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Discussion Paper

Author: Manufacturing and Quality Expert Group ● **Date:** 22/05/2020 ● **Version:** Final

MQEG Discussion Paper: Digitalization in Pharmaceutical Manufacturing

Purpose

Pharmaceutical manufacturers face the challenge to acquire and apply digitalization know-how, while still working within regulatory quality/Good Manufacturing Practice (GMP) frameworks. Regulatory bodies face the challenge to interpret, adopt and develop the regulatory quality/GMP requirements, without creating obstacles to innovation and allowing modernization of manufacturing, testing and release of safe and efficacious products for patients. It is in the public interest that the pharmaceutical sector balances regulatory scrutiny with the necessary agility for change.
This paper highlights selected regulatory quality/GMP framework aspects of digitalization in order to support the development of consistent interpretations of requirements and needs. It also proposes advocacy topics for EFPIA.

Introduction

Faster mobile communication (5G), the Internet of Things (IoT), artificial intelligence (AI), robotics, blockchain, and virtual and augmented reality (VR, AR) and others are technologies that currently drive the 4th industrial revolution. Machines and devices are communicating, continuously and in real-time. Large amounts of data are generated, validated and stored and become subject to use by advanced data analytical tools for predicting, modelling, controlling, and trending.
EFPIA companies are aware that digitalization in pharmaceutical manufacturing plays an essential role to provide innovative medicinal products with high quality to their patients, within economic considerations of the modern healthcare sector.
A number of initiatives have been proposed and started using various technologies, from advanced analytics and augmented reality via IoT and robotics in packaging, and virtual reality in training. To implement these innovations, the interpretation of GMP regulations has to be considered. While certain applications can be implemented and used without any regulatory restriction, other applications need to be considered in the context of the applicable regulatory framework.

Scope and approach

The authors have reviewed current industry approaches to introduce digitalization in the manufacturing area with regard to their compliance with current regulatory framework., It is concluded that many applications can be handled within the GMP framework, whereas others may warrant either further discussion with regulators to clarify regulatory expectations, or re-interpretation or adaption of current regulations.
Selection criteria included

- "urgency" to clarify appropriate regulatory requirements,
- "simplicity" of implementation, and
- "strategic relevance" from EFPIA member perspective.

Subjects in scope have been reviewed and assessed as to what are the desired outcomes from digitalization, e.g.

- enhanced access to data, information, and knowledge, as basis of the transformation of input data into impactful information,
- enhanced process control, robustness, and/or performance, or adaptability of processes, or enhanced process understanding in general,
- leveraging human expertise,
- quality decisions based on data rather than documentation review,
- ability to exchange information with agencies, to overcome traditional forms of electronic- or hard copy submissions, both for initial approvals and post approval situation,

or what are the 'prerequisites and tools', e.g.

- personal capabilities (mindset, digitalization expertise, new responsibilities and roles),
- organizational enablers and conditions (set-up, culture), transformational agility (how to realize rapid changes in a regulated environment),
- data architectures (master data, data model use), systems and system connectivity ('data warehouse'), artificial intelligence.

EFPIA companies analyzed digitalization approaches in manufacturing projects, structured and prioritized them. From this approach, the following projects have high priority:

- Augmented Reality in Manufacturing,
- Use of adaptive process models; Automated and standardized manufacturing processes, interpretation of stability data,
- QA/QC (especially QP release) - use of artificial intelligence and 'at time' release,
- Automated and standardized review processes internally and externally with multiple Agencies,
- Use of robotics.

Other related subjects are currently discussed on their own merits or in different context, and have therefore been excluded from the scope of this review (i.e.: cybersecurity, data privacy and –integrity, supply chain security and counterfeit protection, electronic labeling, personalized medicine, software as medical device, or digital health).

Augmented Reality in Manufacturing

Description

In a computer-generated augmented reality, a real-world environment is enhanced by perceptual information for real-time use, that allows individuals to act on, or interact with a given subject or process. Augmented reality implies that a tool or device interface is used, and that the information is accessed from a remote source.

Current status

Augmented reality applications have been proposed to enable training (knowledge sharing), various supporting activities (trouble shooting), execution of certain GMP activities (line clearance) or maintenance of production equipment, as well as remote audits and inspections, incl.:

- remote virtual and interactive training (e.g. clean room training, Google glasses, digital twins),
- technical staff remotely supporting on-site experts, or
- operation guided by augmented reality (sensor calibration, machine assembly processes).

Further developments are anticipated to enable

- full remote audits and inspections,
- full remote control for maintenance and manufacturing operations, incl. line clearance,

Challenge and opportunity

Technical prerequisites for augmented reality are well understood and are assessed as being possible to interpret and apply with current GMPs. Future extensions of augmented reality applications seem to be attractive where they provide e.g. more effective training by visualization and interaction, and/or in cases where more flexible use of resources is possible, e.g. to overcome geographical limitations.

Use of Adaptive Process Models - Automated and Standardized Manufacturing Processes

Description and current status

The use of process models is common in manufacturing, to support e.g. real time release, continuous processing, generation of process understanding, or investigations. Adaptation of such traditional process models follows general GMP principles.

With the possibilities of digitalization, learning (adaptive, self-learning) models are attainable. Unlike 'traditional' models, the learning models are not freezed after validation at some time point, but continuously updated, powered by the growing pool of observed data and a designed learning mechanism in the modeling algorithm. This evolving nature is expected to improve the model performance (i.e. "quality of the model") continuously over time.

Challenge and opportunity

Adaptive models are automated to evolve continually as new data is processed, while the type and source of input data and the learning mechanism itself are fixed (invariate). Hence there are no discrete 'lifecycle stages' of model development, where 'version updates' can be referred to as subject of inspection or approval. Conventional validation evidence regarding the model development (i.e. used data and correctness of estimated model) is hard to be archived for every continuous model update. In addition, conventional evidences focus on repeatedly demonstrating the correctness of the fixed learning algorithm at a time point, while they miss to validate its expected performance over time.

Flexibility in regulatory documentation is needed to implement adaptive models in agile and fast way. This should be safeguarded within the company quality system, to allow the application of the adaptive models in productive environment. Key aspects to be documented about an adaptive model are (1) sources and types of input data, (2) learning mechanism, (3) conventional validation evidence at a fixed time point, (4) expected model performance over time, and the post-hoc monitoring results.

Use of Artificial Intelligence in QA/QC

Description

Where large or complex data sets need to be processed as prerequisite of quality decision making, automated processes may be applied to support or replace human (manual) activities. For instance, batch (QP) release using an automated process may be based on review by exception.

Artificial Intelligence may be instrumental in this automated process to translate from data to a decision, while minimizing the potential of human error.

Current status

Release activities are mainly manual processes where production and laboratory data, specifications, manufacturing methods, and many other records need to handled and assessed. Related data and information is often held in multiple places, different IT systems, or in paper-based records.

Challenge and opportunity

Quality decisions, specifically batch release, are critical activities and therefore prescriptively regulated by current GMPs.

Potential opportunities for automation (partly or full) incl. review and verification of procedures like

- comparison to QC limits or manufacturing parameter limits,
- Electronic Batch Record (EBR) inputs or completed batch record review,
- validation status, environmental conditions,
- deviations investigations, and changes,
- the regulatory compliance check.

This could contribute to automated real time release, which is supported by an artificial intelligence analysis of related deviations and changes, as well as fully automated control of supply. As prerequisites, validated IT solutions and manufacturing processes, control strategies incl. control methods, and trending and monitoring of quality and process attributes. AI in QA/QC should be safeguarded within the company quality system, to allow its application in productive environment.

Automated and Standardized Review Processes

Description

The traditional GMP paradigm requires review of critical step documentation by experienced personnel. Particularly where 'review' is prerequisite to 'quality relevant decisions', human 'confirmation' is seen as indispensable.

GMP regulations do not rule out or prohibit automated review processes, but also do not provide guidance as to what are acceptable performance criteria or controls for it (to 'justify' trust and reliance on the decision).

Introduction of automated review processes in regulated industry areas is therefore slow and justification approaches are 'conservative'.

Mindset and behaviour is still 'document focused', not 'data focused'.

Prerequisite and tools

Automated and standardized quality review processes are based on data provided directly from the shopfloor.

In addition, a model is needed that represents the relation between the data and the quality attributes of the final product.

The tool is needed to select relevant information to enable assessment and decision making based on these data.

The selection mechanism of the tool needs to be clearly documented and verified against testing scenarios, as well as confirmed through monitoring and trending of actual outcomes. Traceability and reproducibility of any decision needs to be achieved.

Challenge or opportunity

The challenge is to reverse mindsets and behavioural pattern in the pharmaceutical sector to 'data focus' quality review and decision making, rather than 'document focus'.

The opportunity is to have 'live data' available and accessible for multiple purposes like e.g. review and process control by different users, and to enable faster decisions.

Application areas could be processes that can easily be standardized, as e.g.:

- audit trail review and acceptance,
- batch record review and acceptance,
- generation and review of SOPs, qualification or validation documents, or any other kind of manufacturing and/or quality document.

Further extensions could involve e.g.:

- 'digital advisors' aiding root cause analysis for deviations, or
- no touch release approaches i.e. automated real-time-release of batches.

Automated and Standardized Review Processes could be extrapolated further to use in Regulatory licence applications with 'living data' to allow submission of an initial dossier that can be based on available data sets at time of submission, and allowing these to be further added to and interpretations reviewed during Agency review and approval. This could be particularly valuable in situations of accelerated pathways submissions but also allow for any licence to improve lifecycle build of data sets, and therefore refinement of control strategies and specifications. This is a practice already under examination by some companies and Agencies e.g. KASA and may assist application of developing regulatory concepts under ICH Q12.

Use of Robotics

Description

Modern robotics offers pharmaceutical production many new opportunities:

1. Simple tasks in logistics, packaging and quality control can be automated more easily and thus more cost-effectively than in the past. Examples include removing bottles from the conveyor belt or inserting samples into magazines. More complex processes in Quality Control, such as dissolution testing, have been fully automated since years. In these robotic systems all steps from preparation of the medium and filling the medium into the vessels, the insertion of the tablets, sampling at specified time points and analysis are carried out without human intervention. For the next run the robotic system cleans the vessels and the next set of tablets can be analyzed.
2. Image recognition and tactile sense give modern robotics the opportunity to offer automation solutions even where object diversity, process complexity or process variety have so far prevented classical automation. Examples here are sampling in the incoming goods department or sample preparation in the microbiological laboratory (bioburden testing).
3. In the future, self-learning robotic systems will be able to handle the variety and variability robustly without having to be programmed. An example of this is the handling of the many different containers or the sub-bottles in the laboratory.

Challenge and Opportunity

While the applications in 1. and 2. above are covered by existing regulatory requirements for validation, self-learning systems pose new challenges for qualification and validation.

The self-learning robot learns to optimize process steps based on collected data. In case of traditional robots, the process steps are fixed and defined by the program (locked algorithms). An example for a learning system is a robotic system, which learns to open different inliners in different drums. Even though it is important from the GMP perspective that the product remains undamaged and cross contamination is avoided. The validation of self-learning systems with adaptive algorithms needs alternative approaches compared to the traditional robotic systems with locked algorithms.

Conclusion

The intention of this internal EFPIA discussion paper is

- to help introduce and understand the concepts of digitalization,
- to build consistent interpretation guidelines for digitalization aspects and build global harmonization where possible.

EFPIA believes that the following items can be covered within the company quality system.

- augmented reality,
- automated and standardized review systems,
- Artificial Intelligence in QA/QC.

However, where novel approaches are proposed by industry, EFPIA believes that the clarificaton of regulatory expectations will be helpful, for instance with regard to flexibility in regulatory documentation to implement adaptive models or algorithms and self learning robotics.