



Pioneering science delivers vital medicines™

IABS Reference Standards for Therapeutic Proteins

Essential Reference Standard Program Questions

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

For what purposes are reference standards used?

One purpose of a reference standard is to demonstrate through biological and physicochemical tests that a product lot accurately represents the intended product and is of acceptable strength, identity, purity, and potency.

Additionally, reference standards have particular uses for method development and validation, calibrating equipment and continuity of reference standards themselves.

As they relate to product, reference standards are obviously critical in the demonstration that each lot of material is suitable for release and patient use.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

For what purposes are reference standards used?

Reference standards also demonstrate consistency in the process between lots, for comparability after process changes, technology transfer and aid in the identification of drift in quality attributes over time.

A carefully managed reference standard program establishes a link in the material through the product lifecycle, from the early stage clinical trials to the commercial product following licensure, ensuring that quality attributes are tracked throughout the product lifecycle.

Reference standards are necessary to qualify future primary and working reference standards. They protect against drift in a quality attribute between current and candidate standards and to demonstrate the long-term stability of other reference standards.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How are reference standards used in analytical methods?

As they relate to analytical methods, reference standards are used in trending programs to ensure that method performance is consistent over time as well as being used to validate the assays themselves.

Reference standards are also used in analytical methods for the direct calculation of a test sample result or as a component of system suitability and/or assay acceptance criteria.

A reference standard may be used to directly quantitate a quality attribute. The most obvious example of such a use is the determination of relative potency, in which the biological activity of a test sample is calculated by direct comparison to the reference standard response.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How are reference standards used in analytical methods?

Reference standards are also used to generate a test sample response through the qualitative comparison of a quality attribute. Gel methods (e.g. SDS-PAGE) can be used to aid in the determination of product purity by demonstrating that the banding pattern of the test sample is sufficiently similar to that of the reference standard, or “conforms to standard”.

Similarly the chromatograms from methods such as HPLC are compared between reference and test sample if ‘conforms to standard’ or ‘no new peaks’ are part of the acceptance criteria.

Reference standards, therefore, are used in both a quantitative and qualitative capacity to determine the quality attributes of a product lot.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How are reference standards used in analytical methods?

Standards have an even wider use in various analytical methodologies as a component of the system suitability. When used for this purpose, the reference standard is intended to verify performance of an analytical method in accordance with validated parameters each time that it is performed.

For example, HPLC purity assays (cation exchange, reversed phase, and size exclusion) include multiple criteria that establish, through the reference standard chromatogram, that the assay demonstrates precision, efficiency, recovery and resolution that is sufficiently similar to the historical behavior of the method.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How are reference standards used in analytical methods?

A separate type of material can be prepared solely for verifying the capabilities of an assay (e.g. to show it can detect stability related moieties) termed a 'Reference Material'.

These additional reference materials may be required to ensure identity, accuracy and precision of different sample types (e.g. product in various process streams).

This material does not necessarily have to be derived from the primary or working reference standard and may not need to be compared to them depending on use, but this should be justified.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How are reference standards used in analytical methods?

Therefore, one can use the primary reference or working standard for all of the aspects of assays described, but reference materials can be used instead for certain aspects of analytical development/validation and control.

Reference materials may be used in certain aspects of the routine QC lot release/stability program (especially those where quantitation or direct qualitative comparison occur). For example, stressed product samples may be used for identification of expected impurities.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How should one select a reference standard?

Core considerations for initial and subsequent reference standards include production schedule, material availability, the quantity required as well as its intended use. For the identification of the initial (or 'interim') reference standard, the selection may be restricted due to time constraints and limited production.

Because of limited product knowledge at the time of selection and qualification of the initial standard, the production schedule is likely to act as the primary input in standard selection.

At all stages of product development, the reference standard should be 'representative of production and clinical materials' (ICH Q6B). The concept of "representative" will change as product knowledge increases; however, the quality attributes of the standard should represent the desired characteristics of the production lots as understood at each development stage.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How should one select a reference standard?

For example, a reference standard should not demonstrate an impurity profile that is substantially different, either in identity or quantity of impurities, than the lots for which it is intended to support release and stability testing.

While there may be exceptions to this guidance, such as the use of a separate lot of material as a potency standard, in general the quality attributes of the standard should reflect the product that is intended for patient use.

For a potency reference standard, within a particular bioassay, the reference standard must have a biological activity that is identical to the biological activity of the test sample (i.e. shows parallelism). It should be free from substances that may interfere with the assay. Links to the material used in clinical material is essential.

The reference standard must be evaluated to ensure it is a homogeneous preparation (i.e. minimal vial-to-vial variation).

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How should one select an immunogenicity standard?

The use of an immunogenicity standard is different from that for most assays. In general, it is agreed that antibody standards are not that helpful in attempting to quantitate immunogenicity, and thus a titer assay readout is recommended

Different antibody preparations can have very different properties (avidity, affinity etc.) that can give different readouts in an assay (e.g. non parallel dilution curves).

Obviously polyclonal antibody preparations suffer more from this variability when compared to a monoclonal antibody, but then a MAb will not represent the attributes of a polyclonal human antibody response.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How should one select an immunogenicity standard?

A MAb or well characterized (usually purified) polyclonal can be used to compare the sensitivity between assays to illustrate how well antibody assays perform and/or useful to show changes in assay sensitivity during assay development

If reagents are available for both high and low affinity antibodies, these can be used during assay development and compare different assays.

A 'medium' affinity would be best if only a single reagent is available. However, what is clinically relevant should be considered.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How should one select an immunogenicity standard?

In the clinical diagnostics arena, large collaborative studies have been used to select antibody standards for diagnosis and/or prognosis of disease (e.g. in diabetes).

However, these studies illustrate the complexity of identifying an antibody preparation that would work in different assays to the same extent (even be detected in all assays) whereby hundreds of sera are included in such studies and one (if any) is shown to have utility as a standard.

Standardization of the assay across laboratories is essential if an immunogenicity reference preparation is going to have its maximum impact and to have the ability to compare between clinical studies run by different sponsors.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How do the intended uses of primary and working reference standards compare?

The principal difference between the primary and working reference standards are their uses in qualifying and monitoring other reference standards and frequency of use day to day. The primary reference standard should be used to qualify new primary or working reference standards.

The primary standard is also used in the stability monitoring of working reference standards and is critical in establishing product consistency over long periods of time, both within and between working reference standards.

In order to maintain a consistent product history, sufficient quantities of the primary standard should be qualified for usage over a period of at least ten to twenty years.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

How do the intended uses of primary and working reference standards compare?

The working reference standard is used for lot release and stability testing, as well as other quality activities such as investigations and method transfers/validations and thus the working reference standard is depleted much faster than the primary standard.

Session 1 Questions: Understanding the attributes required for reference standards and the purpose of their use

When is drug substance or drug product suitable for use as a reference standard?

Drug substance may be suitable for use as a reference standard for multiple reasons. First, some products may not be stable enough to serve as a long term reference standard in the final formulation (i.e. frozen).

The formulation and/or concentration of drug substance may lend greater stability to the molecule, such that it may be used for an extended period of time as a reference standard.

In addition, drug substance may be better suited to illustrate the presence of impurities if final product goes through additional purification steps.

However, there may be the need to have both DS and DP reference standards depending on how they react in assays.

Session 2 Questions: Reference standard qualification

What are the essential qualification parameters for a Reference standard and from where are the acceptance limits for qualification derived?

As described, the type of qualification carried out is closely linked to the use of the reference standard.

There is a phase specific approach to the level of qualification during the product lifecycle in both the number of tests and their limits.

Often the first standard (interim RS), derived from either tox material or the first GMP run, would simply be compared to specifications in place at that time and results provided as a 'report' of the test result.

As product development proceeds, acceptance criteria for selection of the standard can be set on manufacturing history and exposure in the clinic to provide assurance the standard is 'representative' of clinically qualified material.

Session 2 Questions: Reference standard qualification

What are the essential qualification parameters for a Reference standard and from where are the acceptance limits for qualification derived?

Meeting specifications (both the test and limits) alone is often not enough to ensure the reference standard fully represents the product - additional characterization tests are usually employed for defining the first primary reference standard and occurs late or post Phase III, preferably creating the primary reference standard from commercial scale material.

Tests may be included or removed during development dependent upon the structure/function and development history of the molecule and especially as use of the standard is more closely defined.

Regardless, the rationale for the selection of qualification tests and the accompanying acceptance criteria must be detailed in the qualification protocol for the first reference standard.

Session 2 Questions: Reference standard qualification

What are the essential qualification parameters for a Reference standard and from where are the acceptance limits for qualification derived?

Qualification tests generally include determination of some or all of the following: potency, concentration (strength), mass, primary structure, secondary structure, tertiary structure, disulfide structure, carbohydrate structure, impurity profile, and thermal stability.

Because product concentration and potency are determined by direct comparison to the reference standard, these parameters must be precisely defined during reference standard qualification.

When comparing directly to a standard profile (e.g. ‘compares to reference, no new impurities’) then having a representative profile is desirable (‘centered’ quantities of the attributes) however, the use of both a ref std and impurity std may be useful.

Session 2 Questions: Reference standard qualification

What are the essential qualification parameters for a Reference standard and from where are the acceptance limits for qualification derived?

For certain characterization tests used for the first primary reference standards, such as secondary or tertiary structure methods, reporting the value is satisfactory although acceptance criteria for all test results should be established when utilizing a protocol for replacing a standard after licensure.

For quality attributes that are known to be critical, it is more likely that acceptance criteria for selection of the first primary reference standard should be predefined to ensure the standard represents attributes similar to those used in pivotal clinical studies and have been clinically qualified.

Session 2 Questions: Reference standard qualification

What are the essential qualification parameters for a Reference standard and from where are the acceptance limits for qualification derived?

Regardless of what was in the protocol to define the acceptance criteria for the first primary reference standard, looking at the results of the qualification assays and comparing them to clinically qualified material and commercial material and assessing how representative the standard is can be valuable (and what the regulators do!)

The number of determinations required to generate a final result during qualification is dependent upon method capability, such that sufficient statistical power is obtained in assigning the reported result.

For critical quantitative product attributes such as potency, there must be sufficient agreement between replicate results to assign a final value (e.g. $CV \leq 5\%$, or using a tolerance interval approach).

Session 2 Questions: Reference standard qualification

Should the intended use of the reference standard (potency determination vs. assay system suitability criteria) dictate the qualification requirements?

Yes – because the level of qualification depends on the use of the standard. For example, if one is never going to use a particular reference standard to test for secondary/tertiary structure (in say comparability studies) then adding those tests to qualification would not be necessary.

A potency standard that is separate from a physicochemical standard may not need the same level of physicochemical analysis, especially if potency impacting quality attributes are well understood – as well as those that don't.

If a reference standard is not going to be used for quantitative analysis but only for system suitability (e.g. is a band or peak there or not) then relative levels of different variants may not be relevant.

Session 2 Questions: Reference standard qualification

Should the intended use of the reference standard (potency determination vs. assay system suitability criteria) dictate the qualification requirements?

Regardless of use, a reference standard qualification protocol should be written prior to the selection of material for a reference standard.

The use of the reference standard/s in different assays should be included in the protocol with justifications for what is and isn't tested.

In addition, the use of the standard can impact the level of 'comparability' or 'equivalence' required to prevent drift or if drift in an attribute is even a concern (e.g. in levels of an impurity to which a comparative quantitation is not required).

Session 2 Questions: Reference standard qualification

Should the intended use of the reference standard (potency determination vs. assay system suitability criteria) dictate the qualification requirements?

It is more likely a potency (or quantitation) standard should be the 'gold' material stored in a stable manner to which all future replacement standards are used.

This is likely not necessary for physicochemical standards that are qualitative in nature where changes to its profile are likely to be more acceptable over time, mainly because physicochemical profiles can be 'visualized' more easily and can be manipulated if necessary.

Session 2 Questions: Reference standard qualification

Should primary and working reference standards be qualified to the same extent?

Primary reference standards should be qualified to the fullest extent possible for the use of the standard as previously described.

Current guidance does not adequately address the qualification of working reference standards, specifically how (and if) the approach should differ from that used for primary reference standards.

In the absence of available guidance, qualification of working reference standards should consist minimally of several activities but should be justified on the product type and the use of the working standard – as well as how the working standard is derived - the more manipulation from the primary standard, the more study is required to ensure attributes have not changed.

Full specification testing should be performed at a minimum.

Session 2 Questions: Reference standard qualification

Should primary and working reference standards be qualified to the same extent?

Additional levels of testing of all product quality attributes that are calculated by direct comparison to the working reference standard, such as protein concentration and potency, should be performed.

The minimum requirements for working reference standard qualification should therefore sufficiently demonstrate that the material is representative of the intended product to which it is being compared and/or to illustrate that the working standard is fit for purpose for its particular use.

Qualification against the primary reference standard with the full range of assays does establish the necessary link to the product development history if the working standard is not directly derived from the primary standard.

Session 2 Questions: Reference standard qualification

Should more than one testing laboratory participate in qualification activities?

When calibrating a standard, method variability should be reduced as much as possible and since side by side analysis occurs, the concern for any analyst bias is not relevant – the number of repeats to ensure the most precise estimate is the vital factor.

However it depends on the use of the study – estimating a true value of an attribute is one type of study and requires the least variability (best analyst, best machine).

Another study would be to use more than one analyst/machine etc. to confirm if the calibration carried out by a single analyst is actually correct – how can you confirm your true value is true!

Session 2 Questions: Reference standard qualification

Should more than one testing laboratory participate in qualification activities?

An additional type of study is one to assure that the qualification assays used to calibrate or qualify the standard adequately represent the inherent variability of the analytical methods and that method transfers will be successful, whereby qualification should be performed by more than one laboratory.

This is accomplished by varying the days, analysts, equipment, and critical reagents used to complete the required testing.

These measures help to ensure that the reference standard qualification represents the actual conditions of use following implementation.

Session 2 Questions: Reference standard qualification

What differences are required for selecting and qualifying a vaccine, protein particle or host cell reference standard?

Compared to 'well characterized' products, vaccines, protein particles and HCPs are inherently more complex and heterogeneous.

As for any product, an understanding of what the purpose of the reference standard is for is critical to its qualification.

For protein particles, the properties of the particles have to be considered - and we are at the stage of simply trying to understand which attributes are impactful for their detection in the different assays available (size dispersion, refractive index/contrast, diffraction, shape etc.). Prior to the development of a suitable standard the methods themselves need to be better characterized and standardized.

Session 2 Questions: Reference standard qualification

What differences are required for selecting and qualifying a vaccine, protein particle or host cell reference standard?

For HCPs, one is dealing with a very complex mixture of proteins. On top of that, the mixtures can be cell line and process specific.

Thus there are potential issues with creating an HCP mixture 'standard' depending on how it is prepared and its relevance to HCPs in product produced by actual manufacturing.

Plus manufacturing changes can impact the type of HCPs in product.

Thorough characterization of the HCP protein profile allows confidence in the 'representativeness' of the standard (e.g. 2D gels) and the need for, or not, a change.

Session 2 Questions: Reference standard qualification

What differences are required for selecting and qualifying a vaccine, protein particle or host cell reference standard?

Antibodies raised to the HCP mixture then add to complexity in the assay. Use of 2-D gel western blotting should be used to illustrate the immunoreactivity of the antibodies. Showing such coverage is essential to understand the readouts of the assays.

One needs to understand whether the HCP mix represent the proteome of the cell line used and does the antibody preparation recognize that appropriately?

Over representation against a few proteins can be as bad as antibodies to many (but not all) the proteins limiting signals – thus a medium coverage appears most desirable.

The comparison of HCP levels between manufacturing runs can illustrate the run to run differences in HCP reactivity to assess the cross product utility of a single HCP/antibody preparation.

Session 2 Questions: Reference standard qualification

What differences are required for selecting and qualifying a vaccine, protein particle or host cell reference standard?

For vaccines, one is also dealing with a complex of proteins. Plus, there are combination and adjuvanted vaccines.

Old physiological activity has been replaced by either absolute quantities (e.g. CFU's for live vaccines) for potency standards or titers of antibody production for clinical serology tests as well as in potency assays that test the immunogenicity of the vaccine.

Vaccine standards are usually used quantitatively to create a standard curve but can also be used as assay controls as for other biotech products.

Session 2 Questions: Reference standard qualification

What differences are required for selecting and qualifying a vaccine, protein particle or host cell reference standard?

Basic qualification of a vaccine reference standard is similar to other biotech products.

However, when qualifying anti-vaccine antibody standards, other factors have to be considered as described for anti-drug antibody reagents,.

This can involve the use of different species, considering the age of subject providing the antibodies, immunizing protocol etc. Multiple standards are often created.

For vaccines, as for many other products, IU's are often not transferrable between assay types (e.g. functional versus ELISA) unless confirmed by a collaborative study.

Session 3 Questions: Reference standards and their replacement

What are the main considerations when replacing a reference standard?

It is clear that minimizing drift is the most essential consideration when moving from one reference standard to another.

When to replace a reference standard is critical to ensure:

1. You don't run out of the first reference standard (one should try to always have enough 'primary' reference standard to calibrate against regardless of how many standards have been made after it)
2. You have enough of the appropriate material to create a new standard.
3. You know how to create the new standard – for example, changing formulations between standards can dramatically alter the stability of a standard and this needs to be assessed (snap freezing etc.), understand volume requirement, numbers of vials etc.
4. Give yourself enough time to do all the necessary work.

Session 3 Questions: Reference standards and their replacement

What are the main considerations when replacing a reference standard?

5. Have a plan including justification for the need to replace a reference standard (as this may influence your activities) and an appropriate protocol with acceptance criteria are essential.
6. Investigate the availability of an international standard and if there isn't one, consider working with a public standards organization to create one.
7. Plan ahead to track the performance of assays and their results in your trending program to ensure subtle changes aren't missed

Session 3 Questions: Reference standards and their replacement

How do you prevent drift when implementing a new potency standard?

The accurate determination of the relative potency of a candidate reference standard is a critical component in maintaining a consistent product linkage for potency throughout the development lifecycle.

The relative potency testing design and acceptance criterion in the qualification protocol must be such (e.g. tight enough) that any difference in the potency between the current and candidate reference standards can be shown to be due to either a real difference or the characterized variability of the analytical method, which should be minimized as much as possible.

Other signals beyond the actual potency result (such as slopes, asymptotes etc.) can be tracked as well to illustrate if there are subtle differences between standards.

Session 3 Questions: Reference standards and their replacement

How do you prevent drift when implementing a new potency standard?

Keeping the first primary reference standard as the calibrator each time another standard is developed (ensuring it is stable) as A-B, A-C, A-D and not A-B-C-D.

A sample size should be such that there is sufficient statistical power to demonstrate equivalency in potency between the standards.

The equivalency acceptance criterion (EAC) must also be established in relation to the intermediate precision of the potency method. In general, it appears FDA recommend around 30 individual estimates of potency.

One also needs to take into consideration physicochemical tests as indicators of potential drift as well. In vitro bioassays do not necessarily detect all aspects of biological activity.

Session 3 Questions: Reference standards and their replacement

How do you prevent drift when implementing a new potency standard?

To further aid in demonstrating a lack of potency drift between standards, the internal control lot should not be changed at the same time as the reference standard lot.

An overlap in the internal control potency data over time provides further evidence that there is no change in the activity of the reference standard.

Session 3 Questions: Reference standards and their replacement

How should the impact to method trending be evaluated when implementing a new standard?

Analytical parameters are trended for quantitative methods that use a reference standard or internal control to test the purity, potency, or integrity of active product or the formulation of placebo.

As described, the reference standard usually has direct consequence on only very few trended parameters, such as the protein concentration and relative potency of the internal control.

If stringent selection and qualification practices are executed, there should be minimal impact to trended parameters that are directly influenced by the reference standard.

Nonetheless, all trended parameters that are derived from the reference standard should be evaluated for a shift in the assay results following the implementation of a new reference standard lot.

Session 3 Questions: Reference standards and their replacement

How should the impact to method trending be evaluated when implementing a new standard?

In the event that a shift in a trended parameter should occur directly following the implementation of a new standard, the consequence to the program and the impact in relation to the current trending limits must be determined.

The decision to reset trending limits must be fully evaluated and justified when a change in a parameter is identified.

Session 3 Questions: Reference standards and their replacement

Under what circumstances does a process change require the implementation of a new standard?

A change in the manufacturing process does not necessarily automatically require the implementation of a new reference standard.

One has to consider what the effect of the process change has on the critical quality attributes of the product. In addition, the intended use of the reference standard in question also dictates if it needs replacing or not.

A reference standard should ensure that the product's properties are representative of the clinical trial material not production processes that make a comparable product.

Session 3 Questions: Reference standards and their replacement

Under what circumstances does a process change require the implementation of a new standard?

However, a new reference standard is not necessary if a process improvement slightly alters the impurity profile without an accompanying impact on potency nor the ability to compare to the impurity profile of the existing standard i.e. no new impurities or total loss of an impurity.

Therefore, even if the reference standard is no longer entirely representative of the product delivered by the process, but does not impact any of its uses, a new reference standard may not be necessary following process changes.

In fact, a new reference standard lot should be implemented only when absolutely necessary in order to ensure that the historical link to the clinical material is maintained without disruption.

Session 4: The role of Public Reference Standards

How should public reference standards be utilized in the reference standard program?

Public reference standards can be used to augment the reference standard program because they represent an independent and externally available material that is widely assumed to be stable for long periods of time.

The continued stability of an internal primary reference standard can be supported by periodic calibration against the international reference standard. ICH guidelines stipulate that an internal primary reference standard must be periodically compared to the international standard, when available (ICH Q5C, Q6B).

The comparison to an international potency standard should minimally consist of potency determination with a relative potency method and a sufficient number of replicates to ensure an accurate comparison.

Session 4: The role of Public Reference Standards

How should public reference standards be utilized in the reference standard program?

However, the frequency with which this comparison is required, as well as the necessary or preferred analytical tests, are not specified in the guidelines.

Unless there are data to suggest that the primary reference standard is not stable long-term, it is generally sufficient to calibrate against the international standard on an annual basis or longer.

This frequency can align with the reference standard stability program, for example, where the reference standard stability time points occur annually after the second year of the study.

How often one is required to compare to a pharmacopoeial standard remains obscure.

Session 4: The role of Public Reference Standards

How should public reference standards be utilized in the reference standard program?

Beyond being a stable 'reference point' to which in house reference standard stability can be compared, if a product is labeled and dosed in units, an International Standard is also intended to ensure similar products manufactured by different companies that can be used interchangeably have the same unitage and thus no efficacy impact when switching.

Thus the establishment of a continuous unitage when replacing an IS is essential.

However, one has to be sure that every product responds the same way when compared to the IS and there is a need to define a specific assay unless it has been proved that the IS performs similarly in different bioassay systems.

Session 4: The role of Public Reference Standards

How should public reference standards be utilized in the reference standard program?

Interim public standards or reference reagents can be created early on in the development of products to aid research and product development.

Pharmacopoeia standards are also used for compliance purposes to state that your product meets compendial requirements (which does have legal implications for things like the use by pharmacies and for reimbursement) and thus can be labeled 'USP' or "EP' compliant.

Session 4: The role of Public Reference Standards

How do/should public standards (NIST, WHO, Pharmacopoeia) inter relate to one another?

In order to prevent drift, the relationship between one public standard and another must be carefully controlled.

A proliferation of standards, especially potency standards, can cause issues for pharmaceutical companies.

A best practice is to create WHO and pharmacopeia standards at the same time (e.g. endotoxin standard), with greatly increased volumes of material, to reduce the need to continuously change standards as they run out.

Pharmacopeias do collaborate to try to harmonize monographs through the PDG (but it takes for ever.....) and efforts are made to harmonize standards across organizations.

Session 4: The role of Public Reference Standards

Should public standards be established for all commercial products?

International standards are established by the World Health Organization (WHO) as are other reference standards such as those from the Pharmacopoeias or specific scientific/government organizations such as NIST, ISICR or the Diabetes Foundation.

These materials are intended to establish standards for efficacy, quality, purity and safety of a biological material, and allow for activity to be reported consistently throughout the world as International Units (IU) or other units defined by the standard.

Public standards are usually established through a collaborative study that involves candidate preparations independently tested with the analytical methodologies of participating laboratories.

Session 4: The role of Public Reference Standards

Should public standards be established for all commercial products?

One potential hurdle to the establishment of public standards for proprietary molecules is the potential for intellectual property risk. It could be argued that a public standard, as a globally recognized quality standard, only makes it easier for competitors to infringe upon intellectual property. However, because the product is already available commercially, the public standard does not represent the only means of acquiring the molecule in question.

In fact, because public standards are commonly lyophilized in sealed glass ampoules, a combination of product formulation and primary packaging that is not utilized in any innovator product, a better representation of innovator drug products is the commercially available material, although drug substance provided may still be easier to analyze than re-engineering publicly available drug product.

Session 4: The role of Public Reference Standards

Should public standards be established for all commercial products?

Although the provision of drug substance might be seen as improving the ability to analyze the material, a greater inherent risk is the possibility that a similar molecule could be designated as the public standard should the innovator choose not to lead or participate in the collaborative study.

This could result in a scenario whereby the innovator would need to compare in-house primary reference standards to a public reference standard that was established from a biosimilar.

Session 4: The role of Public Reference Standards

Should public standards be established for all commercial products?

Given these considerations, it is advisable that the innovator lead or participate in collaborative studies, when feasible, to establish public standards for their products at a time when patents are about to expire and yet give enough time for the standard to be created.

This approach will ensure that an innovators' own molecules are recognized as the global standard.

An additional benefit is that it establishes an independent material to which the in-house primary reference standards can be periodically calibrated without the concern that there may be subtle differences between the two preparations.