PRA Health Sciences

WHITE PAPER

Chemistry, Manufacturing, and Controls (CMC)

CMC in Drug Development and Life Cycle Management

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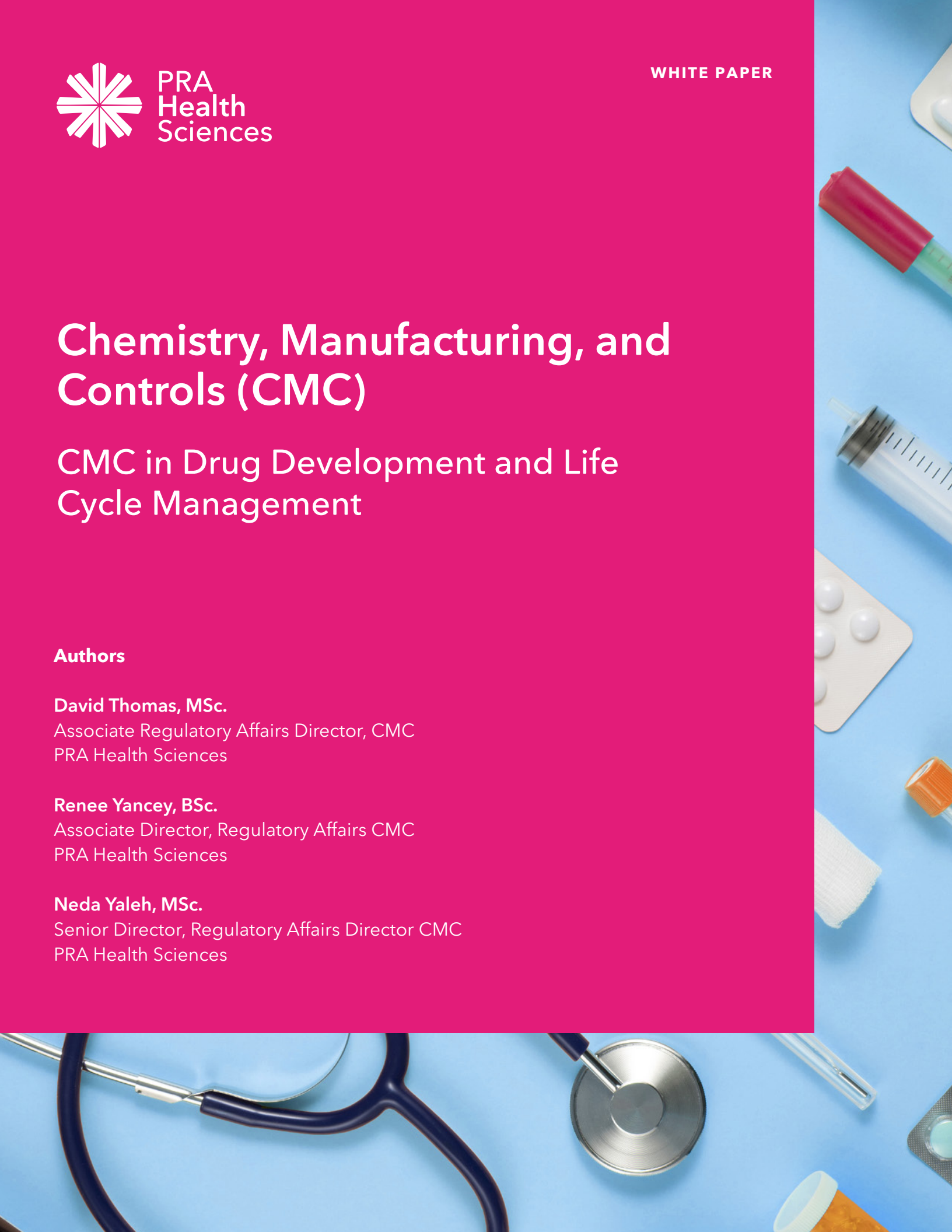

Executive Summary

The United States Food and Drug Administration (FDA) and other health authorities (EMA, etc.) require a well-defined and consistent drugs and biologics development process. This is possible by the chemistry and manufacturing and controls (CMC) activities during the development process. The CMC activities ensure methods are validated, raw materials are chosen and tested, and the product meets the set specifications for purity according to the established guidelines.

The US FDA and other health authorities also require that manufacturers of drugs and biologics determine category(ies) and report changes in the CMC information (e.g. production process, quality controls, equipment, facilities, etc.) of an approved license application. Although not legally binding, numerous guidance has been published by the US FDA1,2 that describes the current thinking of the agency on the topic and provide recommendations on the reporting categories.

During product development, the CMC helps maintain the connection in quality between the drug used in clinical studies and the marketed drug as changes in manufacturing impacts drug quality according to the current Good Manufacturing Practices.

In post-approval, the CMC ensures all required criteria for quality and regulatory are met for change implementation to ensure product quality continues to meet the standards.

The CMC is essential for drug approval and lifecycle management and it must comply to the FDA regulations known as the Current Good Manufacturing Practices. Current Good Manufacturing Practices or Good Manufacturing Practices are referred to as “cGMP” or “GMP.”

Goals of the cGMP:

- The marketed drug product is demonstrated to be safe and effective in the clinical target animal safety and effectiveness studies
- The manufacturing process consistently yields a product meeting approved quality attributes
- The drug product will maintain its quality attributes throughout its shelf life

This white paper provides emerging companies and biotech companies a significant overview of the considerations for CMC. There are a multitude of complexities and points to consider when developing an asset, and product development is at the center of all development. It is imperative that companies that are developing small molecules, large molecules, and biologics have a full understanding of what will be required in the development of their asset. What is required will vary whether it is a biologic or drug. Selection of the right development partner, who has experts in all aspects of CMC, is a critical first step as an asset is developed. This begins ‘at the beginning’ and includes both the FDA and other health authorities (EMA, for example). Both emerging and biotech companies need to consider the investigational product (IP) for clinical trials. This paper will provide greater detail and discussion on how the right development partner can ensure there is a consistent ‘end-to-end’ process and continuity in the development of your asset.

At PRA Health Sciences, we work closely with our clients to understand their product and processes to ensure compliance and supply continuity while adhering to the applicable regulatory requirements. Our global teams have the expertise to assess CMC changes in major markets, are able to determine global CMC strategies, file necessary regulatory applications, and work with local affiliates and governments to establish a single point of contact and respond to queries to ensure timely approval.

The identification of a promising target/monoclonal antibodies (mAb)/biologic is just the start of a long journey to a successful product approval. While the focus of development is typically focused on pre-clinical and clinical aspects, an early focus on Chemistry, Manufacturing and Controls (CMC) is essential to ensure a successful product and the shortest path to approval.

This is especially important and pertinent for companies which are focusing on mAbs (and other biologics), as opposed to small molecules. MAbs cannot undergo complete characterization like in small molecules due to size, while the variable and hypervariable sections are important for antigen binding specificity. This, along with other issues which your development/CMC partner can help to identify, are critical to find early; issues found later on can be very costly in time and money.

Some of the major CMC related steps to consider are listed below:

CMC Considerations

- Upstream process
- Downstream process
- Structural characterization
- Functional characterization
- Process/Analytical
  - Formulation
  - Glycosylation
  - Impurity profile
  - Stability

Why is CMC a critical component in drug development?

As a product is developed, the manufacturing process and controls increase in complexity, so it is critical to assure all of the CMC components are captured and managed. Development of a new biologic requires overcoming a number of technical challenges, but lack of knowledge in the following areas can result in unnecessary delays in product development:

- Agency expectations for CMC data at each stage
- Knowledge of acceptable changes during development
- Comparability requirements with product scale-up
- Factors to address with manufacturing site changes
- Identification of appropriate analytical methodologies
- Defining the acceptable level of impurities/degradants
- Providing the necessary information from clinical trial formulations to commercial presentations

Why is it important to ID issues early?

It is very expensive and time consuming to have to go back and re-start development due to an issue with the chosen process or molecule. A knowledgeable partner can be a valuable resource providing understanding of the issues allowing early Agency contact to request insight and direction and help address areas such as:

- Identification of current CMC gaps
- Regulatory strategy to proactively address CMC concerns
- Identification of potential future issues with scale-up
- Conducting risk analysis and contingency plans
- Providing expert resources with multi-company and regulatory authority experience
- Adding needed technical expertise to address Agency questions
- Meeting and Briefing book preparation

Why are Contract Manufacturing Organizations (CMO) critical to success?

- A relationship where you work well with the CMO is beneficial to your supply chain – the ability to make changes or consistently meet supply chain demand can make or break a product
- Stock outs, equipment issues, methods issues, and out-of-specifications (OOS), along with the associated investigations, are crucial to be successful managing a CMO
- Response time back to clients, response time to health authorities, and top notch change control are some of the things that allow success at CMOs
- Need to understand and weigh the nuances/risk of where you want to manufacture – some CMOs with facilities that are working on the "edge of GMP" = cheaper price per unit is not always better

- The GMP facility is critical to the life of the product. CMO or internal sites – if they do not function well, then product supply is impacted, and patients are ultimately impacted.
  - PRA has two GMP facilities in which they offer CMC services in a role as a small CMO under full cGMP

What are other key issues to consider?

- Early sample retention is essential to be able to bridge early development tox/ Pharmacokinetic (PK)/Pharmacodynamics (PD) work to later manufacturing processes and improved assays
- Perform enough assay qualification to prove suitability with your product – don't rely on what others are using
- Onsite tech transfer presence will result in fewer issues and a more successful manufacturing campaign
- Evaluate the product "for now" while also looking to the future, as most products grow and expand (i.e. do you need in-vitro in-vivo correlation (IVIVC) or Bioequivalent (BE) studies, or various zone stability studies to support future growth)

Small molecules remain prevalent in both development pipelines and on the market in today's Pharma world and are still the majority of the therapeutic dosage forms manufactured today because they consistently deliver results to patient. It's about a good old-fashioned organic group of small chemical compounds with a small molecular size made from synthetic chemical reactions. Small molecules do not necessarily mean old drugs, but many have been around for years, even being reinvented for new indications. The growing trend is cutting edge drugs, often tailored to fit very specific genetic subsets of patients.

One critical issue that the FDA has been more focused on is the evaluation of the chemical properties and the criticality of excipients in the formulation and when making changes. Recent experience shows that the following should be included in this type of change:

- All monograph and manufacturer specification parameters
- A comparison of these test results for the excipient pre- and post-change, to determine if there is a statistically significant difference
- A comparative evaluation of physical properties based upon the physical form of the excipient and its functionality as well as the specification between the RM manufacturer and user
- The effect of the change on bioburden, particularly for excipients susceptible to microbial growth
- Change in origin can involve the country of origin, geological origin, or species of origin for the raw material, Bovine Spongiform Encephalopathy (BSE), Transmissible Spongiform Encephalopathies (TSE), and Genetically Modified Organisms (GMO)

At PRA, our teams provide the expertise in the small molecules and large molecules/biologics space and they are able to assist organizations do the necessary work to obtain marketing authorization and maintain products in the market. Our regulatory affairs CMC team focuses on the manufacturing and quality control changes, which include but not limited to, the following post approval changes in (1) components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) container closure system, and (6) CMC related labeling, as well as (7) miscellaneous changes and (8) multiple related changes. Our CMC team also supports the writing of the Investigational Medicinal Product dossier (IMPD), which is an essential document that forms part of the Clinical Trials Authorization (CTA) submitted to the EU Competent Authorities for non-authorized IMPs.

PRA's Early Development Services offers CMC services in a CMO role in one of our two GMP facilities, based in US and EU, to support manufacturing, packaging, and labeling of the IP.

Summary

CMC is a critical component and a 'first step' component in the creation of a development strategy for an asset. Without a solid development plan for the investigational materials used in clinical studies, HAs will not be able to adequately assess the efficacy or safety of a product.

Your development partner will work closely with you in the development of an appropriate CMC program for your investigational product. Ideally, your development partner can provide an 'end-to-end' service to support manufacturing, packaging, and labeling of the IP, which will ultimately improve timings for clinical studies.

References

1. https://www.fda.gov/files/drugs/published/Changes-to-an-Approved-NDA-or-ANDA.pdf

2. https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/cmc-and-gmp-guidances

3. https://prahs.com/insights/onsite-manufacturing-early-clinical-development

Contact Information

For further information, or to discuss any aspect of PRA's services offered in the field of chemistry, manufacturing, and controls (CMC), please contact your Business Development Manager or the employee listed below:

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