Potency Assignment to Clotting Factor Concentrates: AN EASY TASK?

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Determination of a biological parameter follows, in principle, the same paradigm: one needs an assay, a standard, possibly a reagent, then performs the test and the result in valid everywhere on this planet.

In reality, the situation is often much more complex as highlighted in the recent workshop on “Characterization of new clotting factor concentrates (FVIII, FIX) with respect to potency assays used for labelling and testing of post infusion samples.” The workshop, sponsored by the European Medicines Agency (EMA), the European Directorate for the Quality of Medicines and Health Care (EDQM) and the Council of Europe (COE), was held to share scientific information on the challenges of translating traditional potency testing outcomes to new product manufacturing technologies. The EDQM is increasingly concerned that the
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Issues observed with existing recombinant clotting factor concentrates, when transferring labelled potency into the clinical laboratory, will be even more challenging with new recombinant and/or modified products that are currently under development. The Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (ISTH/SSC) “recommendations on the potency labelling of Factor VIII and IX concentrates” were praised for their systematic and harmonized approach during the workshop and it was concluded that new products fall into the flow diagram of the ISTH/SSC recommendations. When linking assay results for recombinant products to clinical efficacy, the variability is acceptable when the available plasma derived standards are used, but there is more variability with new long-acting products. This increased variability leads to the question of whether actions should be taken to make the testing results more accurate and meaningful. There are several options:

» Could product specific standards overcome these limitations and what would be the implications of such an approach?
» Do we need a new set of requirement for these new products in the form of individual European Pharmacopoeia (Ph. Eur.) Monographs?
» Should regulatory guidance determine the assay that has to be used for potency labeling, or give more than one option or leave the choice entirely to the manufacturer?

Currently in the Ph. Eur., only the chromogenic assay is described for labelling of clotting factor concentrates, while in clinical laboratories and regulatory areas outside of Europe, e.g., in the U.S., the one stage assay is predominantly used. In view of the fact that each test system produces a different result, there is a need to correlate one assay with the other, for example, by applying a conversion factor. In conclusion, there is a lot of variability. Even within one assay system there is an abundance of permutation between the individual assay systems, which could create different test results.

Discussions during the workshop led to noting steps to help remedy the problem. One remedy to improve the situation is the usual call for harmonized approaches among the different global regulatory agencies. In addition, there should more exchange of information between and within the regulatory agencies and the medical community.

The ultimate goal is to assist the clinician in managing his patients. It is generally known and accepted that the current testing technologies and measurements are crude. So when observed variability is the reality, what implications does it have for clinical decision making? How much variability can be tolerated when transferring the labelled potency into the clinical laboratory? A similar decision tree as in the above mentioned ISTH/SSC recommendations would be helpful for clinical decision making, providing different evidence based options. It could also be considered to provide information on how the individual product performs in real life.

There is evidently no “one size fits all” solution. But it should be kept in mind that there is a significant amount of clinical experience which should not be underestimated. In view of the fact that variability within assays of up to 40% has not caused an issue, one may conclude that the most important factor is still the knowledge, experience and judgment of the clinician.

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