Analytical Platform Technologies

Concept and Case Study

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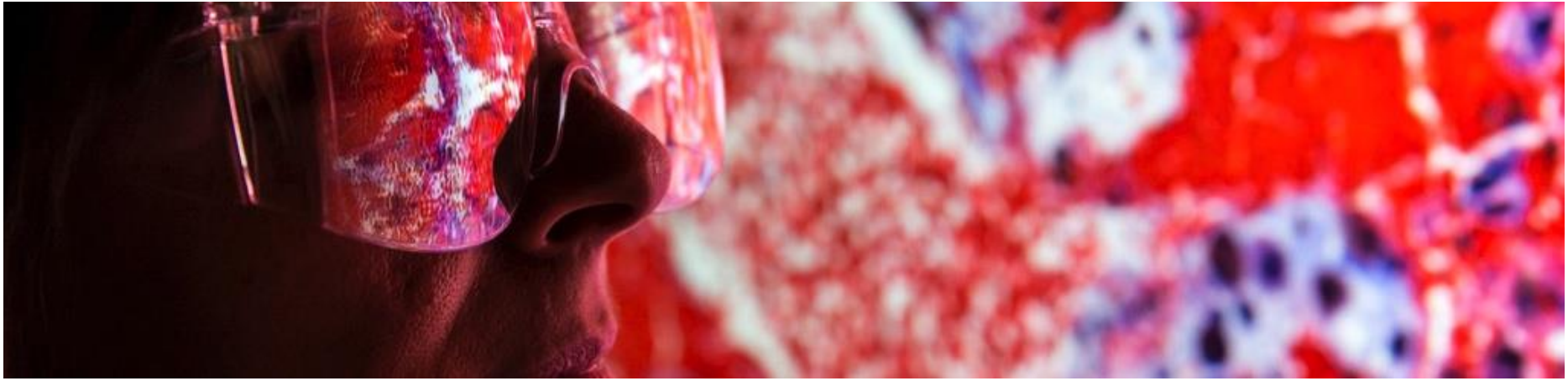

Agenda

Analytical Platform Technology (APT) Concept

APT Case Study

Brief Summary and Points to Consider

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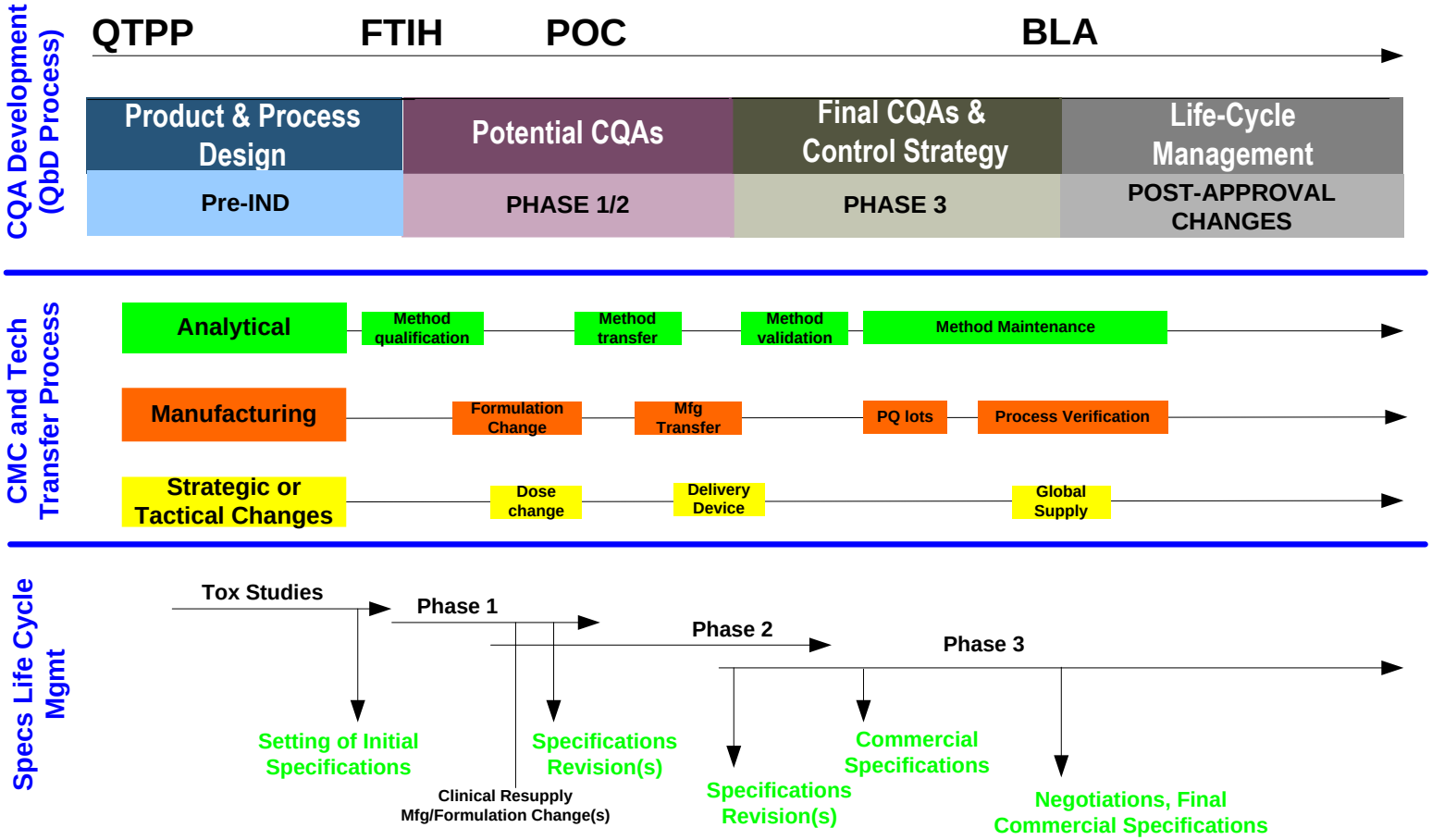
Analytical Platform Technology (APT)

An APT method is an analytical method used for multiple highly similar products or product sample matrices without modification of the procedure.

Suitable for use as APT methods are those methods which by design and intent can generate accurate and reliable results without any significant product-specific interference.

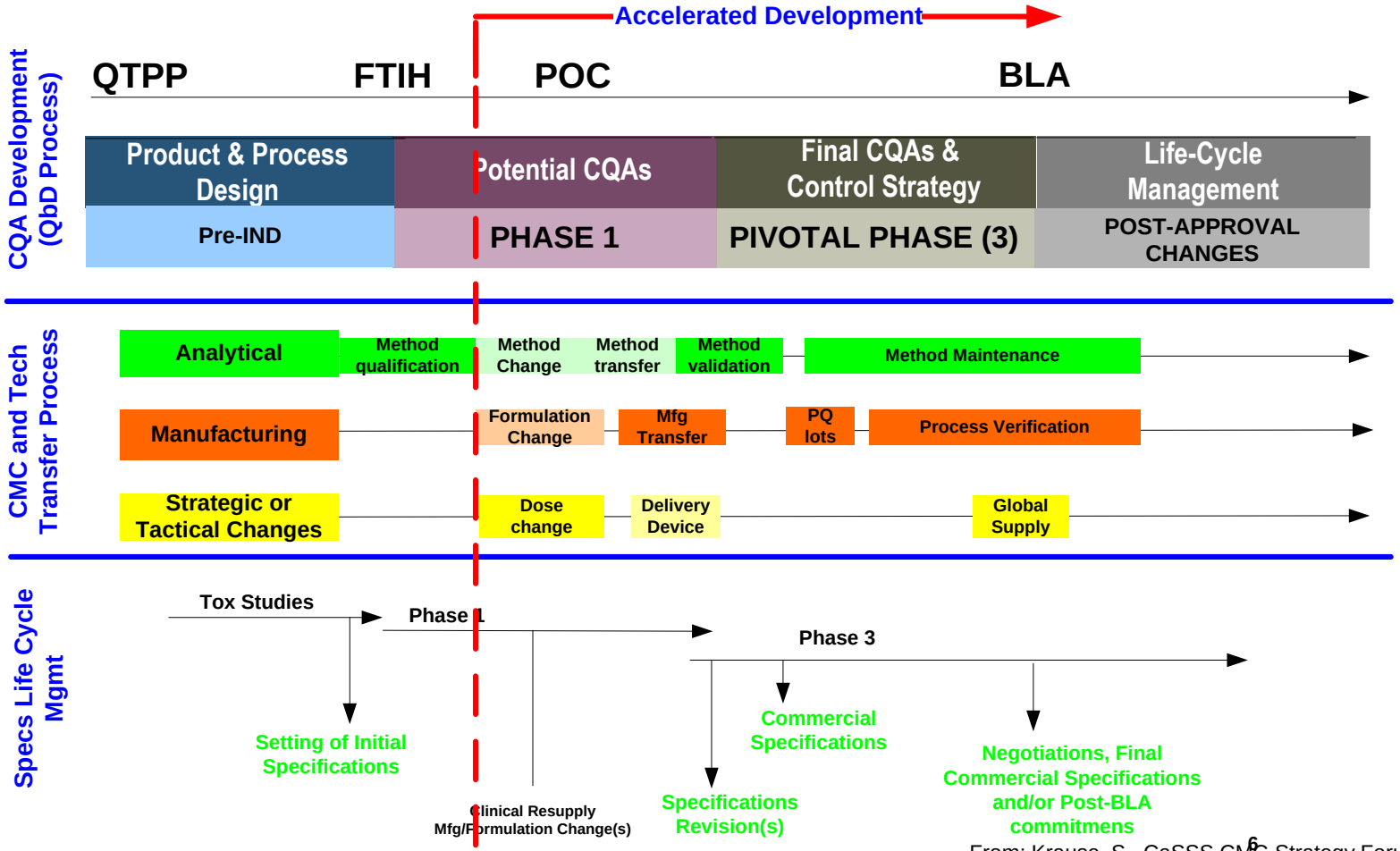
Similar to compendial methods, an APT method may not require full validation for each new product or sample type.

CQA Development, CMC Changes, and Specifications



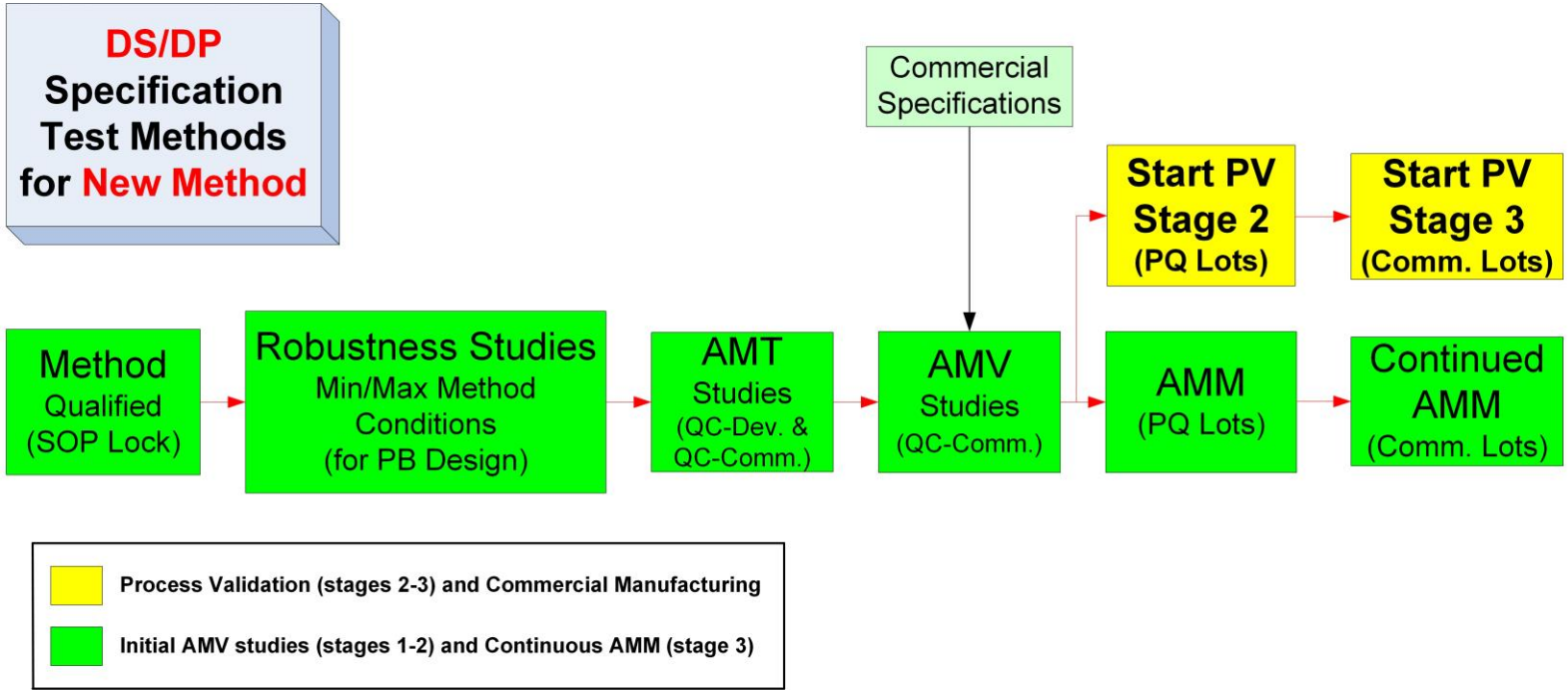
From: Krause, S., WCBP, 30Jan13, Washington, DC.

Accelerated CQA Development, CMC Changes, and Specifications



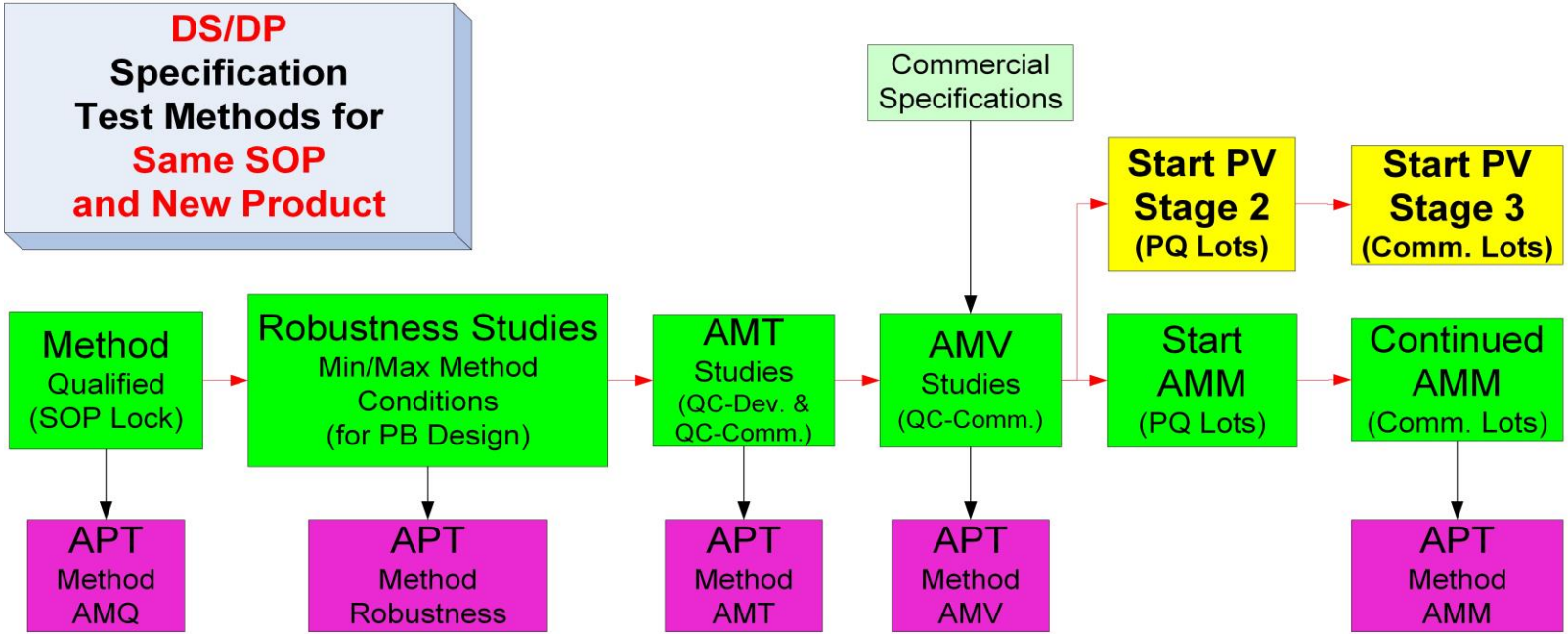
From: Krause, S., CaSSS CMC Strategy Forum, 27Jan14, Washington, DC.

Typical Lifecycle Steps for a New Routine Test Method



From: Krause S, *Using Analytical Platform Technologies to Support Accelerated Product Development Â– Concept Review and Case Study*, PDA J Pharm Sci Technol (submitted for publication in 2021).

APT Opportunities following AMV Study Completion



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AMV Categories and Prospective Validation/Verification Studies

AMV Category Description			Risk/Uncertainty Level (1=Low, 5=High)	Prospective Studies
AMV Category No.	Analytical Method	Product / Process Sample		
A	New	New	4-5	Full Validation
B	New	Old (Validated)	3-4(1)	Full Validation Plus AMC Studies
C	APT No major change(s) (2)	New	1-2	Formal Verification (A plus C)
D	Compendial	New	1-2	Formal Verification [USP <1226>]

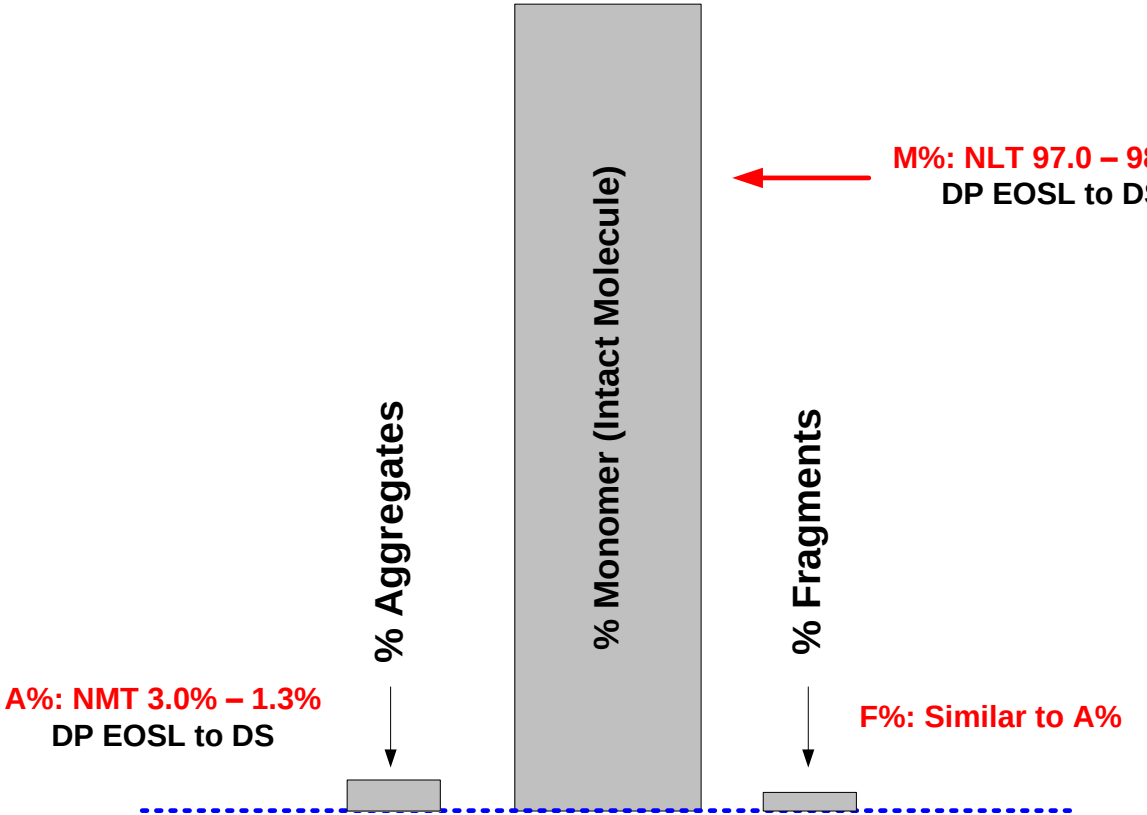
(1) Category B applies when a validated analytical method is replaced by a new method. If a new analytical method (forced method replacement) is needed due to supply reasons, the risk level can be generally considered higher because no other option may exist. Unforced test method replacements can be considered to be a lower risk level as more time may be available to optimize the method performance.

(2) Some changes to validated APT methods such as a different sample preparation step or the use of a different detection system may not require a full validation as only a part of the validated test system changes, whereas most of the system remains unchanged.

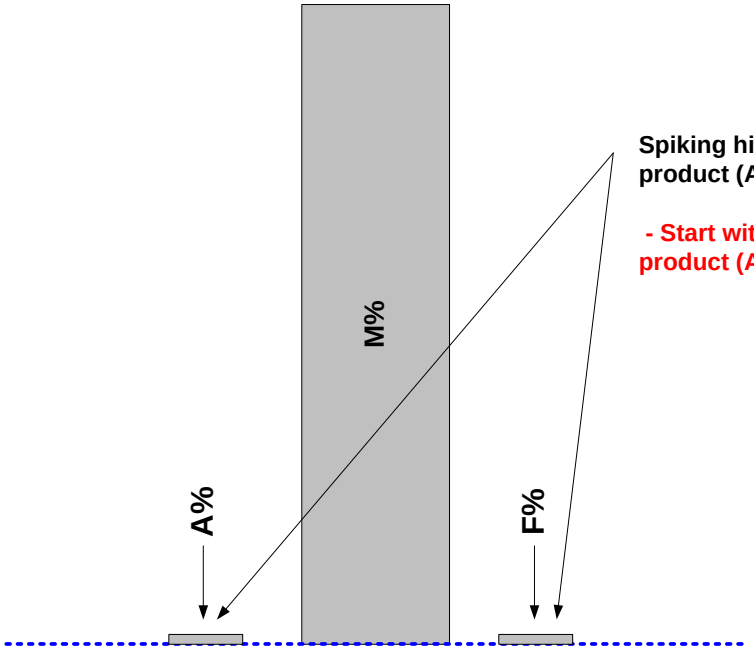
Typical mAb Late-Stage DS Specification Tests and Specifications (Intended Use)

Test Method	Possible Method Status	Example DS Specifications
Appearance	Compendia	Practically free from visible particles
Total protein	APT	nominal value ± 10.0%
cIEF	(Potential) APT	Monomer: NLT 65% Total acidic peaks: NMT 30% Total basic peaks NMT 10%
MOA-simulated bioassay[1]	Validated	90-120% (symmetrical) of Reference Standard binding
Reducing gel electrophoresis	APT	Area percent purity of heavy + light chains: NLT 98.5% Total area percent of impurities: NMT 1.5%
Non-reducing gel electrophoresis	APT	Major product peak: NLT 98.5% Total area percent of impurities: NMT 1.5%
HPSEC	APT	Major product peak: NLT 98.3% Aggregates: NMT 1.7% Fragments: NMT 1.7%
Host cell DNA	APT	LT 20 pg DNA/mg protein
CHO host cell protein	APT	NMT 20 ng/mg protein
Protein A	APT	NMT 10 ng/mg protein
Bioburden	Compendia	NMT 10 CFU per 100 mL
Endotoxin (LAL)	Compendia	NMT 0.20 EU/mg protein

mAb AMV Study Example(s): Purity by HPSEC – Initial AMV Study

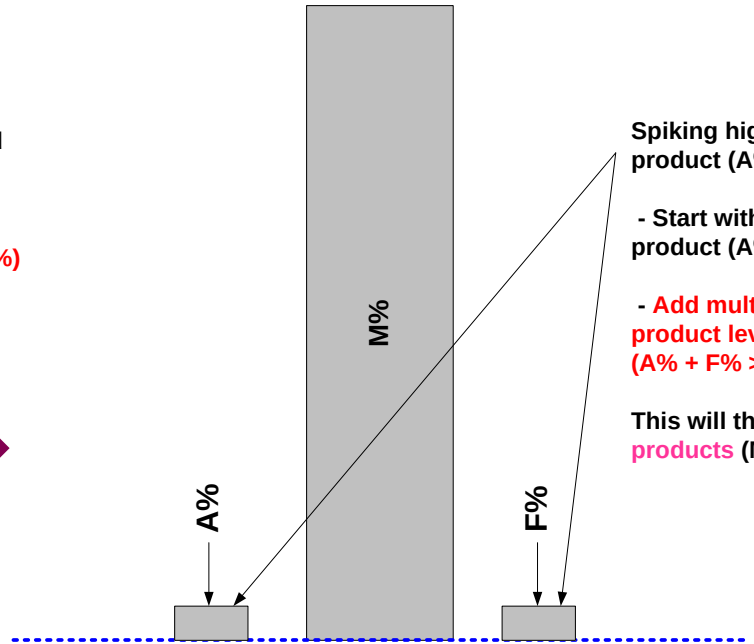


AMV Study: Purity by HPSEC – Initial AMV Study



Spiking highly degraded product (A% and F%)

- Start with high purity product (A% + F% < 1.0%)



Spiking highly degraded product (A% and F%)

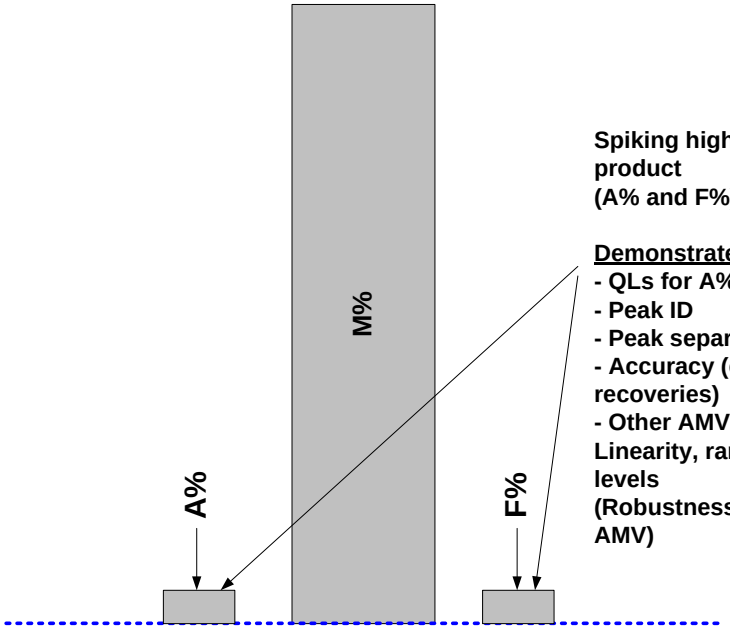
- Start with high purity product (A% + F% < 1.0%)

- Add multiple degraded product levels, so that: (A% + F% > 5.0%)

This will then cover future products (M% NLT 95.0%)

mAB AMV Study Example(s): Purity by HPSEC

Initial AMV Study

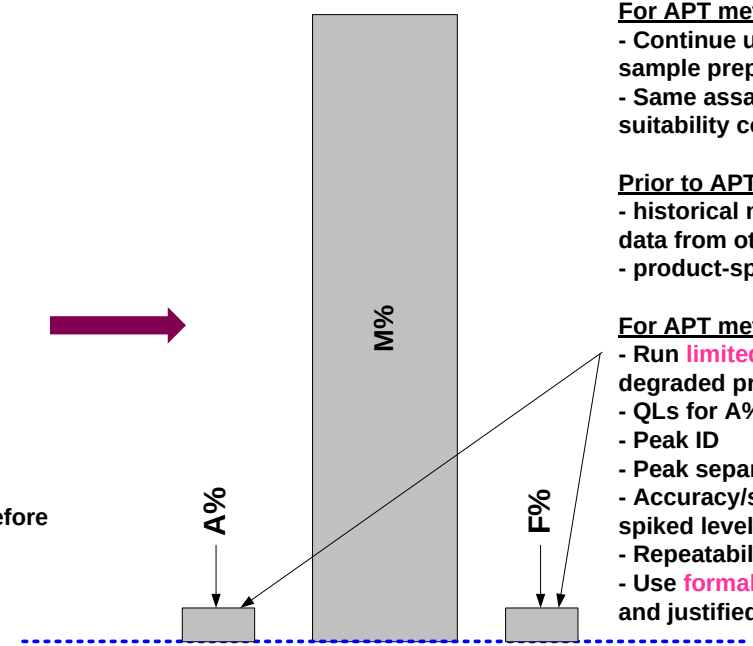


Spiking highly degraded product
(A% and F%)

<u>Demonstrate</u>:
- **QLs for A% and F%**
- **Peak ID**
- **Peak separation**
- **Accuracy (expected peak recoveries)**
- **Other AMV parameters: Linearity, range, precision levels**

(Robustness completed before AMV)

APT Verification Study



<u>For APT method</u>:
- **Continue use of validated sample preparation**
- **Same assay control and system suitability conditions**

<u>Prior to APT method verification</u>:
- **historical method performance data from other product(s)**
- **product-specific data**

<u>For APT method verification</u>:
- **Run limited spiking study with degraded product to confirm:**
- **QLs for A% and F%**
- **Peak ID**
- **Peak separation**
- **Accuracy/specificity for all spiked levels**
- **Repeatability precision**
- **Use formal verification protocol and justified acceptance criteria**

Prospective APT Verification Study Design for HPSEC Method

ICH Q2(R1) Validation Characteristic	Analyst Number	Day Number	Instrument Number	Validation Design (Spiked Analyte Concentration)
Accuracy	**1**	**1**	**1**	**Spike A%/F% (to final %): 0.5, 1.0, 2.0, 4.0% (run each 3x)**
Repeatability	N/A	N/A	N/A	From Accuracy
Specificity	1	1	1	**Formulation matrix interference (3x)** (and inferred from accuracy)
Linearity	N/A	N/A	N/A	From Accuracy
Assay Range	N/A	N/A	N/A	From Accuracy
QL	N/A	N/A	N/A	From Accuracy

Combined Retrospective and Prospective APT Validation Results for HPSEC Method

ICH Q2(R1) Validation Characteristic	Retrospective Data/Results	Prospective Data/Results	Option(s) and Consideration(s)
Accuracy	No	Yes	Number of spiked levels; Number or replicates
Repeatability	No (see option)	Yes	Could consider using initial AMV study results if insufficient replicates (see above)
Intermediate Precision	Yes	No	Use long-term AMM assay control data instead or in addition to initial AMV study results
Specificity	No	Yes	Only infer lack of matrix interference from Accuracy (see Accuracy)
Linearity	No	Yes	Number of spiked levels; Number or replicates (see Accuracy)
Assay Range	No	Yes	Number of spiked levels; Number or replicates (see Accuracy)
QL	No	Yes	Number of spiked levels; Number or replicates (see Accuracy)
Robustness	Yes	No	N/A
System Control(s)	Yes	No	Use AMM data or combination of data sets (Initial AMV plus AMM)

Summary

Using an APT concept can significantly support accelerated product development by reducing prospective laboratory testing.

In the HPSEC case study, the initial AMV (stage 2) and AMM (stage 3) study results become the foundation for the reduced prospective APT verification studies.

A strong foundation is required for the successful use and approval by the agencies. This is accomplished by demonstrating a continuously controlled and validated state.

When submitting APT verification study results in marketing applications, the sponsor should consider submitting rationale for APT suitability and all relevant initial AMV study conditions and results and evidence for continuously controlled AMM state for this APT method.

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