How and Where to Control and What to Put in the File

Setting specification: Session 4

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Control of raw and starting materials
Product
Control of process parameters
Control of intermediates
QUALITY
Control of drug substance and drug product
Process validation & evaluation
Good manufacturing Practice
Process

How to control

- Control Strategy (ICH Q10) :
  - A planned set of controls, derived from current product and process understanding, that assures process performance and product quality.
  - The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

How to control

- Quality Attributes
  - Directly controlled at relevant step(s)
  - Indirectly controlled at relevant step(s) – e.g. surogate QA…
  - Parametric control(s) at relevant step(s) – e.g. causality and/or correlation between PP(s) and QA(s), design space…
  - Process robustness – e.g. demonstration of high clearance capability…

- Process parameters
  - Directly controlled
  - Indirectly controlled – e.g. correlated to other parameter(s)…
  - Procedural – e.g. sequence of operation…

- “Limits”:
  - Acceptance criteria
  - Internal action limits

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How to control

- Frequency of monitoring and control.
  - Routine
    - Performed for each run
  - Periodic
    - Performed at defined frequency and/or conditions (e.g.: skip testing, revalidation, continuous process verification…)
  - Occasional
    - Performed in specific situations (e.g. evaluation/validation, characterisation, comparability, investigation…)

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How to control

- Alternative to routine end-product testing
  - Full testing according to the specifications may be required during a running in period
  - Real Time Release
    - 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
    - RTR testing applicable to Drug Product, Drug Substance, and Intermediates

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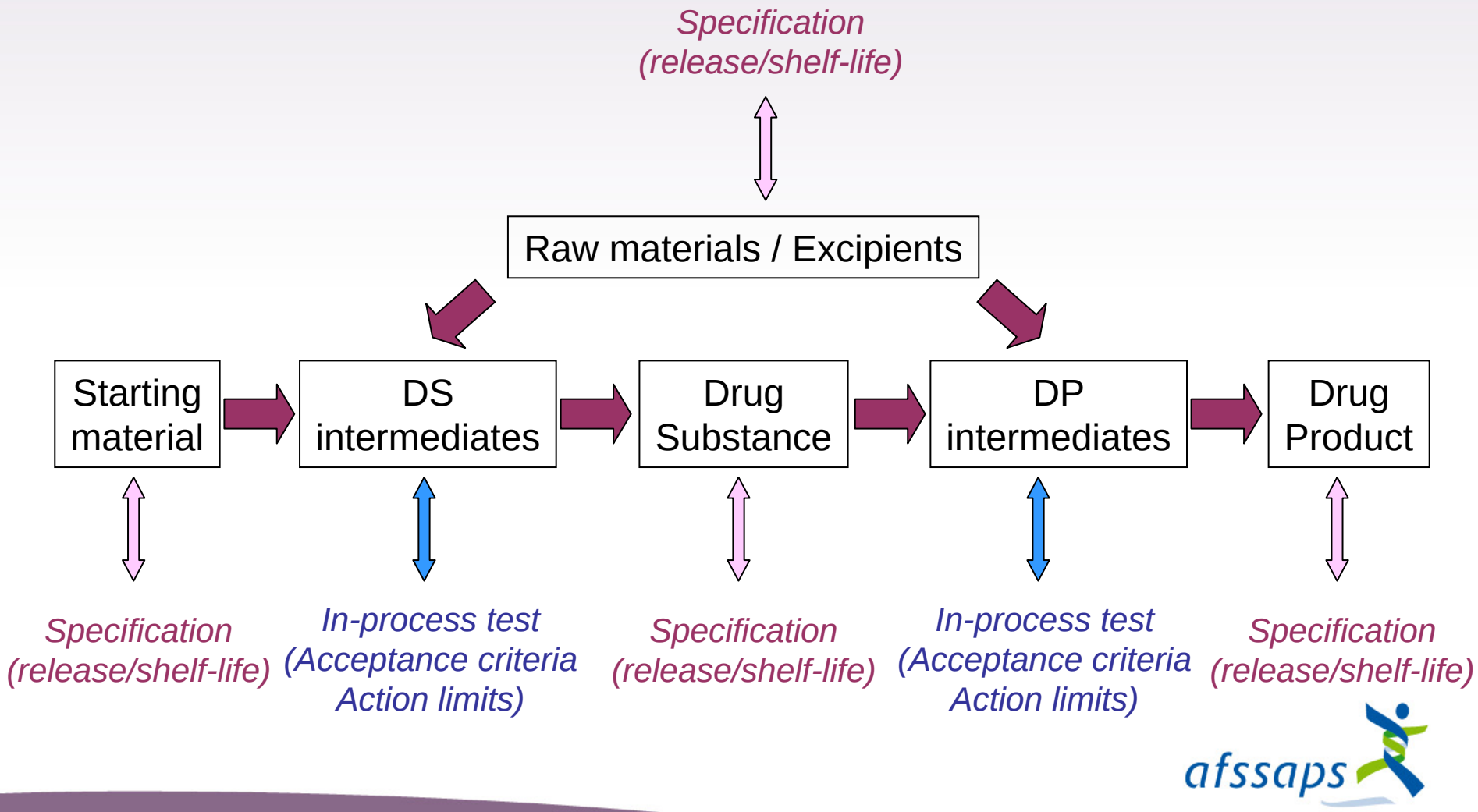
Where to control

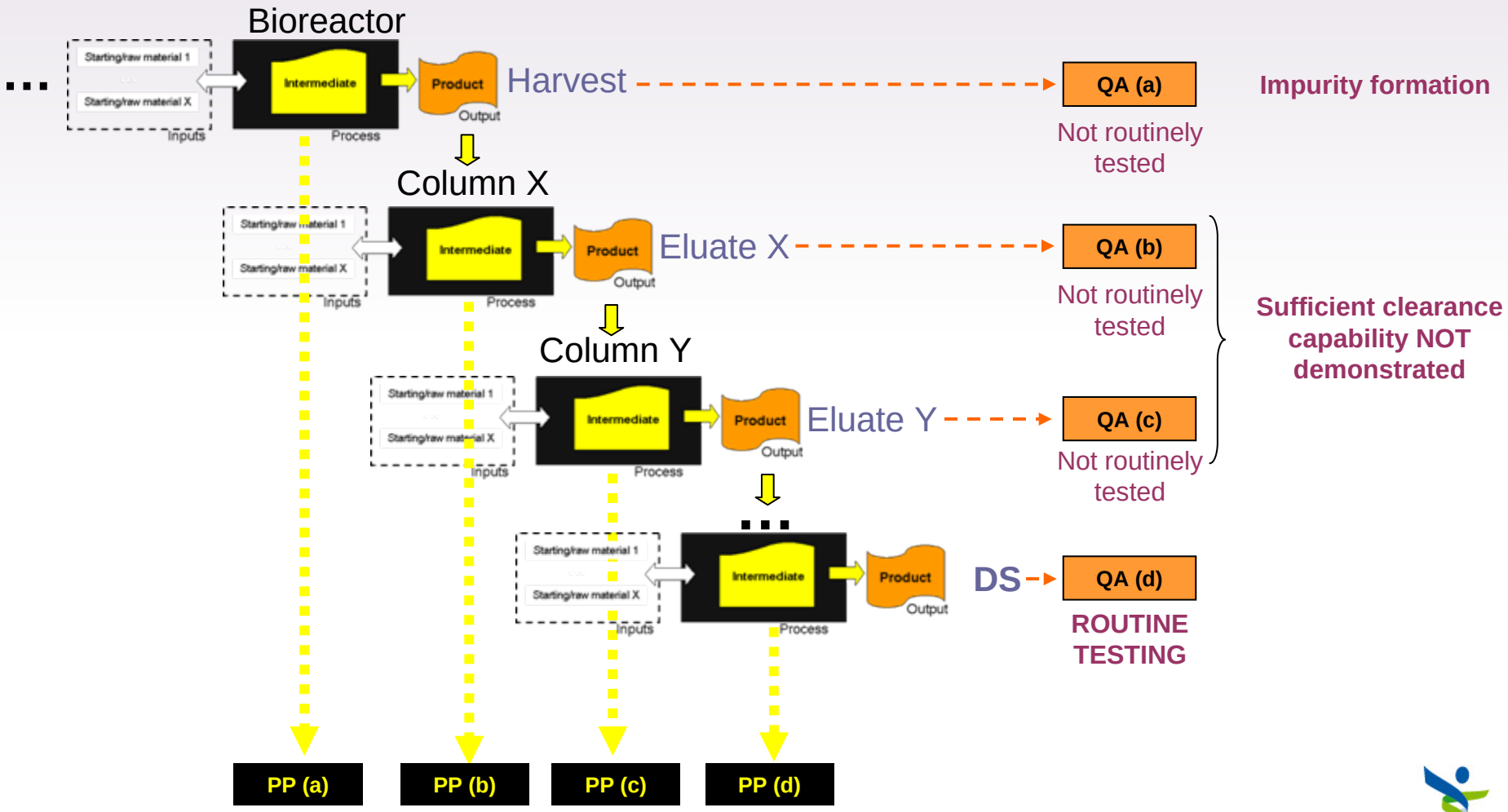
- Routine testing approach and/or a validation approach:
  - Routine testing approach: monitoring of the quality attribute at appropriate step(s) of the process, in order to ensure acceptable levels in the final product.
  - Validation approach: based on evidence of successful validation of the manufacturing process (e.g. establishing consistent and satisfactory impurity clearance); in such situation, process monitoring may be carried out without direct measurements of the quality attribute.
  - Combination of routine testing and validation approaches (e.g. routine testing at an earlier step of the purification process and demonstrated reduction by validation in order to ensure a limit at the final product level, if tested).

Where to control



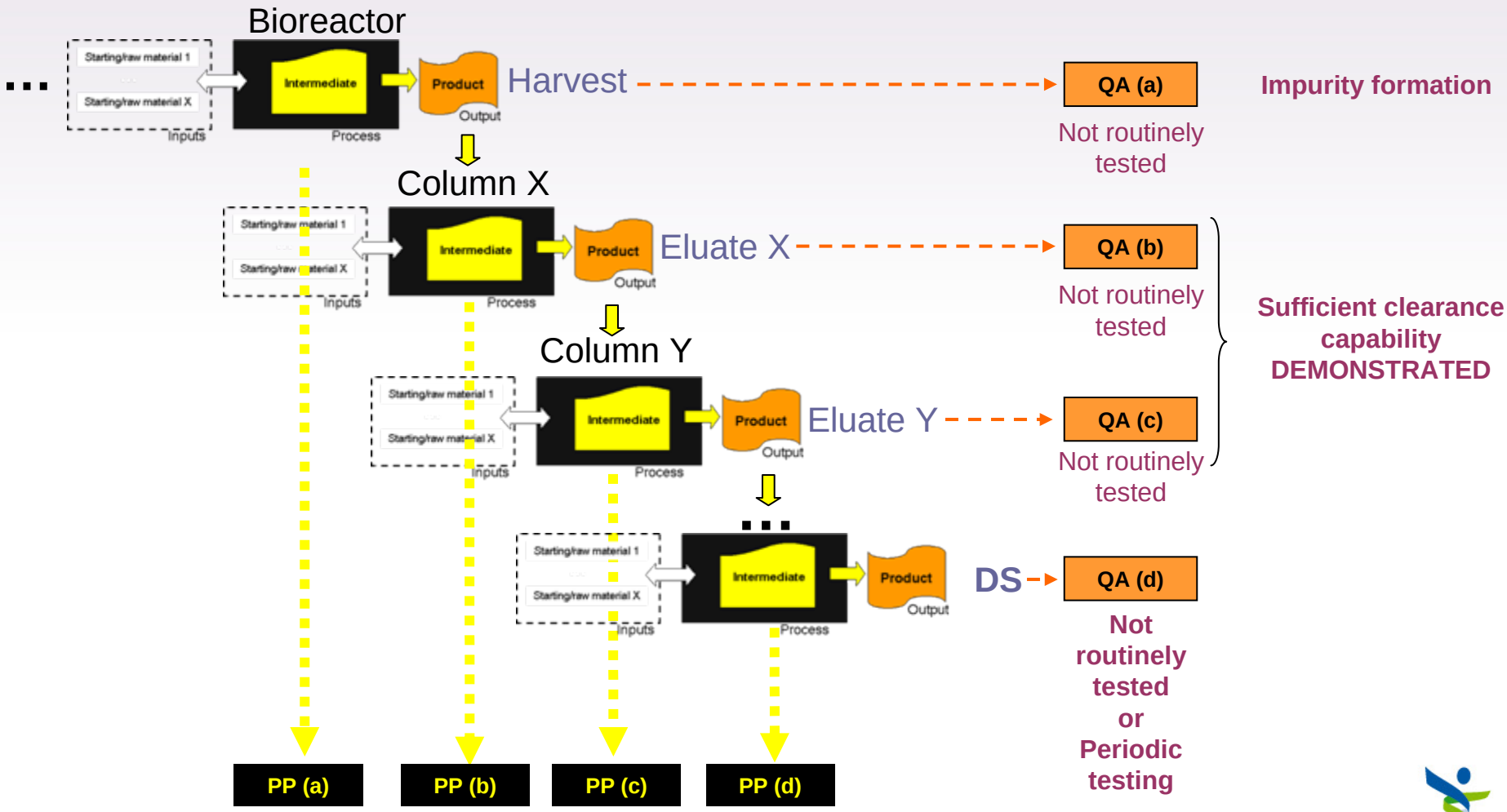
Where to control

Case study 1: “Routine testing approach”



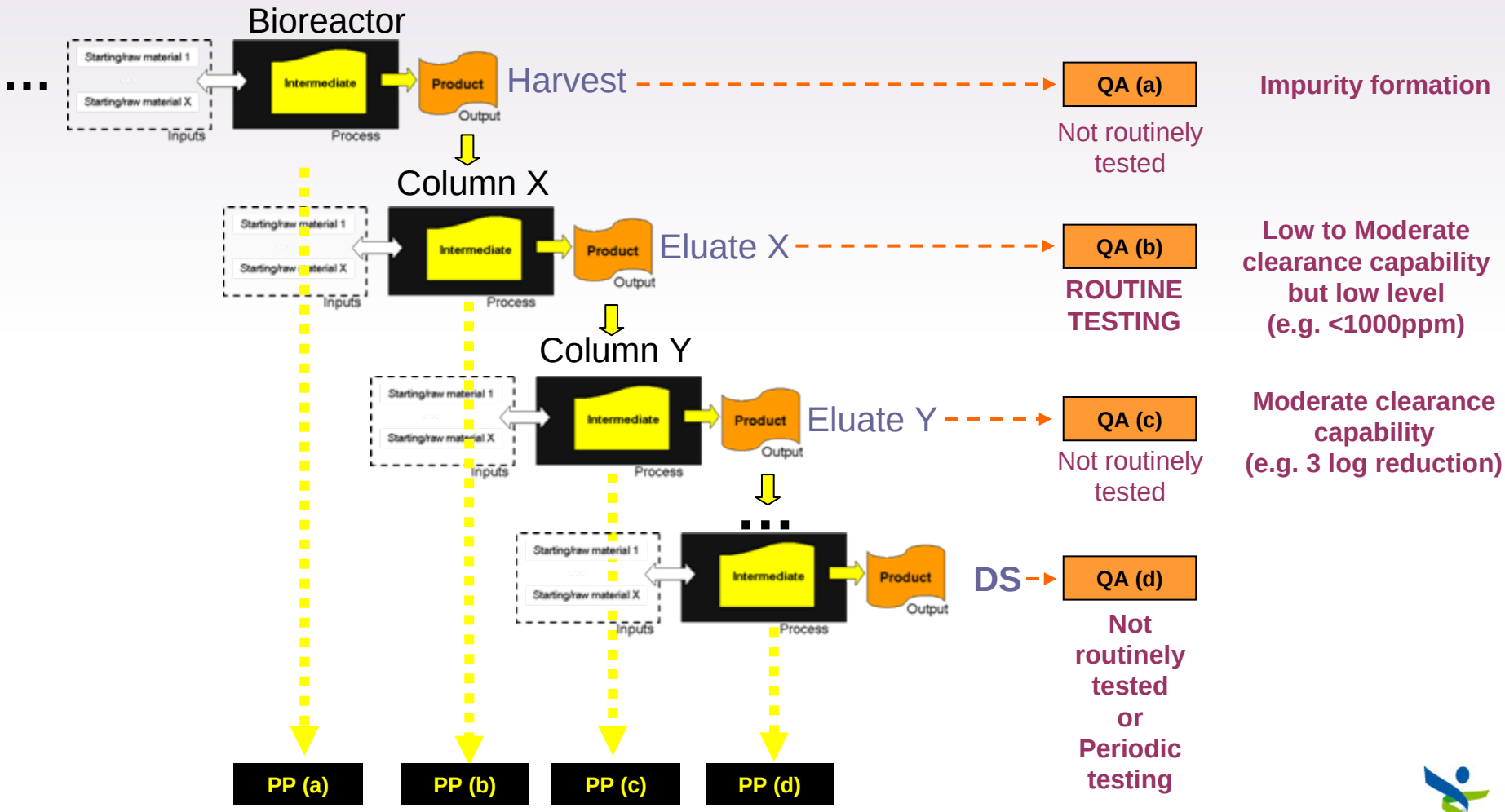
Where to control

Case study 2: “Validation approach”



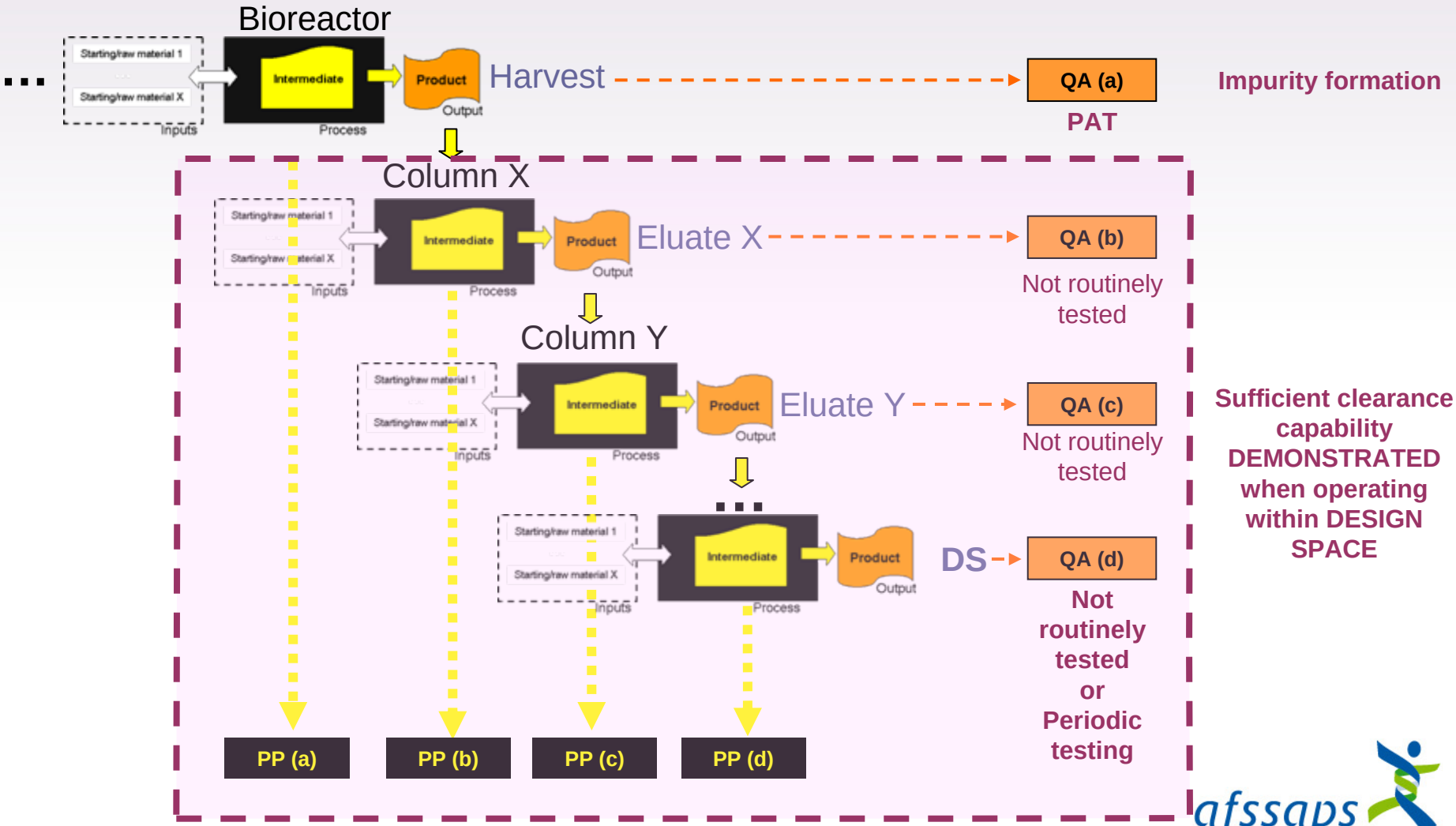
Where to control

Case study 3: “Routine testing & Validation approach”



Where to control

Case study 4: “Enhanced approach”



What to Put in the File

- Marketing Authorisation Application
  - Justification of control strategy:
    - Justification of drug specification (S.4.5 and P.5.6)
    - Specifications release and shelf life (S.4.1 and P.5.1); should comply with them if tested
  - Process description (scale, column characteristics…) and control (CPP, non-CPP, acceptance criteria, action limits…):
    - Description of manufacturing process and process controls (S.2.2 and P.3.3),
    - controls of critical steps and intermediates (S.2.4 and P.3.4),
  - Description of control of materials
    - Control of materials (3.2.S.2.3),
    - Control of excipients (P.4),
  - Process evaluation/validation
    - Results of in-process tests (S.2.5 and P.3.5) and batch analyses (S.4.4 and P.5.4) on an appropriate number of consecutive batches produced with commercial process and scale
    - Evaluation of relevant process steps and/or intermediates (hold time, clearance…)
  - Evolution of the control strategy
    - Description in manufacturing process development (S.2.6).

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What to Put in the File

- Marketing Authorisation Application with enhanced product/process evaluation
  - Justification of control strategy
    - Comprehensive mapping of tests and acceptance criteria/action limits
    - Justification of how and where tests are performed
  - Process evaluation/validation
    - Detailed information on studies (DOE, analysis, outcome…)
  - Depending on study design, objective and outcome, could justify:
    - Alternative to end product testing (RTR testing…)
    - Leverage data requirement for process validation (protocol for continuous process verification…)

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What to Put in the File

- Marketing Authorisation Application with enhanced product/process evaluation and design space
  - Justification of control strategy
    - Comprehensive mapping of tests and acceptance criteria/action limits
    - Justification of what, how and where tests are performed
    - Comprehensive information of risk ranking/filtering tool used
  - Process description and control
    - Clear description of step covered by design space(s)
    - Summary of design space(s)
  - Process evaluation/validation
    - Detailed information on studies (DOE, analysis, outcome…)
    - Interaction between CQA(s) and CPP(s)
  - Depending on study design, objective and outcome, could justify:
    - Alternative to end product testing (RTR testing…)
    - Leverage data requirement for process validation (protocol for continuous process verification…)
    - Reduced details for process description and control (scale, acceptance criteria…)

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	MAA	+ Enhanced evaluation (e.g. DOE)	+ Design space
Specification	Justification +++	Justification +++	Justification +++
CQA Risk ranking filtering tool	+/-	+	+++
CPP interaction with CQA	+/-	++	+++
Process description and control	+++	+++	+ (depends on aspects covered by design space)
Alternative to end product testing	-	+ (depends on study design and outcome)	+ (depends on study design and outcome)
Process evaluation	+/-	++	+++
Process validation	+++ Detailed results of IPT and batch analyses on consecutive batches (final scale and process)	++ Detailed results of IPT and batch analyses on consecutive batches (final scale and process) Could be leveraged from process understanding	+ Mainly based on process evaluation + continuous process verification