Biopharmaceutical Emerging Best Practices Association

Impact of Product Mechanism of Action on Potency Assay Development

BEBPA Technical Note

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What are the scientific and regulatory requirements for a potency bioassay designed to release commercial product in a cGMP quality control laboratory?

Most of us developing potency bioassays understand the analytical requirements for a quantitative method. We have typically been trained to develop methods which contain a standard material used to quantify the test material. However, determining if a method is the right assay for a given product is a far more subtle question. This requires a discussion about the Mechanism of Action (MoA) of the product.

In order for a therapeutic product to be efficacious, it must arrive at an appropriate location, often times, enter a cell and usually act upon this cell by stimulating a specific metabolic pathway or releasing a toxic substance. Common MOAs of therapeutics include direct binding to soluble targets (e.g., ligands, cytokines and enzymes), binding to cell-surface receptors in either an inhibitory or agonistic manner, entering a cell and either stimulate the cell to produce specific proteins or deliver either a needed protein or lethal toxin to the cell.

Potency assays typically need to demonstrate the final biological activity, however, what is usually not required for a potency assay is the testing as to whether a therapeutic will travel through the body to its site of action. These studies are typically performed as onetime studies early during development in the guise of PK and PD studies.

Although each product is unique, specific questions are typically asked during the method development, these include:

1. What is the target cell (or soluble target) for the therapeutic product?
2. Is there a specific receptor to which the therapeutic must bind?
3. Does the drug need to enter into a cell and, if so, is this a specific destination within the cell? For example, lysosomal enzymes must not only enter the target cell but must end up in the lysosome.
4. Once the therapeutic product enters the cell, does it upregulate a specific metabolic pathway? Or does it need to retain a specific activity? For example, if it is an enzyme replacement product, the enzyme must be biologically active within the cell. Or, if it is an antibody drug conjugate, the antibody must arrive in the cell with the conjugate still attached.

Once these questions are answered, then method development can begin as the biological components (cells, receptors, animals, etc.) can be selected and specific readouts can be explored. However, the method must specifically address the above questions.

Sadly, there is no specific guidance on how to select an appropriate MoA-reflective bioassay for your specific product, however, it is critical to remember there must be a ***biological*** impact on the target cells. Thus, do not convince yourself that a binding ELISA is a biological function assay (unless, of course, that is all your product does – bind to a ligand and not block or elicit a functional pathway in the body).