Improving Post-Approval Change Processes as a Way to Ensure Technical Innovation and Drug Product Availability


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The Apparent Dilemmas

• **Regulatory capacity demands a balance between:**
  – the degree of regulatory oversight to ensure safe and effective health products
  – the barriers to timely access to those products

• **As global regulatory capacity increases so does oversight, but at a potential risk to timely access to medicines**

• **Pharmaceutical companies must balance between:**
  – necessary changes as well as voluntary changes to innovate, remain CGMP compliant and ensuring drug product availability
  – satisfying stakeholders/owners expectations to financial performance

• **As regulatory complexity for post approval changes and cost pressure continue to increase, so does the logistics challenge at a potential risk to drug product availability**

• **Together our objective is to improve public health**
EU GMPs,
Part I, Chapter 1

"Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge."

ICH Q10
Pharmaceutical Quality System
Objectives

Product realization
State of control
Continual Improvement

Process Analytical Technology (PAT) was supposed to facilitate innovation, but it hasn’t been successful. Why? And why are we struggling with innovation as an industry?

Guidance for Industry
PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
Product Realization:
Drug Shortages Happen Often

86% of respondents say medicines shortages are a current problem in the hospital they work in, in terms of delivering the best care to patients and/or operating the hospital pharmacy.

66% of all respondents are affected on a daily or weekly basis.

Source: EAHP, European Association of Hospital Pharmacists. EMA Workshop on Shortages due to manufacturing and quality problems, London, UK, 09-Oct-2015
Our Industry is Working on solutions to Drug Shortages Caused by Quality and Mfg Problems

Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems

1. Introduction

Ensuring the safety and Good Manufacturing Practice (GMP) compliance of the manufacturing supply chain is an important responsibility of the Marketing Authorization Holder (MAH) to ensure appropriate and continued availability of medicinal products for human use to meet the needs of patients in accordance with Article 8 of Directive 2001/83.

There is evidence that deviation in quality of medicines can lead to incorrect, or failure to treat, the use of less efficacious or inferior products, under-dosage of medicinal products, increased potential for error and poorer patient outcomes, described by adverse or delayed impact or occurrence of preventable adverse effects associated with alternative medicinal products or dosage forms.

Recent unexpected disruptions to the manufacturing supply chain due to manufacturing/GMP compliance problems have resulted in acute and severe shortages of important medicinal products in the European Union (EU), requiring changes to prescribing instructions, and initiation of patient allocation programmes.

U.S. legislature currently requires mandatory pre-notification by firms of anticipated supply in the case of permanent or temporary consistent 7 and for manufacturers of medicines in the case of a defect that would lead to an abnormal registration in supply.

In the United States (US), as a result of a high number of shortages of medicinal products, the Food and Drug Administration (FDA) published at the end of last year a draft "Final Rule" regarding...

So what are the root causes?
The Heterogenous Regulatory PAC Landscape Makes it a Challenge Being a Global Supplier

Example: One pediatric vaccine protecting against several diseases
Pentavalent Vaccine: a Pediatric Combination Immunizing Against 5 Diseases

- Hib
- Pertussis
- Diphtheria
- Tetanus
- Polio

Each vaccine consists of not 1 but 8 antigens (drug substances).
Formulation is critically important to efficacy.
The Pentavalent Vaccine in Numbers. Yes – It’s a Patchwork Picture

Change is natural, and necessary to innovate, but variances in regulatory approval processes lead to multiple version of same product and a logistics challenge

Approved in 105 countries
Example, Continued….

- 83 batches produced in one year
- 1/3rd of the Changes impacting more than 50% of the batches
- No more than 7 batches ‘version’ identical
- 55 batches totally different from one to another
- 81 batches impacted by new autoclave
- 78 batches impacted by new reference standard
- 43 batches impacted by updating analytical method to new pharmacopoeia version
- 36 batches impacted by change from pyrogen to LAL endotoxin testing
- 26 batches impacted by new raw material supplier

\[
\text{Number of possible changes in Established Conditions} \times \text{Number of different regulatory processes} = \text{a lot!}
\]

Sustainable? Does this kill innovation?
We are here!

The current situation leads to drug shortages & inadequate innovation.
And what about the state of control?

Together we must do a better job to ensure the Q10 objectives of
- Product Realization,
- State of Control
- Continual Improvement

& to improve public health

But how?
# Common Objectives

## Industry
- Globalization
- Improved efficiency
- Reduced process variability
- Improve public health globally

## Regulators
- Nationalization
- Safeguard public health locally
- Sustainable supply
- Enforcing cGMPs

- Safe, efficacious quality products
- Availability of drug products - sustainably
- Innovation
- Improved controls
PAC Processes Need to be Improved to Ensure Technical Innovation and Drug Product Availability

- Some elements of regulatory oversight can be shared
  - Evaluation of quality, efficacy and safety

- Other elements of regulatory oversight must be local
  - The licensing decision
  - Local manufacturing oversight
  - Pharmacovigilance
  - Appropriate distribution controls (stability and cold chain)
  - Product security (protection against counterfeiting and adulteration)

- Shift the dialog to be scientific and evidence based, case studies
- Emphasize that our industry is global – changes should be assessed globally
- Set expectations for PAC global approval time limits & publish data
Improving PAC Processes - Thoughts

• Enhance Regulatory Agency reliance on each other

• Reduce regulatory submission burden
  – Shift the dialog upstream to protocols instead of reports (PACMPs)
  – Shift many more changes to be covered only in an effective Pharmaceutical Quality System (PQS) (no regulatory submission)

• Articulate the need for innovation based on scientific facts

• Plan together through Lifecycle Management Plans (LCM)

• Standardized global Change Protocols
Articulate the Need for Technology Innovation

• **Articulate expedited & harmonized PAC approvals when**
  – Enhanced redundancy
  – Improved process & product controls
  – Improved cost-efficiency, reduced lead times
  – New technologies bring added value

• **Recommend specific validation/comparability studies for new technologies***
  – Single Use Systems
  – Continuous manufacturing
  – Modernization of aging facilities
  – Technologies to manufacture products for new therapies
  – Etc..

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This dialog needs to extend from Quality & Regulatory Affairs professionals to Operations leaders and experts

* PDA: global Change Protocols
Reduced Regulatory Submission Burden. What if we....

- Used the Pharmaceutical Quality System (PQS) and Post Approval Change Management Protocols (PACMPs) to downgrade PACs using a risk-based approach, while maintaining a state of control.

- Changes to non-Established Conditions (non-ECs)
  - Manage in the PQS

- Changes to Established Conditions (ECs). Risk and science based approach
  - PACs having no potential impact to quality, safety and/or efficacy of the drug product handle and manage in the PQS only (“Do & Record”)
  - PACs requiring prior approval by national legislation consider submitting the planned change(s) in a PACMP for evaluation by Regulators. Based on assessment implement either a) only in the PQS (“Do & Tell”) provided all acceptance criteria of the approved PACMP are met or b) after written report summarizing the completed PACMP activities approved by the Regulators (“Tell & Do”). An approved report should be required for any PAC described in the box here

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1. Addition/elimination of a CQA
2. Addition/elimination of a method on the control system
3. Widening of specifications
4. Changes to CPPs
5. Changes to shelf life
6. Changes to novel excipients
A Lifecycle Management Plan (LCM Plan) is part of the company's product lifecycle strategy; it is optional and may be submitted with a new application or for an existing product.

Opportunity for company to:
- prospectively and transparently provide information for managing the post approval phase of the product lifecycle globally
- enhance transparency of planned changes and globally harmonized approaches
- summarize globally agreed upon Established Conditions (ECs) and the company’s Control Strategy
- summarize plans to ensure product supply and availability
- explain and link planned post approval changes to the development summary and the PQS
- describe how the company ensures an effective PQS is developed and maintained

Describes planned changes at high level including product quality impact assessment comparability approach, and suggested reporting category.

A summary of all planned major changes, their interdependency and suggested reduced burden of post approval changes reporting.

Optional structured approach to engaging in a dialog between company and the Health Authorities about planned changes.
LCM Plan – Potential Benefits

• Facilitates ICH Q8 - Q10 objectives
• Harmonizes ECs across several countries for the drug product. Summarizes the Control Strategy and how it is linked to the ECs.
• Summarizes in one place how the product is planned to be managed in the commercial stage of the product lifecycle.
• Opportunity to link planned post-approval changes needed to ensure continued product availability.
• Mutual understanding of post approval commitments and planned changes between the company and the Health Authorities (Assessor and Inspector).
• Expedites reviews and implementation of planned post approval changes.
• Enhances predictability, certainty and transparency of studies to implement a change.
• Provides an opportunity to reduce the reporting category
• Ability for company to communicate to assessors the company’s approach to ensuring an effective PQS, how post-approval changes are managed in the PQS, and how product knowledge is managed during the commercial stage of the product life cycle.
• Where considered necessary, summarizes the company’s plans for supply and drug product availability including identified risks in one place.
Conclusion

• Industry & regulators have many objectives in common, but we are coming from different positions; active dialog is critical to success
• Current regulatory process complexity is not sustainable, it is causing drug shortages & it hampers technology innovation
• Some elements of regulatory oversight can be shared; others must be local
• As an industry we can advance technology if we
  – speak up and work together to drastically improve innovation pace
  – shift the dialog to be more scientific
  – articulate the need for technology innovation, & have more Operations leaders involvement
  – articulate the need for reduced regulatory burden
• PDA is actively supporting the ICH Q12 work connecting people, science and regulation in the areas of LCM Plan template, global Change Protocols, defining an effective PQS, and specific examples of potential reduced regulatory burden
Back to the Vaccines: hexavalent vaccine on market, i.e. penta + one...

Public health convenience, but also added complexity from a manufacturing perspective. All stakeholders must work together to encourage innovation.
Thank you

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