Incurred sample reproducibility

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First draft submitted: 1 October 2018; Accepted for publication: 10 October 2018; Published online: 13 November 2018

Keywords: bioanalytical • incurred sample reproducibility • industry experience

For more than a decade, incurred sample reproducibility (ISR) has been one of the most debated discussions in regulated bioanalysis. By and large, the industry acknowledges the value and importance of ISR to ensure the reproducibility of a newly developed method as a postvalidation experiment when applied for the first-time incurred samples. However, concerns remain about the cost efficiency of the practice. As guest editors, we thought it is time to reflect on ISR application and practice and to bring a few industry opinion leaders together in a special issue of this journal to learn from their experiences and vision on the theme.

In the first two editorials, the guest editors have provided the historical perspectives on ISR, its genesis and evolution with an outlook on how we can build on what we have learned during the past decade [1,2].

In his thoughtful editorial, Fluhler discusses the extent of the ISR currently applied by the industry. Although the editorial clearly acknowledges that ISR adds scientific value and rigor during its first application early on, and when changes in the matrix composition and metabolism are anticipated, it questions the extent of it beyond the mentioned activities [3]. In particular, it draws attention to take caution in its requirement, when ISR is used as an extra quality control measure, given the increasing costs associated with drug development.

Timmons *et al.* reflect on the advantages of the ISR and regards ISR application to all studies as a sensible decision as it reveals human error, instrument error, reagent issues and population differences in addition to method reproducibility issues [4].

The European Bioanalysis Forum (EBF) has conducted three surveys in 2016 and 2017 to collect feedback on ISR from the EBF community. These surveys, which covered data from more than 5000 studies, were quantitative with a focus on the ISR scope as well as failed IS and ISR failure rates. Kall *et al.* describe the surveys and propose recommendations [5] on ISR conduct based on the survey results and further discussions at EBF meetings, and at the Weehawken and Lisbon bioanalytical method validation harmonization sister meetings cosponsored by the American Association of Pharmaceutical Scientists (AAPS), EBF and Japan Bioanalysis Forum [6,7]. Importantly, they bring to the reader's attention the inclusion of the biomarkers in the US FDA 2018 guidance [8], broadening the scope of ISR further.

Summerfield *et al.* [9] share their experience with ISR from over 1000 bioanalytical studies. Only 26 cases out of all cases reviewed required any types of investigation. Furthermore, only a few of ISR investigation cases lead to the rejection of full or partial bioanalytical datasets. They have provided the reasons for these failures. The group has also reviewed the variability in passing ISR studies (scatter of results and flyers), which provided further insight into the sample selection.

Arfvidsson *et al.* [10] share the learning and experience in application of ISR at AstraZeneca over the last 10 years. They discuss the implementation of ISR for capillary plasma microsampling, a strategy used by AstraZeneca for rodent blood sampling since 2012. They also call to attention the importance of the transfer of knowledge between preclinical and clinical method development and production runs in mitigating ISR failure in early clinical development.

Verhaeghe offers [11] examples of ISR failures encountered by his group since its implementation within Janssen R&D. The majority of the examples were tied to instability issues or human error. Based on the low failure ratio (only 2%), the root cause of the failures observed, and the cost of sample analysis, they recommend limiting the number of studies requiring ISR, as well as the number of required ISR samples within the selected studies to a minimum.

Lee and Wickremsinhe [12] take a deep dive into each study conducted after the implementation of ISR within his group and provides stats on the individual failed ISR samples per year in five independent laboratories. A few examples are provided with the action taken and the conclusions. In general, the overall reported ISR failures are less than 5%. The majority point to human error with a few caused by instability or method issues. Based on the observed failures, they recommend ISR to be performed early to detect method issues and analyte characteristics.

We hope you will enjoy the contributions to this special issue and hope it can contribute to the continued scientific discussion and, importantly, that ISR can bring the best value in balance with the resources it requires.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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