Whitepaper

"The application of artificial intelligence in the process validation of medicinal products in compliance with GMP requirements"

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Content

1 Foreword and sample topic

In the age of digitalization and globalization, the pharmaceutical industry continues to focus on continuously improving product quality and ensuring patient well-being. With the implementation of continuous improvement measures, higher quality levels are achieved, which at the same time leads to ever-increasing demands on the industry.
Rapid new technological developments lead to new applicable possibilities in the industry. When applying new concepts and technologies, care must therefore be taken to ensure that the accompanying quality processes are designed and applied to ensure high product quality.

In 2011, the US Food and Drug Administration (FDA) published guidelines on process validation to draw attention to the need to use modern quality assurance tools when applying advanced technologies in the pharmaceutical industry. In recent years, the pharmaceutical industry has developed and established new concepts and processes in order to best meet all requirements in the age of digitalization and globalization.
One of the biggest challenges is the value-adding handling of "big data". According to Gartner, the definition of "big data" is a large amount of diverse data that is generated at high speeds.

In January 2011, the FDA's new Guidance for Industry Process Validation: General Principles and Practices adapted the process validation activities that were first defined in May 1987 to a life cycle concept.
The new guidance combines the basic principles of process validation from 1987 with some of the objectives of the FDA's "Pharmaceutical CGMPs for the 21st Century" initiative and the FDA's experience from the ICH's guidance for industry: (Q8 R2, Q9, Q10).
With the new approach to process validation, the FDA creates a link between product and process development, the validation of the industrial manufacturing process and the maintenance of the process in a controlled state during routine manufacturing via the life cycle approach.

The EMA followed the paradigm shift in process validation with the EU GMP Guideline on Process Validation in July 2014 and the update of Annex 15: Qualification and Validation in October 2015.
In addition to the systematic/strategic approach, the determination, processing and evaluation of the data also represented a major hurdle from a technological perspective.

2 The challange for a company in the pharmaceutical industry

Based on the current state of technology, fully automated data collection of critical process parameters from the manufacturing plants and critical material attributes from the raw material laboratories as well as critical quality properties from the release laboratories cannot be easily realized in many pharmaceutical companies.

The transmission and processing of large volumes of data generated during the manufacture of multiple products leads to an increased risk to data integrity as complexity increases.

In most cases, technologies from the early 1990s are used for production, which only allow automated data acquisition under very complex conditions via a hardware/software interface. In order to be able to process large volumes of data and thus achieve a high standard of product quality, companies have been investing large amounts of capital and resources for several years.

With the progressive establishment of partially and fully automated solution concepts for evaluating and monitoring the available data from a statistical perspective, it is essential to face the next major challenge. The large amount of diverse data that is generated at high speeds must be usable in a GMP-compliant manner with a value-adding concept.

The constant increase in diverse data and the economic pressure to process it in a timely and value-adding manner is creating a complex working environment in which GMP-compliant and value-adding execution will no longer be feasible in the future without the use of artificial intelligence.

There are already various scientific studies that have addressed the problem from different angles. However, these focus more on the sub-area of machine learning. Many questions arising from the overarching consideration of how artificial intelligence can be used for process validation throughout the entire product life cycle in the pharmaceutical industry are still largely unanswered from a scientific perspective.

3 Solution approach

The aim is to develop a solution approach for the application of artificial intelligence for the process validation of manufacturing processes in the pharmaceutical industry.

3.1 Methodology

In a first step, it is discussed how the data of the critical input and output variables of a pharmaceutical manufacturing process from pharmaceutical development to the market release of a drug are determined and used in machine learning.

In a second step, it is shown how an AI unit independently evaluates process results and events that occur in the manufacturing process and makes the necessary decisions to maintain product quality. In addition to clarifying the process structure with the hardware and software components and their interfaces in compliance with regulatory requirements, data is generated with an experimental model to support the thesis of the applicability of AI in process validation in the pharmaceutical industry.

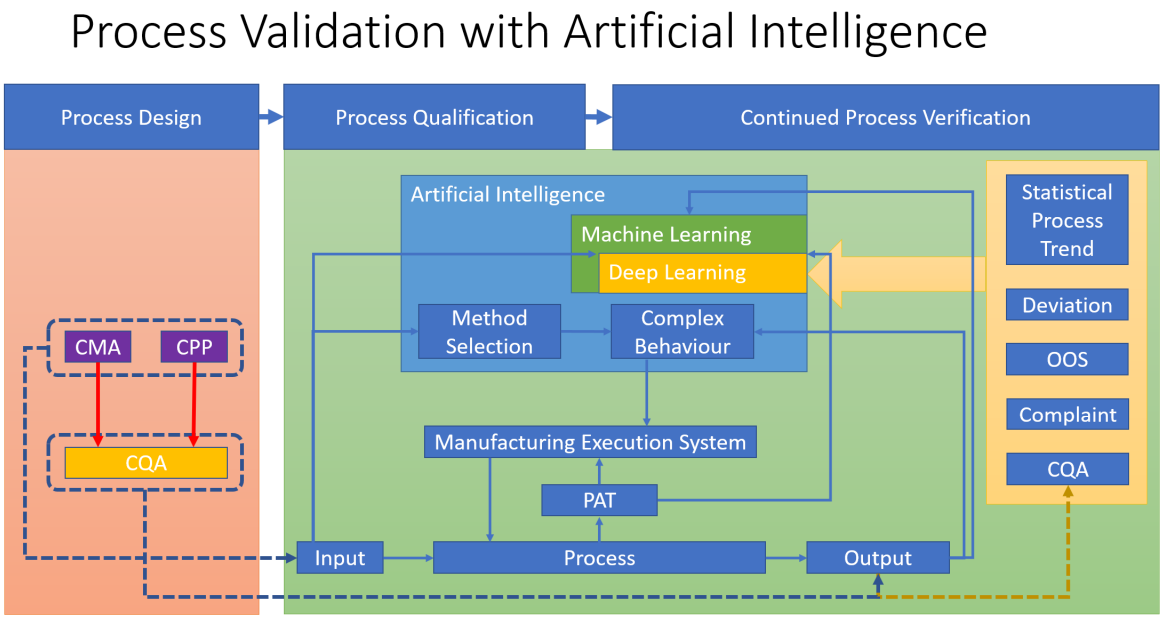

Table 1: Process Validation with Artifical Intelligence

4 Materials and methods

- Risk management instruments according to ICH Q9
- Pharmaceutical development concept Quality by Design according to ICH Q8
- Process validation concept according to FDA Guidiance for Industry and Annex 15 EU GMP Guideline
- Validation concept for computerized systems according to CFR 21 Part 11 and Annex 11 EU GMP Guideline
- Software tools / programming language
- Mathematical operation models
- Deviation management system
- Complaint management system
- Development and manufacturing data for a marketed medicinal product / alternatively: generation of data on a pilot scale or from a simulated process

5 Task definition

5.1 Process Validation Phase 1: Prozessdesign

5.1.1 Pharmaceutical development according ICH Q8

1) Determination of critical quality attributes of the finished medicinal product CQA (Critical Quality Attributes)
2) 2) Determination of critical material attributes of active ingredients and excipients CMA (Critical Material Attributes)
3) 3) Determination of critical process parameters of the manufacturing process CPP (Critical Process Parameter)
4) 4) Definition of the "design space"
5) 5) Creation of a process control strategy

5.1.2 Learning Process 1

How can the data of the critical input variables CMA and CPP (critical material properties of the active ingredients and excipients, critical process parameters) and output variables CQA (critical quality properties of the finished drug), which are determined in the process design phase, be used for machine learning within the AI unit?

5.2 Process Validation Phase 2: Process Qualification

5.2.1 Learning Process 2

How can the data of the critical input and output variables used in phase 2 "Process Qualification" be expanded to include machine learning within the AI unit?

5.3 Prozessvalidierungsstufe 3: Kontinuierliche Prozessverifizierung

5.3.1 Learning Process 3

How can the data of the critical input and output variables used in phase 3 "Continued Process Verification" be used to continue machine learning with artificial intelligence?

5.4 Evaluation Process

How can the events in the manufacturing process be transferred to the decision-making process in compliance with GMP using the AI unit with an automated evaluation process?

5.5 Decision-Making Process

How can the results from the assessment process lead to decision making by using the AI unit while maintaining GMP compliance.

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