Table 31: New Modalities and Technologies (other than CGTP)

Facilitators –
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Scope:

Drug development has expanded tremendously from small molecules to complex biological modalities, and this trend has accelerated with a greater diversity in the types and applications of new modalities and new technologies. The conjugated drugs in anti-body drug conjugates (ADCs) have been small molecules, but there is a wide variety of new types of conjugated modalities under investigation. The growth represents a challenge for pharmaceutical industry as well as global regulatory authorities while the regulations will need to adapt to the everchanging landscape.

This round table will serve as an interactive forum to discuss current challenges, learnings and best practices across industry and regulators.

Questions for Discussion:

1. Types of new modalities and technologies
    a. Innovative antibody therapeutics
    b. New developments in preventive biological products
    c. Multifunctional modalities
    d. Emerging technologies
2. What are the main challenges for new modalities and technologies?
    a. Lack of specific regulatory guidance and no clear legislative pathway
    b. Registration classification dependent requirements
    c. Designation of starting materials and intermediates
    d. Comparability and characterization
    e. Process related impurities and product related impurities
    f. Potency and stability
3. Any best practices and lessons learned from industry and regulators
    a. Antibody drug conjugates (ADC)
4. Considerations for global drug development in US, EU, China, Japan and other markets
    a. Harmonized regulatory requirements
    b. Science and risk-based approach

Discussion Notes:

January 26 –

Session Background:

Drug development had expanded from small molecules to new modalities. What are the challenges with these new modalities?

Topics & Notes:

1. Types of new modalities

a. Innovative mAbs

b. Multi-functional modalities

c. Emerging Technologies

d. mRNA - growing quickly.

2. Challenges of new modalities

a. Potency

i. What is a potency assay for an mRNA product? Tim to share more information on Amgen potency assays.

b. Stability

c. Comparability and characterization

i. What are you using for comparability (new use/different use of therapeutic)

ii. For mRNA, comparability seems similar than vaccine or mAb. An overview consists of:

1. Accelerates stress studies

2. Forced degradation

3. Challenges to transfer methods from sites to sites

a. Robust method and hopefully they don't change the analytical methods otherwise they have to do a bridging study.

b. Method transfer is very difficult. A few submissions recently had a lot of questions from the agency around transferring methods.

4. QC methods remain traditional HPLC methods, however characterization will be newer technologies.

a. For major changes, especially deploying method to new labs is challenging.

d. Process/product related impurities

i. During scale up, there are issues with impurities that show up later in the process. There is a need for more sensitive methods that can handle these questions which can arrive later in the development process.

3. Best practices / Lessons learned from new modalities

a. What kind of products belong in this category? For one company it may be a new modality, but other companies it could be a platform so the term new modality is relative.

b. Should introducing existing therapies for new indications also be covered here?

c. Regulatory filing for an ADC, unexpected finding for mAb conjugated to a synthetic small molecule. Filing resulted in a requirement to register multiple drug substances and 1 drug product. This increased the workload and requirements.

i. In certain cases, companies have taken a hybrid approach. Part of the filing was from the small molecule template and part was from the large molecule template. (CDER vs CBER)

4. Considerations for harmonizing global drug development

a. Lack of specific regulatory guidance

b. Designation of starting materials and intermediates

c. NCL (National Control Labs) are a focus for in-country testing, however it is not clear if you should follow guidance from CDER vs CBER

d. China filings are difficult due to regulation changes and lack of clarity. Even when questions are submitted to regulators

January 28 –

- How do you define new modalitites?
    - Whether to go to CBER or CDER
    - Different reviewers for each type
    - Fits outside the traditional mAb, e.g. multispecifics, nanobodies, ADCs
- What is considered new technologies?
    - MAM, HCP at Pfizer using mass spec as new technologies for newer areas of applications where it was not used before
- Trying to bring mass pec into QC areas. Can transfer to different CROs be a challenge?
- Begin with the end in mind, start the method with QC in mind, set it right away with little tweaking needed to transfer to QC. Need to make sure method is robust s less tweaking needed.

    - Do prevalidation of method especially robustness right at front to make sure can transfer to QC with minimal tweaking
- Some of these new technology won't replace traditional assays but provide supplemental data. Get a lot of data from MS without running multiple assays
- Challenge to move new technologies into QC is the lack of CFR21 compliance of the new method
- Need to implement the new aspects of the process which takes time. Do things in parallel to accelerate the process, with better&faster methods, more resource and at a higher risk. Get buy in from leadership to get the right resources for accelerating the process.
- With new modalities always a challenge to figure out the release specs.
- Comparability assessment at Pfizer done at high level looking at severity of change and what phase of development. Assess risk which drives to how much work needs to be done.Supplements lots with more analytical data e.g. mass spec data, biophysical, done at phase1. Similar requirements in EMEA regulators and FDA, their decision is more science based. Filing in China seen favorably by regulators if accepted by FDA. More challenging in China compared to FDA or EMEA regulators. Requirements and expectations can be different for compendia between the regions.