# Manufacturing Innovation - PDA Annual Meeting 2017, Anaheim

8 min. reading time

*by Thomas Peither*

The topics at this year's PDA Annual Meeting ranged from repairing genetic defects to disposable materials and continuous manufacturing. In Anaheim, California, approximately 800 participants got together to discuss the challenges in the production of medicinal drug products for today and the future. Interesting presentations demonstrated the breadth of the topics:

- Continuous manufacturing
- Manufacturing innovations
- Knowledge management
- Post-approval changes and
- Big data

**Continuous Manufacturing**

Several presentations dealt with continuous manufacturing and also picked up on aspects such as knowledge management at the same time. The fact that a high degree of process mastery, process knowledge and, to some extent, a changeover to manufacturing processes that can be operated continuously are required for continuous manufacturing was highlighted and emphasised once again. According to Dr. Rapti Madurawe, FDA, the benefits of continuous manufacturing are obvious:

- Reduction in manufacturing costs
    - Smaller facilities
    - Fewer solvents and less waste
    - Smaller ecological footprint
- Improvement in quality
    - Improvement of process understanding
    - Faster development of manufacturing systems
    - Better product quality in real time
- Satisfied patients
- Faster market supply
- Agile and flexible production
- Quick reaction time for emergencies and drug shortages



 

These are good reasons to concentrate on continuous manufacturing, particularly for new approvals. It was underlined in several places that a "deceleration" in production often goes hand in hand with this. The processes can also take place more slowly on smaller machines – continuous & fault-free manufacturing will soon make up for these supposed disadvantages.

This is likely to trigger a rethinking process for more than just a few equipment manufacturers.

**Isolators are an Example of Innovation in Manufacturing**

"Where is the innovation in pharmaceutical production?" asked Barry Starkman, DPS Engineering, in a presentation focusing on flexible manufacturing equipment for product launches. The triumph of isolators for him represented a clear example of how it is possible to improve product quality and, at the same time, reduce production costs and times. He emphasised that he would wish for more of these kinds of innovations, but there were hardly any around.

Manufacturing equipment for new biotechnology-based or molecular-based therapies might be fundamentally different, which also raised many questions concerning GMP compliance. In the presentation by Prof. Bruce Conklin, Gladstone Institute of Cardiovascular Disease, this went as far as discussing the question of whether genetic modification using the CRISPR technique is a surgery or pharmaceutical treatment. The question could not be clarified, but the answer will nonetheless have a significant influence on the applicable quality requirements for the use of this new technology. Therefore, some presentations gave their participants a glimpse far into the future!

**Knowledge Management**

According to Dr. Ursula Busse, Novartis "Trust is a significant success factor for regulatory flexibility". She added, that this trust could be lost quickly. But where is the impact on knowledge management? Well you can't just lose trust, it has to be earned first, e.g. through transparency. Anyone sharing process knowledge with the authorities often earns trust in return, or the trust increases. And now we're on the topic of knowledge management. If the authorities are involved here then they are able to support some decisions more based on this knowledge. But in general it is a long road to get there – because many relationships in GMP surveillance are still burdened by the past. And some companies do not have the knowledge yet. Tacit knowledge has to be turned into explicit knowledge first.

This transformation of knowledge is already very difficult because tacit knowledge is not obvious. For the process of identifying tacit knowledge alone represents an enormous increase in knowledge.

Every pharmaceutical manufacturer should think about which knowledge they are providing authorities within the context of the life cycle model. Because when it comes to post-approval changes, for example, a great deal has to be disclosed to the authorities anyway. So why not make knowledge available sooner – perhaps post-approval changes might also proceed more quickly as a result. But that's a topic discussed in another session.



 

## Post-approval Changes (PAC)

Emma Ramnarine, Genentech/Roche, presented the survey results from the PDA Task Force PAC iAM (Post-Approval Changes for Innovation in Availability of Medicines). "Knowledge leads to product and process understanding" she repeated an often-heard statement. And in the end this will lead to post-approval changes to improve the manufacturing process through commercial manufacturing. 85 respondents form quality, regulatory, manufacturing, technical operations and development answered the questions. The survey represents all kinds of products (1 - >100 products) and product variations (1 - >10). The respondents proceed between <50 up-to >1000 PACs/year) in <25 and >100 countries.

**Why do companies make PACs?**

| | |
|---|---|
| Process improvements | 89% |
| Expansion/reduction of manufacturing capacity | 76% |
| Manufacturing site changes | 73% |
| Upgrade or replacement of obsolete equipment | 71% |
| Tech transfer | 69% |
| Specification/testing change | 69% |
| Raw material replacement | 64% |
| Regulatory commitment | 60% |
| Introduction of innovative technologies | 60% |
| Compliance to new regulations | 53% |
| Product-related change (e.g., combination product, new formulation) | 47% |
| Others | 4% |

The bottleneck is the preparation time for a change, whether it is the time that is required from change initiation to submit the PAC to regulators or from PAC submission to approval.
The time to implement is insignificant compared to the preparation and application phase.

For most respondents, the complexity of a PAC correlates with country specific requirements.

Mostly positive is the use of post-approval change management protocols (PACMPs) or comparability protocols. 70% of all respondents said, that PACMPs are accepted globally.

But there is still a lot to be done, to make further progress in this field. 97% think, that the current PAC process hinders technology progress and more than 50% said, that sometimes or often changes that had been proposed were not implemented due to the regulatory burden/complexity.
After the OOS result is detected and the process initiated, the costliest but most important phase of the process begins: the error analysis. The check is generally documented using a checklist. To identify possible non-obvious laboratory errors, confirmatory measurements are carried out.

## Big Data

What would a modern conference be without the topic of "big data". The goal provides the approach here: "What do I want to achieve with the data?" The audience became aware that data can be interpreted in a wide variety of ways which do not necessarily lead to the desired result. But those who do not have a goal, rarely stumble upon it by accident. As for many activities, defining a goal is difficult and information technology (IT), as well as programmers and analysts, have an easier time if a goal is specified.



 

**Dr. Michele D'Alessandro, Merck & Co., showed the progression of data analysis:**

| | Operational View | Strategic View |
|---|---|---|
| Hindsight | What happened? | standard reports |
| | How many, how often, where? | ad hoc reports |
| Insight | What exactly is the problem? | query/drill down |
| | What actions are needed? | Alerts |
| | Why is this happening? | statistical analysis |
| Foresight | What happens if we try this? | simulation / randomized testing |
| | What will happen next? | predictive modelling / forecasting |
| | What's the best that can happen? | optimization |

The following guiding principles were described as helpful:

- Self-service as the default
  This means that people should pull information and data
- Embed analytics/information into processes, change them if needed
  The process should have the lead and the ownership for data
- Work towards "one stop shop" for routine information for key roles
  Dashboards can deliver helpful information/data for activities
- Expose information in its current state and work to improve quality
- Push data creation responsibility to appropriate process
- Push ownership/accountability of data accuracy to process/people who create it
- Develop consumable solutions; experiment frequently, throw away, adjust whenever needed

The ownership of data seems to be a very critical aspect and Michelle D'Alessandro recommended to "treat data as a resource through focused information stewardship". Another tip was to start with "minimal investments in infrastructure and software" to allow a rapid scale-up/scale-down. It is important to share data and to make them visible throughout the organization.

**Sources**

Emma Ramnarin, Post-approval Change and Knowledge Management – Where are We? Results from the PAC iAM Task Force Survey, PDA Annual Meeting 2017, Anaheim, CA

Rapti D. Madurawe, FDA, Continuous Manufacturing – An FDA Perspective, PDA Annual Meeting 2017, Anaheim, CA

Michele C. D'Alessandro, Big Data to Optimize Manufacturing, PDA Annual Meeting 2017, Anaheim, CA



 

Barry Starkman, The Emerging Environment of Aseptic Filling, PDA Annual Meeting 2017, Anaheim, CA

Ursula Busse, The Future State – Knowledge Management and Sharing to Reduce Regulatory Burden, PDA Annual Meeting 2017, Anaheim, CA

## Author:

**Thomas Peither**
Editor-in-Chief
Maas & Peither AG – GMP Publishing
E-mail: thomas.peither@gmp-publishing.com



 