Roundtable Session – Table 7 – Sustainability and the 3Rs

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Abstract:

Environmental sustainability and the 3Rs (Replacement, Reduction and Refinement of animal use) are increasingly recognized as important considerations across the lifecycle of medicinal products, including analytical development, control strategies and standard-setting activities.

Discussion Questions:

1. Analytical procedures and sustainability

Analytical procedures represent a key area for potential improvement. Current reflections include awareness of solvent and reagent use (greener analytical approaches); considering lifecycle aspects in method development; identifying where more sustainable alternatives could exist. To what extent is sustainability currently considered in analytical procedure development? What are the main barriers (e.g. regulatory, technical) to implementing greener analytical approaches?

2. Reduction of animal use (3Rs) in quality control and development

Scientific developments increasingly explore alternatives to animal testing (e.g. *in vitro* methods, advanced analytics), but their applicability remains context dependent. Current reflections focus on exploring where transitions from *in vivo* to *in vitro* could be feasible, understanding the role of emerging analytical techniques, identifying opportunities to avoid duplicate testing. Where do you see realistic opportunities to reduce animal use in CMC and quality control? What are the key scientific or regulatory hurdles to broader adoption of alternative methods? How can confidence in non-animal approaches be strengthened?

3. Testing strategies, lifecycle management and sustainability

Sustainability is also linked to how much testing is performed and how data are used. Reflections include promoting risk-based approaches and better use of existing data, reducing unnecessary testing through improved comparability and control strategies, exploring how standards could support more efficient and sustainable manufacturing. Where do you see the biggest opportunities to reduce unnecessary testing? How can regulatory frameworks better support data reuse and risk-based approaches? Are current expectations aligned with sustainability objectives?

Notes:

- When **developing new products**, companies consider opportunities to reduce waste, solvent consumption, reagent use and containers/packaging materials to achieve a greener footprint (how to reduce containers? Solvents?) Any challenges? The more testing you need to do the more waste you get in terms of reagents, containers etc. It is **not easy to find greener alternatives**.

- For **approved (commercial) products** it is more difficult to move to more sustainable materials or methods (e.g., move out from plastic bags etc). It is easier if you **introduce sustainable materials from the start** in early stage of the development of a new product.

Examples provided by participants:

- In clinical facilities it is easier to switch from LAL to recombinant factor C (rFC) method for endotoxin testing. For commercial products it is difficult to switch because you must update your process/method and demonstrate to regulators it is acceptable (data and comparability). *Of note: rFC was introduced in the Ph. Eur. general chapter 2.6.14. Bacterial endotoxins and, as of the publication of the revised general chapter in Issue 13.1 (April 2026, with an implementation date of 1 January 2027) is fully integrated as one of the seven official methods available for bacterial endotoxin testing (see EDQM FAQ Pyrogenicity).*

- Looking at the example of using **recombinant cascade reagents (rCR) instead of recombinant factor C**. Sometimes it is long waiting for the pharmacopoeia to be updated, and if the method is not yet implemented in a pharmacopoeia, companies need to file a variation for the introduction of a new, non-pharmacopoeial method. *To be noted that BET involving rCR or any other new reagents are considered to be alternative methods replacing a pharmacopoeial test, as described in the General Notices. Generation of robust data, including practical experience and approval of medicinal products using rCR, is essential to support their future consideration for inclusion in the Ph. Eur.*

- When **working with CDMO** it is difficult to make them switch to recombinant factor C (or recombinant cascade reagents), even for new projects. Adoption timelines may vary across CDMOs depending on their technical readiness, existing platform capabilities and investment priorities.

- Challenge for companies: when switching method, during the **transition period** companies have to do **double testing**, which puts a burden on companies (in terms of time, resources). Need to demonstrate comparability and continue to generate data with the old assay (including stability data). It is also considered a risk taken from the companies to implement a new, alternative method, not knowing whether it will be approved by all health authorities globally. **Need to engage very early** discussion with authorities in EU and outside of EU. Reference made to QIG listen-and-learn focus group which aims to support proactive adoption and implementation of innovative technologies to advance sustainability goals in the pharmaceutical sector

- **Double testing question** when switching to a new method: if you have approval from major markets, can you implement the new method at risk? This is considered a **company quality risk** / depends on the company quality system maturity. If implementing at risk, companies may

face supply issues because they don't have any pre-change batch any longer to supply to those countries where the change is not yet approved.

- How **can regulators help companies make** these changes?

  - Sustainability initiatives and evolving regulatory expectations are encouraging companies to evaluate opportunities for more sustainable practices.
  - **Discussions with HAs** are appreciated by industry and seeing HA's engagement is really appreciated by industry.
  - **Enabling change** is seen as crucial / how can HAs help accept the alternative testing to have streamlined approaches?
  - **Carefully designed methods** by companies
  - Industry **needs clarity on what will happen long-term** and consider also more countries (global submissions)
  - Legal issues differ from countries
  - The phasing out of the RPT in Europe is highlighted as a good case (fast in EU but still requires implementation in other regions - need for pioneer companies to bring the alternative methods forward. However, companies don't take the risk of not submitting it as they may face rejection by HAs)
  - **Flexibility supported by pharmacopoeia**, no barriers to use innovative methods

- where are the **biggest opportunities** to reduce unnecessary testing?

  - companies are interested in opportunities to reduce unnecessary testing (for cost reduction). Where testing is required by the pharmacopoeia, it remains an important component of the control strategy. Opportunities may exist to explore alternative methods with a lower environmental footprint (e.g. reduced solvent consumption), where scientifically justified and appropriately validated.
  - Is there any possibility of **streamlining the sites that are performing the testing**? Usually many sites are involved in testing (e.g., proposal having one single centralized testing site performing QC testing of DS/DP for different manufacturing sites but this is risky; preferred to have a back-up site).
  - **Shipment of samples** from one site to another is an aspect of sustainability.
  - HA requirement for **local testing for some countries** creates a double testing / additional burden
  - BET is tested at every step of the process for each batch, is **there any opportunity to reduce** the testing (based on process and product knowledge)? Unfortunately, some issues are observed by regulators. The risk of reducing the number of batches tested is considered high (**low probability but high impact**). Risk-based approach: test endotoxins later in the process, once you have validated the process (for LCM).

- Companies have their **own policies** on how to approach sustainability. **Ongoing engagement between industry and regulators can help build a broader understanding of the practical sustainability challenges faced by companies**.

- **PFAS are a huge sustainability challenge**, especially for inhalers (used in the manufacturing line). But because of patient's needs it is risky to switch to different ways of manufacturing or testing. What substitutes are available? **Significant number of open questions and uncertainties on this topic**.

- 3Rs: pushing to moving out from animal testing, replace by in vitro test methods.

- for development of new products, are new designs considered compared to old products that are in the market? Flexibility in control strategies for newer products; **difficult to bring the older products up to the new standards** or new testing strategies.

- Both pharmacopoeias and regulators support the use of new non-pharmacopoeial/alternative methods **(flexibility provided by the European Pharmacopoeia),** but methods need to be validated and compared to the established methods. To bring new methods into pharmacopoeia, the methods need to be mature enough and used for approved products.

- For companies who want to implement new methods, is there anything that can be **leveraged (guidance/data)?** Is there a description of an approach that can be taken to implement and verify a new method?

    - **Bioforum and EFPIA** are working together to provide a step-by-step approach that companies can use when implementing new methods. We see some pioneer companies moving out from LAL test and could be used as case study.
    - **Publications on Collaborative studies** (e.g. method standardization coordinated by the EDQM)
    - **Generic validation** and product specific data are required

- **AI/digitalization** is seen as a big sustainability issue, although the environmental cost is not visible.