Roche

The use of AI and ML in pharmaceutical manufacturing –

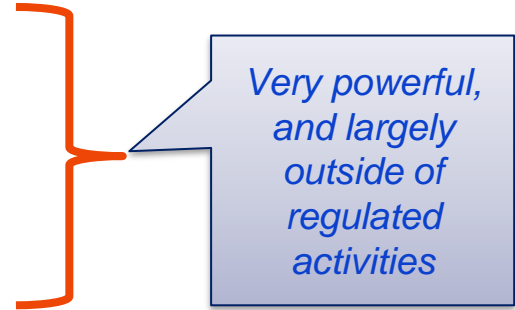## Presentation Material Dump

Dr. Gert Thurau
Head of Manufacturing Technology and Innovation Advocacy in CMC Reg Policy

Image reference: https://www.simplilearn.com/advantages-and-disadvantages-of-artificial-intelligence-article

➢ **Application Examples of AI/ML in Manufacturing**
➢ **Regulatory Considerations/Recent Health Authority Interest**
➢ **The Unique Regulatory Challenges of AI**

Roche

Applications of Artificial Intelligence resp. Machine Learning in Pharma are plentiful

- Many applications of «AI» in Pharma manufacturing and technical development use Large Language Models for text
  - Regulatory: Content generation for dossier, Q&A analysis
  - Technical development: Report generation, advanced search and knowledge mgmt

Very powerful, and largely outside of regulated activities

- *Then*, there are applications of AI that are <u>closer or in the</u> regulated space
  - Often => *use of ML for different types of modeling*
- Example Applications:
  - Natural language processing for trend analysis of Quality observations
  - Use of ML for «Digital Twin» process monitoring
  - Use of ML for fault detection in visual inspection systems

Use of AI in deviation trend analysis
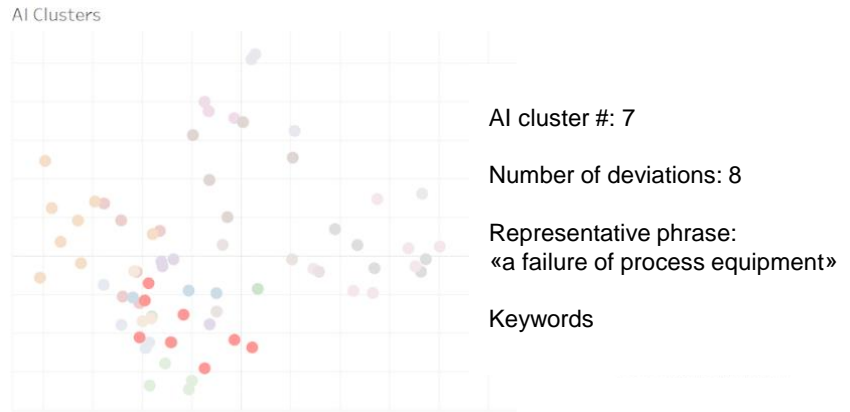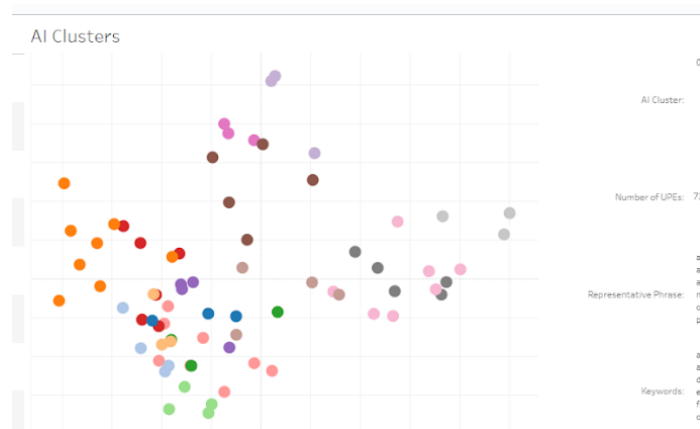
Natural Language Processing

An application for Trend Monitorin/Targeted continuous Improvement in Manufacturing and Quality

- Trend Analysis of deviations is very time consuming for site because of high amount of manual work
- AI model can search free text field and identify topic clusters (no prior tagging/metadata entry)

Clustering from all data → *Drill down to focus areas for improvement*

AI Clusters

AI Cluster:

Number of UPEs: 7:

Representative Phrase:

Keywords:

AI Clusters

AI cluster #: 7

Number of deviations: 8

Representative phrase:
«a failure of process equipment»

Keywords

Employed Technologies
- Topic modeling to extract group of similar records
- Cross Lingual (German & English) Embedding by Language Models

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Machine Learning in Digital Twins for Process Monitoring

Most modeling approaches can use machine learning algorithms

Digital Twin of a manufacturing process
- Could be of entire process or individual steps
 - Here: prediction of titer/yield for mAb DS process
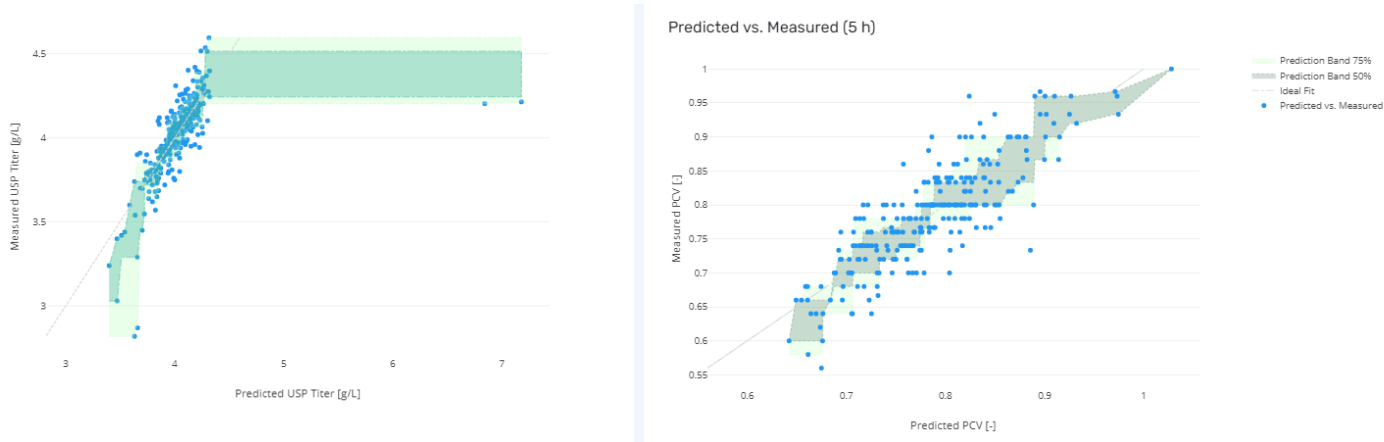
- Predictions Model identifies most impacting Factors
- Predictions Model anticipate mid-term risk of excursions from Golden batches

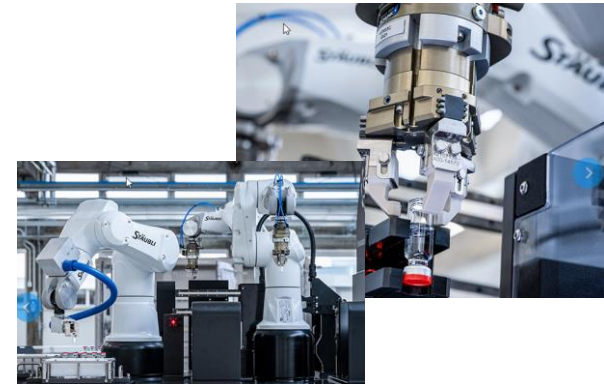# Visual Inspection Algorithms informed by Deep Learning

Reality today, potential for autonomous learning tomorrow

Visual Inspection Robot, powered by Deep Learning/neural network algorithms for image processing

From here...
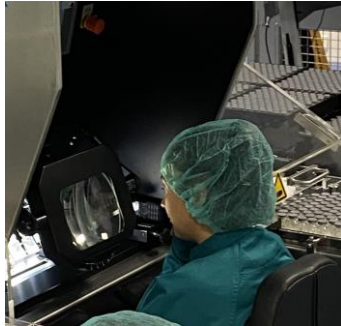
...to here

..No AI....   ..via AI....

Regulatory Considerations/Recent Health Authority Interest

"Artificial Intelligence" in Pharma Regulatory Topics

*For AI in **Manufacturing** the topics are different from the more prominent **"Big Data"** space*

Patient/Medical Data Space

Top regulatory topics are:

- *Data privacy*
- *Personal/medical data ownership*
- *Ethics (includ. Bias introduced by AI against certain parts of populations)*
- *Explainability of AI algorithms*
- *Documentation*
- *Life cycle management*

Manufacturing/CMC Data Space

Top regulatory topics are:

- ~~*Data privacy*~~
- ~~*Personal/medical data ownership*~~
- ~~*Ethics (includ. Bias introduced by AI against certain parts of populations)*~~
- *Explainability of AI algorithms*
- *Documentation*
- *Life cycle management*

..lets go straight to the tech innovation part..

One of the first discussions to have in Manufacturing is the <u>impact</u> and <u>regulatory consideration</u> about the different applications, i.e. are they even <u>GxP relevant</u> and if so, how (dossier vs. Inspection)

The Compliance & Regulatory Spectrum of AI and ML

■ The freedom to operate along the Regulatory/Quality Continuum….can depend on the usage
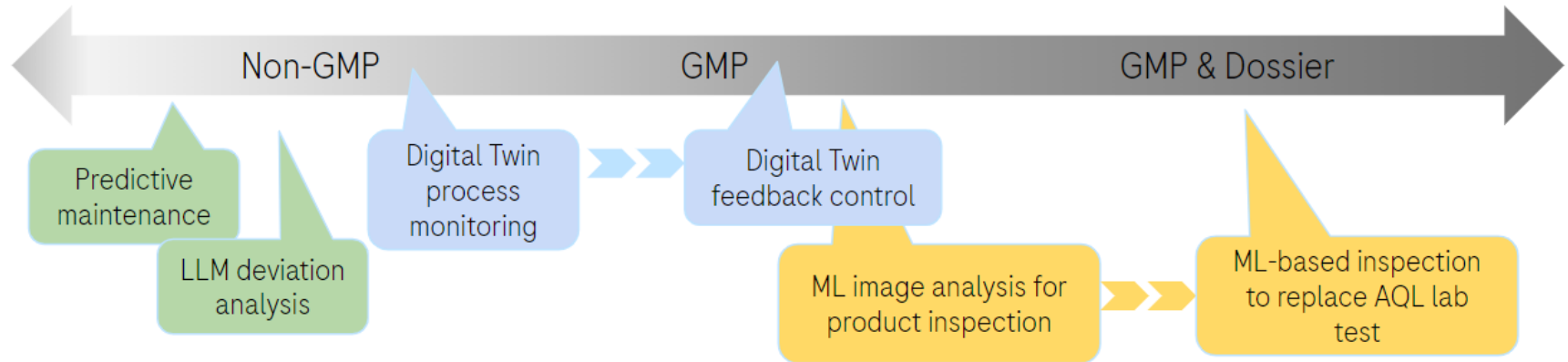
LLM: Large Language Model

Recent Regulator's Interest - FDA

- CDER Framework for Regulatory Advanced Manufacturing Evaluation ([FRAME](#)) Initiative
- 2 Discussion Paper
    - "AI in Drug Manufacturing" (March 2023)
        - Focus solely on applications in CMC
    - "Using AI & ML in the Development of Drugs & Biological Products (May 2023)
        - Combines use of AI & ML in clinical and CMC development
- FDA/PQRI workshop on the Regulatory Framework for the Utilization of Artificial Intelligence in Pharmaceutical development
    - September 2023

What applications does the FDA consider?

- Examples from FDA Paper "AI in drug manufacturing" *(all quotes)*
  - *"**Vision-based** quality controls..of **glass vials**... that are analyzed by AI"*
  - *"**Monitor equipment** to ... trigger **maintenance activities**"*
  - *"AI..used in **manufacturing operations** such as...s**cheduling and supply chain logistics**"*
  - *"**Trend monitoring**...AI to **examine deviation reports**...to **identify cluster problems** and prioritize...continuous improvement"*
  - *"Characterizing raw materials"*
  - *"Advanced process control...AI methods **predict progress of a process** ..in combination with real-time sensor data"*
  - *"Process Design and Scale-up"*

More evolved - FDA «Device/Combination Product» Space

Software as a medical device (SAMD) has more immediate use of software for medical treatment/patient impact

> *=> regulatory framework already more evolted*

- 2019 Discussion Paper
  - «Proposed Regulatory Framework...modifications to AI/ML..software as a medical device (SaMD)»
- Jan 2021 Action Plan
  - «AI/ML based SaMD Action Plan»
- Guidance on Models in device development (Dec 2021)
- Apr 2023 Guidance on life cycle mgmt of AI models (inclding autonomous learning)
  - «Marketing Submission Recommendations...for pre-determined change control plan...for AI/ML in device software functions»
  - Including options for autonomously learning models(!)

Principles used in regulatory guidance used for device regulations might be used for drugs and biological products as well
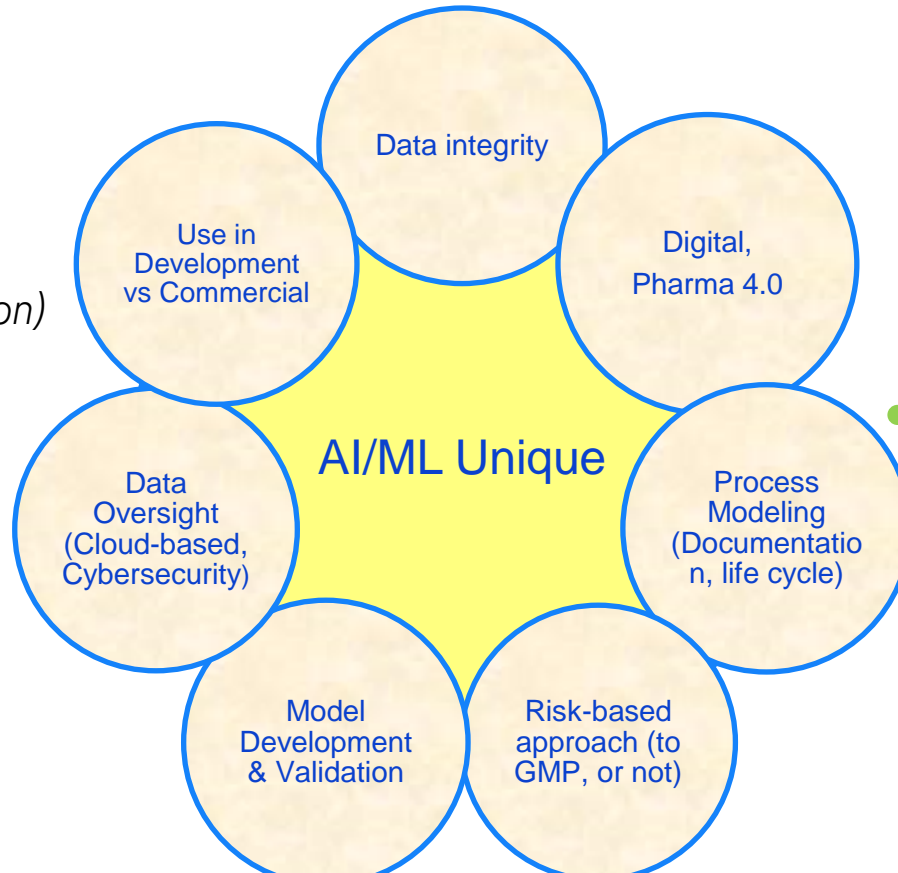
Recent Regulator's Interest - Europe & Beyond

- Europe/EMA
  - New EMA Quality Innovation Group – 2nd «Listen & Learn» Focus Group October 2023,Topic «Digital»
    - 2 day focus group with industry and other stakeholder representation
    - Application examples in two areas, 1.) Digital Twin/Process Modeling, 2.) ML to enhance existing specific GMP relevant applications
- Elsewhere
  - WHO inspector workshop in 2023 with «Advanced Manufacturing» Topics
    1. Continuous Manufacturing
    2. Artificial Intelligence in Manufacturing
    - WHO might consider «Points to consider» guidance for inspectors
  - PIC/S is expressing interest in trainings/learnings on advanced manufacturing

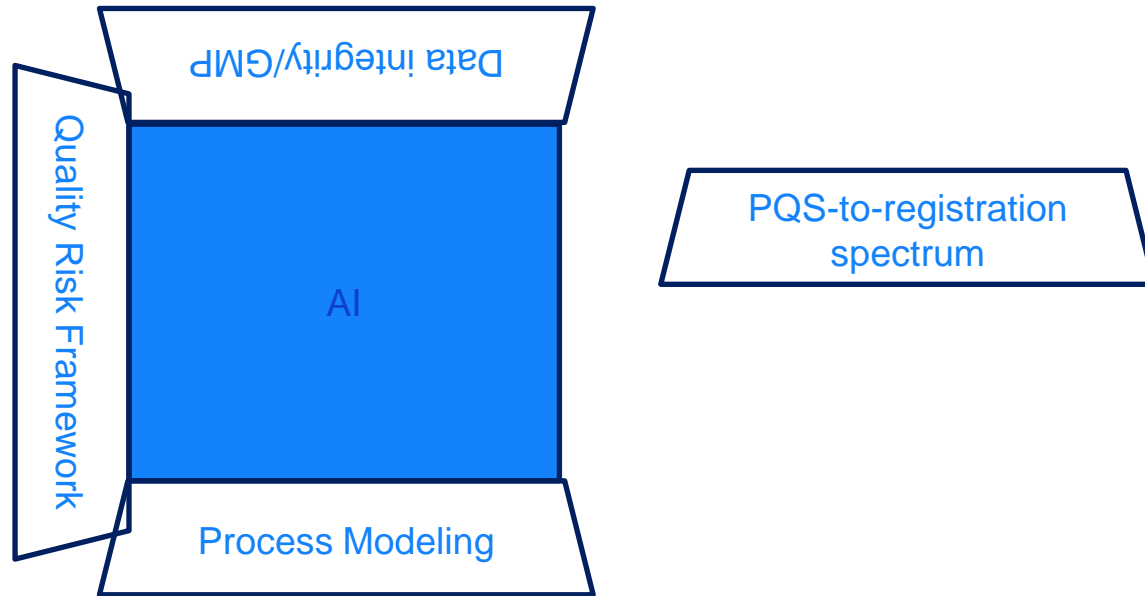# The Unique Regulatory Challenges of AI

The AI Regulatory Topic "Flower"

AI blossoms in the middle of a lot of existing topics
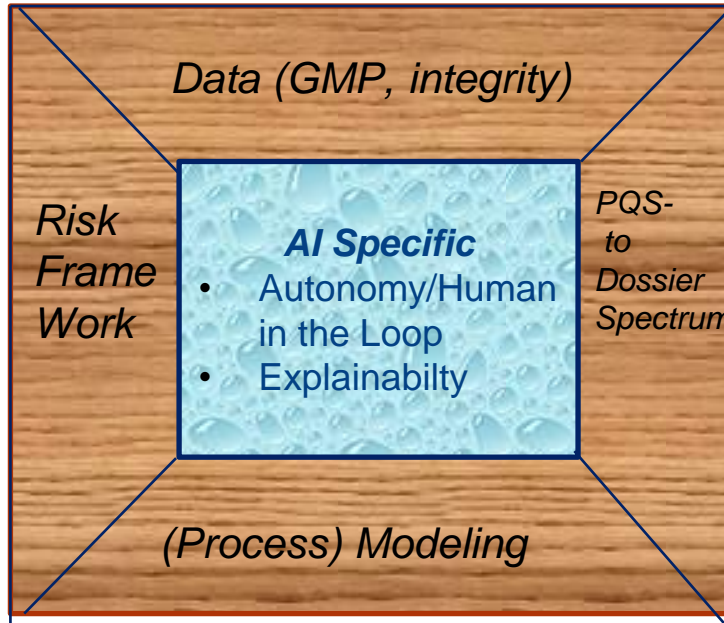
(which might need additional interpretation)

Data integrity

Digital, Pharma 4.0

Use in Development vs Commercial

AI/ML Unique

Data Oversight (Cloud-based, Cybersecurity)

Process Modeling (Documentation, life cycle)

Model Development & Validation

Risk-based approach (to GMP, or not)

...and while all other regulatory/GMP topics deserve proper attention and advancement..

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See the whole picture (including the frame)

Data integrity/GMP

Quality Risk Framework

AI

Process Modeling
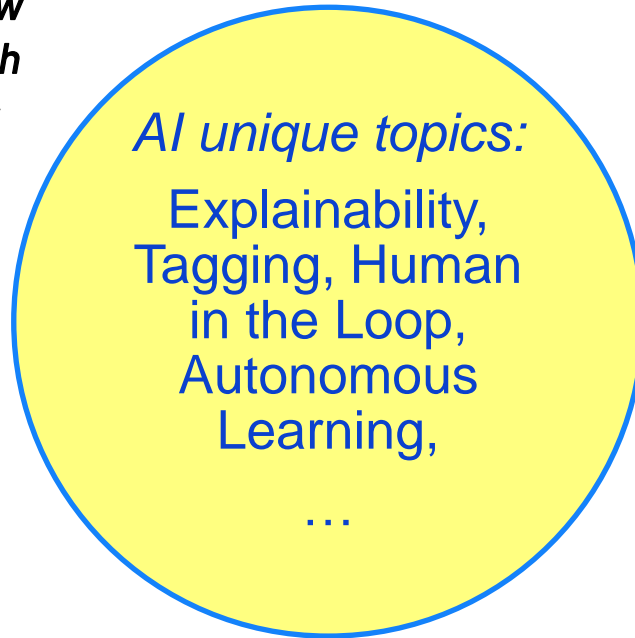
PQS-to-registration spectrum

See the whole picture of AI
(including the frame)

The AI Regulatory Topic Flower – at the very core of it

*...there are also **those few which are really new with AI** and we need principles and solutions to enable these technologies*

AI unique topics:

Explainability, Tagging, Human in the Loop, Autonomous Learning,

…

A Special AI/ML Topic: *Explainability*

Explainability has it's origin in «Acceptability» of AI in the societal setting

- Explainability has a lot to do with:
  - General perception of the use of AI in «real life» - impact of AI in socitiey
  - Level of understanding/skill of the particular audience

Within the GMP space

- GxP is about ensuring **an acceptable balance of risks** to patient safety and their benefits.
- **Explainability** is one means to **bridge the gap** between what can be drawn from the data and **what needs to be assessed by humans' intelligence**
  - However **can we bridge** GxP oversight **with statistical methodology**, analogue to "spectral outliers"

- Choices in model development
- Some models may be more easier to explain than others, *typically at the cost of predictive power*
  - Is this the **"Keep it simple"** or the **"How low can you go?"** principle?

Can be influenced/mitigated by

A Special AI/ML Topic: *Autonomous Learning*

Autonomous Learning

- Ability of AI/ML models to further incorporate and learn about data it ingests during operation
  - Includes then updating/improving the previous algorithms = highest level of autonomy

- Autonomous learning/updating of algorithms is a challenge to the conventional GMP framework for models
  - Documentation principles usually assume «locked» algorithms which then get validated/tested
  - No human decision maker in the devlopment/continuous improvement loop

Summary

- The use of Artificial Intelligence and Machine Learning are promising new tools also for applications in the regulated manufacturing space
- Recently regulators (FDA and EMA) have reached out towards industry via discussion papers, workshops on the use of AI in manufacturing
- There are many enabling regulations to AI which require updating or adjustment
  - But also the unique features of AI deserve forward looking attention to allow to use the full technical potential of the technology

Doing now what patients need next