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Validation, documentation vs. registration and life cycle management of AI and ML models

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The Bigger and Diverse picture of AI legislation and guidance

Policies and Regulation of Artificial Intelligence

It ‘s a hot topic, and it’s a diverse and divisive topic

THE WHITE HOUSE

BLUEPRINT FOR AN AI BILL OF RIGHTS

MAKING AUTOMATED SYSTEMS WORK FOR THE AMERICAN PEOPLE

MIT Technology Review

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POLICY

Three things to know about how the US Congress might regulate AI

POLITICO

TECHNOLOGY

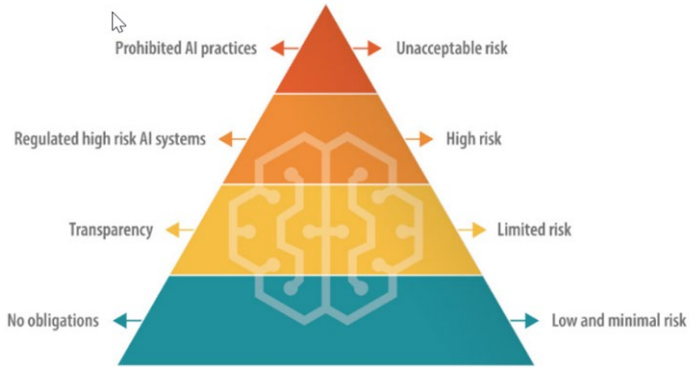
Congress unlikely to pass sweeping new AI laws, key GOP senator says

News
European Parliament

EU AI Act: first regulation on artificial intelligence

Society Updated: 14-06-2023 - 14:06

Pyramid of risks



Data source: European Commission.

Recent Regulator's Interest - FDA

AI/ML in pharmaceutical Manufacturing

- 2 Recent discussion Paper
  - "AI in Drug Manufacturing" (March 2023)
    - Focus solely on applications in pharmaceutical manufacturing
  - "Using AI &ML in the Development of Drugs &Biological Products (May 2023)
    - Combines use of AI &ML in clinical and CMC development

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
- Jan 2021 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 «automatic implementation by software» (=autonomously learning models?)

Recent Regulator's Interest - Europe & Beyond

- Europe/EMA
  - New EMA Quality Innovation Group – 2nd «Listen & Learn» event October 2023
    - Selected topic «Digital», including AI and ML
- Elsewhere
  - WHO inspector workshop in June 2023 with «Advanced Manufacturing» Topics
    1. Continuous Manufacturing
    2. Artificial Intelligence in Manufacturing

AI/ML Regulatory and Quality topics in Pharmaceutical Manufacturing

"Artificial Intelligence" in Pharma Regulation - *Diverging Focal Points*

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Patient/Medical Data Space

Top regulatory topics are:

- *Data privacy*
- *Personalized data ownership*
- *Ethics (includ. Bias introduced by AI against certain parts of populations)*
- *Explainability of AI algorithms*
- *Data Quality Risk assessment*
- *Documentation*
- *Life cycle management*

Manufacturing/CMC Data Space

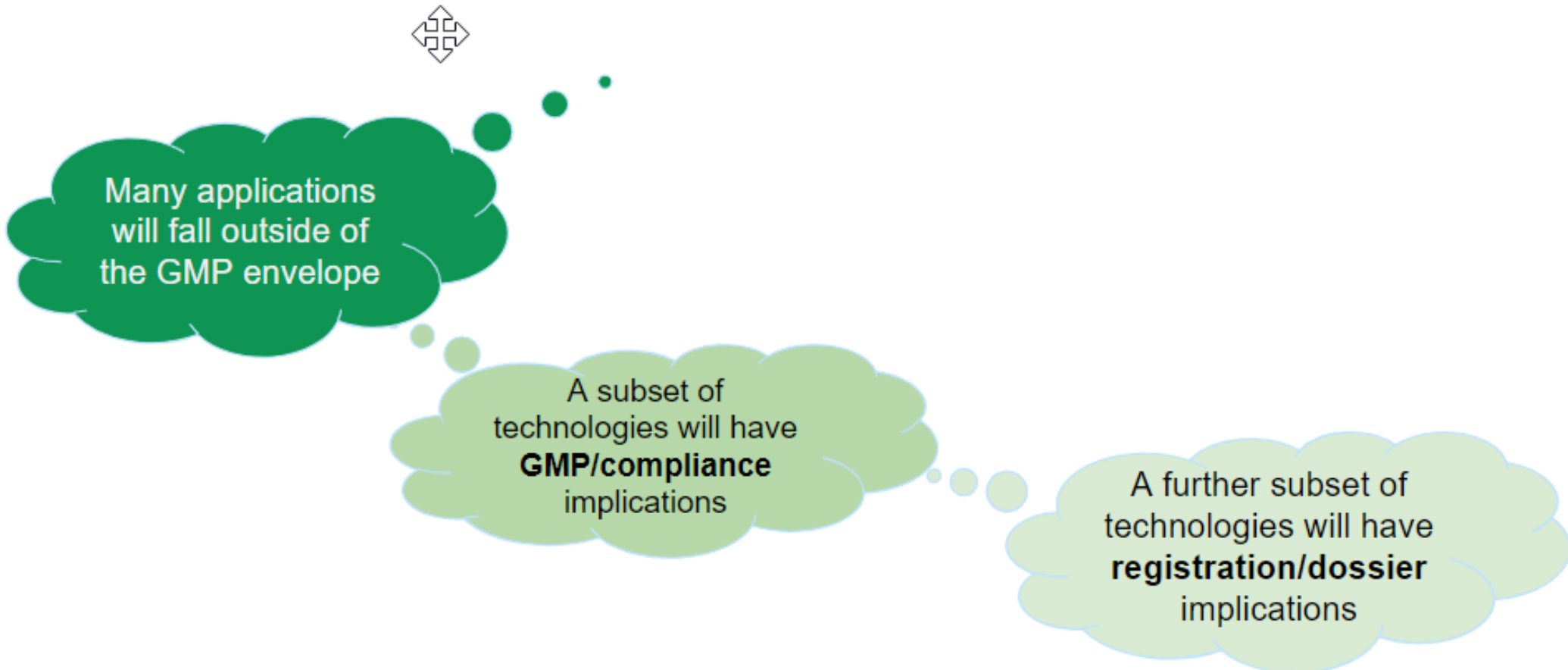
Top regulatory topics are:

- ~~*Data privacy*~~
- ~~*Personalized data ownership*~~
- ~~*Ethics (includ. Bias introduced by AI against certain parts of populations)*~~
- *Explainability of AI algorithms*
- *Data Quality Risk Assessment*
- *Documentation*
- *Life cycle management*

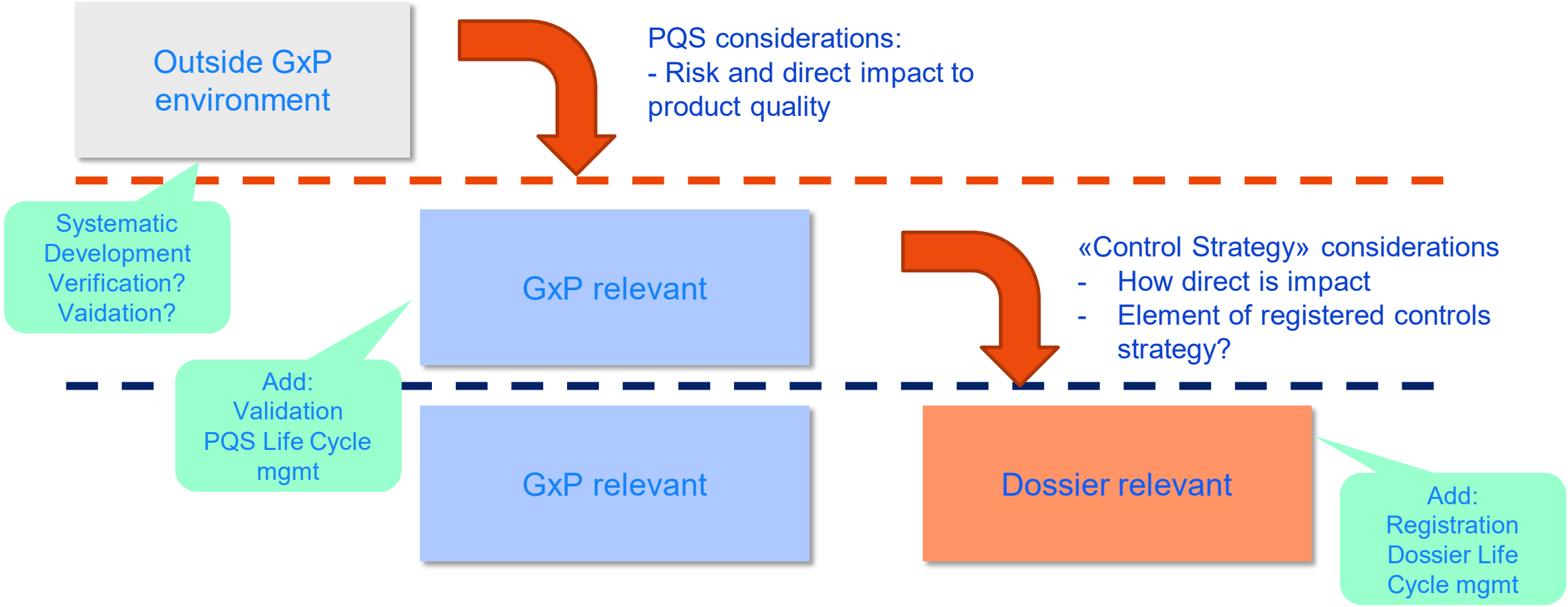
*For AI in **Manufacturing** the topics are different from the more prominent **"Big Data"** space*

1. *First discussion: impact/risk and regulatory consideration for different applications*
   - *i.e. non-GxP, GxP, dossier*
2. *What existing regulation can be applied (and which elements of AI are so unique they don't map well)*

All Technology Innovation in Pharma Manufacturing will benefit patients only with an implementation on a product.

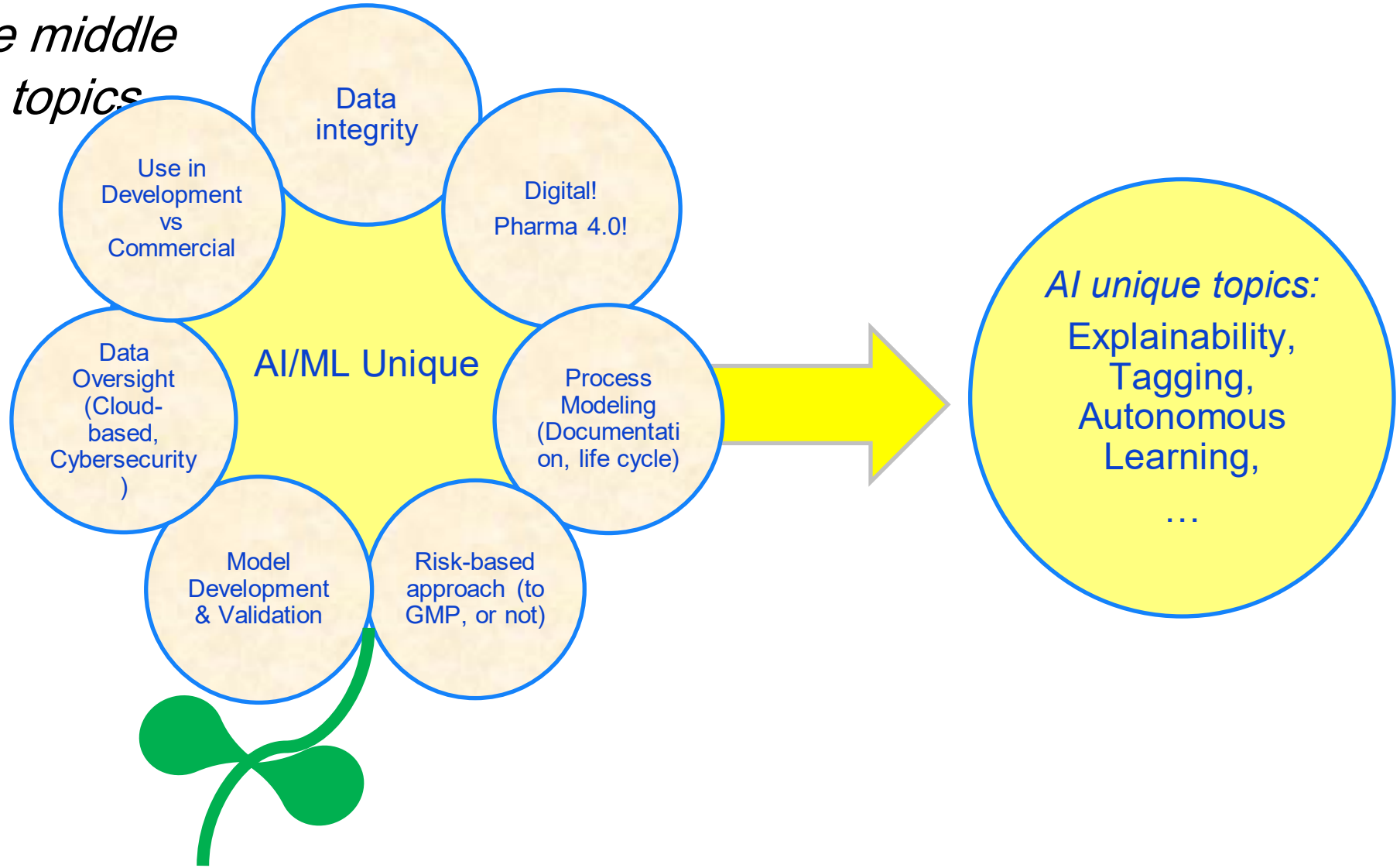


The Layers of GMP/Regulatory Relevance



The AI Regulatory Topic “Flower”

AI blossoms in the middle of a lot of existing topics



An Evolving Topic: Validation of AI

There is no specific regulatory guidance for the validation of AI applications that defines how to handle the specific characteristics of AI

There are concepts

- Maturity models (ISPE)
  - Control design: How much human involvement in the decision (parallel, approved by human,autonomous (control itself and corrects itself)
  - Autonomy stages: From a fixed algorithm all the way to autonomous learning
- Practical Details of AI model development and validation
  - Life cycle: modeling and evaluation
    - …requirements...development...deployment.monitoring..retirement
  - Data sets
    - Training-validation-test sets

Reference: AI Maturity Model for GxP Application: A Foundation for AI Validation, Nico Erdmann, PhD Rolf Blumenthal Ingo Baumann Markus Kaufmann, Pharmaceutical Engineering March/April 2022

Existing Guidance for classification of Models in Pharmaceutical Development and Production- overview

- ICH QbD IWP points to consider document (high level)
  - 3 Levels of risk/impact – many levels of interpretation
- Analytical method guidelines
  - Q2/Q14 – only for models in analytical applications
- Near-Infrared Spectrosopy
  - Most prominent example of more complex modeling algorithms (PCA, PLS)
  - Principles might be helpful, however..
    - Stark regional differences exist for life cycle mgmt of registered methods

Application of existing guidance on two case studies

&

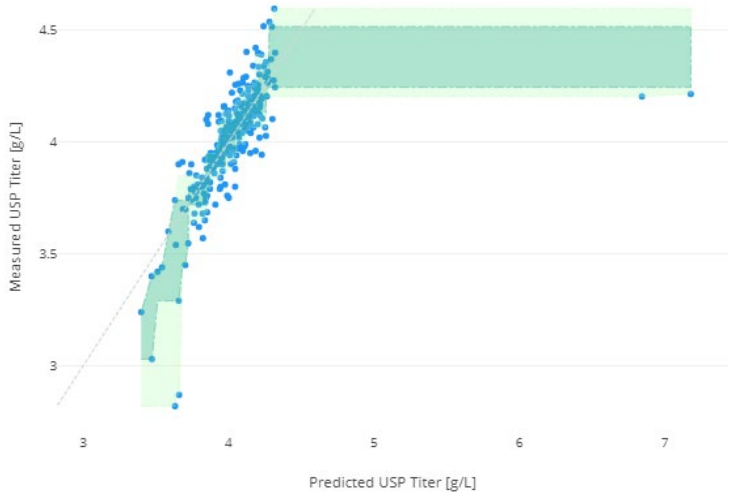
AI/ML specific topics

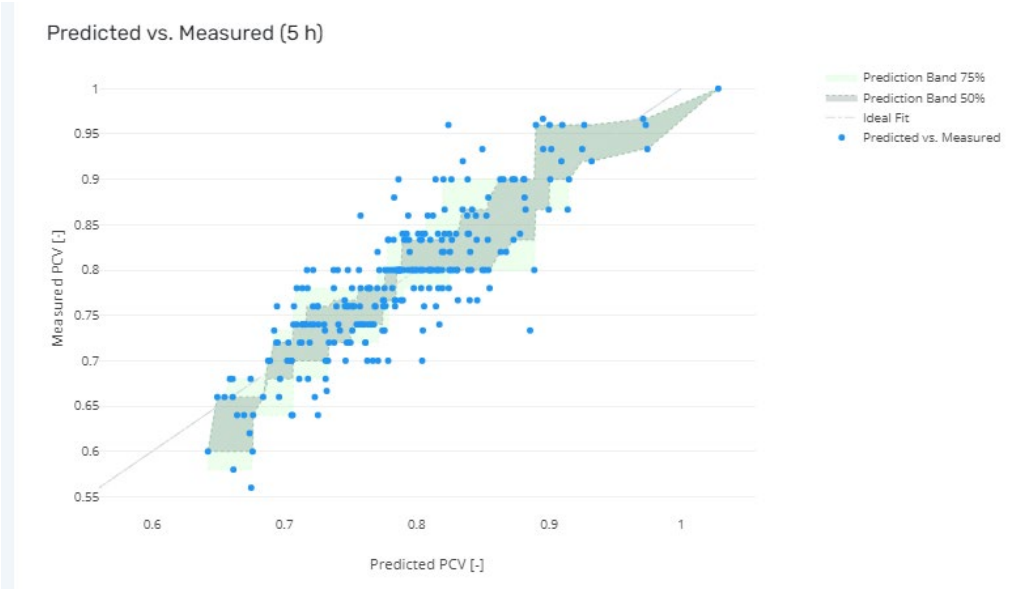
2 Examples of AI/ML Applications

Illustration of regulatory challenges

1) Digital Twin of a manufacturing process

- Could be of entire process or individual steps
  - Here: prediction of titer/yield for mAb DS process



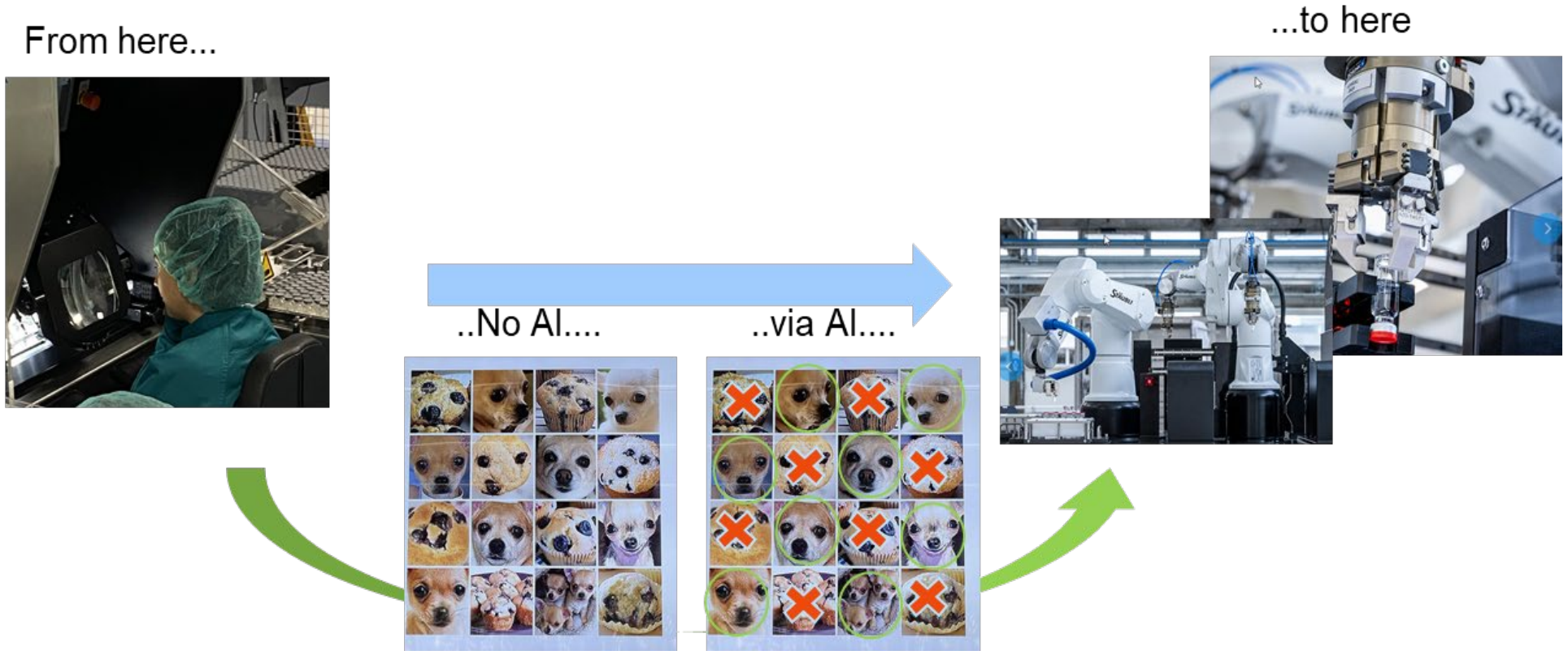


- Predictions Model identifies most impacting Factors
- Predictions Model anticipate mid/term risk of excursions from Golden batches

2 Examples of AI/ML Applications

Illustration of regulatory challenges

2) Visual Inspection System (100% inspection)



Sources:Muffin photo:https://medium.com/@ahffank/solving-the-famous-problem-of-puppy-vs-muffin-using-a-simple-web-application-on-google-app-a3264e2be49c Robot: https://www.stevanatogroup.com/en/offering/visual-inspection/vision-robot-unit/; Robot photos: https://www.stevanatogroup.com/en/offering/visual-inspection/vision-robot-unit/

Applying the existing modeling guidances to AI applications has its limit/requires interpretation

- **Machine algorithms (Visual inspection system)**
  - These exist today, just not yet AI/ML based
  - Remit of GMP/conventional validation and documentation => *should remain in GMP space*

- **«Digital Twins»** = process models (ICH Points to consider applies - but requires interpretation)
  - What use of a digital twin is «high vs. Medium impact»?
  - Only when it replaces end-product testing = equivalent to real-time release testing?
  - Replacement of in-process controls
    - Only when it replaces end-product testing (equivalent «RTRT»)
    - For replacement of important in-process?

Let's project existing guidance on these two examples

- **Visual product inspection example**
  1. In-process testing locked algorithm (still doing end-product QC check=AQL)
  2. In-process testing self-learning algorithm (still doing end-product QC check=AQL)
  3. Finished product AQL with AI/ML (replaces human)
  4. In-process testing in lieu of AQL (replacing human, replacing finished product testing)

GMP only, PQS

GMP only, life cycle mgmt PQS?

Alternative analytical technology, dossier relevant

Real-time release testing, dossier relevant

Let's project existing guidance on these two examples

- **Digital Twinexample**

1. Parallel prediction of attributes (=supports operator who executes validated GMPand registered control strategy, knowledge build, «guiding IPC sampling point»)

Non-GMP Validation required?

...does it matter what type of attribute it is? Non-CQA vs CQA?

2. Prediction is basis of decison inprocess, but retain finished-product testing

GMP, medium impact model according to ICH points to consider? Or PQS only

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"

Can be influenced/mitigated by

- Choices in model development
- Some models maybe 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?

Reference: «The Road to Explainable AI in GXP-Regulated Areas, by Elias Altrabsheh Martin Heitmann, FRM Patrick Steinmüller Bruna Pastori Vinco, Pharmaceutical Engineering Jan/Feb 2023

A Special AI/ML Topic: *Autonomous Learning*

AutonomousLearning

- 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
  - No human decision maker in the devlopment/continuous improvement loop
  - Documentation principles usually assume «locked» algorithms which then get validated/tested

A Special AI/ML Topic: *Autonomous Learning, cont.*

- FDA guidance on use of AI/ML in device development (software as a medical device) has provisions for this
  - Submit pre-approved update and verification protocol – execute, potentially within own PQS

This assumes dossier documentation of algorithm, i.e. high impact scenario
-What if algorithm is part of machine control (GMP space only)?

- Also: verification of the GMP framework of such autonomous learning models requires skill set by inspectors
  - Analogue to other complex models, i.e. Spectrosopic models – inspect the PQS, not the model itself?

Conclusions

- The utilization of AI and ML methodology holds promises also for pharmaceutical technical development and manufacturing
  - An initial important aspect is to position this use vs.many other applications of «AI» discussed in the public a
- With the breadth of applications under development a solid classification approach is needed
  - Keeping in mind currenty similar applications *without* AI
- Many AI/ML compliance and regulatory topics are a continuation discussion on previously existing themes (Data, Modeling, CSV and validation)
  - Many of these topics (process modeling) still require resolution as these topics have matured in recent years
  - And yet some topics are truly AI-unique where mapping of existing guidance might have limitations

Acknowledgement

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Doing now what patients need next