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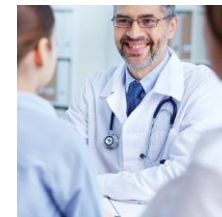


# CMC Regulatory Considerations for ADCs

Karoline Bechtold-Peters on behalf of ADC Workstream, 11 May 2020



CASSS European Strategy Forum,  
May 11 – 13, virtual meeting, EFPIA  
MQEG Biomanufacturing Satellite  
Session



# Thanks

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<sup>1</sup>at the time of compiling the white paper

# Problem Statement and Status

- As mixed modalities, ADCs are more complex to manufacture and analyse. After more than 10 years of experience with this class of molecules, they can be produced consistently and redundant analyses and stability studies should be avoided. In case of changes, risk-based approaches should be allowed to be used and only relevant process steps should be included in a comparability study. Acceptance of different dossier structures would give the sponsors flexibility and reduce redundant work. Similarly, the classical, sequential validation approach leads to unnecessarily long overall validation times.
- Status:
  - Final draft of White Paper practically available,
  - will be sent to BioManufacturing WG and MQEG in ca. 1 – 2 weeks for review; submission to AAPS Pharm Sci Tech and also publication via EFPIA website soon



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Draft



Final



## EFPIA-White-Paper-on-CMC-Regulatory-Considerations-for-ADCs

Author: EFPIA Date: April 2020 Version: FINAL-DRAFT



### Executive Summary

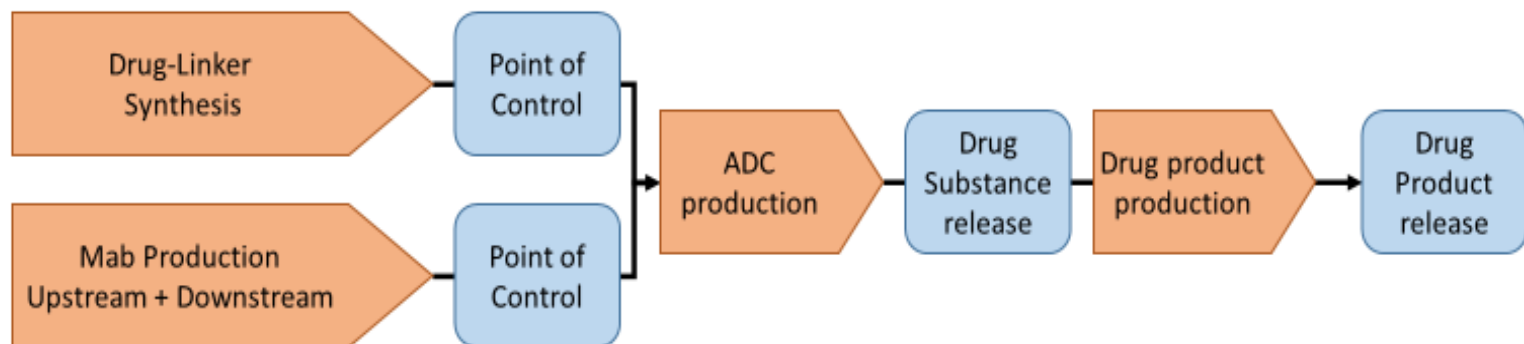
Antibody drug conjugates unite the specificity and long-circulation time of an antibody with the toxicity of a chemical cytostatic drug using smart-linkers to reduce systemic toxicity and increase therapeutic index. This combination of a large biological molecule and a small synthetic molecule creates an inherent increase in complexity. Multiple production processes are required to produce the naked antibody, the drug and the linker, followed by conjugation of aforementioned 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 an increased load of analytical characterization.

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

The structure of a module 3 global technical dossier 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.

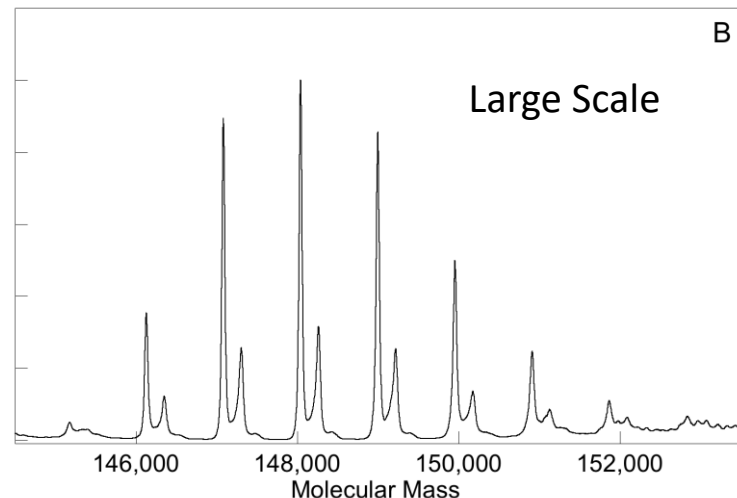
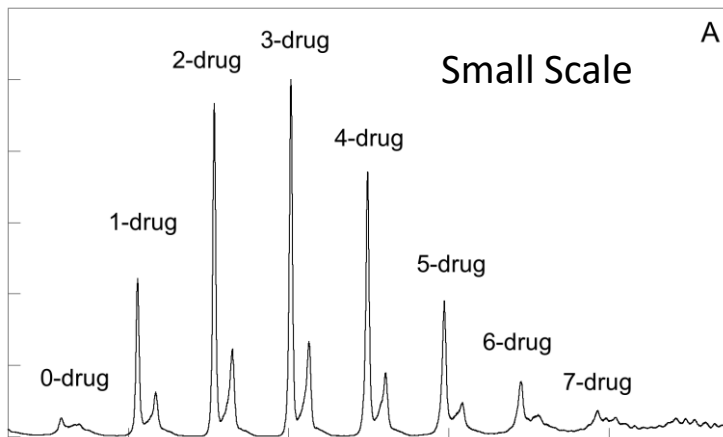
# Points of Control vs Release Specification

- 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 to form an ADC, and their suitability for this use should guide the control required.
- A distinction must be made between analytical parameters that are collected 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 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 be avoided in Drug Intermediate, in Drug Substance and in Drug Product.



# Example DAR and DAR Profile

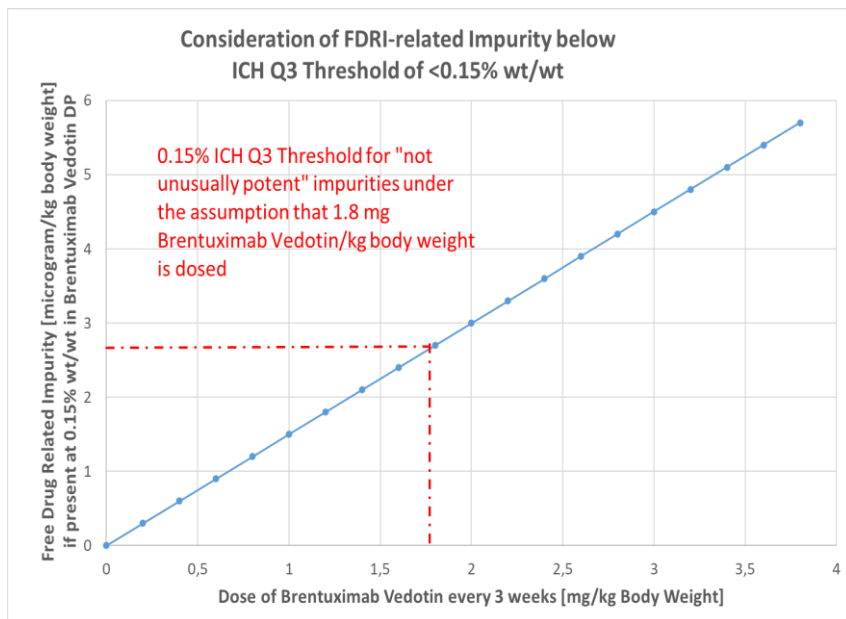
- Direct correlation between average drug to antibody ratio (DAR) and the DAR profile for most ADCs → tight control over average DAR results in highly controlled drug distribution, including the level of DAR0 species
- Experiences with ADCs on the market and in late development have shown that they can be manufactured consistently. Figure below shows the comparability of the drug distribution between trastuzumab emtansine produced at a small lab scale and at full, commercial scale
- In the case of engineered monoclonal antibodies (e.g. Genentech's THIOMAB™) with a predetermined number of conjugation sites, the DAR distribution is less of a concern and shouldn't need to be controlled at the level of DS or DP production. DAR is controlled by the antibody intermediate sequence and drug distribution should only need to be verified during product characterization and comparability studies



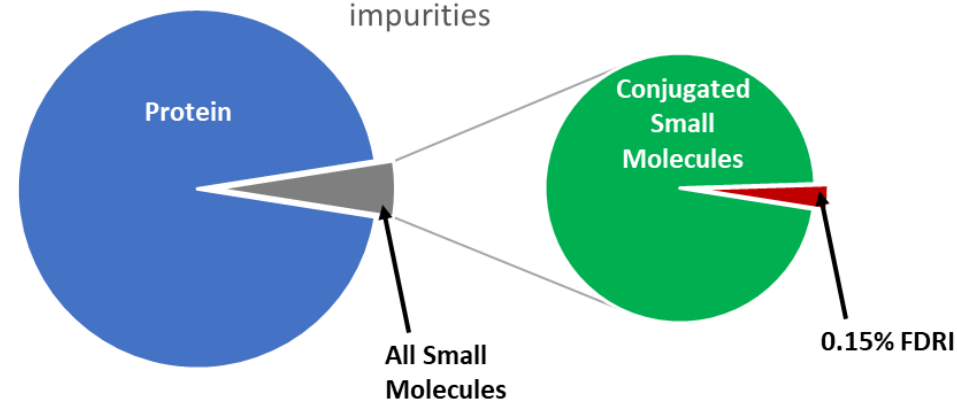
Drug distribution of trastuzumab emtansine produced at a small lab scale and at full, commercial scale both with average DAR of 3.5, assessed by RP-HPLC-ESI-MS

# Example FDRIs (Free-drug-related Impurities)

- 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
- ICH Q3 could be used to revise specifications and beneficial to reduce a historically high burden of testing and controls to a risk-based approach: a threshold of 0.15% FDI as impurity is acceptable, if the impurity is not “unusually potent”. As regards of our example brentuximab vedotin it has been confirmed at time of registration that the MMAE small molecule part or impurity is not pharmacologically active at doses up to 2.7 microgram/kg (equivalent to 0.15% of the impurity at 1.8 mg/kg every 3 weeks) and thus free MMAE should be categorized as “not unusually potent”.



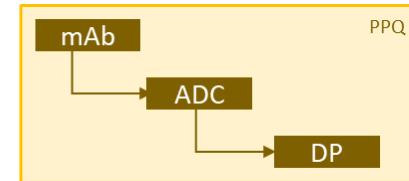
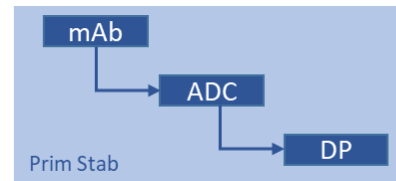
Mass ratio protein to small molecule, and mass ratio conjugated drug-linker to free-drug-related impurities



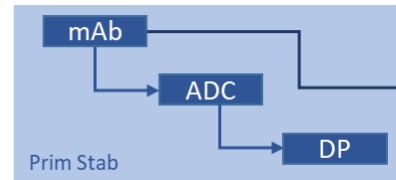
# Validation Concepts

- The manufacture of ADCs is a very long process that requires many steps and can be spread over several months. Classical validation (PPQ) of ADCs requires validation of finished product batches (DPs) using validated drug substance (ADC), itself made from a validated naked antibody and validated drug-linker intermediate as shown in scenario A
- An alternative strategy is to validate each manufacturing phase independently which would allow for some work to proceed in parallel. This is predicated on the idea that the main objective of the PPQ is the demonstration that the process performs as intended, and yields a product meeting its predefined quality criteria (scenarios B and C)

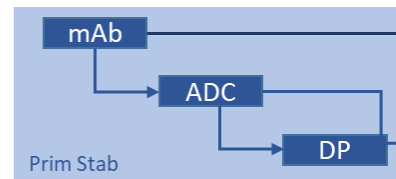
**A**  
Classical  
validation



**B**  
DS + DP in  
sequence



**C**  
DS from  
prim stab



# Flexibility in CTD interpretation and structuring

- **Option A: One DS folder dossier:** Drug, linker, drug-linker and naked mAb are drug substance intermediates (DI) which CMC information are presented within DS modules 3.2.S.2.4 and other relevant sections, division by subsections for each DS intermediate as necessary.
- **Options B: Multiple DS folders dossier (generally up to five) -** each folder has one set of documentation, 3.2.S.1 through 3.2.S.7.
- **We 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 (such as mAb DI) and DS. It should be the goal to reduce unnecessary or redundant work in order to facilitate the development of ADCs.**
- **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). This approach has been used successfully in the United States and Canada and we would like to encourage also other regions to consider introduction of DMFs**





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Thank you

# Backup Slides



# Take home message

- Modern validation concepts should allow parallel approaches and the combination of primary stability batches and PPQ batches, otherwise ADC validations are a time challenge due to the complex manufacturing processes.
- The submission of ADC products following the requirements of the Common Technical Dossier is not easy, because chemical small molecular raw materials, several intermediates and the drug substance have to be described. Flexibility in the design of the CTD up to the possibility of a DMF concept would be helpful.
- Finally, risk-based approaches for process changes should be accepted as naturally as is already the case for normal biologics.
- For the formulation aspect it should be emphasized that the stabilization of several intermediates, the drug substance and the drug product must be achieved, the formulation requirements cannot always be reconciled. As with other well-defined biologics, the trend is to provide liquid drug products.



## Knowledge and Experience gains as regards ADCs

- Compared to the early days of antibody-drug conjugates in the 2000s, we have now achieved major advances in process & product understanding (e.g. through intensive characterization work, improvements in linker technology, targeted integration, etc.)
- We have also gained increasing confidence in the good process consistency even for older methods based on data, and have obtained clinical data on the toxicology of impurities such as Free Drug Related Impurities.
- Overall, the progress achieved on this fascinating class of biotherapeutics is exciting. We are confident that both the Industry and the Regulator will take into account these improvements at the time of dossier generation/submission and subsequent review

# Overview over Conjugation Processes

