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Perspective

CMC Regulatory Considerations for Antibody-Drug Conjugates

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ABSTRACT

Antibody-drug conjugates unite the specificity and long circulation time of an antibody with the toxicity of a chemical cytostatic or otherwise active drug using appropriate chemical linkers to reduce systemic toxicity and increase therapeutic index. This combination of a large biological molecule and a small molecule creates an increase in complexity. Multiple production processes are required to produce the native antibody, the drug and the linker, followed by conjugation of afore mentioned entities to form the final antibody-drug conjugate. The connected processes further increase the number of points of control, resulting in necessity of additional specifications and intensified analytical characterization.

By combining scientific understanding of the production processes with risk-based approaches, quality can be demonstrated at those points where control is required and redundant comparability studies, specifications or product characterization are avoided. Over the product development lifecycle, this will allow process qualification to focus on those areas critical to quality and prevent redundant studies.

The structure of the module 3 common technical document for an ADC needs to reflect each of the production processes and the combined overall approach to quality. Historically, regulatory authorities have provided varied expectations on its structure. This paper provides an overview of essential information to be included and shows that multiple approaches work as long as adequate cross-referencing is included.

Problem Statement and Goal of the Position Paper

The combination of a large biological molecule and a small molecule as a mixed modality is an inherently more complex product to develop as illustrated in Fig. 1. Manufacturing processes for the components (antibody, drug-linker, or linker and drug) and the conjugation process, all need to be characterized and well understood in terms of process and product. Different types of risk can occur which provide an opportunity to build up the scientific understanding at all manufacturing points of control so as to focus on the relevant parameters and measurements and remove redundancies. Advances in conjugation technologies[1] as well as in antibody engineering[2,3] also offer

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[1] At time period of writing the white paper

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Glossary

AA	= Amino Acid
ADC	= Antibody-Drug Conjugate
ADCC	= antibody-dependent cellular cytotoxicity
CDC	= complement-dependent cytotoxicity
CMC	= Chemistry, Manufacturing, and Controls
CMO	= Contract manufacturing organization
CTD	= Common Technical Document
CQA	= Critical Quality Attribute
DAR	= Drug-to-Antibody Ratio
DI	= Drug Intermediate
DP	= Drug Product
DS	= Drug Substance
DL	= Drug-linker = molecule that has both the drug and the linker
Fab	= fragment antigen binding region
Fc	= fragment crystallizable region
FDRI	= free drug (and related) impurities
HC	= Heavy chain (of monoclonal antibody)
IPC	= In-process control
LC	= Light chain (of monoclonal antibody)
MAA	= marketing authorization application
mAb	= monoclonal antibody
MMAE	= Monomethyl Auristatin E
MOA	= Mode of Action
PACMP	= post approval change management protocol
PC	= Process characterization
PPQ	= Process Performance Qualification
PV	= Process validation
TDI	= total daily intake
UF/DF	= ultrafiltration / diafiltration

improved control over the conjugation of the drug-linker to the antibody (e.g. site- specific conjugation), therein reducing risks like conjugation heterogeneity that may have been presented in earlier production processes. Applying the knowledge built up in characterization of products, intermediates, and production processes should lead to a science-based overall process control strategy and product release specifications, and therein prevent redundant analyses or even specifications on non-relevant attributes which have historically been requested by some regulatory authorities.

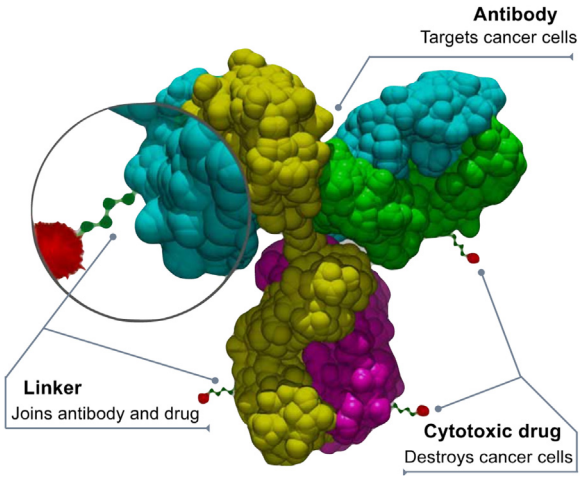


Figure 1. Structure of a typical antibody-drug conjugate (22 *Courtesy: By Bioconjugator – Own work, CC BY-SA 4.0,* https://commons.wikimedia.org/w/index.php?curid=58772304)

Through knowledge management and process understanding, changes in the ADC manufacturing processes can be adequately addressed and managed. Not all changes in early manufacturing steps, e.g. the drug or the linker, would lead to changes in the ADC conjugation process or product quality. Identifying points of control, which could include in-process tests or formal release of material, and demonstrating nonimpact of changes at these points should lead to a reduced change control burden. The authors would therefore propose a risk-based approach regarding comparability assessment which emphasizes critical quality attributes. A case study is used to illustrate the approach.

Another unique consideration for ADCs is the format of the dossier. There is no internationally unified approach defining where the information on the native antibody and the drug-linker are to be placed within module 3. A regulatory review is facilitated most readily by a CMC module complete with all the components included, however in some scenarios, such as when a component (e.g. linker, drug, drug-linker or antibody) is used across multiple ADCs a cross-reference to a master file is the most efficient. Furthermore, in cases where a common intermediate is manufactured by multiple suppliers, dossier maintenance may be simplified if the information about each component is held in a separate CTD 3.2.S section. Not all solutions are available globally, currently making it difficult for sponsors to create one globally suitable document. The authors support continued regulatory flexibility with sponsors adopting the structure most appropriate for their particular submission, i.e. using one file or several files dependent on the specific situation.

This position paper strives to provide additional clarity to the ADC CMC strategy and how the increased scientific understanding of ADC manufacturing processes facilitates a science-based approach. While our focus is ADCs for oncology, many of the principles can be easily applied to Fab or non-antibody protein drug conjugates as well as emerging ADCs for non-oncology applications.

Justification for Quality Attribute Testing and Specification Setting During Lot Release and Stability Testing - Using ADC Experience and Prior Knowledge

Since the first antibody-drug conjugates emerged into the clinic and then the pharmaceutical market, significant progress has been made in the control and understanding of the manufacture of ADCs. This increased knowledge can, and should be, used to create control strategies that adequately address the quality of the ADC products while avoiding addressing risks that are no longer present in modern production systems. This paper will present cases for a number of quality attributes that are specific to ADC products.

- Free drug (and related) impurities (FDRI)
- Unconjugated antibody
- Conjugated small molecule impurities
- Drug-to-antibody ratio (DAR)
- Conjugate variants
- Potency (as mechanisms of action whilst conjugated)
- Charged species

In case of new products, more up-to-date technologies and increased process and product understanding may lead to more focused control strategy development. For more established processes, the increased understandings offer the opportunity to update the control strategy, reflecting the learnings gained from scale-up and technology transfers in all areas of the process and providing prior knowledge for next projects to leverage.

Experience with brentuximab vedotin (internal cysteine, DAR ~ 4, MMAE = Monomethyl Auristatin E) is used to illustrate the

1st year of clinical investigation	Commercial product Available in >65 countries
Single-source supply • Clinical facilities	Redundant suppliers • Commercial facilities
Clinical scale production • mAb Intermediate: kilograms • Drug-linker intermediate: 10's of grams • Drug substance: 10's of grams • Drug product: 10's of grams (lyophilized product)	Commercial scale production • mAb intermediate: kilograms • Drug-linker intermediate: 100's of grams • Drug substance: kilograms • Drug product: kilograms (lyophilized product)
Limited process experience Assumptions about Quality Attrubute criticality Conservative strategy for controls	Well understood processes Better understanding of Quality Attributes

Figure 2. Differences and advancements 2007 vs. 2017 for brentuximab vedotin.[23]

development of product and process understanding from early clinical stages to the current standings.

Example of How a Control Strategy Might Evolve Based on Increasing Scientific Understanding (Summarized in Fig. 8)

ADC license and marketing authorization holders have an obligation to ensure drug availability just as all other pharmaceutical drug suppliers do. Given the complexity of ADC manufacture, there is a complex network of production sites that frequently entails the use of CMOs. Creating this network requires many technology and material transfers, and will lead to multiple changes to control, which may occur simultaneously in different sections of the production processes.

ADC manufacture for early phases of clinical studies may be based at a single location and depending on company structure it may be in-house or outsourced. A mature and marketed ADC will typically have multiple sources of supply for an increased quantity of product and its intermediates. The scale-up and technology transfer efforts which support the commercialization lead to increased understanding of product quality and process controls, as is illustrated in Fig. 2 for brentuximab vedotin manufacture.

The Addendum and its Tables 1 - 5 further elaborate examples of a possible ADC control strategy where test parameters can be "validated out" over time due to an increase in process and product knowledge.

Control Strategy

Examples for quality attributes specific to ADCs are presented in the subsequent sections. The control strategy for an ADC (see Fig. 3, further details are given in the Addendum) product must guarantee a consistently safe and efficacious drug for the patients. While the expectations for drug product and the drug substance are clear in regulatory guidance for small & large molecules, the expectations for control over the drug-linker or the monoclonal antibody, i.e. drug intermediates (DI), are less well defined. The intended use of both these drug intermediates is to be conjugated into an ADC, and their suitability for this use should guide the control required. The control strategy for drug intermediates should reflect control over those quality attributes that are required to support the quality of DS and DP, rather than the traditional level of control required of a native monoclonal antibody or small molecule drug substance. The fact that a DI is used in a subsequent production process, which may in itself introduce further impurities or purification steps, should be taken into account for the overall control strategy. This strategy is analogous to the approach taken with intermediates in a chemical manufacturing process or in-process materials during the manufacture of biologics.

Early ADC processes typically used stochastic non-site-specific conjugation technologies and therefore could have variability in the position and amount of drug-linker per antibody.

Modern conjugation technologies and their control strategies have progressed to produce very consistently conjugated ADCs both in the amount and position of the drug-linker on the monoclonal antibody (see Fig. 4). If there is no technical basis for a diversified payload distribution as in the case of site-specific engineered cysteine-conjugation (with branched or non-branched linkers) due to mutations in the HC and/or LC as opposed to lysine-linked ADCs or conjugates after reduction of interchain disulfides,[24,25] this should also be reflected in the control strategy; i.e. a specification of the payload distribution here is of limited value as depicted in Fig. 4 right graph. If, in another example, the conjugation process and linker is very specific to react with cysteine, monitoring for non-cysteine conjugation is similarly of limited value.

On the other hand, years of experience with non-site-specific conjugations have shown that they also produce very consistent products. While native lysine conjugation is not specific to a single site, it gives a consistent product, since only a subset of all lysines is modified. So here too a control strategy can rely on control of the DAR, i.e. the average number of conjugated drugs rather than specifying a particular profile. This is illustrated by an example in section entitled *Control of ADC Potency and of DAR Profile*. Similar considerations apply to conjugation at the interchain cysteines, for which the disulfide bridges must first be reduced (Fig. 4, graph in the middle). Depending on the reduction and conjugation regime, ADC products with heterogeneity can also arise here. It is clear that the consistency and repeatability of the data must be included in the submitted or updated data package given the potential influence of the payload profile on in vivo behavior.

Quality Attributes of a Monoclonal Antibody Intermediate Used for ADC Production

A monoclonal antibody used as drug intermediate (mAb DI) will provide one primary quality attribute to the ADC in its specificity of binding to the intended target molecule. The other quality attributes of the mAb DI are mostly concerned with the lack of potentially harmful impurities and contaminants. This difference in intended use should lead to a difference in control strategy for a monoclonal

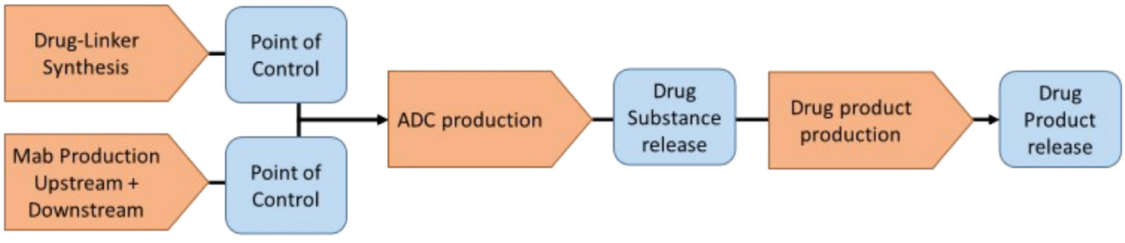


Figure 3. Example of components of an ADC production and control strategy (other sequences of processes possible).

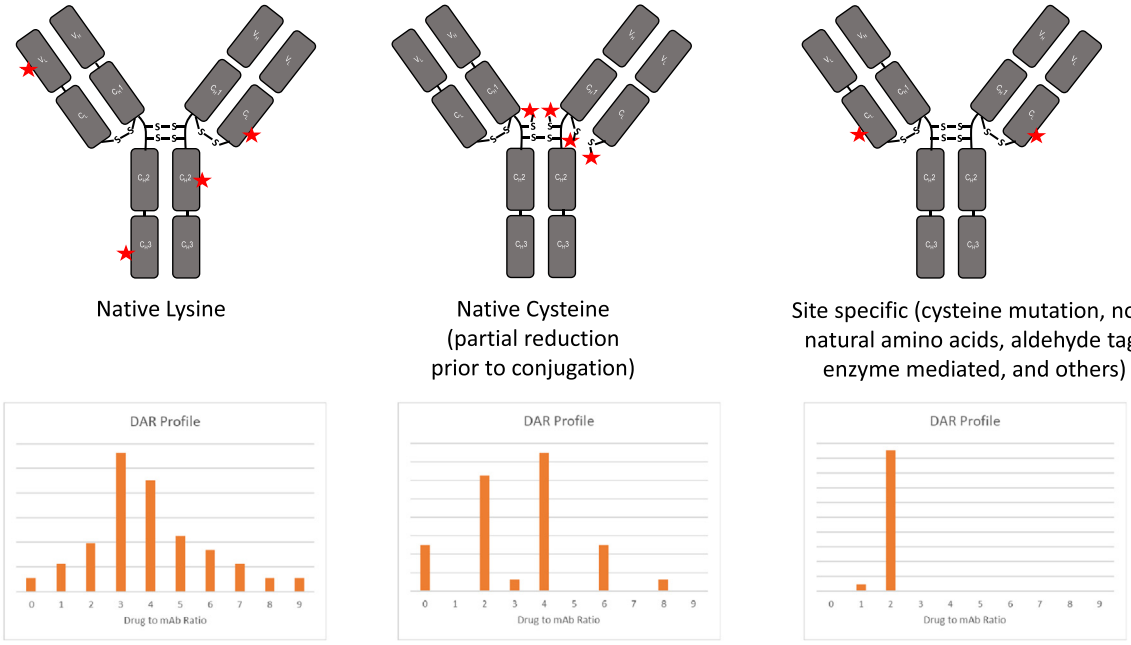


Figure 4. Examples of different conjugation chemistries for ADCs (figure modified from [5,26,27]).

antibody used as a drug substance/drug product, and a monoclonal antibody used as a drug intermediate (see Table 2 in the Addendum).

Quality attributes of the DS and DP that are dictated by the monoclonal antibody should be controlled at the mAb DI level, e.g. trisulfides content in mAb intermediate[4] when conjugation uses the cystine approach. Examples of this may include, but are not limited to,

- Adventitious viral agents, with the highest risk in the production process residing in the cell culture stages, are controlled by both cell culture IPCs and viral removal capacity in the downstream purification. Neither ADC DS production nor DP production represents a significant source or mitigation of adventitious viral agents. Therefore, control at the mAb DI is appropriate.
- Glycosylation of the mAb occurs in the cell culture stages and the level and pattern may be influenced by the downstream purification. Unless the conjugation involves the glycans directly, neither the ADC DS production process nor the DP process influences the glycosylation. Thus, control at the mAb DI is sufficient.
- Host cell proteins and residual DNA, originating from the cell culture stages, are mitigated by removal capacity in the downstream mAb purification. Neither ADC DS production nor DP production represents a significant source or mitigation of these impurities. Therefore, control at the mAb DI is appropriate.

Quality attributes that are influenced across the manufacturing of intermediates, drug substance and drug product may require limitations on the mAb drug intermediate to ensure that the DS and DP reach their desired quality. An example of this may be:

- Oxidation levels of the protein. Since the ADC production process can influence the oxidation level of the antibody, there may be a reason to limit the allowable level of oxidation in the mAb DI to a lower level than would be acceptable if the mAb were a drug substance. This may also hold true for other potential post-translational modifications like deamidation or aspartate isomerization.

Regulatory agencies have in the past approached the use of a monoclonal antibody as a DI with the similar expectations of a monoclonal antibody drug substance. Whereas many quality attributes may be common between the two applications, it is of little value to apply such expectations too early in a production process for ADC. For example, elemental impurities should be addressed on the final drug product and not at a stage where a manufacturing process, with potential to introduce such impurities, can still take place. These should therefore not be part of the control of a monoclonal antibody drug intermediate.

Overall demonstrating control of a mAb DI used to produce an ADC will focus on providing a consistent performance across the development and manufacturing history, including representative batches and comparability studies, and an understanding of the impact on stability over time. Where initially quality attributes may be measured at multiple points in a production processes, single "points of control" for the mAb DI and the linker DI other than a "release" as required for DS and DP can be implemented based on scientific and product knowledge ensuring the quality of both the mAb DI and the resulting ADC. This will alleviate some of the analytical burden from the DS and DP release (Fig. 3).

Quality Attributes of a Drug-Linker Intermediate Used for ADC Production

A comprehensive discussion on a risk-based control strategy for small molecule impurities in ADCs and drug-linker intermediates can be found in Gong et al.[5] Here we briefly summarize some of the key conclusions.

A drug-linker molecule used as a DI will provide two primary quality attributes to the ADC in its linker's ability to react with certain residues in the mAb to form a covalent bond and the toxicity of the drug. The other quality attributes of the drug-linker DI are mostly concerned with the lack of potentially harmful impurities and contaminants. Hence, again, this should lead to a difference in control strategy compared to DS and DP.

As with monoclonal antibodies, regulatory approaches to drug-linker production have taken an analogy from the reviews of small molecule drugs as drug substance and drug product. Again, this is in part warranted, but may result in burdensome requirements which results in the application of tests which would be better to

implement at later stages of manufacture. As an example, control of elemental impurities in the drug product must be assured, but this may be achieved by means other than requiring compliance with ICH Q3D limits at the drug-linker DI stage. Another example is given in Table 4 of the Addendum (removal of conjugatable impurities testing on Drug-Linker DI level during stability testing if demonstrably not changing during storage).

Quality attributes that propagate across the manufacturing from drug-linker DI into DS and DP may require acceptance criteria on the drug-linker DI to ensure that the DS and DP robustly meets the defined quality requirements.

Examples of this may be:

- Conjugatable drug-linker impurities levels. These impurities are typically generated during the drug-linker manufacturing process and may lead to conjugated impurities in the ADC. The detectability of impurities in the ADC drug substance or drug product can be very challenging and a proven approach is to limit the levels of such impurities in the drug-linker DI. Non-conjugatable drug-linker impurities may be tested at the stage of drug-linker DI but their ultimate control would typically include an FDRI test on the DS (see section entitle)
- For new conjugation technologies where the linker connects to multiple drugs, further understanding of quality attributes and heterogeneity is recommended to mitigate any risks related to safety and efficacy.

Control Over of Unconjugated Monoclonal Antibody Levels in the ADC

Early ADC production processes could result in variable levels of drug-linker being conjugated to the monoclonal antibody, sometimes resulting in a significant amount of unconjugated monoclonal antibody remaining in the ADC DS. The unconjugated antibody is sometimes referred to as the DAR0 species. This constitutes a risk of unconjugated antibody binding to target in the patient, thereby blocking binding sites and preventing the conjugated antibody from delivering its full therapeutic potential, and any variability in DAR0 content could result in variable efficacy. In vitro and in vivo studies have demonstrated that, in many cases, DAR0 is not an effective inhibitor of ADC activity, or may even have a beneficial effect.[6] More modern conjugation technologies result in reproducible conjugation patterns, efficient conjugation and, in many cases, a low level of unconjugated monoclonal antibody in the ADC DS. If low or reproducible levels of DAR0 can be demonstrated in product and process characterization, there may be no need for an ADC DS and DP release specification for DAR0 species.

Control of Free-Drug Related Impurities (FDRIs)

Free drug, free drug-linker, free drug-linker impurities or any other forms of free cytotoxic drug that are not conjugated to the monoclonal antibody are defined as “FDRIs”. They may be process-related impurities or degradants, arising either during the manufacturing process or over time during storage, and may originate from different sources. FDRIs are an important quality attribute directly affecting the safety and efficacy of an ADC.

The level of control to be imposed should be based on a number of factors:

- Patient risk due to the FDRIs - both safety and efficacy impact should be reviewed. Impurities may be less cytotoxic than the drug itself, and understanding their biology may provide justification for allowing certain (higher) impurity levels. Where these data are not yet available, a conservative approach can be adopted to assume similar cytotoxicity to the drug. Since these FDRI are available systemically immediately following an intravenous infusion, a safety and toxicology assessment should take that into account.
- Process and product characterization will lead to understanding where in the process FDRIs are created or reduced.
- Stability data, including stress studies on DS and DP, can be used to understand how FDRI levels change over time. If stability is consistently demonstrated during development, then including FDRI test in further stability protocols could be eliminated (see Table 3 in the Addendum). Furthermore, by varying the structure of the linker it was possible to reduce the susceptibility of the conjugate to hydrolytic processes and avoid uncontrolled release of the drug from the antibody.[7] This needs also to be factored into the risk strategy.
- Consistent performance across scales, manufacturing processes and batches all demonstrating acceptable low levels of impurities can also provide justification for removal of FDRI from specifications.

For both ADCs in early development and marketed ADCs a risk-based approach to FDRIs control is recommended. This should reflect the uncertainty and the degree of criticality of the specific impurities based on their potential patient impact. This may lead to clinical specifications that can later be “validated out” of the final marketed release specifications. This is analogous to the way residual DNA limits may be included in clinical specifications for monoclonal antibody products but are later removed from the specifications of marketed products. Advanced process and product characterization can be used to validate impurity removal and thus, justify FDRI’s removal from the specification.

For products that are marketed ADCs, this approach may be beneficial to reduce a historically high burden of testing and controls to a science-based approach that does not impact either safety or efficacy of the marketed drug. ICH Q3A(R2) presents concepts that can be used to justify limits on FDRI: according to this guideline a threshold of 0.15 wt percent for FDRI could be acceptable, if the impurity is not “unusually toxic”. As an example, for brentuximab vedotin it has been confirmed that MMAE, the conjugated small molecule drug, is not pharmacologically active at doses up to 2.7 μg/kg. This level is equivalent to 0.15 wt% of the active ADC when administered at the indicated dose level of 1.8 mg/kg every 3 weeks. Thus, free MMAE should be categorized as “not unusually potent” (see Fig. 5) and if it were present as an impurity at 0.15 wt% in the DS it would not present a safety concern.

If low levels of FDRI are consistently observed during development and process validation, and the observed or potential impurities are not considered to be unusually potent, then removal of the FDRI test from the routine control system may be justified.[5]

Control Over Conjugatable Impurities in the ADC

The conjugation process to create the ADC may also link some small molecule impurities to the reaction positions on the monoclonal antibody. To prevent a reduction of the ADC potency or a safety risk to patients, typically such conjugatable impurities are controlled at the drug-linker DI stage. Implementing controls over conjugated impurities after conjugation is challenging as the detectability of the conjugated impurities in the ADC is typically low.

The level of control to be implemented is based on a number of factors:

- Patient risk due to the conjugated impurities; both safety and efficacy impact should be reviewed.

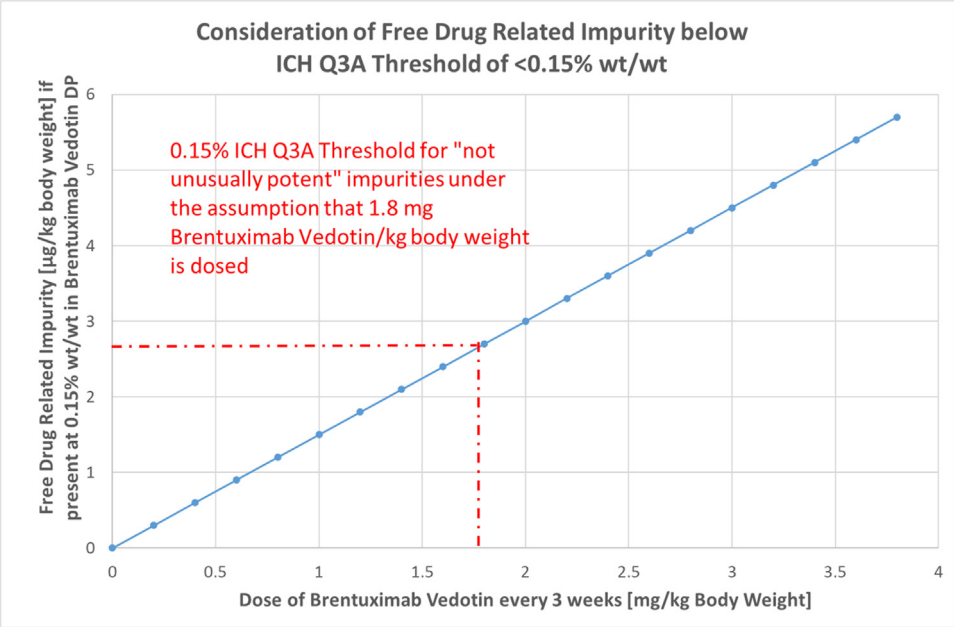


Figure 5. Toxicity consideration for FDRIs example in brentuximab vedotin.

- Process and product variability; a consistent impurity profile will help to demonstrate process control and ensure consistent DS and DP quality.
- The drug, linker, and drug-linker intermediates are small molecules with typical molecule weight of < 4000 Da (considering also dual payloads[8]), which accounts for < 10% of the total mass of the final ADC product (~160,000 Da) (assuming the average DAR = 4). Process design will, in effect, lead to dilution of the DI drug-linker and its impurities as DI is converted to DS and DP. This may be used to support a higher impurity limit in the DI than the 0.15% impurity level that is traditionally used in small molecule APIs (ICH Q3A).

For control strategies for small molecule impurities estimates were made that 3.0 wt% of small molecule impurities originating from drug-linker intermediate, assuming all are capable of conjugating to the mAb, will result in 0.15 wt% of impurity in the final ADC drug substance and drug product (see Table 1[5]). If ADC is dosed at a level of 50 mg once every 3 weeks, the resulting impurity dose is 75 μg and the average daily dose for the impurity would be 3.6 μg. This is well below the 200 μg total daily intake (TDI) of an impurity that requires qualification by ICH Q3B.

Control of ADC Potency and of DAR Profile

The potency of the ADC will typically be part of the release specifications of both drug substance and drug product. The component that brings the cytotoxicity to the ADC is the drug-linker intermediate, and controls are typically in place to ensure that this DI is of the correct structure and composition.

Some of the monoclonal antibodies used in the manufacture of an ADC may have ADCC or CDC functionality in themselves. However, the potency of these activities would typically be an order of magnitude lower than the potency of the ADC so that there is very limited value to verifying these activities in the monoclonal antibody DI. Simply verifying binding to the target (e.g. epitope, receptor, other structures on the target cell) should be sufficient nevertheless regulators continue to ask for additional evidence of an ADCC or CDC activity, especially to reveal comparability after process changes. For comparability, since ADCC and CDC can be correlated to glycan profile, a glycan assay can be enough. In cases where the monoclonal antibody has purposely been designed to eliminate ADCC or CDC functionality, there is a scientific rationale to not include those tests for the mAb DI (see Table 2 in the Addendum).

The authors acknowledge that a binding assay for the final DS is not meaningful by itself. In early development when a cell-based functional assay may not yet be available, a binding assay is often the only option, but for late-stage development, a cell-based potency assay should be included in the specification for DS and DP.

For most ADCs, there is a direct correlation between the average drug-to-antibody ratio and the DAR-profile. In the case of cysteine-linked ADCs such as brentuximab vedotin the DAR-profile can be analyzed chromatographically. From that profile the average DAR can be calculated. For an overview of methods applicable to characterize DAR see.[9–13] In the case of lysine-linked ADCs such as trastuzumab emtansine, average DAR is determined by UV spectroscopy, and mass spectrometry or imaged isoelectric focusing can be used to quantify the drug distribution. In the case of trastuzumab emtansine, there is a linear relationship between the MS measured average DAR and the UV determined DAR. Mathematical modeling demonstrates a Poisson distribution relating average DAR to the MS determined DAR profile.[14] Therefore, tight control over the average DAR determined by UV spectroscopy results in highly controlled drug distribution, including the level of DAR0 species. Fig. 6 shows the comparability of the drug distribution between trastuzumab emtansine produced at a small lab scale and at full, commercial scale where both have an average DAR of 3.5.

Table 1
Calculations on intermediate impurities and consequences, example assumes DAR = 4, and a molecular weight of 1000 Da for the payload and of 1000 Da for the linker, in total of 2000 Da.

- Assure patient safety by controlling conjugated impurities to a level that assures exposure will never exceed ICH Q3A level in DS or DP

$$DS\ Impurity\% = Intermediate\ Impurity\% \times DAR \times \frac{Intermediate\ MW}{DS\ MW}$$

  - 0.15% Impurity in DL Intermediate → 0.0075% Impurity in DS/DP
  - 3.0% Impurity in DL Intermediate → 0.15% Impurity in DS/DP

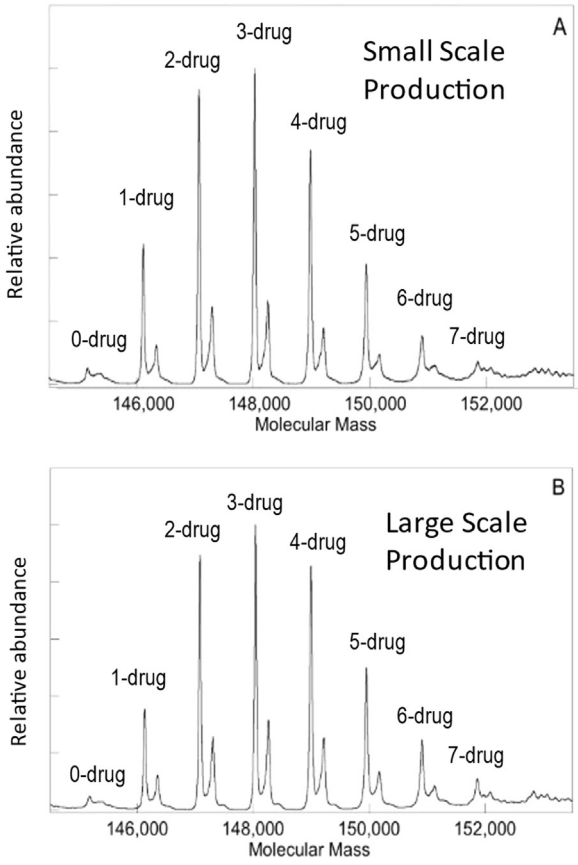


Figure 6. Drug distribution of trastuzumab emtansine produced at a small lab scale and at full, commercial scale both with average DAR of 3.5; assessment by RP-HPLC-ESI-MS.

For genetically engineered monoclonal antibodies used to produce ADCs with a predetermined number of conjugation sites, e.g. developed for site-specific conjugation,[15,16] DAR distribution is less of an issue, although some underlying heterogeneity may be observed.[17] Therefore, the DAR profile need not be controlled at the level of DS or DP production. DAR is controlled by the sequence of the antibody intermediate, and therefore the DAR profile only needs to be checked during product characterization and comparability studies.

Independent of the conjugation technology used, all processes should have appropriate controls that demonstrate that the process as a whole has proceeded correctly (for example, addition of the correct drug-linker, addition at the desired concentrations, application of the planned reaction conditions).

Validation Considerations

The manufacture of ADCs requires many steps and can take place over several months. Traditional validation (PPQ) of ADCs requires validation of finished product batches (DPs) using a validated drug substance (ADC), which in turn is prepared from a validated mAb intermediate (antibody) and a validated drug-linker intermediate, as shown in Fig. 7A = Scenario A.[18] Developmental material, such as pivotal clinical material, may be used as supporting data only. This linear sequence of validation, which requires completion of PPQ for one component before starting validation of the next component, may ultimately delay MAA submission because validation data must be available in the registration dossier.

An alternative strategy is to validate each manufacturing phase independently so that some work can be performed in parallel. This is based on the idea that the main objective of PPQ is to demonstrate that the process works as intended and produces a product that meets predefined quality criteria. This strategy requires a high degree of demonstration that the process inputs are representative of the intended commercial materials, similar to the justification of primary stability lots.

Scenario B (see Fig. 7B) is only one example of a decoupled validation strategy that could be used, and other scenarios could be proposed. In this example, GMP batches of mAb DI would be used to produce primary stability batches of DS and DP but would also be used as input for validation of the DS and DP processes. Another example is found in Scenario C, where the primary DS stability batches additionally serve as input for validation of DP.

Such alternative strategies not only save time, but also enable efficient use of the material and can ensure multiple lots are represented throughout validation batches.

Antibody-Drug Conjugate Products - N-Nitrosamines Risk Evaluation

An N-nitrosamine risk assessment must be performed for all antibody-drug conjugate products, taking into account the individual manufacturing steps, i.e., the synthetic drug-linker intermediate, the biological mAb intermediate, the conjugated drug substance, and the drug product. In particular, however, the issue is whether conjugation with the synthetic drug, linker, or drug-linker intermediate introduces new risks into the antibody product.

Synthetic Drug-Linker and Antibody Intermediates

The review of the synthetic drug-linker intermediate, and the antibody intermediate, should be evaluated for the potential introduction and/or formation of N-nitrosamines. Details of this type of assessment can be found in the EFPIA Position Paper on Risk Assessment of N—Nitrosamines for Synthetic Agents[19] and the EFPIA position paper on the N-nitrosamine risk of products of biological origin[20] respectively.

If a potential risk is identified (e.g. [21]), it should be further evaluated to provide an indication of the likely elimination of the resulting N-nitrosamine residue by subsequent steps. If a significant nitrosamine risk in an intermediate cannot be ruled out, further discussion and consideration of depletion or removal (e.g. chromatography of UF/DF steps) is required in the downstream steps.

Drug Substance (ADC)

If the synthetic and biological intermediates have been shown not to pose a risk for the presence of N-nitrosamine impurities, the focus of the risk assessment should be on the risk posed by the conjugation process. Again, it should be demonstrated that no nitrosating agents or N-nitrosamine residues are introduced as part of the conjugation process.

In the event of the introduction of a nitrosating agent, the persistence of N-nitrosamine species from a previous stage of manufacture, or the possible introduction or formation of N-nitrosamine residues, the potential of the process to remove these agents should be evaluated. As with the antibody intermediate, any UF/DF step will result in the removal of low molecular weight N-nitrosamine species from the drug substance to a high degree.

The storage conditions for the drug substance as well as the primary container of the drug substance should also be considered. Storage at low temperatures or in a frozen state in conjunction with formulation in a physiologically acceptable pH (typically 5−7) should slow reaction kinetics to the point that formation of N-nitrosamines is unlikely, even in the presence of a nitrosating agent. Typical drug packaging materials do not contain materials of concern such as nitrocellulose.

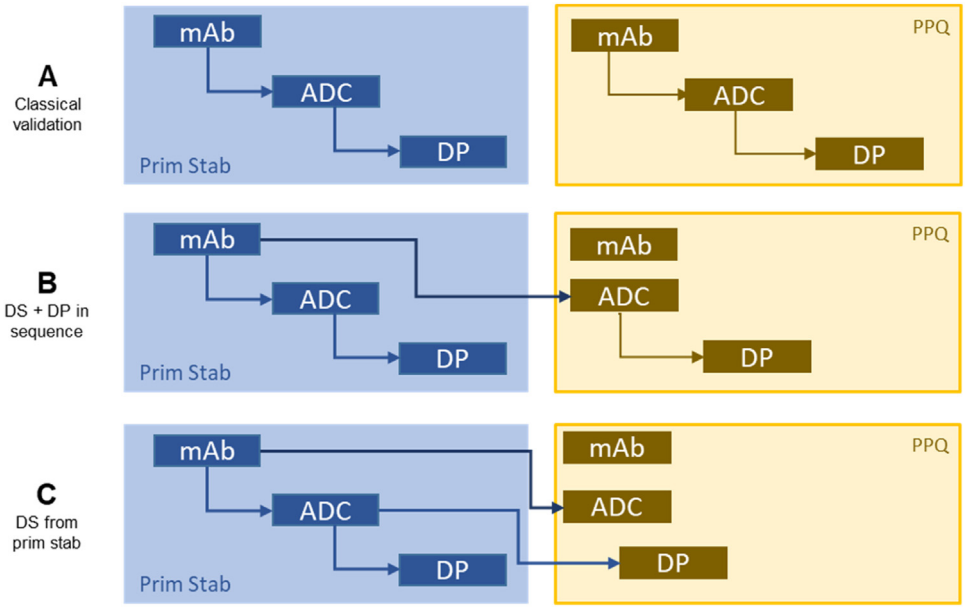


Figure 7. A – C: Three different validation strategy scenarios connecting primary stability studies and PPQ. The scenario C shows an example where representative ADC could be used as input for the DP PPQ.

Drug Product

If the drug substance has been shown to pose no risk of carryover of N-nitrosamine contamination, the focus of the risk assessment should be on the risk posed by the drug product process, the excipients introduced, and the packaging components (primary containers) used. Again, it should be demonstrated that no nitrosating agents or N-nitrosamine species are imported from any of these potential sources.

Like the active ingredient, the drug product is usually stored at low temperatures. This means that in the unlikely event that a sensitive amine and a nitrosating agent are present in the drug product, the reaction kinetics are extremely slow.

Of course, if after this risk assessment N-nitrosamine contamination of the drug product cannot be ruled out, an appropriate level of control for N-nitrosamines must be established, taking into account the recommendations in regulatory guidance. In most cases, however, the risk assessment should reveal no further steps needed given e.g. the purification processes removing small molecule impurities and the presence of scavenging reactive groups on the antibody.

Process Change Considerations for ADCs

Changes to the manufacturing processes of ADCs, as with other biological molecules, occur during development or post-approval due to expectations to improve the robustness or simplify the process, to change or add manufacturers, to increase scale even in the course of a post-approval change management protocol (PACMP), to improve product quality or stability, or to adapt to changing regulatory expectations. The complexity of the overall ADC manufacturing process (Fig. 3) introduces additional challenges in determining how to adequately address the impact of a change. It is the responsibility of the developer/sponsor to evaluate whether process changes would negatively impact the safety and effectiveness of the ADC product. This section discusses some key aspects of comparability studies during ADC development and commercial manufacturing, highlighting considerations specific to ADCs. The key recommendations in the section entitled apply to process or manufacturer changes after pivotal phase has been reached or after regulatory approval, while specific recommendations for changes at earlier stages of development are provided in section entitled. Process change considerations for intermediates, DS and DP are presented below.

Process Changes for Drug, Linker, or Drug-Linker Intermediate

The drug, linker, and drug-linker intermediate are small molecules, which means they are well characterized, and comprehensive analytical methods are usually available to demonstrate consistency of structure, purity, and impurity profiles. Changes in the production process or manufacturing site can affect these intermediates, but with the help of modern analytical technologies, the tools to elucidate structure, screen purity and impurity profiles, and monitor stability are sophisticated and sensitive enough to detect any differences that could adversely affect the subsequent ADC manufacturing process. Hence a science-based approach can be recommended as regards impurities and stability.[5] Impurities are a quality characteristic that deserves special attention, as outlined in the Control Strategy ion 2 of this paper. Checkpoints within the drug linker manufacturing and release process typically provide the best opportunity to control impurities that affect the ADC. In a typical ADC conjugation process, a UF/DF step is provided after the conjugation reaction to provide additional opportunities for removal of reagents, solvents, and other low molecular weight impurities that originate from the drug-linker intermediate. In some ADC processes, a chromatography step is also provided, which offers another opportunity for removal of small molecule impurities. Therefore, the risk of non-conjugated impurities resulting from changes in the manufacture of the drug linker carrying through to the final ADC drug substance and drug product can often be sufficiently controlled within the drug linker manufacturing process.

If an analytical evaluation of the drug-linker intermediate demonstrates the same structure, comparable purity profile, and reactivity for the drug-linker intermediate before and after the process changes, the evaluation generally does not require a comparability study for derived ADC DS or DP. If a significant difference in purity/impurity profile is identified, a risk assessment is recommended to evaluate the impact of this difference on the safety and efficacy of the final ADC drug product, and care should be taken to do so consistent with the intended use of the drug-linker and not based on expectations for an ADC DS or drug product. Decisions about whether to require

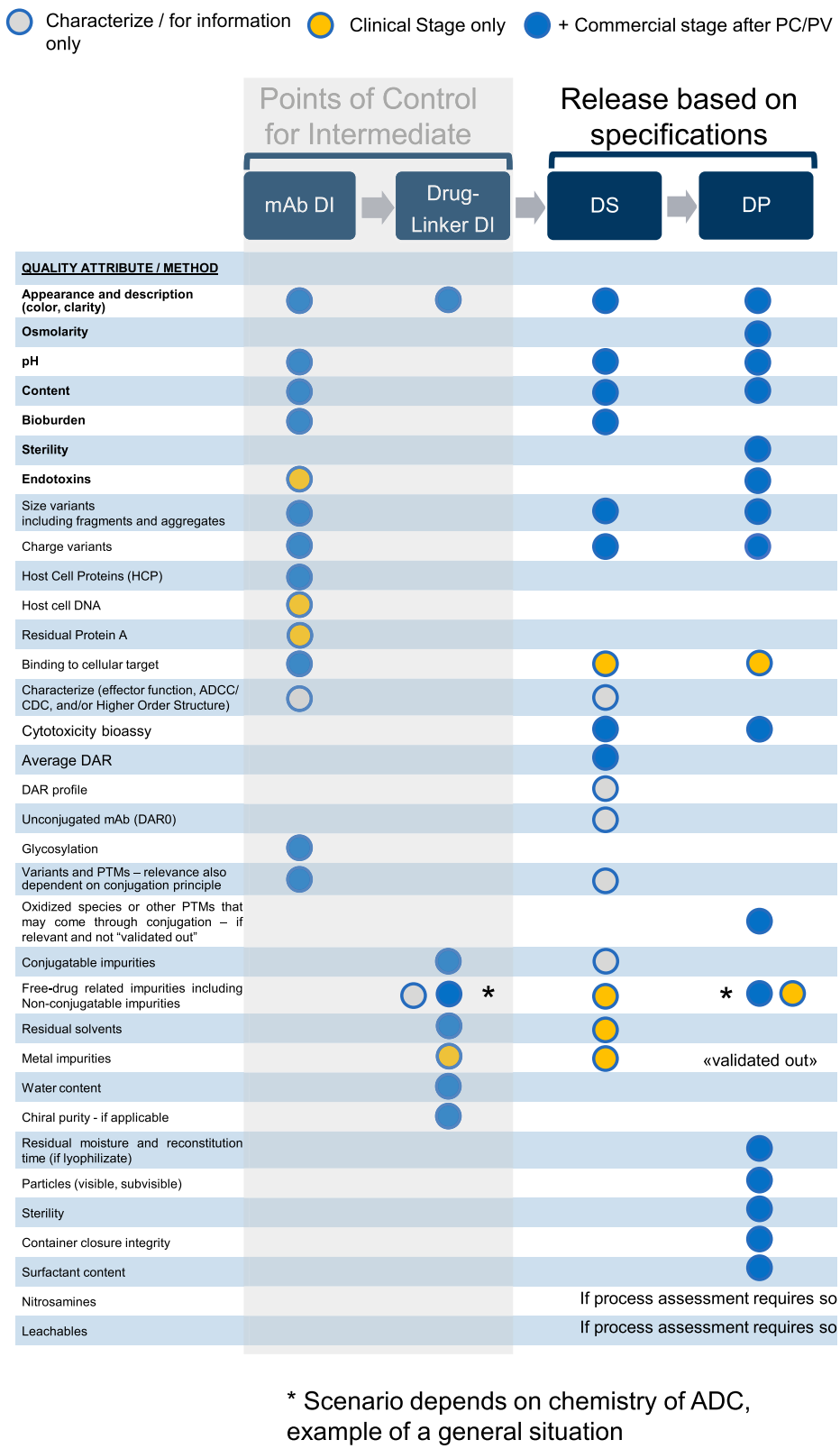


Figure 8. Potential expansion of product and process understanding during development or due to prior knowledge leading to an advanced control strategy – example brentuximab vedotin as Lesssons Learned from the body of data generated and as outlined in the section entitled.

Clinical stage = during clinical stage but not retained for commercial; Commercial stage = in place during clinical and continued after process characterization/validation.

Please note: Tests not continued in the commercial stage or moved to downstream, e.g. drug product level, need a sound rationale such as consistency demonstrated during development & process characterization ("validated out") or controlled by IPC or reliably ensured at last stage. Control of the Intermediate ("point of control") could be an IPC or release test.

qualification of new impurities should focus on the risk posed by the level of the impurity in the DS and DP, see also section entitled control.

A decision tree for Drug-Linker DI is proposed in Fig. 9A.

Process Changes for mAb Intermediate

The mAb intermediate, as a large molecule, is inherently more complex in terms of complete analysis of its quality attributes. With the development of advanced analytical tools, the ability to characterize the structures of mAb intermediates and monitor the critical quality attributes (CQAs) has become more mature, ("well characterized biologics"). However, there is still a risk that the analytical tools used may not be sensitive enough to detect all quality attributes that may impact the safety and efficacy of the final ADC products.

Process changes in cell line, cell culture, purification, or isolation of the mAb intermediate should be evaluated. Quality attributes that are controlled at the mAb level should remain under control there, as with any mAb agent, e.g., glycosylation, adventitious viral agents and host cell proteins. Quality attributes that determine whether the mAb DI is suitable for the mode of action and the conjugation process, e.g., target binding and the presence of the correct amino acids at which conjugation occurs, should be tested during the mAb production process and may require comparability testing.

If a comparability study at the intermediate mAb stage successfully demonstrates a comparable profile in terms of purity, impurity, and stability after process changes, no further action would need to be taken at the drug substance and drug product stages, since quality is sufficiently assured and need not be demonstrated again in DS or DP. If comparability of the mAb intermediate cannot be established, but comparability of the drug substance and/or drug product has been successfully demonstrated, a risk assessment for differences in the mAb intermediate is recommended.

Differences in non-critical quality attributes (non-CQAs) that do not adversely affect the subsequent conjugation process or the CQAs of the ADC drug substance should not disqualify the mAb process changes. For example, cysteinylation and glutathionylation at engineered cysteine sites in mAb intermediates are not typically CQAs. Prior knowledge supports that cysteinylation and glutathionylation are completely removed during the reduction step preceding the conjugation process, and do not affect the conjugation process and the quality of the final drug substance. Difference in the ratio of cysteinylation and glutathionylation as post-translational modifications therefore does not disqualify the implementation of changes in the mAb intermediate process.

Further differences in posttranslational modifications, such as glycation of lysines in a mAb intermediate, could also affect the drug localization profile of lysine-conjugated ADCs, which in turn may have implications for the in vitro and in vivo stability of ADCs. A significant difference in the modification of lysine-amine groups in a mAb intermediate intended for lysine-conjugated ADCs therefore warrants a comparability study at the level of ADC-DS- and ADC-DP.

A decision tree for mAb DI is proposed in Fig. 9B.

Conjugation Process and DS Formulation Changes for ADC Drug Substance

The purpose of the conjugation process is to produce the ADC from intermediates, remove impurities, and formulate the drug

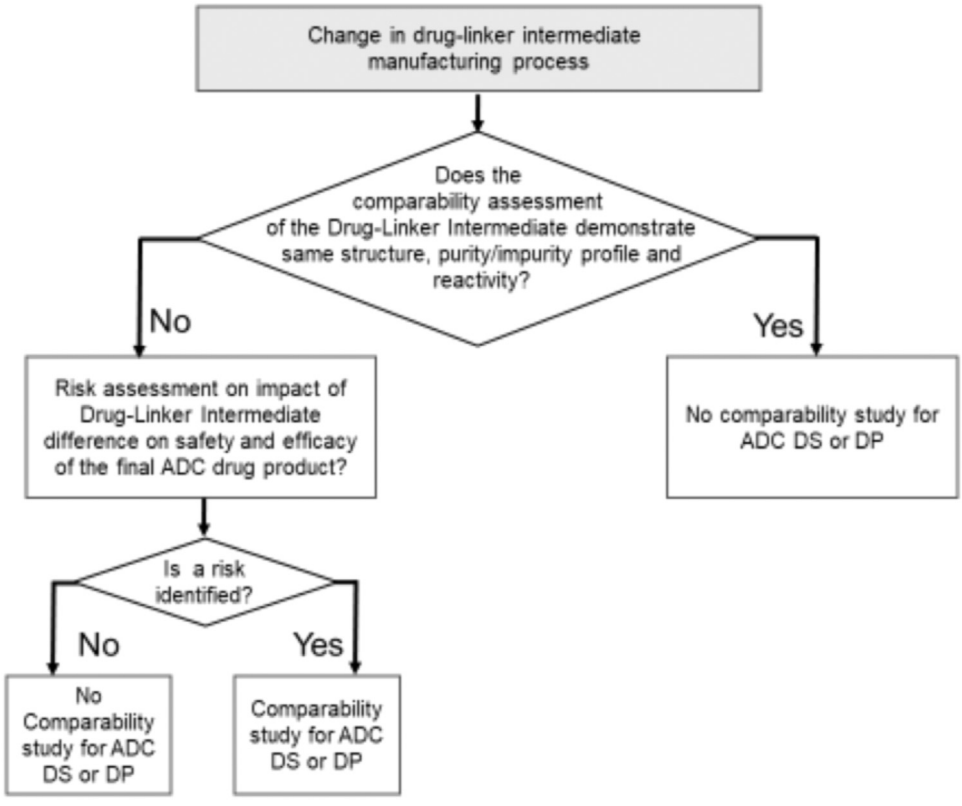
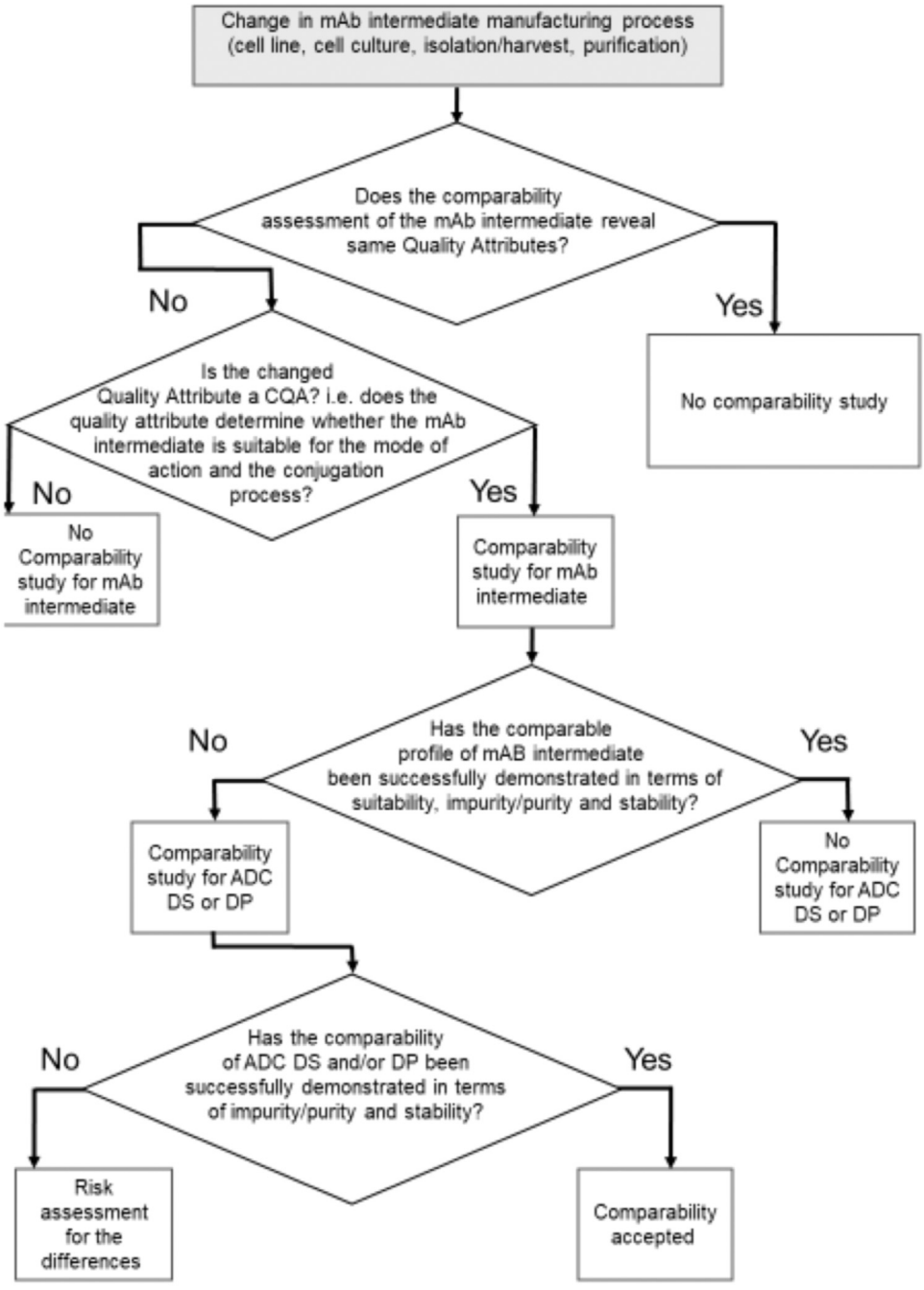


Figure 9. A – C Comparability assessment decision trees for process changes at various stages in the ADC manufacture (A) Process changes for drug, linker, or drug-linker intermediate (B) Process changes for mAb intermediate (C) Process changes for Conjugation process and DS formulation for ADC drug substance.



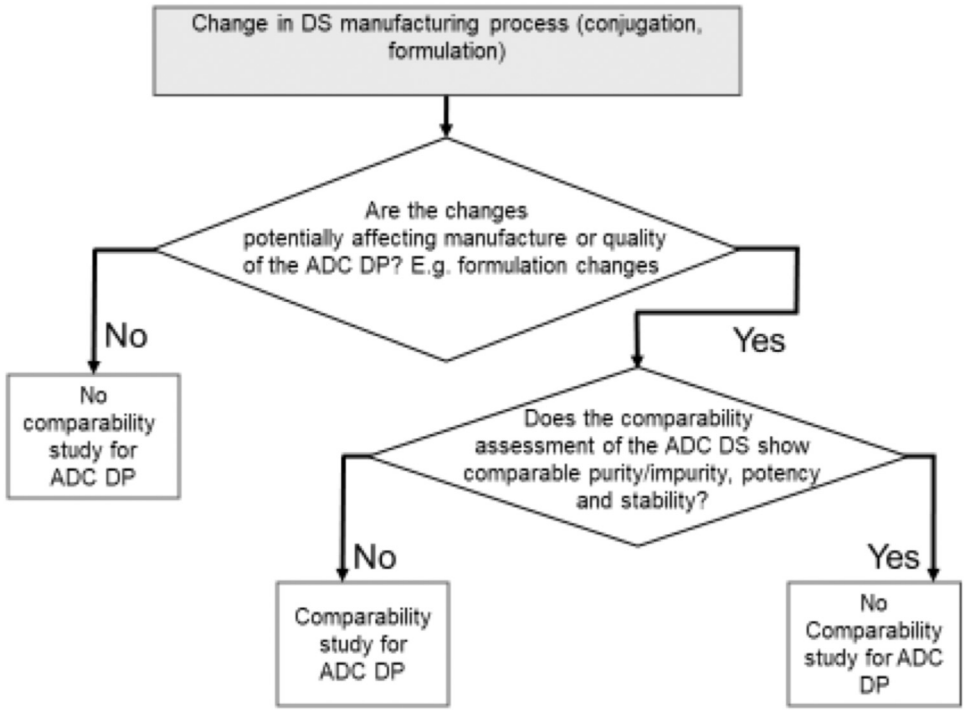
(b)

Figure 9. Continued.

substance. Advanced analytical tools are used to detect the quality characteristics, such as DAR, in the combined molecule.

Changes to the ADC manufacturing process should be treated similarly to changes in other large molecule products. The general recommendation is to perform a comparability study based on a risk assessment only at the ADC DS level to demonstrate comparable purity, impurity, potency, stability, and safety for the ADC DS before and after the process changes. Changes that may justify experimental assessment of comparability include a change in the formulation, a change in the buffer matrix during the conjugation reaction(s), or changes in the manufacturing site or scale. However, if the process changes result in a non-comparable DS or if the changes are likely to affect the manufacture or quality of the drug product, an additional comparability assessment should be considered at the drug product level. For example, if the formulation of the drug substance (pH, sugar, concentration) is changed, comparability studies at both the drug substance and drug product levels may be required. This would be the case, for example, if the drug substance is a frozen liquid and the drug product is a lyophilized vial, so that the stability of the DS cannot be directly derived from the stability studies of the ADC DP.

A decision tree for DS is proposed in Fig. 9C.



(c)

Figure 9. Continued.

Process Changes for ADC Drug Product

For any process change in an ADC drug product, a risk assessment, comparability study, or prospective stability study may be required at the DP stage to evaluate the impact on the purity, efficacy, and stability of the drug product, similar to other large molecule drug products.

Examples where a risk assessment may be sufficient include a minor adjustment in the fill volume of a liquid DP or a minor change in the coating material of the stopper.

Considerations on Analytical Comparability Studies as Applied to ADCs – Steps to Take for a Comparability Study

The factors to consider in assessing comparability are described in ICH Q5E and have been discussed extensively in the literature. A full treatment of this important topic is beyond the scope of this white paper but will rely on one of the main tenets of comparability assessments namely that if product comparability can be demonstrated solely by analytical comparability studies, no further actions will be required. In the next section a few considerations for analytical comparability studies of ADCs are set forth.

Selecting Quality Attributes and Analyses to Demonstrate Comparability

Table 2 lists the potential quality attributes selected for comparability studies for mAb intermediates, drug-linker intermediates, DS and DP. In addition, the selection of quality attributes can be justified based on the risk profile of a particular modification, process knowledge gained from previous process characterizations, and specific characteristics of, for example, conjugation technology.

For mAb intermediates, purity/purity profile, binding specificity, primary structure, and high-order structures are suggested to be compared after process changes. The type of comparability studies that address potency will depend on the mode of action of the ADC. If there is no evidence that ADCC or CDC activity is relevant for the efficacy of the ADC, there is no value in studying these and they could be omitted. Of course, the binding ability of the mAb intermediate should be investigated.

Comparability studies of drug-linker intermediates focus on comparison of purity and impurity profiles as well as identity. For impurities or modifications identified in the mAb intermediate or drug-linker intermediate, it is recommended that their impact on the subsequent conjugation process (differentiating between conjugatable and non-conjugatable impurities) and the potential to affect DS and DP quality attributes be considered.

Quality attributes selected for DS comparability studies include drug-to-antibody ratio (DAR), purity/purity profile, potency, and primary and higher order structures. If process characterization and product knowledge are already available, this information can be used to justify the design of comparability studies. For example, if it is demonstrated that the DAR for a DS is comparable before and after a change and the DAR distribution does not change during stability, it is justified not to test stability at the DP level.

Stability (Side by Side Accelerate / Stress Study)

As regards the stability aspect, the basic principles valid for other biologics are applicable:

- In the comparability study conducted between GLP toxicology materials and GMP clinical materials, side by side comparative stability data are generally not required.
- However, if the process changes happen during the clinical study or post commercial approval, the comparability studies should include side by side comparative stability data, i.e. the stability protocols foresee the comparison of the stability results.

For mAb intermediate, DS and DP comparability, forced degradation studies of limited duration, with side-by-side comparison can be more informative than real time and stress protocols.

Table 2
Recommended quality attributes selected for comparability studies for mAb intermediate, drug-linker intermediate, drug substance, and drug product.

Manufacturing stage	Quality attributes
mAb intermediate	■ General test such as Appearance ■ Purity/Impurity ➢ Size variants (fragments and High Order Structures / aggregates) ➢ Charge variants ➢ HCP ➢ Host cell DNA ➢ Residual Protein A ■ Biological activities ➢ Binding ➢ Effector functions – if significant for MOA (i.e. killing effect relevant compared to killing effect due to drug conjugation) ■ Primary Structure ➢ Amino acid sequence ➢ Glycosylation profile ➢ PTMs – relevance also dependent on conjugation principle
Drug-linker intermediate	■ General test such as Appearance ■ Purity / Impurity profile ➢ Drug-linker related purity & impurities (as appropriated by e.g. UV, IR, NMR, MS, elemental analysis,. . .) ➢ Residual solvent ➢ Heavy metals ➢ Water content ➢ Chiral purity if applicable
DS (risk based)	■ General test such as Appearance ■ Drug Antibody Ratio (DAR and DAR distribution) and conjugation sit ■ Purity/Impurity-mAb ➢ Size variants (fragments and High Order Structures / aggregates) ➢ Charge variants ➢ Unconjugated mAb ■ Impurity-Drug ➢ Free drug and its related substances ➢ Residual solvents ➢ Elemental impurities ■ Potency ➢ Binding ➢ Cytotoxicity ➢ Effector functions if it is significantly part of the MOA ➢ Conjugated Peptide Map
DP (risk based)	■ General test such as Appearance ■ Residual moisture and reconstitution time (if lyophilizate) ■ Purity/Impurity - ADC mAb ➢ Size variants (fragments and High Order Structures / aggregates) ➢ Charge variants ■ Impurity-Drug ➢ Free drug and its related substances – may be waived for stable linkers ■ Potency ➢ Binding ➢ Cytotoxicity ➢ Effector functions if it is part of the MOA ■ Particles (visible, subvisible) ■ Sterility/Container closure integrity ■ pH ■ Surfactant content

If differences in chemical or biochemical characterization are obvious, analytical comparability studies are insufficient to establish comparability post process changes and/or very accelerated developments require a parallel approach (i.e. initiating the animal study before having the analytical results), it is considered appropriate to include additional evidence from nonclinical or clinical studies – similar to other biologics. The extent and nature of nonclinical and clinical studies will be determined on a case-by-case basis per individual sponsor's discretion. The purpose of these studies is to enable comparison of pre- and post-change materials. As an example, a change affecting residence time or binding affinity could justify a PK study in rodents (instead of doing this in human), if sufficiently powered. Where appropriate, these studies should be direct comparative studies.

The design and extent of those nonclinical and clinical studies are out of the scope of this manuscript.

How to Design and Set Criteria for an ADC Analytical Comparability Study

Comparability Protocol and Lot Selection for Comparability Study

Comparability considerations are similar to those for biologics; therefore this subsection provides a brief summary. A comparability protocol is not required for comparability studies conducted during early development, such as the comparison between GLP toxicology lot and GMP clinical lot. In early development it is not feasible to set appropriate acceptance criteria for the comparability protocol, due to limited knowledge and experience for the specific project. However, a formal analytical comparability protocol is highly recommended for comparability studies conducted during late phase clinical development or post commercial approval. In these later development stages, enough manufacturing experience and clinical data should be able to support setting of appropriate acceptance criteria.

Representative lots from both the existing and new process should be included for the comparability study. The number of lots selected depends on the development stage. Specifically for ADCs care should be taken to assess that the lots selected represent the variation to be demonstrated. If there is an intent to demonstrate the effects of a mAb intermediate change in the DS, the ADC lots should represent sufficient variation in mAb lots used.

Comparability Strategy for Different Development Stages

The extent of comparability study depends on development stage of the project.

Early Stage (GLP Tox vs. GMP Clinical)

The comparability studies conducted during the early development usually focus on evaluating quality attributes related to safety, such as impurity profiles, drug load (DAR) and potency. One lot from the GLP toxicology process and one lot from the GMP clinical process are sufficient to assess comparability at this stage of drug development. Generally, the GMP clinical materials should have comparable or improved quality attributes (e.g., improved purity) relative to the GLP toxicology materials. Comparable DAR should be maintained between toxicology lot and clinical lot. The potency of the ADC should be included in the assessment and comparable cytotoxicity between toxicology and clinical product should be demonstrated. Comparative stability data (accelerated and/or stressed stability) are generally not required to demonstrate comparability unless the GMP production process differs significantly from that of the GLP toxicology.

Late Stage (Clinical Process vs. Pivotal Process)

The comparability studies conducted during late development should include assessment of quality attributes related to safety, efficacy, quality and stability. Purity/impurity profile, drug load (DAR), potency, primary and high order structure should be compared. Suitable lots from both the existing and the new process are recommended to be included and should cover process variabilities. Comparable DAR and potency should be demonstrated. Compared to the initial process, a comparable or improved impurity profile is

acceptable. Stability data (accelerated and/or stressed stability) should be generated to support a determination of comparability.

Formulation of the ADC and Linker Technology Aspects

In early ADC technologies the linker was the least stable element in the ADC drug product. Over the past decade, ADC researchers have turned their attention to optimizing linker technologies, not only in terms of in vivo efficacy of the ADC, but also in terms of modulating the physicochemical properties of the conjugate. This has guided the development of more stable Fc molecules with better biophysical properties, such as higher unfolding temperatures (Tm), but the introduced Fc mutations can also sometimes be associated with instabilities. Improved understanding of our linkers, drugs, and antibody components has led to a more informed formulation strategy for ADCs, with formulation scientists able to determine the process parameters for a stable drug product. Advances have been made in the drug dosage form, moving away from frozen and freeze-dried drug product and paving the way for a stable liquid formulation. Although a freeze-dried ADC dosage form allows for faster technical development and a higher likelihood of suitable long-term product stability, a liquid ADC dosage form may be even more attractive given the ease of use for the end user and the low exposure of potentially toxic ADC material for healthcare professionals when handling a liquid formulation. Given the increasing experience with certain linker/drug formats and the improved stability properties of antibody formats, liquid ADC formulations may be technically feasible without significantly delaying product development timelines.

Formulation Development Considerations

In general, it might be appropriate to choose a formulation for the mAb intermediate that is compatible with the subsequent conjugation process, e.g., stable under freeze-thaw cycles and suitable for further manufacturing. Due to the heterogeneous nature of many ADC formats, analytical evaluation of chemical stability is challenging and resource and time intensive. In the lyophilized state, ADCs are less prone to chemical instability, and the optimal pH can be selected to increase the net molecular charge and reduce the aggregation tendency of the molecule. However, when handling ADCs with cleavable linkers, pH selection should focus more on controlling linker degradation, and even in the lyophilized state, pH selection is guided primarily by the need to avoid excessive free-drug formation. Wherever possible and applicable, it may be appropriate to retain the same excipients in all formulations of mAb intermediate, drug substance, and drug product, but the amounts of excipients may vary. In this case, the preformulated DS can simply be diluted and then freeze-dried. Conversely, it is also possible that solubility or stability issues may result in different excipients being used in the different formulations of the mAb intermediate, drug substance, and drug product if, for example, there are incompatibilities between the excipients and the conjugation reagents.

Structure of the CTD

The ICH Common Technical Document quality section M4Q provides guidance on a harmonized structure and format for presenting CMC information in a registration dossier for drug substances and drug products in a registration application. There should be no limitation to a specific structure of dossier, such as for ADCs, as long as the information of chemistry, manufacturing and controls are located appropriately in the dossier and are easily found. However, in reality, to determine the applicability of a format for a particular type of products such as ADCs, applicants are according to the authors' experiences advised to consult with the appropriate regulatory authorities, ahead of dossier submission, so that the reviewer/assessor expectations can be met. The applicants benefit from the flexibility to choose the most appropriate format, based on the specific situation encountered.

The two most common dossier formats for ADC registration applications which do not follow strictly the eCTD format (but were reported to be accepted) are briefly described below and illustrated in Fig. 10. Hybrids between the two dossier formats are also conceivable, depending on the product and the situation.

Option A: One DS folder dossier: Drug, linker, drug-linker and naked mAb are ADC drug substance intermediates (DI) which CMC information are presented nested within the DS modules 3.2.S.2.4, 3.2.S.4 and other relevant sections. Section S.2.4 can be divided by subsections for each DS intermediate including partial or full 3S granules (e.g. S.1 − S.7) as necessary.

Option B: There are separate and multiple 3.2.S folders (e.g. one each for ADC drug substance, drug-linker intermediate, mAb intermediate, potentially also for drug intermediate and linker intermediate if applicable). Each folder has one set of documentation, 3.2.S.1 through 3.2.S.7. According to ICH M4Q guidance Q&A (R1), when more than one drug substance is used in a drug product, information should be presented separately as one complete Drug Substance section followed by other complete Drug Substance sections under the same license.

Both one DS folder (option A) and multiple DS folders (option B) dossiers have their own advantages.

In one DS folder dossier, then drug substance intermediates are presented in 3.2.S.2.4 as typical intermediates. The number of subsections for the intermediates is determined as needed, in reality, authorities may waive the need for a detailed subsection for an intermediate (particularly the chemical ones). As an example, a drug-linker intermediate to be used in drug substance conjugation reaction shortly after its synthesis may not need a full stability subsection if short-term stability data is available or can be submitted upon request.

A multiple DS folder dossier (option B) approach is recommended by the authors, since it facilitates dossier preparation by industry and review by health authorities. It also enables efficient management of subsequent life-cycle activities, excels in simplicity of organization, and provides clarity for the CMC information about ADC drug substance, drug-linker intermediate, and mAb intermediate.

The dossier format option B, however, could imply that the regulatory expectations for the drug-linker and mAb intermediates for characterization, comparability, release and stability are the same as they are for a final drug substance. The authors would like to emphasize that, regardless of which format option is adopted, they do not project the expectations and requirements as being comparable for DI (specifications designed to enable conjugation and prepare for proper end product) and DS (specifications designed to describe safe and efficacious active principle). It should be the goal to reduce unnecessary or redundant work in order to facilitate the development of ADCs as explained earlier in this paper.

In the choice of dossier structure it is advised to provide an explanation of the chosen structure to guide the reviewers, e.g. in the module 2.3 Introduction, and to provide clear and consistent naming, cross referencing and links between sections.

In cases where multiple ADC products use the same drug-linker or mAb, each separate folder for drug-linker or mAb could be reused, or cross referenced between products. The use of an ADC component across multiple ADC products generates a clear opportunity to leverage prior knowledge from the platform, which should be appropriately presented in the dossier. Alternatively, Drug Master Files (DMFs) can be utilized to support multiple products utilizing a single dossier (applicable to all options). A folder 3.2.S.1.1. Drug-Linker DI might be created to cross-reference to the Letter of Authorization in

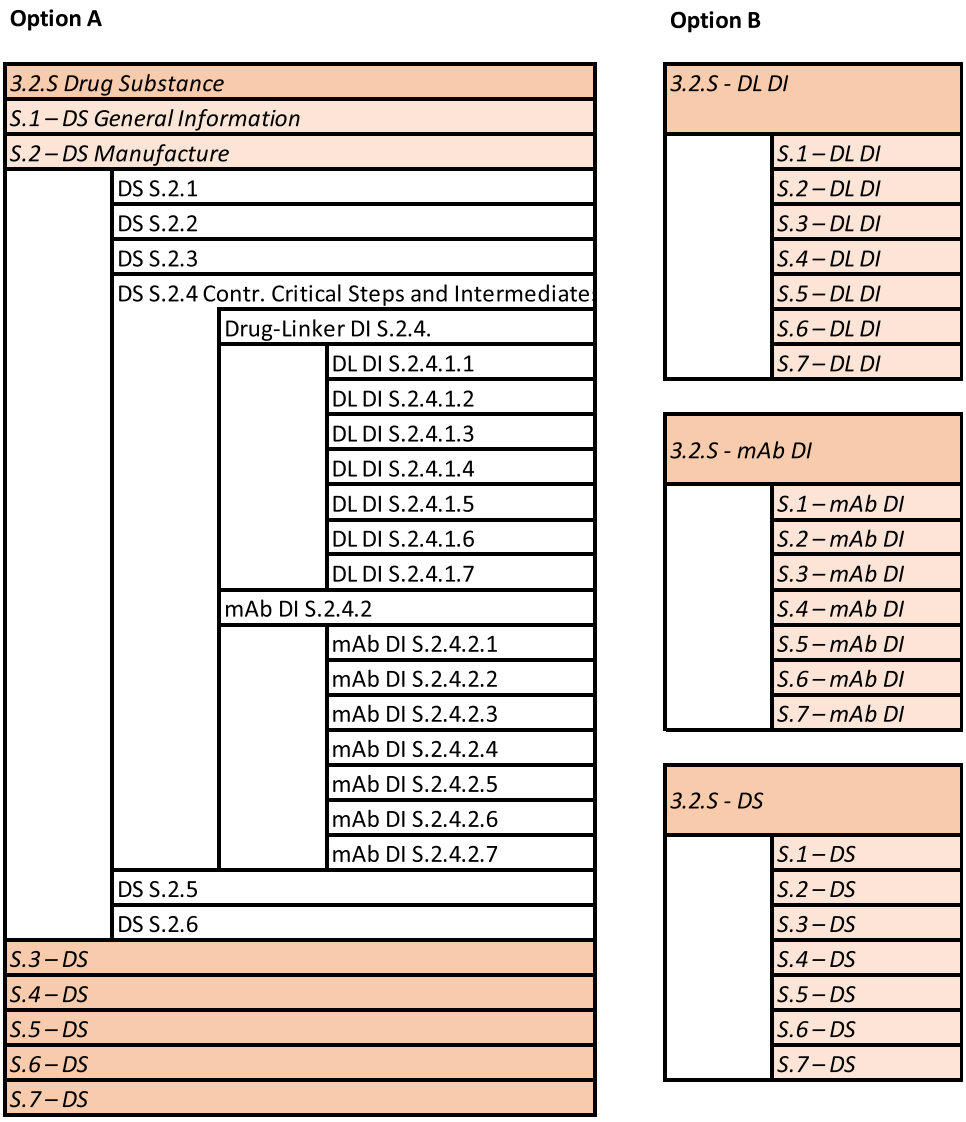


Figure 10. Possible structures for an ADC common technical document.

Module 1. This approach has been used successfully in the United States and Canada but is not currently an available option in many regions.

The authors would like to encourage also other regions to consider introduction of DMFs.

Conclusions

Compared to the early days of antibody-drug conjugates in the 2000s, researchers and industry have now achieved major advances in technology through intensive characterization work, improvements in linker technology and targeted integration/site specific conjugation, and, in addition, have gained increasing confidence in process consistency, even for older methods such as native lysine conjugation based on data. And we have obtained additional data on the toxicology of impurities such as FDRIs which can now be taken into account.

A distinction must be made between quality attributes that are monitored as points of control and those that are part of a release specification. In addition, a differentiation must be made as to whether certain parameters and/or properties can be influenced by a process step at all. If this is scientifically and demonstrably not the case, repeated testing and stability testing should not be required in Drug Intermediates, in Drug Substance and in Drug Product. Prominent examples in this context are the acceptance criteria for unconjugated antibody (DAR0) in DS and DP, effector functions of the monoclonal antibody as drug intermediate, DS and DP, and for a specific drug-antibody profile in DS and DP. These are still required by some authorities, as well as unnecessarily low limits for FDRIs.

Modern validation concepts should allow timewise parallel approaches of Drug-Linker, DS and DP and the combination of primary stability batches and PPQ batches, otherwise ADC validations are a time challenge due to the complex manufacturing processes.

The application of ADC products following the requirements of the Common Technical Document involves making tactical choices. Document flexibility in the design of the CTD up to the possibility of a DMF concept would be helpful.

Finally, science-based approaches for process changes should be accepted as naturally as is already the case for normal biologics.

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Author Contributions

All listed authors have contributed by writing and reviewing this White Paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xphs.2023.09.007.

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