Case Studies
(Articles / Position Papers)

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

Training / Workshops
Goals and objectives

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

Training / Workshops
Outline of the training

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

Proposed additional activities

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

医薬品研究
Pharm. Regul. Sci.
40(12)848～852(2009)

品質に関するトピックの動向
Q-IWG：品質実施作業部会**

槍山行雄*

1. はじめに

本稿ではQ8，Q9及びQ10のImplementation Working Groupについて報告します．

グループの活動目的は，Q8，Q9及びQ10の一貫した導入と実践を世界的に行うこと及び，この三つのガイドラインを相乗効果でより大きい成果を上げることです（Table 1）．グループが組織された背景として，2003年のブラッセル会議が起点となります．その後，製剤開発（Q8），品質リスクマネジメント（Q9），医薬品品質システム（Q10）が作成されました．これらガイドラインは，概念的であり，今後の方針に関わることが多く，またなじみのない概念も含まれていました．これらの内容を明確にして，曖昧さや不確定さを取り除くことが背景になっています（Table 2）．

2006年のQuality Strategy Meetingでは，Q8，Q9及びQ10の導入・実践に関しては今後注意深く，ある程度精密に作業を行っていかなければその実現は難しいという認識がされました．2007年になり，非公式のQ-IWGが開催され，その後，3回のface-to-face MeetingがIWGとして行われ，2009年6月に横浜で3回目のQ-IWGが開催されました（Table 3）．

2. Q-IWGの検討課題と運営

検討課題は，審査と査察の領域を対象に，用語の共通理解，Q8，Q9及びQ10のガイドラインの相互関係の理解を進めることです．また導入後，申請資料の中にどの様に書き込むのかといった調和の程度も課題として取り上げます．Q8，Q9及びQ10の導入・実践を行った場合に，今まで作成されたICHのQualityガイドラインに何らかの影響が及ぶことが考えられるので，それらの課題を洗い出して対応していきます．

また，Q8，Q9及びQ10ガイドラインに関するコミュニケーションとトレーニングを行います．具体的には，Q＆Aや教育資料を作成する，外部団体と共同作業を行う，ワークショップを開くことなどです．

具体的なQ-IWGの運営は，当初，Quality by Design，知識管理，医薬品品質システム・査察の三つの領域について，IWGの成果物である，Q＆A，White papers，Position papersや事例の作成，ワークショップ開催などを実行することです．

またIWGでは，ICHのweb siteを通してIWGに対する提案を受け付けます．Q＆AのQuestionsとAnswersをセットでも，Questionsだけでも，提案を受け付けます．また，外部の非営利団体との共同作業を行う予定です（Table 4）．

2008年のポートランド会議で，先の三つの領域で分科会を設け，Brain Stormingを行いました．その結果得られた課題について，知識管理は日本，Quality by Designはアメリカ，Pharmaceutical Quality System/Inspectionは欧州がそれぞれ担当して，具体的なQ＆Aの作成を行いました．また，外部団体との共同作用についても議論をしました．

2008年秋のブラッセルでは，分担して作成した各領域のQ＆Aを持ち寄り，face-to-faceの会議で40以上を採択しました．その後，会議で合意したQ＆Aは各極でreviewし，2009年3月の電話会議

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** 当協会主催の第20回ICH即時報告会（平成21年6月12日：東京）における講演による．

Table 1 Objectives

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

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

Table 2 Background

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

Table 3 History

- Quality Strategy Meeting, Fall 2006 Chicago
- Quality Strategy Meeting, Spring 2007 Brussels
- Quality Satellite Roundtable, Fall 2007 Rockville
- Informal Q-IWG, October 2007 Yokohama
  - Final Concept Paper endorsed by Steering Committee
- First Q-IWG Meeting, June 2008 Portland
  - Three breakout sessions on Knowledge Management, Quality by Design, Pharmaceutical Quality System/Inspection.
- Second Q-IWG Meeting, November 2008 Brussels
  - More than 40 Q&A' s agreed by IWG. Feedback collected.
- Teleconference on March 11, 2009
  - 30 Q&A' s adopted
- Third Q-IWG Meeting, June 2009 Yokohama

で最終的に30件のQ&Aを採択しました．このQ&AはICHのweb siteに掲載されています（Table 5）．

3. ガイドライン理解のためのQ&A

Q&Aを紹介します．Quality by Designのセクションの Real Time Release Testingの採用により，バッチの出荷判断にどのような影響があるかとの質問です（Table 6）．

Table 4 Q IWG operation

- Areas of Topics
  - Quality by Design, Knowledge Management, Pharmaceutical Quality System/Inspection
- Outcome/Product from IWG
  - Q&As
  - White papers
  - Examples and Case studies
  - Training, Workshops
- Work processes/Collaborations
  - Within IWG
  - Proposals to IWG at the following ICH Q-IWG web site (http://www.ich.org/cache/html/5050-272-1.html)
  - Collaborations with non-profit organizations

Table 5 Progress in and after Brussels meeting

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

Batch releaseというの市場への出荷時の最終的な判断で，Real Time Release Testingを行うか，品質の試験，つまり規格の試験をするかに関わらず，Batch releaseは行われます．回答には，GMP下で行われる通常の出荷の判断の基本的なことが書いてありますが，Real Time Release Testingの議論は，ICHのQ8(R1)に定義されています．ところが，実際の生産現場はGMPに沿って作業は行われます．すなわち，一つのガイドラインで規定したことが，他のpracticeに少なからず影響を及ぼします．この例はGMP下での出荷に影響する部分ですから，このようなQ&Aを出して明確化を図るということです．

Table 6 2. Quality by Design: 2.2 Real Time Release Testing

Q 01: How is batch release affected by employing real time release testing?
A: Batch release is the final decision to release the product to the market regardless whether RTR testing or end product testing is employed. End product testing involves performance of specific analytical procedures on a defined sample size of the final product after completion of all processing for a given batch of that product. Results of real time release testing are handled in the same manner as end product testing results in the batch release decision. Batch release involves an independent review of batch conformance to predefined criteria through review of testing results and manufacturing records together with appropriate GMP compliance and quality system, regardless of which approach is used.

Table 7は医薬品品質システムの導入 に関するQ&Aを，Table 8には，GMP査察へのインパクトに関するのQ&Aの一例を示します．

Table 9は，ICH Q8，Q9及びQ10の発効により，知識管理の重要度と使い方はどのように変わるのか，あるいはどのように変わったのか，という質問です．

Q10には，知識管理の定義が収載され，「製品，製造プロセス，及び構成資材の情報を獲得，分析，保管，伝播するための体系的な取り組み」とされています．知識管理は新しい概念ではなく，Q8，Q9及びQ10の発効に関わらず重要です．ただ，Q10では，最近のいわゆるenhanced approach，Quality

Table 7 3. Pharmaceutical Quality System

Q 01: What are the benefits of implementing a Pharmaceutical Quality System (in accordance with ICH Q10)?
A: The benefits are:
- Facilitated robustness of the manufacturing process, through facilitation of continual improvement through science and risk-based post approval change processes.
- Consistency in the global pharmaceutical environment across regions
- Enable transparency of systems, processes, organisational and management responsibility.
- Clearer understanding of the application of a Quality System throughout product lifecycle.
- Further reducing risk of product failure and incidence of complaints and recalls thereby providing greater assurance of pharmaceutical product consistency and availability (supply) to the patient.
- Better process performance.
- Opportunity to increase understanding between industry and regulators and more optimal use of industry and regulatory resources. Enhance manufacturer's and regulators' confidence in product quality.
- Increased compliance with GMPs, which builds confidence in the regulators and may result in shorter inspections.

Table 8 4. ICH new quality guidelines' impact on GMP inspection practices

Q01: How will product-related inspections differ in an ICH Q8, Q9 and Q10 environment?
A: In the case of product-related inspection (in particular pre-authorisation) depending on the complexity of the product and/or process, there could be a need for greater collaboration between inspectors and assessors for example for the assessment of development data. The inspection would normally occur at the proposed commercial manufacturing site and there is likely to be greater focus on enhanced process understanding and understanding relationships e.g. Critical Quality Attribute (CQAs), Critical Process Parameters (CPPs). It will also extend into the application and implementation of quality risk management principles, as supported by the Pharmaceutical Quality System (PQS).

Table 9 5. Knowledge Management

Q 01: How has the implementation of ICH Q8, Q9, and Q10 changed the significance and use of knowledge management?
A: Q10 defines knowledge management as: 'Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components'.
Knowledge management is not a system; it enables the implementation of the concepts described in ICH Q8, Q9 and Q10.
Knowledge Management is not a new concept. It is always important regardless of the development approach. Q10 highlights knowledge management because it is expected that more complex information generated by appropriate approaches (e.g. QbD, PAT, real-time data generation and control monitoring systems) will need to be better captured, managed and shared during product life-cycle. . In conjunction with Quality Risk Management, Knowledge Management can facilitate the use of concepts such as prior knowledge (including from other similar products), development of design space, control strategy, technology transfer, and continual improvement across the product life cycle.

by Design, あるいは process analytical technology を採用した場合の知識管理は，より複雑な内容を扱うので，より知識管理の重要度が上がると回答では記述されています．

もともと Knowledge Management は Q10 で定義され，説明されていますが，Q8 の中でいわれている enhanced approach を実際の現場で運用するときに，enhanced approach の知識をどのように保存して，どのように site に供給していくかと回答には示してあります．

4. 横浜会議での Q-IWG の成果

横浜では大きく分けて三つの領域で議論が行われました．

Q&A については追加が議論され，その結果，10 件の Q&A が新たに採択されました．

新しく採用された 10 件の一つを紹介します (Table 10)．これは製造所では，どんな製剤開発の情報や文書が必要かという質問です．医薬品開発情報は通常，開発部門で利用できる状態であるべきです．製剤開発から入る情報は，製造あるいは製造管理に必要な重要な情報なため，製造部門で活用できる状態になければならないと回答されています．そのことが技術移転を成功させる鍵になると述べています．

Case Studies を採択するためには，外部論文を review して引用するには，多くの労力が必要となるため断念しました．それに代わり，IWG 自身が外部団体と共同で Position Papers や White Papers を書くことになり，Task force を作り，今後取り組みます (Table 11)．

トレーニングは，Q8，Q9 及び Q10 の implementation を世界中で行うために実施します．Q-IWG が主体となったワークショップの開催を提案し，運営委員会で承認されました．Table 12 にワークショップの達成目標を示します．Q8，Q9 及び Q10 と Q&A を取り込み，製品のライフサイクルに合わせ，全般にわたってトレーニング・プログラムを組む計

Table 10 2. Pharmaceutical Quality System

Qxx: What information and documentation of the development studies should be available at a manufacturing site?
A: Pharmaceutical development information (e.g. supporting information on design space, chemometric model, risk management,…) is available at the development site.
Pharmaceutical development information which is useful to ensure the understanding of the basis for the manufacturing process and control strategy, including the rationale for selection of critical process parameters and critical quality attributes should be available at the manufacturing site.
Scientific collaboration and knowledge sharing between pharmaceutical development and manufacturing is essential to ensure the successful transfer to production.

Table 11 Case Studies (Articles / Position Papers)

- Q-IWG findings
  - Many publications, workshops etc. available
  - Q-IWG will not endorse existing articles
    - Resource intensive: reviewing, decision, maintenance etc.
    - Potential regulatory concerns
  - Q-IWG will initiate, encourage and collaborate on paper development consistent with Q8, Q9, Q10 guidelines and Q&A
- How can this be achieved?
  - Task force within Q-IWG
    - Identification of topics and potential collaborators
    - Establish process for outside contribution
    - Recommend the topic and potential collaborators to Q-IWG
  - Q-IWG to assign topic cordinator(s) among its members
  - Final review and approval by entire Q-IWG (e.g. by telecon)

Table 12 Training / Workshops: Goals and objectives

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

Table 13 Proposed additional activities

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

画です．トレーニングの対象は企業関係者だけではなく，行政の審査や監視の担当者を含めて行う予定です．

計画の概要は，講義を半日，分科会を1日，パネルディスカッションを半日ぐらいの正味2日の計画を検討しています．開催時期は，欧州は2010年のブラッセル会議に，日本では2010年秋の横浜会議前に，アメリカではその間あたりを予定しています．

5. おわりに (Table 13)

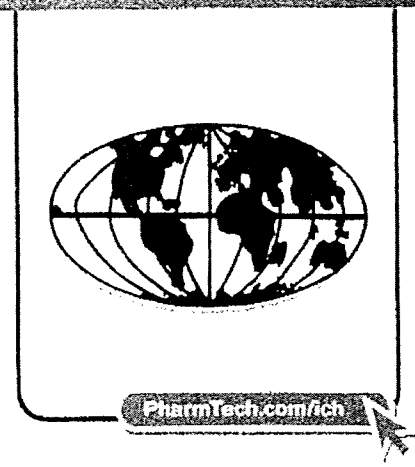
今後，Q8からQ10までを導入することで，既存のQualityガイドラインに影響を与えることになり，そのためどのような問題が発生するかを検証し，手当てを行う予定です．

また，新たに多くの技術や考え方が出てくるので，それらをどのように扱うか，IWGで議論していきます．今までにQ-IWGがカバーしてきたのは，Q10と最後にStep 4に達したQ8(R1)です．その後，約1年でQ-IWGの活動は終了すると提案されていましたが，少し新しいタスクを加えることで活動が延長されることになります．今後の活動経過はセントルイス会議において運営委員会へ提案をすることになります．

INSIDE ICH–MHLW

Working Groups Ramp up Quality-based Implementation

Tsuyoshi Ando, Yukio Hiyama, Yoshihiro Matsuda, Tamiji Nakanishi, and Haruhiro Okuda



Representatives of Japan's MHLW report on recent ICH activities and what the ministry expects from Q11.

The International Conference on Harmonization's Implementation Working Group for the quality trio (Q–IWG) held its third meeting in Yokohama, Japan, this past June. Established in October 2007, the group's mission is to promote consistent implementation of ICH Q8 *Pharmaceutical Development*, ICH Q9 *Quality Risk Management*, and ICH Q10 *Pharmaceutical Quality System* around the world and to help industry and regulators maximize the benefits that can be gained from interaction between the guidelines.

Quality-trio implementation

Because the concepts and principles within ICH Q8, Q9, and Q10 are rather new, it is important to provide clarity on how they can and should be used. Since April 2009, Q–IWG has published 40 questions and answers on the ICH website addressing common questions and concerns. Topics addressed include design space, real-time-release testing, good manufacturing practices, knowledge management, and software solutions. The relationship between continuous-process verification and process validation, and the topic of postapproval product-related inspections have been identified for further discussion.

In June, Q–IWG assigned case-study topic coordinators to write and publish articles and position papers on the quality trio guidelines. In addition, Q–IWG agreed to sponsor three workshops in 2010—one in each ICH region (North America, Europe, and Japan)—to enhance harmonized implementation training among industry and regulators. The workshops will be conducted by ICH experts involved in the guidelines' development.

Q11 makes headway

Representatives of the ICH Q11 expert working group discussed the pending guideline on *Development and Manufacture of Drug Substances*, including chemical entities and biotechnological/biological entities, during the Yokohama meeting. The group prioritized items that need improvement in the guideline's text, which currently exists as a concept paper.

Participants agreed that the scope of Q11 should not be limited to what to file in a common technical document (CTD)—the bulk of the concept paper—but also should address the more general concepts of drug-substance development and manufacture. The group also discussed sections on starting materials, process validation, development, and control strategy. The group intends to create a revised draft of Q11, including a new product life-cycle section, at its St. Louis, MO, meeting in October 2009. A Step-2 signoff (i.e., consensus by all ICH parties) of Q11 is expected in June 2010.

Japan's perspective

One challenge facing Japan's Ministry of Health, Labor, and Welfare (MHLW), an ICH party, with regard to Q11 is that the quality of information on drug substances submitted in new drug applications (NDAs) is often inadequate, especially when using the drug-master-file (DMF) system. This inadequacy occurs because DMFs are often prepared by companies that are unfamiliar with NDAs. Despite being created in a CTD format, in many cases, the DMFs' description of manufacturing process and justification of control strategy are insufficient, leading to increased review time and workload on the part of the regulators.

In addition, Japan's Pharmaceutical Affairs Law was revised in 2004 to introduce the use of marketing business licenses. These new licenses, which replaced traditional manufacturing business licenses, enabled pharmaceutical drug marketing authorization holders (MAHs) to outsource their products, a practice that is expected to increase significantly in the coming years. MHLW also expects MAHs to appropriately carry out technology transfer and to perform change-management controls based on knowledge obtained in development studies, with the goal of accelerating continual improvement.

MHLW hopes that Q11 can be a useful tool to encourage communication, not only between industry and regulators, but also between manufacturers and outsourcing partners. Under Q11, pharmaceutical companies will be encouraged to clearly state the rationale for their manufacturing process and control strategy in their NDA documents and within any outsourcing activity agreements. **PT**

Tsuyoshi Ando is a reviewer in the Office of Biologics of the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and serves as the Ministry of Health, Labor, and Welfare (MHLW) Q11 deputy topic leader; **Yukio Hiyama*** is section chief for the Division of Drugs at the National Institute of Health Sciences (NIHS) and the MHLW Q9 and Q10 topic leader; **Yoshihiro Matsuda** is a reviewer in PMDA's Office of New Drugs (OND) and the MHLW Q11 topic leader; **Tamiji Nakanishi** is a reviewer in PMDA's OND and the MHLW Q–IWG topic leader; and **Haruhiro Okuda** is director of the Division of Organic Chemistry at NIHS, all in Tokyo, Japan, hiyama@nihs.go.jp. Industry is welcome to submit proposals to Q–IWG at www.ich.org.