Roundtable Session 1 – Table 7 – Managing/Leveraging CMOs and CTOs for Marketing Application Success

Facilitator: Dawn Spiller, *Astra Zeneca*

Scribe: Claudia Gributs, *Eli Lilly and Company*

Abstract:

An increasing number of Complete Response Letters (CRLs) are being sent in response to biologic license applications (BLA) with an increase in the frequency of facility deficiencies cited. Managing the relationship with CMOs/CTOs is essential for marketing application success globally. Scientific innovation has fostered an increase in accelerated approval pathways, novel modalities and emerging technologies. Strategies to expedite manufacturing facility readiness is key to enabling success and patient access.

This session will discuss the tools, best practices and strategies that can be leveraged to tap into experience and knowledge from both parties as well as lessons learned from Industry and Regulatory perspectives.

Discussion Questions:

1. How can companies effectively partner with CMOs/CTOs to enhance global marketing applications, and what best practices have proven successful?
2. What approaches have been successful to ensure inspection readiness for both partner and CMO?
3. How has your company successfully handle submission of confidential information (when DMF is not an option)?
4. How does your company approach delineating activities and roles to ensure cGMP compliance?
5. How does your company manage multiple agency inspections or inspections covering multiple products at once or in short span of time?

Notes:

Throughout these notes, the term "CMO" is used as an abbreviation for "CMO/CTO".

Quality Agreements and Contracts

Good quality agreements are key for successfully navigating the marketing application process with CMOs. Issues may arise, for example, if the agreement does not sufficiently define roles and responsibilities or data turn-around time expectations.

Some best practices to consider when establishing quality agreements and contracts with CMOs:

- The FDA guidance "Contract Manufacturing Arrangements for Drugs: Quality Agreements" is a useful resource.
- Include technical stakeholders as authors or reviewers of quality agreements. QA, project managers, or external manufacturing representatives may not have visibility to all critical items that should be included.
- If a CMO is used for multiple projects, consider creating appendices for each project and subject matter. Clearly state the communication mechanisms. List contact names for each area at both parties (e.g., regulatory, QA, each technical function).
- Include enough detail to ensure that key information can be accessed in an appropriate time frame if needed (e.g., during responses to questions or inspections).
- The business contract can be used to reinforce key points of the quality agreement and the expected role of the project manager in ensuring that information is available within time required by health authorities. Often, exact turn-around-time requirements cannot be specified in the contract as they may change between health authority requests. However, communicating the spirit of the expectation helps build a more collaborative relationship with the CMO.
- The quality agreement must define how and when information related to inspections at the site will be communicated to the client. The client should be informed of observations and findings that may impact their product(s), even when they originate from the inspection of another company's product. For example: an inspection on one line/lab might impact a product on another line/lab. Timely communication is very important, because the sponsor needs as much time as possible to implement a mitigation strategy for their BLA/MAA.
- Awareness of quality agreement details may be poor when one pharma company is taken over by another. Read the quality agreements to gain familiarity with their contents (do not assume that they are the same as what you are used to).

BLA/MAA preparation

The group discussed to which extent CMOs are included during BLA/MAA preparation, and what visibility they have to the contents that is submitted to the health authorities.

- Third parties should participate in authoring or reviewing BLA/MAA sections. Most commonly, the sponsor authors and the CMO reviews the content related to their activities before submission. This practice gives high confidence that the information is correct and complete, and awareness of commitments. Only relevant sections are shared with the CMO, not the entire submission.

- Leveraging the CMO to write the BLA/MAA can accelerate the submission process and increase engagement in the project.
- Contracting all analytical testing to one company could decrease the complexity of data compilation activities during BLA/MAA authoring. Risk: the contracted laboratory may not have all analytical technologies in-house and may subcontract, which leads to less direct Quality oversight.
- Where possible, write separate BLA/MAA sections for each site. This reduces the need for the sponsor to create a redacted version for each CMO.
- If a site is added after first approval, then it may be useful to share the original site's submission contents with the CMO to ensure understanding of the expectations.

<u>Inspection readiness, and inspections</u>

- PLI readiness:
    - The group recommended being as transparent as possible about timelines and information requests with the CMO during regular project meetings. This puts both parties are on equal footing and builds a partnership mindset.
    - Sponsors help CMOs prepare for the PLI. The sponsor performs a quality audit before submission. The sponsor typically travels to the CMO's site for a scheduled inspection. However, there are cases where the inspection is unannounced.
    - Sponsors proactively inform the CMOs of new submissions and possible inspection dates. The two parties agree on which product will be on the line for the inspection, and whether a surrogate will be used.

- PLI:
    - The sponsor is sometimes on-site for the PLI, sometimes nearby in a different location (depends on the CMO and the health authority).
    - The CMO must be given a copy of the final BLA/MAA sections that relate to their site to avoid difficulties during the PLI. The site must be able to demonstrate to the inspectors that they have enough information to comply with the marketing license.
    - In case of findings, partner with the CMO to develop the responses.
    - The sponsor very rarely participates in regular inspections after PLI.

- After BLA/MAA approval: the sponsor must share the commitments with the CMO to ensure that the expectations are understood.

<u>Confidential information</u>

- The process for submitting confidential information to health authorities can create friction between the sponsor and the CMO, especially when the CMO does not have in-depth knowledge of the regulatory constraints in each country. The CMO may want to submit information directly to the health authority rather than through the sponsor, but this is not allowed in some countries. For example: in China, CMOs must give power of attorney to the sponsor's China affiliate or a law office.
- As much as possible, define in the quality agreement how confidential information will be submitted to health authorities in countries where DMFs are not allowed.

- Sharing parts of the sponsor's submission strategy with the third party could be beneficial (e.g., "we will hold back this confidential information for now and submit if asked"). However, this gives the CMO access to company confidential strategic information, which may not be desirable.
- Experienced third parties sometimes want to know in detail where their information has been submitted. This becomes difficult to manage for the sponsor.

Idea for a future WCBP round table topic: China importation testing.