regulatory approaches,



Examples of more flexible regulatory approach

- Risk-based regulatory decisions (reviews and inspections)
- Manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review
- Continual improvement
- Reduction of post-approval submissions
- Real-time quality control, leading to a reduction of end-product release testing

Structure of Q8



Former objectives of Q8(R)

- Solid oral, liquid oral, parenterals
 - Focus on exemplifying Quality by Design concepts to enhance product and process understanding
 - References to the opportunities to use relevant tools from Q9
- Ver.4

- Illustrative examples of acceptable pharmaceutical development approaches
 - Solid oral
 - Baseline vs enhanced approach
- Ver.5

Evaluation of Ver.5

- Current Pharmaceutical Development: Continuum practice between baseline and enhanced approach
- Obsolete; too prescriptive
- Need more explanation on QbD

Focus on

- Quality by Design
- Terms and Definitions including examples
- Glossary

Objectives of Ver.7 (Current version)

- To provide further clarification of key concepts outlined in the core guideline
- To show how concepts and tools (e.g., design space), as outlined in the core Q8 document, could be put into practice by the applicant for all dosage forms
- To describe the principles of Quality by Design (QbD), and the use of Quality Risk Management (QRM)

Table of Contents (Step 2)

1. Introduction
2. Elements of Pharmaceutical Development
 - Target Product Profile; Critical Quality Attributes (CQA); Linking Material Attributes and Process Parameters to CQAs – Risk Assessment; Design Space; Control Strategy; Product Lifecycle Management and Continual Improvement
3. Submission of Pharmaceutical Development and Related Information in CTD Format
4. Glossary
 - Appendix 1 and 2.

Quality by design (QbD):

High Level Definition

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

Examples of points to be discussed in Yokohama

- Reference to API or analytical procedures
- Non-predictive design space (DS)
- Relation between proven acceptable range and DS
- Critical process parameter (CPP)
- Lifecycle management on DS
- Definition of critical, control strategy
- An adaptive process step (a step that is responsive to the input materials) to assure consistent product quality

Approaches to Pharmaceutical Development

- In all cases, the product should be designed to meet patients' needs and the intended product performance.
- Strategies for product development vary from company to company and from product to product.
- The approach to, and extent of, development can also vary and should be outlined in the submission.
- An applicant might choose either an empirical approach or a more systematic approach to product development.

Design space (Core Guideline)

- The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.
- Working within the design space is not considered as a change.
- Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.
- Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Selection of variables for establishment of design Space

The risk assessment and process development experiments:

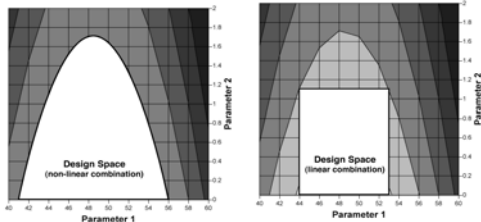
- can lead to an understanding of the linkage and effect of process inputs on product critical quality attribute (CQAs)
- help identify the variables and their ranges within which consistent quality can be achieved.

These input variables can thus be selected for inclusion in the design space

Defining and describing a design space in a submission

- A design space can be defined in terms of ranges of input variables or parameters, or through more complex mathematical relationships.
- It is possible to define a design space as a time dependent function or as a combination of variables such as principal components of a multivariate model.
- Scaling factors can also be included if the design space is intended to span multiple operational scales.
- Analysis of historical data can provide the basis for establishing a design space.
- Regardless of how a design space is developed, it is expected that operation within the design space will result in a product meeting the defined quality attributes.

Illustrative examples of presentation of design space



Design space for granulation parameters, defined by a non-linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

Schedule

- Translation of Q8(R) into Japanese
- Public consultation
- EWG reconvenes late 2008 to reach step 4

Thank you for your attention

Quality: New Paradigm

Jean-Louis Robert, *EU*
Rapporteur

Abstract

The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use was born in April 1990 at a meeting in Brussels. Since then, a lot of progress has been made.

In the Quality area, the following guidelines have been drafted in order to ensure robust protection of public health through quality: Technical oriented: Stability (Q1), Analytical validation (Q2), Impurities (Q3), Biotech series (Q5), Specifications (Q6), Pharmacopoeial Harmonisation (Q4); Format oriented: Common Technical Document (M2); Technical and conceptual oriented: Pharmaceutical Development (Q8); System related: Good Manufacturing Practice of APIs (Q7A), Quality Risk Management (Q9), Pharmaceutical Quality System (Q10) (step 2).

In Brussels 2003, after a long discussion, the following vision on quality has been agreed on:

Pharmaceutical Quality – A New Vision

“ Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science.”
Brussels July 2003

Q8: Pharmaceutical Development (step 5)
Q8 (R): under discussion
Q9: Quality Risk Management (step 5)
Q10: Pharmaceutical Quality System (step 2)

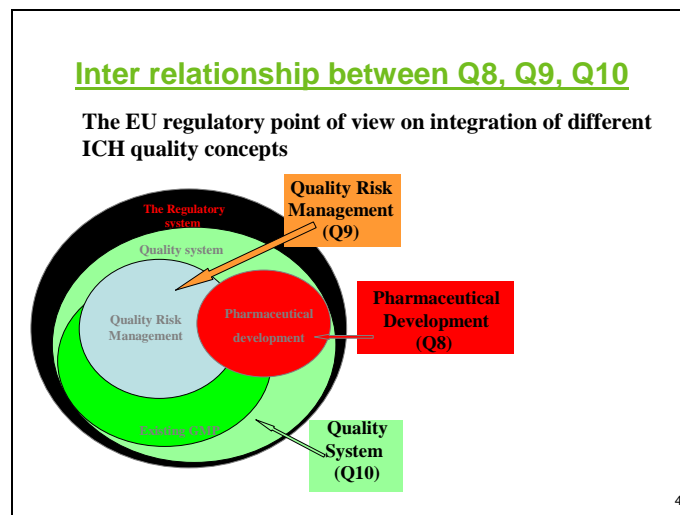
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This new vision or paradigm considers the medicinal product during its lifecycle, i.e. starting from development through technical transfer to routine manufacturing, emphasises on a better product and process understanding and on deriving specifications from this understanding. The whole should be achieved by having a more systematic approach to development, by using risk management tools and by working within a Q10 type quality system.

Q8 has defined several concepts like PAT, design space, real time release, control strategies, systematic approach to development. If Q8 addresses the drug product, experts agree, that the same principles and concepts described there, are also applicable to the drug substance, both chemically and biotech derived. It is rather the complexity of the product than the type of product itself which will impact implementation.

The presentation will address all these different principles and/or concepts and also the opportunities which ‘potentially’ can be derived from this new paradigm.

Relationship between Q8, Q9 and Q10



Questions and Answers

Tominaga: So, probably as a starter, looking at your diagrams on the process, the quality by design approach and quality space approach, it is complicated and almost daunting, in my opinion. So my question is, does the quality by design approach automatically increase the regulatory requirements and hence the resources imposed upon the applicant? What do you think about those aspects?

Robert: The question is a little tricky. Personally, I do not think that this will trigger new requirements or that an enhanced level of resources will be required. It always depends on how you look at it. Pharmaceutical development has to be done anyhow, so before a company releases a product onto the market it has to perform pharmaceutical development studies in order to make sure that the product will be of consistent good quality and be meeting performance requirements. If we understand, by “quality by design”, a more systematic approach to development, I am sure that this will help the applicant or the manufacturer, to reach faster the same degree of knowledge. Of course, if one wants to do what we refer to as “achieving enhanced knowledge”, then you will be able, for instance, to establish a design space or to perform real time release. So, if a manufacturer wants to go in this direction, to take advantage of these opportunities, this will require more investment. Short-term you might have to do more investment, but long-term I would say you will also have some benefit from it. To my opinion, I think, that also for the basic or the traditional development approach, a systematic way will lower your cost. If you want to achieve “enhanced knowledge”, it will require more resources, but long-term it will also be of some benefit for the company. So if one makes the balance at the end, it will probably not raise the cost or raise the resources compared to the benefits which a manufacture can get.

Tominaga: Thank you so much. That is a relief for us with fewer resources! Do we have any other questions? In that case, thank you so much, Dr. Robert. In the interest of time, we would like to move on.

ICH Tokyo Symposium: Hot Topics and Influence on Asia Quality New Paradigm

Jean-Louis ROBERT, Ph.D.
European Union
National Health Laboratory, Luxembourg
Tokyo November 2, 2007

Overview

- Reminder: Evolution of ICH quality guidelines
- Pharmaceutical Development Q8, Q8R
- Quality Risk Management Q9
- Pharmaceutical Quality System Q10
- Conclusions

Reminder

- Objective of ICH:
Technical and scientific harmonisation between Japan, Europe and USA.
- ICH Quality Topics so far
 - Scientific/technical guidelines:
stability, method validation, impurities, specification, Q5 series (biologicals)
 - System oriented: GMP for APIs
 - Structure: Common Technical Document

Pharmaceutical Quality: A New Vision

“ Develop a harmonised pharmaceutical **quality system** applicable across the **lifecycle** of the product emphasizing an integrated approach to quality **risk management** and **science**.”

Bruxelles July 2003

- Q8: Pharmaceutical Development (step 5)
- Q8 (R): under discussion
- Q9: Quality Risk Management (step 5)
- Q10: Pharmaceutical Quality System (May 07, step 2)

Pharmaceutical Development

- Quality cannot be tested into products; i.e., quality should be built in by design.
- The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.
- The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls.
- Information from pharmaceutical development studies can be a basis for quality risk management.

Pharmaceutical Development

- At a minimum approach
- Enhanced approach
 - Opportunities to be gained (design space, real time release)
- The regulatory process will be determined by region.
- New EU publication on Variation Regulation:
 - Public Consultation Paper (Nr 2)
“Better regulation of Pharmaceuticals.
Towards a simpler, clearer and more flexible framework on variations”
 - Draft regulation version 24 October 2007.

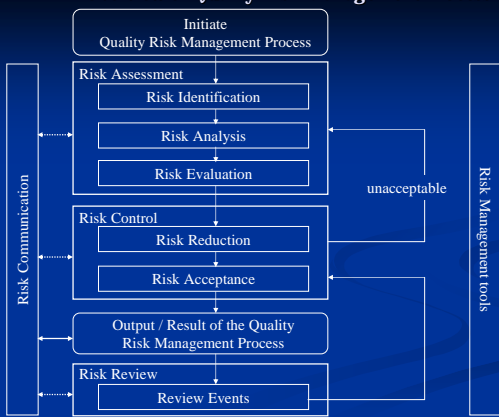
Pharmaceutical Development

- Quality by design
 - Systematic approach to development that begins with predefined objectives and emphasises product and process understanding and control, based on sound science and quality risk.
 - A more systematic approach to development may include, for example, incorporation of *prior knowledge*, results of experimental studies using *design of experiments*, *use of quality risk management*, and *use of knowledge management* (see ICH Q10) throughout the *lifecycle* of the product.

Pharmaceutical Development

- A systematic approach will facilitate the process to achieve quality and should automatically generate more knowledge.
- Not necessarily new requirements:
 - Pharmaceutical development has anyhow to be done
 - The level of development will depend on the complexity of the process and product and on the opportunities chosen or wanted by the applicant.

Overview of Quality Risk Management Process

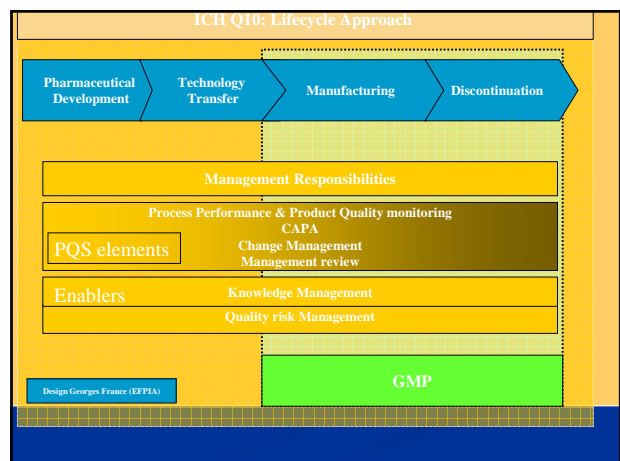


Fishbone diagram as a QRM tool



Q10: Pharmaceutical Quality system

- Pharmaceutical Quality System: Management system to direct and control a pharmaceutical company with regard to quality (Q10 based upon ISO 9000-2005)
 1. Introduction, Scope, Objectives
 2. Management Responsibility
 3. Continual Improvement of Process Performance and Product Quality
 4. Continual Improvement of the Pharmaceutical Quality System
 5. Glossary
 - Annex 1: Potential Opportunities for Science and Risk Based Regulatory Approaches



Definition of Product Lifecycle (Q10)

Development	Technology Transfer	Manufacturing	Product Discontinuation
<ul style="list-style-type: none"> - Drug substance development - Novel excipient development - Formulation development (including container/ closure system) - Delivery system development (where relevant) - Manufacturing process development and scale-up - Analytical method development 	<ul style="list-style-type: none"> - New product transfers from Development to Manufacturing - Transfers within or between manufacturing and testing sites for marketed products 	<ul style="list-style-type: none"> - Procurement of materials - Provision of facilities, utilities and equipment - Production (including packaging and labelling) - Quality control and assurance - Release - Storage - Distribution (excluding wholesaler activities) 	<ul style="list-style-type: none"> - Retention of documentation - Sample retention - Continued product assessment and reporting

Continual Improvement of Process Performance and Product Quality

Four elements:

- Process performance and product quality monitoring system
- Corrective action and preventive action (CAPA) system
- Change management system
- Management review of process performance and product quality

These elements should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages

e.g. Monitoring

Development	Technology Transfer	Manufacturing	Product Discontinuation
<p>Quality risk management and monitoring conducted throughout development to establish a control strategy for manufacturing</p>	<p>Monitoring of scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Monitoring of transfer and scale-up activities can be useful in further developing the control strategy</p>	<p>A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas (knowledge management)</p>	<p>Monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.</p>

ICH Satellite Meeting (Sept. 27/28, 2007)

- Common meeting between chem. and biotech experts
- Issues identified as crucial for a common understanding:
 - Systematic approach to pharmaceutical development (better than Quality by design)
 - Quality Risk management
 - Pharmaceutical Quality System
 - Control strategy(ies)
 - Design Space
 - Real Time Release
 - Lifecycle approach

ICH Satellite Meeting (Sept. 27/28, 2007)

- All these concepts/principles were found acceptable for both the product and the active substance (chemical + biotech);
- The application of these principles are depending on the **complexity** of the molecule rather than of the type of the molecule itself;
- Focusing on enhancing the knowledge of the product and the process for ensuring quality and away from any specific terminology.

ICH Satellite Meeting (Sept. 27/28, 2007)

- Other issues found important:
 - Information needed in an application file
 - Basis for releasing a product on the market
 - Communication
- Preparation of a guideline on APIs (chemical and biotech origin, S2 of CTD-Q)

Recommendation by the participants and accepted by the Steering Committee (31 October 2007).

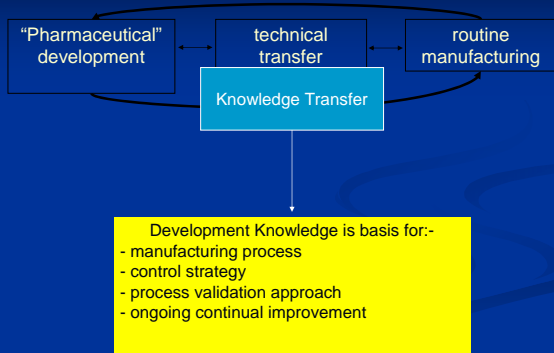
Implementation Q8, Q9, Q10

- Creation of an implementation Expert Group decided by the Steering Committee (31 October 2007).
- Issues to be addressed:
 - Technical issues & related documentation
 - Additional implementation issues: influence on existing ICH guidelines
 - Communication and training
Q&A, briefing packs from ICH, external collaboration, workshops

Conclusion

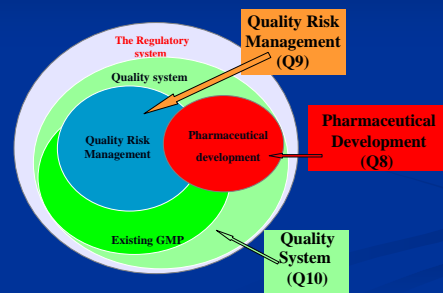
- The new Paradigm to Quality is based on science, risk management tools and the establishment of an efficient Quality System.
- An integration of these three elements should enhance the process for ensuring quality and facilitate continual improvement.

Lifecycle Goals



EU Regulators Vision on ICH

The EU regulatory point of view on integration of different ICH quality concepts



M2

Andrew Marr, EFPIA
Rapporteur

Abstract

Preliminary presentation slides submitted as abstracts are omitted.
On-site presentation slides are attached below.

Question and Answers

Tominaga: So as to the items being worked in your IWG, the number of tasks that you shoulder is so large, and the eCTD alone is no small task. Do you have any idea about the future of M2, especially in terms of eCTD?

Marr: Yes, if you saw on my slide, I had version 3.3 on one slide that became version 3.2.1 on another slide. We were originally intending to progress a minor version that involved a technical change that would involve costs to applicants and regulators to implement. There was also a question as to whether that was going to be value for money to make that change. Coupled together with the knowledge that, again, the FDA had got exactly the same problem with the eCTD, in that it needs to work with electronic submissions for medical devices and veterinary medicines, and wants to have one standard. So it needs a new major version. By law, it now has to deliver the ability to do two-way communication by the end of 2012. So that is why we were looking at this question: If we were going to do a minor version that was going to cost us, and then we were going to have to do another version that would cost us to implement, the next major version, then can we minimize this change of 3.3.2?

We agreed to go two ways. One is to go forward, plan for the next major version, which in my personal opinion, will almost certainly be within the SDO processes. We are gathering the requirements to allow us to know what it is that we need to take forward. Then, we have gone back and said, "Let's do with some small, narrative changes that help with implementation at the moment." So M2 is the group that has the knowledge about those requirements, and I am sure that it will work to create those. But we are learning all the time, on these SDO processes – the ICSR and the vocabularies – and we want to make sure that we use M2's resource efficiently. I think we can learn to do perhaps more in the SDOs than actually doing it all inside ICH, doing too much work in ICH, and having to redo things in the SDOs. It is a matter of getting that balance right. So we are certainly looking to reduce the resources that we are utilizing inside M2. But at the moment they are setting up these processes, monitoring and making sure it all works to ICH's satisfaction. It is taking a large amount of resources, which hopefully as we move on to the next project, will be much reduced. Thank you.

Tominaga: Thank you. Do we have any questions? Yes, Dr. Molzon?

Molzon: Andrew, maybe you could talk about the benefits to your company of the transition to electronic submissions. In the FDA, the eCTD has been very helpful to the review staff, because they are able to access documents quicker, and the consistent format of the CTD has

really provided for more consistent and efficient reviews. I thought you could discuss the company's benefits.

Marr: OK, I will talk about my company which is GlaxoSmithKline, because that is obviously what I know. The benefits to us have been a large amount in the U.S., because it is electronic-only. We do not need to ship hundreds of thousands of pages to FDA. We can now actually stream it electronically directly into the agency, get the acknowledgment immediately, and in five minutes it is on the reviewer's desk. So that, to us, in terms of speed and cost of delivery, is great. It also gives us an internal record, a complete record, available to us to refer back to and et cetera. So it is a very good history of the product. From a European perspective, we still are caught with this having to provide paper. So we are getting benefit from access to information, but we have not yet reduced the cost. But all of the agencies are moving towards the electronic-only approach. Our experience in Japan is relatively large, compared with most companies. I think what we are seeing there is fewer benefits at the moment, because it is being used as an electronic version of paper. At least, that is my opinion. It is not, perhaps, using the opportunities that electronic information, and processing it differently, might have. The fact that the CTD has got a common structure all the way across is of great help, because it allows electronic reuse of information globally. That, in itself, has brought benefits. So CTD has brought some and eCTD has brought us much more. But it is not yet evenly distributed between regions. Thank you.

Tominaga: Thank you. Any other views on the use of the eCTD? Its benefits or its downside, perhaps from any end users? Then, the last question... Are there any ideas regarding more enhancement of the use of the eCTD?

Marr: There are some new requirements that will come out of this major review. I think it is important to look at the opportunities that it provides – things like two-way communication. At the moment, we manage the information being sent to the agency, and then we get back some paper or an e-mail or something, and it is not able to be integrated. I think there is much to be done. It is not about how you review. You are not expected to do a different scientific review. But I think some of the functionality could be supported by improved specifications, to give more opportunity to the agencies to do things better, to do things differently. Yet, it might not be much more difficult for the applicant to do that if we know what the agencies want to facilitate in their business process.

Tominaga: Thank you so much. Increased functionality and increased efficiency. That is a good message when we are increasing the use of eCTDs. Thank you so much, Dr. Marr.

M2

Andrew Marr, PhD
EFPIA

ICH Hot Topics
2 November 2007
14.20 - 14.55

Outline of Presentation

- M2 Responsibilities
- Current status of eCTD
- Use of Standards Development Organisations (SDO) to develop ICH-related standards
 - Rationale
 - Status of Current Projects

M2 Responsibilities

- Facilitate international electronic communication by evaluating and recommending, open and non-proprietary - to the extent possible - Electronic Standards for the Transfer of Regulatory Information (ESTRI) that will meet the requirements of the pharmaceutical companies and regulatory authorities.
 - Recommendation of Standards
 - General - Gateway
 - Physical Media
 - File Format
 - Information Transfer
 - Electronic message for the Individual Case Safety Report (ICSR)
 - Electronic Common Technical Document (eCTD)
 - New standards at the Steering Committee's request

eCTD

eCTD

- Status of current specifications
- Implementation status regionally
- Change control process
- CTD-Q related issues
- Specification for v3.3.3
- Next major release

Current Specifications

- CTD – Revised 2002
 - Organisation & Granularity Annex – Revised 2003
- No current plans to modify CTD
 - Steering Committee has just endorsed the re-establishment of CTD-Q IWG to address eCTD Change Requests
 - Potential for a series of CTD-Q-related Q&As in 2008
- eCTD
 - Current specification v3.2 – issued 2002
 - + Study Tagging File v2.6 – issued 2004 (implemented only in US)
 - Regional specifications in support of Module 1 in US, EU, Japan & Canada

eCTD Implementation - Scope

- Submissions for Human Pharmaceuticals in
 - USA
 - NDA/BLA
 - ANDA
 - IND
 - DMF
 - EU
 - MAA
 - Japan
 - Japan NDA (excluding applications for generic products)
 - Canada
 - NDS

eCTD Implementation

Region	Status	Type	Applications	Sequences
USA	<ul style="list-style-type: none"> •CDER – eCTD only e-submission format from 1 January 2008 •CBER – eCTD accepted. Other guidances (eBLA, eIND) still in operation 	IND NDA ANDA BLA DMF FDA Internal	501 264 358 48 112 180 1448	8518 3946 1110 1813 147 319 15853
Europe	<ul style="list-style-type: none"> •eCTD to be accepted in lieu of paper in all Member States by 31-12-2009 –Centralised e-only from mid-2008 (Barge) •eCTD currently accepted by most agencies •Non-eCTD submissions accepted in all agencies 	Centralised National/ Mutual Recognition/ Decentralised	98 (~30% of products) Varies significantly between agencies 0 – 100+ >2800 across 17 member states	400
Canada	eCTD accepted in lieu of paper for Modules 3,4 &5	NDS & SNDS ANDS & SANDS Notifiable Changes	86	366 187 48 591
Switzerland & Australia	Have initiated eCTD projects to implement in 2009			

eCTD Implementation - Japan

- Different model for eCTD adopted in Japan
 - Much narrower scope – each submission is a different eCTD
- Most submitted as reference applications (e.g., electronic support of paper application)
- MHLW statistics as of September 2007

Original Applications	5 (10 sequences)
Reference Applications	47 (62 sequences)
Total	52 (72 sequences)

eCTD Change Control Process

- Any individual, organisation or party can submit a Question or Change Request to the ICH M2
 - Urgent
 - none received to date
 - Routine
 - 171 received since January 2003
 - 13 reviewed in Yokohama (September 2007)
- Each is carefully reviewed – could lead to
 - Approved
 - Approved for Q&A
 - Approved for Specification Change
 - Assigned to sub-group for testing
 - Deferred
 - Rejected
 - Out of Scope
- Spreadsheet re-issued after every ICH meeting
- Specification change
 - Minor version release
 - Major version release

CTD-Q-related Change Request

- Increasing number of CTD-Q related questions/change requests
 - Due to greater implementation of eCTD globally
 - Increasing experience of dealing with lifecycle submissions
- Joint group actioned in Yokohama to
 - Recommend how to address change requests
 - Proposed re-establishment of CTD-Q IWG
 - Resolutions to be limited to
 - CTD-Q Q&As
 - Joint CTD-Q/eCTD Q&As
 - Minor changes to the eCTD specification

eCTD v3.2.1

- Release of minor update to specification being progressed
- Key changes proposed are :
 - Incorporation of approved change requests
- Step 4 – target February 2008
- Regional implementation to follow

Next Major Release

- A number of proposed changes will require a major update to eCTD specification
 - E.g. Two-way communication, interoperability with other product types, enhanced metadata
- In Yokohama, Steering Committee has endorsed the initiation of definition of the business requirements for the next major version
 - Plans are in development

SDO Initiatives

SDO Initiatives

- Background
- Proposal
- Pilot projects
 - Rationale for selection
 - Current status
- Key issues being addressed

Drivers

- US Presidential mandate to utilise standards and bring about a joined-up health-care service
- FDA also responsible for Veterinary Medicines, Medical Devices, Food Additives
 - Also need e-submissions & adverse event reporting
 - Wishes to have a single standard that can support all

Initial FDA Proposal

- Cease to initiate message specifications within ICH alone
- Collaborate with Standards Development Organisations to develop what ICH needs – but in a wider context
- Move current standards initiatives into an SDO process
- Considered by Steering Committee in November 2005
 - M2 actioned to develop options for how standards could be developed for ICH

Options Considered

- Option 1 – no change to M2
- Option 2 – M2 processes change
 - 2a – M2 formalises processes
 - 2b – M2 becomes an SDO
 - 2c – Process involves SDOs but M2 responsible for testing
 - 2d – M2 provides facilitation between EWG and SDO
- Option 3 – Eliminate M2
 - 3a – Admin group to negotiate with SDOs
 - 3b – EWG works directly with SDO
 - 3c – ICH no longer develops message standards

Selected Process

- Steering Committee agreed to adopt the use of SDOs as the method for the development of message specifications
 - 2c – Process involves SDOs but M2 responsible for testing
- A number of 'critical conditions' should be met
 - An assessment of the critical conditions and a risk mitigation plan was considered and adopted by the Steering Committee
- Steering Committee agreed to progress standards initiatives with SDOs as an evaluation of the process

Standards to be Initiated

- E2B(R) – ICSR Message revision
- M5 - Data elements and standards for drug dictionaries
- Both projects closely related and therefore logical to progress together

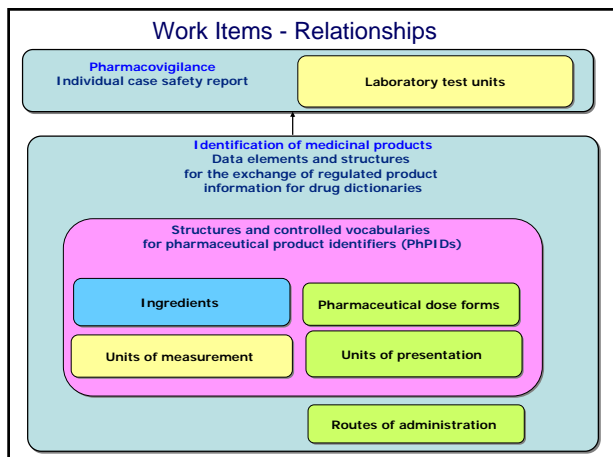
ISO/CEN/HL7 'Joint Initiative'

- A joint initiative has been established between three major standards bodies in the health care area
 - ISO Technical Committee 215
 - CEN Technical Committee 251
 - Health Level 7
- To collaborate on the development of standards rather than compete
- Charter has been agreed between SDOs
- Detailed working practices still to be establish

ICH & ISO

- ICH is now a Liaising Organisation with ISO TC 215
- Allows the proposal of New Work Items
- E2B(R) and M5 requirements proposed as 7 New Work Items to ISO
- Agreed by Joint Initiative that ISO would lead these items
- Two Task Groups established
 - Pharmacovigilance
 - Medicinal Product Identification

Work Items - Relationships



ICH-proposed New Work Items

- All 7 items have passed ballot
- Comments received on all which will need to be resolved
- Additional resources nominated from countries eg. Korea, Australia, Turkey, Malaysia
- ISO confirmed that is critical that a strong linkage between the regulatory and clinical worlds will be created and sustained

ISO - ICSR

- Have agreed scope to cover all types of products
- First phase is human pharmaceutical medicines
 - Expertise is available already
- Agreed multi-part standard to be produced
 - E.g. Part 1 – Overview of structure applicable to all types of product types
 - Part 2 – human medicinal products
 - Part 3 – medical devices
 - Part 4 – veterinary medicines
 - Etc.
- Full gap analyses of HL7 standard and draft JPMA schema being undertaken
- Task Group meeting held pre-ICH in Yokohama

ISO - Vocabularies

- ICSR-related : Laboratory test units for the reporting of laboratory results
- Medicinal Product Identification
 - Med ID
 - Ingredients
 - PhPID
 - Dose Forms, Units of Presentation & Routes of Administration
 - Units of Measurement
- Discussed the adoption, adaptation or development principles
- Identified potential sources of terminologies
- Key issue for ICH is whether a single ISO-endorsed terminology will be identified to which regional terminologies may need to be mapped

Key Issues to be Addressed

- Establishment of the working practices of the Task Group
 - in relationship with ISO, CEN, HL7 and those interested in establishment of international standards
- Clarification of document set to be produced
 - Within the SDO processes
 - Within ICH
- Clarification of balloting process in ISO & HL7
- ICH consultation process
 - SDO documents
 - ICH documents
- ICH testing process
- Definition of evaluation criteria
 - To assess progress, performance and results of initiatives
 - Will be leveraged for continuous process improvement

M3 (R2)

Joseph J. DeGeorge, *PhRMA*
Rapporteur

Abstract

Preliminary presentation slides submitted as abstracts are omitted.
On-site presentation slides are attached below.

Question and Answers

Tominaga: As to the expansion of the scope of the guidelines, there are issues such as abuse, liability and such things, and also initial dosage setting, of course that is on the consideration as to that monoclonal antibody incident. Could you elaborate a bit more on these newer movements in your working group, please?

DeGeorge: As for the new topics that we are taking up, there was a lot of interest from the pharmaceutical representatives in the working group, to talk about the combination drug testing. This is because the world is moving to a lot of combination products as lifecycle extension approaches greater value. As for the guidance that is out there, I do not believe the European guidance gives any recommendations on timing. The FDA guidance actually gives recommendations that are very difficult to understand, in terms of the difference between marketed products and products in development, particularly as where one product is in development and another is marketed, and this is further complicated when by early versus late-stage development candidates. So we need to get more clarity around what the recommendation really is going to be, for a global process. Again, we are trying to make global drugs we can get globally approved. The problem is that, absent any agreement – or even, in some cases, absent guidance from the regions – it is very difficult for the regulatory authorities to come to a consensus about what makes sense on timing. We also do not want to make the M3 guidance be a guidance which now creates requirements for regions where certain requirements do not exist. So we are working through a lot of these difficulties, in terms what is the agreed language and how do we approach that to say “it should be done here” (for this region but not that region), if it needs to be done at all... One experience to date is that where we have had about four lines in the guidance on one of these topics in the guidance before, we have spent the entire morning and half of the afternoon discussing those four lines. By the end of the day we now have three paragraphs on that section. So adding these topics to the guidance has and will extend our timeline. But they are critical particularly on, as I said, something like combination testing.

Tominaga: So, again, might there be some spin-off from your working group to another guideline, like the one you mentioned? What about the possibility of spinning off some of the work, some guideline starting from your EWG? Or are you going to do it by yourself forever?

DeGeorge: If at the end of this we determine there is a lot of non-harmonized guidance that we have to capture, the Steering Committee ought to look at those guidances and see if there

is not a reason to drive harmonization on those topics. If this was done sooner, it might make our job revising M3 easier, but I do not think the ICH process can get a new guideline done before June, when we would like to be signing off on M3.

ICH M3 Revision: A status update

Joseph J. DeGeorge,
Safety Assessment, Merck & Co

Scope of ICH M 3 Guidance

- M 3 Guidance was intended to attempt to provide a unified approach to the timing of all non-clinical studies to support global clinical development
- M3 Guidance was not intended to define which studies were needed for specific drug products and did not specifically apply to biologics therapeutics
- M3 Guidance was at the time of its inception the only ICH guidance which did not produce a harmonized approach, but denoted regionally specific recommendations

Need for M 3 Guidance Revision

- While M 3 provides the “timing template” for global development, it is not global:
 - Currently Clinical Trials are much less frequently conducted as regional trials to support global marketing applications
 - To shorten development times simultaneous multiregional trials are becoming the norm
 - The previously non-harmonized regional recommendations of M3 have now become a burden for global drug development, particularly where they exist without scientific basis
 - Major burdens needing to be addressed in M3 Revision are
 - Duration of toxicology testing in relation to clinical duration and phase
 - Duration of nonrodent chronic toxicology studies
 - Toxicology studies needed to support inclusion of WOBB

Need for M 3 Guidance Revision

- Since ICH M3 was finalized, additional testing recommendations have been developed.
- ICH M3 does not cover these new recommendation
- Some of these guidances have no or unclear timing recommendations, or provide conflicting recommendations with those of other regional guidances
- New multiregional and ICH guidances needing to be addressed include:
 - ICH S6 Immunotoxicology
 - EU and FDA Juvenile animal testing to support use in pediatrics
 - FDA and EU and Combination Drug product toxicology testing
 - EU Abuse liability testing
 - Phototoxicity testing

Need for M 3 Guidance Revision

- ICH M3 does not address current clinical development needs and current toxicology understanding in its recommendations
- Exploratory clinical trials are a new approach in the overall drug development process necessitated by the high rate of development failure (>90%) and enabled by the increasing availability and utility of “biomarkers” in understanding drug activity (PK, safety and efficacy).

Need for New Approaches to Development

- Development costs approach \$1 B and 7-10 yrs
- > 90% of compounds entering clinical stage FAIL
- Human genome project has yielded numerous unproven drug targets with greater risk for failure
- Significant advances in chemistry and HTP screens have yielded many more drug candidates
- Public demanding safer, more effective, less expensive medicines
- In vivo toxicology testing is a bottleneck to early human studies
- Traditional clinical “PoCs” come too late and more biomarkers are becoming available

Need for M3 Guidance Revision

- M3 does not address new paradigms in early development
 - There is great interest in these new paradigms and there are several Regional and National Guidances or guidances in planning
 - FDA Exploratory IND Guidance
 - EU Microdosing Guidance
 - Belgium Guidance on support of Exploratory Clinical Trails
 - Japanese and German Health Authority Meetings on Exploratory Clinical Studies
 - ICH M3 guidance could provide a global framework for non-clinical studies to support exploratory clinical paradigms

Need for M3 Guidance Revision

- Misinterpretation, misapplication, and missed opportunities within the context of the ICH M3 guidance have resulted in misuse of non-clinical resources (animal, human and financial).
 - Clarification of the applicability of ICH M3 is necessary:
 - (as a timing document, rather than a studies recommendation document, particularly in the context of biologics and vaccines development)
 - Inclusion of recommendations for cross application of toxicology data rather than conducting additional, stand alone studies to yield more efficient drug development
 - Application of dose ranging studies to support acute toxicity endpoints
 - Combination of endpoints in toxicity studies (Reproductive toxicity endpoints from general toxicology studies, teratology hazard identification from dose-ranging studies, and chronic toxicity studies to address juvenile development issues)

Evaluation of Non-Rodent Chronic Study Duration (acceptability of uniform 9 m design)

- While ICH M3 recommends 9 m non-rodent is acceptable, FDA has many exceptions requiring 12 m
- ICH process in place to evaluate data from nonrodent studies of 3, 6, 9, or 12 month duration since original agreement.
- Approximately 160 study pairs identified
 - Several study pairs not evaluable as inadequate comparative data sets (e.g. only 1month and 12 month results, and 12 month findings not detectable in life)
 - Data indicates some new findings post 6 m
 - No cases identified where 9 m study could be considered inadequate

Evaluation of Developmental Toxicity Exploratory Studies for Use in Risk Minimization

- ICH M3 recommends exclusion of WOCBP in clinical trials absent completion of definitive Development Toxicity studies, except in US if adequate prevention methods are included
- ICH process in place to evaluate data from exploratory and definitive reproductive tox studies to see if significant risks were identified in exploratory studies
- Approximately 240 study pairs identified
 - JPMA data set most evaluable: over 100 study pairs
 - Data indicates reproductive risk can be limited and address for limited scope clinical trials based on appropriately conducted exploratory studies.

Issues Discussed At Yokohama

- Of all the topics mentioned above, none have general resolution with the exceptions of:
 - Use of Dose-Ranging studies to support Acute toxicity endpoints
 - Clarification of the application of M3 as a Timing document, not a studies document, especially for biotechnology products
 - Inclusion of specific non-clinical support for Exploratory Clinical trails (5 approaches are proposed)
- Discussion at the Yokohama meeting focused on:
 - Agreement on the general duration of non-rodent chronic studies
 - Agreement on timing of studies needed to support inclusion of WOCBP
 - Timing aspects of newly developed guidances
 - Finalization of Exploratory non-clinical paradigms
 - Attempt To Reach Agreement on a New Step 2 ICH M3 guidance

5 Different Exploratory Clinical Trial Options Agreed Upon at Yokohama

- 2 Microdosing Options Supported Rodent only testing
- Details of nonclinical study are provided in ICH M3
 - Total human dose of up to 100 ug given in up to 5 dose
 - Useful for human PK and PET
 - Supported by extended acute toxicity test in rodent with 2 sacrifice time points
 - Genotoxicity testing not required
 - Safety pharmacology core battery not required
 - Understanding pharmacological profile is necessary
 - Total human dose of up to 500 ug given in up to 5 doses of no more than 100ug
 - Useful for human PK and PET
 - Supported by 7 day repeat toxicity study in rodent
 - Ames test required
 - No Safety Pharmacology required
 - Understanding pharmacological profile is necessary

5 Different Exploratory Clinical Trial Options Agreed Upon (cont.)

■ 3 (sub) Therapeutic Dose Options

- Single Dose Clinical Studies that allow Evaluation Therapeutic or Sub Therapeutic Range (depending on ICH region)

Supported by extended acute toxicity test in rodent and non-rodent with 2 sacrifice time points using MTD, MFD, or limit dose

Ames Test required

Safety pharmacology core battery required

Understanding pharmacological profile is necessary

Non-clinical TK (AUC) and metabolism data required

5 Different Exploratory Clinical Trial Options Agreed Upon

■ 3 (sub) Therapeutic Dose Options (cont.)

- Dosing up to 14 Days Into Therapeutic Range

Clinical starting dose not more than 1/50th the NOAEL, and top dose not to evaluate clinical tolerance

Supported by 14 day toxicity test in rodent and non-rodent at 10 X or greater of the maximum clinical AUC

Ames Test and assay for clastogenicity required

Safety pharmacology core battery required

Understanding pharmacological profile is necessary

Non-clinical TK (AUC) and metabolism data required

*In Japan, female fertility study or 1 month rodent study is required to include Women of Child Bearing Potential

5 Different Exploratory Clinical Trial Options Agreed Upon

■ 3 (sub) Therapeutic Dose Options (cont.)

- Dosing up to 14 Days Into Therapeutic Range

Clinical starting dose not more than 1/50th the NOAEL, and top dose not to evaluate clinical tolerance

2-wk toxicity study in rodents

Confirmatory study in non-rodent (n = 3), minimum duration of 3 days up to intended clinical duration

Ames Test and assay for clastogenicity required

Safety pharmacology core battery required

Understanding pharmacological profile is necessary

Non-clinical TK (AUC) and metabolism data required

*In Japan, female fertility study or 1 m rodent study for WOCBP

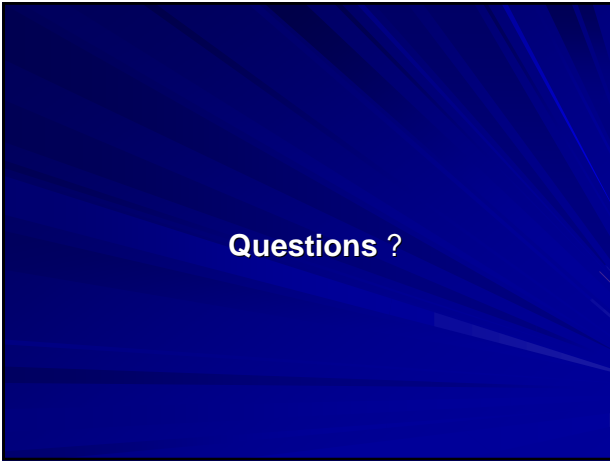
Other Harmonized Topics

- Chronic toxicity testing limited to 9 months in non-rodent
- WOCBP inclusion criteria
 - Up to 2 weeks without teratology testing provided appropriate controls are in place
 - Up to 150 WOCBP for up to 3 m with exploratory teratology studies (GLP still being discussed)
- Acute toxicity testing replace by application of non-GLP repeat dose dose-ranging studies

Other Harmonized Topics

- Timing of newer Toxicity Testing Guidances agreed for inclusion in M3 (phototoxicity, immunotoxicity, abuse liability, and combination drug products)
- General language for initial starting doses in FIM now in guidance

Great progress made, but unfortunately, signoff on Step 2 delayed until June 08!



Chairperson's Closing Comments

Toshiyoshi Tominaga, *MHLW*
Member of the Steering Committee

Everybody, before concluding this particular session, I would like to make a few comments. The latest trends of our quality-related guidelines have been presented. I think you have the feeling that the scope has expanded, and the impact is more far-reaching than ever. I agree with you. The situations about our M guidelines illustrate how grave the effect of ICH guidelines are and how actively electronic development is being incorporated into the process.

As was clear from the presentation, the ICH guidelines currently being made are of very high technical level and with a broad scope. Being a member of the Steering Committee, I am always feeling the challenge.

However, ICH guidelines in themselves are not the goal. We are not formulating them for the sake of having them. As Dr. Okuda aptly pointed out, in the end, or all the way from the beginning to the end, the guidelines are for patients. They are to help deliver better and safer drugs to patients as soon as possible. We have to always bear that in mind as the ultimate goal of the ICH. A part of our effort to achieve this difficult goal has been presented today.

With that, I would like to conclude this session. Thank you very much.

PANEL DISCUSSION
Clinical Development in Asia and ICH:
Implementation of ICH Guidelines in Asian Countries

(1) GCG/Industry

Kohei Wada, JPMA
Member of the Steering Committee

Abstract

In the last 10 years, along with the development and establishment of ICH principles and guidelines, the arena of clinical trials expanded into non-ICH regions including Asia, Eastern Europe, Central/South America, Gulf countries and South Africa. Many clinical trials have been conducted on a multinational basis.

Many of the non-ICH countries adopted or adapted ICH guidelines. In terms of GCP guideline, regulatory authorities of the ICH regions basically accept clinical data from abroad as long as the studies are conducted under local GCP requirements.

However, even a slight difference in GCP guideline sometimes requires additional effort on the industry side. Such differences can be overperformance or underperformance of ICH standards, in either case will be an obstacle for the industry.

When a company plans to conduct clinical studies in non-ICH regions, they (1) cross-check the similarities and differences of the local clinical guideline versus ICH guideline; (2) analyze and interpret the differences and (3) adjust the procedures as needed. Even if there is a big difference in the description of the guideline, sometimes the actual implementation is very similar. On the other hand, even if there seems to be no difference in the guideline, sometimes the actual implementation is different. It takes extra effort for the industry to identify the actual situation, and such effort would not be required if the guideline differences are minimized.

As will be introduced by my other Co-chair Mr. Mike Ward, GCG (Global Cooperation Group) is a sub-committee of the ICH Steering Committee, with the mission to promote ICH principles and guidelines to non-ICH regions, such as APEC, ASEAN, GCC, PANDRH and SADC. The regional harmonization representatives (RHIs) are representing each organization to promote this activity.

GCG activities are very important for the industry to conduct effective global drug development. In this panel, the RHIs from the Asian region (APEC and ASEAN) will discuss the ICH status of their countries with special focus on clinical GCP guidelines.

APEC: Asia-Pacific Economic Cooperation

ASEAN: Association of Southeast Asian Nations

GCC: Gulf Cooperation Countries

PANDRH: Pan American Network on Drug Regulatory Harmonization

SADC: Southern African Development Community

Clinical Development in Asia and ICH: Implementation of ICH-GCP guideline in Asian countries

Kohei Wada
Co-chair, Global Cooperation Group (GCG), ICH

ICH Tokyo Symposium,
Nov 2, 2007

Clinical Trials are now conducted in non-ICH regions

- Arena of clinical trials:
to non-ICH regions including Asia, Eastern Europe, Central/South America, Gulf countries and Africa.
- Many of the countries adopted or adapted ICH guidelines.

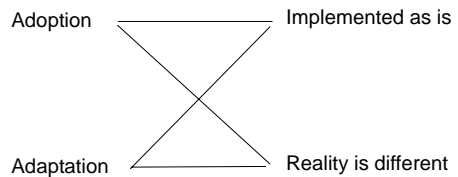
Adopt = そのまま採用

Adapt = 修正して採用

Issue Statement

- Even there is big difference in guidelines, sometimes the actual implementation is very similar.
- On the other hand, even if guidelines look the same, sometimes actual implementation is different.
- A slight difference in guideline or implementation sometimes requires additional effort on the industry side.

Issue statement



Today's Topic

In this panel, the representatives of the Asian region (APEC and ASEAN) will discuss the ICH status of their country focusing on GCP guidelines.

Panelists

K.Wada, JPMA, GCG Co-chair
[Introduction](#)

Mr. Mike Ward, Health Canada, GCG Co-chair
[GCG: Overview and report](#)

Dr. Jianhua Ding, SFDA: APEC representative
[GCP in China](#)

Dr. Dong Sup Kim, KFDA: APEC representative
[GCP in Korea](#)

Dr. Yuppadee Javroongrit, Thai FDA: ASEAN representative
[GCP in Thailand](#)

Clinical Development in Asia and ICH: Implementation of ICH Guidelines in Asian Countries

(2) GCG/Regulator

**Mike Ward, *Health Canada*
*Steering Committee Observer***

Abstract

The Global Cooperation Group or GCG was created in 1999 as a subcommittee of the ICH Steering Committee in response to a growing interest in ICH and ICH guidelines by countries beyond the three ICH regions. Originally formed with the intent of responding to information requests on ICH matters, the GCG has evolved into an active partnership with regional harmonisation initiatives (RHIs) from across the globe that seeks to more effectively facilitate the adoption and implementation of ICH guidelines in non-ICH regions.

Towards this end, the GCG has made substantial progress in promoting a better understanding of both ICH guidelines and the issues associated with their implementation in non-ICH regions, including those surrounding the adoption versus adaption or modification of guidelines.

As training has been identified as a key enabler of successful implementation, the GCG has focussed much of its effort to date on developing a strategy, process and tools that will allow maximum benefit to be derived from the investment of ICH and RHI resources. With these elements in place, the GCG expects to devote more of its collective resources to training and is committed to ensuring the delivery of training that responds to the needs of RHIs and the public health priorities of ICH members.

The GCG has also taken important measures to improve the transparency of GCG operations, identify potential means of encouraging feedback from RHI countries on draft ICH guidelines and promote good harmonisation practices. Further improvements to operations and procedures are under consideration.

It is noteworthy that these accomplishments would not have been possible without the spirit of trust and cooperation that exists between ICH and representatives from fellow harmonisation initiatives – perhaps the most important outcome of all.

ICH Symposium: Hot Topics and Influence on Asia The GCG Story

ICH Public Conference
November 2, 2007
Tokyo, Japan

Harmonization

Harmonization as a *concept* is straightforward

Definitions:

“The adjustment of two or more standards or procedures until they are the same”

– Bruce Farquhar and Alex Donahue

“The establishment, recognition and application of common standards and regulatory measures”

– WTO SPS Agreement

Harmonization in Drug Regulation Occurs at Different Levels

- Technical and science requirements
(ICH: yes)
- Format and content of dossiers
(ICH: yes)
- Assessment and review practices
(ICH: no, but influence)
- Regulations
(ICH: no, but influence)

The Benefits of Using International Standards and Guidelines

- Provide for a scientifically sound means of establishing the quality, safety and efficacy of therapeutic products
- Improve the **transparency, predictability** and efficiency of the regulatory process
- Contribute to reducing unnecessary regulatory burden and promoting industry compliance

The Benefits of Using International Standards and Guidelines (2)

- Promote bilateral and multilateral regulatory communication and cooperation – common regulatory platform
- Facilitate the earlier availability of new therapies while also promoting trade and investment
- Level playing field good for export market

ICH

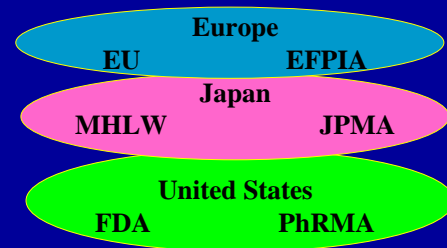
**INTERNATIONAL
CONFERENCE ON
HARMONISATION**

of
Technical Requirements
for the Registration of
Pharmaceuticals for Human Use

A Unique Approach

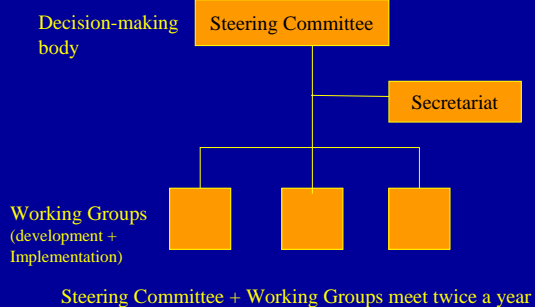
- ICH created in 1990
- Objective: Improve efficiency of development and registration process for *new* drugs
- How: Through development and implementation of harmonized technical guidelines and standards

The ICH World



Observers: WHO, Canada, EFTA

ICH Structure



Accomplishments

- 50+ harmonized guidelines on technical requirements (safety, efficacy, quality)
- Medical dictionary (MedDRA)
- Electronic standards (ESTRI)
- Common format and electronic specification for market applications : CTD and eCTD
- Scope of ICH products now extends over the product life cycle and beyond new drugs

The World Beyond....

- For the first decade of its existence, ICH focused intently on the development of guidelines and standards for use in the ICH "regions"
- However, ICH parties gradually recognized there was a growing interest in ICH products beyond the ICH countries

Why a Growing Interest?

- 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

Global Cooperation Group (GCG)

- Established March 1999 as sub-committee of ICH Steering Committee
- Formed to respond to this growing interest in ICH guidelines
- Name reflective of desire to establish links with non-ICH regions
- Same membership as ICH

ICH Structure



Mandate

- Role: Promote a better understanding of ICH and ICH guidelines
- How: **information-sharing**
 - Information brochures (posted to ICH website)
 - Presentations by GCG members at international meetings
 - Respond to questions
- Note: Not a technical body!

Good intentions, but ...

...Not Very Effective

It soon became clear that a more proactive approach was necessary in order to effectively respond to this growing interest

What better way to understand the interests and challenges of non-ICH regions in using ICH guidelines than by inviting representatives from these regions – and specifically regional harmonisation initiatives - to be part of the GCG?

Important Guiding Principles

- ICH will not impose its views on any country or region – rather, role to facilitate understanding and use of ICH
- The GCG will work with the WHO and other international organisations to achieve its goals
- Recognition that non-ICH countries may not be in a position to utilize ICH guidelines

ICH 6, Osaka, Nov. 2003: An Important Milestone

Endorsement by ICH SC of new mandate and Terms of Reference that called for

- the **ongoing participation** of regional harmonization initiatives (RHIs)
- greater **transparency**

New Mandate and Approach

- Expanded membership:
 - To include (2) ‘**Permanent Representatives**’ from other harmonisation initiatives
 - Criteria established for such participation
- More strategic, proactive approach
- Greater transparency

Criteria for Participation

- Harmonisation initiative engaged in efforts to harmonize drug requirements across a defined group of countries
- Science-based; clear scientific harmonization objectives
- Active – regular meetings
- Possess or develop mechanism to disseminate information on activities with ICH GCG

Regional Harmonization Initiatives (RHIs) now part of GCG

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

Progress Since Osaka

- June 2004, Washington:
 - RHIs invited to attend technical working group meetings and Steering Committee discussions
- May 2005, Brussels:
 - Adopt new GCG mission statement
- June 2006, Yokohama:
 - Endorse strategy on training and capacity-building

New Mission Statement

“To promote a mutual understanding of regional harmonisation initiatives in order to facilitate the harmonisation process related to ICH guidelines regionally and globally, and to facilitate the capacity of drug regulatory authorities and industry to utilise them”

Training: a Key Focus

Framework and mechanisms established:

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

ICH/APEC Q8,Q9,Q10 Workshop: September 13-14, 2008, Seoul, Korea

- First training request endorsed and coordinated through GCG
- Workshop confirmed value of such events in promoting a better understanding of the ICH guidelines and opportunities/challenges associated with their use
- Over 200 participants from 17 countries
- Model for future training workshops:
 - Shared responsibility: APEC, ICH, KHIDI/KFDA
 - Interactive session
 - Representation from across three ICH regions

Additional Training Activities Under Development

- APEC workshops on clinical trial assessment (Bangkok: March, August 2008)
- APEC workshops on GCP inspection (Bangkok: June, November 2008)
- PANDRH (Mercosur region) Quality workshop related to risk-based GMP inspection approach (Sao Paulo: early 2008)

Other Progress to Date

GCG is also actively working on ways to:

- Improve transparency of activities (redesigned webpage, publication of RHI profiles, etc.)
- Identify options for promoting feedback from non-ICH countries/regions on draft ICH guidelines (mini-symposiums, regional pool/network of experts, etc.), and
- Promote awareness of the GCG and ICH in the regions (branded workshops, etc.)

Important New Developments

ICH Steering Committee, at its meeting October 30-31, 2007 in Yokohama, has endorsed proposals to create an 'Expanded GCG' and establish a 'Regulator Forum'

Expanded GCG

- ICH has recognized need for certain changes to current GCG principles and procedures to mirror global face of drug development
- The SC has therefore decided to invite a number of individual Drug Regulatory Authorities to participate in the GCG, even if in some cases not part of an existing RHI

Expanded GCG (2)

- Such participation would be distinct and complementary to participation of official RHI representative/observer
- Expansion of GCG would be based on considerations such as
 - Source of APIs, medicinal products and clinical data for ICH regions;
 - Use or intended use of ICH guidelines

ICH Regulators Forum

- New forum for discussion and sharing of best practices between regulatory authorities on issues related to the implementation of ICH guidelines and impact on regulatory systems
- Discussions would assist in identifying training and capacity needs for action by GCG
- Forum would therefore serve to complement activities and objectives of GCG in promoting a better understanding and use of ICH guidelines
- Principles for participation in forum would mirror those for the expanded GCG

Shared Objectives - Complementary Actions: Facilitate understanding and use of ICH Guidelines

Expanded GCG

Forum for dialogue:
Regulators, RHIs, industry
Translate identified
training needs into action
based on priorities
of non-ICH and ICH regions

Regulators Forum

Forum for discussion
between regulators on issues
related to use of
ICH guidelines and
impact on regulatory systems

New Leadership

- Two co-chairs of GCG, selected from regulatory and industry SC members from different ICH regions
- Two year terms of co-chairs staggered to ensure continuity
- Co-chairs: Mr. Kohei Wada (JPMA)
Dr. Peter Arlett (EU) *new*

Conclusion

- Considerable progress to date in promoting a better knowledge of ICH guidelines and the challenges faced by other regions in their use
- GCG efforts have evolved from information sharing to active dialogue to results-oriented actions
- Important new developments should further accelerate progress
- Spirit of trust and cooperation established between ICH and colleagues from RHIs perhaps most important key to future success

Thank you!

Clinical Development in Asia and ICH: Implementation of ICH Guidelines in Asian Countries

(3) APEC: China

Jianhua Ding, APEC
Member of the Global Cooperation Group

Abstract

China has established its clinical trial requirements since 1998, by which the first GCP was published, and several clinical trial technical guidelines related to pharmaceuticals, bio-product and traditional Chinese medicine were introduced to regulatory practices. Since then, guidelines for clinical trials have been revised by adapting many concepts from ICH guidelines, with some being adopted as regulatory enforcements to the Provisions for Drug Registration. As a new move, more clinical trial guidelines are going to be set up on each main category of diseases.

Many challenges have been emerging in the areas such as the timing for the approval of clinical trials application, documentation requirements for IDN in the part of CMC, IDN and NDA differentiation.

In July, SFDA published its revised Provisions for the Drug Registration and has become effective since October 1. By then, a CTD format of application package can be accepted with the administrative part to follow the requirements by the Chinese Regulation particularly.

China GCP and ICH GCP

- Challenges and Opportunities

Ding Jianhua
Division of Pharmaceuticals
Department of Drug Registration
State Food and Drug Administration, China
2007-11-2, Tokyo

History Briefing

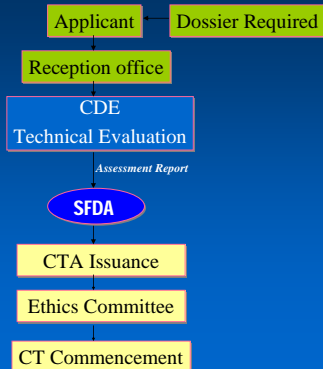
- March, 1998, First China GCP, Published by Ministry of Health
- September, 1999, Second China GCP, Revised and published by State Drug Administration
- August, 2003, Last China GCP, Revised and published by State Food and Drug Administration

Introduction of China GCP

13 Chapters, and 70 Articles

- Chapter 1, Principals
- Chapter 2, Preparations before Clinical Trials
- Chapter 3, the protections of subjects
- Chapter 4, the protocol
- Chapter 5, Investigator
- Chapter 6, Sponsor
- Chapter 7, Auditor
- Chapter 8, Record and report
- Chapter 9, Data management and statistics analysis
- Chapter 10, Investigational product handling
- Chapter 11, Quality Assurance
- Chapter 12, Multi- center clinical trials
- Chapter 13, Supplementary rules

CT Approval Procedure Briefing



Application Dossiers

Part I: General data and Administrative Documents
Part II: Chemical, Pharmaceutical and Biological Data
Part III: Pharmacological and Toxicological data
Part IV: Clinical Data Related

Technical Data Requirement(1)

- Part I
- Certificate of Pharmaceutical Product (CPP) (Import)
 - Patent Certificate (Import)
 - Applicant Authorization Letter (Import)
 - Summary of the research, study, product characteristics
 - Package, label design
 - Insert sheet design
 - Introduction of the R&D
 - others

Technical Data Requirement(2)

Part II

- the Chemical Structure, Physical Characteristics
- Ingredients and Formulation
- Manufacturing Process
- Specifications and Test Methods of API, Finished Product, Excipient, Immediate Materials for Packaging
- Validation of Test Methods
- Quality Analysis Report of 3 Batches
- Stability Data

Technical Data Requirement(3)

Part III

- Principal Pharmacodynamic Study
- Immunological Study
- General Pharmacological Study
- Acute Toxicity
- Long Term Toxicity
- Mutagenicity Test
- Reproductive Toxicity
- Carcinogenicity Test
- Drug Dependence Study
- Animal Pharmacokinetics

Technical Data Requirement (4)

Part IV

- Protocol and Design
- Clinical Trial Data
- Human Bioavailability Study
- Bioequivalence Study

CGCP –ICH GCP Comparison (1)

- The principals and must parts of CGCP are the same with ICH GCP
- Some parts of CGCP are stipulated and enforced by China Pharmaceutical Law by National People's Congress, The Implementation Regulation of Pharmaceutical by State Council, the Provisions for Drug Registration by SFDA
- CGCP published by SFDA as regulation, with more legal enforcement and obligation requirements; ICH GCP is more voluntarily intended.
- Some parts of CGCP are less in details due to its legal orientation. But with many supplementary official explanation, notification for each detailed issue in conforms with ICH GCP

CGCP –ICH GCP Comparison (2)

- Medical institutions are pre-qualified and pre-approved by MOH and SFDA according to the Law. A List of Clinical Trial Medical Institutions is established. 251 Institutions in the List
- Any clinical trial shall be conducted by Investigators from among medical institution in the List only.
- Any trial with the participation of medical institution not in the list, shall be approved by SFDA in advance at case by case bases
- Amendment of protocol up to IRB/IEC approval, and with a notification to SFDA afterwards

CGCP - ICH GCP Differences

- A clinical trial has to be approved and a Certificate of Clinical Trial Approval issued by SFDA, prior to IRB/IEC approval.
- An application for clinical trial approval with strict CMC part requirement
- The establishment of IRB/IEC is required to notify SFDA
- IRB/IEC shall be male and female balanced in proportion
- Record shall be kept for 5 years, ICH is 3 years
- For Bio-product, the investigational products must be tested before its supplying, by SFDA designated official Quality Control Institute

Challenges

- GCP is relatively a new area, investigators lack of experiences
- China regulatory system currently without IND and NDA differentiation in technical dossier, procedure, and timing. Causes delay for clinical trial application
- EC is separately established by each hospitals involving a trial
- Lack of social supportive policy is a bottle-neck for better GCP implementation, such as insurance.

Opportunity

- The new Provisions for Drug Registration is implemented in Oct. 1, 2007 in China
- CTD format of application package can be used first time for China, despite the administrative part
- Must of the test requirement for investigational products are dismissed since Oct. 1
- China regulatory system became more open and transparent , with more international communications, cooperation
- International common practices plays a very important role for the improvement of CGCP

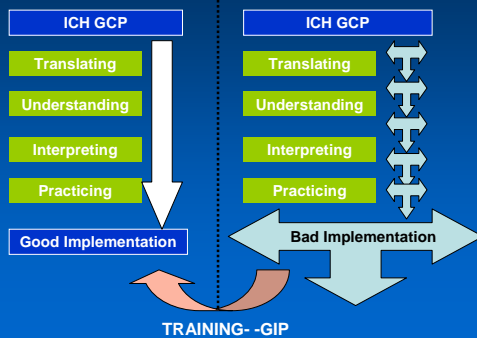
Discussion

- The same parts in wording of GCP might not be interpreted, understood, conducted into the same comprehensive way , by different users during practices
- Is there a sound confine of *Adaptation and Adoption*? If some things are the same in principal, only with the difference in structure of contents, and wording, but in practices everything turns out to be the same.
- There are varies of copies of translation of ICH GCP to different languages. This is a area of mistakes and conflicts between different versions of translation in the same language and between languages.

Suggestion

- How to put ICH GCP to practices by the same manner for each sponsors, investigator, monitor, auditor, is something worth consideration and more important
- The same in content of a Guidelines might not necessarily become the same in understanding and in practices , then *Practical training* is a crucial way for better implementation of ICH GCP

Implementation Model -GIP



Thank you for your attention !
ありがとうございました !



Clinical Development in Asia and ICH: Implementation of ICH Guidelines in Asian Countries

(4) APEC: Korea

Dong Sup Kim, APEC
Member of the Global Cooperation Group

Abstract

KGCP (Korean Good Clinical Practice) was established in 1987 and became the mandatory guidance to any clinical trials in Korea. To harmonize the aim of GCP in ICH guideline E6, which is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials so that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected, we revised KGCP in 2000. Bridging study was introduced in 2001 for the new drug registration, and the IND approval system was introduced as part of the new drug approval system in 2002 for enhancing new drug development and allowing multinational clinical trials easier.

We tried to harmonize ICH guideline E6, to protect trial subjects and safety, to give investigators clear responsibility and to strengthen IRB's function, and we are adapting this guideline to KGCP continuously.

ICH-Tokyo Symposium Nov. 2, 2007


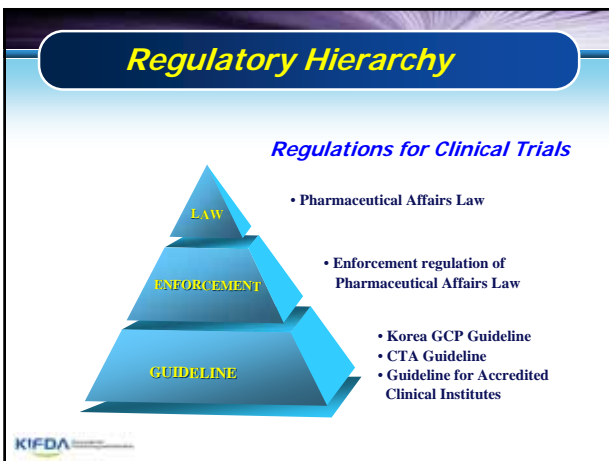
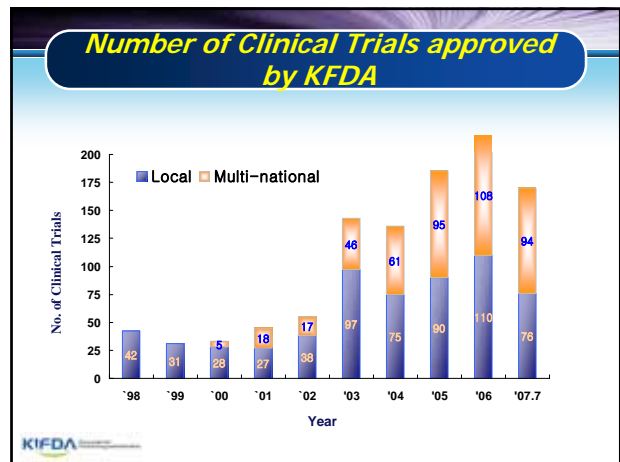
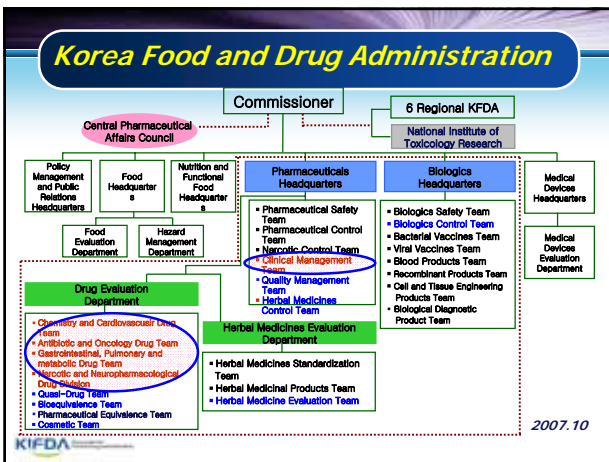
Clinical Development in Korea

Dong Sup Kim, Ph.D.
Director
Drug Evaluation Department
Korea Food and Drug Administration



Contents


- 1 Introduction of KFDA
- 2 Current Status of Clinical Trials in Korea
- 3 Challenges for implementation
- 4 Future changes on Clinical Trials in Korea

History of KGCP

- ❖ Established on December 28, 1987
- ❖ Enforced since October 1, 1995
- ❖ Revised on January 4, 2000
- ❖ Legislation of IND system on August, 2001
- ❖ Preparation of detailed regulations for IND system on December, 2002
- ❖ Introduction of Joint-IRB on January, 2007

- Harmonize with ICH guideline E6
- Clarify the responsibility of investigator
- Reinforce the function of IRB
- Protect the rights and safety of subjects



Major Regulatory Changes (1)

1. Dec. 28, 1987	• Establishment of KGCP (recommendation)
2. Oct. 1, 1995	• Requirement for compliance of KGCP
3. Dec. 12, 1999 (enforced Jul. 1, '00)	• Adoption of the Bridging Concept - Harmonized to ICH guideline E5 - Diverse bridging strategies were required
4. Jan. 4, 2000 (enforced Jan. 1, '01)	• KGCP Amendment for Harmonizing with ICH GCP - Harmonized with ICH guideline E6 - Protect the rights and safety of subjects - Responsibility of investigator

KIFDA

Major Regulatory Changes (2)

5. Aug. 14, 2001	• Establishment of Pharmaceutical Act Article 26-4 (07.4.11 Changed to Article 34) - Require to approval of clinical trial from KFDA - Prohibition for selecting "Vulnerable Subjects" - Protect the rights and safety of subjects * penalty: servitude under 3year (fine under 10 Million Won)
6. Dec. 3, 2002	• Introduction of IND System - Separation between developmental clinical stage and commercial product approval, such as IND and NDA - Participation in international study enabled
7. Apr. 19, 2007	• Providing a guidance for Clinical Trial - prudent review of clinical trials exempt from KFDA approval - Strengthen IRB functions

KIFDA

Essential Elements in Clinical Trials

- Pharmaceutical Affairs Law -

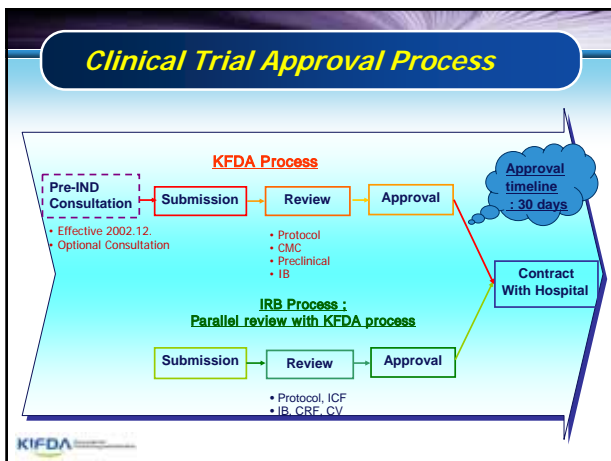
- Protocol approved by KFDA
- Only at the accredited clinical sites
- Qualified investigator
- Protect the right and safety of subjects
- Informed consent before enrollment of subjects
- Investigational drugs

KIFDA

Guidance of Accredited Clinical Institutes

- Purpose
 - To assure the quality of clinical study and institutes
- What are essential to accredit?
 - Appropriate facilities and equipments
 - Pool of personnel to support the clinical study
 - Activities of IRB
 - Education program of GCP
 - Structures and activities to manage the clinical study

KIFDA



Challenges for implementation

- ❖ Qualification of Investigator
- ❖ Importance of IRB review
- ❖ Importance of SOP
- ❖ Need for Clinical Research Resources
- ❖ Need for Regulatory Service from Authorities
- ❖ Need for communication and harmonization with Foreign Authorities

KIFDA

Improvement in Clinical Study Institutes

Hospital	IRB
<p>Improvement in hardware</p> <ul style="list-style-type: none"> Increased number of accredited hospital Major hospitals have specialized clinical trial centers and laboratories 	<p>Improvement in software</p> <ul style="list-style-type: none"> IRBs are well-organized and well-operated in accordance with the KGCP requirements IRBs hold regular training as to KGCP and ICH-GCP for the investigators, pharmacists, CRC and other medical staffs

KIFDA

Improvement in Clinical Trials Staff

Investigator	Clinical Research Coordinator
<p>Improvement in qualification</p> <ul style="list-style-type: none"> Increased opportunities to participate in global study since 2001 and good awareness of GCP Enthusiastic to join in early development stages of new drugs Proficiency in strict regulatory inspection 	<p>Improvement in qualification</p> <ul style="list-style-type: none"> Increased number of research nurses with clinical expertise Major hospitals are able to utilize CRC pools in and out of the hospitals Well-organized and qualified annual trainings for CRCs are available

KIFDA

Future Changes on Clinical Trials

- ❖ IRB management
- ❖ Resource management
 - Support the training course for investigators, CRC, CRA, IRB members
 - Develop the training program for reviewers
 - Keep the transparency of review process
- ❖ Supporting plan for Clinical Centers by MOHW
 - 9 Regional centers designated in 2004-2006
 - Support for Facilities, Operation systems, R&D etc.
 - \$ 0.5 ~ 1 million/center/yr for 5 years
- ❖ Continous harmonization of the regulation with ICH guidelines
- ❖ Encouragement the industries to participate in multinational clinical trial

KIFDA ➤ MOHW : Ministry of Health and welfare

Goal for Clinical Trial Management

KIFDA

Thank You For Your Attention

Tel: 82-2-380-1701, Fax: 82-2-387-7857, Homepage: www.kfda.go.kr

Clinical Development in Asia and ICH: Implementation of ICH Guidelines in Asian Countries

(5) ASEAN: Thailand

**Yuppadee Javroongrit, ASEAN
Member of the Global Cooperation Group**

Abstract

As Co-chair Country of ASEAN-PPWG (Pharmaceutical Product Working Group), as well as a Lead Country on Clinical (Efficacy) Data, Thailand has devoted and put optimal endeavor to comply with ASEAN Harmonization Agreement/Requirement. In this regard, fully implementation of the ICH E guideline, which is the adopted International Technical Guidelines by the ASEAN-PPWG, is our attempt among all.

Dr. Javroongrit will present the Clinical Trial system and situation of Thailand. She will focus on the details of relevant GCP stakeholders, which are the ECs, Investigators, Sponsors and Regulators in particular.

Clinical Trial system and situation of Thailand

by
Yuppadee JAVROONGRIT, Ph.D.
* Head of International Affairs and Investigational Drug Group
Drug Control Division, TFDA, Thailand

The Tokyo ICH Symposium
Marunouchi Hotel, Tokyo, JAPAN
02 November 2007

Good Clinical Practice

Stakeholder

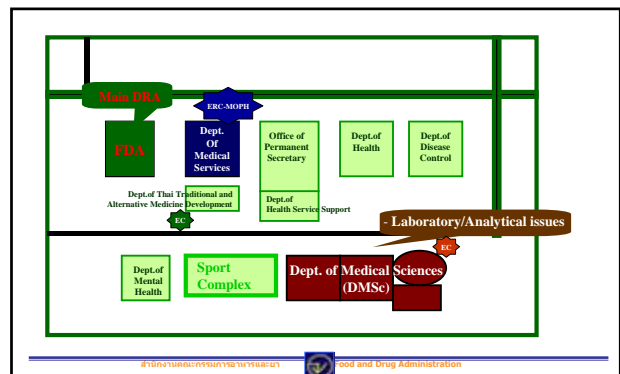
- Ethical Committee (IRB/IEC)
- Investigator
- Regulator
- Sponsor

→ By the *National Seminar !!!*

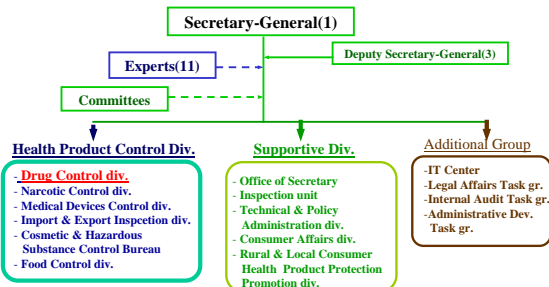
Clinical Trial 'system and situation' of Thailand

Regulator- *the TFDA*

(Thai Food and Drug Administration)



Organization of TFDA



Main Group of Drug Control Div.



Law

- Drug Act, B.E. 2510(A.D. 1967)

Main Responsibility

- Control on *Non-License Drug Product*
- Pre-marketing control (*Registration :- product , premise*)
- Surveillance program on Product Safety
- Surveillance system on Advertisement
- International Affairs regarding P'cals

The current laws and regulations

The Drug Act B.E. 2510 (A.D.1967)

Amendments :-

- Drug Act (No.2) B.E. 2518 (1975)
- Drug Act (No.3) B.E. 2522 (1979)
- Drug Act (No.4) B.E. 2527 (1984)
- Drug Act (No.5) B.E. 2530 (1987)

- Supported by Ministerial – Regulations / -Orders, and Notifications
- Amendment is from time to time

→ working on New Act !!!

Surveillance (1)

- ☉ Type of Surveillance
 - Quality
 - Safety
- ☉ Surveillance on Quality
 - Manufacturers
 - Importers
 - Private pharmacies
- ☉ Surveillance on Safety
 - Uppsala-WHO
 - Report from Professional/Company/Consumer
 - routinely Formal Report from provincial/central Hospitals

Surveillance (2)

- ☉ Regular surveillance of Drug & Advertisement through public media
- ☉ Monitoring at Port of Entries :-
 - 25 port of entries (7 in Bangkok)
 - 2 Minilabs :- Bangkok / Chiang Rai
 - checking documents
 - identify products / chemicals by Minilab at port entries
 - collect samples for analysis

Non-License Drug Product

- for Clinical Trial
- for Conference and Donation
- for prevention / cure Diseases
- of Placebo for Clinical Trial

→be Monitored !!!

by Ministerial Notification #14

Ministerial Notification #14 (A.D.1989)

The drugs, which are intended to import into the Kingdom on following purpose, are exempted from registration;

- Clinical trial/study,
- Analysis,
- Exhibition, or
- Donation

- Authorization NEEDED!
- only to the “rightful Organization/Person”
- need Application + specific Data/Information

Note: Notification = Regulation

TFDA Notification

“Criteria for Importation of Investigational Drugs”

Requirement / Standards

- GMP
- Controlling ‘Quality & Administration’ of imported CT Drugs
- GCP
- Un-Expected SADR’s Report
- Reporting at the end/termination of the Trial
- Destroy/Re-export the remain Drugs, after the Trial

Note: Notification = Regulation

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In-Process & Future Activities

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In-Process /Future Activities (1)

1. Scientific Review on Clinical Trial Protocol

- developing Template/Check-list/Criteria of Evaluation
- provide Training/Strengthening the Evaluators
- establish “Evaluation Unit”

The Aim

- on CMC, Pre-clinical, Dose escalation, Design-Mat. needed,
- Independent decision system

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In-Process /Future Activities (2)

2. Formalize Linkage b/w TFDA & IRB/IEC

- collective of all related Trial Information
- for Subject Protection

3. GCP/Clinical Trial Inspection

- setting Template/Check-list/Criteria of Inspection
- establishing of the GCP/CT Inspection Unit
- training/strengthening the Inspector

4. Amendment of Ministerial Notification #14
(at step of Public Hearing now)

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In-Process /Future Activities (3)

5. Strengthening the Work ‘efficiency + quality’

- competitive Timeline
- consultative service
- support the IND → NDA
- Good Regulatory Practice

6. Implementation the Adopted ICH-S&E gls of ASEAN

- adopted gls = 15+11

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Implementation of the ASEAN-Adopted Tech. gls.

- Law & Regulation
- Criteria
- Forms & SOPs
- Translation *English to Thai* Document
- Dissemination Information + Requirement
- Official Announcement
- Implementation System

Great Commitment + Resources + Working Hard...NEEDED !!

สำนักงานคณะกรรมการอาหารและยา Food and Drug Administration

Clinical Trial 'system and situation' of Thailand

The National Seminar

- **1997 -1999 :- Preparatory phase**
- **Since 2000 :- Annual Seminar**
 - Title...*"Thailand Towards Center of Excellence in Clinical Trials-Annual Seminar"*
 - Composition...*GCP's Stakeholder*
 - Speaker... *National, and invited International Experts*
 - Host... *rotation*

สำนักงานคณะกรรมการอาหารและยา



Food and Drug Administration

The 7th Annual Seminar (1)

by TFDA (29-30 Aug.07)

- **subTitle...***"Being Number One-Clinical Trial Hub of Asia/ASEAN"*
- **Sessions...**
 - (1) **The Global New Trend**
 - The Global Drug Development :- by *Mr.Hironobu SAITO*
 - Perspectives, future directions and use of P'genetics in Clinical Drug Dev. Thailand Experience :- by *Dr.Chanin LIMWONGSE*
 - Multinational / Multi-centers Studies-the Nature and Opportunity :- by *Ms.Poi Ting LIM*
Prof.Dr.Pyatat TATSANAVIVAT
 - (2) **The Update Strategy and specific roadmap to ensure Hub Fulfillment**
by *Stakeholder Rep.(Fercit, Investigator, PReMA, TFDA)*

สำนักงานคณะกรรมการอาหารและยา



Food and Drug Administration

The 7th Annual Seminar (2)

- **Sessions...**
 - (3) **The Competitive Situation and Environment**
 - Experiences, Success Stories, and Recommendation by *PReMA, Fercit, and TFDA*
 - Way to Improve and Enhance Competitiveness by *HIVNAT, Disease Control Dpt. MOPH, Investigator, and TFDA*
 - (4) **Unify the Regulation for the Ease & Success of the Country**
 - All Rules & Regulations involving CT of Thailand by *3 Speakers of relevant MOPH-Dpt./Institutes*
 - Development of IEC and IRB in Thailand by *Fercit*

สำนักงานคณะกรรมการอาหารและยา



Food and Drug Administration

Clinical Trial 'system and situation' of Thailand

Situation, Outcome, and the Plan

สำนักงานคณะกรรมการอาหารและยา



Food and Drug Administration

The Outcome

Overall :-

- **Amendment of National Strategy & Roadmap**
 - appropriate-specific Target
 - clear/feasible Indicator
 - Competitiveness
- **Next Annual Seminar**
 - in Chiang Mai (Jul/Aug. 08)
 - host by Faculty of Medicine-ChiangMai

Plan

- set-up Organizing Committee
- start the Work early in 2008

สำนักงานคณะกรรมการอาหารและยา



Food and Drug Administration

Ethical Committee (IRB/IEC)

current ECs - Governmental , Academic, & Private

(3 in MOPH, 1 in Army Medical Dpt., > 15 in Academic (mainly Faculty of Medicine) private Hospital, foundation)

Standards - the EC (CIOMS, ICH-GCP, Declaration of Helsinki, WHO)

- Members (Training, Study Visit)

Networking - Fercit

- Fercap

Plan

- SIDCER / Fercap audit-recognition
- OHRP/FWA Registration
- Joint IEC/IRB
- acceptant of the TFDA
- competitive Timeline

สำนักงานคณะกรรมการอาหารและยา



Food and Drug Administration

Investigator

current Situation:-

- Experienced, but need MORE Investigators
- **Pharmaceutical & Biological Trials**
 - Phase I, II, III, and IV
 - Vaccine
- **Networking -**
 - CRCN
 - ICRC

Plan

- increasing in Numbers
- enhancing the contribution to the R&D

สำนักงานคณะกรรมการอาหารและยา



Food and Drug Administration

The Clinical Trial

current Situation:-

- **Local & Multinational trials**
- **Areas-**
(Infectious diseases, HIV/Aids, Cancer, Digestive system diseases, Hepatitis, Cardiovascular, Mental disorders&behavior study, D.M...)
- **Numbers-**
(increasing from 184 to 291 (58% increased))

Plan

- public-private partnership (TRUST)
- public education
- competitive timeline/enrollment
- set-up "Trial Centres"

สำนักงานคณะกรรมการอาหารและยา



Food and Drug Administration

Thank You ...

สำนักงานคณะกรรมการอาหารและยา



Food and Drug Administration

Clinical Development in Asia and ICH: Implementation of ICH Guidelines in Asian Countries

Discussion

(Chairpersons: Kohei Wada and Mike Ward)

Wada: May I now invite the panelists to the stage? I thank all the speakers very much for talking about the situation in their country. From what I heard about the GCP adoption or adaptation, in China it is adapted, and in Korea it is mostly adopted?

Kim: Yes, mostly adopted.

Wada: In Thailand is it adopted? I hope I am differentiating the pronunciation. Anyway, now under this situation, I would like to talk a little bit about the actual implementation issue. Can I ask each of you: What do you think are the most important issues right now, related to the implementation of GCP or regarding conduct of clinical studies in your country? For example, the investigators' side, IRB side, or the industry side, would be one perspective. Or, I think many of you do the inspection; what have you found from the inspection that is significant? Or, you do a lot of training; what do you put focus or emphasis on in such training? – Anything that you can bring up as an example would be nice.

Kim: In the case of Korea, the main problem is the difference in the quality in clinical trial centers and IRB. Because of that, the Korean FDA tried to persuade hospitals, IRBs and CRCs to keep the KGCP and ICH rules. The KFDA and the MHW in Korea invested nine regional clinical centers point five to one million dollars per center for the development of an education program, especially in clinical centers and IRB/CRC. Another problem is following the adverse clinical results. Nowadays, hospitals and other clinical trial centers are not too frank about results with adverse reactions. It is a problem. Thank you.

Wada: Thank you.

Javroongrit: I also would like to share about the importance or the difficulty in terms of implementing the GCP. I think that in the case of Thailand it may be the same as in other countries in Asia. One of the important issues is to ask the consent from the subject. As an oriental culture, most of the patients always leave everything up to the doctor, and they just do whatever the doctor asks them to do, without any attention whether it is a clinical trial. The point is that the PI (principal investigator) should donate available ample time to the clinical trial. Since only a good physician can be a good investigator, they might face difficulty in donating sufficient time to the trial due to their busy schedules with their other routine work. Therefore, I think on this point we might need to strengthen our consenting system, in terms of the work on asking consent and recognition of the subject. I think this is really important, on the view of a regulator. We need the subject to really realize and get all the information

before they get into any trials. The second thing, which is quite difficult in my country, is the monitoring issue. You know, clinical trials in the past were kind of voluntary. Medical schools have to do teaching and also research. When we started to have the GCP, a part of that was the monitoring. It is quite difficult for the Thai FDA. What we need to do, really, is to discuss and then to set up the standards and the policies on how to work on these. This is, I think especially either from the regulator, the Thai FDA, or from the ethical committee, how to do the monitoring over the clinical trials. Even though we have achieved successfully from sponsor-internal audit and from the US FDA and the EMEA inspection, I think we still need to work more on how to do the appropriate monitoring over the clinical trials. Thank you.

Wada: Thank you, Dr. Javroongrit. Dr. Ding, please?

Ding: I believe, as I mentioned in my presentation, that training for GCP is the most important issue – not only in China, but in some other countries as well. This is because, in considering the nature of it, GCP cannot be implemented by a single person unlike other ICH guidelines. They should be understood and practically used by investigators, monitors, sponsors and many other authorities. One single clinical trial will, at the same time, involve many factors rather than a single entity to finish it. Conversely, even if a single investigator is to do things wrong within one clinical trial boundary, then the clinical trial as a whole can turn out wrong. In other words, a single wrong step can cause a wrong result. It is a systematic issue. Only training can ensure all the system, without any problems so that they can be assured that the ICH would be practically implemented. Otherwise, because the technical guidelines are in fact without boundaries, regardless of whether the country has adopted or adapted from the Web or from a publication, the technical experts can utilize the guidelines with the language they know, whether it is English or another language. I know some Chinese professionals and experts that indeed read Japanese, and so they understand Japanese more than English. Then the issues are greater issues. Because of the non-boundary of the technical guidelines, the issue that becomes more important is how to train people who are involved in the clinical trials – for all, not for only one person. Thank you.

Wada: Mr. Ward, who is sitting next to me, has been involved in these GCG activities for many, many years, and I know you have a lot of thoughts about adoption/adaptation and implementation of guidelines. Can you share some of your thoughts with us?

Ward: We have certainly had some very productive discussions within the GCG over the last year or so, involving the presenters today, on the adoption versus adaptation and the complexities associated with this issue. Really, there are two categories. One is where there is a deliberate intention to apply some of a particular guideline and maybe transition into applying the entire ICH guideline. Then there are other situations where it is not intentional and it is matter of language, of interpretation, of training, et cetera. It is also true that adoption is not the same as implementation, and that to truly implement a guideline as it was intended, you have to have a good understanding of the objectives of the guideline; and you have to have – and I think this was repeated several times – training of all the players. When it comes to GCP, we do have many players: we have the investigators, the IRBs, the sponsors and the regulatory authorities. Other considerations include: having the right skill sets and qualifications to make use of certain ICH guidelines; awareness of new requirements; the barriers that regulations pose, as we have heard: for example, if regulations do not allow for

particular guidelines to be applied; the need for collateral guidances to integrate an ICH guideline in a regulatory framework; and as we have heard again from Dr. Ding, the difficulties translation of words and even concepts pose. So, clearly, the actual understanding and effective and complete implementation of a guideline really relies on a number of different things within any country.

Wada: Thank you. Now we are running out of time. But do any of the panelists want to share any information specific to their country?

Javroongrit: I would like to share something, but not specific to my country, maybe on behalf of the region. As an RHI I really would like to express our sincere thanks to the ICH, especially in the GCG, which is the forum for the information changing as well as the forum to build understanding and trust among us. With the GCG I think that our ICH party understands our obstacle or difficulty in terms of implementing the ICH technical guidelines and lead to a valuable offer - for example, from the ICH's Regulators just now has created a forum for the regulator of non-ICH countries, and used that to open training for the non-ICH. In addition, each of them, as well as Health Canada, try to provide support as requested, if possible. Right now the ICH GCG is trying to expand the facilitation. I think that this is really a good way or mechanism to help the non-ICH countries to understand and be able to implement the ICH guidelines with understanding and know how to do so better. So I just would like to thank you.

Wada: Thank you for your statement. Before closing this session, I would like to ask Mr. Ward to make a short statement on where he thinks the GCG is heading, or the future of the GCG.

Ward: Well, I think we are really at a crossroads right now. It has taken a certain amount of time to set up mechanisms to bring in regional harmonization initiatives, to have dialog, to get to know one another, to understand some of the issues. And I think we really have established a partnership. ICH has better understanding of the challenges faced by non-ICH regions. Let's face it: the implementation of ICH guidelines can sometimes be a challenge even for ICH regulators and industry within the ICH regions. Imagine: if you are not part of the process, not part of the dialog, how can you be expected to fully understand the intent behind these guidelines? So I believe the GCG will play an increasingly important role in promoting global implementation of ICH guidelines, to the benefit of all countries involved. We do rely on our colleagues from the regions. We have, I think it is fair to say, established a considerable level of trust and respect and understanding for one another. We are all in the same game. We are all looking at promoting public health. ICH guidelines are essential to achieving that goal. I think the new mechanisms that are being set up, that will bring in other countries and allow for frank discussion amongst regulators on some of the issues that were raised today, and then feed that back into the Global Cooperation Group for specific training, will be vital. I believe that we have a very bright future ahead of us, under the leadership of Wada-san and Dr. Arlett.

Wada: Thank you.

So I hope, for the audience, this session was useful. I apologize that we do not have enough time to discuss more, but we will continue with this GCG activity within the ICH framework, and we would like to share with you any new progress or advancements we make along the

way. Before I close, I would like to ask you to give big hands to the four speakers from abroad. Thank you very much.

CLOSING REMARKS

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

Ladies and gentlemen, upon closing, as a member of the Steering Committee of ICH I would like to say a few words. For today, we covered many hot topics. It has been a long day and I thank you all for your attention.

As Mr. Wada mentioned this morning, in the past, ICH results have been presented every three years or so at the big conventions or conferences. However, with the cancellation of the major conference this spring, we decided to have a very region-tied symposium on the following day of the SC expert meetings to report on the latest meeting results to the audience.

We decided to invite Rapporteurs amongst the committee members to give direct presentations to the audience of interest. They had to stay an extra day for this presentation, but they are the central figures embedded in the entire work of that particular subject. I am sure that you had a very good understanding of the themes presented.

Since this was the very first arrangement of this kind, we had many worries. However, this turned out to be a very rich program. I was privileged to be a part of it and feel that this was a tremendous success. I would like to thank the speakers for their extra effort that made this possible.

I do not want to go into lengths, but as for myself, I believe that this particular symposium will contribute to the global development of innovative new drugs.

With this, I would like to conclude my short speech. Thank you very much.