A
nalytical methods used for characterization, release, and stability testing of biotechnological/biological products are often automatically referred to as “bioanalytical” methods by some in the field. Many times the term is used to distinguish between test methods applied to small-molecule chemical products and those for macromolecular, biologically based products. It seems sensible enough: We use analytical methods to test chemical pharmaceutical products, so aren’t test methods used for biopharmaceutical products therefore bioanalytical methods?

Anyway, who cares whether the term is misapplied in this manner? What difference does it make so long as we understand what we mean? But that’s precisely the problem: Does everyone really understand what is meant by the term bioanalytical methods? Apparently not, based on its (mis)use in publications and presentations in our field over the past decade. Although ramifications can be minor, for some people (including me) this mistake is akin to people pronouncing the word nuclear as “nucular.” It is like the sound of fingernails on a chalkboard. And it can have regulatory implications: Bioanalytical studies are typically conducted under GLPs, whereas biotech product release and stability tests follow GMP quality requirements.

According to a May 2001 FDA guidance (www.fda.gov/cder/guidance/4252fnl.pdf), a bioanalytical method is used for “quantitative determination of drugs and/or metabolites in biological matrices such as blood, serum, plasma, or urine . . . tissue and skin samples.” The applications of such methods are “pharmacology, bioavailability, bioequivalence, pharmacokinetic, and toxicology studies” conducted in humans and animals. Immunogenicity tests are also considered bioanalytical methods, in that their target analytes are antiprotein antibodies in serum or plasma. Bioanalytical methods are not intended for elucidating quality parameters (e.g., identity, purity) of a biotech product; they’re intended to determine the quantity of a drug (or the presence of induced antibodies) in biological samples.

For that reason, technologies used to perform bioanalytical methods vary according to the molecule’s nature. With chemical products, the biological components of test samples can be removed by precipitation or extraction, allowing remaining small molecule(s) to be analyzed with technologies such as LC–MS or GC–MS. With biomolecular products (or antiprotein antibodies), processing away the biological components of a sample can equally remove the target analyte, making accurate quantitation technically impossible. So for biotech products and antiprotein antibodies, bioanalytical methods require technologies that can specifically measure one biological moiety (the protein(s) of interest) in the presence of a biological milieu (which contains many proteins).

Immunological methods that use specific antigen–antibody recognition (e.g., ELISA-like methods) are usually chosen for bioanalytical assays applied to biopharmaceutical products because they can “fish” the one protein of interest out of the protein mixture. Similarly, immunogenicity screening assays use ELISA-like methods to capture reactive immunoglobulins. Perhaps the confusion between “bioanalytical methods” and “analytical methods used for the testing of biomolecular products” is more prevalent in the biopharmaceutical community because of the nature of our products. The most accurate term for the analytical methods used to assess the physiochemical parameters of these products is thought by many to be biomolecular methods.

One major professional scientific organization, the Association for Biomolecular Resource Facilities (www.abrf.org), recognized the distinction in terms over two decades ago when selecting its name. “Biomolecular resource facilities” are laboratories that conduct physiochemical characterizations of biologically based molecular entities. Several years ago, a contract testing facility launched its analytical services group — to perform characterization, release, and stability testing of biopharmaceutical products — under the name “Bioanalytical Services.” Numerous inquiries for solid-phase extraction and GC–MS of e.g., pharmacokinetic samples (which the laboratory did not intend to perform) demonstrated clearly that the name was not appropriate, so it was changed to “Analytical Services.”

If you don’t believe the choice of terms is a problem when searching for specific kinds of biotech product testing services, try this experiment. Search the Internet for contract laboratories using the term bioanalytical, and most hits come up for facilities that predominantly test biological specimens (for preclinical, GLP/GCP studies). Searching for immunogenicity laboratories can generate hits for bioanalytical testing labs that perform this subset of bioanalytical tests.

But searching with the term biomolecular is much less productive in calling up facilities that perform the physiochemical analysis of biopharmaceutical products. The cumbersome string analytical testing of biotechnology products is more productive but still misses many contract laboratories offering such services. So here’s the conundrum: Do we simply accede to the will of the masses and live with the erroneous use of the term bioanalytical both for analyzing biological samples and assessing the physiochemical characteristics of a biotechnology product? Or do we use the same nomenclature as for chemical pharmaceuticals, with bioanalytical methods used only for studies of preclinical and clinical samples, and use analytical methods for identity, purity, potency, concentration, and stability testing of our products? And not to complicate matters, but perhaps next we should review applications of the term bioassay.

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