BREAKOUT SESSION D: **Communication**

Moderators: Gordon Johnston, GPhA; Jeff Blumenstein, PhRMA; Doug Ellsworth, FDA; Helen Winkle, FDA

Focus:

Pharmaceutical Quality Assessment in the 21st Century raises challenges to the historic communications processes between Agency and Applicant. This session will explore new ways to share knowledge and exchange points of view during the development/pre-registration, registration, and post-approval phases of a product's life cycle. In addition to formal information exchanges the breakout will also examine the benefits and issues surrounding informal communications mechanisms, as well as dispute and conflict resolution processes. New roles for communication processes to facilitate the introduction of new technologies, as well knowledge sharing in new regulatory processes will also be discussed.

Questions:

1. How do you suggest managing conflict resolution for CMC review issues?

    - What have we learned from the newly implemented CGMP dispute resolution process for scientific and technical issues?
    - What are the advantages/disadvantages related to informal and formal approaches to conflict resolution?

2. What are the expectations for access and availability for the management of communications on CMC review and related issues between industry and FDA?

    - Is there appropriate accessibility for both informal and formal communication?
    - Is timeliness a problem? If so, what do you think causes problems - lack of adequate resources? Lack of adequate process controls?

3. What are the perceived barriers to good communications between industry and FDA on CMC issues?

    - Some firms advocate minimal communication with FDA while others seek opportunities for communication. What are the reasons for these widely

divergent corporate philosophies?

- Does industry perceive risk related to open communications with FDA? If so, why?
- Does FDA perceive risk in communicating with industry? If so, why?

4. What is the best way to communicate changing processes and new technologies which affect the CMC review process?

- Do guidances provide value to FDA and industry?
- As issues evolve, how can the FDA best communicate with industry to ensure that everyone is well informed?
- Is there some other form of communication that would be more effective than guidances?
- What are the best approaches for FDA and industry training with changing technologies?

5. Are there concerns regarding FDA internal communications?

- How effectively does the Field and Center communicate as review requirements/technologies change?
- Does communication between disciplines during review lead to slow down in timeliness and efficiency?
- What has been the experience of industry when inter-disciplinary discussions are required?
- What concerns or recommendations does FDA have for these internal communications?
- Will the ONDC reorganization create additional challenges for communications?
- How will ONDC assure consistency?
- What are the concerns of industry related to reorganization?

BREAKOUT SESSION E: Design Space

Moderators: Ajaz Hussain, Ph.D., FDA; Scott Reynolds, Ph.D., Merck; Chris Potter, Ph.D., AstraZeneca; Susanne Keitel, Ph.D., EU

Focus:
Considering how we work today and how we could work better in the future

Questions:

1. What is the value for industry and regulators of mapping the formulation, manufacturing process and analytical method Design Space over the lifecycle of a product?

2. Can Design Space be as simple as a finished product specification and associated bioequivalence and stability criteria?

3. How do we move away from processes controlled based on fixed process parameters and equipment (e.g. time, rotation speed) to move towards use of quality attributes (blending acceptable) of unit processes, or relevant attributes of the finished product?

4. How can we use experience of manufacturing multiple batches for the market to improve knowledge and better define and/or extend Design Space?

5. Can the Design Space be mapped and justified using modeling and predictions and verified by actual experimentation (test of hypothesis)?

    a. must the test of hypothesis always extend to an edge of "failure"?

    b. how can prior knowledge be utilized to develop, justify and/or extend the Design Space?

6. What kind of regulatory relief are companies suggesting they would request given increased levels of product and process understanding and knowledge?

Deliverables:
A better understanding of:

- how to develop Design Space and how it could be presented in P2
- how to update Design Space
- what factors would be useful to include in Design Space
- what companies will expect in terms of differentiation by regulators between varying degrees of knowledge in applications and companies

BREAKOUT SESSION G: **Quality Overall Summary (QOS)**

Moderators: Norman Schmuff, Ph.D., FDA; Richard Poska, MS., Abbott; Yukio Hiyama, Ph.D., MHLW, Japan; Gary Condran, Health Canada

Focus:

The ICH's Common Technical Document (CTD) contains a single Module 2 summary for the CTD's Quality section (CTD-Q). The Quality Overall Summary (QOS) is currently described in terms of all of the level 1 and 2 headings of Module 3, but none of the lower level headings. As CTD-Q (ICH M4Q) focuses on format, and not content, there are very sparse examples of the kinds of information to be submitted in each section. This suggests that regional variations are likely.

The stated purpose of the QOS is to "... to provide the Quality reviewer with an overview of Module 3..." while emphasizing "... critical key parameters of the product..." And it is further suggested that the QOS "... should include a discussion of key issues that integrates information from sections in the Quality module and supporting information from other modules..."

It has been suggested that it might be beneficial to repurpose the QOS, and rethink its role in the assessment process. Already, based on their practice of the past 10 years, Health Canada is using the QOS as a review template, and Japan's MHLW is using a more extensive QOS, akin to their previous Gaiyo. It might be that, as in Health Canada's approach, the QOS could serve as a template for the assessment report, where the assessor's comments are written just after the applicant's summary. Alternatively, some version of the QOS could serve a role as an adjunct, to be attached to the reviewer's assessment.

Questions:

1. What are the pros and cons of the QOS different models?

2. How could the QOS be repurposed/redefined to be a more useful document for industry and regulatory agencies?

3. What are the challenges to achieving a better QOS?

4. Should a harmonized QOS be an ICH topic?

Deliverables:

If there is a consensus that the QOS should be re-examined, the deliverables expected from this session are:

- Items and level of detail to be included in a revised QOS
- Steps to achieve a harmonized QOS

BREAKOUT SESSION H: **Innovation and Continuous Improvement**

Moderators: John Berridge, Ph.D., Pfizer; Joe Famulare, FDA;
Tim Marten, D.Phil., AstraZeneca; Christine Moore, Ph.D., FDA

Focus:

This session will explore the necessary framework to implement innovation and continuous improvement under a modern pharmaceutical quality system. The new paradigm proposes regulatory flexibility for firms to implement changes under their quality systems, in many cases, without prior approval. In order to implement such a system, changes will be needed for both the information submitted to the agency and its review and/or inspection. Regulators would like assurance that any changes and improvements are scientifically sound and are of acceptable risk. Sponsors would like clear delineation of the "conditions of approval" to support continuous improvement under a quality system. In this session, we will discuss the mechanisms for process or specification changes of new and existing products, and what information and systems are required to support such changes.

Questions:

Submissions & Review

1. What aspects of the current NDA supplement system most need revision? How can a new regulatory system increase continuous improvement efforts?

2. What information is required in regulatory submissions to support continuous improvement implemented through a firm's quality system?

3. What outputs are required from a scientific risk-based assessment to enable continuous improvement?

Design Space

1. How should continuous improvement be implemented for changes within a design space? Outside of a design space?

2. What mechanisms can be utilized to modify a design space based upon increased process knowledge or understanding?

Established Products

1. How can older established products fit into the new paradigm for continuous improvement?

2. How can cumulative knowledge from existing products be used to support continuous improvement?

Deliverables:

This session will define the information and systems required for continuous improvement/post-approval changes for both new and existing products. The aim is identify the type of information required for new paradigm submissions and the associated reviews/inspections, and to capture any perceived hurdles to implementation of the new system.

BREAKOUT SESSION I: Post-marketing Changes (Supplements / Variations)

Moderators: Eric P. Duffy, Ph.D., FDA; Leo J. Lucisano, GlaxoSmithKline; Sue Schniepp, Hospira

Focus:

The FDA has reorganized its review activities to streamline the approval process for drug applications. This reorganization coupled with the new paradigm "Quality by Design" will facilitate changes to current process employed by companies and regulatory authorities for post-approval changes to filings.

Questions:

1. With in the concept of "design space", what type of process changes made in the design space parameters should be reported to the agency before they can be employed by the manufacturer? What should the reporting mechanism be?

2. How does the current reporting system work within the context of "Quality by Design"? Are the CBE-30 and CBE reporting mechanisms still practical with the new paradigm?

3. How can the annual product review and the annual product update activities be merged into one process with in the company? What is the annual update process that would best fit the "Quality by Design" paradigm?

4. What is industry's expectation for this new FDA post-marketing approval group?

5. How can the utility of comparability protocols improve streamlining the post approval process within FDA? Within Industry?

6. Do you have any suggestions/ideas for criteria for supplement downgrade or reduced data submissions?

Deliverables:

This session will seek input from participants on defining what types of changes would be considered within the "design space" definition and the reporting requirements for various types of changes. An overview of the CMC section (manufacturing process validation, method validation and product specifications) will be explored.

BREAKOUT SESSION J: **Integration of Review and Inspection**

Moderators: Keith Webber, Ph.D., FDA; David Horowitz, Esq., FDA; Neil Wilkinson, Ph.D., AstraZeneca; John Franolic, Ph.D., Lachman Consultant Services

Focus:

The new paradigm of submitting greater knowledge / less data in submissions and the stated desire of FDA to push back the ownership of post approval changes to the industry and facilitate continuous improvements will require changes in the traditional roles of reviewers and inspectors to deliver the appropriate regulatory oversight.

Questions:

1. What is meant by "integration of review and inspection"?

    - Participation of reviewers in preparation for inspection?
    - Reviewers participating in on-site inspections?
    - Investigators participating in the review process by providing inspectional observations pertinent to the review?

2. In what ways can the integration of review and inspection add value to the regulatory process?

    - Under the new QS approach, could some 'review' data be better evaluated in inspections, and vice versa?
    - How can the inspection provide data that is usually not submitted in the application?
    - Should this data be available at the manufacturing site or submitted in the application?

3. How could regulators use information and knowledge gained from application / supplement review in prioritizing and conducting inspections?

    - What documents (e.g., QOS Summary and CMC agreement), or other information, will be useful for an investigator to have during an inspection?
    - Could a firm's Annual Product Review (APR) be better aligned with its

annual report submissions and redesigned to facilitate a more efficient inspection / review of its facility and products?

4. How could industry use the information and knowledge generated in support of the application review in its quality systems implementation?

Deliverables:

This session will try to identify ways in which a more integrated regulatory system can provide synergy between the review and inspection components to give the appropriate regulatory oversight whilst facilitating risk-based regulatory flexibility for companies demonstrating a high degree of product and process knowledge and robust modern Quality Systems (Q10 / FDA QS Guideline).

BREAKOUT SESSION K: Pharmaceutical Assessment Practices

Moderators: Lawrence Yu, Ph. D., FDA; Diane J. Zezza, Ph. D. Schering Plough; John Kovaleski, Teva Pharmaceuticals

Focus:

Good pharmaceutical assessment practices will be critical as an element for successful implementation of the new paradigm. Developing an assessment process that focuses on product design, manufacturing, and critical pharmaceutical attributes will ensure drug product quality. Consideration of developing tools, such as a reviewer guide, can assist the reviewer in the evaluation of product quality and in the determination of the level of risk associated with the manufacture and design of the product. Communication of the process that reviewers will invoke during the CMC reviews can provide transparency to sponsors. One such model is being implemented in the Office of Generic Drugs (OGD). OGD has proposed a question based review (QbR) system for its Chemistry, Manufacturing, and Controls (CMC) evaluation which includes important scientific and regulatory review questions which will transform the CMC review into a modern, science and risk-based pharmaceutical quality assessment. Elements of QbR can be considered in developing new pharmaceutical assessment practices.

Questions:

1. Elements of the pharmaceutical development report, risk assessment, and the review process must be considered in developing best practices for pharmaceutical assessment. What elements are critical to achieve a new paradigm?

2. What best practices for pharmaceutical assessment exist today? What additional practices should be considered?

3. As we transit to a new pharmaceutical assessment process, what issues do you anticipate we will have? What can we do to enhance a smooth transition?

Deliverables:

- Identification of critical elements for regulatory assessment to achieve the quality by design paradigm

- Recognition of the best practice of the current review system

- Discovery of issues when we transit to the new regulatory quality assessment process

（外国旅行記録書別添資料３）

FOOD AND DRUG ADMINISTRATION
An official visit to CDER Office of Pharmaceutical Science by Drs Yukio Hiyama and Tomoaki Sakamoto from Japan

Details of the visitor

Tomoaki Sakamoto, Ph.D.
Senior Research Scientist, Division of Drugs, National Institute of Health Sciences, MHLW, 1-18-1, Kami-yoga, Setagaya-ku, Tokyo, 158-8501 Japan
Phone: +81-3-3700-1141 (Ext.230); Fax: +81-3-3707-6950; E-mail: tsakamot@nihs.go.jp

Oct 4th (Dr. Sakamoto along with Hiyama)

Meeting location: Khan's office, White Oaks Life Sciences Building.

Overview of the DPQR/OTR functions - Khan
Chemistry team projects overview - Faustino/Khan
Physical pharmacy team projects overview - Everett/Lyon
Biopharmaceutics team projects overview - Volpe/Khan
Drug delivery systems projects overview - Khan
Stability projects overview - Almetia/Khan
Laboratory tour - Lyon

Tuesday, 10/11/2005 (Only Dr. Sakamoto)

Meeting Location: Office of Generic Drug and Office of ONDQA

(Dr. Lawrence Yu will pick up Dr. Sakamoto from his hotel between 8:00 to 8:15 AM and take him to Office of Generic Drugs)

8:30 to 9:00 am: Meet with Mr. Gary Buehler, Director, Office of Generic Drugs – General discussion about the approval of generic drugs

9:00 to 9:30 am: Meet with Dr. Frank Holcombe, Director of Chemistry – CMC review of an ANDA

9:30 to 10:45 am: Meet with Dr. Lawrence Yu & QbR Working Group – Question-based Review for Generic Drugs: An Enhanced Pharmaceutical Quality Assessment System

10:45 to 11:30 am: Meet with OGD Science Team – Research projects to support approval of generic drugs

11:30 to 12:30: Lunch with Lawrence (After lunch, Dr. Yu will drop Dr. Sakamoto in the Office of New Drug Quality Assessment)

1:00 to 4:00 PM: Dr. Guirag Poochikian and other ONDQA Managers

(At 4:00 PM, Dr. Poochikian will drop Dr. Sakamoto at his hotel).

Wednesday, 10/12/2005 (Only Dr. Sakamoto)

Meeting Location: Conference Room 112, Rockwall-2 Building
5515 Security Lane, Rockville, MD 20852

9:00 - 9:30	Welcome, introduction, and discussion on goals for the visit, and professional expectations
9:30 - 10:30	Role of OPS in CDER, and its organization
10:30 - 10:40	Break
10:40 - 11:20	FDA's Critical Path Initiative

11:20 – 12:00	FDA evaluation of Drug Products through their life-cycle
12:00 – 1:00	Lunch
1:00 - 2:30	FDA Interactions with United States Pharmacopeia (USP) and National Formulary (NF)
2:30 to 2:45	Break
2:45 – 3:30	CGMP Initiative, Pharmaceutical Inspectorate, Product Specialists, Quality by Design, Process Analytical Technology
3:30 – 4:15	Activities of OPS Coordination Committee; Guidance Development and Publication, and Changes to Guidances
4:15 - 5:00	Question and Answer Interactions, and Conclusion of Visit

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
小山靖人 檜山行雄	医薬品製剤 GMP ガイドライン—これからの GMP のあるべき姿と国際調和	PHARMA TECH JAPAN	21	1367-1376	2005
檜山行雄 坂本知昭	GMP をめぐる動向について	医薬品研究	37	42-56	2006
檜山行雄	品質に関するトピックの動向—Q9-	医薬品研究	37	131-139	2006

医薬品製剤GMPガイドライン

GMP Guideline for Drug Products

これからのGMPのあるべき姿と国際調和

Vision of the Future GMP Orienting to Global Harmonization

日本イーライリリー株式会社 医薬開発研究所 品質保証・品質管理[1)]
国立医薬品食品衛生研究所 薬品部[2)]
小山靖人[1)]，檜山行雄[2)]
YASUTO KOYAMA[1)], YUKIO HIYAMA[2)]
Quality Assurance/Quality Control, Pharmaceutical Development Laboratories, Eli Lilly Japan K. K.[1)]
Division of Drugs, National Institute of Health Sciences[2)]

はじめに

医薬品の品質確保は「医薬品及び医薬部外品の製造管理及び品質管理の基準に関する省令」(平成16年厚生労働省令第179号)(以下「医薬品・医薬部外品GMP省令」という)への適合が義務とされ，そこでは品質を確保するために必要な基本要件が示されている。しかし，その内容は包括的な事項にとどまり，具体的な要求事項や品質システムの運用の子細が定まっていない。このため，医薬品・医療機器等レギュラトリーサイエンス総合研究事業（厚生労働科学研究)として，檜山行雄を主任研究者とし，「医薬品の最新の品質システムのあり方・手法に関する研究」が平成14年度より３年計画で実施された。本研究では，グローバルに通用する指針を提供することを目的とし，医薬品開発，製造，流通，行政規則等を取り巻く技術や状況に相応した品質システムのあり方・手法が研究された。

医薬品製剤GMPガイドラインは，**表１**に示す研究経緯を経て，本研究の成果の１つとして公表されたものである[1, 2)]。ガイドラインの作成に直接関与した研究班の構成員は**表２**に示した。平成16年には第２年度に作成し公開した「医薬品GMPガイダンスの提言」に対し，日本製薬団体連合会GMP委員会，日本PDA製薬学会をはじめ各社各位よりパブリックコメントをいただき，本ガイドラインに反映させることとなった。また，同年末に医薬品・医薬部外品GMP省令が改正され，本年３月にはバリデーション基準が改正された[3)]ことを受け，本ガ

表１　ガイドライン検討の経緯

平成14年度	GMPへの提言“薬事法制とガイドライン”
平成15年度	医薬品GMPガイダンスの提言 ・パブリックコメント(平成16年７～９月)
平成16年度	医薬品製剤GMPガイドライン ・医薬品・医薬部外品GMP省令の改正(平成16年12月) ・改正バリデーション基準(平成17年３月)

表２　医薬品製剤GMPガイドライン研究班

座長	小山靖人(日本イーライリリー)
	石井勇司(静岡県庁)
	伊井義則(小野薬品工業)
	香川一浩(東京都庁)
	河村浩史(静岡県庁)
	紀井良明(メルシャン)
	栗原陽子(大阪府庁)
	原　芳明(ザルトリウス)
	柳原義彦(医薬品医療機器総合機構)

(敬称略)

イドラインにはこれらの新たな基準を取り込んでいる。

本稿では，医薬品製剤GMPガイドライン研究の概要と，本ガイドラインにおける品質に関する考え方の基本となる品質管理監督システムを，ガイドラインの記述に則して紹介する。

1．医薬品製剤GMPガイドライン研究の概要

本ガイドライン研究の主旨は，医薬品・医薬部外品GMP省令の補完を目的とした，ICH Q7Aガイドライン[1]（以下「Q7A」という）に相応の医薬品製剤を対象とするGMPガイドラインの提言にあった。

(1)医薬品製剤GMPガイドライン策定の方針

本ガイドラインの策定は次の方針によることとした。

1) 現時点で最善・最適と見なされる医薬品製剤の品質保証のあり方を標準化し，これからのGMPのあるべき姿を具体的に提言しようとするものであること。
2) 医薬品製剤GMPの包括的なガイドラインとして，GMPに求められるすべての要件を取り入れること。
3) 法的要件である医薬品・医薬部外品GMP省令にとどまらず，国際的に確立し，あるいは共通認識が形成されつつある管理項目を積極的に評価・検討し，取り入れること。例えば「品質管理監督システム」「技術移転」などである。
4) 国際的な評価にも耐えうるよう，Q7Aあるいは欧米のGMPなどとの整合性にも配慮すること。
5) GMPの対象として，改正薬事法との関連で製造販売会社および製造所（製造業者）の立場があるが，本研究では製造所を主体とする自律したGMPシステムの構築を目指した。
6) 無菌製剤や生物学的製剤等の製剤特性に伴う特別な管理事項については，本ガイドラインでは取りあげず，他のガイドラインを参照すること。
7) 本ガイドラインの構成などはQ7Aに準拠することとし，Q7A各条を製剤GMPの観点より検討して再構築すること。その上で，必要に応じてわが国の医薬品・医薬部外品GMP省令との整合を図ること。

(2)医薬品製剤GMPガイドラインの特徴

このような策定方針の下で研究を実施した結果，本ガイドラインは次のような特徴を有するものとなった。

1) 本ガイドラインは，医薬品・医薬部外品GMP省令が適用されるすべての医薬品製剤を対象としていること。結果として，本ガイドラインのすべての項目が求められるものは，再審査期間中の新薬等となることが想定されるが，これ以外の医薬品についても，製造所や製品の特性等に応じて該当する事項について適用することが望まれること。
2) 本ガイドラインには，医薬品の製造管理および品質管理に求められるすべての要件を取り入れるよう配慮したこと。このため，結果として，わが国の改正薬事法のもとではGQP省令[5]などにおいて実施され得る事項なども含まれていること。

   ちなみに，改正薬事法では製造販売業者と製造所の関係として次の３つのビジネスモデル（①～③）が考えられるが，製造所の自律したGMPシステムの構築という観点から，③の受託製造専門業者の場合を考察の前提とし，必要に応じて③，②，①の順に考察を進めた。

   ①製造所が製造販売業者社内の１部門である場合
   ②製造所が製造販売業者の分社である場合
   ③製造所が製造販売業者と経営上の関係がない受託製造専門業者である場合

3) 本ガイドラインには，承認や許可の要件として強制力を伴って実施を求めたり，承認や許可の適否の判定基準とすることが，必ずしも適当ではない事項が含まれていること。すなわち，事業者が自らの責任と判断で自主的に取り組むべき事項についても，その指針を示そうとの意図からこれを取り入れていること。例えば「内部監査」や「製品品質の照査」などである。言い換えれば，本ガイドラインは医薬品製造業者における望ましいGMPの具体化に主眼を置いており，行政査察などにおける評価事項を示すことを意図するものではないこと。

(3)医薬品製剤GMPガイドラインとQ7Aとの関連

本ガイドラインの各条を策定するにあたり，Q7Aを製剤GMPの観点から検討するため，Q7A各条を次のように分類し，考察した。

①Q7Aの記述内容に即して，本ガイドラインに採用できる事項
②原薬に特有の事項であり，Q7Aそのままでは製剤を対象とする本ガイドラインに適用できない事項

③Q7Aには規定がないが，本ガイドラインには規定すべき製剤特有の事項，または現在の一般的なGMPの見地から規定すべき事項

④さらに①～③を通して，わが国の医薬品・医薬部外品GMP省令に規定がないか，あるいは一部内容の異なる事項

なお，Q7Aを製剤GMPの観点から検討するにあたり，Q7A全般に対して次の対応を行った。

・Q7A各条における「中間体」と「原薬」を，それぞれ原則として「中間製品」ならびに「製品」と読み替えた。ただし，医薬品・医薬部外品GMP省令では製品の概念に中間製品を含むことから（第２条第１項），特に中間製品を明示すべき場合以外は，中間製品と製品を区別せず「製品」と表記した。また，「原薬」を「医薬品」または「製剤」とするなど，文脈に応じた対応を行った。

・Q7Aでは，同一の要求内容が複数の章文に分散して記載されていることがある。本ガイドラインでは，同一の要求内容は可能な限り主たる章文１カ所に集約するように努めた。

・Q7A各条に記載された事例のうち，原薬に特化したものについては必要に応じて製剤の事例に置き換えた。

・Q7A（ICH Q7Aの日本語訳）の文言については必ずしも達意とは言えない箇所があるが，意図を明確にするための補足や改変が必要な場合を除き，Q7A由来の文言の変更は行わなかった。

表３　医薬品製剤GMPガイドラインの章構成　Ⅰ本文　Ⅱ解説

第1章	序文	第11章	試験検査室管理
第2章	品質管理監督システム	第12章	バリデーション
第3章	職員	第13章	変更管理
第4章	構造設備	第14章	不適合製品及び再加工
第5章	工程装置	第15章	品質情報
第6章	文書化及び記録	第16章	回収処理
第7章	原料及び資材の管理		
第8章	製造及び工程内管理		
第9章	包装及び表示		
第10章	保管及び製造所からの出荷		

(4)医薬品製剤GMPガイドラインの構成など

本ガイドラインは「本文」編，および「解説」編の２部構成である。「解説」編においては，ガイドライン本文の根拠または留意点，あるいはこのガイドラインの作成にあたって参考にしたQ7Aとの関係などについて説明を行った。本文ならびに解説の章構成を表３に示した。