

Uniting Small Molecule and Biologic Drug Perspectives

Analytical Characterization and Regulatory Considerations for Antibody–Drug Conjugates

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Cosponsored by CASSS (an international separation science society) and the US Food and Drug Administration (FDA), the January 2010 CMC Strategy Forum explored antibody–drug conjugates (ADCs), which are monoclonal antibodies (MAbs) coupled to cytotoxic agents. The ADC platform of products is being used more and more for clinical evaluation in oncology. More than a dozen companies are developing several types, including products conjugated with calicheamicin, auristatins, and maytansinoids. Such products use the specificity of a MAb to deliver a cytotoxic drug to tumor cells. Depending on the chemistry of linkage, sites of attachment, and synthetic route for the small-molecule component, various chemistry, manufacturing, and control (CMC) issues arise during development and regulatory review of ADCs.

Determining the appropriate assays for characterization and quality assurance (QA) is important, as is identifying potential critical quality attributes (CQAs) for the conjugate, antibody, cytotoxic agent, and linker.

Conjugation technologies have improved significantly since Wyeth's Mylotarg approval in 2000, so this forum provided a good opportunity to discuss CMC requirements and regulatory approaches for an evolving



class of products. In addition to a provided list of potential discussion topics (as listed in the “Topics” box), plenary presentations by experts from both industry and FDA (listed in the “Speakers” box) provided the framework for the forum. Topics ranged from considerations for characterization, QA, and comparability to content and regulatory review of product submissions.

The general conclusion reached about ADCs at this CMC Strategy Forum was that it is best to have dialogue (formal meetings) with health authorities during the development of such products. Whether submitting to the US FDA, Health Canada, the EMA in Europe, Japan's PMDA, or any other regulatory body, ADC developers are covering new territory. At this stage, product sponsors and regulators are both learning as they go. Because ADCs are composed of both a MAb and a small-molecule cytotoxic drug,

TOPICS FOR DISCUSSION OF ANTIBODY–DRUG CONJUGATES

Regulatory approach for submission of products that incorporate both a small molecule and a biologic

Analytical methods for characterization and quality assurance of conjugates and their components; analytical challenges posed by ADCs; assessment of heterogeneity; biological assays for assessing potency and stability

Designation of different components as starting materials or intermediates or drug substances — and practical implications of such designations

Approaches and timing for process validation for ADCs and their critical components

Comparability assessments following manufacturing process changes for conjugates or their components

regulatory submissions will be reviewed by one or more health authority individuals who have the appropriate expertise to ensure that each aspect of a product is addressed.

DISCUSSION

What Assays Are Appropriate for Quality Control Testing and Characterization of ADCs? Quality control (QC) testing of an ADC needs to account for its identity, purity, concentration, and activity (potency or strength) — the same as for other

biopharmaceutical and pharmaceutical products. However, some specific features need special consideration because of the structural complexity of ADCs and the presence of their cytotoxic agents. In certain cases, assays developed for a MAb control system may not provide the same type of information about an ADC. As with all biopharmaceuticals, a significant number of methods can be used for molecular characterization of an ADC. This extended set of assays establishes its physicochemical and biological attributes and is appropriate for understanding the impact of the manufacturing process on the product. The entire set of assays may not be necessary for routine lot-release testing, but they are appropriate for significant comparability studies.

Identity: Methods used to determine identity must be adequately specific for an ADC to confirm that the product contains both essential components (the MAb and the cytotoxic drug). This is particularly important if an ADC is manufactured in facilities that may handle multiple products containing either the same chemical drug or the same MAb. At such multiproduct facilities, identity testing is essential to distinguish one product from another.

Both physicochemical and functional assays could be used orthogonally to confirm product identity. It might be possible to perform an immunoassay for the MAb moiety and a chemical identity assay for the small-molecule moiety, but both would require validation of specificity for the ADC.

Potency: In early development of ADCs, both ELISA and cell-based assays are valuable for generating data in assessing both target binding and cytotoxicity (the biological effect). For MAb products, an ELISA is often in place before a cell-based assay is available and is therefore the only potency assay used during early phases of development. For ADCs, however, it is expected that both an ELISA and a cell-based assay will be in place at such an early stage of development. Cell-based assays are important to demonstrate a product's mechanism of

action, which is to bind to an extracellular target, be internalized, and then kill the cell.

As discussed during the morning session, it may be possible in some cases to omit the ELISA from routine QC testing late in development (or upon commercialization) based on data demonstrating that the two methods produce similar information about the product. This decision would need agreement by the regulatory authorities. In such cases, the ELISA should continue to play an important role in characterization and comparability studies. Such an assay may be the only functional bridge between an unconjugated MAb and its conjugated form in an ADC. As a 1997 FDA points-to-consider document states, "Immunoreactivity should be assessed before and after conjugation" (1). So an ELISA or suitable alternative (e.g., surface plasmon resonance technology) for assessing binding can provide information about the effect of the conjugation reaction on an antibody. Even if some change is observed, as long as the ADC exhibits consistent binding from batch to batch (monitored during development), its affinity for the antigen may be measured as part of cell-based potency and thus not necessarily require a separate assay.

The terms *potency* and *strength* have different meanings depending on whether you're working with large or small molecules. ICH Q6A doesn't use the term *potency* for small molecules, but instead lists *strength* (or *assay*) as a measure of the amount of an active pharmaceutical ingredient (API); Q6B (for large molecules) uses the term *potency* as a quantitative measure of biological activity (2,3). An ADC includes both components. So its total function (or potency) would be measured with a cell-based assay that assesses overall structure, antigen binding, drug loading, and drug delivery. In this context, *strength* applies to the quantity of product (per milliliter for a liquid or per vial for lyophilate).

Heterogeneity: Because conjugation can occur at multiple, but not necessarily all, available sites on an antibody, many species of conjugate

SPEAKERS AND THEIR PRESENTATIONS

The morning and afternoon sessions each comprised presentations followed by interactive discussion among subject matter experts on the panel and the audience.

Morning Presentations

"Overview of the Antibody–Drug Conjugate Landscape" by Godfrey Amphlett (ImmunoGen, Inc.)

"Regulatory Considerations When Developing Assays for Characterization and Quality Assurance of Antibody–Drug Conjugates" by Marjorie Shapiro (CDER, OBP)

"Selecting Appropriate Assays for ADC Lot Release and Stability," by Fred Jacobson (Genentech, Inc.)

Morning presenters were joined on a panel by Himanshu Gadgil (Amgen), Claudia Jochheim (CMC consultant), and Sarah Pope-Miksinski (CDER, ONDQA). Session Chair Kathleen Francissen (Genentech) moderated.

Afternoon Presentations

"Current Review Processes and Regulatory Considerations for Antibody–Drug Conjugates (ADCs)" by Michael Folkendt (CDER, ONDQA)

"Antibody–Drug Conjugates: Development of Regulatory Submissions" by Tish Webber (Pfizer)

"Analytical Characterization and Scale-Up for Brentuximab Vedotin (SGN-35)" by Nathan Ihle (Seattle Genetics)

Afternoon presenters were joined on a panel by Chana Fuchs (CDER, OBP), Rajesh Krishnamurthy (ImmunoGen Inc.), and Anthony Ridgway (Health Canada). This panel was moderated by Jonathan Harris (Genentech).

molecules are generated for a given ADC. Because an ADC product is thus a mixture of conjugated species, appropriate tests are needed to measure heterogeneity and ensure product consistency. Routine QC testing and/or characterization may measure aggregates and fragments, charge variants, unconjugated MAb, average drug:antibody ratio, and drug distribution. Because of the heterogeneity of an ADC, isoforms derived from the antibody intermediate (e.g., glycosylation and other posttranslational modifications) are

most appropriately controlled at the point of MAb release. Techniques shown to be useful for analyzing ADC heterogeneity include hydrophobic-interaction high-performance liquid chromatography (HIC-HPLC), size-exclusion chromatography (SEC-HPLC), reversed-phase chromatography (RP-HPLC), capillary electrophoresis with sodium dodecyl sulfate (CE-SDS), mass spectrometry, and peptide mapping.

Some assays developed for MAbs will provide different information when used to test ADCs. Depending on the nature of the drug, linker, and site of conjugation, tools that typically work for MAbs may not provide an informative charge variant profile for an ADC. For cases in which the drug or linker is charged or linkage occurs through a charged amino acid (such as lysine), the underlying MAb charge heterogeneity (e.g., due to asparagine deamidation) is difficult to assess because conjugation affects the overall charge of the conjugated molecule. In such cases, the “charge profile” is often more of a “conjugation profile.” After discussing whether charge-variant profiles are important to ADC activity, forum attendees acknowledged that measuring the distribution of charged species can be a good way to demonstrate process consistency and thus should be included in an ADC comparability tool kit.

One sponsor’s presentation included evidence that within approved parameters of the company’s manufacturing process, average drug:antibody ratio (DAR) highly correlated to drug distribution. In this case, a specification was defined for DAR instead of distribution (which was measurable only using mass spectrometry). Information about the level of unconjugated antibody is included in either the DAR or the drug distribution data.

An ADC may include a previously approved MAb. In such instances, new analytical technologies that have emerged since development of the original antibody product should be evaluated for use in characterizing the related ADC. Consistent with the principles of quality by design (QbD),

THE CMC STRATEGY FORUM SERIES

The CMC Strategy Forum series provides a venue for biotechnology/biological product discussion. These meetings focus on relevant chemistry, manufacturing, and controls (CMC) issues throughout the lifecycle of such products and thereby foster collaborative technical and regulatory interaction. The forum committee strives to share information with regulatory agencies to assist them in merging good scientific and regulatory practices. Outcomes of the forum meetings are published in this peer-reviewed journal with the hope that they will help assure that biopharmaceutical products manufactured in a regulated environment will continue to be safe and efficacious. The CMC Strategy Forum is organized by CASSS, an International Separation Science Society (formerly the California Separation Science Society), and is cosponsored by the US Food and Drug Administration (FDA).

regulators expect sponsors to use the most current and effective technologies available to build product and process knowledge in controlling product quality.

Impurities: Because the small-molecule drug in an ADC is generally highly toxic, residual free drug will be a CQA. One approach to free-drug analysis for ADC drug substance and drug-product preparations is to precipitate the proteins (along with protein-bound drug) and analyze the resulting supernatant using a method that is effective for detecting the small molecule. It may be possible to present a comparison of free-drug levels in an ADC relative to the impurity level shown in ICH Q3(R2), which “sets out a rationale for the reporting, identification, and qualification of such impurities based on a scientific appraisal of likely and actual impurities observed, and of the safety implications, following the principles elaborated in the parent guideline” (4). In addition, the fate of impurities originating in the cytotoxic small molecule and/or linker should be considered to determine whether they are cleared during conjugation or are

carried over to the ADC drug substance or product (DS/DP). However, it may be impossible to detect such carry-over impurities in the drug substance and product because those amounts are likely to be very low.

Inclusion in a certificate of analysis (CoA) for routine testing of other product-related impurities — aggregates, fragments, charge variants, and unconjugated antibodies — discussed above should be assessed product by product. For example, data could be generated to show that unconjugated antibody is adequately monitored and controlled as part of DAR testing.

Regulatory agencies have expressed concerns regarding the presence of subvisible particulates (SVPs) in ADCs as well as in other biotherapeutic products. There are as yet no suitable analytical tools for consistently measuring particles with sizes below 10 μm in a release testing environment. To address potential immunogenicity concerns and demonstrate product quality and consistency, sponsors are expected to collect data on the particulate population between 1 and 10 μm . As new particulate characterization assays become available, sponsors will be expected to implement them. Particle characterization is required at the MAb intermediate level as well as the ADC DS/DP levels, with attention paid to any notable difference in size or characteristics between the MAb intermediate and the DS/DP.

Other process-related impurities — e.g., cosolvents used to increase the solubility of a drug or linker for conjugation — either need to be tested lot by lot to demonstrate clearance by the downstream purification process or included in process validation to demonstrate adequate removal relative to ICH Q3C (5). Chemical impurities other than free drug or drug-related substances may be evaluated with both ICH Q3(B) limits and pharmacology/toxicology input for the specific product (6). Some process-related impurities might be omitted from release testing with sufficient data and process experience over multiple ADC

lots or multiple ADC products using the same conjugation platform.

Reference Standards: Each intermediate (MAb, linker, and drug) should have reference standards in addition to the ADC reference standard, which will be used in designated release and stability tests. These standards are critical reagents used for analytical method system suitability and in characterization, stability, and bridging studies, as is currently expected for pharmaceutical and biopharmaceutical products.

Stability Testing: Sponsors must use stability-indicating methods to collect data to monitor the stability of ADC intermediates and a DS/DP throughout its shelf life. Companies will be expected to conduct comprehensive, systematic, forced-degradation studies to demonstrate inherent product degradation pathways. The morning panel recommended that a stressed sample panel be created to validate the stability indicating capabilities of methods for both the ADC and its intermediates. An ADC requires the same justifications as for any MAb when choosing or omitting methods in a stability protocol.

It is proving to be a challenge to measure the stability of a chemical drug once it has been conjugated to create an ADC. This is partly due to the size of cytotoxic agents relative to MAb moieties, and partly to the heterogeneity of ADC products. One suggested approach was the use of a surrogate study to monitor the stability of unconjugated (free) cytotoxic agents in the ADC formulation buffer and in the container-closure system. However, toxin stability tested alone in formulation buffer might not indicate the stability of the cytotoxic agent attached to the antibody because conjugation may change the nature and rate of degradation pathways. Additionally, the hydrophobicity and poor solubility of many drugs used for ADCs could make this approach impractical or fail to represent a protein-bound drug's stability.

Regulators are also interested in the cumulative stability of starting

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materials, intermediates, and drug substance through to the drug product.

Retained Samples and Test

Omission: Many analytical tests are necessary during ADC development for generating sufficient data to assess product consistency and stability. Some of these tests may be removed from a control system if sufficient data are available to support doing so, but such tests could still be valuable for characterization/comparability studies. Deciding to remove tests from the control system would require regulatory agreement. It is also important to consider that, although justification and approval may be granted to delete technically challenging tests, there is a risk that data on process consistency may not be obtained. Such data could eventually end up being very valuable to support postapproval process changes. To mitigate that risk, retain samples should be collected for retrospective analysis with previously omitted tests (and/or new methods) just in case additional data are needed to support postapproval changes.

Batch retains are also valuable materials to bridge testing if a better analytical method emerges later in a product's life cycle. New specifications may be appropriately established from historical lots with retrospective testing. However, this strategy may not be effective for all quality attributes. For example, particulates are likely to change over time, and test results at time of release may differ significantly from those of archived material.

How Do the Analytical Requirements Compare for the Conjugate and Its Components? An investigational new drug (IND) application is expected to have a complete CMC section for the small-molecule component (cytotoxic drug and linker) of an ADC, including a stability program. This expectation involves having stability-indicating methods developed and validated appropriate to the development phase. Adequate stability data should be submitted in an IND.

Some or all of that information may be filed in a small-molecule/linker drug master file (DMF) with the governing regulatory agency. However, a DMF might not be open to an ADC sponsor for review. The agency can review cited DMFs and may notify a sponsor about deficiencies, which then would need to be resolved by the DMF holder. But responsibility rests with the ADC sponsor to assure that all components are adequately characterized and controlled. The panel noted that sometimes third-party reviewers can be used to audit DMFs under confidentiality agreements with DMF holders and report gaps to the ADC sponsor.

For small-molecule intermediates that have compendia monographs, regulators consider such monographs to be the minimum standard for those chemical components when used in ADCs. If newer technologies are available, sponsors will be expected to have appropriate characterization and stability information necessary to assure the quality and stability of an intermediate above and beyond what is in its monograph. Chemical drug characterization must use current analytical methods, whether the drug was developed separately or as a part of an ADC.

MAb Component: In most cases the MAb intermediate in an ADC will be a novel entity that requires a complete CMC section of its own. ADCs also may be newly conjugated forms of previously developed but never-approved MAbs — or previously approved MAbs. In those cases, all MAb CMC information should be reviewed and updated to current

regulatory expectations for characterization, comparability, release, and stability testing. ADC sponsors need to perform gap analyses on the old CMC packages to find and correct deficiencies before submitting their IND to a regulatory agency.

In general, new and relevant analytical technologies that have emerged since the original small molecule, linker, or MAb was developed or approved should be evaluated for potential use during ADC development. Regulatory agencies expect that current analytical technologies will be used wherever appropriate to assure the quality and consistency of component materials.

Immunogenicity: Immunogenicity testing will be included in a clinical review. Assays for clinical immunogenicity testing (screening and neutralizing) are described in Module 5 (reports of biopharmaceutical studies) of the common technical document (CTD) used for submissions in Europe and the United States. Neutralizing assays must measure MAb binding as well as cytotoxicity function of the ADC.

What About ADC Process

Robustness, CPPs, and CQAs? For an ADC, CQAs are defined in the same way as they are for other therapeutics — namely, as a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure desired product quality (7). Detailed risk assessment and understanding of a conjugate's characteristics are used in determining which properties are CQAs. In some cases, the CQAs for an ADC may be shared with those of the starting MAb (e.g., aggregates and fragments); in other instances, they may be unique to the ADC (e.g., DAR, drug distribution, and free drug).

Robust ADC manufacture is possible because the chemistry of conjugation is well understood and is usually a simple chemical reaction. Process steps for clearance of unbound species are also fairly simple. Optimization of the conjugation process is amenable to statistical process development tools such as

single and multifactorial design of experiment (DoE) matrices. For example, reaction temperature, time, and pH can be studied using a DoE approach. Based on such studies and an assessment of the impact of process conditions on CQAs, it is possible to define critical process parameters (CPPs) and then set appropriate operating limits to yield a reliable manufacturing process. Examples of robust conjugation processes were presented at the forum, showing the reproducibility of resulting average DAR and drug distribution for an ADC product as well as the consistent removal of impurities. Those examples also demonstrated reproducibility of conjugation at multiple process scales.

Regulators at the forum noted that anything that could induce variability in a drug and/or linker during conjugation would require data to demonstrate process consistency. Justification and rationale for CQAs and CPPs can be evaluated using risk-assessment tools, an approach they highly encourage. Because only one ADC has been approved to date, regulators have little experience to leverage with regard to what might or might not be considered CQAs for an ADC.

Chemical drug product risk assessments have been useful to many regulators because they present a product sponsor's perspectives “on the record” and can stimulate discussion among reviewers very early in a review process. Biologic product risk assessments also are now beginning to be used in formal submissions for regulatory review. It will undoubtedly be valuable for ADC (and other biologics) manufacturers to outline their scientific rationale for CQAs and non-CQAs in their submissions. For small molecules or biotech products, such information is typically located in the pharmaceutical development section of their CTD submissions. For ADCs, it could be provided individually in sections for the respective components — or collectively in the DS/DP section (S.2.6 or P.2).

What Particular Challenges Are Associated with ADC Comparability Studies? To assess the effects of process changes on an ADC's safety

or efficacy, comparability studies should be conducted with a strategy similar to that used for biologics. Changes may be made in the MAb, linker, and/or cytotoxic agent manufacturing processes — or in the conjugation process itself. Product heterogeneity, process-related impurities, and product stability should be assessed. It is particularly important to distinguish expected lot-to-lot heterogeneities and variations in ADC impurity levels from differences related to a given process change.

Structural and functional elements of an ADC and all affected intermediates should be characterized for possible changes resulting from a manufacturing process change. Product sponsors are expected to use sensitive and specific separation methods with various sample treatments. Those could include separation based on charge, hydrophobicity/hydrophilicity, polarity, mass, native and denatured sample treatment, reduced and nonreduced sample treatment, and pre- and postconjugation sample analysis.

Regulators expect late-phase comparability studies to include selected side-by-side analyses of prechange and postchange lots. As mentioned, archived retains of all ADC batches and intermediate components produced during development, stored at -80°C or as appropriate for long-term stability, provide valuable material to use in comparability testing. Selected forced degradation of previous and current process lots should also be included to confirm comparability. If such a comparison shows differences in degradation profiles among those lots, it will be important to demonstrate that the new batches yield degradants that are comparable to those observed for the original process, providing a link back to the product used in earlier clinical studies. Another approach to evaluating old and new lots could be the use of aged (rather than new) MAb in the conjugation reaction. The results could show that aging the MAb does not negatively affect the quality of the ADC.

Changes made in linkers or cytotoxic drugs might be managed

under existing scale-up and postapproval changes (SUPAC) guidance for chemical products. However, it is the sponsor's responsibility to show that a changed chemical does not affect the ADC made with it. SUPAC might not include all elements that could substantially affect the use of a small molecule for an ADC. If the changes are not scale-up changes, then suitable small-molecule and ADC characterization should assess the potential effect of the change on both small-molecule and ADC quality and consistency. Changes to the synthesis that result in a different impurity profile are considerably different from changes only to scale.

What Regulatory Challenges Come in Filing an NDA for an ADC? At the time of this workshop, ADCs were regulated as drugs in the United States, so they would be subject to new drug application (NDA) filing. However, the regulatory landscape has evolved since then, and the Patient Protection and Affordable Care Act has been signed into US law. Reflecting the FDA's evolving consideration of ADCs, the agency has categorized two such products (brentuximab vedotin and trastuzumab emtansine) subsequently as BLA products. At the workshop it was stated that ADCs are not combination products; however, subsequently at least one ADC was classified as a such. Regardless of how ADCs are classified, because they comprised both small-molecule and antibody components, the CMC component of their regulatory submissions will continue to be reviewed by both ONDQA (Office of New Drug Quality Assessment) and OBP (Office of Biological Products) staff. But here we recap the workshop discussion that occurred before it was known that these categorizations would evolve.

NDA or BLA: In the United States, ADCs were regulated as drugs — with an NDA required. These products were not considered to be combination products. But the review paradigm continues to evolve. In Canada, ADCs are regulated as biologics; the country has not yet

approved an ADC, but many are in development for its market. Health Canada will draw from several existing regulatory approaches as needed, as will the FDA, to provide the most effective review for an ADC using the most appropriate subject matter experts.

Designation of Materials: Gemtuzumab ozogamicin for injection (Mylotarg), the first and at the time of our forum the only approved ADC, has recently come off the market. Its NDA was submitted by Wyeth (now Pfizer) including data on the linker, which was identified as an active component in the mechanism of action. Since then, Pfizer has had success in jurisdictions outside the United States with designating the linker instead of drug substance as its starting material. That designation does entail certain data requirements, but they are less onerous than a drug-substance designation, which facilitates making postapproval changes. Starting materials are discussed in ICH Q7 and in the draft of ICH Q11 (8, 9). For an ADC, key points to consider regarding designation of material include quality control for the starting material and the impurity profile's potential effects on the ADC DS.

Terminology can be both important and misunderstood. Due to differences in US regulations for drugs and biologics, the same terms may mean something different to small-molecule experts and antibody experts. We recommend that sponsors discuss with regulators what is intended by such terminology (e.g., *raw materials*, *starting materials*, *intermediates*, and *components*). These terms could ultimately determine the requirements for an ADC's control strategies.

CMC Review and Inspections: CMC reviews of ADCs in development are assigned by teams in the Office of Pharmaceutical Science (OPS) that include reviewers from ONDQA and the OBP. The Division of Monoclonal Antibodies (DMA) is the office within OBP that reviews ADCs. With each new ADC product, the lead review responsibility alternates between ONDQA and DMA.

Postapproval changes are also managed jointly by DMA and ONDQA. It was noted at the forum that “there is no brick wall between the offices. Open communication exists at the FDA.”

Regardless of which office has the lead review role, ONDQA and DMA each have specific responsibilities for different aspects of an ADC. The small-molecule components (linker and drug) and conjugation reaction are reviewed by ONDQA. The antibody component — by itself before conjugation, and then as part of the ADC — is reviewed by DMA. Reviewers noted that a common deficiency in ADC submissions is inadequate information regarding linkers.

In the United States, inspection logistics for ADC products are still evolving with regard to which FDA group(s) will send experts to the manufacturing sites for preapproval inspections. Many internal organizational changes have occurred at the agency since the first ADC was approved 11 years ago, and so far no other such product has reached the inspection phase. Although the offices of regulatory affairs and the commissioner (ORA and OC) were not represented at this forum, other FDA staff members expected that the team-based approach will always be the best for ADC inspections. Two ADC products have since been reviewed as BLAs, so the BMT/DMPQ (Biotechnology Manufacturing Team from the Division of Manufacturing and Product Quality), which takes the lead for inspections of biologics, will also take the lead for inspections of ADCs reviewed as BLAs.

Communications Between Sponsors and Regulators: The current increase in ADC products under development presents a mutual learning curve for both regulators and sponsors. Regulatory attendees strongly recommended early and continuing discussions with regulators, particularly at critical points such as before IND submission, at the end of phase two (EOP2), and before submission of an NDA/BLA. These conversations will help both sponsors and regulators navigate the learning

curve. Sponsors can get input on proposed strategies to stay aligned with emerging expectations and logistics for ADC product review — interactions that would be useful to discuss and document rationales for development strategies. Regulatory personnel would greatly benefit by learning early and throughout development what experimental techniques and analytical approaches have been used. Specifically, regulators commented that the FDA is rarely told what didn't work. Knowing what hasn't worked would be very helpful so that reviewers could adjust their expectations for submission content accordingly. The agency welcomes data-driven discussions about what has been shown not to be technically feasible or informative with regard to analytical characterization of ADCs.

What Is the Correct ADC Submission Content and Format? Because regulatory submissions for ADCs must cover the antibody, linker, and small-molecule cytotoxic agent, they are more complex than dossiers for either biologics or small-molecules alone. Following the standard format is not as straightforward as it might appear. Therefore, sponsors should discuss with regulators the best approach to using the CTD format (Module 3). One approach suggested at the forum is to create separate CMC subsections using the CTD outline for each component (drug, linker, and MAb), which then would be embedded in the DS section, although this might make that section unwieldy.

Another approach mentioned was to create a separate Module 3 for each component. Differences in formatting between biotech products and new chemical entities (NCEs) could be motivation enough to prepare separate outlines for these individual intermediates. This strategy could make it easier to update a file when process changes to components or conjugate are made later in the product life cycle.

Global Experiences: Regulatory agencies worldwide are mindful of comparability and stability issues that are possible in ADC development.

Inquiries have been made about the cumulative shelf life of ADCs spanning from the intermediates through DS and DP. Heath Canada and the EMA are evaluating ADCs as biologics. Although some guidance is available through ICH documents, more is needed. Currently no FDA guidance is in progress for ADCs, but it would be helpful given the rapidly growing ADC platform. The EMA has some limited guidance available, with more promised.

A MUTUAL LEARNING CURVE

At present, the ADC regulatory process represents a mutual learning curve for product sponsors, reviewers, and inspectors alike. The more sponsors discuss their ADC efforts with regulators, the more everyone will learn. Regulators want to hear from sponsors “early and often” regarding ADC plans, successes, and failures alike. Some gaps have been identified in the ADC analytical toolkit. The number of ADC programs currently under way indicates tremendous potential for this class of product. As regulators begin evaluating these programs, regulatory personnel and sponsors will be writing a new chapter in drug development together.

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