Managing regulatory expectations throughout the product lifecycle

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ICH reform (2015) leads to enhanced expectations for global harmonization

- Name change: International Council for Harmonisation of technical requirements for pharmaceuticals for human use
- Virtual inauguration took place on October 23rd, 2015.
- ICH Assembly took place in Jacksonville Florida, Dec. 5-10, 2015, and in Lisbon, Portugal, June 11-16, 2016.
- Governance and transparency: Improve transparency and openness of ICH and its processes
- Structure: ICH Assembly – overarching body
  Management Committee – is in charge of administrative matters
- Membership: Assembly – includes drug regulatory authorities and international pharmaceutical industry associations, who apply to become an ICH Member and meet the eligibility criteria
  - Observers – includes authorities and organizations that are not (or not yet) eligible for or interested in becoming ICH Members
- International outreach: Increase participation of other regulators and affected global industry sectors
- Permanent members: Founding members: US FDA, EU, PMDA/MHLW, PhRMA, EFPIA, JPMA
  - Standing members: Health Canada, Swiss Medic
- Other members: Standing observers: WHO, IFPMA
  - First observers under the new rule: SADC, GCC, ANVISA, PANDRH, APEC

Source: ICH Public Meeting, May 6, 2016
ICH Quality Guidelines

**Enabler**
- Quality Risk Management (ICH Q9)

**Systems**
- Pharmaceutical Quality System (ICH Q10)
- GMP for APIs (ICH Q7)
- Analytical Validation (ICH Q2)
- Life Cycle Management (ICH Q12)

**Process**
- Development & Manuf. of APIs (ICH Q11)
- Pharmaceutical Development (ICH Q8)
- Biotechnological Products (ICH Q5A-E)

**Product**
- Specifications (ICH Q6A-B)
- Pharmacopoeias (ICH Q4)
- Impurities (ICH Q3A-D & ICH M7)
- Stability (ICH Q1A-F)

**Common Technical Document (CTD)**
(ICH M4Q, eCTD: ICH M8)

Courtesy: S. Roenninger
Quality by Design

Current ICH “Q” Activities

- Q3C – Guideline for Residual Solvents
- Q3D – Guideline on Elemental Impurities
- Q11 – Q&As: Selection and Justification for Starting Materials for the Manufacture of Drug Substances
- Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
- M4Q – Addressing CTD-Q Related Questions/Change Requests Raised by eCTD

Enabler: Knowledge Management as part of Quality Risk Management (ICH Q9)

Courtesy: S. Roenninger
Industrial Product Life Cycle Management has many dimensions and aspects

- Environment – see e.g. carbon footprint and ISO 14040
- Analytics
- Manufacturing
- Supply and Logistics
- Cost and profit
- Therapeutic value added to the patient
- Regulatory

In this presentation we focus on the regulatory aspects of Lifecycle Management of Product Quality, on product quality life cycle management.
Product quality lifecycle management encompasses:

1. the regulatory dossier and regulatory commitments for manufacture and control
2. the pharmaceutical quality system and its risk/change/knowledge management components
3. the use of post-approval change management plans and protocols
Regulatory quality expectations for the pharmaceutical product:

1. Developed with the patient in mind
2. Manufactured with appropriate apparatus and robust processes with adequate control
3. Manufactured under GMP and distributed under GDP

How can this be achieved?

Lifecycle: All phases in the life of a product from the initial development through marketing until the product’s discontinuation. (ICH-Q8)
Modern pharmaceutical development employs Quality by Design concepts as described in ICH-Q8:
- starting by defining the Quality Target Product Profile and
- using science and risk based approaches and
- knowledge management.
Patient @ center employs the therapeutic trinity to optimize value for the patient

Patient stratification:
- Age groups e.g. pediatric patients, elderly
- Disease groups with specific impairments e.g. arthrose patients
- Individual patients with need for personalized medicine
Use benefit/risk approaches to select the most appropriate pharmaceutical dosage form for the targeted patient population.
Select appropriate mfg processes and adequate control over all Quality Systems during the entire lifecycle.

Layers of manufacturing processes to be governed by good manufacturing practices:

1. Processing of API, excipients and packaging into a Drug Product (PQS, ICH-Q10)

2. Processing of starting materials into API (ICH-Q7), excipients, and packaging

3. Processing of API starting materials (ICH-Q11 Q&A), excipient starting materials and packaging starting materials
The ICH Q7 document is intended to be read in its entirety regardless of the nature of the manufacturing activities being conducted to fully understand the linkages between certain sections and successfully implement appropriate GMPs at all stages of the API supply chain, including distribution.

ICH Q7 Q&A, Introduction, 2015
The Pharmaceutical Quality System encompasses all stages of the Product Lifecycle including all changes
Change management

**Change Control** (WHO, EU GMP)
A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.

**Change Management** (ICH Q10)
A systematic approach to proposing, evaluating, approving, implementing and reviewing changes.

**Variation** (EU) (regulatory change)
An amendment to the contents of the marketing authorisation for a medicinal product.
Keeping a process in its validated state requires a Lifecycle Approach

Regulatory agencies are emphasizing the need for a more thorough understanding of product and process prior to validation.

**Traditional:**
- Based largely univariant and empirical approach to development
- Three validation lots
- Not a lot of emphasis on material variability
- Utilizes proactive process monitoring/PAT for trending/continuous verification
- Continuous proactive improvement (we are always learning)

**Process Validation Lifecycle Approach:**
- A holistic QbD lifecycle approach to development supports a robust validation.
- Uni/multi variant
- Use of modeling tools
- Use of prior knowledge
- Leverages control strategy implementation
- Utilizes proactive process monitoring/PAT for trending/continuous verification
Process Validation requires Lifecycle Management due to accommodate process changes.

Grace E. McNally, FDA
Change is an inherent part of the development process and its documentation is good scientific practice.

Changes could be incorporated in and tracked through the development plan.

The formality of application of the change management process should be consistent with the stage of pharmaceutical development: clin phase III > clin phase II > clin phase I.

Investigational products are subject to formal change management - adapt EU Product Specification File and Investigational Medicinal Product Dossier (IMPD).

Changes can potentially impact on INDs/CTAs – notification of competent authorities (if applicable).
Technology Transfer may take place at different points in the lifecycle e.g.
- prior to phase III clinical manufacture,
- post-approval to additional or alternative manufacturing site, and
- to contract manufacturing partners.

Technology Transfer forms the basis for commercial manufacturing and supply and strongly benefits from QbD practice.

GMP standards for Technology Transfer when close to or equal to commercial manufacture requires full application of the change management system.

Changes could be part of the Technology Transfer plan.

Need to consider impact on emerging or approved regulatory filings since Technology Transfer may trigger the need for many changes in the registration file.

Impact on existing facilities (if not new build or dedicated).
Utilization of QbD ensures a robust Technology Transfer

- Form a diverse/skilled and collaborative development team
- Review the process flow diagram for key inputs/outputs that could impact quality (QRM)
- Uni/multi variant experiments should have been completed to study relationships and gain information on potential sources of variability. (need to know where quality could be impacted)
- Make sure you understand your measurement capability (i.e. repeatability, precision)
- Critical Process Parameters (CPPs), Critical Quality Attributes (CQAs) and other important parameters are identified
- Design space should be defined and understood consisting of a set of input ranges (CPPs) that provide high probability that CQAs will meet specification.
- A control strategy needs to be in place to assure focus on critical points
- Full GMP standards apply as is full application of change management
- Extent of markets supplied and different GMP requirements need to be considered during change management to evaluate the impact on regulatory filings.
- Impact of change on upstream activities e.g. component and raw material supplies
- Impact of change on downstream activities e.g. subsequent manufacturing packaging and distribution steps
- Impact on Control Strategy
Control Strategy is the quintessential element of QbD

A planned set of controls, derived from current product and process understanding, that assures process performance and product quality.

The controls can include:
- parameters and attributes related to drug substance and drug product materials and components,
- facility and equipment operating conditions,
- in-process controls,
- finished product specifications, and the associated methods and frequency of monitoring and control.
Control over the Control Strategy must be managed during the entire product lifecycle.
Where are we in the Life Cycle of the concept of Quality by Design?

Quality life cycle element, as defined in the following:

1. **Adoption**: the implementation stage of a new quality initiative.

2. **Regeneration**: when a new quality initiative is used in conjunction with an existing one to generate new energy and impact.

3. **Energizing**: when an existing quality initiative is refocused and given new resources.

4. **Maturation**: when quality is strategically aligned and deployed across the organization.

5. **Limitation or stagnation**: when quality has not been strategically driven or aligned.

6. **Decline**: When a quality management system (QMS) has had a limited impact, initiatives are failing and the QMS is awaiting termination.

The science and risk-based **QbD approach needs energizing** to provide Health Authorities, the pharmaceutical industry and patients with the benefits.

Denis Leonard and Rodney McAdam, Quality’s Six Life Cycle Stages, AUGUST 2003 | www.asq.org
Despite ICH Q8 – Q11, in daily practice QbD did not deliver regulatory flexibility and continual product and process improvement.
Change during the Product Lifecycle

Change management often is a major hurdle to achieve continual improvements during the latter parts of the product lifecycle:

- **non-harmonized** between ICH-regions and beyond!
- **assessment** of impact of change **varies** both in risk and in time
- no agreement on use of **comparability protocol**
- no agreement how to define **regulatory change in registration file**
- **differences** in task division between **assessors and inspectors**
Global Change Management is complex

The inefficient, non-harmonized change management process spills regulatory capacity both from the side of HAs and companies, obstructs continual improvement and, most seriously, let patients suffer.
# Final Concept Paper

## Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

dated 28 July 2014

**Endorsed by the ICH Steering Committee on 9 September 2014**

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The science and risk-based QbD approach needs energizing to provide Health Authorities, the pharmaceutical industry and patients with the benefits. Energizing is achieved at least partially by expanding the ICH community and involve organizations like ANVISA, and by introducing new standards like ICH Q12.
Regarding the **Regulatory Dossier** the ICH-Q12 IWG will

- Explore the development of a harmonised approach to “regulatory commitments” for inclusion in the guideline. Such approaches could enable post approval changes that facilitate continual improvement and encourage the adoption of innovative technologies.

- Delineate the appropriate level of detail and information necessary for regulatory assessment and inspection in the dossier, in order to create a more enabling post approval change management system.

*Concept Paper ICH Q12, dated 28 July 2014*
Regarding **Pharmaceutical Quality System aspects** the ICH-Q12 IWG will

- Establish **criteria** for a harmonised risk-based change management system based on product, process and/or clinical knowledge that effectively evaluates the **impact of change on quality**, and, as applicable to safety and efficacy.

- Clarify expectations and reinforce the need to maintain a **knowledge management system** that ensures **continuity of product and process information** over the product lifecycle.
Regarding **Post-Approval Change Management Plans and Protocols** the ICH-Q12 IWG will

- Introduce
  - a) the concept of a *post-approval management plan* that can be used to *proactively identify* post-approval changes and
  - b) the mechanism to *submit and assess* these changes by regulatory authorities (Assessors and Inspectors)

- Establish *criteria for post-approval change management protocols* that can be adopted by the ICH regions (enabling a harmonised proactive approach for lifecycle management)

- Encourage enhanced product development and control strategy approaches (*Quality by Design (QbD)*) providing opportunities for scientific and risk based *foundations for post-approval change management plans*.

*Concept Paper ICH Q12, dated 28 July 2014*
Dealing with changes according to ICH Q12

1. Established and non-established conditions?

2. Pre-approval change management plan?

Figure: Lifecycle Management workshop EMA, London, 28-29 October 2015
Product Development and Lifecycle Strategy

PDLS is summary of:
- product development
- control strategy
- proposed established conditions
- proposed regulatory regulatory filing for future changes (optional?)

Can also be used to develop and use PACMPs, which will provide manufacturers the opportunity to propose how to manage future mfg changes, rather then wait, submit and discuss with HAs.
Change is beautiful .... a strong need to adapt the current state of immobility!

In the current regulatory climate everybody hates to change:
- Companies try to avoid change because of the immense regulatory burden it creates.
- Regulators because of uncertainty and lack of trust.

To avoid current hiccups for patients such as drug shortages and inefficiencies for companies we have to realize that change is fundamental to quality improvement. The registration file is no end product, but a document that should facilitate change. The registration process should support making changes.
If change is crucial for the patient, the health system and the companies ..... 

Let companies take full responsibility to handle changes within their Quality System including change management and CAPA 

Let companies be monitored and inspected for adequacy of their Quality System, their Quality Culture and Processing Capability (metrics) 

Enable the registration file to be equipped for change 

Let Health Authorities align using risk based principles for regulatory change management
My conclusions

The ICH organization is reinventing itself and the new ICH process deserves to be owned by all global pharmaceutical organizations, including ANVISA.

In the CMC area Quality by Design is the way forward, since it is based on science and risk, rather than ‘case by case’ and it enables continual improvement.

Continual improvement is needed to maintain and increase quality of products and processes; change therefore needs to be facilitated e.g. by introducing Pre-Approval Change Management Protocols, and by dealing with changes more in a ‘Do first and Tell later’ mode.

Lifecycle approaches are needed to ‘close the loop’ and ‘avoid loose ends’. Solutions should work throughout all stages from development till discontinuation.

It is important that pharmaceutical industry is given full responsibility for quality over the entire lifecycle, including changes of product design, manufacturing process including control strategy, and analytics, be it with adequate oversight from health authorities.

Moving to Do and tell, where possible ....
Let’s use the ICH QbD standardization process to bring even better quality medicines to our patients!!

Medicines with improved Quality by Design