ATMP POTENCY ASSAY STRATEGIES:

Adding Value to Your Asset and Avoiding Delays in Development

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Introduction

Potency assays are used to monitor the quality, consistency and stability of medicinal products and are crucial to chemistry, manufacturing and control (CMC), as well as clinical development.

Potency assays are a legal requirement for medication approval, so deficiencies in assays can delay or prevent medications receiving a marketing authorization. Furthermore, deficiencies in potency assays can result in significant clinical development delays. For antibodies, approaches for creating suitable potency assays throughout a product's development are well established; however, this is not true for the evolving field of cell and gene therapies (CGTs), where the complexity and heterogeneity of products make the creation of a standardized approach challenging, if not impossible. Regulators evaluate the adequacy of CGT potency assays on a case-by-case basis, according to the unique characteristics of the CGT. This means that potency assays need to be carefully designed and planned, in a product- and therapeutic-modality specific manner, to ensure that they will meet regulatory approval. This can pose some risks to product developers, who generally focus on clinical efficacy and safety in early development, often at the expense of potency assays, which are perceived as more relevant to laterstage manufacturing. Given the vital importance of potency assays to the eventual license and release of a therapeutic, it is crucial that sufficient focus is given to their development earlier in the product life cycle.

This shift in mindset regarding clinical development and manufacturing of CGTs is best captured in a 2018 quote from Scott Gottlieb, the former U.S. Food and Drug Administration (FDA) Commissioner.

Although some CGTs may receive accelerated or fast-tracked designation, CMC, and in particular the potency assay, will not be afforded any shortcuts.

The investment in CGT investigational new drugs (INDs) continues to grow, although many products fail to receive a license (Figure 1). Product failures may have multiple reasons. A recent survey of CGT developers investigated the major barriers companies faced in licensing their therapeutics via the European Medicines Agency (EMA). Among a cohort of 68 commercial developers, the most frequently cited challenges were those associated with regulatory requirements (34%) and manufacturing (30%) – the latter including scale-up challenges related to product inconsistency and quality standards including potency assessment.[1]

This white paper discusses the value of planning potency assays early in the clinical development process, explains some of the barriers to potency assay development and regulatory acceptance, and provides some top tips on how to overcome potential hurdles.

> A lot of the complexity with gene therapy is in product-related issues, not the clinical issues. Whereas with normal drug review, I'd say 80% is the clinical portion and 20% is the CMC and product portion of the review, I think with gene therapy and cell-based regenerative medicine, it's completely inverted. We're having to think very differently about the regulatory issues with these.

Figure 1: A Snapshot of the CGT Market[2-5]

A NOTE ON TERMINOLOGY
In the European Union, CGTs are categorized as Advanced Therapy Medicinal Product (ATMPs), a legal term that covers gene therapy, somatic cell therapy and tissue-engineered products. We have used the term cell and gene therapy (CGT) throughout this article.

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The Value and Challenges of Potency Assays

Potency is a critical quality attribute (CQA) of any CGT. Without validated potency assays, a therapeutic product cannot be licensed and lots cannot be released. Potency assays are not a just a final checklist for manufacturing – they can be leveraged to smooth the regulatory and development journey of a therapeutic, reducing development and licensing delays.

The Purpose of Potency Assays

Potency is a fundamental element of product characterization. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) definition of potency in quality guideline Q6B is "Potency (expressed in units) is the quantitative measure of biological activity based on the attribute of the product which is linked to the relevant biological properties."[6] This definition clearly links potency to mode of action and clinical efficacy, meaning that any potency assay should correlate with the expected clinical response.

Potency assays, therefore, provide information about the clinical effect expected from a dose of product and reassurance that the manufacturing process is performing reliably to produce consistent doses. Potency assays may be *in vivo*, *ex vivo* or *in vitro* tests (Table 1) and can employ a wide range of technologies; what is important is that the assays are specifically designed to provide an adequate measure of potency appropriate to each product.

Potency Assays for CGTs

Detailed product characterization is essential for CGTs, which are complex products, given their nature and heterogeneity. While traditional biotechnology products tend to be large molecules with complex higher-order structures, CGTs, in most cases, include a cellular component which increases their complexity almost exponentially. Compared with small molecules or recombinant therapeutics, they have less clearly defined structure-function relationships and the processes used in their manufacture are more complex.

Table 1: Examples of Potency Assays

Type of Assay		Assays and Readout
In vivo		Animal death / survival / tumor shrinkage
Ex vivo		Dose administration – humoral / cellular response / cytokine profiling
In vitro/ ex vivo	Level 1	Cell proliferation / growth arrest / cell death / motility / differentiation / infectivity
	Level 2	Alteration of intracellular pathways / presence of active transgene products
	Level 3	Expression of transgenes / alteration in transcriptome

Unlike traditional biotech products, which can use a wide range of orthogonal physicochemical assays for product characterization, orthogonal methods for CGTs may be unavailable or provide unclear results.

In such cases, the potency assay may be the linchpin for CMC. However, given the complexity of CGTs, a single assay may not provide all the information needed, so a matrix of potency assays may be required.

Each assay in the matrix addresses an individual aspect of the mode of action of the CGT, with the overall potency assessment represented by the totality of the results for the battery of individual tests.

Tables 2 and 3 summarize some of the benefits and challenges associated with potency assays.

Table 2: Summary of the Values Associated with Potency Assays

Value of a Potency Assay
• Prerequisite for biological license application (BLA) approval
• Prerequisite for release of manufactured lots of therapeutics – evidence of conformance to standards related to potency, sterility, purity and identity is required
• Demonstrates the product activity, quality and consistency at all stages of the development process
• Acts as an early indicator of manufacturing quality – like the "canary in the mine"
• Enables comparability of a therapeutic before and after changes to the manufacturing process
• Enables the generation of data to support specifications for lot release
• Evaluates product stability and helps establish shelf life
• Required to establish compatibility of the therapeutic with product contact materials
• Controls clinical dosing consistency

Table 3: Summary of the Challenges Associated with Potency Assays

Challenges Associated with Potency Assays
• Variety of CGTs means that assays are dependent on the therapeutic – there is no "one-size-fits-all"
• Amounts of the therapeutic that are available for testing may be limited
• The viability or stability of the test materials may be limited
• Mechanism of action may not be fully understood
• A well-established reference standard may not be available
• It can be difficult to accurately predict in vivo fate
• It can take time to develop and validate potency assays; if this is left late in development, it can cause regulatory delay

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When to Start

The best time to start evaluating potency assays is in the early stages of product development (preclinical onward) as data and knowledge about a CGT are being generated. Relevant information should be reviewed to establish the data that might be useful and different methodologies should be screened to establish which techniques could form the basis of potency assays.

As further data is built throughout preclinical and clinical development, potency assays need to be refined and enhanced to optimize their measurement of the biological activity, so that established assays can be easily validated in a timely manner – ICH Q2.7 The assays and acceptance limits need to be established in advance of Phase III, as they will be needed for Phase III release lots (Figure 2).

Investment in potency assay design during the early stages of development can enhance the clinical development program and also reduce the need for greater expenditure further down the line – think of Benjamin Franklin's old adage, "an ounce of prevention is worth a pound of cure."

Figure 2: Potency Assays Through the Clinical Development Process

	Early Product Development			Late Product Development	Biologics License
	Preclinical	Phase I	Phase II	Phase III (pivotal)	
Potency assay focus	• Patient safety is the main concern and focus for testing • Establish broad acceptance criteria evaluated with physicochemical and biochemical testing data as the basis for further testing and assay development			• Establish appropriate limits for potency to ensure that product lots are well-defined, biologically active and consistently manufactured • Establish stability to inform expiry date for licensure	• Describe and justify a validated potency assay within defined acceptance criteria • Use for lot release, product stability and product comparability
Challenges	• Difficult to set appropriate acceptance criteria for potency assays, because of limited manufacturing experience, product lots and lack of assay validation			• Trials may be placed on hold if potency assays are inadequate because the trial will be deemed to have a deficiency in its design	• A license cannot be granted and lots cannot be released if you do not have an accepted, validated potency assay

Assays and limits must be established for Phase III release lots

Validated assays ready for manufacture and release

Product characterization
- Understand the mode of action and the attributes that contribute to biological effect to guide assay development

Refine acceptance criteria
- Broader acceptance criteria become narrower towards clearly definably limits
- Panels of assays are refined and revised

Validate assay(s)
- Refined assay panel validation

Investment in potency assays
- Early investment of resources and funding can reduce later costs

Ongoing quality assurance and quality control

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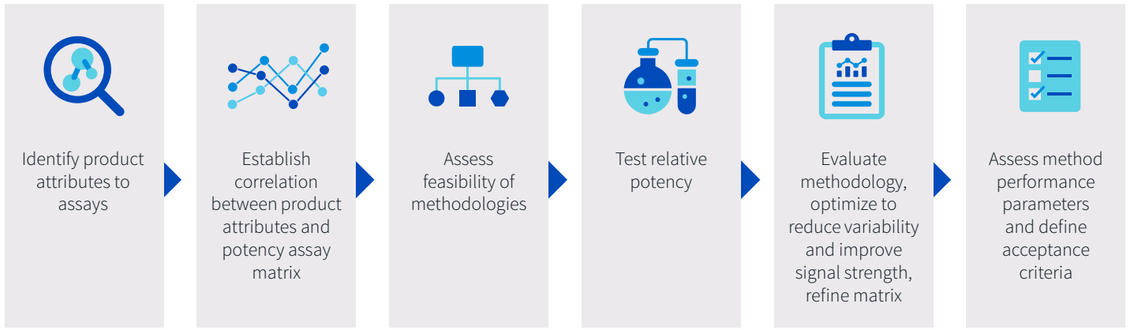
The Need for a Matrix Approach

It is highly unlikely that the potency of a CGT can be represented by a single assay, so a matrix of potency assays is usually required, certainly at the start of development. The data accumulated during development should, therefore, be reviewed to identify possible methodologies to build into a potency assay matrix. Figure 3 summarizes the key steps in developing a potency assay matrix.

Figure 3: Process for Potency Assay Development



The matrix will evolve over development as product knowledge increases and different methodologies are evaluated, leading to a reduction and refinement of the matrix. For programs that require a matrix approach, data-driven rationale to reduce the tests in the matrix could be derived in some cases, once a substantial knowledge base has been accumulated for all the assays in the panel.

It may be appropriate, for example, to replace a complex biological activity assay with a fast, quantitative polymerase chain reaction-based (qPCR-based) approach if it can detect quality issues as reliably and robustly as the functional assay. When replacing assays, it may be necessary to conduct a bridging study to demonstrate the adequacy of the replacement test.

Characteristics of Ideal Potency Assays

Although there is no “one-size-fits-all” model for potency assays, as the “ideal” will be unique to each product, some key characteristics, from both a practical and a regulatory perspective, should be considered when designing assays. The ICH quality standards provide essential information on relevant specifications.[7]

Reflects the Mode of Action (MOA)

Potency assays should represent the intended therapeutic activity of a product; that is, they should reflect its MOA.

> For example, if a therapeutic induces the expression of a protein that is otherwise absent or defective, then an appropriate assay of its MOA would be the measurement of the presence of the biologically active protein. If a cell-based therapeutic is designed to kill tumor cells, then assaying the death of these cells would indicate the MOA.

The MOA of CGT products can be complex, however, as multiple biological systems may be involved in producing the final therapeutic effect and it may be difficult to reproduce these biological pathways in their entirety. In such cases, it may be necessary to focus on specific aspects of the MOA.

> For example, if the biological activity of a therapeutic is conveyed entirely via cytokine secretion, a potency assay that demonstrates the presence and activity of these cytokines may be appropriate, rather than an assessment of the impact of each cytokine on the wider biological system.

It is important to consider all the ingredients in a therapeutic that contribute to the MOA, although the focus should be on those that are most relevant.

> For example, a gene therapy may rely on both the ability to transfer genetic material into the cell via a vector and the biological effect of the expressed gene. The potency assay needs to measure the gene transfer as well as the biological activity of the transferred gene.

Predictive of Product Quality

Potency assays are a CQA for the development and manufacture of therapeutics. They play an essential role in product characterization testing, comparability studies and stability protocols that ensure the therapeutic is manufactured to a consistent standard through all phases of clinical investigation. Crucial to this is the ability to correlate the potency of the product to its clinical efficacy. Ideally, a potency assay would unambiguously and reliably predict clinical efficacy, but this can be difficult to achieve. Instead, potency may have to be measured via surrogate markers or functional bioassays.

Stability

Stability and degradation are important aspects of product quality, as they determine the product shelf life – see ICH Q5C.[7] For non-CGTs, stability can often be measured using a physiochemical attribute of the product; however, this may not be possible for CGTs, as minor changes in potency, detected through physiochemical measurements, may have a massive, but unpredictable, impact on the biological activity of the product. Establishing the impact of degradation products on the performance of potency assays is important. It is expected that degraded products of a CGT may result in shifts in potency, but they may also cause an aberrant dose response, confounding the estimation of relative potency. The ability of the potency assay to differentiate between degraded products and the target product, therefore, needs to be tested. This should be done early in development by testing multiple intentionally degraded samples. In some cases, the stability-indicating properties of the potency assay may be at a gross level, rather than a finely tuned quantifiable change.

Quantitative

In theory, potency can be quantified absolutely, with an assay reporting potency expressed in absolute units and the result derived from a standard curve. Although this is the gold standard, absolute quantification may not always be achievable.

> For example, the number of animals required for *in vivo* assays may be prohibitive or there may be too much variability to make quantification possible. In other cases, the biological dose response may not follow a standard sigmoidal path. The latter is true for assays where an immune response constitutes the endpoint; in such cases, the response is often binary (i.e., on or off).

Good Performance Parameters

Accurate, Sensitive and Specific

Potency assays should be able to detect changes in the measured parameter with accuracy, sensitivity and specificity; however, it is important to understand that the limits of performance can be highly variable, depending on the assay type.

> As a result, relative potency is generally used for CGTs. Relative potency is estimated by calibrating a response against a recognized reference standard. Rather than being expressed in absolute units, relative potency is expressed as a percentage drift of the sample compared with the reference standard, and it is reported with confidence intervals. Selection of a suitable reference standard is crucial to the success of these quantifications.

The reference standard is often generated internally; therefore, complete characterization of the standard with evidence of comparability may be required. Initially, the reference standard is usually a development batch, which has been well characterized and is available in sufficient quantity for the necessary assay development studies.

Nevertheless, it is possible to change the reference standard during development with appropriate comparability studies as product and process knowledge increases. Hence, the initial selection of a reference standard is not an ultimate commitment.

An assay that can detect a relative change in potency of as little as 5% is considered a good assay, but a change of 20–30% may be considered to be perfectly appropriate and would be expected for some cell-based assays. This highlights how important it is to define acceptable performance limits for assays, using information from other analytical methods. Part of the decision-making will be driven by the purpose of the specific assay, the information it provides and how a single potency assay fits into the wider assay matrix.

For some products, a performance precision of 50–150% may be acceptable. This may be true, for example, for an assay on *ex vivo* materials such as primary cells or cells mixed with populations, while much tighter performance limits would be appropriate for other assays. When assessing assay performance, it is important to keep in mind the intended specification that the potency assay will measure and that both the performance and the specification limits are scientifically justifiable.

Easily Reproducible, Reliable and Consistent

Potency assays that are difficult to reproduce and those that produce unreliable or inconsistent results are of limited value. Looking at standard ICH assay performance parameters, the worst performing assays are *in vivo* assays, followed by assays based on primary cells or cell lines and then by physicochemical methods, which usually perform best. There are also ethical and commercial judgments to be made here – for example, given the high variability of outcomes, are *in vivo* experiments, which are costly, time-consuming and require the use of animals, really justifiable?

Fast and Inexpensive

A potency assay or assay matrix will be used repeatedly to monitor manufacturing consistency throughout the product life cycle; therefore, having a fast and inexpensive assay is beneficial. Potency assays are complex by nature but should be designed to be simple and practicable. It is important to quickly differentiate the assays that are “good in principle but not in practice” from assays that provide “good enough” results but are easier to implement cost-effectively. The number of steps in an assay should be kept as low as possible, as each additional step introduces variability. In addition, each step should be risk-assessed and tested for criticality, and those that are unnecessary discarded.

Fast Assays

In vivo assays often require a lot of time to run, as they can include animal sourcing, acclimatization and dosing, etc. In fact, *in vivo* potency assays can take as long as two months to complete, which makes the assay unfeasible for stability programs. An additional issue with such a long-duration assay is that it can be impossible to repeat the analysis in a timely fashion if the assay is invalidated for some reason.

Inexpensive Assays

There has been a huge increase in the number of very complex analytical platforms, such as high-content imaging or next-generation sequencing, and it can be tempting to use these novel, cutting-edge platforms for potency assays. Those platforms may not be widely available, however, as the equipment may be unique and expensive, while their use will increase the cost of the potency assay and limit its transferability and reproducibility. A good example is flow cytometry used to assay for cells expressing specific biomarkers. It is also worth considering how the regulators might view a CGT advocating the use of a new technology that has yet to be proven in the field. Unfamiliarity with novel approaches may lead regulators to request a more comprehensive data package.

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How Achievable Is the Ideal Potency Assay?

Although cell therapies and gene therapies have been grouped thus far in this review, these are very different types of therapeutics, and the potential to reach each ideal characteristic varies. Table 4 summarizes the challenges related to each category of CGT. It should be noted that data demonstrating attempts at overcoming some of these challenges may be requested in order to gain regulatory acceptance of alternative approaches. Simply "hand waving" that a potency assay is too difficult will generally not be accepted.

Table 4: Challenge of Achieving Ideal Potency Assay Characteristics for Cell and Gene Therapies

Ideal Characteristic	Cell Therapy	Gene Therapy
Reflects the MOA	Multiple steps in the MOA	Multiple steps in the MOA
Predictive of product quality	Assay may lack sensitivity	Assay may lack sensitivity
Quantitative	Reference standards may be hard to define	The most downstream steps in MOA may necessitate an *in vivo* assay
Good performance parameters	Cell-based assays generally have high variability	Gene transfer steps as part of the assay add to overall variability
Fast and inexpensive	A fast assay may be required but this can be difficult to achieve	Fast assays possible but usually require a substantial knowledge base and data

Key: Ease of Achieving Ideal Potency Assay Characteristics **Relatively Difficult** **Difficult**

Top Tips to Create Potency Assays That Meet Regulatory Requirements

This section provides practical advice on building potency assays that will be able to pass regulatory scrutiny.

TIP 1: Base the Approach on Sound Science

Focus on the science behind the potency assays to enhance regulatory acceptance. Potency assay decisions should be based on what is scientifically sound, rather than what is easy and cheap to do. This makes any regulatory arguments more convincing and justifiable. It is crucial to identify and measure essential product attributes and correlate these to specific potency assays.

TIP 2: Know the Regulations and Work Collaboratively with Regulators

The regulatory framework for approval of CGT potency assays is flexible and open, with product developers left to propose assays appropriate to their specific, unique product. This can be daunting, and it may be difficult to know where to start. Regulators understand this and encourage product developers to engage with them early to help with scoping. Before approaching a regulator, however, it is important to understand what regulations apply in different jurisdictions – see Table 5 and Table 6 for an overview.

Table 5: U.S. Regulations and Guidance on Potency Tests

Regulation	Code of Federal Regulations Title 21[8] Part 600 outlines general information for biological products • 600.3 provides definitions for potency • 610.3 provides definitions for potency tests
Regulator	FDA Center for Biologics Evaluation and Research
Guidance	FDA Guidance for Industry: potency tests for cellular and gene therapy products[9] United States Pharmacopeia chapters on bioassays: • 1032: design and development of biological assays[10] • 1033: biological assay validation[11] • 1034: analysis of biological assays[12]

Table 6: EU Regulations on Potency Assays

Regulation	Regulation No 1394/2007 and Directive 2001/83/EC[13]
Regulator	EMA: • Committee for Advanced Therapies reviews and evaluates • Committee for Medicinal Products for Human Use adopts final opinion
Guidance	• Guideline on human cell-based medicinal products[14] • Guideline on potency testing of cell-based immunotherapy medicinal products for the treatment of cancer[15] • Guideline on quality, nonclinical and clinical aspects of medicinal products containing genetically modified cells[16] • ICH Topic Q 6B. Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products[17]

Working with Regulators

Develop a dialogue with regulators early in the development process to explore the potency assay framework, establishing what may be acceptable and what may need revision. Leverage their expertise to test scientific justifications and arguments.

> For example, to evaluate the potency of a gene therapy, it is usual to use a matrix of assays, including a simple gene-expression assay as well as more complex, labor-intensive functional bioassays. The tendency is to try to drop the bioassays at some point, with the most common justification being that the variability of the cell-based assay is too high. The regulator may accept this argument if scientific due diligence has been empirically demonstrated. This can usually be achieved by providing a complete method development report showing that a thorough attempt at reducing the variability of the cell-based assay has been undertaken.

TIP 3: Potency Is Not a Single Outcome – Think of the Matrix

The number of assays needed for effective potency testing may be dictated by the number of steps in the MOA, with more steps requiring more assays. It is important to think strategically and focus on assays that will provide the most meaningful and relevant information.

Fight the tendency to perform only the easiest assay, unless there is a sound scientific justification as to why this is appropriate. Does an enzyme-linked immunosorbent assay (ELISA), for example, provide as much information, if not more than, the bioassay? Is the ELISA, due to its quantitative nature, perhaps more sensitive to product degradation?

Think in practical terms when compiling the matrix. Some potency assessments may, for example, require a fast turnaround time; accommodate this by including several assays with varying turnaround times, both fast and slow. The payoff for a fast assay may be that it is less accurate and sensitive. Consideration should, therefore, be given to which assay provides the most information on product quality in the least amount of time.

The matrix approach is all about targeting and balance.

TIP 4: Consider the Unique Properties of the Cell or Gene Therapy

The development of potency assays for a cell therapy product differs from that of a gene therapy product.

The next section examines specific advice for each therapeutic category.

Cell-Based Therapies

Cell Types

There are multiple types of cell-based therapies, each requiring specific considerations; for example:

- Autologous cell therapies: variability of patient cells can be difficult to control and, similarly, reference standards can be difficult to define
- Allogeneic cell therapies: donor variability is a challenge
- Stem cell therapies: it may be difficult to assess the final cell population or measure biological activity until the cells are *in situ*

Assays designed using healthy donor material often pose problems when used with cells derived from a patient cohort, as they can behave differently. It is essential to challenge assays with material from actual patients as early as possible to identify issues in a timely manner.

MOA Complexity

The MOA of cell therapies is usually very complex, so traditional potency assays are not appropriate. One reason for this is that the cell population administered can contain many different types of cells with multiple, interrelated activities.

If the cell therapy comprises a gene therapy component, this also needs to be assessed (see below).

Cell Therapy Requires Potency Assays with a Fast Turnaround Time

Turnaround time becomes an issue with some cell therapies, since the time from manufacture to infusion is extremely short; therefore, this practical consideration should be prioritized when designing the assay matrix.

Gene Therapies

MOA Usually Comprises Multiple Steps

The MOA of gene therapies involves transfer of genetic material and, subsequently, the biological effect of the expressed gene. A matrix assay approach is crucial, especially during development of the manufacturing process, as each aspect of the MOA must be assessed separately; for example, infectivity, expression of the transgene (measurement of transcript levels), presence of the transgene and finally confirmation of transgene biological activity.

TIP 5: Allow Time and Invest Resources into Characterizing the Assays

The design of a potency assay matrix can take up to a year or more from initial kick-off to final validation.

After identifying the possible matrix of assays, methodological feasibility must be assessed and the relative potency approach tested. This is followed by further evaluation and optimization, with the aim of reducing variability and improving signal strength. The value of each assay in the matrix should be assessed and further refinement made. In the final stage, method performance parameters are measured and acceptance criteria defined. It is important, and can be crucial, to characterize each assay in detail through this process, so that it will meet regulatory requirements for validation.

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Conclusions

Potency is a CQA. Without a suitable assay to measure the potency, a CGT product cannot be licensed and lots cannot be released.

Given the complexity and variability of CGTs, it can be difficult to establish a set of potency assays that meets regulatory requirements – especially when those requirements are open-ended and considered on a case-by-case basis. It is prudent to start thinking about these assays very early in development, selecting a matrix of assays that can be evaluated and refined over time, focusing on those assays that provide the most meaningful and relevant information.

What the ideal assays are will be determined by the CGT, but they should reflect the MOA, be predictive of product quality, be quantitative and have good performance parameters. It is beneficial if such assays allow rapid results turnaround and are inexpensive to run. It is unlikely only a single assay will suffice, so building a matrix of assays with a strategic and practical focus is essential. This all takes time: the design of a potency assay matrix can take up to a year or more from initial kick-off to final validation, which must be factored into the planned development timelines. In addition, decisions based on sound science will be more successful and justifiable to regulatory authorities worldwide.

Short Bios

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