# 4th FDA/PQRI Conference on Advancing Product Quality Breakout Summaries

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Hilton Rockville

PQRI
Product Quality Research Institute

FDA U.S. FOOD & DRUG ADMINISTRATION

# *TRACK 3:* NOVEL MANUFACTURING TECHNOLOGIES AND CHALLENGES FOR THE PRODUCTION OF PATIENT-CENTRIC DRUG PRODUCTS

# SESSION 4: REGULATORY SUBMISSION LIFECYCLE MANAGEMENT

Moderator: Susan Rosencrance, FDA

Speakers: Andrew Chang, NovoNordisk

Mahesh Ramanadham, FDA

Bhagwant Rege, FDA

# Presentations

1. Overview of ICH Q12 Guideline Development: Current Status

   Andrew Chang, NovoNordisk

2. The Concept and Proposed Global Applicability and Benefit of PACMP (Post-Approval Change Management Protocol)

   Mahesh Ramanadham, FDA

3. Established Conditions and its Application

   Bhagwant Rege, FDA

# Key Points from Talk #1 Andrew Chang (Novo Nordisk)

## *Overview of ICH Q12 Guideline Development: Current Status*

- Andrew Chang is a member of ICH Q12 Expert Working Group, representing PhRMA.
- Updated on current status and next steps for EWG.
- Provided an general overview of ICH Q12 and highlighted key chapters (2, 5, 6, 7, & 8).

Purpose of ICH Q12

- ICH Q12 introduces a *globally harmonized risk-based categorization system for managing post-approval CMC changes under ICH framework*
- Designed to address global variation in regulatory framework for managing post-approval changes.
  - *For instance, expected lead time for worldwide approval of a new filling site is on average 4 years.*
- ICH Q12 builds off the existing framework for product lifecycle management outlined in ICH Q8-11 but is intended to be more operational.
- Moves management of post-approval changes to a prospective mechanism to facilitate understanding of reporting category and time to approval.
- Emphasizes control strategy as a key components of the dossier and enhances regulatory tools for prospective change management.
- Brings envisioned operational/regulatory flexibility to fruition by demonstrating how enhanced product and process knowledge contribute to a reduction in the number of post-approval regulatory submissions
- Encourages innovation and continual improvement – annexes allow for ad hoc updating of guidance

# Key Points from Talk #1 Andrew Chang (Novo Nordisk)

## *Overview of ICH Q12 Guideline Development: Current Status*

*Chapter 2: Categorization of Post-Approval CMC Changes*

- Considers a risk based system for categorization of changes and regulatory communications (prior approval, notification and no reporting)
- Provides clarity to distinguish between ECs and supporting information in a regulatory submission
- Global implementation will allow timely and efficient introduction of CMC changes
- Lowest risk changes are only managed and documented within the PQS and not reported to regulators (May be verified on routine inspections

*Chapter 5: Product Lifecycle Management (PLCM)*

- **This was a contentious chapter for many on the EWG but have since reached consensus and there is strong support for this piece*
- PLCM document serves as central repository of the established ECs, reporting category for making changes to approved ECs, PACMPs, and post-approval CMC commitments. Meant to be a living document.
- Updated list should be submitted in post-approval submission for CMC changes
- ECs should be updated passed on knowledge gained

# Key Points from Talk #1 Andrew Chang (Novo Nordisk)

## *Overview of ICH Q12 Guideline Development: Current Status*

*Chapter 6: Pharmaceutical Quality System (PQS) and Change Management*

- Not meant to make changes to quality systems established in Q10; provides a benchmark
- Highlights need for active KM and QRM in driving change and maintaining ECs as well as relationship between sponsor and site's PQS
- Discusses inspection impact on ECs – Following an inspection violation, particularly those indicating problems with ability to manage change, ECs may be reviewed and modified

*Chapter 7: Relationship Between Regulatory Assessment and Inspection*

- Encourages communication between assessors and inspectors to implement Q12 but does not change their relationship or roles
- Communications between agencies will proceed in accordance with present arrangements (e.g., EMA and FDA can communicate bilaterally)

*Chapter 8: Post-Approval Changes for Marketed Products*

- Regulatory tools are applicable to new and marketed products
- Described a strategy for structures approach to frequent CMC analytical changes and the data required to demonstrate stability of those changes

# Key Points from Talk #1 Andrew Chang (Novo Nordisk)

## *Overview of ICH Q12 Guideline Development: Current Status*

*ICH EWG Status and Next Steps:*

- Open for public comment Q1-Q4 2018
- Discussed comments at February 11-15 meeting in Tokyo , Japan
- Still reviewing comments and addressing them, aim to complete this process in time for Step 4, Q2 2019 – June 2019 Amsterdam, The Netherlands
- Plan to develop a training program – a training subteam has been established

# Key Points from Talk #2 Mahesh Ramanadham (FDA)

## *ICH Q12: Post Approval Change Management Protocol (PACMP)*

Dr. Ramanadham is a FDA representative to the ICH Q12 Expert Working Group (EWG)

Discussed chapter 4 and explained how ICH envisions it being utilized and for what purposes

### About PACMPS

- Prospective agreement between applicant and regulator on changes to be implemented, studies and acceptance criteria, and implementation of lower reporting category
  - A predictable and transparent change approach
  - Allows for shorter review time for change implementation, when appropriate
- ICH process is highly aligned with FDA draft guidance on comparability protocols (2016) with exception that ICH requires discussion on suitability of the approved control strategy and confirmation that ongoing verification will be performed under PQS

### PACMP Expectations

- Generally not suitable for quality changes that require supporting safety or efficacy data
- Prior to implementation of change, applicant will need to periodically re-evaluate and confirm validity
- After approval of PACMP step, modifications made to the PACMP may require a supplemental depending on the ability to assess product quality under change

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# Key Points from Talk #2 Mahesh Ramanadham (FDA)

## *ICH Q12: Post Approval Change Management Protocol (PACMP)*

PACMP Expectations- cont'd

- If risk of implementing change has increased or failure to meet acceptance criteria, applicant must default to regional reporting requirements
- Changes monitored after execution under PQS; update the PLCM

PACMPS Role/ Benefits in ICH Q12

- Although PAMPS (comparable to FDA comparability protocols) are an existing tool, felt it was important to include since it would ensure transparency, ability to apply for reduced reporting categories, and flexibility to choose this tool over others in ICH Q12 for streamlined change management.
- Development approaches and timelines may not always allow for risk based definitions of ECs and reporting categories beyond those established by regional regulation.
- PACMPS allow for broader implementation of Q12 beyond new products or single product approaches.
- Enhanced transparency between regulator and MAH regarding approach to risk assessment and control.
- Predictable approach to change implementation.

# Key Points from Talk #3 Bhagwant Rege (FDA)

## *Established Conditions and its Application*

Dr. Rege is a FDA representative to the ICH Q12 Expert Working Group (EWG)

Discussed Established Conditions (EC), which is the subject of chapter 3

<u>Established Conditions (EC) – What are they?</u>

- ECs are legally binding information [within an application] considered necessary to assure product quality
- As a consequence, any change to ECs necessitates a submission (PAS, CBE, AR) to health authorities
- Examples : DS name and structure, DC and DP manufacturing sites, DP batch formula
- ECs govern the scope of reportable post approval changes
- All changes require management under the pharmaceutical quality system (PQS)
- All regulatory submissions contain a combination of ECs and supportive information (supportive information is not an EC but used to provide sufficient detail to justify initial selection of EC and their reporting category)
- Currently, though each approved NDA application has “conditions established” they are interpreted through regulations and guidance. In the future ECs may be specified and documented when FDA approved application.

# Key Points from Talk #3 Bhagwant Rege (FDA)

## *Established Conditions and its Application*

Established Conditions in ICH Q12

Although the term "established condition" has been used (21 CFR 314.70), historically there has been confusion about the appropriate interpretation which has led to underreported changes, supplements at wrong categorization level, or confusion over which changes are supplements vs. managed under PQS. This was part of the motivation for ICH Q12.

- Request for post-approval changes may indicate that a correction needs to be made or that a quality system has matured and gained sufficient understand to reduce monitoring conditions. There could also be an opportunity to advance manufacturing and analytical technologies.
- FDA would like to:
  - Encourage behaviors where applicants take more responsibility for product quality
  - Incentivize deeper and holistic implementation of ICH Q8-11 principles
  - Ensure appropriate and well-functioning PQS is in place (ICH Q10)
  - Facilitate the streamlined implementation of changes that improve quality
- In ICH Q12, ECs provide a platform to:
  - Reduce submission of unnecessary supplements
  - Encourage pre-application development work and post-application continual process improvements
  - Optimize use of regulators' time: allows FDA to focus on most important changes during assessment and inspection for post-approval changes
  - Encourage monitoring and trending to identify opportunities to improve

# Key Points from Talk #3 Bhagwant Rege (FDA)

## *Established Conditions and its Application*

Identifying ECs

- Based on a number of factors: product and process understanding including an assessment of criticality and risk management approaches (CQAs and CPPs), product characterization, product development strategy, control strategy, and desired product performance.
- There are also different approaches for manufacturing processed and analytical procedures.
- For manufacturing processes, ECs can be identified by unit operation and sequence of steps, considering control strategy inputs and outputs necessary to assure product quality
  - Critical Process Parameters (CPPs). defined in Q8(R2)
  - Key Process Parameters (KPPs) – parameters that may not be directly linked to critical product quality attributes but need to be tightly controlled to ensure process consistency
  - *NOTE: Several comments on KPPs received during open comment period and will be addressed*

- For manufacturing processes, three approaches to identifying ECs were discussed– parameter-based, enhances, performance-based
  - *NOTE: Several comments received during open comment period and will be addressed*

# Key Points from Talk #3 Bhagwant Rege (FDA)

## *Established Conditions and its Application*

Categorizing and Submitting ECs

- Applicant proposes reporting category (PAS, CBE-30, CBE-0, AR) for post-approval changes, which should be based upon potential risk to quality and follow approaches described in Q9
- PLCM - Serves as a central repository of the ECs, reporting category for making changes to approved ECs, comparability protocols, and post-approval CMC commitments. Provides a high level summary of product control strategy to clarify and highlight which elements of the control strategy should be considered ECs. Q12 currently doesn't specify location for ECs which is also under discussion in ICH Q12 EWG.
- List of ECs should be maintained and sent with each annual report

Nest Steps

- EWG has broken into subgroups to address comments received during the open comment period. Aiming to have addressed comments and finalized Step 2 document before June meeting.
- Implementation date to be determined
- Established Conditions Pilot Program: https://www.federalregister.gov/documents/2019/02/15/2019-02364/established-conditions-pilot-program
- CBER ICH Q12 Support Group is being established

# Panel Discussion and Q&As

Q: It was mentioned that the EWG is considering replacing ECs in the PLCM document and if you look at the Japanese system, all ECs and reporting categories are summarized in their document. For PLCM document, are you envisioning that all EC would be reported in the PLCM or would it be possible for companies to experiment and only put their explicit ECs, or the ECs for which they plan to change the reporting category?

A: We want to avoid unnecessary burden and try to find ways to streamline to process – the EWG will be experimenting with ways to report ECs. However, if the applicant is going by the regional guidance, there is no need to define all of the ECs in the eCTD and the focus is on the regional regulations.

A: There is a EWG subteam that will be addressing the PLCM document and is currently considering adding more information or examples to help avoid confusion. Additionally, with regards to the Japanese process, this information is filed under Module 1 in their document and the EWG had a lot of discussion on whether or not they could put that information in one location on all documents however, regional requirement are built into the legal system, which makes it challenging to harmonize. However this is another issue they will discus in the next couple of months (i.e., Japanese are legally required to file that information in module 1, EU in module 3)

# Panel Discussion and Q&As

Q: Once Q12 is launched, how should companies consider related guidances, such as SUPAC, going forward?

A: It will be possible to follow SUPAC but Q12 advises that if you do enough development work then you have a lot more process and product understanding, and with the data package that you are preparing for SUPAC, it may be difficult to justify a reduced reporting category.

Q12 is going to require that FDA look at at all of our related-guidances (ANDA, NDA, Annual Report guidance, comparability guidance) and make sure that we have built in enough flexibility to allow for implementation as well as a science and risk based approach. Everything is going to have to be revised to account for Q12 implementation.

Q: How do you apply ECs to those combination products that incorporate a device and is anyone at CBER or CDER currently working on this issue?

A: If the primary mode of action is either drug or biologic product then it is within the scope of Q12 however within commenting period we did receive comments requesting further elaboration on combination products specifically ECs for device components. The subteam has drafted some additional text and a decision tree for combination products. However, when this was presented to the EWG, PMDA and EU commented that they needed time for an internal review because their regulatory framework deals with combination products differently and they need to make sure it is compatible. The EWG is currently waiting for their reflection.

# Panel Discussion and Q&As

Q: Can you elaborate on the changes the PLCM document will allow as the applicant optimizes their manufacturing processes pre-market?

A: The intent for the PLCM is that as an applicant gets more scientific knowledge and understanding, the ECs may be refined. There are several situations that could trigger these changes, such as when new risks are identified or the applicant is able to demonstrate better control over previous ECs and the risk framework changes. However, when we do find problems with change management during inspections there may be mechanism whereby we change the ECs back to what they were prior until corrective action is taken and we are satisfied with the controls.

A: From industry perspective, the hope is that there will be no changes requested to ECs unless there is an unfavorable inspection that triggers concern for appropriate controls.

# Overall Conclusions

- Q12 provides a framework to facilitate the management of post-approval CMC changes
  - More predictable and efficient manner
  - Benefits increased product and process knowledge

- Q12 is a joint effort between industry and regulators designed to help us reach the:
  - Desired state of pharmaceutical quality in the 21st century
  - Vision for pharmaceutical product lifecycle management

- Transformational guideline that many of us are working to understand and determine how to best implement and make operational

# Session 5: Challenges with Drug Device Combination Products Post Approval

Moderator: Susan Neadle, Johnson & Johnson

Speakers: QuynhNu Nguyen, FDA

John Towns, Eli Lilly and Company

Doug Mead, Janssen

# Presentations

1. The Role of Human Factors Engineering in Combination Product Post Approval Changes

   QuynhNu Nguyen, FDA

2. Types and Handling of Product Complaints for Combination Products

   John Towns, Eli Lilly and Company

3. Combination Products Post Approval Challenges Based on Differences in Global Regulatory Filing Requirements

   Doug Mead, Janssen

# Session Background/Premise/Challenges

- **Combination products are increasingly incorporating cutting edge, novel technologies** that hold great promise for advancing patient care, with the potential to make treatments safer, more effective, or more convenient or acceptable to patients .
- A combination product is assigned to a lead center of the FDA for premarket review and post-market regulation based on the primary mode of action (PMOA) of the combination product or other defined regulatory criteria when the PMOA cannot be determined with reasonable certainty. **In most instances FDA may regulate the entire combination product under one type of marketing application** (e.g., one BLA, NDA, or PMA).
- For a combination product approved under one application, there may be uncertainty for when, how and what to submit for a change to a constituent part or to the approved combination product as a whole. **Applicable drug regulations and drug-centric guidances (ICH) may not adequately address delivery device requirements both for new products and changes to them.**
- The focus of post market change management is to ensure the **continued safety and effectiveness of combination products in the marketplace**. **Human factors engineering and effective complaints handling** are among the approaches used to help meet this goal.
- **Post-approval requirements vary and are evolving** in the dynamic global regulatory environment, presenting application holders with ongoing challenges in managing post approval changes. Increasingly, they are country-specific.

# Key Points from Talk #1

## The Role of Human Factors Engineering in Combination Product Post Approval Changes QuynhNu Nguyen, FDA

- Drug-device combinations with complex controls or unexpected device operation can lead to medication errors.
- **Human Factors (HF)** is a core element in minimizing medication errors. It is a scientific approach to understand the interactions between humans (HCP, patient or consumer) and various points of contact on a medication delivery system, **to optimize human well-being and product safety and effectiveness.**
- The mission of Division of Medication Error Prevention & Analysis, or DMEPA, is focused on increasing safe use of drug products by **minimizing user error** related to **naming, labeling, packaging** or **design** of drug products.
- DMEPA involvement can be as early as pre-IND phase, and carries into product lifecycle management (e.g., post market development, responding to use-related safety reports, complaints or problems, or expanded indications for use or user populations).
- Case study examples were presented, incorporating considerations such as dosing requirements, intended user group(s), impact on critical tasks (i.e.any task that has potential to cause harm), and design of a prefilled syringe user interface.
- A draft guidance was issued September 2018: Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications
  - 6 Types of Submissions: (1) Use-Related Risk Analysis; (2) HF Validation Study Protocol; (3) HF Validation Study Results Report; (4)Threshold Analyses; (5) Comparative Use HF Study Protocol; and (6) Comparative Use HF Study Results Report.
  - Updates to forms 356h and 1571 were made to reflect HF in submissions

## Key Points from Talk #2 John Towns, Eli Lilly and Company

### Types and Handling of Product Complaints for Combination Products

- Reasons/drivers for combination products post-approval changes were bucketed into 4 categories
  - Compliance, Supply (material availability), Capacity, Patient
- The distinction between "**Product Complaint**" under medical devices vs "**Adverse Event**" was reviewed, as well as differences in handling of investigations for combination products vs. medical devices.
  - 820.3(b) Complaint: Any written, electronic, or oral communication that ***alleges deficiencies*** related to the identity, quality, durability, reliability safety, effectiveness or performance of a device after it is release for distribution.
  - Adverse Event (312.32(a): Any untoward medical occurrence associated with the use of a drug in humans, ***whether or not considered drug-related***.
- Combination Product complaints differ from those of strictly drug or device
  - Combination product complaint investigations require a thorough and expedient process
  - Complaint volume trends are unique due to initial introduction of device platform, frequency of use (reusable devices versus single use), and changes to user interface.
- Multiple training and patient education programs may be needed to reduce product complaints for combination products.
  - Strong Human Factors program is an essential component
- Changes to current marketed combination products
  - Need to be cognizant of unintended consequence of patient familiarization
- Social media presents new challenges: Data mining potential and ramifications. New ways to "listen" to patients?

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# Key Points from Talk #3

## Combination Products Post Approval Challenges Based on Differences in Global Regulatory Filing Requirements Doug Mead, Janssen

- Review of post-approval requirements around the world for combination products registered as drugs.
  - Requirements increasingly country-specific
  - Depend greatly on pre-approval requirements
- Best practice sharing
  - Review submissions for details previously provided
  - Apply appropriate device change control and risk managent best practices: Design Controls/Changes (820.30); Design Verification and Design Validation; Bridging principles; Risk Analyses (ISO 14971)
  - Leverage device suppliers documentation, support, and certification
  - Be transparent and timely
- Apply 21 CFR 314.70 Supplement to an NDA: Interpret for the device: "…any change in the drug substance, drug product, production process, quality controls, equipment or facilities that has a [substantial/moderate/minimal] potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."
- Consider ICH Q12- Established Conditions (framework to facilitate more predictable and efficient management of post approval Chemistry, Manufacturing and Controls)

# Key Points from Talk #3

## Combination Products Post Approval Challenges Based on Differences in Global Regulatory Filing Requirements Doug Mead, Janssen

- FDA Draft Guidance: Submissions for Post-approval Modifications to a Combination Product Approved Under a BLA, NDA or PMA (2013) proposed risk-based submissions categories for post approval changes. Industry (CPC) is advocating a risk-based "Decision Tree" framework that distinguishes between low/moderate risk devices (Class I/II) versus Class III device constituent part changes, and consistency with 21 CFR 314.70 for drug products.

- May raise questions of safety and effectiveness:
  - Changes that may impact identity, strength, quality, purity, or potency of the drug product (including the device)
  - Changes to technological characteristics or intended use for the device with the drug
  - Changes that trigger need for clinical assessment, e.g., PK, comparability, or Human Factors

# Key Points from Talk #3

## Combination Products Post Approval Challenges Based on Differences in Global Regulatory Filing Requirements Doug Mead, Janssen

- Global dynamics:
  - EU MDR Article 117: "Substantial" device changes will require an assessment by a Notified Body for conformance to Annex I of the Medical Device Regulation beginning 26 May, 2020
    - *Companies with integral, single-use Combination Products expecting to file MAA's in 2020 should identify and select a Notified Body to provide conformity assessments for device constituents, inclusive of pre-filled syringes.*
  - Post approval changes to approved dossiers in the rest of the world: License/ registration renewals can trigger additional device requirements under newly created regulations. MANY country-specific nuances and differences in expectations.
    - *Health Canada*
    - *Japan*
    - *China*
    - *South Korea*
    - *Latin America*
    - *Malaysia*
  - Asian Harmonization Working Party: Guidance on Regulatory Practices for Combination Products (2016) provides harmonization suggestions.

# Panel Discussion and Q&As

Q: An example was given in which a company is applying for approval of a combination product that involves a needle shield safety device. They had been told by an associate that their documentation was too extensive. Asked panelists for guidance on right sizing to ensure they are considering the appropriate human factors and controlling for safety concerns but not over-doing it in terms of the data package.

A: (Nguyen) From a human factors perspective, for a needle shield safety device MEPA/CDER would need to know details around activation process and the extent to which the company has controlled for risk of needle-sticks. The product profile dictates the safety profile. When you see that there is potential for harm to the user, FDA needs to see appropriate controls. If critical tasks can be performed safely and without harm for a particular COU in the hands of the user, this would be sufficient. However, it was suggested that for a product this complex, they leverage the MEPA office and come in for discussions prior to IND filing.

A: (Mead) The level of detail (based on design controls and validation) that goes into a submission is in part negotiated. Mr. Mead suggested that the company search the FDA drug review database and find a similar combination product and look at the data package that they developed.

# Panel Discussion and Q&As

Q: Are Oral films considered a combination product and if so what are the relevant human factors?

A: (Nguyen) FDA- If is not a combination product however, if there is a risk of the patient not using the product appropriately or safely you would need to conduct a risk analysis. Another example would be Parkinson's disease formulation optimized for patients experiencing motor issues (dissolved under the tongue). The company was asked to do a risk analysis which ultimately led to a human factors study.

Q: How do your control for patients conducting internet searches for instructions rather than following instructions that came with the drug/device?

A: (Towns) This is a problem that we haven't yet developed an effective solution for. There is also a high incidence of drug instructions that appear to be associated with company but are, in fact, not. Even internally, it can be a challenge to define the boundary between a label and promotional material.

# Overall Conclusions

- The focus of post market change management is to ensure the **continued safety and effectiveness of combination products in the marketplace**. **Human factors engineering and effective complaints handling** are among the approaches used to help meet this goal.

- **Post-approval requirements vary and are evolving** in the dynamic global regulatory environment, presenting application holders with ongoing challenges in managing post approval changes. Increasingly, they are country-specific.

# SESSION 6: CMC INNOVATION IN THE 21ST CENTURY – GLOBAL REGULATORY PERSPECTIVES


Moderator: Nina Cauchon, Amgen Inc

Speakers: Sven Stegemann, Graz University of Technology

Yoshihiro Matsuda, PMDA

Celia Cruz, FDA

# Presentations

1. Regulatory Framework and Industrial Initiatives – A European Perspective

   Sven Stegemann, Graz University of Technology

2. Pharmaceuticals and Medical Devices Agency (PMDA) Perspective

   Yoshihiro Matsuda, PMDA

3. FDA Perspective

   Celia Cruz, FDA

# Session Background/Premise/Challenges

*"We live in a moment of history where change is so sped up that we begin to see the present only when it is already disappearing."*

- R. D. Laing

- The theme of innovation in our industry has been in every session
  - Applying cutting-edge science to improving the lives of patients
- This conference has provided an opportunity to view the landscape for novel modalities and emerging technologies in the field of human therapeutics
  - Advances in manufacturing, analytics, modeling, dosage forms, delivery systems
- This session is intended to provide a global regulatory perspective on innovation
  - The rapid rate of innovation will necessitate the evolution of efficient and harmonized regulatory frameworks to ensure global patient access while still safeguarding the expected standards for quality, safety, and efficacy.

# Key Points from Talk #1 Sven Stegemann (Graz University of Technology)

## *A European Perspective of Global CMC Innovation*

- Dr. Stegemann presented a holistic approach to putting patient centricity at the heart of drug development as well as a variety of often overlooked considerations when designing drugs for patients.
- Patients have increasingly being recognized as a major factor in achieving therapeutic outcomes in the real world settings (effectiveness) - they are in control of the last step (Rx compliance) and are becoming more empowered in medical decisions by education and information accessibility.
- There are often gaps between efficacy and effectiveness as well as between clinical trial outcomes and real-world observations. Medication errors, therapeutic failures, adverse drug withdrawal events, and secondary non-adherence account for much of these differences.
- Patients are getting more involved in their health and healthcare decision by ease of information access and lay-person organization in the internet (eroding the white coat authority)
- The pharmaceutical product is beyond simple “health repair”, it is the patient experience with the disease (disease burden), the treatment (therapeutic burden) and the expectation in the personal outcomes

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# Key Points from Talk #1 Sven Stegemann (Graz University of Technology)

## *A European Perspective of Global CMC Innovation*

Patient centric pharmaceutical drug product design:

- It is the process of identifying the comprehensive needs of individuals or the target patient population, and utilizing the identified needs to design pharmaceutical drug products that provide the best overall benefit to risk profile for that target patient population over the intended duration of treatment.
- The patient is the owner of the disease and therapy as well as carried the burdens and outcomes. The benefit to risk might change with age (life expectancy, severity of ADR) and multimorbidity (drug – drug, drug – disease interactions)
- Therefore, industry should design therapies to meet patient–specific needs and make adherence to therapies simple/ seamless. Includes the following considerations / design inputs :
  - Patient (internal influences) – Co-morbidities, Dexterity, Literacy, Memory, Expectations, Illusion of control, Patient Expectations, undiagnosed symptoms, aging process
  - Environment (External influences) – culture, healthcare system, society/status, relatives/friends
- These lead to design outputs such as individual drug/drug combinations, individual dose/dose accuracy, dose range, disease-specific disabilities

# Key Points from Talk #1 Sven Stegemann (Graz University of Technology)

## *A European Perspective of Global CMC Innovation*

- Industry needs to adapt a broader definition of quality beyond technical/chemical
- Provided a list of reflection papers and practice guides that should inform regulatory guidance. Topics included: formulations for pediatric populations, geriatric medicines, potential for medication errors, frailty status.
- The Quality Target Product Profile ((Q)TPP) – forms the basis for product development considering conventional product related characteristics but should also considers patient related characteristics.
  - Individual physiology related factors (e.g. ADME, disease, drug-disease, drug-drug & age related changes)
  - Personality related (e.g. psychological situation, cognitive capacity, health literacy)
  - physical functioning related (e.g. dexterity, sensory, motoric changes)
- Case study – development of an ergonomically designed self-injection syringe for the rheumatoid arthritis compound certolizumab pegol (UCB)
- Multidisciplinary collaborations are required to understand patient behavior and intuitive use of medicines including learnings from the consumer industry
  - Should strive to evolve from products that require instructions to those that are intuitive (as the iPod was in 2001)

# Key Points from Talk #2 Yoshihiro Matsuda (PMDA)

## *PMDA Perspective*

Dr. Matsuda presented PMDA's perspectives on the major trends and challenges on CMC topics such as QbD, Continuous Manufacturing and global regulatory harmonization.

### QbD

- QbD provided (1) higher level of quality assurance, (2) facilitated regulatory assessment, (3) enabled science and risk based regulatory decisions, and (5) improved communication. Design Space – adoption challenges

### Novel Manufacturing Technologies: Continuous Manufacturing (ICH Q13)

- Industry's interest is moving towards Real Time Release Testing, Lifecycle Management (ICH Q12) and Novel Manufacturing Technologies.
- The current ICH Guidelines do not sufficiently address technical and regulatory requirements that are unique to CM.
- Dr. Matsuda is Regulatory Chair of the ICH Q13 expert working group
  - Proposed Timelines: Step 2b: June 2020, Step 4: November 2021
  - Definitions/regulatory concepts; key scientific approaches; regulatory expectations

# Key Points from Talk #2 Yoshihiro Matsuda (PMDA)

## *PMDA Perspective*

Continuous Manufacturing

- CM is trending right now because it may offer industry what is not achievable with batch manufacturing. However, batch manufacturing should remain one of the methods used in the future.

Expectations for CM – Broader choice of manufacturing methods

- Flexible manufacturing - Production in response to demand
- Detectability of poor quality products - Prevention of drug shortage problem
- Prevention of waste - Promotion of Green chemistry and cost reduction

PMDA work on CM

- PMDA Innovative Manufacturing Technology Working Group (IMT-WG)
  - PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry (provisional draft)
- Japan Agency for Medical Research and Development (AMED) sponsored study group.
  - "Points-to-consider" document
  - "State of control in continuous pharmaceutical manufacturing" document

# Key Points from Talk #2 Yoshihiro Matsuda (PMDA)

## *PMDA Perspective*

### PMDA Continuous Manufacturing Learnings

- There are different views on control strategies of CM between APIs, chemical products and biological products.
- We need further discussion about how we can define the acceptable variation of CM as the state of control.
- What kinds of PV strategies would be allowed?
- Issues of lifecycle management such as a batch size change, a formulation change, model maintenance, a change from CM to BM, etc.

### Regulatory harmonization and convergence

- Necessary for pharmaceutical industries to make similar regulatory decisions globally. The ICH is among the most effective vehicles of harmonization.
- Necessary to share knowledge between regulatory agencies, and particularly, to make opportunities to review real assessments with those of other regulatory agencies.

# Key Points from Talk #3 Celia Cruz (FDA)

## *Innovation and Regulatory Landscape*

- Emerging technologies offer the promise of novel therapies for patients and modernizing pharmaceutical manufacture
- FDA supports the implementation of innovative technologies using a science and risk-based approach
- Encouraging innovation in the pharmaceutical sector is an OPQ strategic priority
- The OPQ Emerging Technology Program can be utilized for early and effective interactions between FDA and industry in developing emerging manufacturing technologies
- OPQ science and research activities and collaborations are crucial to informing ETT interactions

# Key Points from Talk #3 Celia Cruz (FDA)

## *Innovation and Regulatory Landscape*

- Emerging Technology Team:
  - Early Engagement, Site Visit, Integrated Quality Assessment (IQA), PAI
  - ETT Maturity and evolution
  - Currently approx. 20 team members, part-time.
- More than 30 requests accepted since late 2014; guidance finalized in 2017
  - Strong positive industry feedback (8.9/10)
  - Shared learning and open communication to accelerate adoption of emerging technologies to advance product quality
  - ETT Grants and Contracts – Rutgers, MIT, Georgia Tech.
- Research and publications include:

  Continuous manufacturing of drug substance/product
  - CM standards development and wide range of products (5 approved)

  Continuous crystallization
  - Publications on continuous crystallization of carbamazepine and monitoring using Raman spectroscopy.

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PQRI Product Quality Research Institute

# Key Points from Talk #3 Celia Cruz (FDA)

## *Innovation and Regulatory Landscape*

- Research and publications include:

  Process modeling, simulation and advanced control

  - Modeling for QRM approaches; modeling in CM control strategy; modeling in quality risk assessment of CM applications.

  Big data, industry 4.0, and artificial intelligence

  - Use of AI to extract more information from process characterization, grants to Rutgers and Purdue.

  Evaluation of 3D printed tablets and additive manufacturing

  - Platform for precision medicine by delivering the ability to tailor production to different patient populations; study of additive materials and controls; risk map for 3D printed tablets.

  Multi-Attribute Method (MAM)

  - MAM is a peptide mapping based LC-MS approach proposed to replace traditional methods for QC of protein therapeutics.

- Journey to the Future of Pharmaceutical Manufacturing/Integration
  - Continue to innovate – integrate multiple innovative technologies together in the future. Regulators should predict the direction for future technologies in order to figure out where and when regulations are needed.

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# Panel Discussion and Q&As

Q: (Stegemann) Thoughts around digital application – what role would or should that play in patient adherence?

A: The current generation of geriatric patients are not digital native so technology is not centric to these patients and may not be beneficial. This may be a different case for the next generation of patients however, there's also a question of validity in digital-based diagnostics as well as challenges with data ownership and security.

Q: (Cruz) Would it be within the scope of the Emerging Technologies Team to develop novel manufacturing processes to address raw materials shortages, such as saline, dextrose solutions, etc., with manufacturing processes that have slim margins ?

A: The qualification criteria for participation in ETT program include (a) the proposed technology has the potential to improve product safety, identity, strength, quality and purity, and (b) the new technology includes one or more elements subject to quality assessment for which the Agency has limited review or inspection experience. It depends on the root cause of the shortage, but if criteria are met it could be considered.

# Panel Discussion and Q&As

Q: Dr. Stegemann and Dr. Cruz both presented very different approaches to meeting patient needs. Dr. Stegemann emphasized increased simplicity and designing with patient-specific needs in mind, such as fatigue, dexterity, technological literacy. Dr. Cruz emphasized emerging, innovative technologies such as bedside 3D tablet printing, which is far more sophisticated than the current state. These approaches seem to be at odds, one advocating for increased complexity, while the other advocated for simplicity. What are your thoughts on how these two can exist in the same space?

A: (Cruz) The FDA does not advocate for a particular technology and the examples given are manufacturing processes brought to us for assessment to meet a specific unmet need. In the case of 3D printing, examples include serving remote populations and battlefield aid in war. However, one could imagine where this 3D model gets leveraged by a pharmacy and allows for manufacturing of specific designs that meet the needs Dr. Stegemann described.

(Stegemann) Depending on design and application, 3D printing has the ability to simplify the process of drug manufacturing and delivery. For instance, if a drug is produced on demand for a patient when he/she needs it, it could reduce burden on the patient to remember to take the drug. He believes that creating standards (colors, shapes identifiers), rather than creating any and all variations of drug products, is key.

Q: How do you envision coordinating the regulation of these emerging technologies between agencies?

A: (Matsuda) In effort to share knowledge between regulatory agencies and create opportunities to discuss real life scenarios, ICH Q13 EWG is planning to visit a CM site.

(Cruz) From ETT Perspective, if the sponsor requests it we can share data with other agencies.

# Overall Conclusions

- There are many CMC challenges facing our industry with the rapidly evolving and innovative landscape
- Emerging technologies offer the promise of novel therapies for patients and modernizing pharmaceutical manufacture
- Industry, regulatory agencies, and academics need to continue to share ideas and information in a transparent manner
  - Consortia, conferences, publications
- Knowledge management will be key as the amount of data grows exponentially (AI and ML applications)
- Harmonization of global approaches to regulatory strategies with consistent data packages will facilitate approvals
- The true benefactors of these efforts will be the patients that are so desperately in need of these life-saving therapies