CMC Strategy Forum Report

Analysis and Structure Characterization of Monoclonal Antibodies

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Disclaimer: *It must be noted that the details contained in this manuscript reflect the discussion that occurred during two workshops, in addition to the personal experiences of the authors. However, this document does not represent officially sanctioned FDA policy or opinions and should not be used in lieu of published FDA guidances and points to consider or direct discussions with the agency.*

Monoclonal antibodies (MAbs) represent a major category of therapeutic and diagnostic recombinant products currently marketed or under development in the United States. The first MAb approved for US use was OKT-3 in 1986. Since that time, 19 other antibody products have been approved for either therapeutic or diagnostic use. These products have a variety of purposes including imaging of tumors and cardiac infarcts, prevention of ischemia, allograft rejection, respiratory syncytial virus–associated hospitalization, and treatment of non-Hodgkins lymphoma (NHL), B cell chronic lymphocytic leukemia, acute myeloid leukemia, metastatic breast cancer, Crohn's disease, rheumatoid arthritis, and severe persistent asthma.

Because of the importance of this category of recombinant products on the market, several statutory and guidance documents have been issued by the FDA recommending approaches for lot release and characterization (**1–5**). The points to consider document developed in 1997 contains the most specific information regarding testing of MAb and monoclonal conjugate (or radiological conjugate) products. Although that guidance document is quite useful to industry in clarifying the recommended approach to testing, many questions remain regarding which tests are most appropriate for lot release testing.

PRODUCT: MONOCLONAL ANTIBODIES

PROCESS FOCUS: TESTING

WHO SHOULD READ: QA/QC, REGULATORY AFFAIRS, PRODUCT AND PROCESS DEVELOPMENT

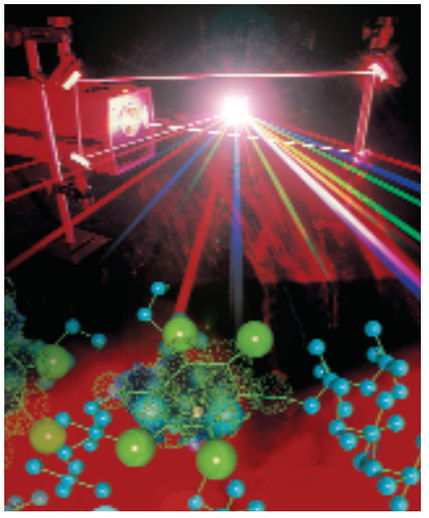
KEYWORDS: LOT RELEASE, POTENCY, CHARACTERIZATION, BIOASSAY, PHYSICOCHEMICAL

LEVEL: OVERVIEW (INTERMEDIATE)

A Strategy Forum

On 6 January 2003, 129 attendees participated in the second Well-Characterized Biotechnology Product (WCBP) Chemistry and Manufacturing Controls (CMC) strategy forum, titled "Analysis and Structure Characterization of Monoclonal Antibodies," held in San Francisco to discuss lot release and characterization test issues specific to MAbs. The California Separation Science Society (CaSSS) sponsored this forum. For a description of the WCBP CMC Strategy forum as well as information on CaSSS and some of its other meetings, see the "Strategy Forum" box (**6**).

The objective of the meeting was twofold: Identify a "core" set of assays most useful for lot-release testing of MAbs and define a mechanism for selecting appropriate potency tests. Two separate workshops were held as a part of the strategy forum discussing these topics in detail. The purpose of this article is to describe the discussion that



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The WCBP CMC Strategy Forum and *BioProcess International*

A Section of the California Separation Science Society (CaSSS): The WCBP CMC Strategy Forum provides a venue for industry and the FDA to discuss innovations and technologies in research and routine testing applications for biotechnology derived products. Of particular interest is the practical application of the latest biomolecular methods and instrumentation to biotechnology products in product characterization, process development, and validated in-process, release, and stability testing. At the annual Well-Characterized Biotechnology Products (WCBP) meeting, the forum will foster an environment for technical and regulatory discussion.

Oversight: CaSSS serves as the primary sponsor of the forum. The CaSSS board of directors and the WCBP permanent committee established a program planning committee (PPC) to govern the strategy forum. The initial committee was established from volunteers: Sid Advant (Diosynth RTP, Inc.), John Dougherty (Eli Lilly and Company), Rohin Mhatre (Biogen, Inc.), Nadine Ritter (American Red Cross), Mark Schenerman (MedImmune, Inc.), Brooks Sunday (Schering-Plough, now retired), and Anthony Mire-Sluis (FDA-CDER). The PPC is responsible for organizing and managing each workshop. It also maintains a WCBP CMC strategy forum topic list. Members solicit input regarding specific topics and their relative priority from numerous venues including WCBP symposium participant evaluations and periodic industry/FDA surveys.

Workshop Format: To provide adequate opportunity for FDA and industry involvement, three one-day workshops are conducted annually, the first scheduled in alignment with the WCBP annual symposium. Each workshop focuses on a maximum of two topics and begins with formal presentations by industry and/or FDA experts chosen and invited by the PPC, followed by breakout sessions for additional discussion on the technical and regulatory details of the topics. Those sessions will be facilitated by workshop presenters and/or other experts (selected by the PPC) and summarized by a PPC member or designee.

The outcome of those workshop discussions is envisioned to be the development of a draft technical/regulatory position regarding the topic of interest. Following the workshop, breakout session facilitators and others selected by the PPC will constitute a topic working committee (TWC) sanctioned by the PPC to draft a document describing the position established during the workshop. Draft documents will be presented to CaSSS members for their information and review and their comments and questions directed to the TWC for their consideration. When a harmonized document is finalized, the TWC will then prepare it in a format suitable for submission to *BioProcess International.* The deliverable from each WCBP CMC strategy forum can then be considered by the FDA in developing or revising good regulatory practice guidelines for biotechnology derived products.

occurred and to define the "core" set of assays that are most frequently used for MAb characterization and lot-release testing.

Physicochemical Test Methods

The morning session featured talks by three experts using a case study format to provide an industry perspective and approach to the test methods used for characterization and release testing of MAbs. Two afternoon discussion sessions provided an opportunity for attendees to exchange ideas with featured speakers and other expert panelists (see the "Panelists" box), providing further insight into the numerous test methods and approaches that can be used for MAb characterization (Table 1) and release testing (Table 2).

The goal of the roundtable discussions was to identity those "critical quality attributes" required to demonstrate product consistency for lot release — and the corresponding test methods used to determine those criteria. Thus, the first discussion focused on examining the physicochemical quality attributes of MAbs and the test methods required for their characterization (Table 1). Some questions considered include the following:

- What quality attributes best define purity and identity?
- Can a "core set" of quality attributes be selected for lot release?

The second discussion examined the question of which physico-chemical test methods should be used to assess the quality attributes of MAbs for lot release (Table 2). The questions considered were

- What if one assay is complementary to and more information rich than another so that it may preclude the use of one or more assays without loss of information?
- Can a "core set" of orthogonal assays be defined for lot release?

Panelists

The panel members were Weseley Wang (Amgen), Mark Plucinsky (Centocor), Wassim Nashabeh (Genentech), Rohin Mhatre (Biogen), Keith Webber (FDA-CDER), and Brooks Sunday (Schering-Plough).

The panelists in the **afternoon potency discussion** session were Mark Schenerman (MedImmune, Inc.), Steve Kozlowski (FDA-CDER), Kathryn Stein (Macrogenics), and Hélène Gazzano-Santoro (Genentech).

Acronyms Used

ADCC: antibody-dependent cellular cytotoxicity

BLA: biologics license application

CDC: complement-dependent cytotoxicity

CGE: capillary gel electrophoresis

CIEF: capillary isoelectric focusing

CZE: capillary zone electrophoresis

ELISA: enzyme-linked immunosorbent assay

ESI-MS: electrospray-ionization mass spectrometry

Fab, Fc, Fv: antibody fragments

FACS: fluorescence-activated cell sorter

HIC: hydrophobic-interaction chromatography

IEC: ion-exchange chromatography

IEF: isoelectric focusing

MOA: mechanism of action

NK: natural killer cells

NO: nitric oxide

PD: pharmacodynamics

PK: pharmacokinetics

QC: quality control

RI, RII, RIII: Fc gamma receptors I, II, and III

SDS-PAGE: sodium-dodecyl sulfate polyacrylamide gel electrophoresis

SEC: size-exclusion chromatography

Table 1: Test methods for drug substance characterization (supplementary tests that should be performed in addition to lot-release testing)

Method	Use (Impurities/Substances Detected)
ADCC, CDC, neutralization, etc.	Potency characterization
Isotyping	Verify IgG isotype
Peptide mapping with electrospray ionization mass spectrometry (ESI-MS) detection	Truncation, deamidation, oxidation, phosphorylation, substitution, alterations in oligosaccharides, incorrect sequence
Focused peptide map	Detect specific product-related impurity/substance (e.g., oxidation)
Carbohydrate composition	Determine monosaccharide and sialic acid content
Oligosaccharide profile	Determine oligosaccharides present
N-terminal and C-terminal content	Determine proportion of C-terminal lysine forms and N-terminal truncation and/or blockage
Western blotting	Heavy and/or light chain related species
Analytical ultracentrifugation	Detect and characterize aggregates
Matrix-assisted laser-desorption ionization time-of-flight (MALDI-TOF) mass spectrometry	Aggregates, breakdown products, verify mass
ESI-MS (intact molecule)	Aggregates, breakdown products, verify mass, nonglycosylated forms, and C-terminal variants

Determination of Quality Attributes and Lot Release Tests

Seven quality attributes and/or common structural characteristics of MAbs were evaluated to determine whether they constituted "critical quality attributes" that should be included in the strategy for release testing (Table 1).

1. Aggregation/Size: Aggregation is a key FDA concern in the development and manufacture of marketed MAbs. SDS-PAGE, CGE, and SEC (see the "Acronyms" box) are used for size analysis of MAbs. Light scattering and analytical ultracentrifugation are recommended and used during development to ensure comprehensive aggregate characterization. Aggregates are typically monitored for lot release and for stability testing with SEC under native conditions to determine both covalent and noncovalent aggregates. However, CGE is often used by industry as a size-based assay to profile MAbs and fragments because it can be more sensitive and easier to quantitate than SDS-PAGE. Both native SEC and CGE are recommended for lot release.

2. Molecular Weight: ESI-MS was demonstrated in a morning presentation as a QC release test for identity to monitor mass isoforms (IgG1s). It was agreed that ESI-MS is an excellent method to use during product characterization for mass determination (the identity testing of intact MAbs and fragments) because of its mass accuracy. Intact molecule ESI-MS also should be useful for elucidating oligosaccharide forms. However, ESI-MS was not regarded as an essential release test.

3. Free Sulfhydryl Groups: Sulfhydryl groups should be determined during characterization as an indication of correct protein folding. Ellman's Reagent — 5,5´ dithiobis (2-nitrobenzoic acid) — is recommended as a sensitive method to determine free sulfhydryls resulting from incomplete MAb folding.

4. Disulfide Structure: Confirmation of disulfide structure should be performed during development and prior to submission of a BLA. However, the FDA does not usually require full disulfide bond mapping unless it is thought that this parameter is related to product safety and efficacy. For example, novel antibody constructs such as Fv fragments may need additional structural characterization.

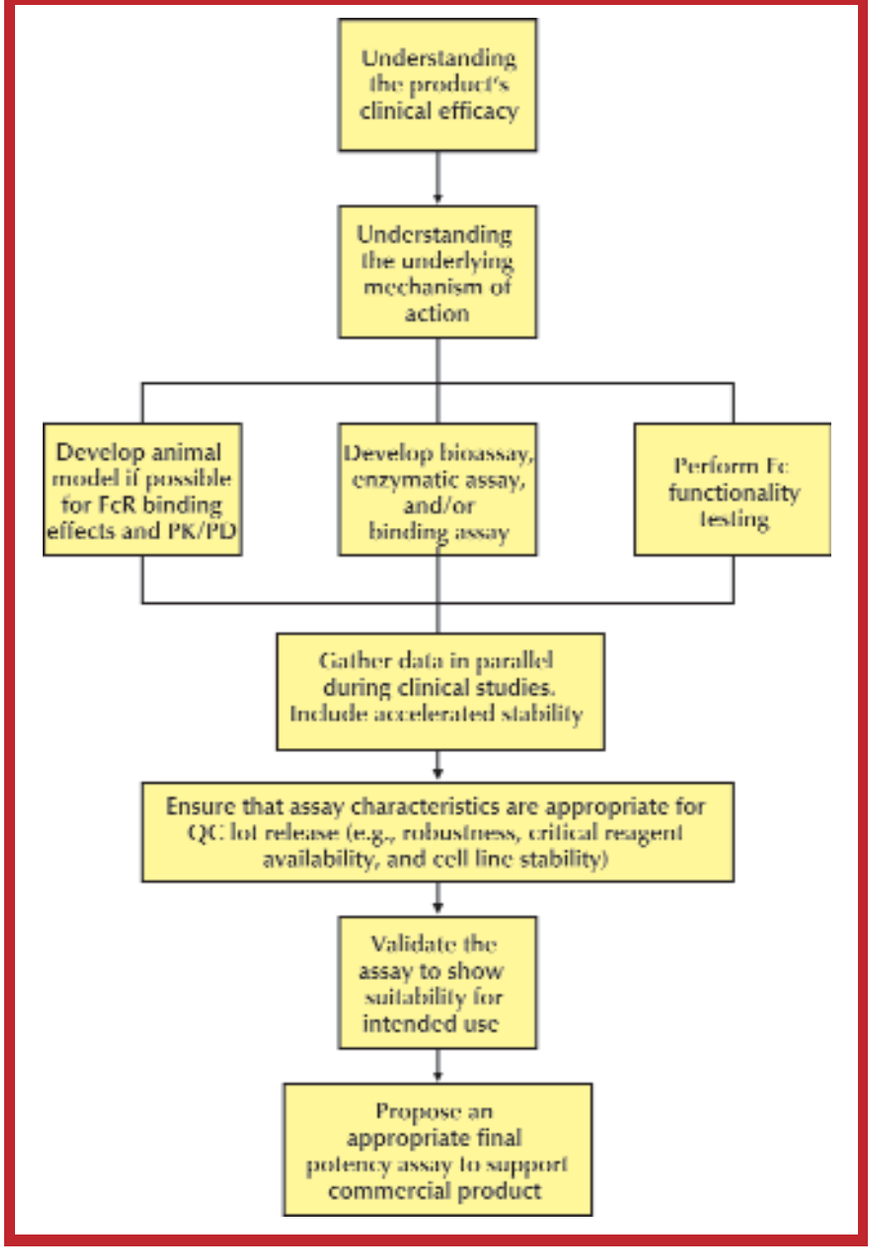
5. Heavy Chain Glycosylation (Oligosaccharides): A variety of methods are used during development to characterize oligosaccharides and monitor the consistency of MAb glycosylation. There does not appear to be a preferred test method to use when glycosylation monitoring is required. Monosaccharide compositional analysis is recommended to confirm qualitative and quantitative lot-to-lot consistency. However, glycosylation is typically monitored

as a release test only when it is directly related to product potency (when it is a "critical quality attribute").

6. C- and N-terminal Heavy Chain Heterogeneity: C-terminal Lysine (Lys) heterogeneity of the heavy chain is a common posttranslational modification present in IgGs that has been the subject of many discussions. Lys truncation does not appear to adversely affect product potency or safety. However, we cannot rule out potential C-terminal Lys effects on all antibodies. Lys truncation should be characterized, and process consistency should be demonstrated during product development. The FDA likes to see the range of C-terminal Lys heterogeneity reported in the characterization and development phases. It is a useful parameter for the characterization of reference standards and to demonstrate lot-to-lot consistency. Pyroglutamination of the heavy chain N-terminus is a common posttranslational modification in MAbs. It should be characterized during product development but is not typically monitored during release testing.

7. Fragments/IgG4 Half-Molecules: IgG immunoglobulins consist of four isotypes (IgG1–4). IgG4 is unique among those isotypes in forming both intact and incomplete half-molecules. IgG4 half-molecules consist of disulfide-bound light and heavy chains that have formed an intramolecular disulfide bridge, preventing intact MAb assembly. IgG4 half-molecules can be monitored using CGE, nonreducing SDS-PAGE, and SEC assays. The half-molecule can be measured in CGE purity analysis of MAbs and thus does not require a separate test. MAbs are typically monitored in their reduced and nonreduced forms during development. However, it should be noted that IgG4s must be tested as the nonreduced form to quantify the formation of any half-molecules. Release testing of the reduced MAb (IgG1–3) is preferred.

Figure 1: Strategy for potency assay selection



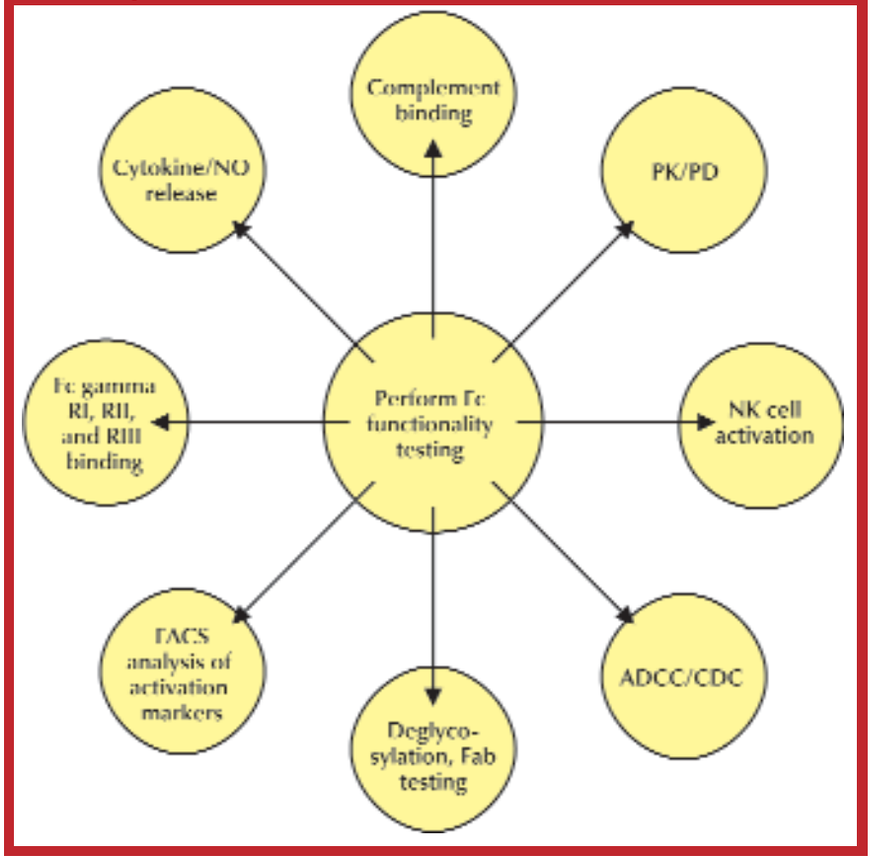
Summary

The preceding discussions led to a generally accepted view that release tests should be performed for those quality attributes that affect product performance (potency/safety) or stability, the "critical quality attributes" (Table 2). However, the agency may require tests for other attributes that might be sensitive monitors of batch-to-batch consistency yet not be critical to safety or efficacy. Such criteria are product-specific and must be defined for each MAb.

Test Method Types: Similarly, a "core set" of generic test methods for MAbs cannot be recommended because the test methods are directly related to those product-specific MAb "critical quality attributes" that affect product potency and safety. However, a "core set" of lot-release test methods (Table 2) can be designated for each individual MAb:

- *Identity* unequivocally identifies the product (by IEF, CGE, or specific binding activity, for example)
- *Native size determination* measures covalent and noncovalent aggregates under native conditions (using SEC or analytical ultracentrifugation, for instance)

Figure 2: A comprehensive set of tests that can be performed to evaluate Fc functionality; depending on the understanding of the MoA, one or more (or none) may be required for lot-release testing



• *Denatured size determination* measures the MAb and MAb fragments (with denaturing SEC, SDS-PAGE, or CGE)

• *Charge heterogeneity* assesses the variety of charged species (by IEF, CIEF, IEC, or CZE)

• *Potency* (see below).

Additional discussion is required to determine whether a "core set" of orthogonal assays may be defined for lot release. For example, charged-based QC release tests may be sufficient to determine C-terminal heterogeneity; CGE purity analysis of MAbs can be used to measure IgG4 half-molecules, and ESI-MS can be used to determine identity and oligosaccharide composition. The discussions indicated that, although it may be possible to use "information rich" test methods (such as mass spectrometry) as orthogonal tests for characterization and lot release, the current state of the art indicates a preference for assays that are easier to perform and control.

Potency Assays

The goal of this session was to discuss the issues regarding development and selection of an appropriate potency assay(s) supporting commercialization. The group (see the "Panelists" box) was asked to try and find a potential algorithm for making decisions about what type of potency testing should be done and when during the course of product development such decisions should be made. The categories of assays discussed included animal-based potency tests, cell culture–based bioassays, enzymatic assays, and binding assays (ELISAs).

Biological assays (bioassays) are intended to act as a measure of the functional capability of a biological product. In relation to biotechnology products — in this case, MAbs — the bioassay is used to determine potency, defined as "the specific ability or capacity of a product to achieve its biological effect." Potency should be considered a quality issue to ensure batch-to-batch consistency and comparability between materials used in pivotal clinical studies and those manufactured postapproval. It is only in clinical trials that the clinical "potency" is determined and dose ranges defined. However, one major consideration in the development of any bioassay format is its link to clinical efficacy because ICH guidelines state, "Mimicking the biological activity in the clinical situation is not always necessary. . ." and yet, "A correlation between the expected clinical response and the activity in the biological assay should be established. . . ." To make the link between a bioassay and clinical response, one needs to have an understanding of the mechanism of action (MoA) of the product.

Therefore, understanding the MoA must play a major role in the process of bioassay selection during product development. However, other factors must be considered during bioassay development so the final assay format closely mimics the MoA and can also function appropriately as a lot-release assay under cGMP-compliant quality control conditions. The development of bioassays required for lot release necessitates appropriate design, validation, and analysis if those assays are to provide reproducible and meaningful data regardless of their format. It is not always possible to completely understand the MoA, in which case more than one potency assay may be necessary. For example, if it is not known what role the Fc function plays in the MoA, additional potency assays testing the activity of the Fc portion may be required. Figure 1 depicts a decision tree of items that might be considered during the process of potency assay evolution.

After many years of experience developing and manufacturing MAbs, the process of bioassay selection does have some common themes. It is not unusual during the research phase of antibody development to have the two

Table 2: Most frequently used lot release tests for drug substance and drug product

Method	Use, Impurities or Substances Detected	ICH Q6B Category	Quality Attribute	Drug Substance	Drug Product
Protein concentration (A_{280} absorbance)	Measure protein concentration	Quantity	Dose	Yes	Yes
High-performance size-exclusion chromatography (HP-SEC)	Aggregates, protein fragments	Purity	Size	Yes	Yes
Ion-exchange (IEC) or hydrophobic-interaction (HIC) chromatography, isoelectric focusing (IEF), or capillary IEF	Deamidation, protein fragments	Identity, purity	Charge	Yes	Yes
Capillary zone electrophoresis (CZE) or native gel electrophoresis	Deamidation, protein fragments	Identity purity	Charge, size	Yes	Yes
Peptide mapping	Primary structure	Identity	Structure	Yes	No
Denaturing gel or capillary electrophoresis reducing or nonreducing	Protein fragments	Purity	Size	Yes	Yes
Antigen binding assay or other appropriate bioactivity assay	Potency	Potency	Activity	Yes	Yes
Host cell proteins[a]	Residual host cell proteins	Impurities	Impurities	Yes	No
DNA[a]	Residual DNA	Impurities	Impurities	Yes	No
Process-related substances and impurities[a]	Various process-related impurities	Impurities	Impurities	Yes	No
Endotoxins (*Limulus* amoeboyte lysate)	Detect endotoxins	Contaminants	Impurities	Yes	Yes
Sterility	Test for sterility	Contaminants	Impurities	Yes	Yes
pH	Measure pH	General	pH	Yes	Yes
Particulates	Impurities	Impurities	Impurities	No	Yes
Volume	Measure volume	General	Volume	No	Yes
Appearance	Evaluate color and clarity	General	Color/clarity	No	Yes

[a]It may be possible to eliminate lot-release testing for process-related substances and impurities if appropriate process clearance (removal) and process validation studies have been performed.

extremes of the assay spectrum, namely the in vivo assay (usually developed for proof of concept), and the binding assay (used for simple quantitation of material being manufactured at laboratory scale and for PK assays). It would be fortunate if some form of cell-based bioassay were available during the early stages of product development, although it is more often the case that cell-based assays are established later in the product development cycle — once a "go" decision for further development has been reached.

It is clear that an animal model with a suitable PD outcome is most likely to be the closest mimic of clinical activity. However, it is unlikely that such an assay would be suitable for lot-release testing for MAbs due in part to the inherent variability and the difficulty in routinely performing such assays within a cGMP-compliant control system. In addition, data available on the MoA may allow for a surrogate assay to substitute for such an animal assay.

The term "surrogate" is probably the crux of the lot-release assay selection process: How much data can we provide to ensure that any changes occurring from batch to batch that may affect bioactivity can be detected by the assay? For MAbs, the answer requires an understanding of the role of the two functional ends of the antibody molecule — the Fc and the Fab — in the MoA. Many techniques can be used to test the functionality of the Fc portion, and some of these are illustrated in Figure 2. However, it would be futile to carry out extensive testing without some understanding of the MoA. Proving that the Fc can induce ADCC, for example, does not necessarily mean that the assay has to become part of lot release if it can be shown that ADCC plays no role in the MoA. Therefore, although it is necessary to test each product using a wide range of Fc assays during product characterization, it is the understanding of the role of the Fc in the MoA that determines which of the various tests are selected for lot release.

The decision-making process concerning a bioassay to test the function of the Fab antigen-binding portion of the MAb is heavily influenced by the intended use and, once again, the MoA of the product. If the product is intended to prevent binding of a protein to a cell receptor (as with tumor necrosis factor binders), then it is likely that some form of cell-based bioassay will have to be investigated during selection of the lot release assay. The same is true for MAbs that bind adhesion molecules and prevent cell attachment and MAbs that bind cell receptors and induce apoptosis.

One question always arises: Because such MAbs function through the binding of their ligand, why is it not enough to use a binding assay as a potency assay

rather than to have a secondary cellular readout? The answer is that a correlation between antigen binding and the cellular/functional endpoint must be validated before one can consider using a binding assay for lot release. Data show that the results of a binding assay do not necessarily correlate with functional assays. An example is the case of a MAb intended to bind to a heterodimeric cell surface receptor and prevent the binding of another protein. The binding assay did not correlate satisfactorily with the functional, cell-based assay due to its inability to mimic the receptor mobility and subtle structure when bound on a microtiter plate. Another example is a degraded product that bound extremely well to antigen-coated microtiter plates and yet had a greatly reduced ability to prevent the same antigen binding to its receptor on the cell surface and induce apoptosis. Many binding assays suffer from this phenomenon because some MAbs may tend to get "sticky" when denatured or degraded.

However, that is not to say that binding assays cannot serve as lot-release assays, just that one should carefully compare them to other functional assays before resting assured that binding to the antigen alone does correlate to the intended biological endpoint. As shown in the examples above, careful consideration should be given during evaluation of the stability-indicating properties of a bioassay intended for lot release. As mentioned earlier, an important consideration when selecting any bioassay format is how well it would perform under the requirements of cGMP compliance. A biological assay used during the course of drug development should be appropriately designed if it is going to serve as a suitable lot-release assay. The bioassay may then be used to determine the suitability of binding assays regardless of whether there is a desire to migrate to a binding assay for lot release. Bioassay characterization plays a major role in this determination and should include the investigation of formats that may reduce inherent variability, statistical analysis to identify potential sources of variability, selection of stable and well-characterized assay components (such as cell lines), optimization of assay conditions, and selection of suitable internal controls and standards. Consideration of critical components/reagents and their availability, stability, cost, and ease of routine use can all affect the bioassay selection process.

Finally, the "validatability" of bioassay formats must be taken into account and should include careful examination of the performance of the active components (1). For cells used in bioassays, one should consider analyzing post-thaw activity and viability, stability, receptor

expression, and response over time as well as other more standard parameters described in ICH guidelines. Statistical tools such as trend charting, factorial assay design, and parallel line analysis are all valuable techniques for the validation of any bioassay format, although unique aspects of assay validation may be required depending on the assay (an enzyme assay compared with a cell-based assay, for example).

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