CONFERENCE "EDQM'S FUTURE PLANS IN THE GENE THERAPY FIELD"
ROME, ITALY, 27-28 SEPTEMBER 2018

Summary of recommendations

On 27 September 2018, the EDQM held a conference to gather feedback from its stakeholders on their needs as regards quality requirements in the field of Gene Therapy. The conference was hosted by the *Istituto Superiore di Sanità* in Rome. A summary of recommendations voiced by participants is provided below.

1. Raw materials

During the conference, industry representatives made multiple references to the need for an improved system in Europe for the acceptance of raw materials and excipients used in the manufacture of gene therapy products (GTPs). In the United States (US), Drug Master Files (DMFs) can be referenced for a critical raw material and the Food and Drug Administration (FDA) may have access to more detail: this is easier for vendors to maintain and update. In Europe and Japan, details are provided directly in the Common Technical Document (CTD); the level of information provided by the vendor to the manufacturer as well as interpretation of certain aspects such as whether the product is of animal origin may vary. Moreover, qualification of multiple suppliers presents a serious burden in particular on Small and Medium Enterprises (SMEs). Therefore, it was mentioned that introduction of a DMF-like system or a certification scheme for critical raw materials in the EU may be preferable for a more globally aligned approach in rapid development programmes.
The need for harmonisation of terminology between Europe and the US was also raised.

2. Testing methods

Genetically modified cells
The audience spent considerable time discussing quality-related aspects of genetically modified cells, a topic raised by the recent approval of CAR-T cell products both in the US and the EU and the steep increase of clinical trial applications for CAR-T cells in particular. The methods used during the manufacturing process of CAR-T cell products are complex, with multiple steps, close to what is usually performed in research. Product inconsistency, largely due to intrinsic variability of the patient's cells used as starting material, may lead to Out Of Specification (OOS) results. However, since these products are often indispensable for extremely ill patients, after evaluation of the risk/benefit ratio with the physician, frequently the OOS product is finally nevertheless administered to the patient, thereby demonstrating a paradigm shift for cell and gene therapy compared to other medicinal products. Other participants, however, stated that this puts a high responsibility on the treating physician in an area in which he or she may not be the best placed to identify potential issues.

In the light of this potentially high variability, it became evident from the discussions that the European Pharmacopoeia (Ph. Eur.) should refrain from setting specifications for individual products. Instead, the majority of participants recommended that the Ph. Eur. concentrate its efforts on describing common methods and providing respective reference standards in order to allow comparability between products and help to establish links to clinical safety and efficacy profiles.

Among others, Vector Copy Number (VCN) standards and cell viability assays were cited as particularly relevant and important to have. There was also a plea for rapid methods to be encouraged, for example in the field of microbiology (e.g. rapid sterility, mycoplasma qPCR) and the wish for compendial methods in this area was expressed. There were mixed feelings about potency assays: a number of participants recognised that some assays may be product-specific and therefore would not be applicable across a range of products. However, the description of standardised assays might be useful for establishment of in-house standards and for bridging studies while the definition of parameters to control assay performance was also indicated as desirable.

It was also mentioned several times during the discussion that allogeneic CAR-T cell products are being developed and, in that respect, guidance documents from Ph. Eur. would be extremely useful. Setting quality requirements for those products would be more feasible than for autologous products due to lower product-related variability, larger batch sizes as well as longer time ranges for their quality control. For these products, usual testing schemes used for other biological medicinal products could be applied.

Participants pointed out that genetically modified cells needed specific handling procedures or acceptance criteria. For example, visual inspection, required for parenteral preparations, is particularly problematic and the Ph. Eur. monograph *Parenteral Preparations* is not always applicable. In addition, the current Ph. Eur. test for sub-visible particles requires large amounts of samples and the possibility of using smaller test volumes is not currently addressed. Similar considerations should be taken into account for the test for sterility (sample size, bioburden versus sterility).

Another example was the necessary cryopreservation of the cells. This requires specific procedures and reagents for which acceptable residual levels in the final products should be considered.

Gene therapy vectors

The rapid growth of the field of adeno-associated virus (AAV) and lentiviral (LV) vectors had trigged a session dedicated to AAV- and LV-mediated gene therapy. Vectors can be considered both as starting materials for genetically modified cells as well as products themselves when administered directly to the patients. Similarly to genetically modified cells, a lack of harmonisation or guidance for vector related Critical Quality Attributes (CQAs) as well as very limited availability of reference standards were highlighted as the main challenges in the field. In addition, the wide variety of vectors and products is extremely challenging in terms of setting standards. Moreover, the safety concerns also differ depending on the manufacturing process applied to a given vector (e.g. mammalian producer cells may carry higher risks of viral contamination than insect cells).

Wishes were expressed for global harmonisation and more specific guidance in areas such as residual DNA quantification (qPCR versus ddPCR; plasmid versus host cell), AAV vector genome quantification (qPCR versus ddPCR), capsid integrity (full versus empty; dose-measurement; deamidation) or viral clearance. The use of more innovative testing methods was suggested as traditional methods such as ELISAs may not be appropriate or sufficient sometimes, and specifications derived from other fields (e.g. vaccines) may not be applicable to gene therapy products given the particularity of these products. Moreover, the relevance of some tests recommended in the European Pharmacopoeia's overarching general chapter *Gene transfer medicinal products for human use (5.14)* (e.g. infectious genomes titre) was questioned by some participants if other tests such as potency assays are performed. Also, guidance for setting limits was considered valuable.

Gene editing
Although not the subject of specific talks, gene editing was referred to in the discussions and, as clinical trials are in the pipeline, the EDQM should remain aware of the corresponding products manufactured using these tools.

3. Innovative technologies

The Ph. Eur. is aware of the need to remain open to new technologies in order to avoid being a barrier to progress. Current Ph. Eur. texts in the field of cell and gene therapies are written in a way which allows for innovative technologies to be further developed and implemented.

4. Continuous manufacturing

The production of autologous products is a continuous process, starting with apheresis at the bed of an extremely sick patient. Each batch is personalised for one patient, and administered as a final product after a complex series of manufacturing steps during which the cold chain and a strict identity traceability are of critical importance. This process raises new challenges as far as quality control and product release are concerned. The definition of a batch has an impact on the testing strategy. The Ph. Eur. already provides possible alternative approaches to quality control and will need to keep this aspect in mind for the future.

5. Standardisation

Associations/operational groups (BioPhorum, Standards Coordinating Body) were given the opportunity to present their work and their role as promoters for partnership and global collaboration, in view of mobilising the gene therapy community. The acceleration of standardisation activities during recent years by bodies which do not have historical presence or experience in the standardisation field, illustrates the need for global technical and written standards. At the same time, the industry appealed for a close collaboration between the various stakeholders in this field to ensure uniform approaches.
The National Institute of Biological Standards & Control (NIBSC, UK) representative informed the audience about the progress of the work on the first World Health Organisation (WHO) International Standard for gene therapy products i.e. the lentiviral vector integration copy number, which is foreseen to be endorsed by the WHO Expert Committee on Biological Standardization (ECBS) in 2019.

6. European Pharmacopoeia texts on gene therapy products

The Ph. Eur. overarching general chapter *Gene transfer medicinal products for human use (5.14)* had been implemented in 2006 with the intention of paving the way for the future and simultaneously providing ample flexibility for further development. Participants expressed the wish for the Ph. Eur. to continue its activities based on current knowledge related to approved products or products in clinical trials but to remain flexible and be able to adapt to a rapidly evolving field. However, advancements will only be possible with strong support from all stakeholders in the field and willingness from all sides to share expertise, data and materials.

7. The General European Official Medicines Control Laboratories (OMCL) Network

OMCLs are actively working on method validation/qualification in order to prepare themselves for testing of GTPs (either during market surveillance of Centrally Authorised Products or during pre-licensing testing). They also strongly support the establishment of robust standardised methods which may eventually be included in the Ph. Eur. texts. Several companies offered to support the EDQM for the OMCL activities by providing materials and participating in collaborative studies aiming at the development of standardised methods and establishment of reference standards.

8. Conclusion

Many participants commented that it had been an extremely valuable meeting and thanked the EDQM for the initiative. There was unanimous agreement on the need for harmonised quality requirements for rigorously chosen quality attributes and testing schemes for gene therapy medicinal products and corresponding reference standards. The recommendations will be carefully evaluated by the relevant Groups of Experts/Working Parties of the Ph. Eur. for further consideration and eventually submitted to the European Pharmacopoeia Commission for decision on the work programme for the coming years. The OMCL Working Group will continue to follow these activities and strive to validate common methods for the quality control of GTPs, in close collaboration with the GTP WP of the Ph. Eur.