Statistical Strategies to Accelerate Development

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Outline

People with unmet medical needs depend on us to accelerate development.

The **Quality by Design** framework supports acceleration.

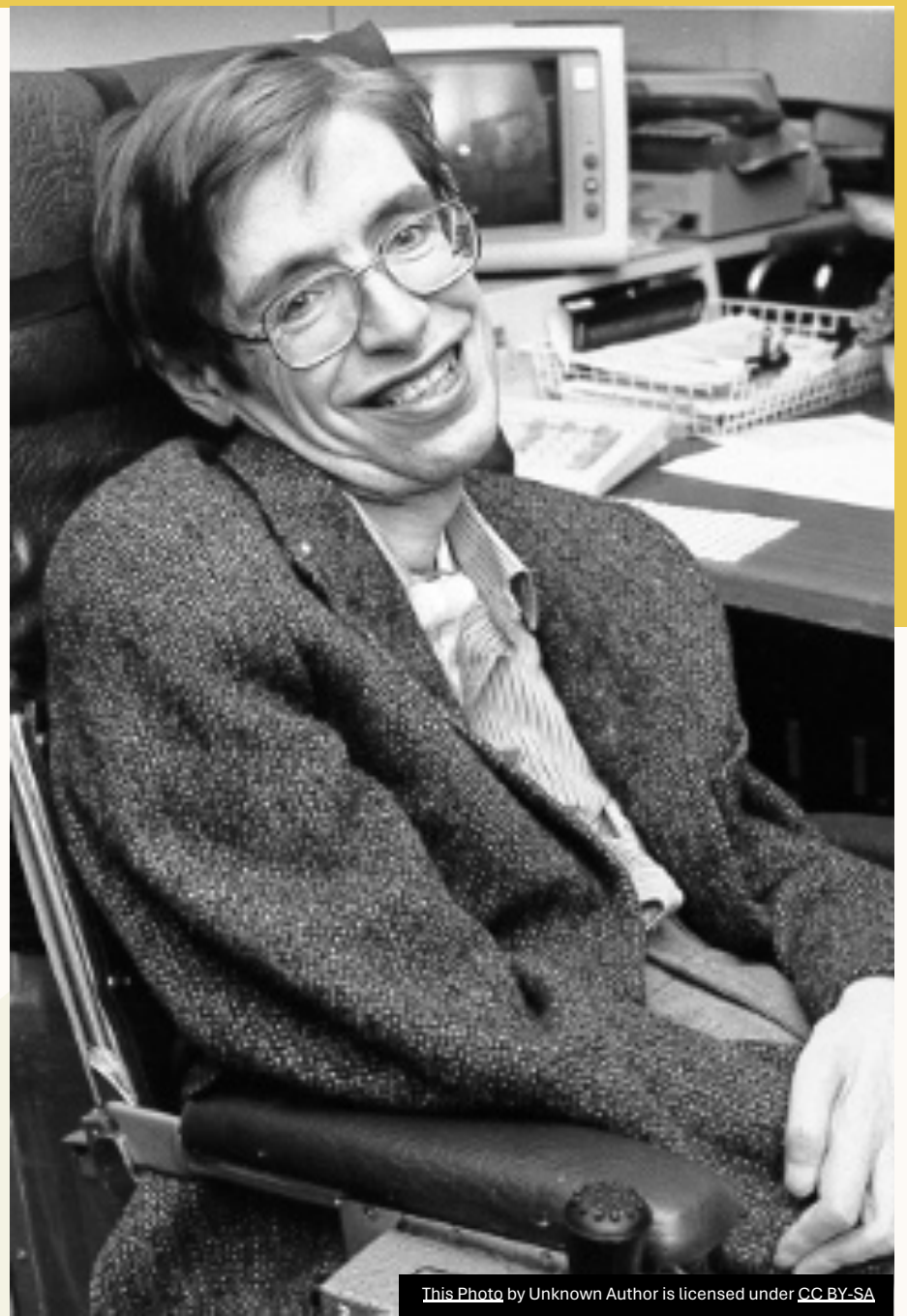
High-impact **product approvals demonstrate the value** of moving from the traditional to Quality by Design paradigm.

People with cancer depend on us to accelerate development.

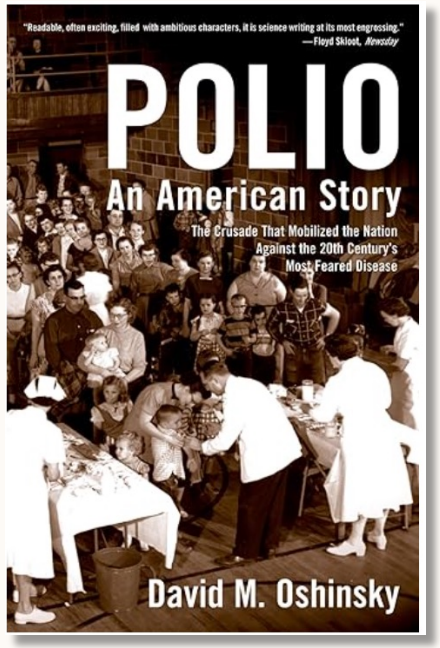
Professor Connie Borror
1966 – 2016
ASU Foundation Professor
ASQ Shewhart Medal 2016

People with degenerative diseases depend on us to accelerate development.

ALS, or amyotrophic lateral sclerosis, is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord. There is no cure for ALS yet.



People under threat from infectious disease depend on us to accelerate development.

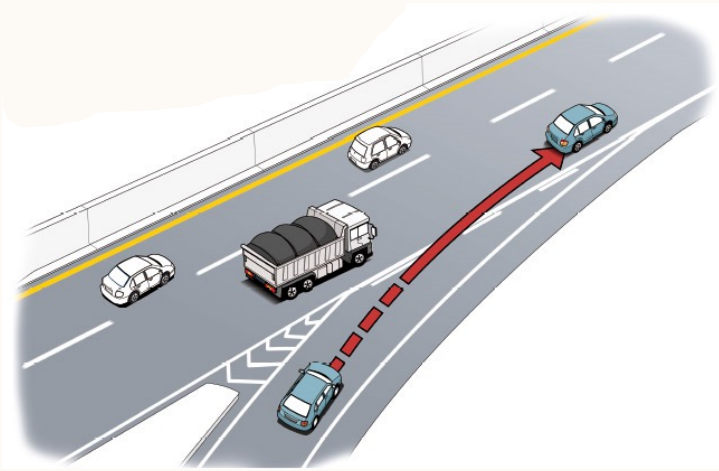


"For 50 years polio stalked parents' nightmares."

Patient Impact Depends on Successful Development.

Molecular Biology
Artificial Intelligence
Genetic Sequencing
Precision Medicine

Quality by Design (QbD)



High-volume affordable reliable supply:
scale-up
manufacturing
testing

DIRECTA

Janet Woodcock, MD, Former US Acting Commissioner of Food and Drugs, advocates for modernizing development.

- J. Wechsler, "FDA Continues to Promote Quality Drug Production," *Pharmaceutical Technology* 41 (7) 2017.

"In the past,

efficient manufacturing scale-up

was not that important because

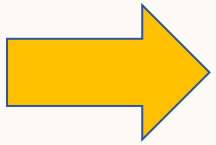
clinical development took so long,

Woodcock observes."

QbD is the modern development and quality paradigm.

Traditional paradigm:

Inspection of product to assure quality



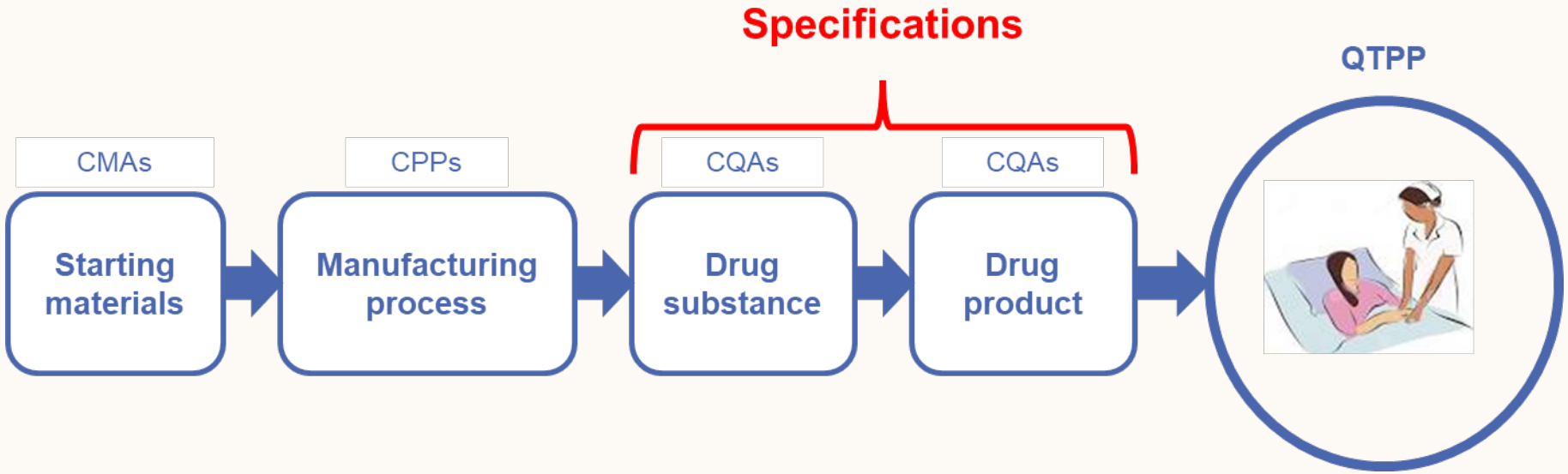
Modern paradigm:

Continuous improvement to assure reliable supply of high-quality product

Quality by Design (QbD) is described in ICH Q8(R2).

- ICH Q8(R2):
- Pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

- Critical process controls ensure product quality:
- *CMA = Critical Material Attribute*
- CPP = Critical Process Parameter
- CQA = Critical Quality Attribute
- QTPP = Quality Target Product Profile

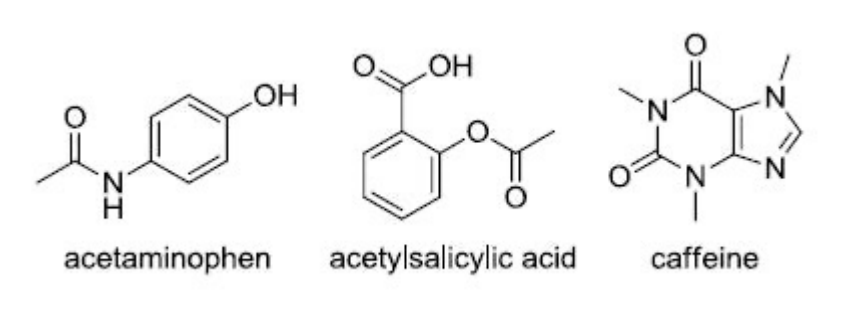


Many statistical methods are used in QbD.

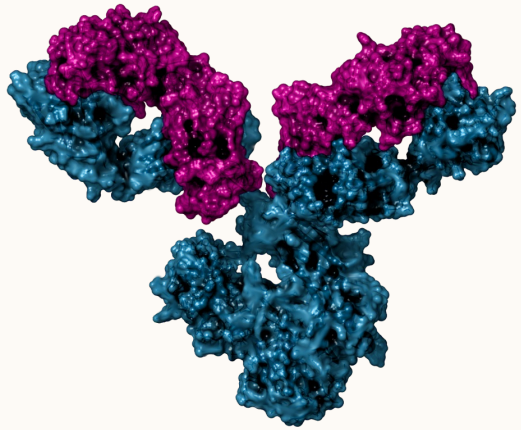
What's most important is how the tools are connected in the QbD framework.

Biologics are larger and much more complex than traditional pharmaceuticals.

small molecules



large molecule



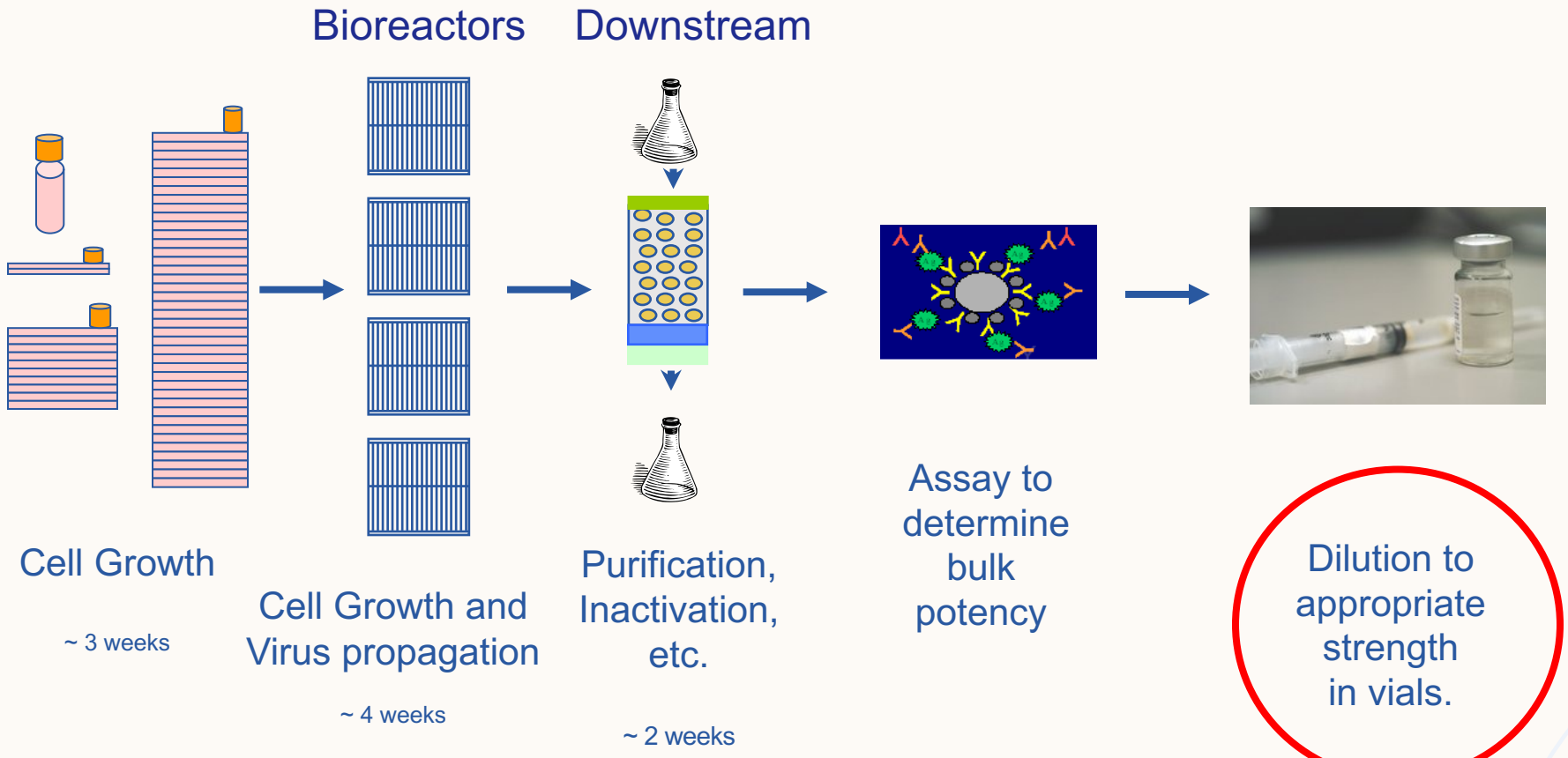
Biological Input Materials are Difficult to Control and Characterize.

Serum

Trypsin

Viral Vaccine Manufacturing Is Complex and Slow

(at least 9 weeks).



The traditional paradigm for biologics was "the process is the product."

Quality by Inspection

not

Quality by Design

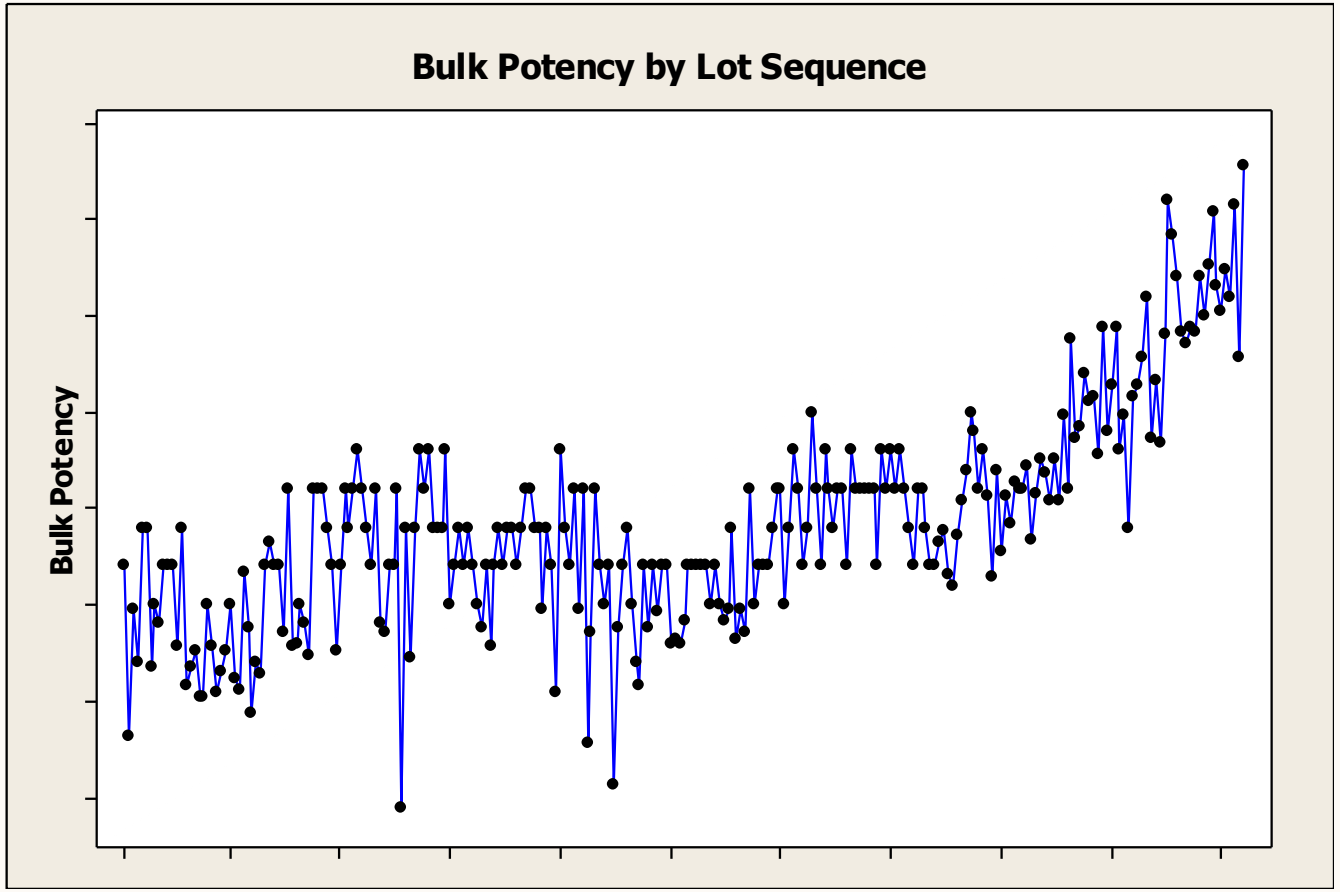
Complex "large molecule" biological products were considered too difficult to fully characterize.

"A fixed process equals a fixed product."

Don't change anything!

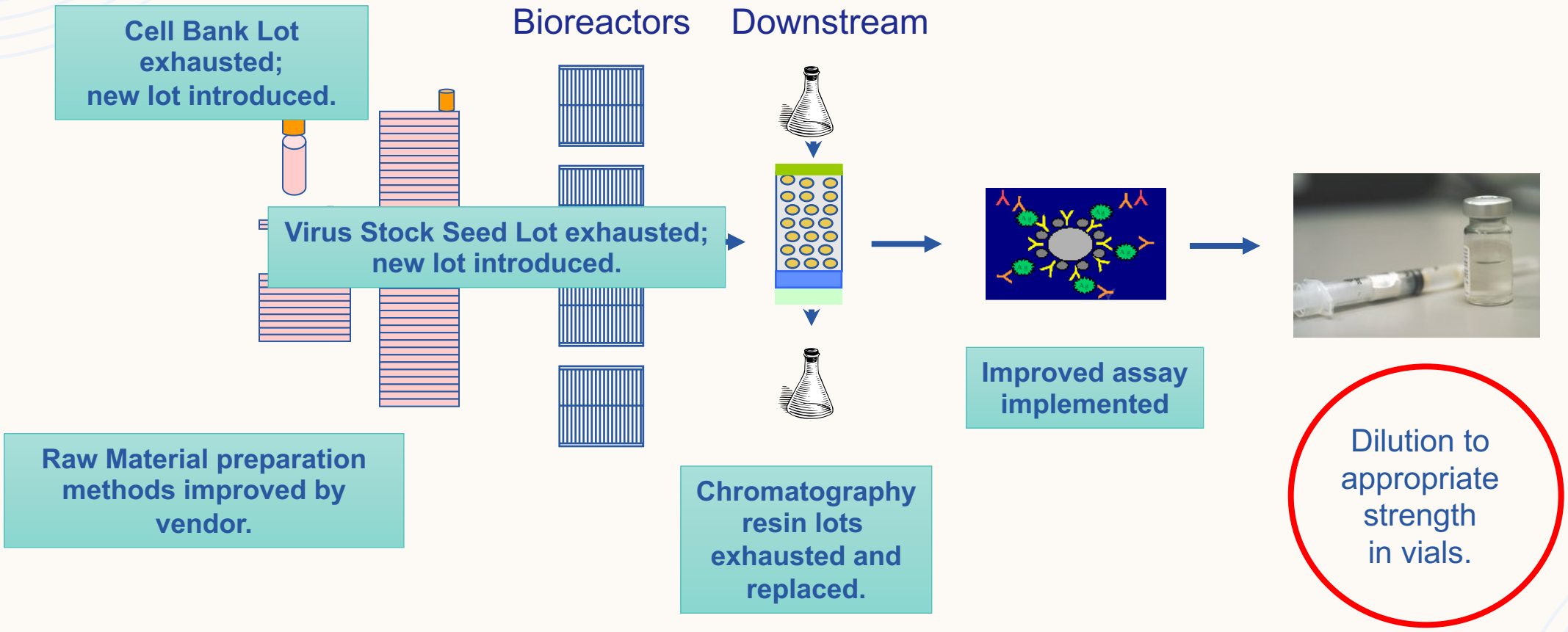
Viral Vaccine Bulk Potency Increased Without an Identified Cause.

Enormous risk when relying on Quality by Inspection: discover out-of-specification material only after it has been produced.



The biologics mantra “the process is the product”

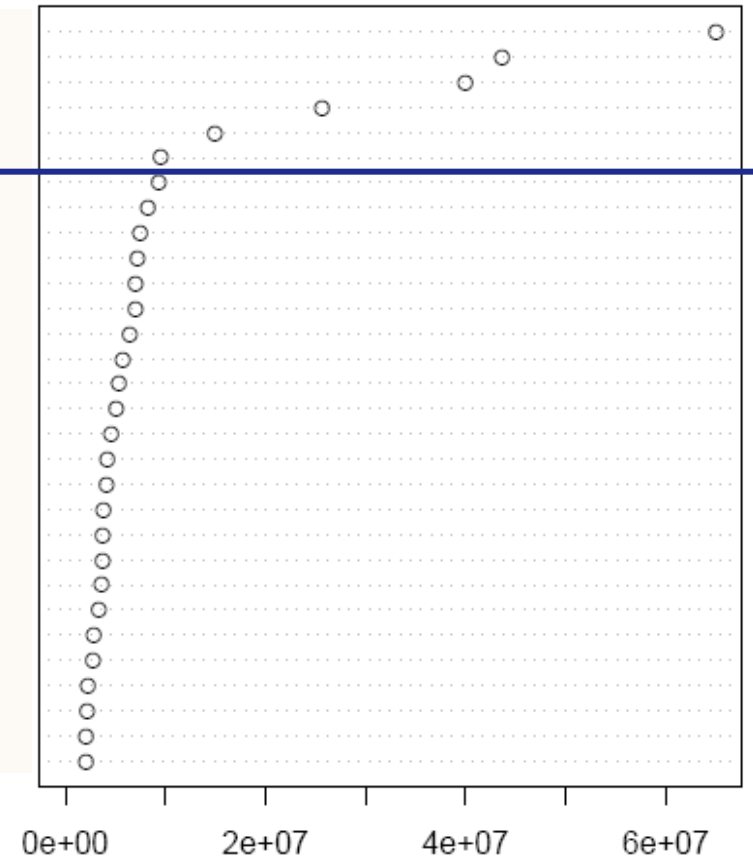
does not allow continuous improvement or insure reliable supply.



A “fixed process” does not guarantee a fixed product.

Variable Importance for Potency by Machine Learning

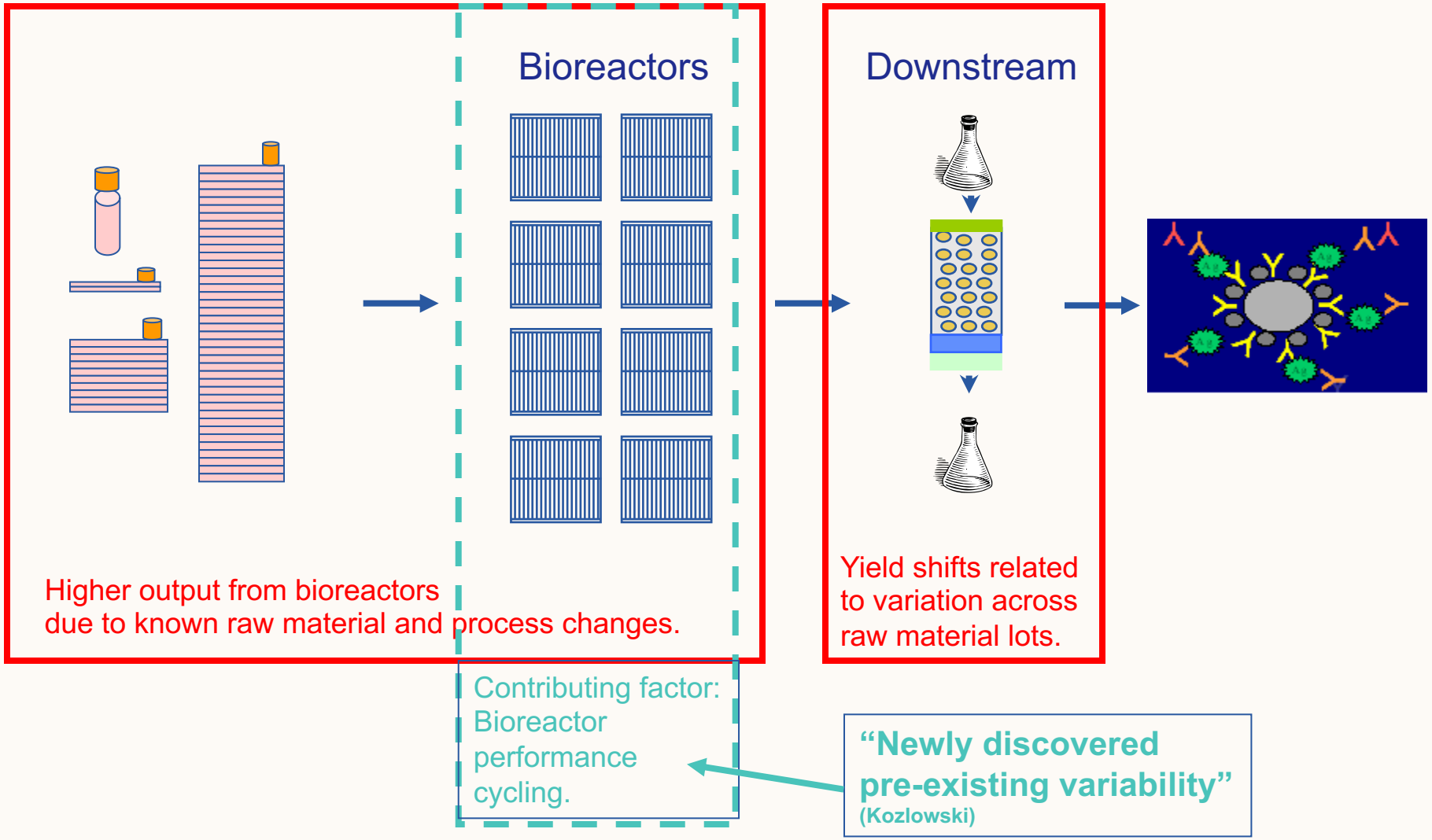
BR	process change 1
BR	raw material change
BR	Day 4 Glucose
DS	raw material change 1
BR	Day 1 DO
BR	input 1
CE	Split II variable 1
CE	Split II variable 2
BR	Day 3 pH
BR	Day 2 Lactate
CE	Split I variable 1
BR	timing variable
BR	GUR
BR	raw material prep
CE	Split III variable 3
CE	Split I variable 1
CE	Split III variable 4
CE	Split III variable 5
CE	Cell Bank lot change
CE	Split II variable 4
CE	Split III variable 1
BR	Day 5 DO
CE	Split II variable 5
BR	Day 8 DO
BR	variable 6
CE	Split III input variable
BR	Variable 7
BR	Day 2 temperature
BR	input variables



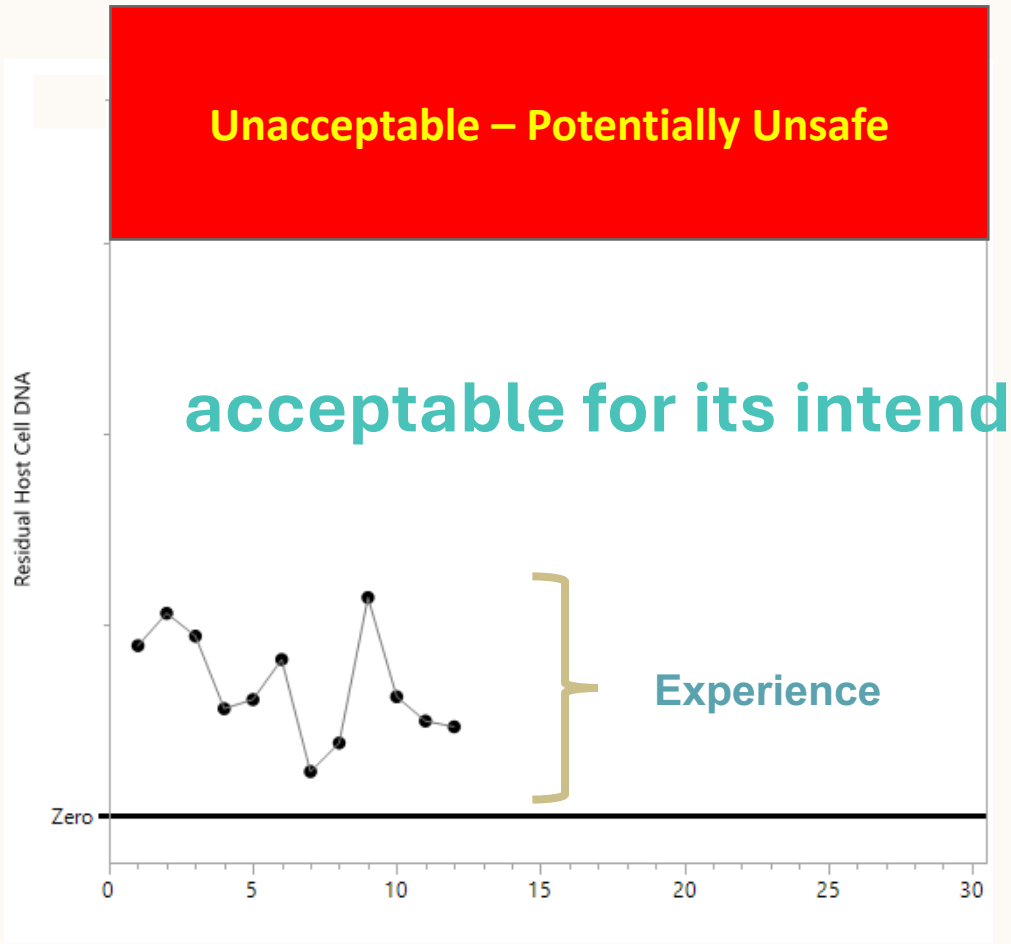
Important variables were suspected in advance of machine learning analysis.

Only 1 variable is Downstream – all others are Bioreactor or Cell Expansion.

Statistical methods provided QbD style control strategy from manufacturing experience.

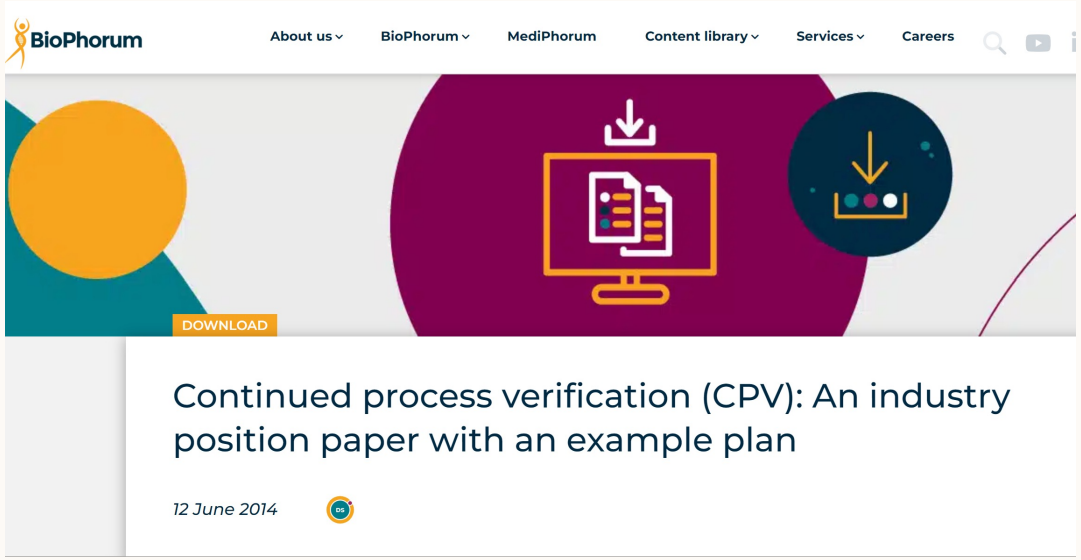


Acceptability should be defined based on knowledge of patient requirements, not manufacturing experience.



Merck sought Keytruda approval quickly by “Moving Heaven & Earth”.

- Ongoing process monitoring with statistical controls allows specifications to occupy a more meaningful role.
- www.biophorum.com



High-impact product approvals demonstrate the value of moving from the traditional to Quality by Design paradigm.

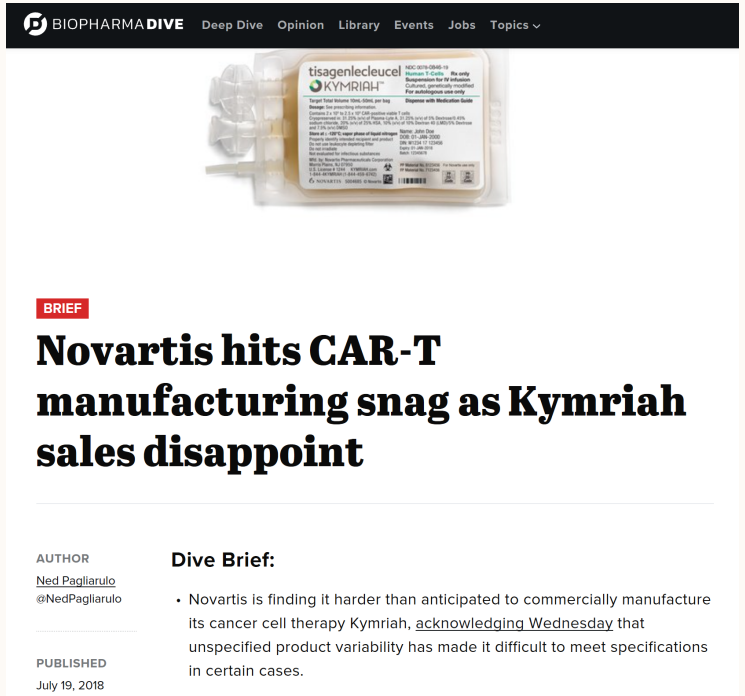
Why Not Make Limits as Tight as We Can?

From Biopharm Dive, Dec 6, 2018:

"…the company is still delivering the treatment to some patients for free, unable to charge for a product that – while OK for use in patients – doesn't meet stricter specifications established for commercial use."

"We are engaged with the FDA, EMA, other regulatory authorities to change the specification to be more in line with the reality of the data we have today,…"

Eligible patients are very sick – CAR-T cell therapy can be a last option.



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BRIEF

Novartis hits CAR-T manufacturing snag as Kymriah sales disappoint

AUTHOR
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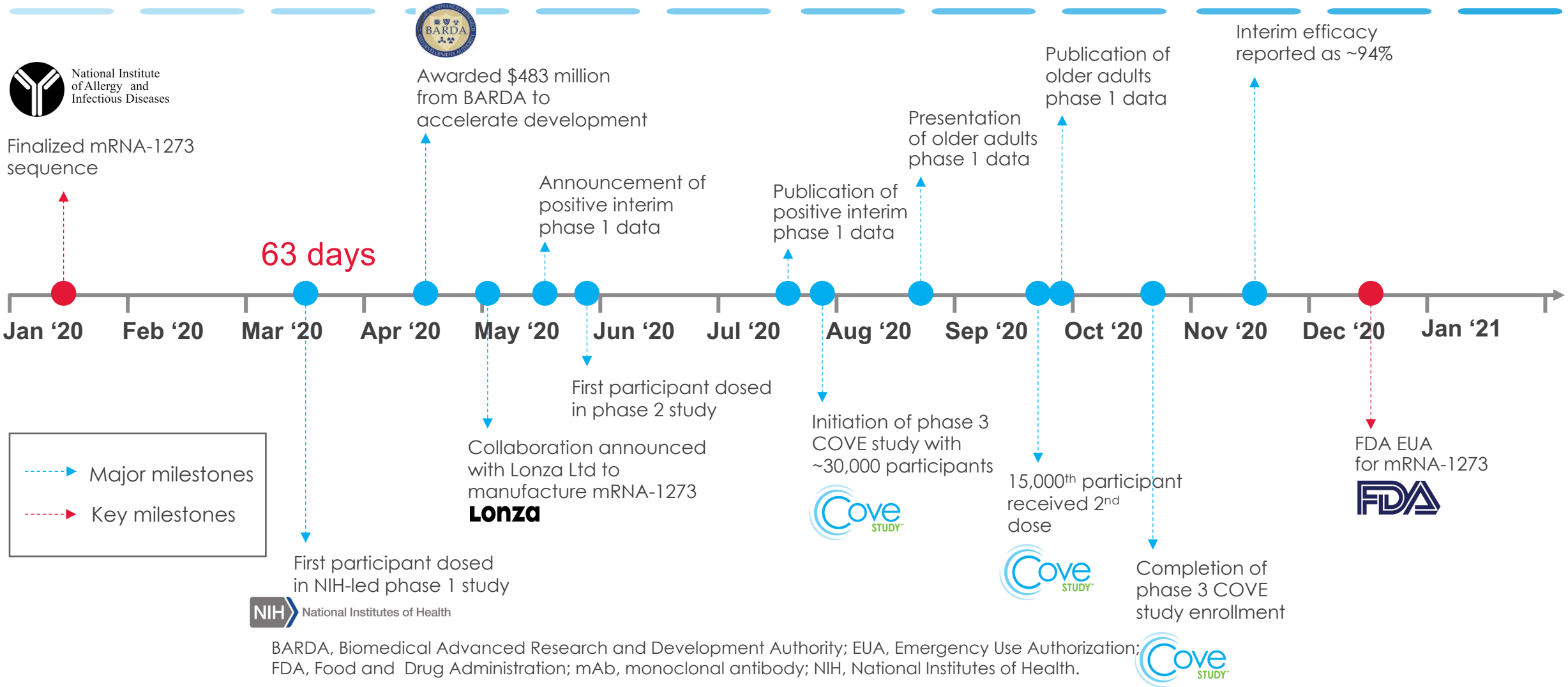
PUBLISHED
July 19, 2018

Dive Brief:

- Novartis is finding it harder than anticipated to commercially manufacture its cancer cell therapy Kymriah, acknowledging Wednesday that unspecified product variability has made it difficult to meet specifications in certain cases.

Clinical Pace Accelerated Spikevax Development to 11 months.



BARDA, Biomedical Advanced Research and Development Authority; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; mAb, monoclonal antibody; NIH, National Institutes of Health.

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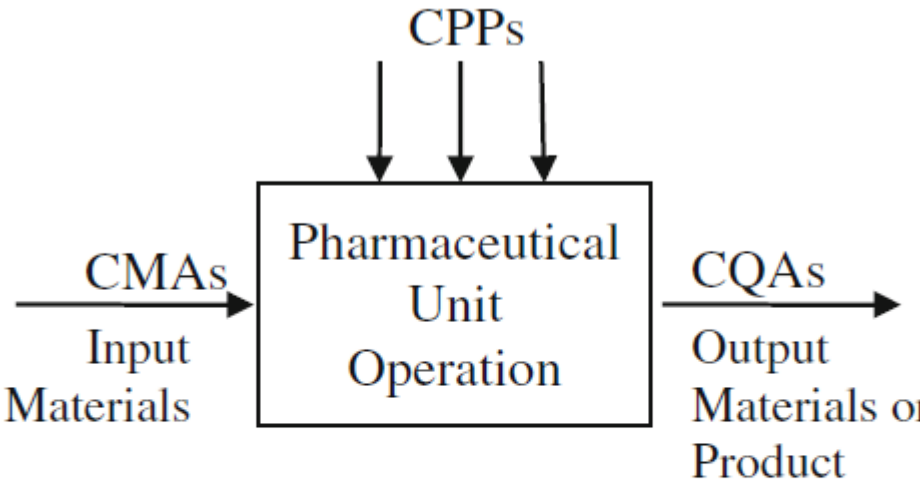
Statistical Design of Experiments Is Used Extensively.

Identify potential CPPs (factors)

Identify primary CQAs (responses)



$$CQAs = f(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

Fig. 1. Link input critical material attributes (*CMAs*) and critical process parameters (*CPPs*) to output critical quality attributes (*CQAs*) for a unit operation

* Yu et al. (2014)

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mRNA-1273 Timeline is Both Global and Personal.

National Institute of Allergy and Infectious Diseases

Finalized mRNA-1273 sequence

Jan '20

Feb '20

Mar '20

First participant dosed in NIH-led phase 1 study

National Institutes of Health

Apr '20

Awarded $483 millio from BARDA to accelerate develop

May '20

Collaboration with Lonza Ltd manufacture m

Lonza

Annou positive phase

First in p

75 State Street January 4 at 12:58 PM ·

blication of er adults ase 1 data

participant ed 2nd

Oct '20

Completion of phase 3 COVE study enrollment

Cove STUDY

Nov '20

Interim efficacy reported as ~94%

Dec '20

FDA EUA for mRNA-1273

FDA

Jan '21

Jan. 4, 2021
Mom's 1st dose

Major milestones

Key milestones

BARDA, Biomedical Advanced Research and Development Authority; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; mAb, monoclonal antibody; NIH, National Institutes of Health.

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Conclusion

- **People** with unmet medical needs depend on us to accelerate development.
- The **Quality by Design** framework supports acceleration.
- High-impact **product approvals demonstrate the value** of moving from the traditional to Quality by Design paradigm.

What's next for QbD in biotech? Hot topics include:

- Patient centric specifications
- Predictive stability
- Potency assays