Molecular Therapy
Editorial

Reference Standards for Gene and Cell Therapy Products

Reference standards are important tools for the calibration of medical products and procedures. They are particularly important when dosing and potency are critical parameters for patient safety and product efficacy.[1] Reference standards benefit the field by fostering best practices for the manufacturing and testing of safe and efficacious medicinal products. As the first commercial gene therapy products are now reaching market approval in the United States,[2,3] there is increased discussion of the need to generate reference standards for the industry. Recently, the American Society for Gene and Cell Therapy (ASGCT) conducted a survey on the topic among its senior members who had product manufacturing expertise. The results were presented in October 2016 at the Cell Therapy Liaison Meeting, a yearly meeting hosted by the International Society for Cell Therapy that brings together representatives from various stakeholder societies with representatives from the Food and Drug Administration (FDA). Although the survey revealed a consensus that reference standards are needed, it also exposed considerable differences in opinion. Interestingly, there was concern that such standards might impede, rather than facilitate, commercialization of gene and cell therapy depending on how they are put into practice. In the following paragraphs, I summarize some of the specific findings of the survey.

The experts were asked a total of ten questions. The first two questions asked whether they thought industry reference standards were important for or a hindrance to the development of gene and cell therapy products. 88% of respondents agreed that such standards were important, with 12% undecided. Interestingly, 36% of respondents were either undecided or agreed with the view that industry reference standards could potentially hinder the field's development. The two primary concerns were whether intellectual property could be used to exclude competition and whether gene and cell therapy products are so diverse and technologically dynamic that industry-wide reference standards could restrict innovation. With regards to the need to be product-specific, the responses were split: 44% of respondents thought that reference standards should be limited to specific products, whereas 36% thought that it would be useful to create industry-wide standards for a product class. On the specific question of whether reference standards are essential for the commercial development of gene and cell therapy products, 72% agreed, with only 16% disagreeing. This supports the view that the resistance to reference standards appears to be related to the concerns noted above, as opposed to their specific utility once products are approved for commercial use. Therefore, the development of reference standards would best serve the industry when created under pre-competitive conditions that foster and do not obstruct competition and innovation.

Adeno-associated virus (AAV) vector reference standards have been previously developed.[4] When asked if these standards were useful, the responses were split: 46% were undecided, with 38% agreeing and 16% disagreeing. However, these standards were generated many years ago, and some respondents commented that it might be useful to develop reference standards for AAV vectors that are currently on track for market approval. The experts were also asked whether it would be useful to develop reference standards for lentiviral vectors (LVs) used in the development of cellular products, with 80% agreeing. Furthermore, 72% agreed that it would be useful to develop defined copy number LV cell standards to calibrate qPCR assays for copy number determination in gene-modified patient cell products. However, the responses were mixed as to whether a T cell line expressing a chimeric antigen receptor (CAR) targeted to the CD19 surface receptor (used potentially to calibrate levels of anti-CD19 CAR expression on the surface of gene-modified patient T cells) would be useful.

Respondents were also asked to identify standards they would like to see developed. The responses were quite broad, reflecting the diversity of the respondents' manufacturing experience, but they included other vectors and cell types, such as vectors based on herpes simplex virus and mesenchymal stem cells (MSCs). There was also interest to develop clinical standards to manage toxicities, such as dosing standards for antibodies used to manage cytokine release syndrome during CAR-T cell therapy.

A few interesting points emerged when experts were asked to comment freely on the utility of reference standards for product development and commercialization. An important comment included the necessity to define the specific need for a reference standard: what product attribute is important to calibrate against a reference standard? For gene and cell therapy products, the consensus key attribute was understanding what constitutes a safe and effective dose. However, it was further noted that dosing attributes will differ widely among different product classes. For example, while AAV vectors are used as a final product, LVs and retroviral vectors are often used as intermediates to generate, for example, gene-modified T cell or hematopoietic stem cell (HSC) products. While the priority clearly should be to calibrate products that are directly administered to patients, the potential need to calibrate manufacturing product intermediates, particularly those critical to the generation of final gene-modified cellular products, was noted. It was also suggested that, as technology evolves within a product class (e.g., new AAV vector serotypes), the concomitant standards would need to keep pace so as not to become obsolete. Clearly, the timing of development and adoption of reference standards is an important consideration for a field that is rapidly advancing and so technologically diverse.

In summary, the survey represents the views of a select group of manufacturing experts who are senior members of the ASGCT. In

my experience, their responses reflect those being discussed more generally by experts in the field. It will be important to discuss these issues more broadly in the gene and cell therapy community. Before embarking upon the expense and effort to develop reference standards, careful consideration should be made to what product attributes are important and how specific standards can be developed to accurately calibrate these product attributes. Ideally, such reference standards should be pre-competitive so that they foster and not obstruct competition and innovation.

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