Roundtable Session 1 - Table 5 – Material Classification for Genome editing components

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Abstract

The classification of gene editing (GE) components depends on their specific application. When GE components, such as nucleases and DNA templates, are administered in vivo, they are considered active pharmaceutical ingredients (APIs) and in their final formulation with e.g. nanoparticles classified as a Drug Product.

On the other hand, if GE components are used ex vivo to genetically modify cells outside of the patient's body, their classification can vary. Depending on the region and the specific regulatory authority, they may be categorized as starting materials or critical components or even as a drug substance.

To establish consistent standards and facilitate efficient global submissions and assessment processes, it is crucial to harmonize definitions, compliance requirements, and the organization of information in regulatory submissions.

By aligning these aspects, the regulatory landscape for gene editing can be streamlined, ensuring that the development and evaluation of GE products adhere to unified guidelines and facilitate their safe and effective use worldwide.

Discussion questions

1. What are the challenges you are facing with classification of GE components used in product manufacturing?
2. How does the classification impact the qualification requirements of GE components used for ex vivo gene editing approaches?
3. What is the level of functionality assessment performed for critical components/ starting materials?
4. What are challenges for global regulatory submissions during development of GE products?
5. What strategies can be used for more regulatory convergence?

Notes

Regulatory classification:

The classification of GE materials depends on the nature of the product, e.g. ex vivo or in vivo. For in vivo, they are considered as DS. For ex vivo, while there is flexibility in the US during the IND stage, the legal framework in the EU would require a starting material classification.

USA:

For ex vivo in the US there is the expectation to consider as critical component (FDA terminology) place the information as a distinct DS section. FDA wants to see full

characterization, process characterization, process qualification at the BLA stage. An activity/Functionality assay is expected.

For raw material definition the US follows USP 10.43 which provides for a 4 tier classification based on a risk assessment. This would not be very detailed during early development, but be more detailed towards marketing authorization.

Previous experience recounted by one company representative where a company pushed back on classification of vector as DS → failed, but that was years ago.

FDA wants to see real time stability data and does not accept supportive data to be leveraged. In contrast, this was acceptable in the EU. In the US this creates (re)labelling issues whenever a new timepoint for shelf life extension becomes available.

Europe:

In Europe, for ex vivo applications, the GE materials are classified as critical starting material. This means, that manufacture is expected under the principles of GMP rather than full GMP and that the information is placed in S.2.3 rather than the DS section.

There are open questions on the regulatory burden at MAA, e.g. → justification for change control processes required e.g. cell line change etc. but unclear how this fits with the variation guideline.

As independent additional challenge at marketing authorization a Nitrosamines risk assessment is required in the EU covering the entire manufacturing process.

Scientific requirements:

In terms of scientific requirements no obvious differences between US and EU were identified, but the placement expectation within the regulatory submissions is different.

Different requirements are expected by FDA for autologous vs allogeneic products, which likely relates to the different amounts of material available, the potential number of patients impacted. For allogeneic products a lot of issues can be addressed on the MCB level

US IND: There are open questions on the need for stability data after process change.

The question was raised whether non-GMP material could be used in non-clinical studies, which is a possibility in the US. It was clarified that this was not recommended for the EU for the following reason: It is not an issue of GMP vs non-GMP, it is an issue of representative material. The EU requires representative material/representative process to be used in non-clinical studies. The case would need to be made that the material is representative and there is less need for justification, if the material used is the clinical material or as close to it as feasible.

Functionality assessment is generally included, clear for the nuclease, but also for the sqRNA and is part of the CoA release tests from vendor. Wider acceptance criteria during development were expected to be tightened at marketing authorization.

Sequencing is considered enough as functional assay (plus impurities, identity) for sqRNA. There was a discussion, if a cleavage assay as required by FDA really should be required and what it contributes.

Adventitious agents evaluation – needs to include the starting materials and requires a risk assessment

Case examples

One developer applied the classification as critical components (FDA) for all countries. Full details were provided for major countries while streamlined information was provided to 2nd tier countries, while being prepared to provide additional information, if questions were asked.

Developer example (US) for in-vivo setting: the sqRNA on its own was defined as DS and once complexed with CRISPR Cas9 this was defined as further DS. Different functional assays were applied for the two DSs; Cas9 on its own was not define as DS.

In contrast, another developer in the same setting, defined the sqRNA as starting material and only the complex as DS