New Science.
Transformative patient outcomes.

Data-driven Root Cause Analysis

An overview of how to identify causes of manufacturing deviations in Pharma

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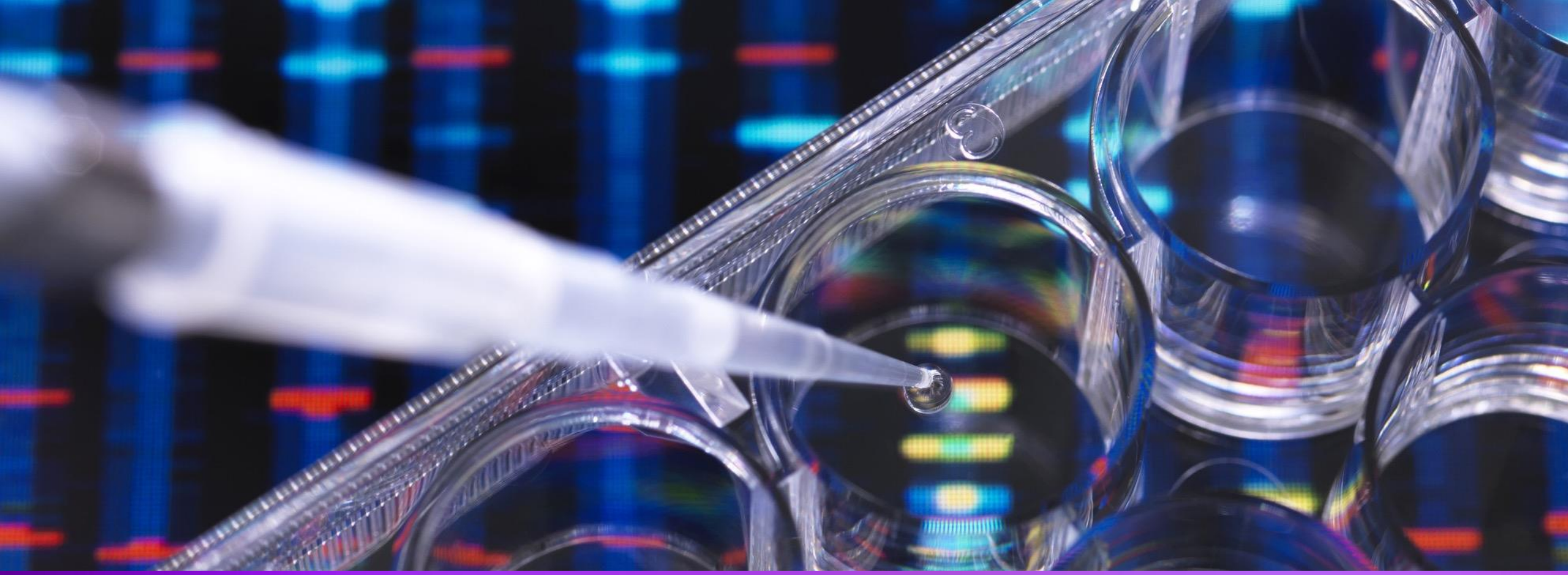

Background

A short overview of BioPharma and their challenges

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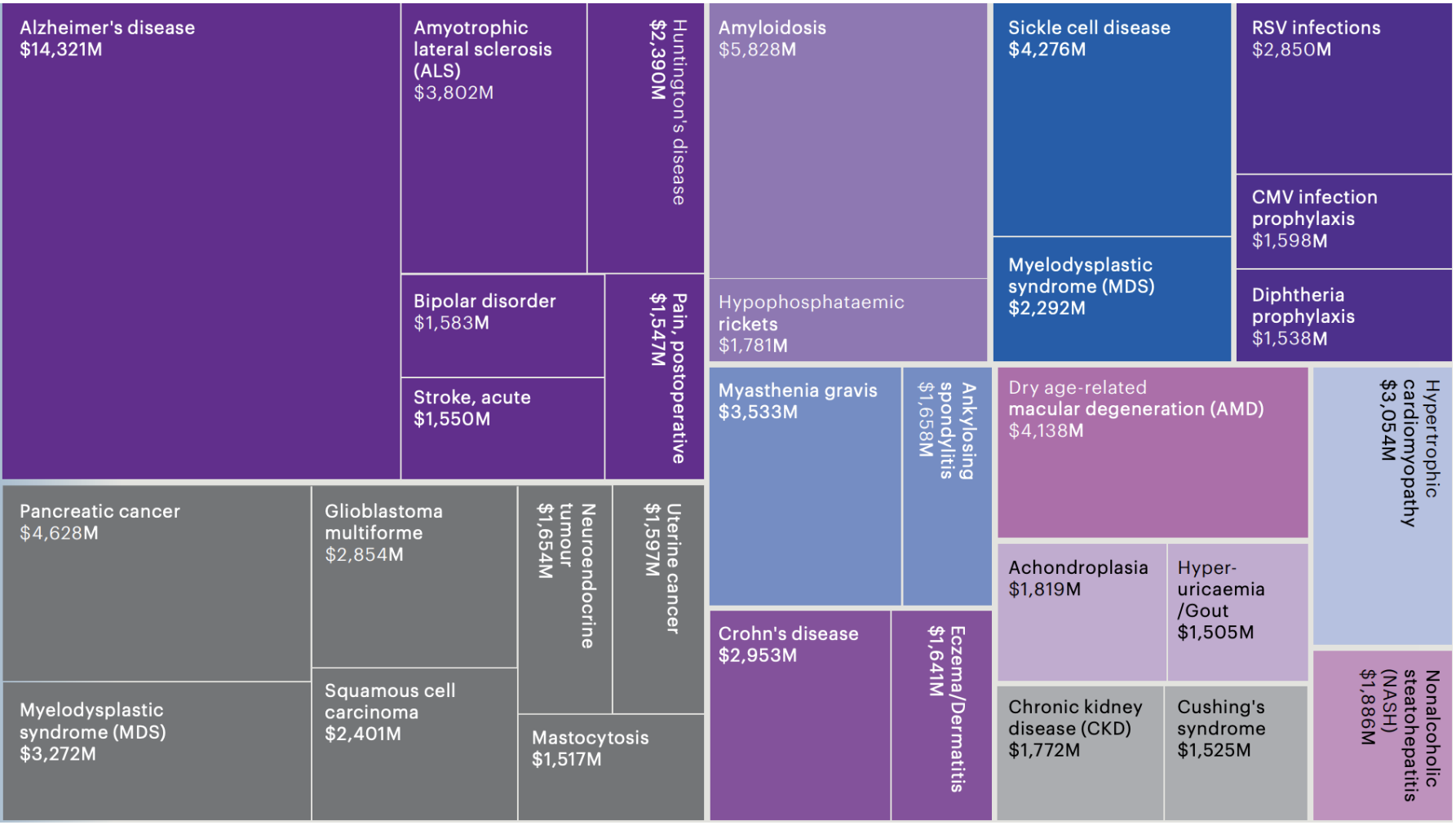
Pharma companies are heavily investing in RnD, as a response to Biosimilar threats



Requires

- **Shift high to low-volume production**
- **Stronger Data & AI focus**
- **Leaner processes**
- **Upskilled workforce**

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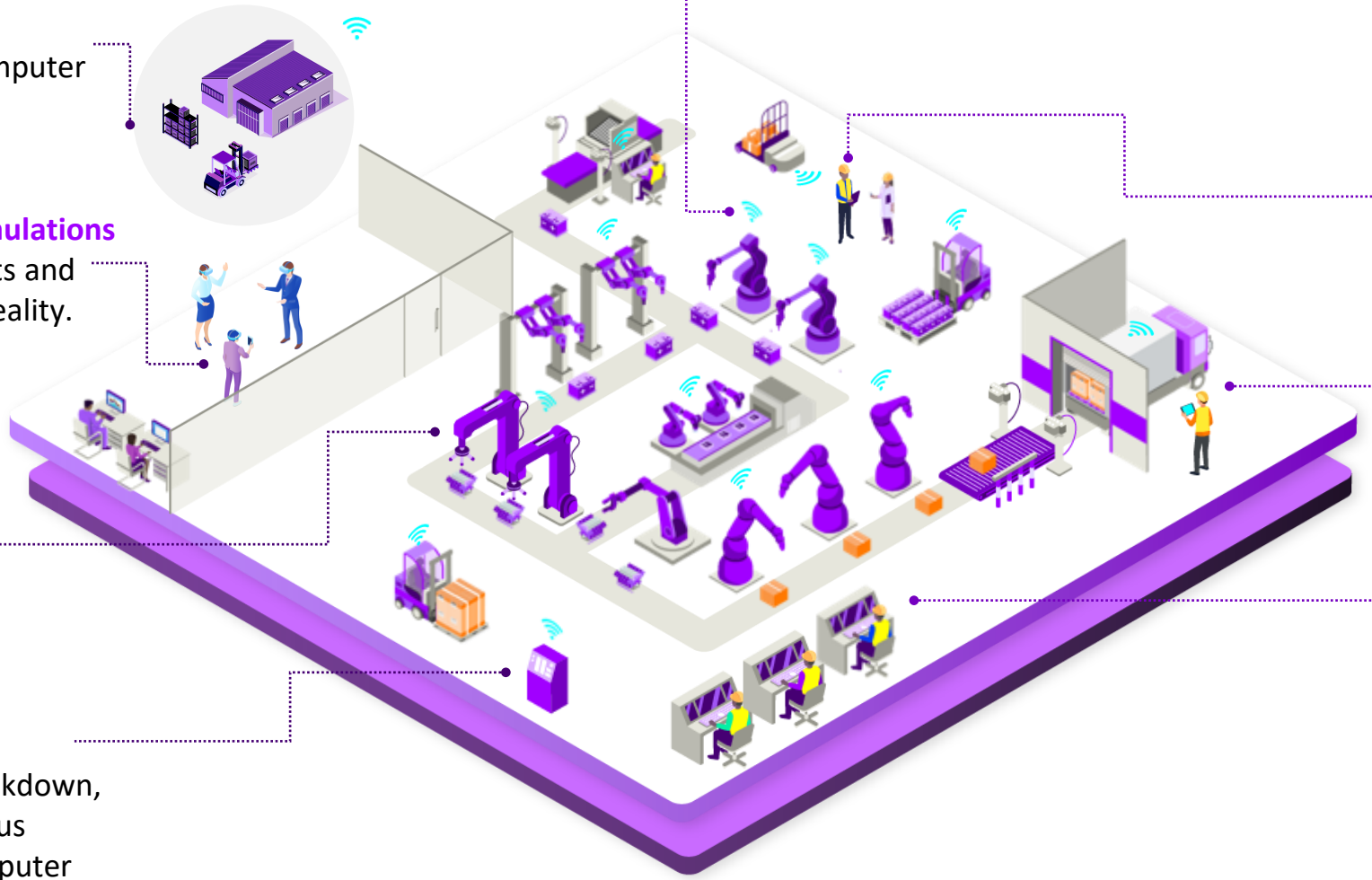
New therapies require to equip manufacturing plants with innovative technologies and A.I.

1 AI supported Supply Chain
Optimising logistics and reducing waste with Computer Vision.

2 Virtual trainings and simulations
Train staff on instruments and processes with Virtual Reality.

3 Single Use Technologies
In the biopharma industry, single-use technologies are disposable products which are intended for one-time use.

4 Digital Maintenance
Prevent machine breakdown, and ensures continuous operations using Computer Vision algorithms on Log files.



5 Robotics in DS and DP
Automate production and quality control with robotics.

6 Connected operators
Operators receive real-time alerts about the process, enabling to prevent deviations and to improve output.

7 Predictive Track and Trending
Evaluating and predicting OOS, OOT events on CPPs, non-CPPs and KPIs continuously.

8 Factory App-store
Suite of easy-to-use applications to support with standard work instructions availability, remote assistance, process alerting.

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One major challenge is to ensure product quality and avoid deviations of the manufacturing process

Deviations

- Manufacturing process detailed in SOPs.
- Deviation of the process, poses a risk to product quality and patient safety.
- Minimizing deviations is top priority to any Big Pharma company.
- Failure to comply, can risk the Right to Operate.

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Business impact

- Large time and resource invest to find Root Cause
- Shift of production to other sites
- Recall of products and additional waste

Root Cause Analysis

- Method to investigate the “root cause” of the deviation
- Main intention is to fix it and prevent re-occurrence
- Carried out by the operator or other Subject Matter Experts

Current RCA process

A rather manual approach

Common RCA methods: lean problem solving to rule out probable causes

Mostly a manual effort, involving little quantitative data analysis

Fishbone

Main observation is the head, potential causes are bones. Discuss each bone and rule out if not probable.

5 Whys

Take a probable cause, ask 5 times the question “Why” until you can rule it out.

Check sheets

Specific list of checks to understand if the process has been followed or not.

Pareto Charts

Involves data analysis to plot observations against frequency to identify most likely cause.

A3 problem solving

Structured problem solving approach that can combine several methods.

Expert meetings

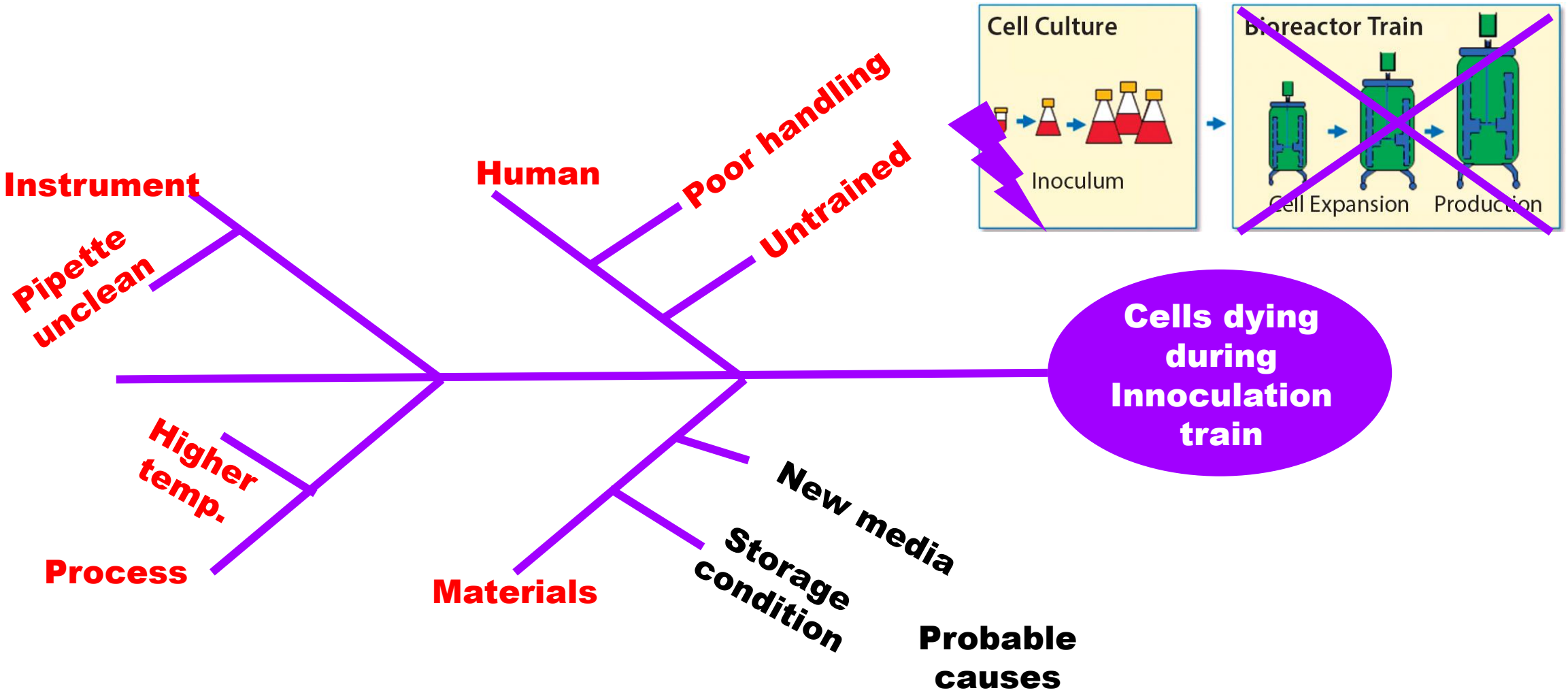
Deep dives into problems with relevant experts to identify root cause.

Limitations

Unidentified root cause

Time consuming

An example: contamination in the upstream cell culture fermentation process



Data-driven RCA approach and its benefits

Several data-centric approaches can be applied before and after a deviation occurs.

1

Real time process control

Adjust process parameters automatically to avoid deviations.

2

Deviation prediction

Utilise process and material data, to predict a deviation in advance.

3

Clustering of deviations

Understand root cause by applying NLP and clustering.

4

Advanced Analytics

Non-linear algorithms to infer combination of hidden causes.

Several data-centric approaches can be applied before and after a deviation occurs.

1 **Real time process control:**
Adjust process parameters automatically to avoid deviations.

2 **Deviation prediction**
Utilise process and material data, to predict a deviation in advance.

3 **Clustering of deviations**
Understand root cause by applying [illegible] and clustering.

4 **Advanced Analytics**
Non-linear algorithms to infer combination of hidden causes.

Clustering of deviations on historic data to investigate patterns of causes, departments and locations

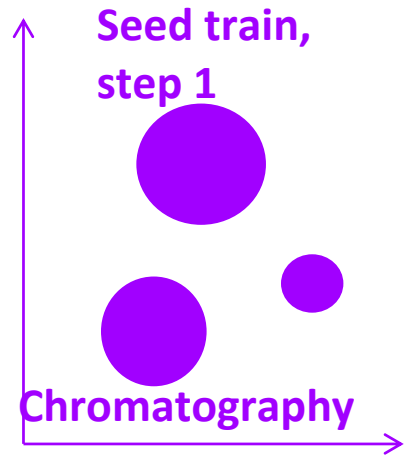
Veeva
Contains structured and unstructured data
- Metadata product, date, staff
- Text about analysis
- Text about cause
- Text about actions

ETL
Python NLTK tokenize, standardize, clean

Clustering
Hierarchical clustering to identify deviations that are similar to each other and optimise clusters.

Auto-Labelling
NLP to extract most common cause and label the cluster

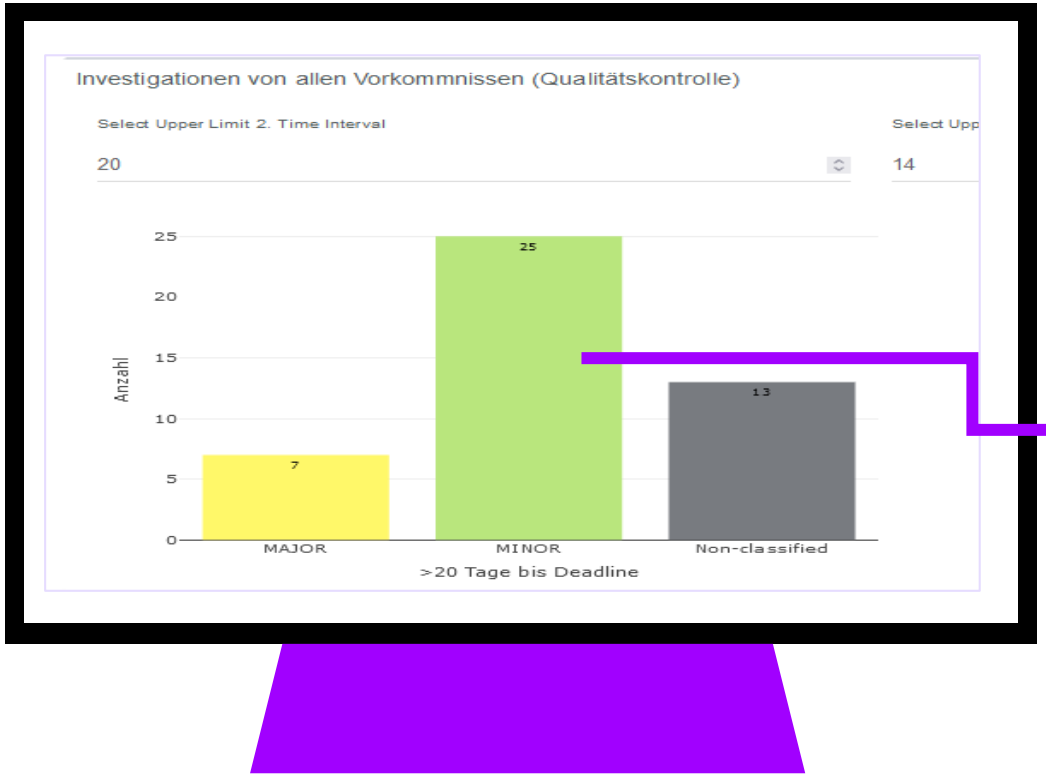
Visualise in a dashboard



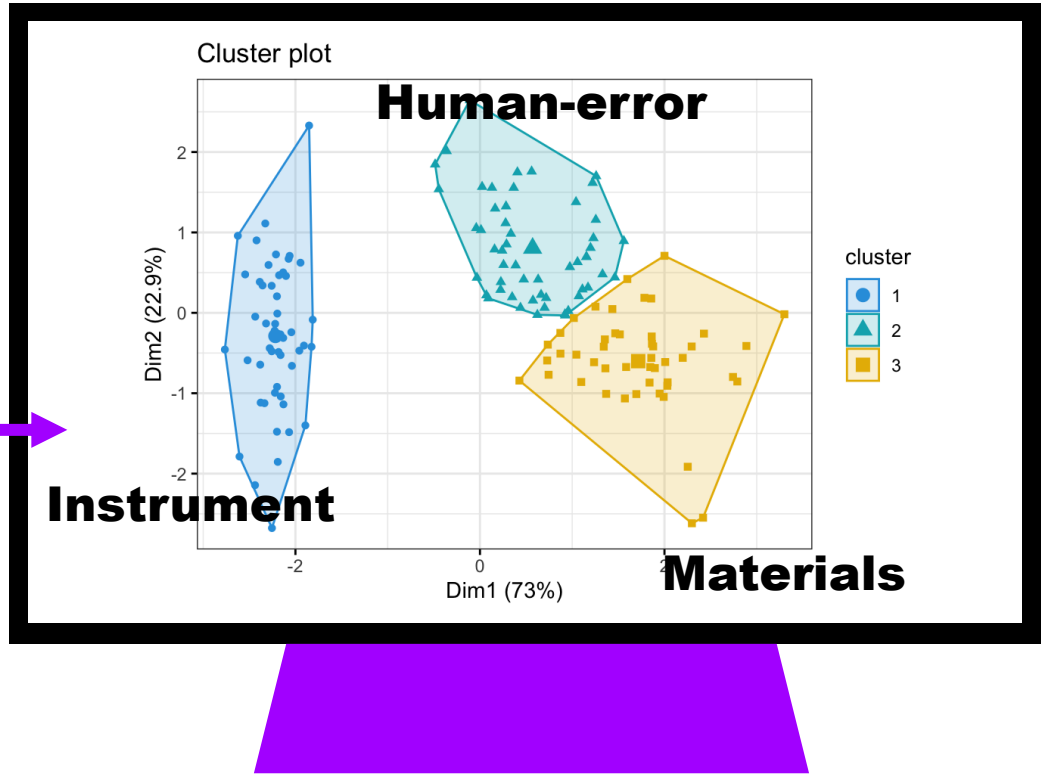
GMP Computer System Validation
- Risk assessment
- Automated unit testing
- User acceptance and functional tests
- Documentation
- Data Audit trail

Dashboard to investigate Root Causes used on a daily basis to reduce deviations overall

Frequency and statistics of deviations



Clustering of Minor deviations based on Deviation title

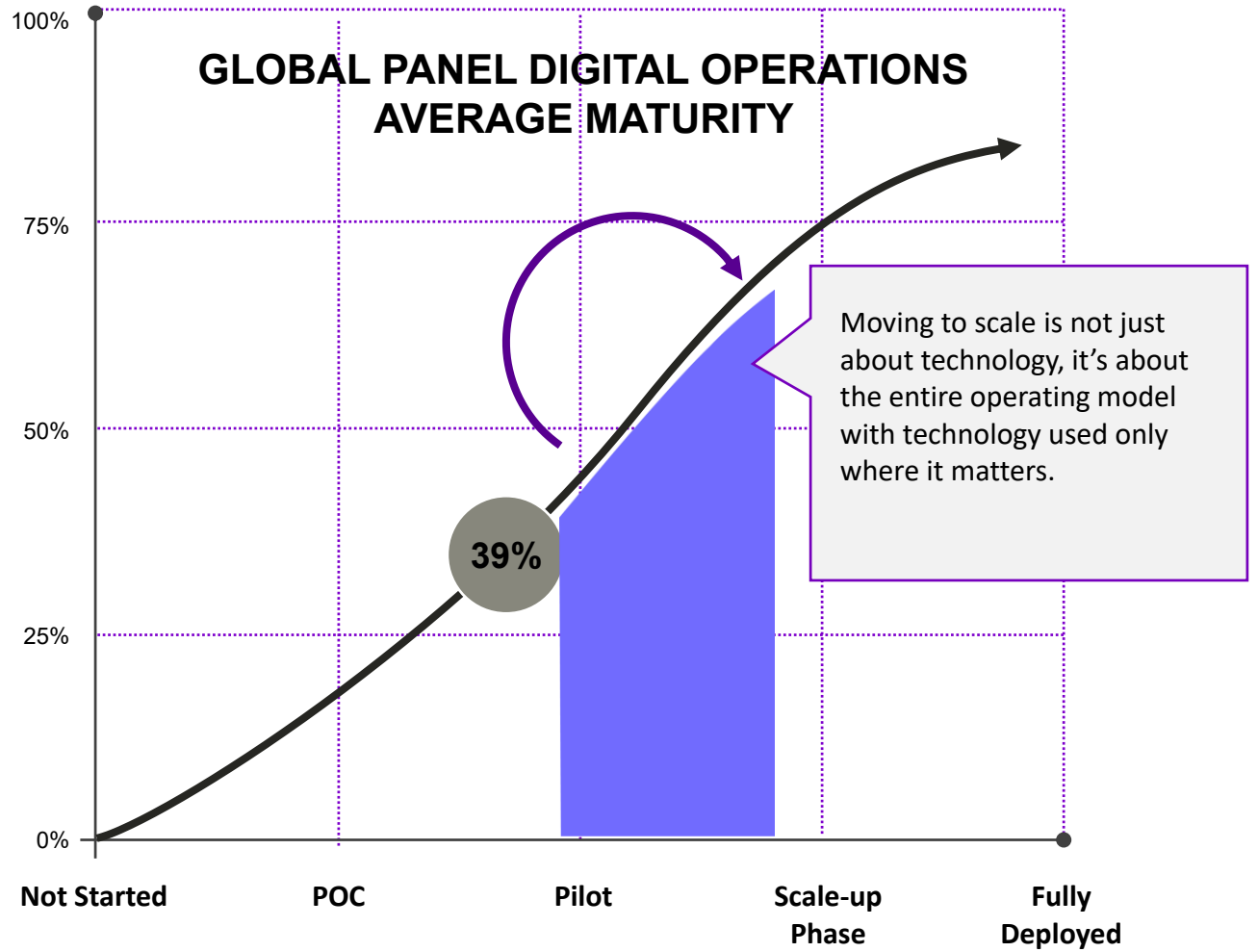


Scaling AI use cases

More than just technology

Scaling digital and AI use cases is not easy

Despite all the possibilities, our research shows that many of the leading manufacturing companies find themselves in a pilot paralysis.



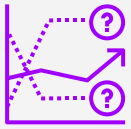
Source: Accenture Industry X Mastery Global Report. Base: All Respondents (n=600)

Common causes on why most companies are stuck in pilot paralysis

Key factors limiting Pharmaceutical companies to scale digital capabilities

Change Management

Insufficent org anizational change management not enabling adoption and lack of top-level executive support.

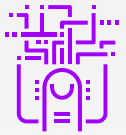


Lack of Solid Business Case

Lack of comprehens ive business cases with costs, benefits, and measures of success.

Insufficient resources

Availability of experts to scale (at site) is not sufficiently prioritized or in place making it hard to scale

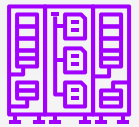


Technology Focus

Pilots are focused on implementing a particular technology, as opposed to resolving a specific problem.

No Path from Pilot to Scale

Lack of concrete path from pilot to scale under-estimating the required governance & roadmap.



Legacy IT/OT Landscape

IT / OT landscape is difficult for digital implementation due to legacy equipment, PLCs, etc.

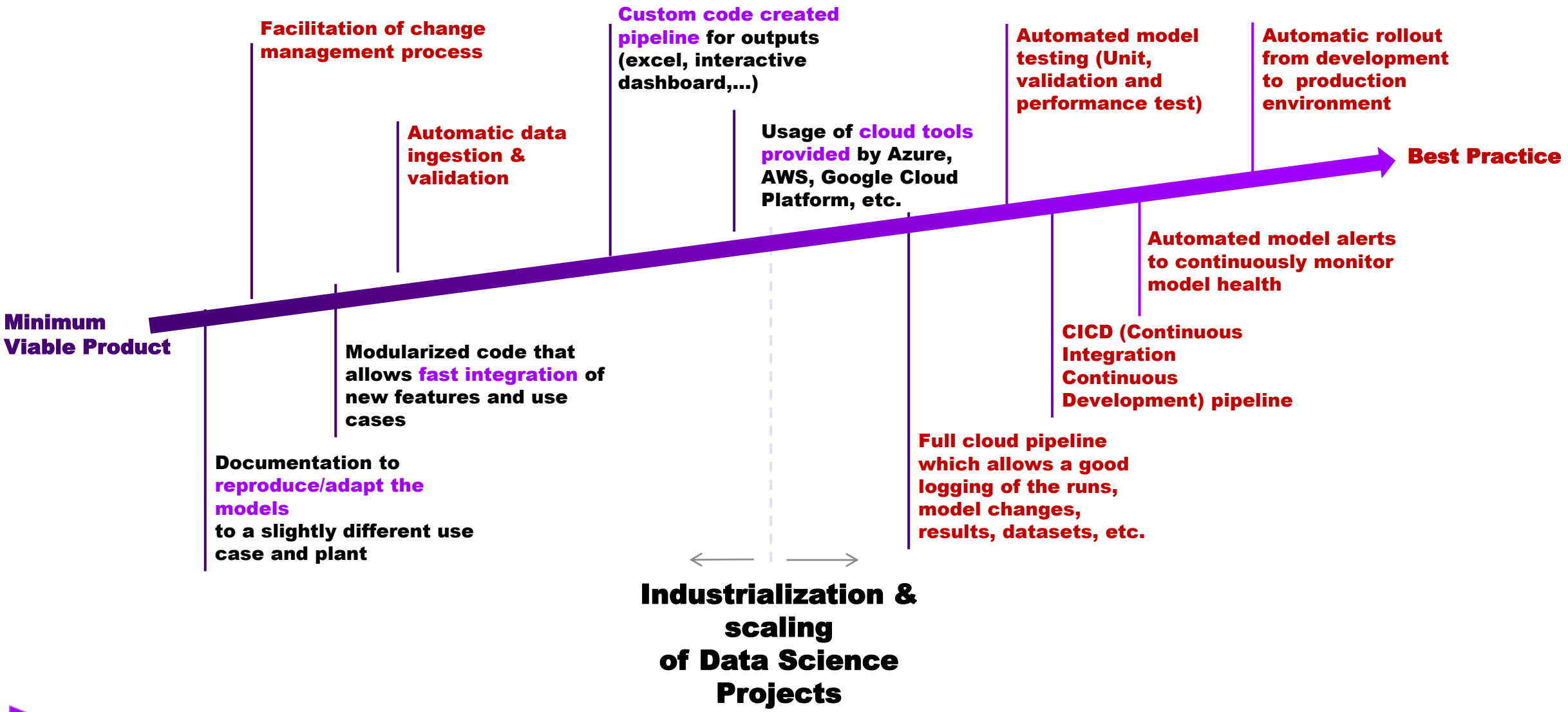
Limited global governance

Pilots often led by IT with limited global coordinate & plan balancing resources and capacities .

Cross-functional collaboration

Not sufficient meaningful decision-making, not reacting on short term change.

To industrialize A.I. use cases from a technological point is also challenging



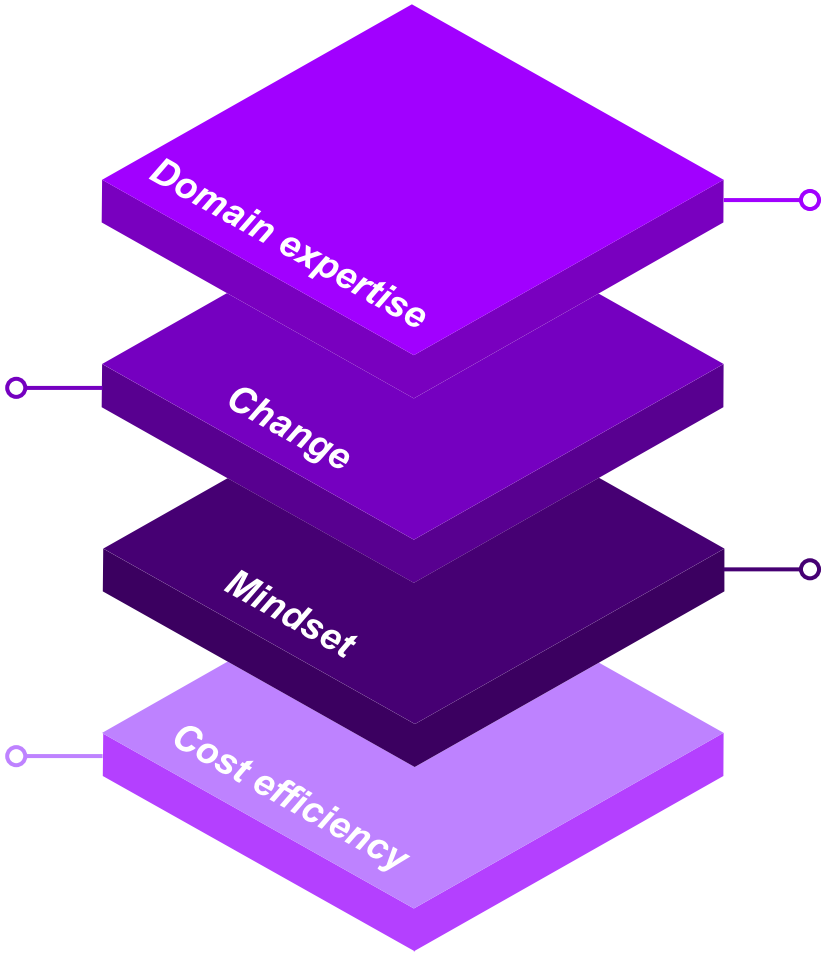
How to accelerate value and user adoption?

Change management

Crucial to actively work on user adoption, have change agents, and promote the solutions.

Cost efficiency

The implemented solutions need to be cost effective as well, to create a cost saving foundation for further expansion.



Data and Domain Expertise

Having data scientists and engineers with actual domain expertise (e.g. Manufacturing) helps enormously to speed up the process.

Organization mindset

Having the entire organization work on data standards and employ a data mindset is essential.

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Real impact is possible with A.I.

But it requires to look beyond technology.

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Appendix

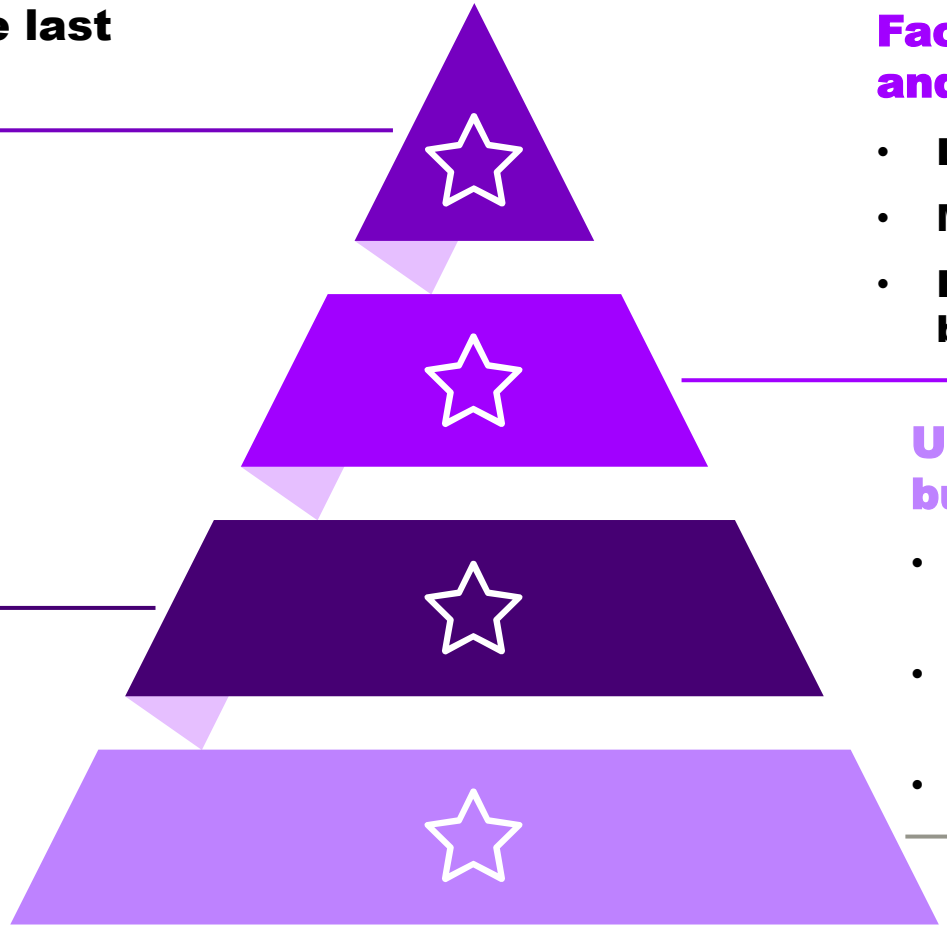
Pharma companies are reinventing themselves, as a response to Biosimilar threats

New modalities in RnD:

- Top 10 invested $157 billion CHF in 2022
- New molecular entities registrations tripled in the last decade

Data, Digital and AI

- AI across all parts in Pharma
- Business processes digitalised
- Replacing legacy systems with modern data platform



Factory of the future: Robust and agile manufacturing

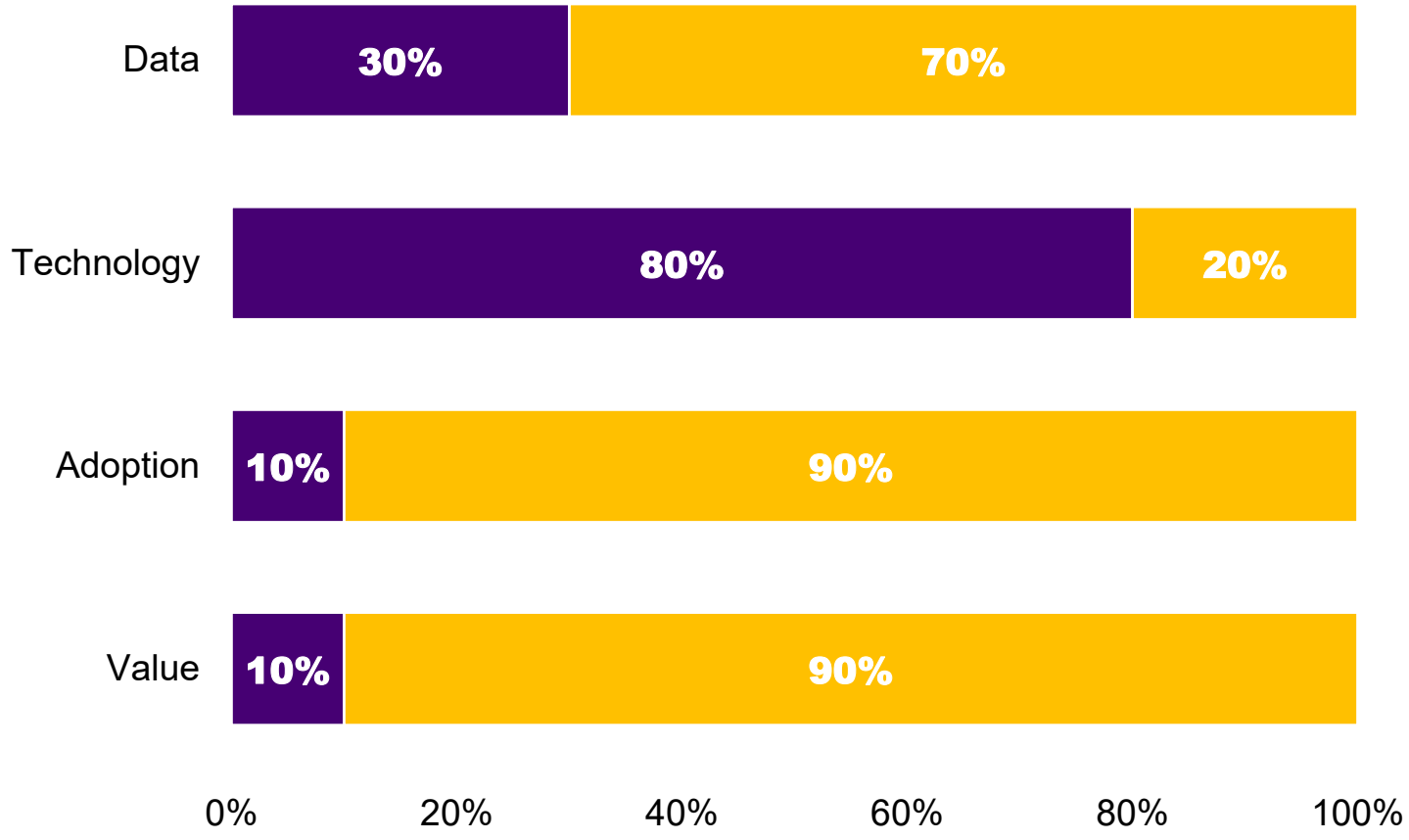
- Low volume production
- More adaptable operations
- Right first time and real time batch release

Upskilled workforce and lean business processes

- Training workforce to adopt new digital solutions
- SOPs and business processes adapted
- Teams more self-empowered

Pilot **Scale**

Achieved Maturity in Pilot vs Scaled



Technology often matured after pilot, but adoption, value and data not.

An example: contamination in the upstream cell culture fermentation process

The cells are dying.

1. **Why?** The cell culture didn't survive the process conditions.
2. **Why?** Temperature was too high.
3. **Why?** It was adjusted to work with the new media that we used.
4. **Why?** New media was tried out with a different profileration parameters
5. **Why?** The previous media was not available anymore and we ordered from a new vendor.