GMP and Personalized Medicine

Biotechnology took over the development of new drugs and personalized medicine is about to deliver first success stories. Presentations at the PDA Annual Meeting 2012 reported of first successes in cell based therapies.

Personalized Medicine

This year Phoenix/Arizona was the host of the PDA Annual Meeting 2012 (Parenteral Drug Association). As in previous meetings it was challenging to choose between many outstanding presentations.

The trends are obvious. This year a session on „personalized medicine“ including ATMPs (Advanced Therapy Medicinal Products) was offered the first time. While this topic is still in its infancy the presentations demonstrated that the field has moved from research to first successes are in application. Tom Finn, Ph.D., FDA (Office of Cellular, Tissue, and Gene Therapies, CBER) gave an outstanding presentation on: „FDA Perspective: Challenges in Manufacturing of Cell Therapies for Personalised Medicines“.

Cell based therapies as targeted therapies can range from a single product aiming at subpopulations of patients through companion diagnostics to highly customized products manipulated and designed for a single patient.

The advantages of cell & gene therapy are:
- Often cell therapies have the potential to work through several different mechanisms of action
- Opportunity to customize products to a very high degree
- Cell therapies are particularly well suited for rare and challenging diseases
- For therapies targeted to individual patients:
  - "Practice makes perfect" - a high manufacturing throughput is an opportunity to learn from manufacturing to a level not seen with traditional biologics
  - Can acquire a unique data set: patient specific product lots tied with clinical outcome data - an opportunity to evaluate relationship between product quality and safety/efficacy

After the advantages Tom Finn highlighted the challenges of manufacturing, quality systems and validation.

Challenges of Manufacturing

The challenges for the manufacturing and quality systems are:
- Involvement of many different kinds of therapies, each with their own manufacturing challenges
- Limited industry experience
- Involvement of partially closed systems or very open systems
- High lot-to-lot variation of specific products
- Establishing release criteria for products with multiple mechanisms of action
- Characterization of single patient-specific products compared to cell bank derived products
A key focus for patient-specific products has to be a rigorous tracking from source material through product administration. Also the qualification of reagents needs to be considered at the earliest stages of development.

Validation of individualized drugs

Tom Finn addressed critical validation topics of such products. Process validation can help identify false assumptions, inconsistencies, variations and contradictions in the manufacturing process that are difficult to address by other means. And control of manufacturing rather than complexity is the important issue in this area.

Challenges in manufacturing consistency are:

- Lot release specifications may not be fully informative (not extensive enough, do not examine most critical product property, specifications may change during product development)
- Potency assay may not be in place early in product development
- Some products have high lot-to-lot variations (traditional statistical approaches may not be practical or informative)

As in other fields of application, final product testing by itself may not adequately capture all relevant information and in-process testing can help to gain important information about the process and the cell production and the cell itself.

In order to get a full picture, process validation studies should be conducted, as they would be for producing the intended product. Representative starting material should be used and ideally worst-case scenarios have to be included, where possible.

Acceptance criteria for release specifications should be based on scientific principles and product characterizations.

Assays and methods must support those criteria.

The importance of the assay validation was emphasized. ICH recommendations should be applied, although not all elements are directly applicable. A simple assay does not necessarily equal easy validation. It was recommended that even assays meant „for informational purposes only“ should be validated as the data might become useful at a later time.

At the end of the presentation it became clear that the current regulations do not justify all the requirement of the cell and gene therapy manufacturing. Some examples show that personal medicines clash with existing regulations. And the FDA recommended to contact them if there are potential conflicts.

Examples:

Regulation: Retain samples for a period of at least 6 months after expiration.
Practice: Some products expire within hours.

Regulation: Each active ingredient shall be retained.
Practice: It is not always clear what the „active ingredient“ is for a cell therapy with a fixed population of cells.

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Summary

Manufacturing and testing should be aligned so that they are consistent with one another and suitable for the intended purpose.

Cell and gene therapies present special challenges that may need novel approaches to achieve the intended goals:

→ Product lot release criteria should relate to the proposed mechanism of action as closely as possible
→ Traditional product comparability approaches may not be sufficient for products with high inherent variability
→ Lot release assays by themselves may not adequately evaluate risk of a manufacturing change
→ Need to think beyond the walls of a cGMP facility about source materials and handling of product at clinical sites
→ Cell therapies and biologics regulations are not always a perfect match, but can be aligned

The FDA is open to meet the challenges of personalized medicine by cell and gene therapy. The further developments in this sector will be interesting. We will see what will happen in the future.

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