

Simulating the DS to DP conversion process in vaccine manufacturing

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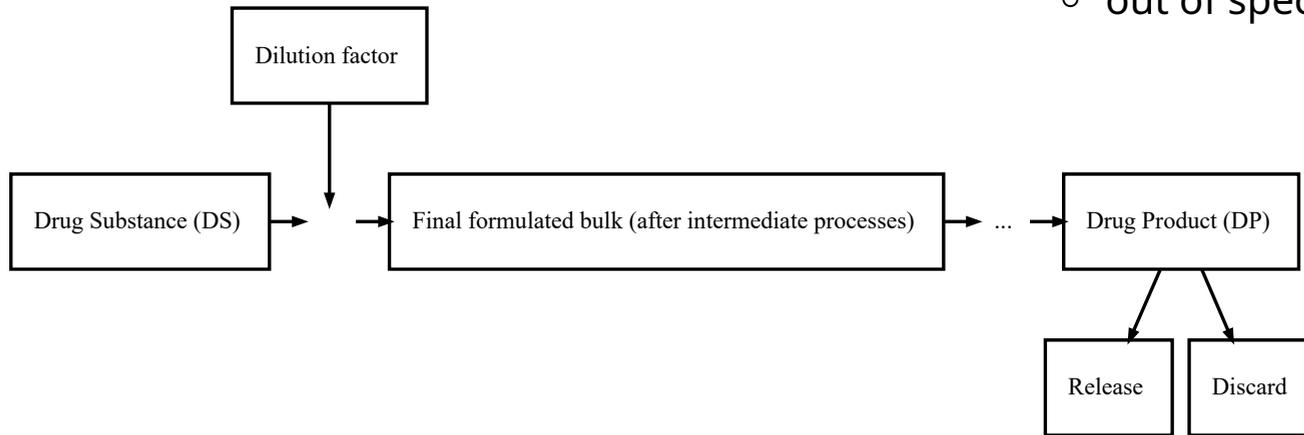
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Dilution

- In vaccine manufacturing, conversion of a concentrated Drug Substance (DS) to a less concentrated Drug Product (DP) involves a dilution step
 - Ensures the final DP meets specifications for different attributes
 - Virus Particles per mL (VP/mL)
 - Infectious Units per mL (IU/mL)
 - VPIU ratio
 - The dilution can be for a single DS or for multiple DSs
- Uncertainty in the titration of DS and DP to account for DP concentration within specifications, otherwise it is discarded
- Determine a safe dilution to ensure released DP is within specifications with high probability
 - Determine an assay format to obtain reliable reportable results

Dilution process flow

- Dilute DS to formulated bulk
 - Dilution factor *known*
- DP stage:
 - in-specifications: release
 - out of specs : discard



Case

- Assess the probability of meeting vaccine DP release specifications for a range of DP formulated bulk target Virus Particles (VP) titres given an assay format
 - Target VP titre for a formulated bulk
 - Dilution factor depends on the measured DS VP value

Modeling VP & IU

- Bayesian bivariate linear mixed model for VP & IU at DS and DP stages
 - Parameter estimates used as inputs in the simulation

Simulation

- Possible approaches
 - Conditional distribution of IU|VP
 - Bivariate normal distribution of IU, VP at DS stage
 - Deming regression
- Main steps for the approach based on the conditional distribution of IU|VP
 - Determine a measured DS VP value for each posterior chain factoring in process and analytical variability
 - Calculate the dilution factor for every measured DS VP value given the target DP VP value
 - Determine a corresponding DP IU value given the DP VP value
 - Simulate measured DP VP and IU by adding assay variability at DP stage
 - Calculate POS for each attribute given an assay format
 - Determine a target DP VP titre with the highest POS