

Table 8: Phase-appropriate Method Validation

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Scope:

Analytical testing is at the cornerstone of a successful development for medicinal products including CGT products, addressing product characterization, manufacturing consistency, product release and stability as well as product and process comparability.

Method validation is required for marketing surveillance post-commercialization to set product specifications and ensure state of control of process and product. Also, validated analytical methods according to ICH Q2(R1) are needed for pivotal trial as it should be performed with fully controlled products.

Throughout development, scientific data generated must be reliable and methods used should be fit for purpose. Method qualification is required for early clinical phases while assays intended to ensure patient's safety should be validated. In fact, viral safety testing of human and animal derived substances or absence of replication competent viruses are required to be validated prior to human exposure.

Noteworthy is that, in the regulatory landscape, revision of ICH Q2(R1) is being prepared and also a new guideline focusing on analytical procedure development - ICH Q14 - is under elaboration. Furthermore, ICH Q5A(R2): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin is also being revised where viral vectors are covered and requirements for new molecular methods are defined.

In this context, it seems relevant to discuss method qualification/validation requirements and the challenges with current revisions under way and their impact for the CGT products.

Discussion Notes:

- Analytical testing is often complex not only for potency measurements but also in terms of overall analytical testing of CGTP due to their inherent complexity.
- There is no guidance to support analytical validation for complex methods. As an example, it was mentioned that flow low cytometry is difficult to validate. Nevertheless, it was mentioned that Ph. Eur. 2.7.24. FLOW CYTOMETRY can be used as a guidance.
- RCV is also a complex assay to be validated as required in early development for clinical trials and also for the GMO aspects at least in the EU.
- In terms of potency measurements, a surrogacy approach for potency testing relies on the fact that - among the qualified characterization assays – a surrogate one is selected and validated for release. It is acceptable as surrogate based on cross validation studies with meaningful functional assay(s).

- R&D knowledge is the starting point to address the quality of the product and what are the most suitable characterization assays. Release methods are established thereafter, selected from the characterization panel, and those are the ones required to be validated for pivotal trials and beyond.
- Analytical methods for process follow-up do not need to be validated. Characterization assays that have to be qualified suffice: the specific setting of process characterization has therefore to be clarified.
- Requirements for qualification vs validation, and lack of clarity about the wording “method qualification” was considered an important aspect that requires urgent action. It is clear there is no formal definition of qualification anywhere or strict pre-defined criteria to be complied with to consider a method as qualified. In the EU, GMP GL for ATMPs the terms suitability/not fully validated are used.
- There is the need to define the term “qualification” and to stress that use of “validation” is not appropriate for characterization assays. There is the need for a common terminology worldwide. ICHQ14 is an opportunity to possibly define the appropriate terminology.

The following considerations on the required clarification were presented:

- The term “validation” is specifically linked to the product release in order to release/stability test the product worldwide, i.e. regardless where the testing takes place. It accounts for strict pre-determined acceptance criteria (rigid conditions) and requires QA approved protocol. It is the method confirmation on the basis of previous studies and it is not a discovery exercise. It implies that there is method failure. Products for confirmatory clinical study should be tested according to validated test methods.
- The term “qualification” during method development is linked to the concept of robustness of the analytics; it is meant as fit for purpose but not to be part of the control strategy. Nevertheless, it requires pre-defined acceptance criteria, but flexibility is acceptable. Therefore, there is no method failure. Qualification represents what can be tolerated while still being confident on the results. As a minimum, specificity, linearity, range, precision in terms of reproducibility, needs to be in place to ensure the method is scientifically sound in a sufficient way.
- ATMPs represent a very complex class of products. Therefore, the requirements as for proteins cannot be directly applied and this is the reason why, in the EU there are stand alone GMP guidelines specific for ATMPs.