Roundtable Session 2 – Table 6 – GMO Environmental Risk Assessment and the Application Process

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Abstract:

It is essential to evaluate the potential environmental impact of medical products consisting of or containing Genetically Modified Organisms (GMOs) before receiving Marketing Authorization (MA). This is accomplished by completing an Environmental Risk Assessment (ERA) and including the assessment in the product MA application. The European Medicine Agency describes a methodology for conducting the ERA and application requirements in *Guideline On Environmental Risk Assessments For Medicinal Products Consisting Of, Or Containing, Genetically Modified Organisms (GMOs)*.

We will discuss the execution of the ERA, what challenges firms have faced in this process, and strategies for engaging regulatory authorities before submission of the ERA.

Discussion Questions:

When does a risk assessment get submitted?

What factors must be considered when assessing environmental risk of GMOs?

What parties must be involved in this assessment?

What are best practices and challenges seen regarding knowledge management for environmental risk assessment?

Notes:

The discussion on *GMO Environmental Risk Assessment and the Application Process* brought together participants from industry who are new to the submission process. This included those preparing their first risk assessment, seeking insight into the requirements for GMO submission as it pertains to early clinical trials, and wishing to improve dialogue and information management with sponsors/clients. Members of this discussion entered this roundtable with a drive to discuss GMO environmental risk assessment (ERA), particularly with regard to Cell & Gene Therapy Products (CGTP).

Definitions

- GMO – non-human biological entity capable of replication/transmitting genetic material in which genetic material has been altered in a non-naturally occurring manner (examples in gene therapy might include CAR-T treatment, and the genetic modification of chicken eggs with human proteins)
- Effects on the environment – effects exerted on any inhabitants of the global ecosystem (including humans) with the *exception of effects on target patients as a direct result of the administration of the product to the patient*

Timing – when does a risk assessment get submitted?

- The ERA is to be submitted with Clinical Trial Application (CTA) rather than waiting for MAA. By addressing this early, a thorough knowledge of the data needed can be acquired.

Considerations

- Key considerations include viral shedding, spills, and impurities present within the GMO, which could include intact DNA or replication competent vectors. The release data on host cell DNA would ideally be provided through a quantitative risk assessment and may assist in removing subjective aspects of risk assessment. Qualitative assessments may be used if quantitative data cannot be provided.

- Harmonization is another key consideration – here discussed from the guidelines proposed by the EMA

Parties involved in the ERA

- Delegation/organization/facilitation is largely regulatory and should include a CMC Regulatory member as well as a Clinical/Medical member.
- Pharmacy technicians should be involved in the root cause analysis (RCA) to identify and analyze underlying risks. Those involved in the processing, manufacturing, and handling of the GMOs should be assessed for competence.
    - GEL S1-3 should outline proper training regarding disposal, handling, and contingency plans regarding first aid/environmental damage control. These should be included in the ERA as omission of these poses a challenge discussed

below. Between gathering data and submission, overseeing body may not always have the information required, posing a challenge in knowledge management

Challenges of determining validity of risk

- Interpretation of regulations should involve obtaining an impartial third-party that can help address confirmation bias, provide objective input on contradictory data,
    - In-house data, so when queried, assumptions may be justified
    - Pulling conclusions from data may at times be sufficient, not always source data
- Assessing risk while still in product development may be challenging for new products GEL-S1 (risk with promoter for instance, in which GMO may be replication competent). If sponsors do not provide key information (such as the promotor sequence mentioned above), the GMO cannot be received or stored for the distributor and this will dramatically slow the entire process. The Analytical and CMC teams also need this information to successfully move forward.
- Filing subsequent ERAs may become easier once initially performed, but those performing the risk assessment should not get anchored into thinking the process will necessarily be identical.

Best Practices of Knowledge Management

- Knowledge management should draw from early development/characterization/tox PK/PD, with practices in place to avoid information loss.
    - Some suggested best practices for managing preliminary knowledge acquisition:
        - Controlling data before it becomes GXP
        - Using repositories that compile regulatory data
        - Managing different versions/change controls
        - Bring in supporting data for GXP qualifications
        - Online box files to access
        - Feeding early data into quality system, which also can aid in identifying best resources for the future

- When implementing process changes, CTA accounts for comparability:
    - When amending comparability, changes likely depend on factors (manufacturing, site, product fill-finish) and risk assessment may be repeated. A change management process may be used to assess whether these changes have an environmental impact.

- While technical changes may be small enough to not initially be considered, changes would ideally be assessed through a change control process that would be written in to the CTA. This would factor in the risk of the change (high risk/low risk), as well as determining whether the change is of a regulatory or technical nature. An example of this would be changing the vial size, where if this changes the regulatory filing, it should be addressed and revisited to determine if further action needs to be taken.

- Other key examples of changes include packing, handling/disposal, dosing/volume changes, specific technical details requested (production specs). Packing, handling, and disposal changes relate directly to accidental spills, and depending on the GMO, may involve the patient. Dosing and volume changes should be looked at and evaluated as needed. If production specs are impacting viral titre, they are also impacting residual virus and should be considered as such.

Reference:

Guideline On Environmental Risk Assessments For Medicinal Products Consisting Of, Or Containing, Genetically Modified Organisms (GMOs) – EMA (2024)