Roundtable Session 2 – Table 9 - ATMPs and Companion Diagnostics - Development Challenges

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Abstract:

The need for a parallel development of a Companion diagnostic adds further complexity to the already mostly accelerated development of ATMPs. This relates not only to the need to comply with regulatory requirements for medicines and in-vitro diagnostics but also to aspects of biomarker qualification, clinical trial and performance study design and interpretation of study results. These aspects different possible approaches will be discussed in the roundtable

Discussion Questions:

1. Are you aware of similarities/differences between US and EU requirements for CDx development?
2. What are the perceived challenges of CDx co-development?
3. Are you aware of ongoing initiatives to facilitate CDx development?
4. Lessons learned from regulatory interactions?

Notes:

What is a companion diagnostic:

- Companion Diagnostic is a status/definition that is confirmed at MAA/BLA stage.
- Primary use is of CDX in ATMPs is currently with AAVs, because WT AAV Neutralizing Ab might preclude the therapy from being efficacious. Any test that is used as inclusion criteria for a clinical trial, it is an interventional IVD/CDx candidate.
- CDx for cell therapy are not excluded, but currently not seen. An hypothetical example could be, when CAR-T product may be considered for a second treatment, there could be a test to include/exclude for re-dosing clinical study patients with Nab against the initial CAR, this would be a CDx also.
- For this conversation, we assume that the biomarker is qualified already, and needs to be shown, independently
- Not every in vitro diagnostic becomes a companion diagnostic but development of a CDx should be progressed with development of the drug. Anything that becomes an exclusion/inclusion criteria in a clinical study generally will be considered interventional IVD/ CDx candidate.

Example: neutralizing antibody test

- If the sponsor tests for presence of Nab, and excludes patients who have Nab --> companion diagnostic

- If the sponsor tests for presence of Nab, but proceeds to dose all patients anyway --> this was only an IVD when the clinical trial ws designed, but the outcome (if there is an efficacy difference in drug efficiency) could be that a CDx was needed, and performance validation work will be required.

Legislative differences globally:

- FDA reviews both device and drugs at clinical studies setting and BLA stage. There is communication between CDER/CBER and CDRH, although there could be a need of two separate applications.

- EU has different organizations which review drugs and device and they follow different legislations. Device / CDx trials are reviewed by national device agencies, but certification is performed by notified bodies.

o COMBINE: EU initiative to clarify requirements for clinical studies based on legislations for both the drug and the device.

- Japan: the drug division makes the determination whether a CDx is needed based on the Clinical Trial execution and data. We need the CDx to be defined very specifically. If CDx is necessary, then the developer has to submit license application for the Drug and a separate submission for the CDx

Considerations for drug developer during clinical Development

- If the purpose of the assay is to be treatment deciding, it will be considered interventional from a device perspective and it will be considered a comp diagnostic --> Company needs to follow IVDR regulations in addition to the regulations for the drug component. Q&A for IVD use in clinical studies (eudralex volume 10).

- Communication between the drug sponsor and the CDx sponsor/manufacturer is key to ensure a CDx development plan is put in place early in development.

- In the US you will be allowed to start the IND without an FDA Clearance of the IDE for a companion diagnostic.

- In the EU, we will not require the assay to be certified at clinical stage, but the assay has to be investigational --> the performance study needs to be submitted to the device agency directly at the same time as the drug clinical trial application.

- In house assay usually do not require performance evaluation but if you are developing it in parallel to a clinical study, it is recommended that it is evaluated, for example if there are multiple sites using each their own in house assay. From a device perspective, there is no need to align those assays, but from a drug perspective the assays differences may be impactful to the performance of the device in the context of the medicine and comparison of performance is required.

Considerations for drug developer at commercial stage

- In EU, even if the MAA for a new drug is approved, the new drug cannot legally reach the market until the CDx has completed MDD certification and has an approved CE mark, which is issued by a notified body. While the drug label may not need to specify the exact CDx, the CDx label will need to reflect which drug has to be used with.

o The first time the medicine review division will see/ask for information about the device is at the MAA stage, because they need to make sure that, if the assay changed during development, the assays have been appropriately bridged and are appropriate for intended use.

o It is too late to think about CDx at MAA stage

- If there is an approved IVD for that indication, in house assays are not accepted.(general IVDR rule)

o e.g. with the current approach, if there is AAV9 Nab IVD, the label for the IVD will say certified for AAV9 for product X. But product Y could develop a new in house assay for AAV9.

Reference:

- Q&A for IVD use in clinical studies (eudralex volume 10).
- Q&A for complex clinical trial design (question 5 on biomarkers) (eudralex vol 10)
- Guidance in preparation for biomarker-guided drug development (will look from MAA perspective).

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