BIOANALYTICAL STRATEGY: AUTHORITIES' EXPECTATIONS TO CONSIDER

__Dr Markus Fido__, analytical characterisation expert and VelaLabs co-founder, looks at the product lifecycle of biopharmaceuticals to describe the methods manufacturers should use to ensure required safety and quality under Directive 2001/83/EC

The term "biopharmaceuticals" comprises a very heterogeneous group of pharmaceutical products that range from monoclonal antibodies, hormones, enzymes, plasma products to biogenerics, also called biosimilars. The reach of the concept results in several challenges for manufacturers and analytical service providers, as well as for regulatory and supervisory authorities, to ensure required safety and quality of the products in accordance with Directive 2001/83/EC.

The manufacturer must have excellent knowledge and complete control of the production process, as the product is defined there. During the manufacturing process, impurities must be eliminated without any negative impact on the product's biological activity. Various materials, media and reagents of consistent quality from qualified suppliers play a key role here. To ensure this, the therapeutic agent must be thoroughly analysed and characterised during the early stages of product and process development.

Appropriate analytical methods must be evaluated and implemented accordingly to allow for sustainable product characterisation. These analytical methods are performed throughout the complete development process – in its early stage during clone screening, *in vitro* and *in vivo* testing during the pre-clinical phase and, finally, during clinical studies by selected contract research organisations (CROs). The samples to be analysed may have different matrices, which needs to be investigated according to guidelines.

Concerning the product lifecycle, this would apply for process validation, in-process controls, batch release testing and, of course, the initial testing of reagents and excipients for the pre-marketing phase. For biosimilars, comparability studies with the reference product (originator) would have to be established in addition in a stepwise approach (according to EMA/CHMP/437/04 Rev.1 and EMA/CHMP/BWP/247713/2012).

During the post-marketing phase, changes in the production process, the production site, or the establishment of a new manufacturer may require further analytics.

Whereas inline, online or at-line methods are commonly used in classical analytics, (matrix-specific) bioanalytics usually requires an off-line methodology; various methods, as well as an increase in time per method and specific measuring systems, are frequently required. It is expected that the method used is sensitive, i.e. that it will detect the smallest structural differences,

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or lowest amounts of impurities that the smallest amount of an analyte can be quantified. High-specificity, precision and robustness are expected to ensure the precise identification of the analyte.

The bioanalytical procedures used should also be qualified and validated according to ICH Q2(R1) as early as possible during development. Especially with high-quality analyses (during proof of similarity of biosimilars or characterisation of critical molecules) it may be reasonable and necessary to use orthogonal methods, i.e. to analyse a parameter with different methods. The increasing focus of European authorities on the 3R strategy (reduction, replacement, refinement) with regards to animal testing should be observed when choosing the method of choice.

Consequently, authorities' expectations can be summarised as follows:

- Relevant guidelines are to be observed, e.g. ICH Q2(R1), the Pharm. EU Product Monographs or, for Biosimilars, "CHMP/437/04/Rev.1 – Guideline on Similar Biological Medicinal Products".
- Qualified and validated methods should be used as early as possible during development – at the latest, during clinical phase III.
- Action mechanisms should be described in detail and clearly demonstrate, e.g. the binding capacity of specific receptors or antigens (possibly through different assays).
- If certain functional structures are not analysed, a scientific justification is required.
- In case of impurities, those should be determined to possess biological activity that influences the potency of the active ingredient and having immunogenic properties (product specific side effects).
- The reduction of contamination within the production process should be examined and limits should be determined according to the relevant industry guidelines if necessary.
- For raw and auxiliary materials, especially for those of biological origin, a content determination in the final product should be available and their possible influence on the active ingredient should be evaluated.
- Concerning the detection of "adventitious agents" (e.g. mycoplasma or endogenous viruses), testing of the starting material and of unprocessed bulk and/or evidence of the effective elimination of viral contaminants by the manufacturing process is expected. A potential contamination with prions must also be examined for some products.

Heterogeneous product groups, such as biopharmaceuticals, require the development of new test methods or the adjustment of existing ones. In that case, a corresponding justification of the chosen method, a short description, a list of differences to the previous method, and relevant comparative data should be presented to the authorities. A good method transfer proving that other test laboratories/devices/etc. deliver comparable results is key.

The challenges in product and process development of biopharmaceuticals will be covered at PharmaLab Congress (20-21 November, Düsseldorf). More information at **www.pharmalab-congress.com**.