

Reliance Practices, Availability of reagents and standards on novel assays: scarcity, costs, complexities on import & characterization



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In this presentation the following points will be discussed :

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- 6. Storage and distribution of antibody critical reagents
- 7. Strategies For Successfully Managing Critical Reagents
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Good Reliance Practices

Good reliance practices (GRelP) are anchored in overall good regulatory practices (GRP), which provide a means for establishing sound, affordable, effective regulation of medical products as an important part of health system strengthening.

- ▶ Reliance represents a smarter, more efficient way of regulating medical products in the modern world, Reliance benefits patients and consumers, industry, national governments, the donor community and international development partners by facilitating and accelerating access to quality-assured, effective and safe medical products.
- ▶ Countries are therefore encouraged to formulate and implement strategies to strengthen their regulatory systems consistent with GRP, including pursuing regulatory cooperation and convergence, as well as reliance.

Good Reliance Practices

In developing a strategy on the use of reliance in regulatory functions and activities, an NRA should consider the needs and characteristics of the national health and regulatory systems, existing capacity, regulatory systems' needs, the availability of an authority on which the NRA can rely with confidence and how reliance could complement the capacity to increase efficiency and make optimal use of resources.

- Reliance is not a lesser form of regulatory oversight but rather a strategy for making the best use of the available resources in any setting. This would allow the allocation of resources to other regulatory functions, such as in-country vigilance and post authorization activities, thereby increasing the effectiveness of local regulatory oversight. In addition, reliance can result in more evidence-based, better-quality decisions.
- **An Intention to build mutual confidence amongst NRAs/NCLs, reduce redundant testing, promote the development of common standards and facilitate the sharing of best practices.**

Good Reliance Practices

Regulatory harmonization through standardization of quality assessment and testing methodology is crucially important for improving access on a regional and global scale. The increased speed of development of information technology and biotechnology has become unprecedented, and keeping up with global harmonization of biological norms and standards is increasingly challenging. As a result, policies, strategies and standards used by NRAs/NCLs for quality assurance and quality control of biological products has become divergent.

- ▶ This therefore necessitates the need to promote regional networking based on commonality of regulatory policies and strategies, existence of market or demand on a particular class of products, existence of domestic biological research and production, and developmental history of manufacturers and control laboratories for each country. A continued exchange of information and sharing of good practices across NCLs is an important mechanism to collectively address these challenges.

The role of industry

- ▶ In line with WHO's belief in reliance on the work of other regulators as a general principle in order to make the best use of available resources and expertise, manufacturers of vaccines too are in support of the same.
- ▶ This principle allows leveraging the output of others whenever possible while placing a greater focus at national level on value-added regulatory activities that cannot be undertaken by other authorities, such as, oversight of local manufacturing , lot release and distribution.
- ▶ Reliance facilitates timely access to safe, effective, quality-assured vaccines /biologicals and can support regulatory preparedness and response, particularly during public health emergencies e.g. Covid 19.

The role of industry

Industry plays a crucial role in successful use of reliance mechanisms by NRAs. While industry widely supports reliance as a concept and practice that can increase efficiency and see meaningful benefits. Industry support and stringent adherence to the factors that validate the reliance process are essential for filing applications in several countries or regions to ensure the sameness of products submitted to reference regulatory authorities and relying NRAs.

- ▶ Collaboration and dialogue among all stakeholders participating in regulatory reliance activities will help to create and build trust, which is the foundation of regulatory reliance. Transparent publication of an NRA's reliance framework and strategies, including the metrics used and benefits achieved, will encourage industry to support and promote the reliance approach.
- ▶ In case of a public health emergency, reliance approaches are even more essential and should be given more importance in order to accelerate access to the medical products required.

Reference Standards

It is important that the reference standard is well characterized and the quality (e.g., purity, identity) of the reference standard and the suitability of the Internal Standard is ensured, as the quality will affect the outcome of the analysis and, therefore, the study data. The reference standard used during validation and study sample analysis should be obtained from an authentic and traceable source.

- ▶ The reference standard should be identical to the analyte. Suitable reference standards include compendial standards, commercially available standards or sufficiently characterized standards prepared in-house or by an external organization.
- ▶ A certificate of analysis (CoA) or an equivalent alternative is required to ensure quality and to provide information on the purity, storage conditions, retest/expiration date and batch number of the reference standard.
- ▶ Stock and working solutions should only be prepared from reference standards that are within the stability period as documented in the CoA (either expiration date or the retest date).

Managing Critical Reagents

Critical reagents are an essential part of bioanalytical testing for large molecule preclinical and clinical studies. Critical reagents can refer to a variety of compounds, including: Antibodies, peptides, engineered proteins, complex biologics and peptide conjugates etc.

- These essential components help determine the accuracy of the analyte, precision and performance of assays, which are key to measuring the efficacy of compounds and providing insights into proper dosing. This means users need to carefully characterize and document critical reagents early in a suitable formulation with demonstrated stability.
- To ensure consistent assay performance, the identity and quality of critical reagents need to be well controlled during their production.

Critical Reagents: Challenges and Risks

The first factor that makes critical reagents challenging to produce and manage is that they are natural biological compounds. That makes them immensely susceptible to variability. “Variability” refers to compounds naturally changing or morphing, which undermines control group validity in a study. Without the consistency a control provides, assay results cannot be fully validated and may be inaccurate.

- ▶ To mitigate variability issues, researchers must monitor critical reagents’ stability to ensure quality and accurate characterization. If the reagent is out of stock or outside the re-test date, scientists should determine if the changes are minor or major to the assay. The current ICH M10 guidance explains that major lot changes will significantly impact the assay, whereas minor changes are those that don’t impact performance as drastically.
- ▶ Regulatory requirements are the second challenge that developers need to consider when dealing with critical reagents. For example, ICH M10 underscores the importance of critical reagents by pointing out that they directly impact assay results—alongside binding agents like binding proteins, antibodies and conjugated antibodies.

Critical Reagents: Challenges and Risks

- ▶ The U.S. Food and Drug Administration (FDA) and the American Association of Pharmaceutical Scientists (AAPS) also provide helpful recommendations for best practices when assessing critical agents.
- ▶ The U.S. FDA [Bioanalytical Method Validation](#) (BMV) specifically advises that “assay validation is important when there are changes to the critical reagents, such as lot-to-lot changes or switches to another reagent.” Other factors that may impact assay functionality, such as changes to labelled analytes, detector reagents and antibodies, should trigger specific processes. It is also guided that a developer needs to evaluate binding and re-optimize assays, verify performance with a standard curve and QCs, and evaluate cross-reactiveness when these changes occur.
- ▶ The AAPS also details processes for managing critical reagents, including designing the reagent, assigning stability, and altering procedures for minor and major lot changes.

Critical Reagents: Challenges and Risks

- ▶ Antibody critical reagents are crucial to regulated (GxP) drug development assays. Poor quality reagents risk generating inaccurate and unreliable results, while failure in supply can delay preclinical and clinical studies. Overall, the potential consequences are losses in time, money and reputation. Read on to understand the key challenges in antibody critical reagent production and supply as the first step to de-risking your product lifecycle.
- ▶ The key challenges in the management of antibody critical reagents relate to:
 - **Generation of initial and subsequent lots**
 - **Characterization**
 - **Storage and distribution**



Critical Reagents: Challenges and Risks

How much antibody critical reagent should you generate and what happens if you run out?

- ▶ As reagents are often generated in large lots, there are difficulties associated with their management. Planning for, and guaranteeing, a continuous supply is challenging because the lifespan of an assay can range from months to years depending on the stage of drug development, which makes it difficult to predict the length of time you will use the reagents. There needs to be a balance between producing a large quantity, which is not cost effective, versus producing too little and not being able to generate consistent additional lots. If needed, one has to create a credible plan and criteria for bridging between lots.
- ▶ ***Ensuring reproducibility between lots***
- ▶ When a new lot of reagent is produced, it must meet a set of established criteria for characterization and assay performance. These criteria provide information to compare initial and subsequent lots to decide whether they are suitable for use. Here, the challenges are to establish the criteria, and to use these criteria to verify assay performance with new lots.

Critical Reagents: Challenges and Risks

- **Characterization of antibody critical reagents**
- The structural integrity and stability of reagents are directly related to assay performance. Therefore, it is important to ensure reagent consistency by regular characterization.
- ***Defining assay performance criteria and ensuring consistency in their application***
- Reagents are characterized in terms of their sensitivity and specificity. These characteristics determine the optimal performance of both quantitative assays (e.g., PK or biomarker assays) and quasi-quantitative assays (e.g., immunogenicity assays).
- ***Defining shelf-life and managing dozens of re-test dates***
- The reagent expiration or re-test date provides the period it will meet established characterization criteria. The expiry/re-test date, which should be based on formulation, storage conditions and available biophysical and functional data, can range from 2–10 years. Managing dozens of re-test dates is challenging.

Storage and distribution of critical reagents

Degradation during storage

- Storage can degrade antibody critical reagents via chemical (e.g., oxidation or deamidation) or physical (e.g., aggregation or misfolding) mechanisms, thus altering the characterization profile. Given this, the formulation must be carefully considered. For example, additives can help minimize changes in the structure or function of the protein on storage (e.g., cryoprotectants, stabilizers, preservatives, etc.).
- ***Poorly controlled storage environment***
- Antibody critical reagents are typically produced in bulk and stored as concentrated samples. Fluctuations in storage conditions, like temperature, can alter the characterization profile of reagents. Facilities without appropriately maintained environmental storage conditions can cause antibody critical reagent degradation. As many antibody critical reagents are stored in freezers or fridges, failure in power supply or damage of facilities due to the impact of natural disasters, such as flooding or tornados, can also put lots at risk.

Storage and distribution of critical reagents

Managing inventory across multiple sites and vendors

Inadequate inventory management increases the risk of running out of qualified reagents, which can cause delays when resupplying the antibodies. It may also cause issues in retrieving important information about the reagent.

- For companies with only one or two products, managing four to five critical antibody reagents per product does not sound too time consuming, but when scaled up per product (especially for larger pharmaceutical firms with multiple assets in various development stages), effective reagent management becomes complex and time consuming.
- **Getting the right reagent to the right place at the right time**
- Assay methods and reagents may move from one laboratory to another, either internally or externally to a CRO. Therefore, efficient distribution between laboratories is necessary for timely data collection. Failure at any point in the distribution chain can have wide-reaching implications, which need to be assessed, communicated and fixed.
- **What are the implications of antibody critical reagent failure or supply delay?**
- Without appropriate generation, characterization, storage and distribution of reagents, there is a substantial risk of stalling preclinical development and/or delaying clinical trials. Without sufficient and consistent management processes, valuable resources are wasted conducting experiments to generate and test new lots of reagents.

Strategies For Successfully Managing Critical Reagents

- ▶ Given the challenges associated with critical reagents, organizations need to adopt productive and efficient management strategies. Chief among these is prioritizing characterization and documentation throughout the process. Researchers must conduct proper validation and bridging testing across lot changes and any substitutions of reagents. It's also recommended that scientists conduct three distinct runs to document performance and limit any variation.
- ▶ To ensure proper critical reagent management, developers should consider working with a testing partner that includes a comprehensive bioanalytical laboratory staffed by experienced scientists. When vetting potential partners, ask specifically about their experience characterizing and managing critical reagents. Collaborating with a testing partner can also reduce testing and expertise barriers and ensure your research methods and results are accurate, reliable and compliant.

Strategies For Successfully Managing Critical Reagents

➤ Regulatory support / Reliance is required in terms of:

- Import and export of critical reagents as stringent rules for cross border trade hampers the free movement of such agents, more so if these are of animal origin or contain live viruses/bacteria.
- Promotion of development of common critical reagents to be encouraged which can be available on Global/Regional or National networks e.g. NIBSC/EDQM supplies International Standards or IRM for many Vaccines/Sera and Biosimilars globally, similarly Regional Working Reference Standards and National Reference Standards are also available. This can be done both for human as well as veterinary vaccines.
- Establishment/optimisation of test methods and make standard operating procedures available to ensure a harmonization between countries and regions so as to avoid redundant testing.
- Conducting Collaborative Studies/ Proficiency Testing Studies between the manufacturers and NCLs thus helping in standardization of the tests/assays using the common/different reagents. This may help in reduction of variability in test results when compared between the two.

Strategies For Successfully Managing Critical Reagents

➤ Vaccine Manufacturers Associations/Networks need to :

- Collaborate in providing training (Hands on, E learning courses, Webinars etc) on the use/validation/verification/characterization of critical reagents.
- Collaboration also required for discussion with industry partners (vendors and users) in 1) Nominal Price Fixation and 2) Developing channelized distribution of the critical reagents so as to avoid shortages and delay in supplies.
- Encourage research and development of reagents in respective regions.
- Enter into discussion with Pharmacopoeia commissions to publish the usage of newer agents including strategies for verification/validation and also implementation of replacement of in vivo assays with invitro assays and finally to push for harmonization amongst different Pharmacopoeias.

Future of critical reagent management

- ▶ The focus on critical reagents is increasing. As the industry continues to increase the number and complexity of biotherapeutic drug molecules, we are witnessing a direct correlation in the demand for high-quality reagents and scrutiny, including regulatory agencies, of these same antibody reagents.
- ▶ Unfortunately, current regulatory guidelines on the management of antibody critical reagents are limited. Certain regulatory guidelines do exist but lack specific recommendations on stability assessments, expiry/re-testing, characterization and monitoring of assay performance. For example, recommendations are unclear on defining in-house re-test dates of commercial reagents when given vendor-specified expiry dates. With limited regulatory guidelines, organizations define and follow their own processes for characterization, qualification and monitoring of reagents. However, regulators are beginning to understand the importance of antibody critical reagents, and a renewed focus in this area of regulation may be likely.
- ▶ Advances in production and characterization of antibody critical reagents to match innovations in drug development are expected, so keeping ahead of those will be important to the future of antibody critical reagent supply chain.

Conclusion

Complications with production/generation and management of critical reagents represent a major risk to the efficiency, effectiveness and cost of drug development process. One can start de-risking the process by carefully reviewing the approaches you take to generate, characterize, store and distribute antibody critical reagents to ensure you join up these different areas to optimize supply.

- A comprehensive, seamless service can protect and optimize the management of your antibody critical reagents
- Through long-term partnerships with large and small pharmaceutical companies who are well aware of the challenges of reagent management, effective risk management can be optimized and help in protecting one's reagent portfolio's integrity and supply.
- Join hands with the vendors who have an expertise to build a comprehensive, end-to-end service that takes the worry and risk out of the generation and management of antibody reagents.
- Ensure that the service delivery agents are consistent and are able to deliver reliable antibody critical reagents: efficiently generated, and well characterized, stored safely and distributed to when and where needed and at an economical price.

To Summarize

In this presentation the following points were discussed :

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I acknowledge that certain material has been extracted from the following published literature and utilized in the preparation of this presentation:

- 1. WHO TRS 1033, 2021 - Annex 10 Good reliance practices in the regulation of medical products: high level principles and considerations.
- 2. ICH Guideline M10 - Bioanalytical method validation and study sample analysis.
- 3. Current and Effective Strategies for Critical Reagent Characterization, Storage, Stability, Retesting and Life Cycle Management for Ligand-Binding Assays and Flow Cytometry : [Lakshmi Amaravadi](#), [Nisha Palackal](#) and [Fabio Garofolo](#) , Bioanalysis; 2021 May;13(10):737-740.
- [4. Webinar: Critical Reagent Management Strategies](#)
- 5. Brochure - WuXi AppTec Laboratory Testing Division



Thank you

Principles of good reliance practices

- ▶ The following principles are meant to complement and extend the basic principles of GRP. They are based on the principles presented in the concept note and recommendations on regulatory reliance principles of PAHO and the Pan American Network for Drug Regulatory Harmonization.
- ▶ **1.Universality**
- ▶ Reliance applies to all NRAs, irrespective of their levels of maturity or resources. Different NRAs use reliance for different reasons. Some use it to increase or build in- house capacity when there is the requisite expertise but not enough to perform their regulatory work as efficiently as they would like. Others use reliance to gain expertise that they do not have locally. Reliance is relevant for all resource settings.
- ▶ **2.Sovereignty of decision-making**
- ▶ The decision to practise reliance and how best to do so rests with the national health regulatory authority. Reliance does not imply dependence; it is not an agency out-sourcing its decision-making authority or responsibility. In applying reliance in daily practice, NRAs maintain independence, sovereignty and accountability in regulatory decision-making.
- ▶ **3.Transparency**
- ▶ Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations, both locally and internationally. NRAs should be transparent about the standards, processes and approaches they adopt in implementing reliance measures. NRAs should engage with all stakeholders, including industry, to ensure the appropriateness and awareness of reliance processes.

Principles of good reliance practices

➤ 4. Respect of national and regional legal bases

- Reliance practices should be coherent with national and regional legal frameworks and policies on medical products, supported by clear mandates and regulations that ensure efficient implementation of reliance as part of government policy on good regulation. Use of reliance does not obviate the need for a capable local regulatory authority; on the contrary, it should be used to maintain and build local capacity for regulatory decision-making. Reliance can be implemented through policy change, as long as it is broadly consistent with national legislation. If application of reliance is prohibited, revision of the legislation should be considered within a reasonable timeframe.

➤ 5. Consistency

- Reliance on an assessment or decision from another authority should be established for specific, well-defined categories of products and processes. The scope of regulatory activities in which reliance may be practised should be clearly defined, and the practise of reliance should be transparent and predictable. Thus, reliance should be expected to be applied consistently for products and processes in the same categories.

Principles of good reliance practices

➤ 6. Competence

- Implementation of reliance approaches requires that NRAs have the necessary competence for critical decision-making. Introduction of the reliance approach usually requires the involvement of senior regulatory staff, managers and experts who are competent to make the best use of foreign information in the local context.
- NRAs should maintain the appropriate scientific expertise of their staff for activities in which they do not apply reliance, such as monitoring local adverse events, market surveillance and control, national labelling and product information activities and for oversight of locally manufactured products.
- Equally, the authorities being relied upon should have and maintain competence and operate within a robust, transparent regulatory system based on international standards and guidelines, as well as GRP, and a well-functioning quality management system. Competence may be benchmarked through transparent processes for developing trust and building confidence in the reference authorities.

Principles of good reliance practices

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 - 1. Universality
 - 2. Sovereignty of decision-making
 - 3. Transparency
 - 4. Respect of national and regional legal bases
 - 5. Consistency and
 - 6. Competence