2

Are Biopharmaceuticals Really Different?

Few drug discovery stories have offered researchers as many chances for dismissive belief as the one William B. Coley launched with his bacterial lysate treatments of cancer. When Coley learned of a cancer survivor who coincidentally had suffered sever skin infection caused by *Streptococcus pyogenes*, he wondered if the bacteria had caused the patient's tumour to regress. In the 1890's he began injecting cancer patients with crude *Serratia marcescens* bacterial preparations that became known as Coley's toxins, with claims that some achieved lengthy remission. Many others who tried to repeat the results failed. Coley endured decades of derision from the American Chemical Society.

Coley's toxin – a possible precursor to today's anti-cancer biopharmaceuticals now known to induce fever (recombinant IFN, IL, TNF, etc.)

1. PERCEPTION OR REALITY?

It can be quite a shock for the person who has been working in the Chemistry, Manufacturing and Controls (CMC) area with traditional pharmaceutical drugs to move over and start working with biopharmaceuticals.

J. Geigert, *The Challenge of CMC Regulatory Compliance for Biopharmaceuticals*

1.1. Five Questions Frequently Asked

Three of the first questions that are often raised by new people about biopharmaceutical operations are:

1. Why does the cost have to be so high for operating and supporting the manufacturing facilities, especially the air handling and water utility systems'

2. 'Why is it necessary to have such a large number of staff, especially Quality staff; to support the manufacturing operations?'

3. 'Why is so costly to validate a biopharmaceutical process, especially the purification steps?'

Then when their attention is turned toward biopharmaceutical product inventory, two additional questions that are often raised are:

4. 'Why does it take so long, possibly even months, for the product to be released by Quality Assurance?'

5. 'Why can't we increase our product shelf-life by extrapolating from the existing stability data?'

1.2. Bottom Line Question

These five questions can be boiled down to the single critical question: Are the differences that are observed between biopharmaceuticals and chemically-synthesized drug products real or just perceived? From those of us who have worked in this industry for so many years, it is surprising that such a question would even be raised today. But then again, there are still people in the industry that feel that the differences are being made up either by the biopharmaceutical CMC consultants (for their job security) or by their own Quality Assurance groups (for their power trip). Unfortunately, this is not a healthy attitude for a company in this business to take.

But if there are real differences, and there are, it is most important that a company recognize such differences and properly address from a corporate strategic perspective the additional CMC regulatory compliance issues for their biopharmaceutical product.

2. REGULATORY AGENCIES SPEAK

The best answer to the question of whether the CMC differences that are observed between biopharmaceuticals and chemically-synthesized drug products are real or perceived comes from the regulatory agencies themselves.

2.1. U.S. FDA

The FDA believes very clearly that there is a difference between biopharmaceuticals and chemically-synthesized drugs:

- FDA answering why more CMC information on container closure systems is required for biopharmaceutical products than other drugs:

  "... there is greater potential for adverse effects on the identity, strength, quality, purity, or potency of biologics and protein drug products during storage or shipping."[15]

- FDA discussing the amount of CMC description of the method of preparation of the drug substance required for their review of Phase 1 INDs:

  "More information may be needed to assess the safety of biotechnology-derived drugs ...."[16]

- FDA discussing the agenda for CMC meetings with the agency:

  "The discussion of safety areas for conventional synthetic drugs is typically brief. For certain type of drugs, such as biotechnology drugs ... it may be appropriate to discuss the CMC information in more detail."[17]

- FDA explaining the scope of their comparability protocol guidance:

  "This guidance applies to comparability protocols that would be submitted in NDAs and ANDAs ..., except for protein products. A separate guidance will address comparability protocols for proteins as well as for peptide products outside the scope of this guidance."[18]

- FDA announcing the plan for moving some biopharmaceuticals from CBER to CDER:

  "It was again reiterated that under the new structure the biologic products transferred to CDER will continue to be regulated as licensed biologics."[19]

2.2. EMEA

EMEA believes that there is a difference between biopharmaceuticals and chemically-synthesized drugs:

- EMEA explaining its note for guidance on process validation:

  "The note for guidance ... It is not intended to apply to products of biotechnological ... since these processes are themselves very complex in nature and have an inherent variability which generally require the submission of more extensive validation data."[20]

- EMEA introducing its concept paper of PK and PD principles for proteins

  "An increasing number of new Marketing Authorization Applications for medicinal products concern peptides or proteins indicated for therapeutic or diagnostic use. The pharmacokinetic behavior of such compounds is generally different from that of "conventional" molecules and, consequently, alternative issues have to be considered when the development process is designed and study results are interpreted."[21]

2.3. ICH

The International Conference on Harmonization (ICH; tripartite agreements reached between the FDA, EMEA and the Japanese Ministry of Health, Welfare and Labor) believes there is a difference:

- ICH Q7A – GMPS for Active Pharmaceutical Ingredients, explaining why there is a separate section for biopharmaceuticals:

  "GMP principles for the manufacture of APIs for use in human drug products are not adequate for APIs manufactured by cell culture or fermentation using recombinant organisms."[22]

- ICH Q6A – Specifications for Chemically Synthesized Drugs, explaining the scope of this document:

  "This guideline applicable to drugs of synthetic chemical origin is not sufficient to adequately describe specifications of biotechnological and biological products."[23]

In fact, because of the difference between biopharmaceuticals and chemically-synthesized drugs, ICH has several documents that cover the same CMC topics but are applicable either only to biopharmaceuticals or only to chemically synthesized drugs:

CMC Topic	Biopharmaceutical Drugs	Chemically-Synthesized Drugs
Stability	ICH Q5C	ICH Q1A
Specifications	ICH Q6B	ICH Q6A

3. THREE UNIQUE CMC CHALLENGES FOR BIOPHARMACEUTICALS

With all of these comments from the regulatory agencies, there has to be a real difference between biopharmaceuticals and chemically-synthesized drugs! As a result, biopharmaceuticals should have unique CMC challenges. In fact they do, and the CMC challenges come from three areas:

1. The use of living recombinant organisms
2. The products themselves
3. The impact of the manufacturing process.

3.1. The Use of Living Recombinant Organisms

Biopharmaceuticals are the result of applying genetic engineering to living cells, whether it be bacteria cells, yeast cells, mammalian cells, viruses, whole animals or whole plants. These living hosts can provide an opportunity for amplification of various types of adventitious agents (e.g., bacteria, fungi, mycoplasma and viruses) during their production. The amplified adventitious agent can overwhelm the standard control procedures of the manufacturer and pose a safety risk to the patients intended to be helped by the biopharmaceutical. Biopharmaceuticals cannot be terminally sterilized which could have provided a barrier downstream of cell culturing.

Adventitious agent contamination is minimized by stringent adherence to current good manufacturing practices (CGMPs) and proper containment procedures, as well as careful, thorough quality controls and testing. But adventitious agent contamination cannot be entirely eliminated from a manufacturing process so contamination does occasionally happen. Should amplification of the agent occur, it is most important for the biopharmaceutical manufacturer to be vigilant for such an event and prepared to do what is necessary to protect the facility, the equipment and downstream processes from the adventitious agent. Ultimately, the manufacturer must demonstrate that the product is free of adventitious agents and thus poses no risk to the patient.

Risk management for biopharmaceuticals is an ongoing process because of working with these living organisms. And it requires staying current with new risks. Who was concerned in the early 1980's with the risk of bovine spongiform encephalopathy (BSE) being possibly present in the bovine components that we were using in the cell culture process? Who was concerned before the year 2002 about the risk of West Nile Virus being present in the human blood-derived components that could be used in their manufacturing processes?[24] Who was concerned before the year 2003 about the risk of the causative virus for Severe Acute Respiratory Syndrome (SARS) being present in these same human blood-derived components?[25]

3.2. The Products Themselves

Biopharmaceuticals, when viewed from a two-dimensional perspective, are really simple molecules composed of a handful of amino acids linked together in various lengths and combinations to form the primary protein chains, and many times having a handful of carbohydrates linked together in various lengths and combinations to specific amino acids on the chain (i.e., glycosylation). However, various manufacturing systems starting from the same gene can yield the same biopharmaceutical but with differing post-translational modifications (e.g., glycosylation patterns and protein heterogeneity). These changes may not always be readily detected by available analysis tools.

But, when biopharmaceuticals are viewed from a three-dimensional perspective, the major CMC challenges can be understood. For biopharmaceuticals, the maintenance of its three dimensional form, its molecular conformation, is critical, as it can have dramatic impacts on either the biological activity of the molecule, or its immunogenicity, or both, when administered to the patient. But the maintenance of molecular conformation is dependent on both covalent forces and non-covalent forces, which are often hard to control during the manufacturing process and also when the product sits in a container on the shelf.

Furthermore, the ability to distinguish one protein product from another is not trivial, after all, for the most part proteins have the same amino acids and carbohydrate components present. This places extra pressure upon the manufacturer to ensure that products are not mixed during manufacture or subsequent handling. Identity for a biopharmaceutical is more than showing that protein is present; it involves demonstrating that the specific protein is present. A simple 1 hour long infrared spectrophotometer fingerprint identity test for a chemically-synthesized drug can become a 1 week long peptide mapping fingerprint identity test for a biopharmaceutical.

3.3. The Impact of the Manufacturing Process

New technologies are often met with ultra-conservative CMC regulatory compliance controls. In the past when biopharmaceuticals were new and their technology and manufacturing processes were new, the FDA was treading cautiously and took the position that 'the process was the product'. CBER required two licenses for each biopharmaceutical feeling the need to control both the product (through a product license application, PLA) and the manufacturing process in its facility (through an establishment

license application, ELA). All biopharmaceutical process changes required FDA pre-approval prior to implementation.

Today, because of considerable experience with the biopharmaceutical products and their manufacturing processes, the FDA has now taken the position that 'the process impacts the process'. The FDA now requires a single license (a biologic license application, BLA, or a New Drug Application, NDA) and even now permits some biopharmaceutical process changes to occur without prior approval or within a 30-day window for pre-approval by the agency.

But this does not mean that there is not considerable concern about the control of the manufacturing process. The process can impact the molecular conformation as stated above, but the manufacturing process can also directly alter the product itself. During a bacterial fermentation process with recombinant *E. coli*, if the culture medium becomes methionine-depleted, the biopharmaceutical produced can have an incorrect amino acid, norleucine, incorporated into the molecule where methionine should be.[26] During a mammalian cell culturing process, if the process is not properly controlled, the resulting biopharmaceutical can have different carbohydrate isoforms present that can impact the *in vivo* activity and/or serum half-life of the molecule.[26] Additional concerns about the process impacting the product are discussed in Chapter 10.

There is considerable discussion today about whether the FDA will move their opinion about biopharmaceuticals to that currently accepted for chemically-synthesized drugs; that is, 'the process can be independent of the product'. While there are generic chemically-synthesized drugs (using an abbreviated NDA, and not being required to perform clinical trials prior to FDA approval), there is no equivalent for biopharmaceuticals. From this author's experiences and based on further CMC discussion in this book, it is difficult to see such a move for biopharmaceuticals. The risk that would be incurred in moving to 'generic biologics' can best be summed up by the following statement:

> "Safe and effective biological products can be assured only by extensive characterization of each drug substance and product, a well-defined and validated manufacturing process, and appropriate clinical trials to establish the safety and efficacy for that molecule".[26]

4. CMC MEETINGS WITH THE FDA TAKE ON GREATER IMPORTANCE

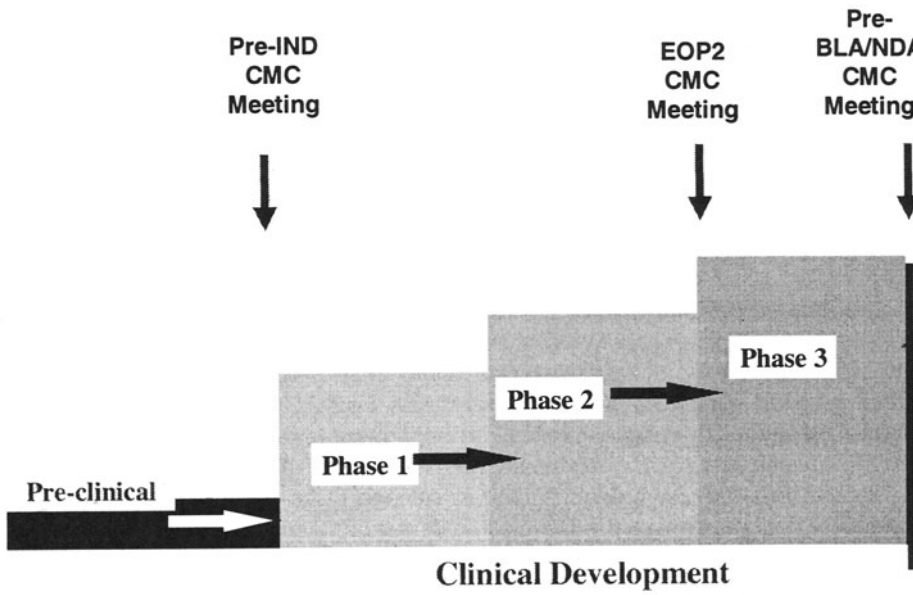
Because of the unique CMC challenges for biopharmaceuticals, maintaining an ongoing open dialogue with the regulatory agencies is critical for moving the biopharmaceutical through the clinical development stages and into the marketplace. The FDA in announcing its new strategic plan for beyond 2002 identified poor communication as a significant factor in causing unnecessary delays in new product approvals:

> "In addition, the findings of these retrospective analyses of causes for delays in approval emphasize the importance of communication between FDA and the sponsor during the product development phase so that various deficiencies can be addressed prior to submission of the application or avoided altogether by

better drug development practices. Clear understandings of agency expectations and timely communications between FDA and application sponsors can increase the likelihood that a submitted application contains the necessary information for timely approval in the first round. For example, insufficient FDA-industry interactions may result in late identification of important problems and other avoidable concerns that lengthen the time and cost of product development when discovered late in the development or review process and necessitate further data development and delays in product marketing approval."[27]

The FDA has identified 3 CMC specific meetings that could be of value to a company during the evolving stages of clinical trial development for a biopharmaceutical (Figure 3).

Figure 3. CMC specific meetings with FDA, of special importance to biopharmaceuticals



4.1. CMC Communication with FDA is Critical

It may not be clear to all why CMC specific meetings with the regulatory agencies are of extra importance to biopharmaceutical companies. There are still some companies that believe that they know more than the regulatory agency reviewers and they view their input as possible interfering with the direction that the company wants to move down: 'Why discuss that with the FDA, they may want us to do something differently?' and 'Isn't it a better use of our limited resources to focus our resources on the clinical meetings instead?' When these questions arise, you may need to convince your senior management of the value of these meetings.

A good start is to bring to their attention the comments from the FDA about the need for these CMC specific meetings, especially for biopharmaceuticals:

- Prior to Filing the IND: "The discussion of safety areas for conventional synthetic drugs is typically brief. For certain type of drugs, such as biotechnology drugs ... it may be appropriate to discuss the CMC information in more detail."[17]

- End of Phase 2: "The CMC portion of the EOP2 meeting is a critical interaction between the sponsor and the chemistry review team to ensure that meaningful data will be generated during phase 3 studies. The goal is to identify potential impediments to further progress at an early stage, thus reducing the number of review cycles for the proposed marketing application. Although the EOP2 meeting is important for all drugs, it is particularly important for new molecular entities, biotechnology drugs...."[17]

Also, it can be helpful to remind senior management that the FDA has continually encouraged companies to discuss CMC issues with them before they finalize their plans:

- "FDA urges manufacturers to consult with FDA prior to implementing changes that may result in comparability testing, in order to avoid delay in review of applications."[28]

- "Sponsors considering novel expression systems not specifically covered by guidance documents are encouraged to consult with CBER."[29]

It should be obvious that no meeting should be held unless there is a genuine reason. For biopharmaceuticals there are at least three primary purposes for these CMC specific meetings:

1. To address outstanding questions and scientific issues that arise during the course of the biopharmaceutical's development

This is especially important for new types of biopharmaceuticals or new manufacturing technologies that produce the biopharmaceutical product, where there may be limited existing CMC regulatory compliance guidance published.

2. To aid in the resolution of problems

   Every biopharmaceutical will encounter problems or challenges, and with the regulatory agencies' willingness to provide direction, they can provide assurance that the approach to be taken to resolve the problem will be satisfactory. Also, they have been known to suggest additional workable solutions that a company might consider for resolving the problem.

3. To facilitate evaluation by the regulatory agency of the biopharmaceutical

   The company, the regulatory agency and the patients all win when a new biopharmaceutical product is approved for the market. To avoid delays in approval, especially if expedited or accelerated drug approval is granted, a company's CMC issues must be handled effectively. Early interaction with the regulatory agencies is essential, as they ultimately have to accept the final CMC strategy and documentation.

4.2. Preparing for the CMC Meeting

But keep in mind, when preparing for a CMC specific meeting, follow the guidance provided by the FDA (Table 4). The FDA has provided detailed instructions on how to request a meeting, how to prepare the CMC briefing document and how to focus the meeting on specific CMC questions. Not following these administrative details can delay the scheduling of a meeting which could impact the forward progress of your product. A background briefing document is mandatory prior to the meeting. The goal of this submission should be to provide an easy to read and easy to understand account of the issues to be discussed.

Table 4. Instructions from the FDA on what companies should include in a request letter when asking for a CMC specific meeting [30]

The product name and IND number, if already assigned
Chemical name and structure
The type of CMC meeting being requested (Type A for stalled drug development programs; Type B for a standard meeting to review drug development progress; and Type C for meetings such as facility design, general product issues or general development)
A brief statement of the purpose for the meeting • This should include a discussion of the types of studies or data that the sponsor or applicant intends to discuss at the meeting • For new products, this should include a description and developmental status of the product, as well as its proposed indication
A listing of the specific objectives or outcomes that the requester expects
A preliminary proposed agenda, including estimated times needed for each agenda item and designated speaker(s)
A draft list of specific questions, as comprehensive and precise as possible
A list of all individuals (including titles) who will attend the proposed meeting from the sponsor's or applicant's organization and consultants
A list of requested participants or disciplines to be represented from the Center
The approximate time that a background package for the meeting will be sent to the Center (i.e., x weeks prior to the meeting), consistent with the type of meeting planned (Type A, at least 2 weeks; Type B, at least 1 month; and Type C, at least 1 month in advance)
Suggested dates and times (i.e., morning or afternoon) for the meeting

4.3. Pre-IND Meeting

The first key CMC meeting between the sponsor and the FDA is the pre-investigational new drug (pre-IND) meeting, which takes place prior to filing the IND to initiate Phase 1 clinical trials. For many first-product biopharmaceutical companies, this might be their first exposure to the regulatory agency.

CMC issues need to be discussed if they could lead to a potential clinical hold, and this especially applies to biopharmaceuticals. To have a rewarding dialogue and obtain the necessary agency guidance, the FDA requires a written briefing document to be submitted to them prior to the meeting (usually 4 weeks in advance). Table 5 presents some of the CMC issues that could be focused on during the pre-IND meeting for a

biopharmaceutical. Not that all of these areas need to be discussed but if there are issues with your biopharmaceutical manufacturing process or the biopharmaceutical itself, this is a great opportunity to seek FDA guidance.

Table 5. CMC issues recommended by the FDA for discussion at a pre-IND CMC meeting[17]

Physicochemical and biological characterization of the product
Manufacturers
Source and method of manufacturing
Removal of toxic reagents
Adequacy of cell bank characterization
Potential contamination of cell lines
Removal or inactivation of adventitious agents
Potential antigenicity of the product
Formulation, especially if novel excipients are used
Quality controls (e.g., identity, assay, purity, impurity profile)
Sterility (e.g., sterilization process, release sterility and endotoxin testing)
Stability information
Linkage of pharmacology and/or toxicity lots to clinical trial lots

From my experience, the regulatory agency's interest in having a pre-IND meeting increases if the biopharmaceutical is manufactured using either a new cell line (especially if there is an endogenous virus present) or a newer technology (e.g., transgenics). Interest also increases if the biopharmaceutical product has challenges (e.g., purification issues or unanticipated structural issues with the biopharmaceutical). Always keep in mind that the 'newness' of either the biopharmaceutical product or its manufacturing process will trigger interest from the FDA, and the unknowns will most likely then trigger a conservative regulatory agency response. Assurances will have to be provided that the

company will be able to exercise adequate CMC control during the manufacturing and release of the biopharmaceutical for clinical trials. Following up on these assurance will bring confidence to the FDA about the company's commitment to quality and compliance.

Less one think that the CMC at Phase 1 is not considered significant by the regulatory agencies, the FDA has stated that if they believe that there are any reasons that the manufacturing and controls for the clinical trial product presents unreasonable health risks to the patients, that they will delay or suspend all or part of the clinical work requested in the IND. Specifically, they include the following CMC examples as unreasonable health risks to the patients[16]:

- Product made with unknown or impure components
- Product possessing chemical structures of known or highly likely toxicity
- Product that cannot remain chemically stable throughout the testing program proposed
- Product with an impurity profile indicative of a potential health hazard or an impurity profile insufficiently defined to assess a potential health hazard
- Poorly characterized master or working cell bank

4.4. End of Phase 2 (EOP2) Meeting

The second key CMC specific meeting between the sponsor and the FDA is the end of Phase 2 (EOP2) meeting, which usually takes place prior to initiating the pivotal clinical trial. Although the EOP2 meeting is important for all pharmaceuticals, the FDA considers this meeting especially important for biopharmaceuticals to ensure that potential impediments to further progress at an early stage are identified.

From my experience, biopharmaceutical companies are not committing adequate resources to properly prepare the written briefing document that must be submitted ahead of time to the agency. The easier that it is for the FDA reviewers to understand the concerns, the more confidence that a company will have in the final agreements reached with the agency. A list of CMC questions should be included in the briefing document and they should be specific, comprehensive and precise as possible to identify the critical issues. Also, sufficient CMC background should be included to allow the regulatory agency to address the specific questions. The company should understand that this CMC meeting provides them the opportunity to present their results of the biopharmaceutical development program to date for evaluation by the agency. This meeting provides the company the ability to identify and resolve, if possible, any specific safety or scientific issues or problems prior to initiation of the Phase 3 studies. This meeting provides the FDA the opportunity to identify additional CMC information that the company might need to generate important to support a future marketing application. In other words, this is a very critical meeting for both the FDA and the company, and the company should

prepare accordingly. The FDA requires the written briefing document to be submitted to them prior to the meeting (usually 4 weeks in advance).

Table 6 presents some of the CMC issues that could be focused on during the EOP2 meeting for a biopharmaceutical. It is important that the company use this opportunity of discussion with the agency to resolve any major CMC issues that could ultimately delay product approval. This is not the time for a company to hold back and be shy about its CMC issues!

Table 6. CMC issues recommended by the FDA for discussion at an EOP2 CMC meeting[17]

Unique physicochemical and/or biological properties of the product
Adequacy of physicochemical and biological characterization studies (e.g., peptide map, amino acid sequence, disulfide linkages, higher order structure, glycosylation sites and structures, other post-translational modifications, and plans for completion, if still incomplete)
Coordination of all manufacturing activities, including full cooperation of Drug Master File (DMF) holders and other contractors and suppliers in support of the planned BLA/NDA
Starting material designation
Adequacy of cell bank characterization (update from Phase 1/Phase 2, plans for completion, if still incomplete)
Removal or inactivation of adventitious agents (update form phase 1, where applicable)
Removal of product- and process-related impurities (e.g., misfolded proteins, aggregates, host cell proteins, nucleic acids)
Bioactivity of product-related substances and product-related impurities relative to desired biopharmaceutical
Approach to specifications (i.e., tests, analytical procedures and acceptance criteria)
Bioassay (e.g., appropriateness of method, specificity, precision)
Approach to sterilization process validation and/or container closure challenge testing, where applicable
Appropriateness of the stability protocols to support phase 3 studies and the planned BLA/NDA
Linkage between formulations and dosage forms used in preclinical, clinical and pharmacokinetic and pharmacodynamic studies, and formulations planned for the BLA/NDA
Major CMC changes, including site changes, anticipated from phase 2 through the proposed BLA/NDA, ramifications of such changes, and appropriateness of planned comparability and/or bridging studies, if applicable
Environmental impact considerations, if pertinent
Identification of any other CMC issues, including manufacturing site, which pose novel policy issues or concerns, or any other questions, issues or problems that should be brought to the attention of the Agency or sponsor

From my experience, the following are the top 5 CMC hot topic issues for a biopharmaceutical product that the FDA wants to discuss at the EOP2 meeting:

- Sufficient product characterization

  Does the company really understand their molecule?

- Product comparability after process changes

  Will the product really be the same after future process changes?

- Management of outsourced CMC

  Who's in charge at the contract manufacturer(s)

- Bioassay (Potency)

  What is the biological function assay?

- Company's approach to justifying specifications/stability

  Does the company have a strategy?

4.3. Pre-BLA/NDA Meeting

The third key CMC specific meeting between the sponsor and the FDA is the pre-biologics license application (BLA) or pre-new drug application (pre-NDA) meeting, which usually takes place about 6 months prior to the submission of the marketing authorization. With respect to CMC requirements, the meeting is to ensure that the proposed dossier submission is well-organized and complete. The goal of the meeting is to resolve any CMC problems that could cause a refusal-to-file recommendation by the agency or hinder their review process. As with the other CMC meetings, the FDA requires a written briefing document to be submitted to them prior to the meeting (usually 4 weeks in advance).

Table 7 presents some of the CMC issues that could be focused on during the pre-BLA/NDA meeting for a biopharmaceutical. Note, that this meeting provides an opportunity for the FDA to obtain assurances from the company that it will have all of the required CMC content in the submitted dossier and that the company is ready for a pre-approval inspection at the time of filing.

Table 7. CMC issues recommended by the FDA for discussion at a pre-BLA/NDA CMC meeting[17]

Discussion of the format of the proposed marketing authorization, including whether an electronic submission will be provided
Confirmation that all outstanding issues discussed at the EOP2 meeting or raised subsequently will be adequately addressed in the proposed filing
Assurance that all activities in support of the filing have been coordinated, including the full and timely cooperation of DMF holders or other contractors and suppliers
Discussion of the relationship between the manufacturing, formulation, and packaging of the drug product used in the phase 3 studies and the final drug product intended for marketing, and assurance that any comparability or bridging studies agreed upon at the EOP2 meeting have been appropriately completed
Assurance that the submission will contain adequate stability data in accordance with stability protocols agreed upon at the EOP2 meeting
Confirmation that all facilities (e.g., manufacturing, testing, packaging) will be ready for inspection by the time of the BLA/NDA submission
Identification of any other issues, potential problems (especially those that could lead to a refuse–to-file recommendation), or regulatory issues that should be brought to the attention of the Agency or sponsor

From my experience, one or more of the following three CMC issues are usually the focal point of the pre-BLA/NDA meetings for a biopharmaceutical:

- Can the company document that it has honored its commitments made previously to the FDA?
- Can product comparability be demonstrated (especially if scale up or process changes are planned after the pivotal clinical studies are completed)?
- Does the company understand the extent of full CMC content needed in the filing of the dossier?

It is important that the company use this opportunity of discussion with the agency to resolve any major CMC issues that could ultimately delay product approval. Since the FDA will see the CMC issues later in the submitted dossier or during its pre-approval inspection, this is not the time for a company to hold back and be shy about its CMC issues!

Having full CMC content in the filed BLA/NDA is not a negotiable issue with the agency. The FDA can issue a refusal-to-file (RTF) for any biopharmaceutical dossier that is incomplete in the following CMC issues[31]:

- Incomplete description of relevant cell banking systems
- Omission of data demonstrating consistency of manufacture
- Incomplete data demonstrating equivalency to clinical trial product when significant changes in manufacturing processes of facilities have occurred
- Failure to describe changes in the manufacturing process, from material used in clinical trials to commercial production lots

And having a dossier RTF'd becomes an issue for public reporting by the company. This is clearly not something that any senior management wants to have to deal with.

5. WHAT ABOUT CMC MEETINGS WITH EMEA?

Unfortunately, the EMEA is not as accessible to biopharmaceutical manufacturers during the clinical development stages as with the FDA. The EMEA relies heavily on published guidances to guide the industry. However, EMEA does have an official procedure where a company can request scientific guidance.[32] But this guidance has the following limitations:

- Scientific advice will be given by the CPMP on questions concerning specific issues relating to the manufacturing of the product
- Scientific advice is restricted to purely scientific issues
- Scientific advice is not binding to the EMEA with regard to any future marketing authorization of the product concerned
- It is not the role of the CPMP to substitute the industries' responsibility in the development of their products

In the United States, we can be thankful for the open door communication policy of our FDA.

6. BIOPHARMACEUTICALS NEED TO BE TREATED DIFFERENTLY

Biopharmaceuticals are truly unique. The use of genetically modified living organisms for production, the uniqueness of the biopharmaceuticals themselves, and the impact of the manufacturing process on the product, all create the CMC regulatory compliance challenges that will be discussed in great detail in the following chapters.

The need for active involvement with the regulatory agencies during the clinical development of these products is paramount. Use every opportunity to obtain FDA guidance. Biopharmaceuticals move faster through the regulatory review process when companies treat FDA reviewers as team members.

The FDA has the major task to keep pace with the development of biopharmaceuticals, and, in my opinion, the / have done a remarkable job, especially considering the diversity of biopharmace ticals that they must regulate. FDA's regulation of these products, as stated by the regulators themselves, "should be based on sound science and good sense".[33] It is the hope of the biopharmaceutical industry that this practice continues.