Pioneering Disruptive Changes to the Manufacture of Biologics

CASSS WCBP 2022

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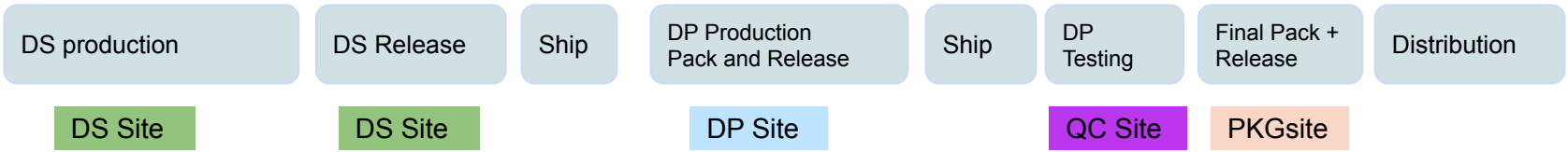
Jan 26, 2022

Typical End to End Processing Times

- The actual “making” of product is not the majority of time spent in processing
- Lead times in the order of several months is typical, can be lengthier if there are more sites involved or deviations to resolve
- Overall goal to decrease these lead times



Definitions

Real Time Release Testing, regulatory definition:

The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls (ICH Q8 (R)).

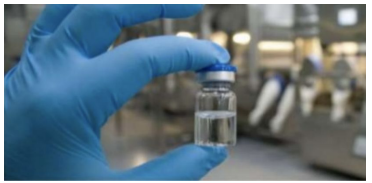
Instant Release*, performance based definition:

Product (DS,DP or FP) can be shipped to patients as soon as it leaves the robust process without waiting periods for quality testing and release.

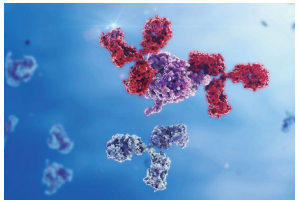
*internal Roche definition only

RTRT Background - Examples In-Use Today

Visual inspection + AQL testing for visible particles (many vials)



Purification process validation demonstrating robust impurity clearance (ProA, DNA, HCP)



PHCCF adventitious agent testing

- Testing at the relevant location

Main elements for a RTRT control strategy

Replacement of conventional QC method(s) with rapid or more efficient analytical method(s)

Movement of release testing points upstream in the process

Replacement of end product release testing with in-process controls, e.g. fill weight checks

Parametric release, i.e. combination of process control and (IPC/QC) analytic results supported by predictive modeling tools (e.g. MVDA)

Drug Product Process

How many of these tests can be moved upstream?

Are certain manufacturing controls better than end product test, i.e. fill weight?

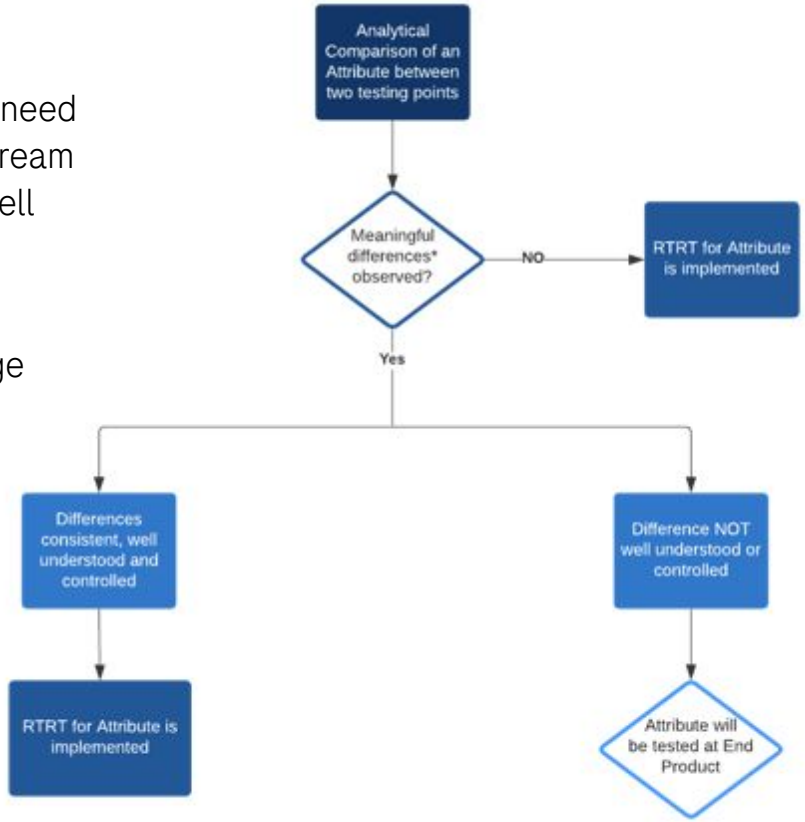
Can we skip some tests for importation?

<u>Conventional</u>
Sterility
Endotoxin
Identity
Potency
Purity Assays
Content
Appearance /COC
Visible Particles
SVP
Extractable Volume

Decision Tree for RTRT instead of End-Product Testing

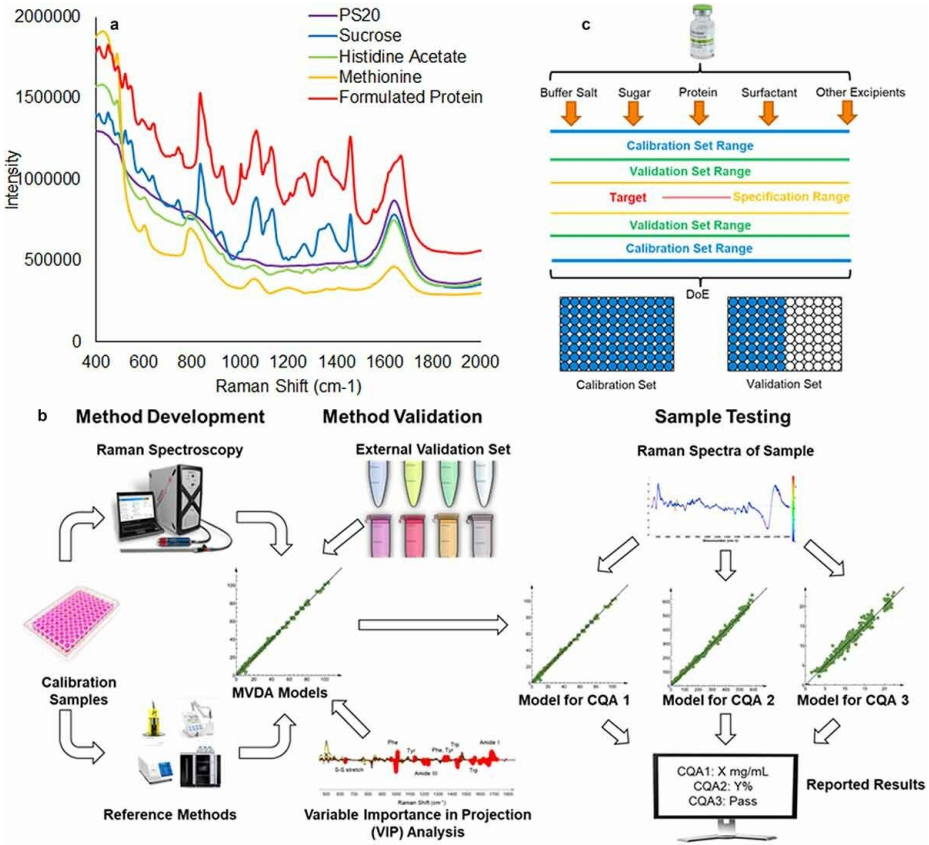
Using **prior knowledge, product-specific data**, we still need to provide assurance that the testing performed at an upstream step are 1) consistent with end-product testing and/or 2) well understood and controlled.

- Understanding unit operations, i.e. what could change could occur
- Process design / validation studies
- Method variability
- Sample matrix



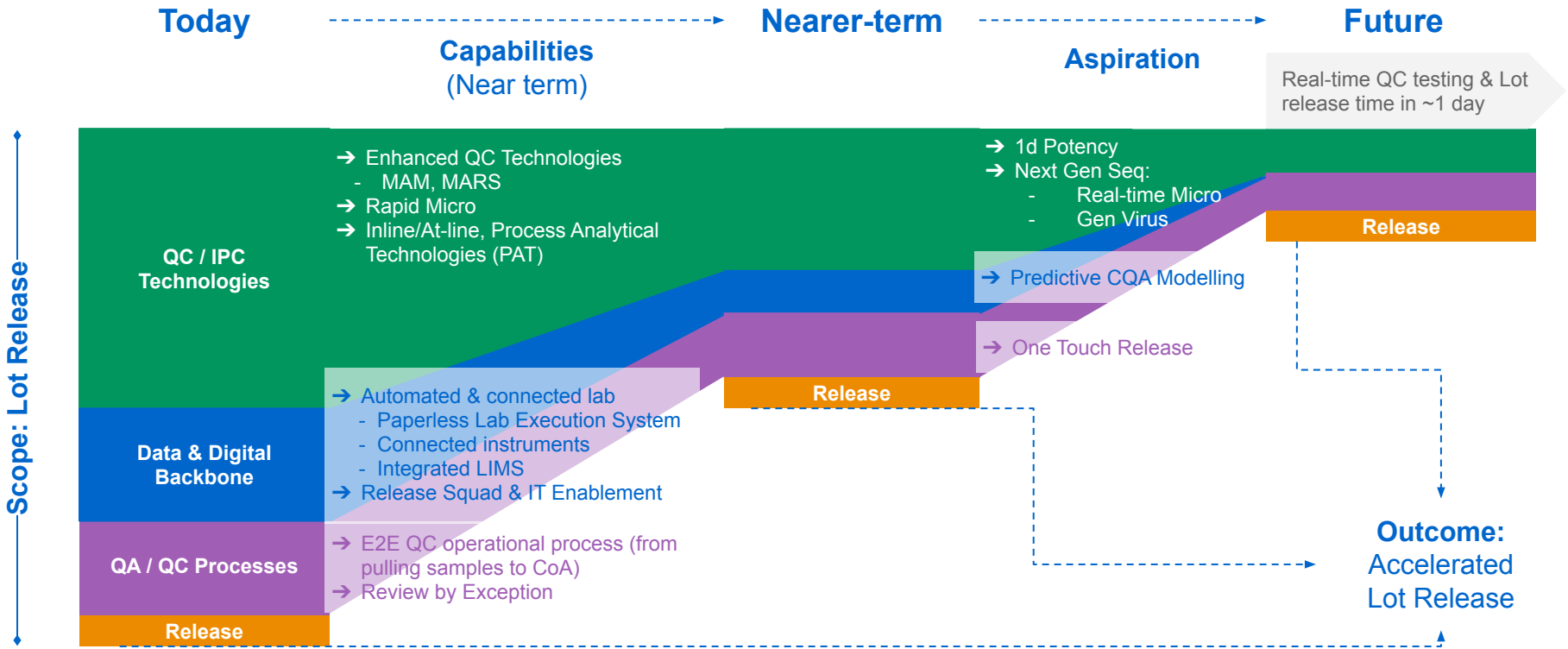
Raman Spectroscopy

- Can be non-destructive test (cuvette or vial), online/at-line/offline
- Being considered a replacement for multiple attributes: identity, pH, osmolality, protein content, surfactant



https://www.tandfonline.com/doi/full/10.1080/19420862.2021.2007564&sa=D&source=editors&ust=1642039682903291&usg=AOvVaw2pJ4KEIL_SU-AU3_o2SnzN

Where we are, where we want to be and what capabilities we need



How can we get from here to there?

Closing Thoughts

- To go fast and do what's best for patients, technologies are enablers and the science is still foundational in what we do
- But we need to rethink how we do things.
  - What information is needed to make decisions
  - Is there a better/faster way to get the information we need to ensure product quality?
  - What information is NOT needed to make decisions

Doing now what patients need next