USE OF A CONTROL FRAMEWORK TO LIMIT RISK OF AI IN GXP

Brandi M. Stockton

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- Charles River Laboratories case study and images from ATEM Structural Discovery are shared with permission from Carsten Jasper.

GAMP ML Risk & Control Framework

PE 2024 January/February GAMP Edition

FEATURE ARTIFICIAL INTELLIGENCE

MACHINE LEARNING RISK and Control Framework

By Rolf Blumenthal, Nico Erdmann, PhD, Martin Heitmann, Anna-Liisa Lemettinen, and Brandi Stockton

Stakeholders across industries are becoming accustomed to using information technology (IT) systems, applications, and business solutions that feature artificial intelligence (AI) and machine learning (ML). Even though some of these uses show phenomenal performance, thorough risk management is required to ensure quality and regulatory compliance are met within the life sciences industry. By leveraging specialized frameworks and methods, we compiled a holistic framework to dynamically identify, assess, and mitigate risks when AI and ML features are in use.

A RISK-BASED APPROACH TO AI AND ML

RAPIDLY EVOLVING AI AND THE NECESSARY RISK MANAGEMENT

Foundation

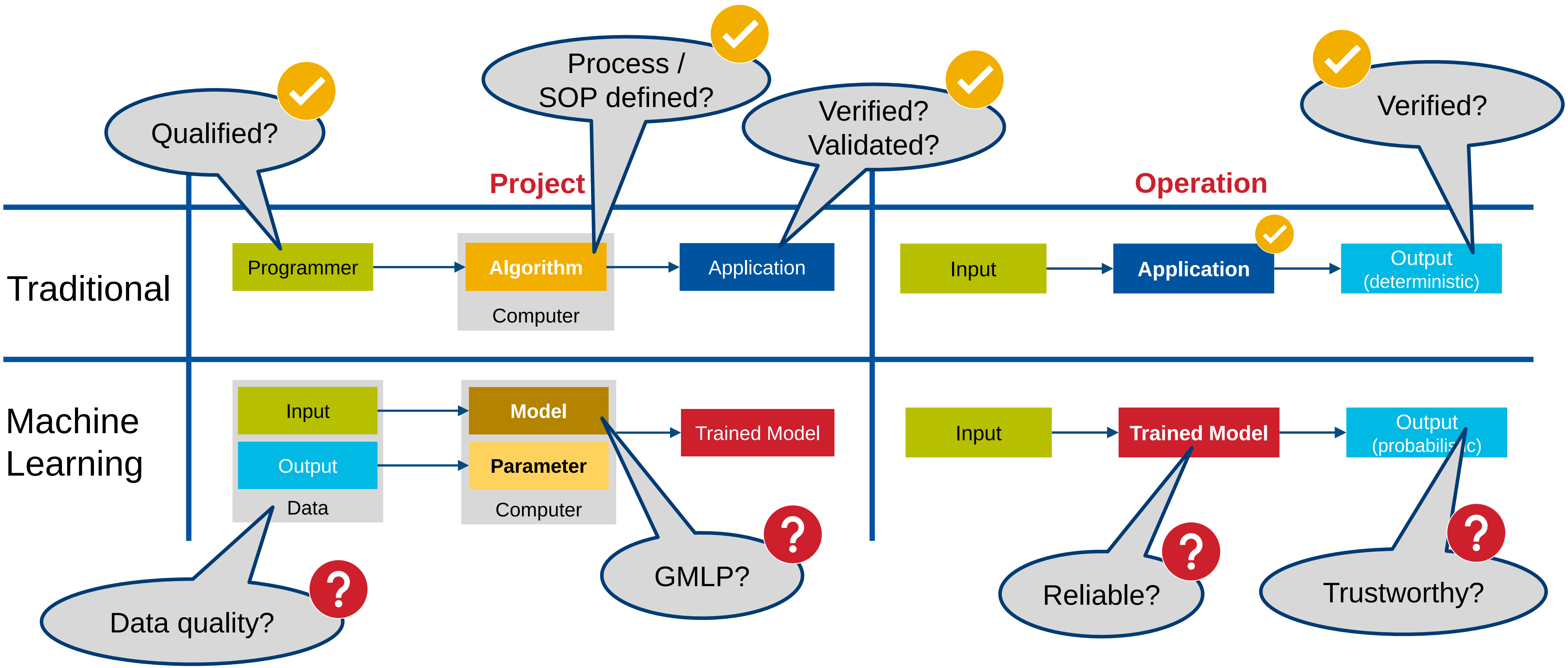
- ICH Q9 (R1)

4 Key Concepts

- AI Maturity Model (2022)
- AI Governance & QA Framework (2022)
- GAMP 5 2nd Edition – Appendix D11 (2022)
- Risk Analysis and Mitigation Matrix (RAMM) (2012)

Based on: A Control Framework to Limit Risk of AI in GxP by S. Münch and B. Stockton 2024 – ISPE European Conference

New Technology! New Trouble?



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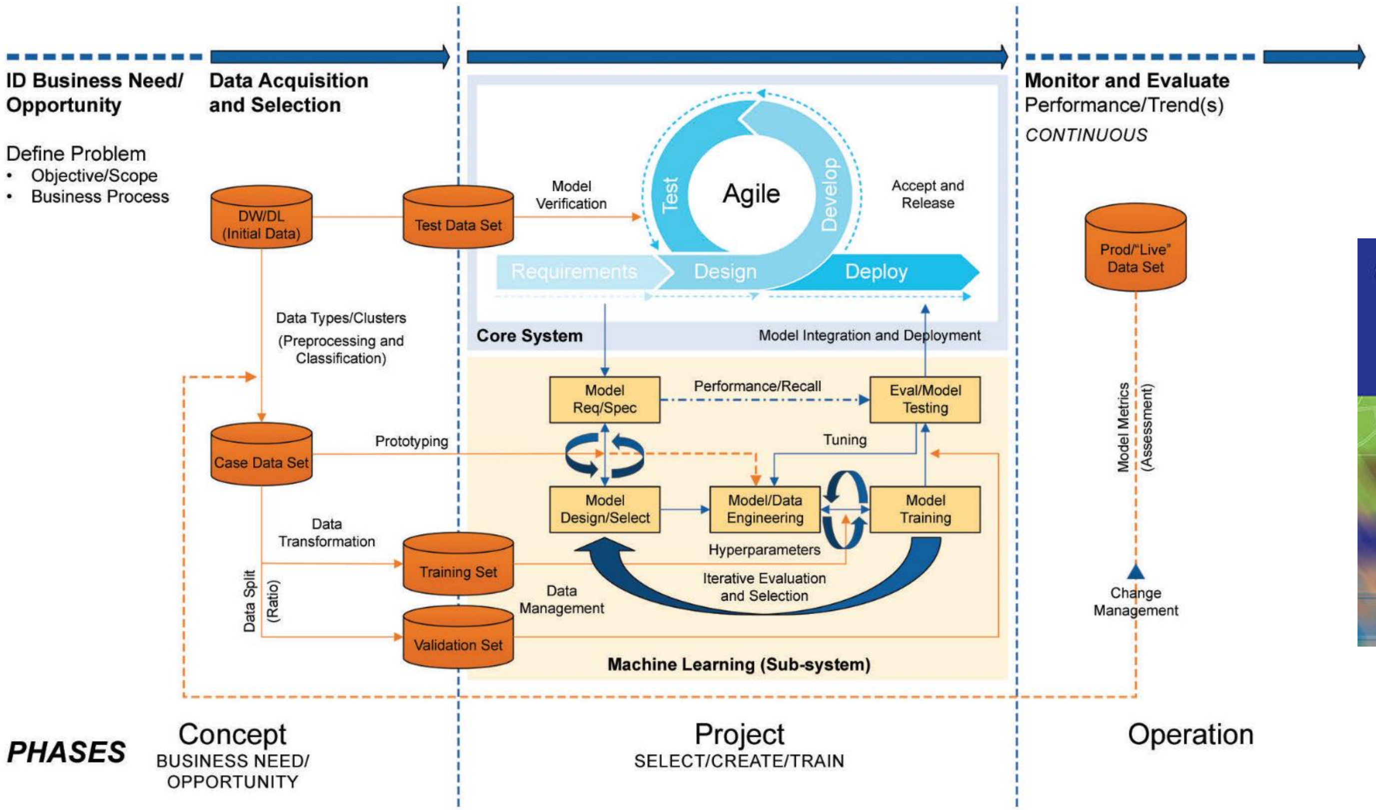
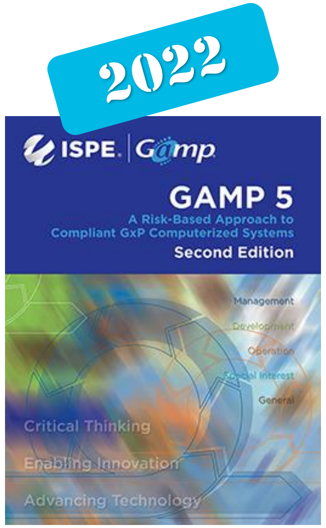
GAMP 5 Second Edition

Machine Learning Sub-System Life Cycle Model (Appendix D11)





Source: GAMP® 5 Second Edition, Appendix D11, Figure 31.1, © ISPE 2022

Why a ML Risk and Control Framework?

Collaboration: Using AI/ML requires new competences and close collaboration between various functions

Critical thinking: Several perspectives need alignment for a process-oriented procedure

Data rules: Based on training, validation, and test methodologies, every single data point counts

Managing risk: A risk inventory assists to identify relevant hazards and supports interpretation of their analysis

Complexity: Models can be highly complex – sometimes the outcome resembles a black box

Maintain control: A dynamic approach to support control during the model's life cycle

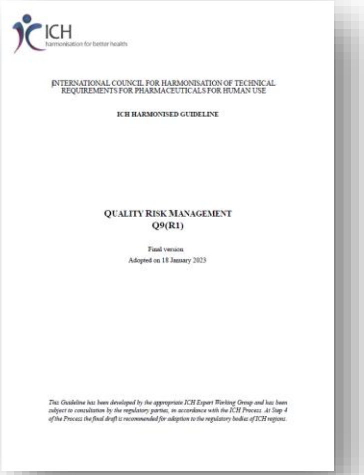
The ML Risk and Control Framework integrates processes, data, and roles

Based on: ML Risk & Control Framework by N. Erdmann, M. Heitmann 2023 –GAMP D-A-CH Forum

ICH Q9 (R1) as Regulatory Background

While ICH Q9(R1) is used as a reference, the ML Risk and Control Framework focuses on the following aspects:

- Initiate Quality Risk Management Process
- Risk assessment
  - Hazard Identification
  - Risk Analysis
- Risk Control
  - Risk Reduction
- Risk Review
  - Review Events

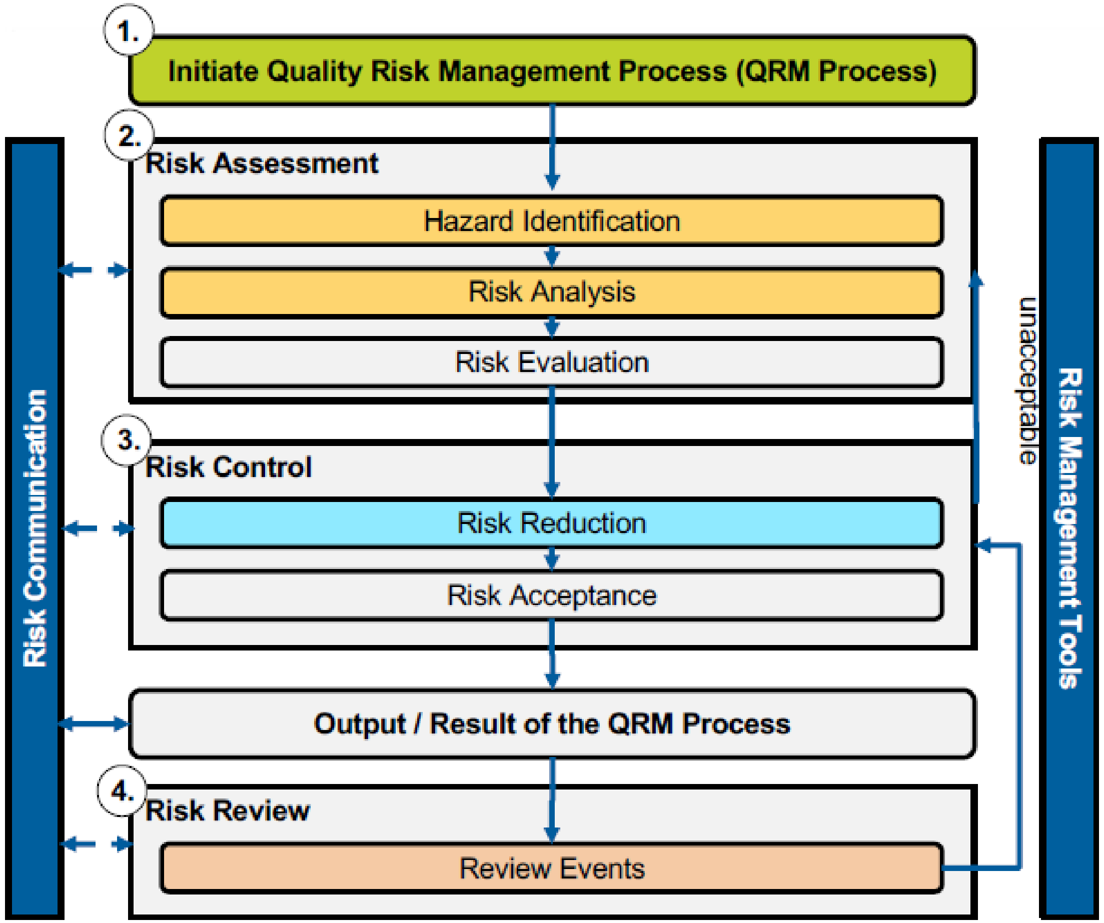

ICH
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

QUALITY RISK MANAGEMENT
Q9(R1)

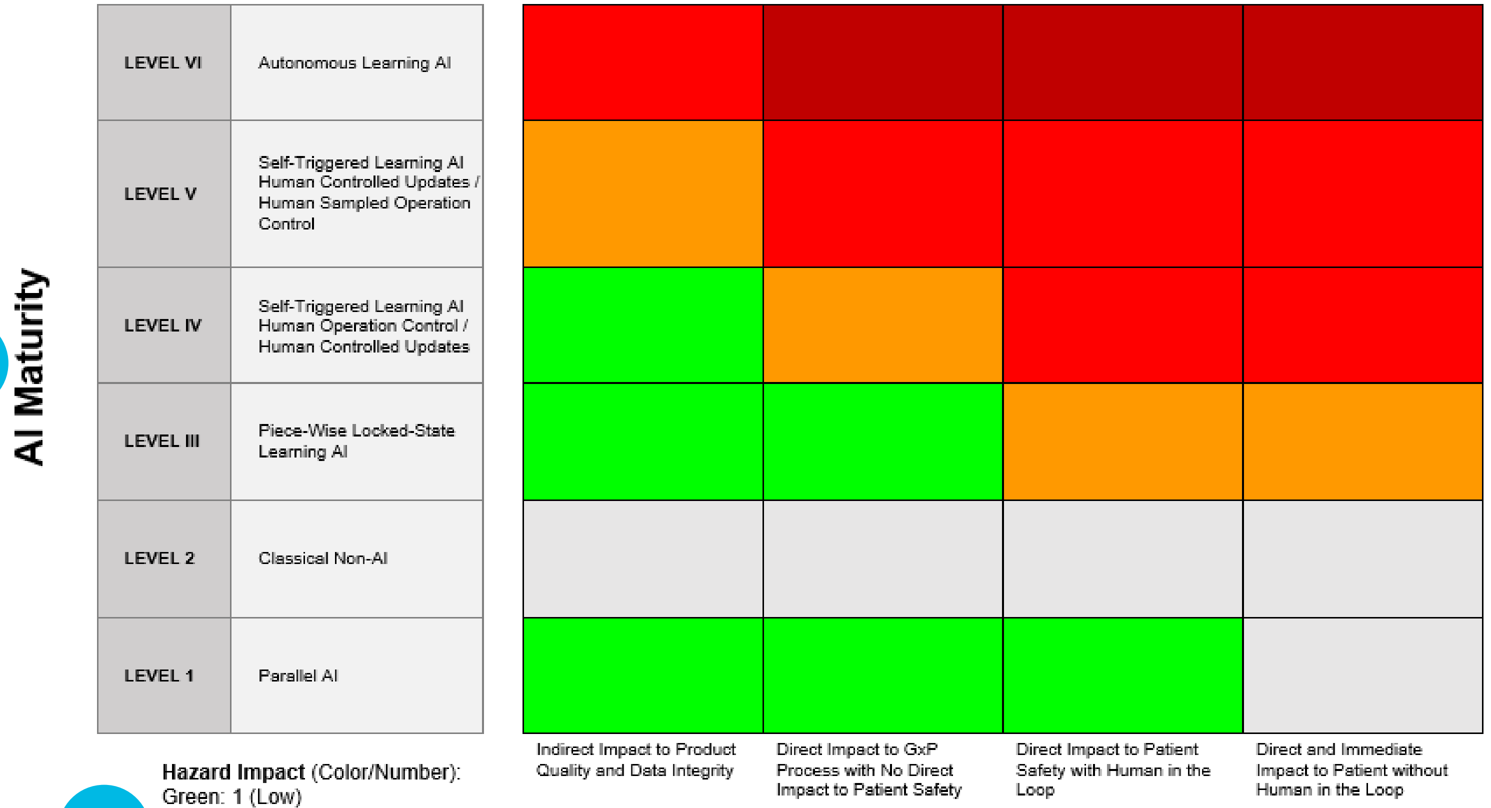
Final version
Adopted on 18 January 2023

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.



Source: ML Risk and Control Framework, Figure 1, © PE magazine Jan/Feb 2024

Risk Severity Matrix for Initial Risk Classification



1

Hazard Impact (Color/Number):
Green: 1 (Low)
Orange: 3 (Med)
Red: 9 (High)
Dark Red: 18 (Very High)

3

Risk Impact

2

Two dimensions:

1 **AI Maturity** – Application & process assessment

2 **Risk Impact** – Proximity and influence on the patient

Resulting Hazard Impact: 3

- Basis for the following risk assessment
- Affects the recommended review cycles
- Should enable comparison between systems and models

Source: ML Risk and Control Framework, Figure 4, © PE magazine Jan/Feb 2024

General Principles

Commensurate effort

Holistic view

ML Risk and Control Framework

Compatibility with accepted methodology

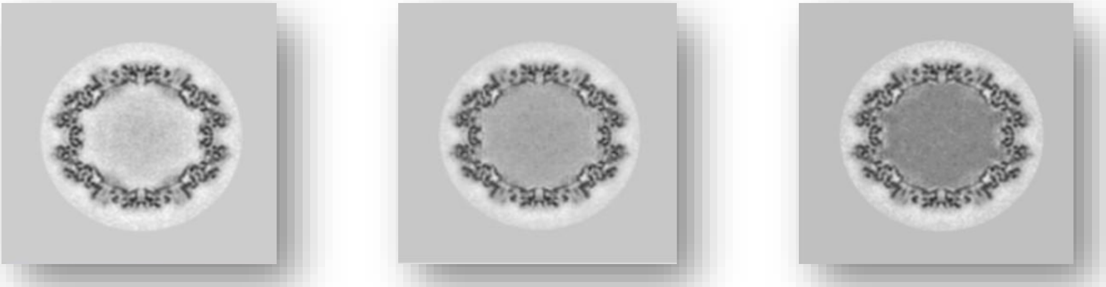
Dynamic process understanding

Source: A Control Framework to Limit Risk of AI in GxP by S. Münch and B. Stockton 2024 – ISPE European Conference

Examples to illustrate some of the hazard clusters

(QC for Adeno-Associated Virus (AAV))

Assess AAV fillings by means of examples



empty | partially filled | full

3 images are easy - how about 1000?

With permission of ATEM

Source: Adapted from AI/ML in Regulated (GxP) Life Sciences Sectors Concept/Project Phase: Data sets and representativeness Brandi Stockton, Martin Heitman, Taylor Chartier, and Tom Williams 2024

Use Case AAV: Challenges & Objectives

Challenges

- Requires highly skilled SMEs for review and analysis
- Original method requires high effort and time
- Existing SW is rarely GxP-ready / compliant (no solution available out of the box)
- Thousands of images need to be generated and processed
- Highly subjective results

Objectives

Fully digital E2E process (image creation, singulation, classification)

Development of a ML-model for the AI-based analysis of image data as part of quality assessment

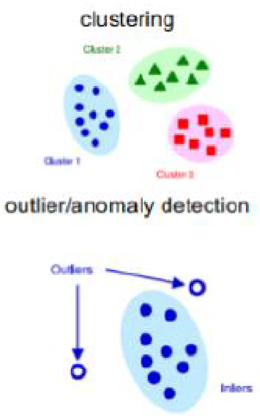
Validation of the model per ML Risk & Control Framework

Based on: Assessment of empty/full ratios of Adeno-associated Virus (AAV) capsids using cryogenic electron microscopy by Dr. Nico Erdmann & Carsten Jasper

Challenges Specific for the Use Case

Unsupervised Learning

- Training with **unlabeled data**
- **Self-induced** clustering



- Currently **no other productive use case in GxP** known

- Uniform availability of real data problematic
- Labeling of existing real data is extremely time-consuming and partly subjective
- Relatively small data difference for clustering
- Difficulties with training, verification, & validation

Based on: Assessment of empty/full ratios of Adeno-associated Virus (AAV) capsids using cryogenic electron microscopy by Dr. Nico Erdmann & Carsten Jasper

Synthetic Data: Background & Challenges

Background

- Synthetic data / images are well-known in GxP environments:
  - Migration of data validation
  - Anonymized test data for productive systems (GDPR)
- Data / image generation:
  - Selective variations
  - Data multiplication
  - Inter- and extrapolation
  - Adding noise
  - Agent models

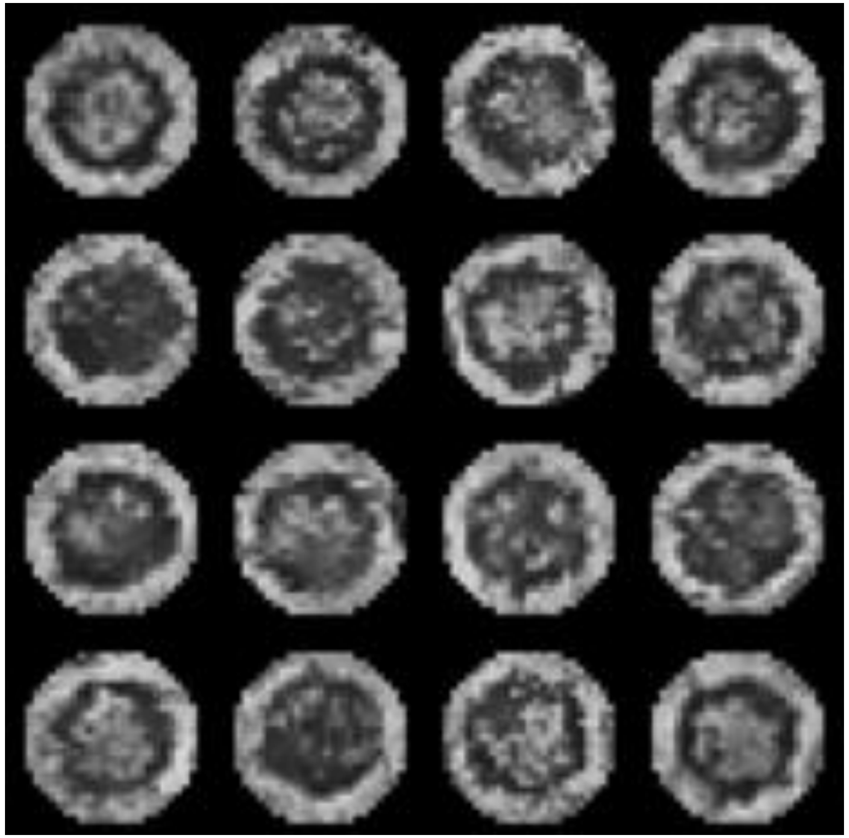
Challenges

- Selecting appropriate source data
- Verifying representativeness and reliability of synthetic data
- Noise in EM is highly complex
- Generation of *partially* filled AAV
- Generation of special cases (e.g., for verification)
- Reality gap: Synthetic data / images are not a replacement for all variations in real data / images

Based on: Assessment of empty/full ratios of Adeno-associated Virus (AAV) capsids using cryogenic electron microscopy by Dr. Nico Erdmann Carsten Jasper

Illustration / Comparison of Random Samples

Real data



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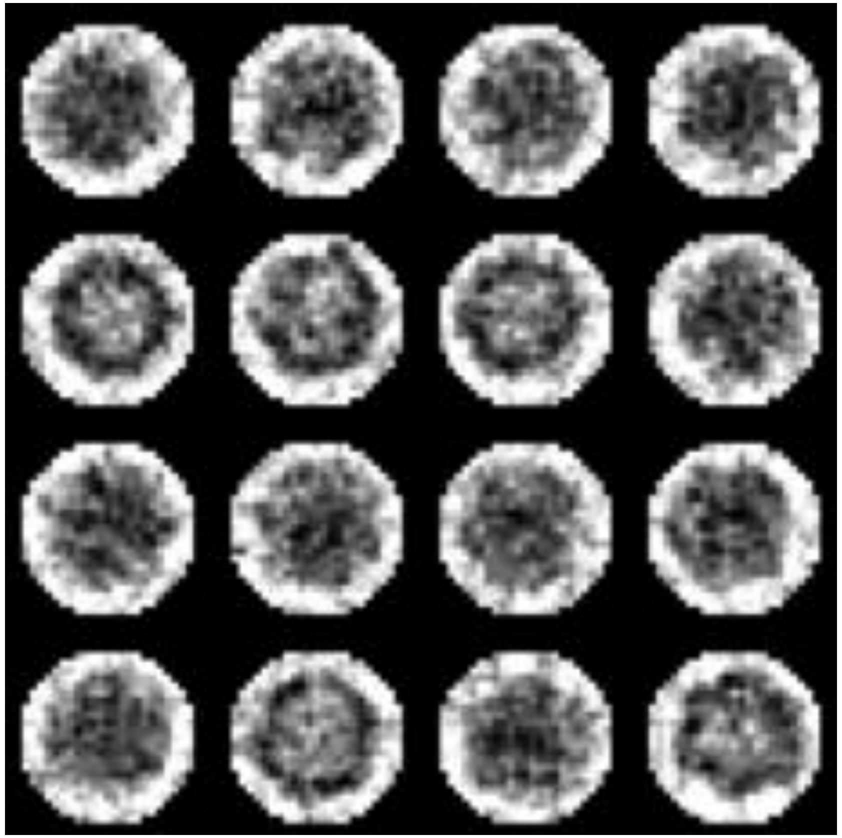
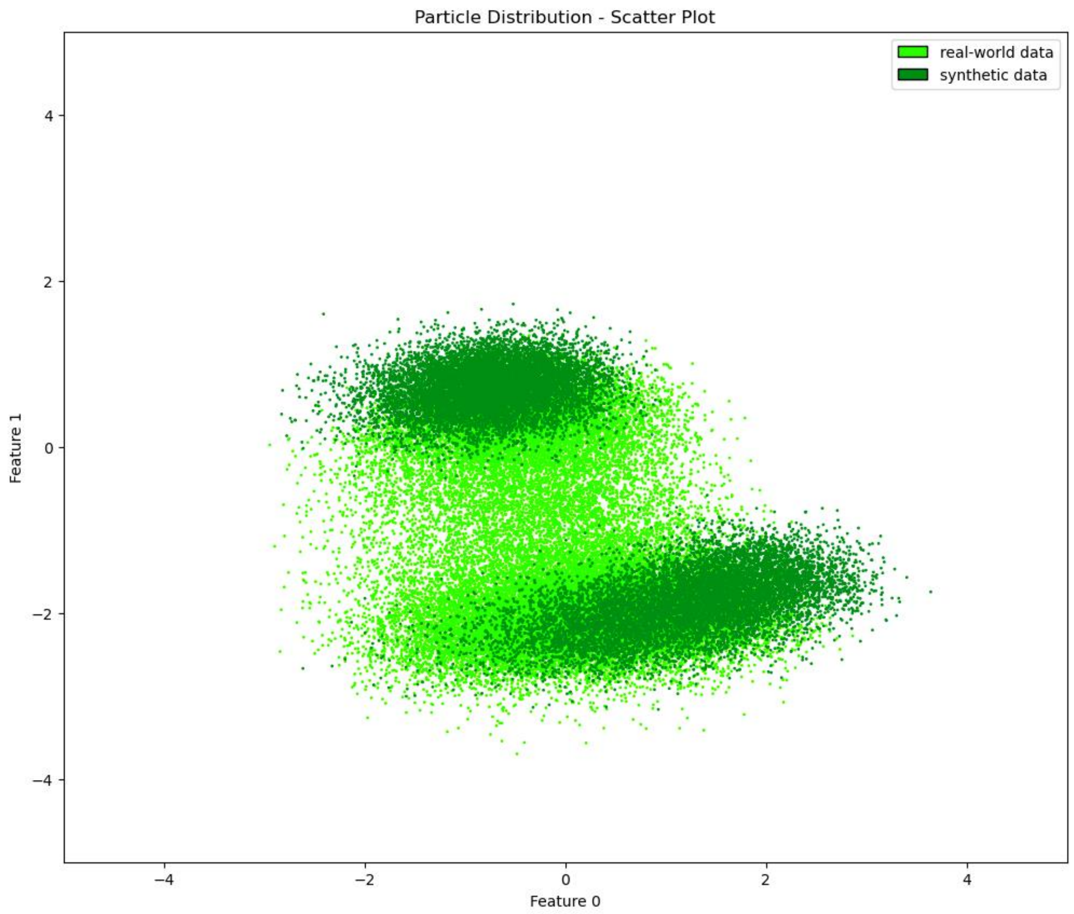
Synthetic data

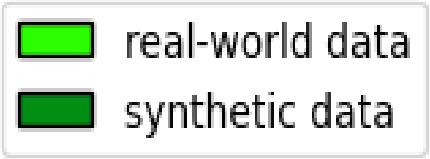


Images provided by ATEM Structural Discovery, thanks to Carsten Jasper

Scatter Plot – Real World vs Synthetic

(Two-dimensional feature space)





Images provided by ATEM, thanks to Carsten Jasper

Let's Look at Two Examples …

1 **Initial Data Set Quality** ←

2 Data Split

3 Model Design

4 Model Training

5 Model Evaluation

6 Deployment and Release

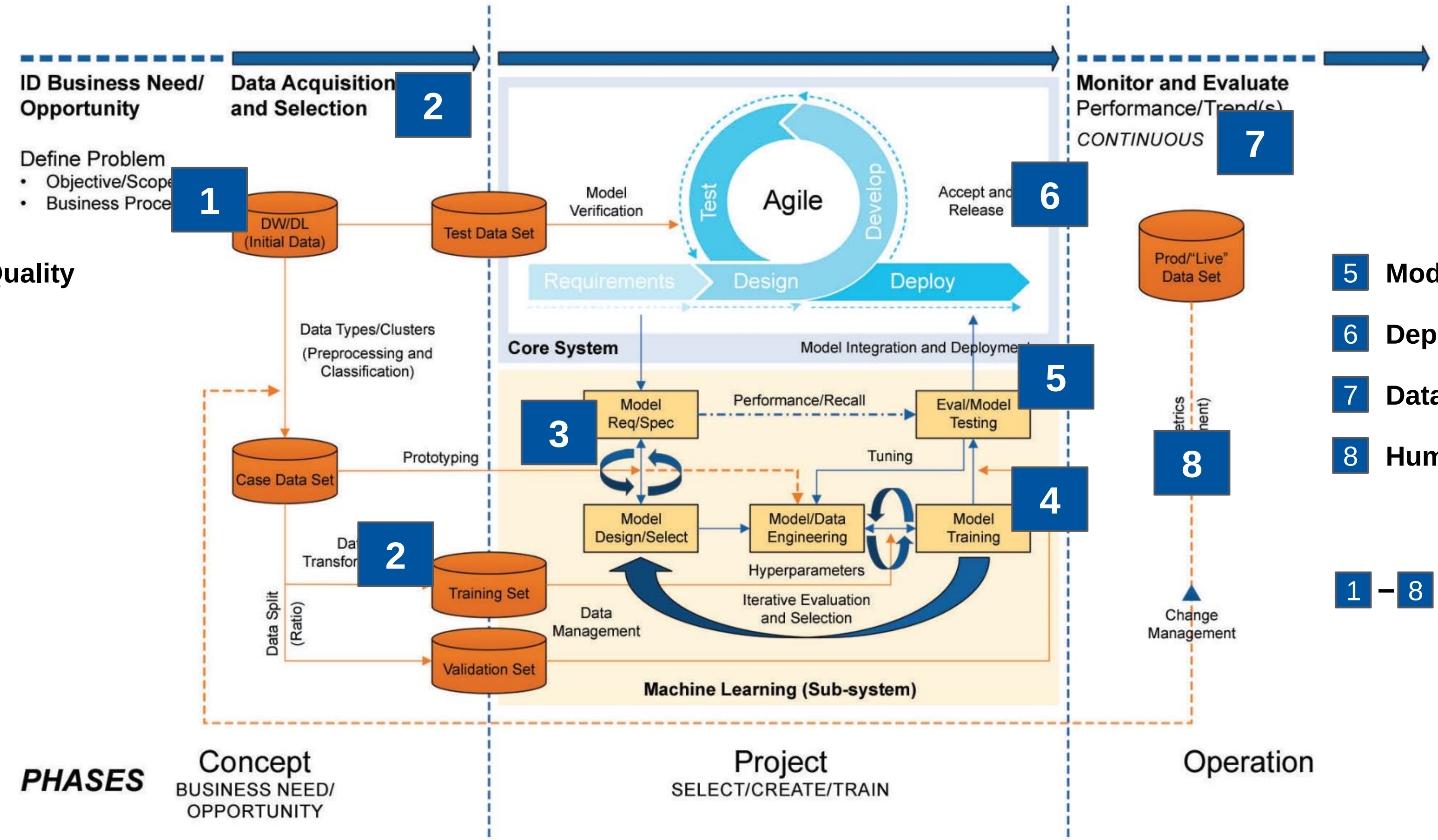
7 **Data Quality in Operation** ←

8 Human Interaction & Monitoring

Based on: A Control Framework to Limit Risk of AI in GxP by S. Münch and B. Stockton 2024 – ISPE European Conference

Risk Analysis with Hazard Clusters
along the G5SE D11 development life cycle

1 **Initial Data Set Quality**
2 **Data Split**
3 **Model Design**
4 **Model Training**



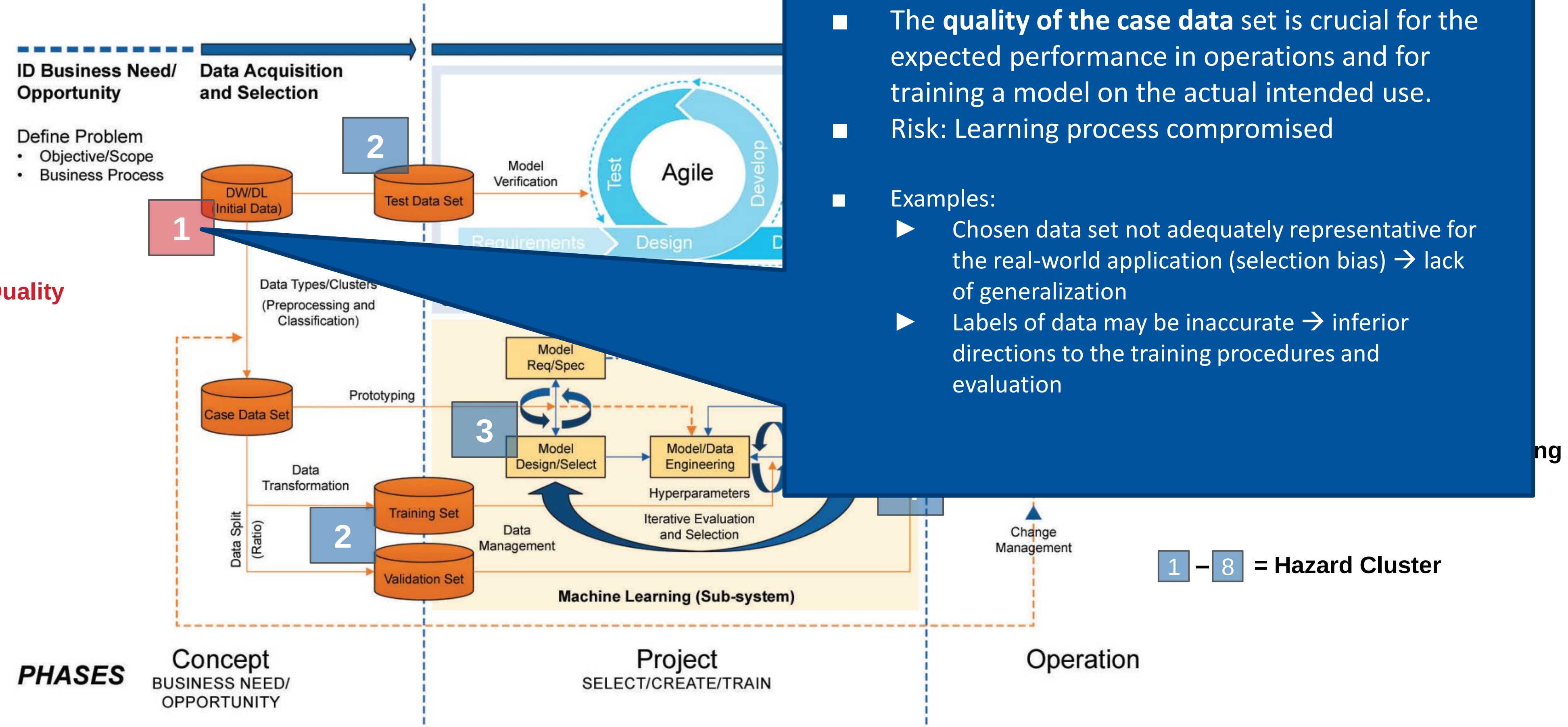
5 **Model Evaluation**
6 **Deployment and Release**
7 **Data Quality in Operation**
8 **Human Interaction & Monitoring**

1 – 8 **= Hazard Cluster**

Based on: ML Risk and Control Framework, Figure 5, © PE magazine Jan/Feb 2024

Initial Data Set Quality

Hazard Cluster #1



1 **Initial Data Set Quality**
2 **Data Split**
3 **Model Design**
4 **Model Training**

- The **quality of the case data** set is crucial for the expected performance in operations and for training a model on the actual intended use.
- Risk: Learning process compromised

- Examples:
  - Chosen data set not adequately representative for the real-world application (selection bias) → lack of generalization
  - Labels of data may be inaccurate → inferior directions to the training procedures and evaluation

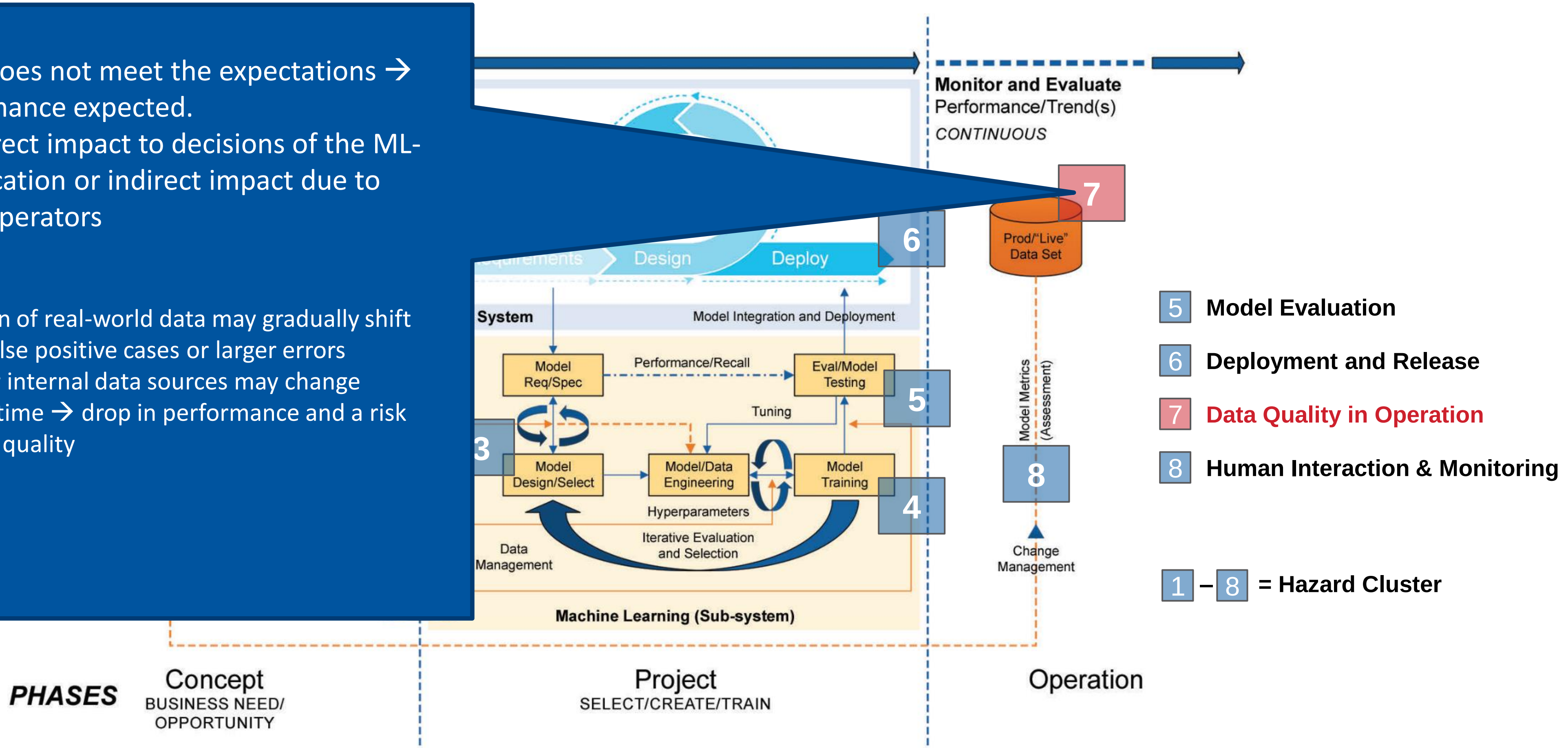
Based on: ML Risk and Control Framework, Figure 5, © PE magazine Jan/Feb 2024

Data Quality in Operation

Hazard Cluster #7

- **Data quality** does not meet the expectations → loss in performance expected.
- Risk: Either direct impact to decisions of the ML-enabled application or indirect impact due to confusion of operators

- Examples:
  - Distribution of real-world data may gradually shift → more false positive cases or larger errors
  - External or internal data sources may change during runtime → drop in performance and a risk to product quality



Based on: ML Risk and Control Framework, Figure 5, © PE magazine Jan/Feb 2024

Risk Analysis and Mitigation Matrix (RAMM)

Originally published in PE magazine Jan/Feb 2012

Monoclonal Antibody		Relative Importance of CQA →	Mycoplasma	Viral Contamination	Identity	Acidic variant levels	Yield	Concentration (UV Assay)	Purity assay (HPLC)	Visual Appearance	Osmolality	pH	Purity	Residual Host cell protein	Residual Host Cell DNA	Bioburdin	Endotoxin	Viral clearance	
			9	9	9	9	3	3	9	1	1	1	3	9	9	9	9	9	
Process Step	**Class**	**Process Parameters or Material Attribute**																	**Total**
N-1 stage cell expansion	Personnel	Equipment setup	3	3	1	3	3	3	1	1	1	1	1	1	1	9	3	1	276
N-1 stage cell expansion	Method	Batch media volume	1	1	1	3	3	3	1	1	1	1	1	1	1	1	1	1	150
N-1 stage cell expansion	Method	Temperature control	1	1	1	9	9	9	1	1	1	1	1	1	1	1	1	1	240
N-1 stage cell expansion	Method	Agitation	1	1	1	9	3	9	1	1	1	1	1	1	1	1	1	1	210
N-1 stage cell expansion	Method	Dissolved Oxygen	1	1	1	9	9	9	1	1	1	1	1	1	1	1	1	1	240
N-1 stage cell expansion	Method	Overlay CO2 flow rate	1	1	1	3	3	3	1	1	1	3	1	1	1	1	1	1	146
N-1 stage cell expansion	Method	Overlay air flow rate	1	1	1	1	3	1	1	1	1	3	1	1	1	1	1	1	128
N-1 stage cell expansion	Method	Sparge air flow rate	1	1	1	3	3	1	1	1	1	1	1	1	1	1	1	1	132
N-1 stage cell expansion	Method	Post-inoculation temperature	1	1	1	9	3	9	1	1	1	1	1	1	1	1	1	1	210
N-1 stage cell expansion	Method	Culture duration	1	1	1	3	3	1	1	1	1	1	1	1	1	1	1	1	132

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Structure of the ML RAMM

Visualization of risk classes based on quality dimensions

Hazard Impact Factor	9						
Quality Dimension		Data Quality	Human-AI Interaction	Predictive Power	Stability & Robustness	Calibration	
Hazard Clusters	**Risks**						**Risk Control Measure**
Hazard Cluster 1	Risk 1						Control Measure 1
	Risk 2						Control Measure 2
Hazard Cluster 2	Risk 3						Control Measure 3
	Risk 4						Control Measure 4
Hazard Cluster 3	Risk 5						Control Measure 5
	Risk 6						Control Measure 6
Hazard Cluster 4	Risk 7						Control Measure 7
	Risk 8						Control Measure 8
Hazard Cluster 5	Risk 9						Control Measure 9

Risks are plotted along hazard clusters

Classification may be performed along Quality Dimensions; a simple version may only classify the risk

Comparison of risks
via *Total Score* per risk
or via Hazard *Cluster Score*

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ML RAMM dynamic application

Risk mitigation and residual risks can be clearly identified

initially

Hazard Impact Factor 9

Quality Dimension			Data Quality		Human-AI Interaction		Predictive Power		Stability & Robustness		Calibration			
Hazard Clusters	**Hazard Cluster Total Score**	**Risks**	**RA**	**RA * HIF**	**RA**	**RA * HIF**	**RA**	**RA * HIF**	**RA**	**RA * HIF**	**RA**	**RA * HIF**	**Total Score**	**Risk Control Measure**
Initial Data Set Quality	198	Risk 1	Low	9	Low	9	Low	9	[illegible]	[illegible]	High	81	[illegible]	Control Measure 1
		Risk 2	Low	9	Low	9	Low	[illegible]	Medium	27	[illegible]	[illegible]	[illegible]	Control Measure 2
Data Split	261	Risk 1	High	81	Low	9	Low	9	[illegible]	[illegible]	Low	9	[illegible]	Control Measure 3
		Risk 2	Medium	27	Low	9	Low	9	Low	9	Low	9	63	Control Measure 4
		Risk 3	Low	9	Low	9	Medium	27	Low	9	Medium	27	81	Control Measure 5
Model Design	135	Risk 1	Medium	27	Medium	27	Medium	27	Medium	27	Medium	27	135	Control Measure 6
Model Training	153	Risk 1	High	81	Medium	27	Medium	27	Low	9	Low	9	153	Control Measure 7
Model Evaluation	117	Risk 1	Low	9	Low	9	High	81	Low	9	Low	9	117	Control Measure 8
Deployment and Release	81	Risk 1	Medium	27	Low	9	Low	9	Low	9	Medium	27	81	Control Measure 9
Data Quality in Operation	63	Risk 1	Low	9	Medium	27	Low	9	Low	9	Low	9	63	Control Measure 10
Human Interaction and Monitoring	135	Risk 1	Medium	27	High	81	Low	9	Low	9	Low	9	135	Control Measure 11

with risk control

Hazard Impact Factor 9

Quality Dimension			Data Quality		Human-AI Interaction		Predictive Power		Stability & Robustness		Calibration			
Hazard Clusters	**Hazard Cluster Total Score**	**Risks**	**RA**	**RA * HIF**	**RA**	**RA * HIF**	**RA**	**RA * HIF**	**RA**	**RA * HIF**	**RA**	**RA * HIF**	**Total Score**	**Risk Control Measure**
Initial Data Set Quality	126	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	9	[illegible]	[illegible]	Medium	27	63	Control Measure 1
		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Low	9	[illegible]	[illegible]	63	Control Measure 2
Data Split	135	Risk 1	Low	9	Low	9	Low	9	[illegible]	[illegible]	Low	9	45	Control Measure 3
		Risk 2	Low	9	Low	9	Low	9	Low	9	Low	9	45	Control Measure 4
		Risk 3	Low	9	Low	9	Low	9	Low	9	Low	9	45	Control Measure 5
Model Design	63	Risk 1	Low	9	Medium	27	Low	9	Low	9	Low	9	63	Control Measure 6
Model Training	99	Risk 1	Medium	27	Medium	27	Medium	27	Low	9	Low	9	99	Control Measure 7
Model Evaluation	63	Risk 1	Low	9	Low	9	Medium	27	Low	9	Low	9	63	Control Measure 8
Deployment and Release	63	Risk 1	Medium	27	Low	9	Low	9	Low	9	Low	9	63	Control Measure 9
Data Quality in Operation	45	Risk 1	Low	9	Low	9	Low	9	Low	9	Low	9	45	Control Measure 10
Human Interaction and Monitoring	81	Risk 1	Medium	27	Medium	27	Low	9	Low	9	Low	9	81	Control Measure 11

- Mitigation measures lead to risk reduction in certain quality dimensions
- Critical aspects and risks can be highlighted and visualized during periodic reviews or audits
- Simplified prioritization of further measures

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Ensure Comparability

Comparison different environments and between applications made easy

Hazard Impact Factor 9

Quality Dimension			Data Quality		Human-AI Interaction		Predictive Power		Stability & Robustness		Calibration			
Hazard Clusters	Hazard Cluster Total Score	Risks	RA	RA * HIF	RA	RA * HIF	RA	RA * HIF	RA	RA * HIF	RA	RA * HIF	Total Score	Risk Control Measure
Initial Data Set Quality	198	Risk 1	Low	9	Low	9	Low	9	Low	9	High	81	117	Control Measure 1
		Risk 2	Low	9	Low	9	Low	9	Medium	27	Medium	27	81	Control Measure 2
Data Split	261	Risk 1	High	81	Low	9	Low	9	Low	9	Low	9	117	Control Measure 3
		Risk 2	Medium	27	Low	9	Low	9	Low	9	Low	9	63	Control Measure 4
		Risk 3	Low	9	Low	9	Medium	27	Low	9	Medium	27	81	Control Measure 5
Model Design	135	Risk 1	Medium	27	Medium	27	Medium	27	Medium	27	Medium	27	135	Control Measure 6
Model Training	153	Risk 1	High	81	Medium	27	Medium	27	Low	9	Low	9	153	Control Measure 7
Model Evaluation	117	Risk 1	Low	9	Low	9	High	81	Low	9	Low	9	117	Control Measure 8
Deployment and Release	81	Risk 1	Medium	27	Low	9	Low	9	Low	9	Medium	27	81	Control Measure 9
Data Quality in Operation	63	Risk 1	Low	[illegible]	Medium	27	Low	9	Low	9	Low	9	63	Control Measure 10
Human Interaction and Monitoring	135	Risk 1	Med[illegible]	27	High	81	Low	9	Low	9	Low	9	135	Control Measure 11

Hazard Impact Factor 3

Quality Dimension			Data Quality		Human-AI Interaction		Predictive Power		Stability & Robustness		Calibration			
Hazard Clusters	Hazard Cluster Total Score	Risks	RA	RA * HIF	RA	RA * HIF	RA	RA * HIF	RA	RA * HIF	RA	RA * HIF	Total Score	Risk Control Measure
Initial Data Set Quality	66	Risk 1	Low	3	Low	3	Low	3	Low	3	High	27	39	Control Measure 1
		Risk 2	Low	3	Low	3	Low	3	Medium	9	Medium	9	27	Control Measure 2
Data Split	87	Risk 1	High	27	Low	3	Low	3	Low	3	Low	3	39	Control Measure 3
		Risk 2	Medium	9	Low	3	Low	3	Low	3	Low	3	21	Control Measure 4
		Risk 3	Low	3	Low	3	Medium	9	Low	3	Medium	9	27	Control Measure 5
Model Design	45	Risk 1	Medium	9	Medium	9	Medium	9	Medium	9	Medium	9	45	Control Measure 6
Model Training	51	Risk 1	High	27	Medium	9	Medium	9	Low	3	Low	3	51	Control Measure 7
Model Evaluation	39	Risk 1	Low	3	Low	3	High	27	Low	3	Low	3	39	Control Measure 8
Deployment and Release	27	Risk 1	Medium	9	Low	3	Low	3	Low	3	Medium	9	27	Control Measure 9
Data Quality in Operation	21	Risk 1	Low	3	Medium	9	Low	3	Low	3	Low	3	[illegible]	Control Measure 10
Human Interaction and Monitoring	[illegible]	[illegible]	Medium	9	High	27	Low	3	Low	3	Low	[illegible]	45	Control Measure 11

initially

adjusted maturity

Easier definition of target maturity for dynamic developments

Comparability of applications in different application areas

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Benefits: The ML Risk and Control Framework …

Alignment

- … aligns with ICH Q9 (R1)

Cohesion

- … connects:
  - Application context
  - Autonomy
  - Model training and development
  - Specific quality dimensions

Transparency

- … supports and simplifies presentation of risks for reviews and audits

Flexibility

- … can be dynamically applied during all steps of model selection, training, and deployment

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References

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ML Risk and Control Framework (2024)

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Abbreviations

Short	Long
AAV	Adeno-Associated Viruses
AI	Artificial Intelligence
ATMP	Advanced Therapy Medicinal Products
D/A/CH	Germany / Austria / Switzerland
E2E	End to end
EM	Electron Microscopy
G5SE	GAMP® 5 Second Edition
GDPR	General Data Protection Regulation
GMLP	Good Machine Learning Practice
GxP	Good … Practice (x = Manufacturing, Clinical, Laboratory, etc.)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ML	Machine Learning
PE	Pharmaceutical Engineering
QA	Quality Assurance
RAMM	Risk Analysis and Mitigation Matrix
SA	Software Automation

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Thank You!

Charles River Laboratories

https://www.criver.com/

ATEM Structural Discovery

https://atem.bio/