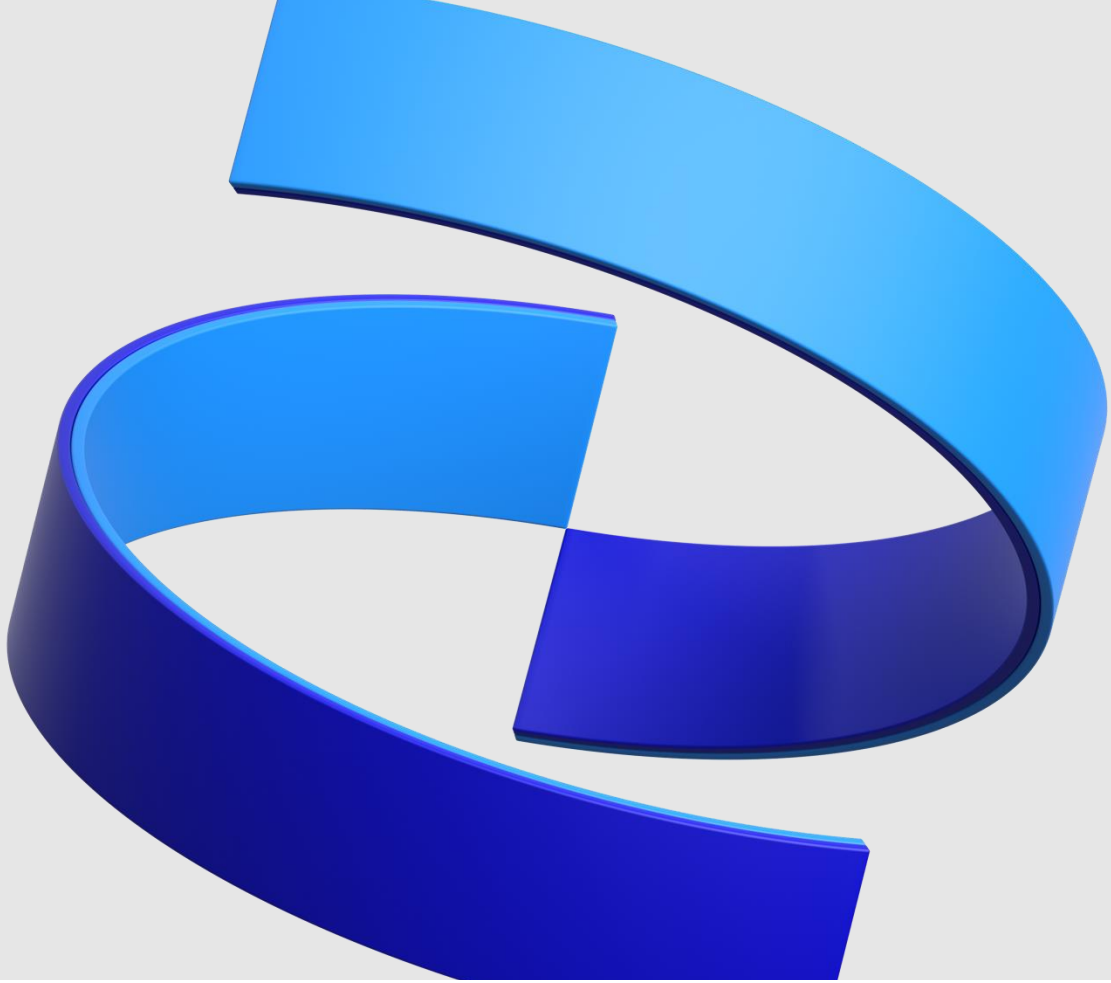
Leveraging platforms to accelerate ADC formulation and drug product development

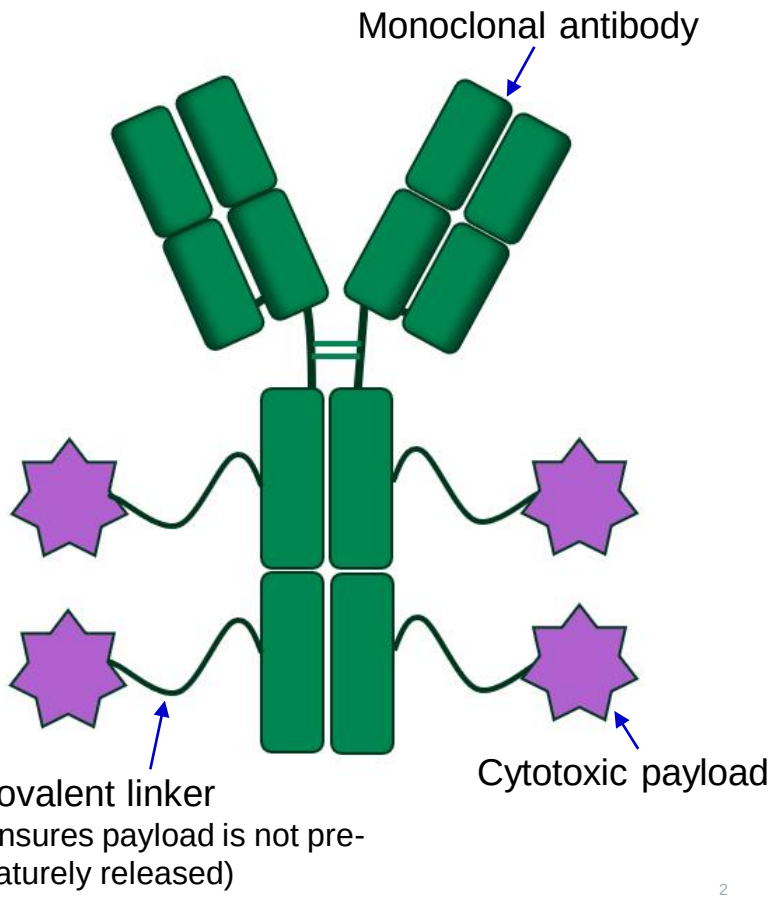


Karen Rutherford

CMC Strategy Forum
North America 2024

Antibody Drug Conjugates

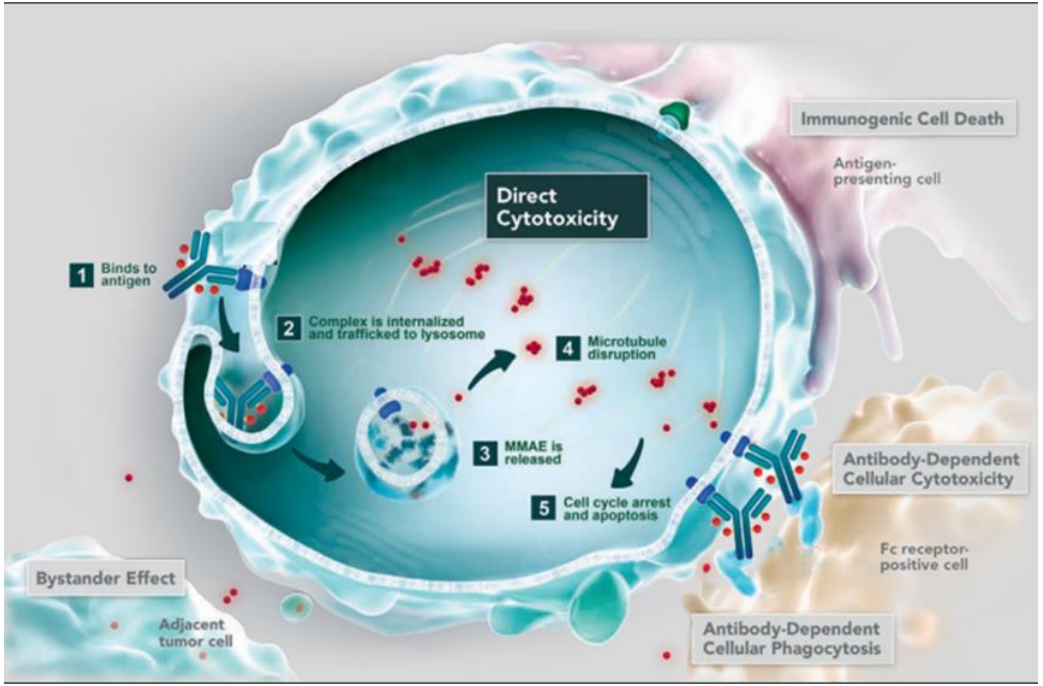
- Complex therapeutic increasingly used in cancer treatment
- Specificity of a monoclonal antibody AND potency of a cytotoxic agent
- Significant diversification in antigens targeted, cytotoxic payloads, linker technologies



ADC = Antibody drug conjugate

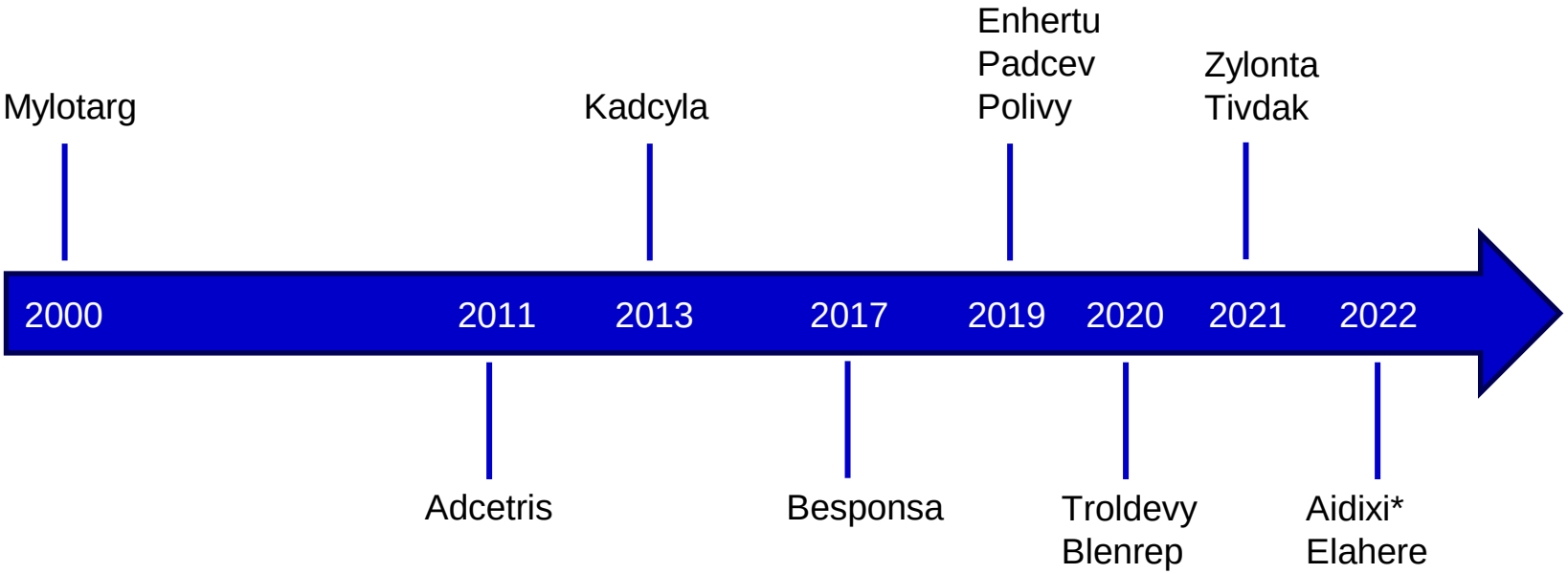
How do ADCs work?

- Preferentially target payload to tumor site
- Cytotoxic payload targets: DNA, tubulin, topoisomerase 1 inhibitors
- May be used in combination with other agents
- Managing ADC-related toxicity is key



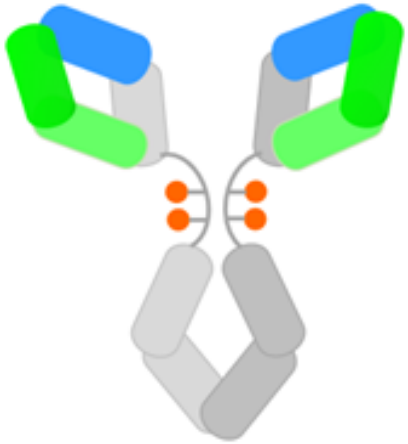
ADC = antibody drug conjugate

Marketed ADCs for targeted cancer therapy



* Approved in China
ADC = Antibody Drug Conjugate

ADCs are complex, heterogeneous molecules



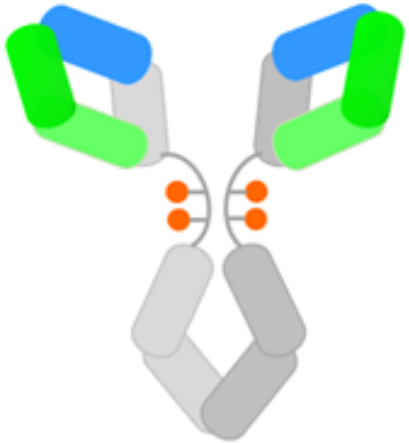
- Post-translational modifications (e.g. glycosylation)
- Conjugation site (e.g. lysine, cysteine, …)
- Linker stability (e.g. hydrolysis, drug exchange, photolysis, …)
- Number of payloads (e.g., 2, 4, 8 …)
- Payload properties (e.g. charged, hydrophobic, …)

ADC = antibody drug conjugate

ADC development requires balancing stability of antibody, drug-linker, and payload

mAb CQAs

- Aggregation
- Fragmentation
- Charge variants
- Deamidation
- Oxidation
- Hydrolysis
- Disulfide Scrambling
- Conformational integrity



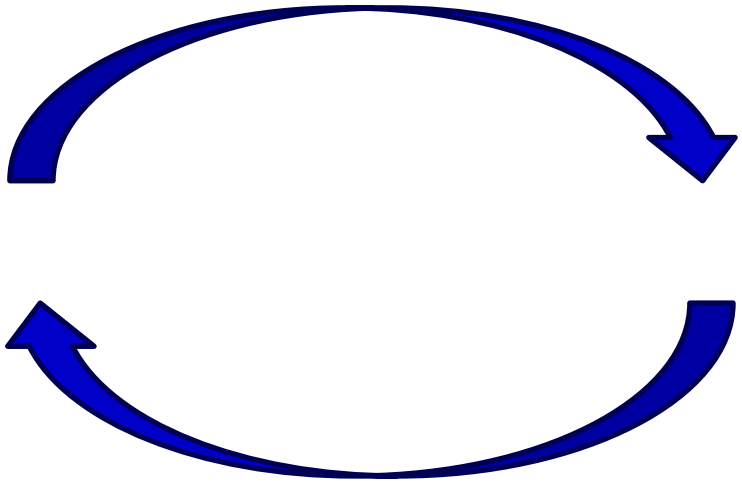
ADC-specific CQAs

- Free Drug Related Impurities (FDRI)
- Drug-to-antibody ratio (DAR)
- Unconjugated mAb
- Cytotoxicity

ADC = antibody drug conjugate
CQA = critical quality attribute

Leveraging platforms and prior knowledge to accelerate ADC development

Information from multiple molecules



Changes / improvements

Platforms

- Common process, set of conditions, operation, approach that work for (most) similar molecules

Prior Knowledge

- Understanding, conclusions established through analysis of historical data for similar processes and/or molecules

ADC = antibody drug conjugate

Antibody platform is consistent between common mAbs
ADC platforms are often grouped by drug linker properties

IgG1 mAb Platform

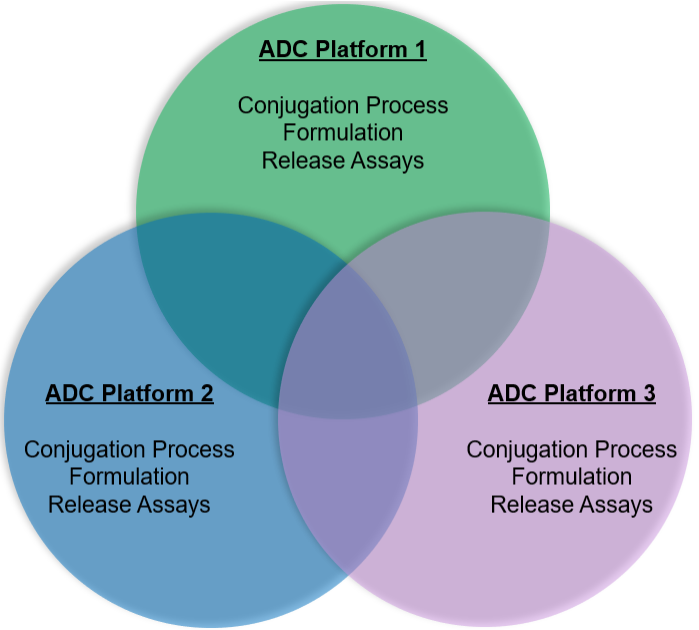
Cell Culture Process

Purification

Formulation

Impurities Assays

Release Assays



ADC = antibody drug conjugate

ADC platforms can be further subdivided by challenges associated with each process step

IgG1 mAb Platform

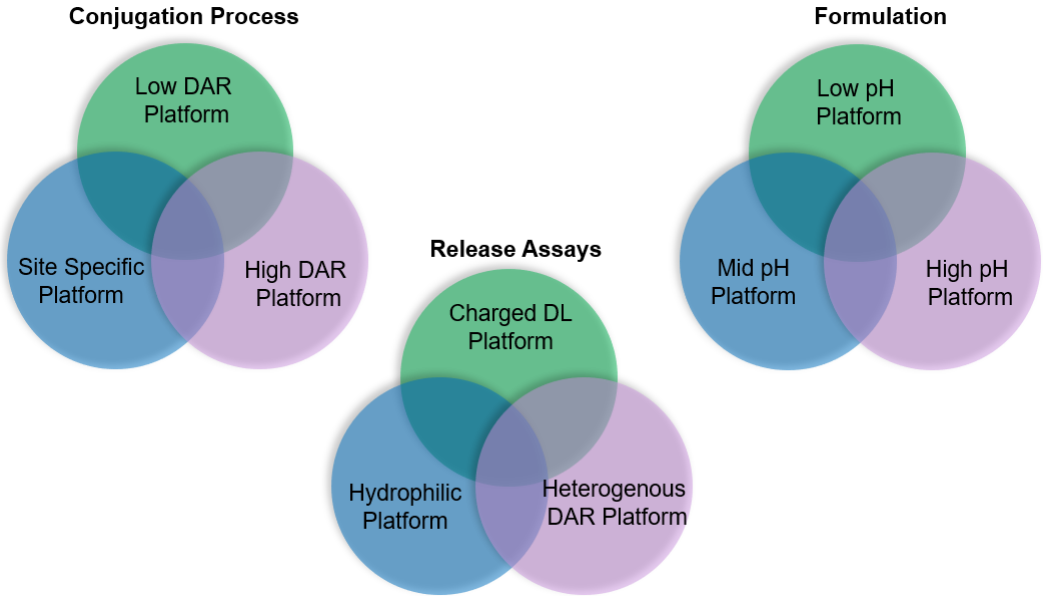
Cell Culture Process

Purification

Formulation

Impurities Assays

Release Assays



ADC = antibody drug conjugate
DAR = drug-to-antibody ratio
DL = drug linker

Drug product development

Successful development depends on understanding how each aspect impacts and is impacted by different DP elements.

Leveraging platforms and assessing prior knowledge focuses development efforts

ADC = antibody drug conjugate
DP = drug product

Formulation development and platform fit

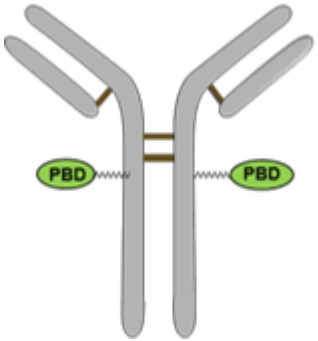
1. Assess drug linker dependent prior knowledge
- Each ADC has unique liabilities under different conditions

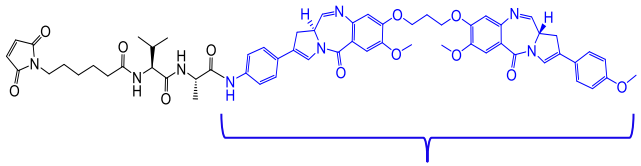
2. Pre-formulation or early molecule assessment
- Is ADC fit to platform?
- Evaluate against experience with similar DL

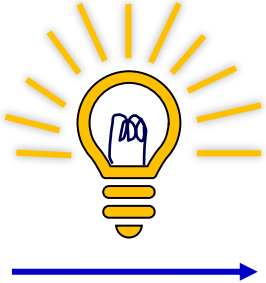
3. Confirm formulation (mAb & ADC)
- Thermal stress forced degradation
- Freeze / thaw
- Light stress
- Agitation
- Clinical in-use

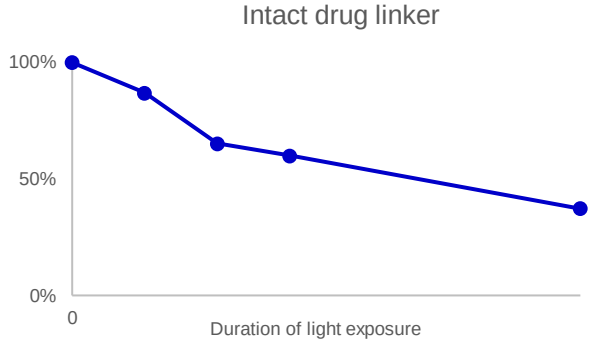
ADC = antibody drug conjugate; DL = drug linker

Light exposure controls to mitigate light-sensitive drug linkers









- Methionine oxidation
- Charge variants

Mitigations implemented for manufacturing, stability / storage, testing, and administration become platforms for ADCs with light-sensitive DL

ADC = antibody drug conjugate; DL = drug linker; PBD = pyrrolobenzodiazepine

Platform ADC dosage forms and strengths streamline FIH development

ADCs are lyophilized drug products

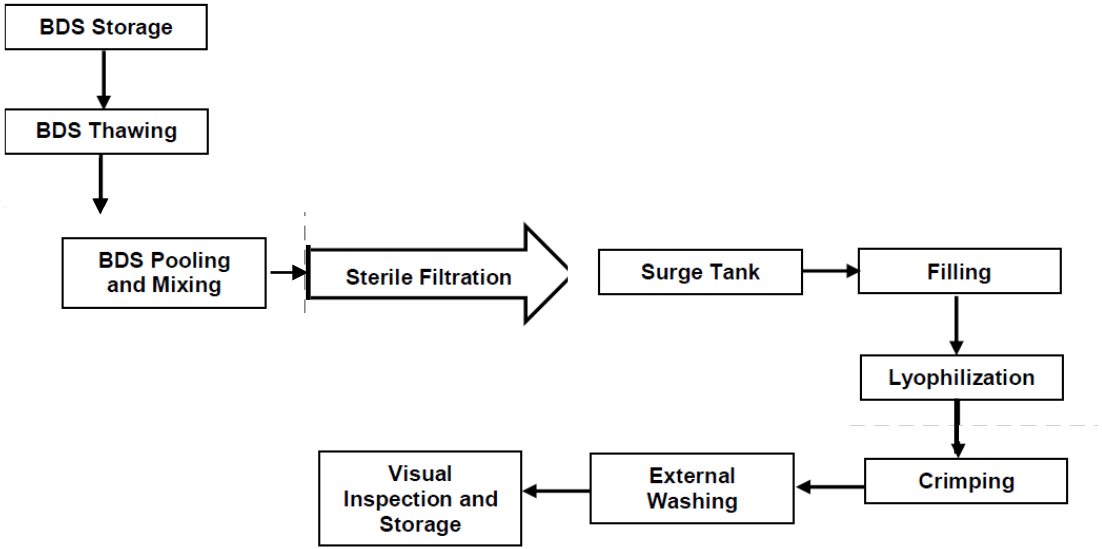
- Linker hydrolysis is major degradation pathway

ADC cytotoxicity profile informs platform strength for FIH

- Intravenous administration
- Platform container closure system
- Platform fill volume
- Platform cake reconstitution

ADC = antibody drug conjugate
FIH = first in human

Robust ADC drug product manufacturing processes to support entire molecule lifecycle

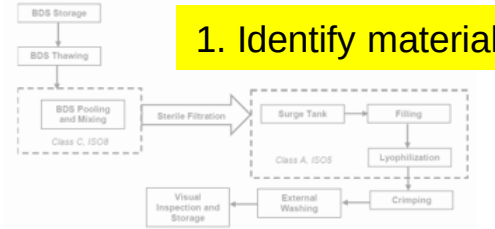


Platform approach to DP processing steps enabled by:

- Formulation
- Dosage form
- Container closure system
- Strength

ADC = antibody drug conjugate, BDS = bulk drug substance, DP = drug product

Leveraging Prior Knowledge: Manufacturing material of contact compatibility assessments



1. Identify materials of contact

Pooling bag, Impeller, Port, Tubing assemblies, Valves, Hoses, Gaskets, Sensors, Filters, Surge tank, Filling needles

→ Polyethylene, Silicone, Pt. cured silicone, Polycarbonate, 316 L SS, PVDF, PETG

2. Assess prior knowledge

- Availability and applicability (ADC type, study conditions, …)

Program	Materials Assessed						
	PETG	HDPE	316 L SS	PTFE	PC	PVDF	Silicone Tubing
A	X	NT	X	X	NT	X	X
B	X	X	X	X	X	X	X
C	X	X	X	X	X	NT	X

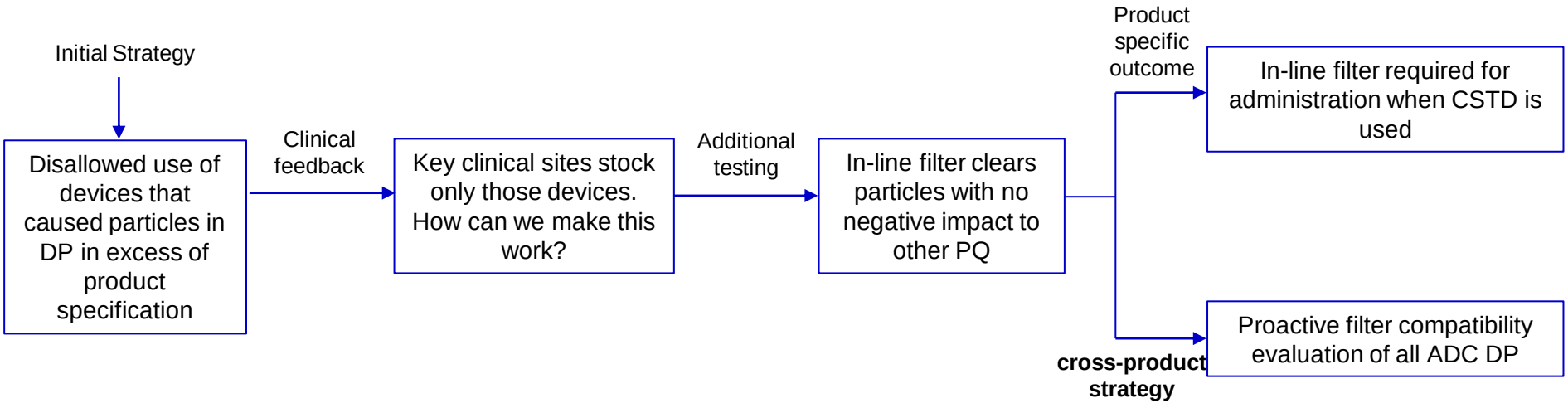
3. Perform study

- Test new MOC or identified risk
- Leverage applicable prior knowledge to reduce testing/scope
- Update prior knowledge with new data

HDPE = high-density polyethylene; MOC = material of contact; PC = polycarbonate; PETG = polyethylene terephthalate glycol; PVDF = polyvinylidene fluoride; SS = stainless steel

Platform approaches to ADC dose preparation and administration

- All ADCs are considered hazardous drugs (USP <800> “Hazardous Drugs-Handling in Healthcare settings”
- Closed system transfer devices (CSTDs) are required for dose preparation
- CSTD use commonly results in particles (visible and subvisible)
- Platform approaches that enable clinical flexibility and ensure patient safety



ADC = antibody drug conjugate; CSTD = closed system transfer device; DP = drug product; PQ = product quality

Summary

Platforms

- Common process, set of conditions, operation, approach that work for (most) similar molecules

Information from multiple molecules

Changes / improvements

Prior Knowledge

- Understanding, conclusions established through analysis of historical data for similar processes and/or molecules
- Develop applicability criteria
- Leverage to reduce scope of work / focus development

ADC = antibody drug conjugate

Thank You