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Ensuring suitable quality of clinical measurements through design

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ABSTRACT

To design and deliver high quality, safe and effective products, manufacturers of in vitro diagnostic (IVD) products follow a structured, traceable process for controlling the uncertainty of results reported from their measurement systems. This process and its results however, are not often shared in detail with those outside of the manufacturing company. The objective of this paper is to facilitate discussion by describing some of the best practices used during the IVD design and development process, highlighting some design challenges manufacturers face, and to offer ideas for how IVD manufacturers and laboratories could work together to drive further improvement to public health.

1. Introduction

The role of the laboratory in delivering accurate and precise analytical results in relationship to the classification of the clinical condition and to patient outcomes is well-defined in literature, including in a comprehensive review by Ferraro et al. [1]. The contributions of in vitro diagnostic (IVD) manufacturers to this process, however, is less well-documented.

Given the importance of analytical performance, the responsibility and design practices used by IVD manufacturers are clearly understood. This paper provides examples of how manufactures of IVD systems can design products to improve the capability to meet analytical quality requirements. In addition, this paper suggests areas where manufacturers and laboratories can further collaborate during this process to improve patient care.

2. Methods

2.1. The design story overview

IVD manufacturers strive to deliver systems that report accurate laboratory results that drive effective treatment decisions leading to the best possible clinical outcome for a patient. To achieve this, the accuracy of the IVD system should be measured against accepted and clinically relevant analytical quality goals.

The importance of the quality goal is a key design input to the design process as it answers the Essential Question, “What amount of medical harm due to analytical error is it OK to let go undetected?” [2] Industry-wide accepted values for this quality goal should be established to provide a consistent design requirement and to allow comparison of analytical performance across IVD systems and laboratories. This action would enable the guiding principle of relating IVD design requirements to the Essential Question – and enable the use of quality goals in the design of all future assays across IVD manufacturers.

While progress has been made in defining the allowable error in measured clinical results and practices for doing so have been established [3] and recently supported and updated [4], this progress needs to reach its logical conclusion with accepted harmonized quality goals for all assays being used in laboratories to classify patient results. One of the biggest challenges for manufacturers and labs is that many analytes do not have published quality goals, and even those that are published have different specifications depending on the source. Another issue is that there are multiple ways to report error performance [5]. Lastly, many analytes are not standardized, leading to problems that have been well documented in literature [6,7]. Programs and leadership to finalizing the harmonization of the varying methods that exist today is overdue and would be a key driver to future improvement in development, performance and monitoring of IVD products worldwide. Achieving general adoption of a single harmonized set of quality goals should be accomplished as a collaboration between Clinical Laboratories, Scientific Societies and Manufacturers and is an outcome the authors of this paper will contribute toward achieving.

Documentation of Quality Goals for a new product is the first step in a design process for establishing highly effective designs. The International Conference on Harmonization (ICH) published a scientific approach to product development and manufacturing using the principles of Quality by Design (QbD) [8] in the document, ICH Q8(R2).

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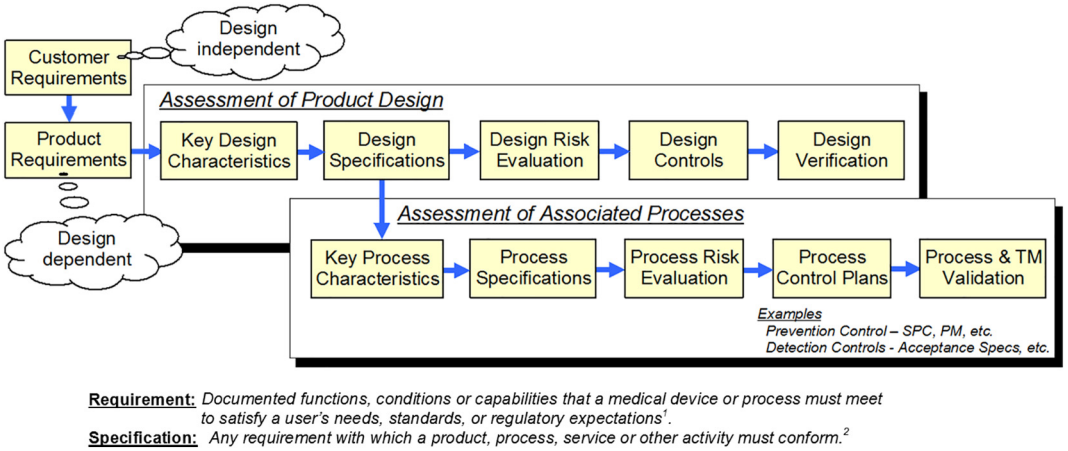

Fig. 1. Translation of customer requirements into product design and production specifications (TM-Test Method, SPC-Statistical Process Control, PM-Preventative Maintenance, Spec-Specification).

The FDA has adopted this as a guidance document in their regulation of product design and its application to IVD manufacturers is well accepted as part of today's design control requirements and practices. Some examples of QbD methods in use with IVD's is referenced in literature [9].

A key element of this process includes the traceability of design activities as illustrated in Fig. 1 including the following actions:

- Establish customer requirements – Design of an IVD product begins with establishing customer requirements as shown at the start of Fig. 1. For diagnostic products, customer needs associated with the intended use of the system including the environment of use, workflow and analytical performance are defined through discussions with customers among other sources. As an example, a key laboratory customer need is that the diagnostic system deliver accurate results to enable the laboratory to provide correct clinical classifications of patient results. Analytical quality goals such as Total Allowable Error (ATE or TEa) are quantitative measures that define the level of accuracy that must be achieved. These quality goals serve as the basis of the analytical system design requirements and subsequent choices on product design and production controls by the IVD manufacturer.
- Establish product/design requirements – For diagnostic products, product requirements translate the customer need for accurate results into more detailed allocations that can be directly designed to and verified. Here, the quality goals (e.g., Total Allowable Error) for each assay are allocated down to system-level design characteristics and specifications such as maximum allowable random (e.g. imprecision) and systematic (e.g. bias) error.
- Establish design controls – Next, choices on product design will be made along with decisions on how to maintain performance over time. These decisions are made by selecting designs and establishing production controls for each component of the product that assure the product meets the systematic and random error allocations of the quality goal. For example, the manufacturer will characterize and optimize the design of an assay's calibrators and calibration method. Specific decisions on the design of the calibrators including the formulation, concentration and calibration model are made based on the allocation of the total allowable error to this component and in turn this is used to set the design and process specifications to ensure this level of performance over the life of the product. This is an iterative process applied across the assay components, commodities and instrument system. This process assures that the IVD sub-systems will perform together to consistently produce results that meet customer needs over the life of the product.
- Verify and validate the design – After the design and production specifications are set, the product design is verified and validated to provide objective evidence that the product meets all customer and product requirements prior to distribution of the product to the end customer. A broad set of study protocols is used to confirm the performance of the design meets the intended use of the device. In some cases, direct measures of design function are used. In addition, protocols such as those from the Clinical and Laboratory Standards Institute (CLSI) are used to evaluate performance consistently with laboratory practices and expectations.
- Maintain production testing and field monitoring – Once the design is verified and validated, the manufacturer then assures that the product performs reliably over the life of the product. Control measures include tight tolerances for raw materials and the manufacturing processes and the use of instrument sensors to monitor the system for undesired performance due to issues such as unexpected wear-out of key components. In this example, the performance of the instrument can be monitored remotely by the manufacturer's service organization to identify the need for potential proactive maintenance to minimize or eliminate any loss of analytical performance or negative impact to laboratory workflow due to unscheduled down-time. This paper will not address this specific element in further detail, but it is important to acknowledge the role of production testing and field monitoring in the overall process of assuring the highest performance of the IVD systems.

2.2. Detailed description of the design story

This section elaborates on four design steps, providing more tangible details on how each step considers and contributes to the control of analytical error.

2.2.1. Establish design requirements

The foundation of the IVD system design is to establish a concept that can meet analytical quality goals established for the assay.

1. Obtain the analytical quality goals for the assay. In this paper, we will illustrate the use of total analytical error (TAE) and the level that can be tolerated based on the maximum, or total allowable error (ATE or TEa) for the assay. This directly links us to the Essential Question and our guiding principle of relating product design requirements to this question. Given that design input is the foundation of the expectations for the design, having well-accepted and clinically-relevant goals is a key need for manufacturers of IVD systems.
2. Establish the top-level allocation of this quality goal down to

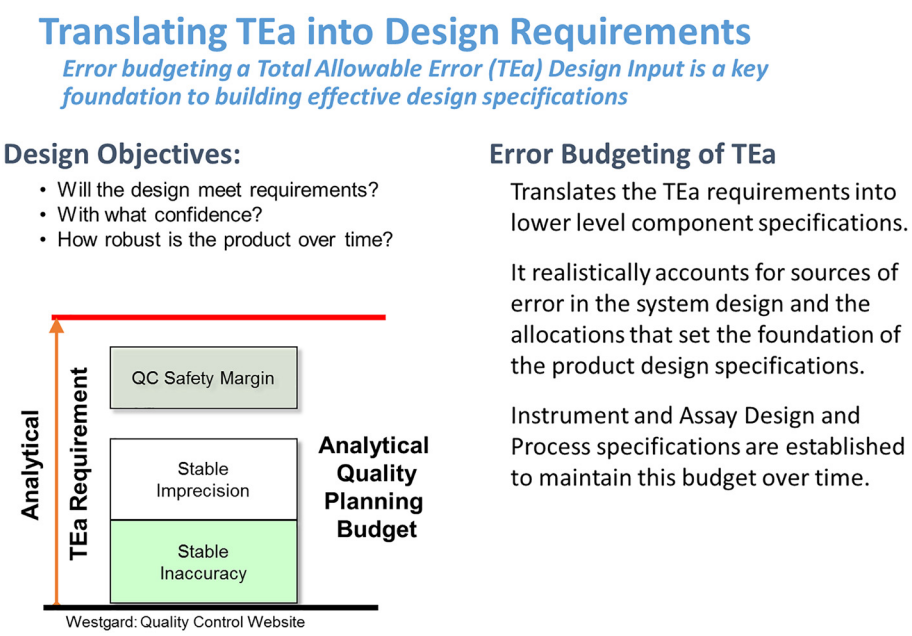

Fig. 2. Translating total allowable error (TEa) into high-level design requirements [10].

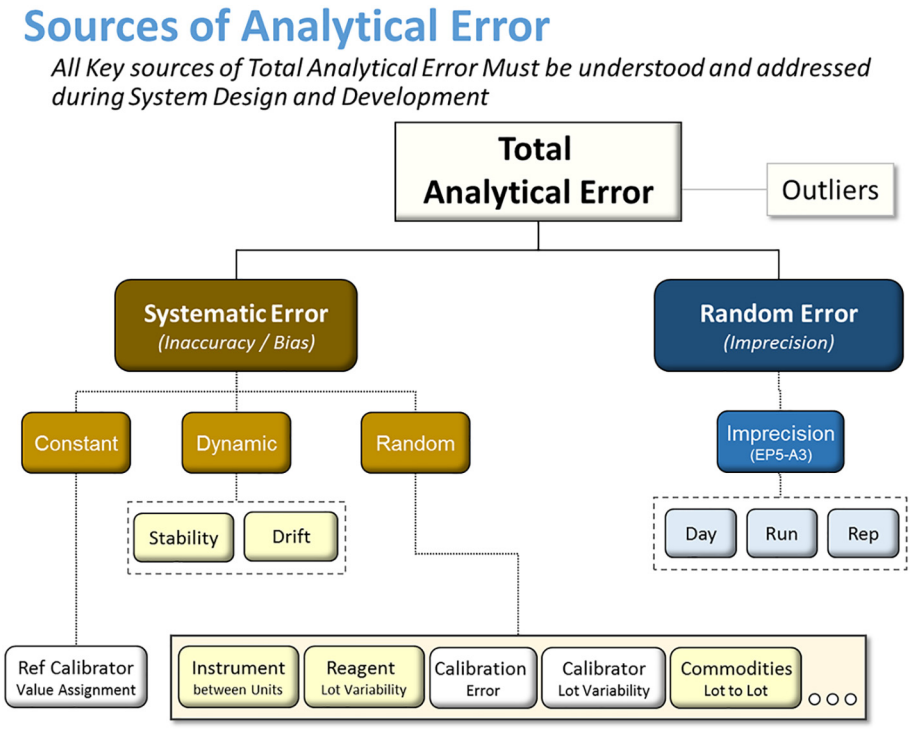

Fig. 3. Sources and allocation of total analytical error [11].

precision and accuracy design requirements. Westgard has proposed a generalized model for taking a specified total allowable analytical error goal and allocating it to components of error associated with random (stable imprecision) and systematic (stable inaccuracy) error [10]. With this method, the need for a laboratory to allocate a portion of this goal to a quality control (QC) safety margin is discussed. This safety margin provides sufficient capability for the laboratory QC system to detect an elevated level of analytical error that would exceed the overall limit within a specified timeframe and with a specified level confidence. This top-level break-down of the Total Allowable Error is illustrated in Fig. 2. Further definition of imprecision and inaccuracy will be discussed in Fig. 3.

For IVD design, the model shown in Fig. 2 is a well-aligned and practical approach that guides specific decisions in the design of the IVD assay and instrument system.

There are many sources in the design of the IVD system that contribute to error. To control for these sources of error, manufacturers can align with engineering and scientific best practices by employing a "tolerance" analysis error stack-up approach. We will use this as the basis for our design discussion.

An important discussion at the end of this paper will address some challenges faced in academia and industry with establishing an accepted standard for quality goals in the IVD industry. The harmonization of the total allowable error and measurement uncertainty

approaches is essential to best enable future progress. A consistent established goal for each analyte is a key to standardized methods, comparability and improved performance. The good news is that both methods have value and can be well-aligned, complementary methods when applied for specific objectives. Alignment on established standards has been elusive but needs to be achieved as a common basis for assessing and directing improvements in analytical performance to best impact patient outcomes.

3. Identify key sources of analytical error in the proposed design. Defining which elements of the total allowable error allocation fall into the systematic error (i.e. "bias") category and which fall into the random error (i.e. imprecision) category is a question of timeframe. From the Westgard approach, the timeframe is relative to the ability to measure bias across batches of patient samples run between QC tests. Whereas, measurement uncertainty takes a long-term view and therefore looks at contributions to total error from sources such as instrument differences or reagent lot variability as forms of random error. Each of these estimates and timeframes are of value, but must be clearly understood in context of an assessment. Our view therefore is not which method to choose, but where to apply each method based on the objective of the assessment being requested
   The error allocation model concept used in the IVD design process described in this paper is shown in Fig. 3.

From a manufacturer's perspective, design components whose deviation from a target value can be controlled through design or production controls are aligned with the systematic error designation shown in Fig. 3. Because sufficient data can be obtained to reliably estimate the deviation from target for these factors, these errors can be evaluated as forms of biases when reporting the error present for a given patient result. The sub-categories listed under the systematic error branch will be discussed in more detail in the next section, but it is important to note that the breakdown of systematic error into these more detailed sub-categories is useful for a manufacturer to understand and to quantify. Since the causes for each of these sub-categories of error can be quite different and therefore any necessary design and production controls may also need to be different.

From a laboratory's perspective, understanding this type of breakdown of systematic and random error can also be useful. Understanding the magnitude and sources of error can lead to more effective and specific discussions with manufacturers when further control of analytical error is desired for an assay relative to standardized quality goals.

As mentioned, dissecting random and systematic error components aligns well with practices used by manufacturers to establish the design and production controls needed for an IVD assay, instrument or commodity. For example, tighter production specifications can be placed on the manufacture of a calibrator to further limit deviations from target. This action further reduces systematic error and its effect on the classification of an individual patient result. Each new control however adds cost to the product and must be weighed against the value it provides before being implemented. This is where measures of performance against an accepted quality goal are key to well-balanced future design choices. Quantifying the level of error for each component relative to the necessary level of control is essential to directing IVD design that will meet clinically relevant quality goals today and in the future.

2.2.2. Identify sources of error

As shown in Fig. 3, error can be either systematic or random. Systematic error can be further categorized into three additional sub-categories. Each type of error is described in this section.

2.2.2.1. Systematic error (bias) – closeness to "truth".

- Constant bias (reference calibrator)
  No manufacturer can build a product based on zero error, as all manufacturing processes, no matter how well controlled, will produce error that will manifest as product bias to a standard. The magnitude of such bias may be larger in some cases or imperceptibly small in other cases, but this effect should always be comprehended and addressed when developing a model of analytical error [10]. This effect should neither be ignored nor assumed to be zero.
- Dynamic bias (stability, drift)
  Dynamic bias is attributed to the fact that some reagents and working calibrators used in a laboratory can change over time and that a mathematical calibration model present on IVD systems cannot always fully calibrate out this effect over time. For example, factors such as protein binding differences or potency changes can sometimes overcome the ability of the calibration model to compensate and to adjust fully for these effects.
  The magnitude of this effect is dependent upon the designated shelf-life of the product and can vary from nearly imperceptible to significant. In any case, it must be part of a complete analytical error model. For this category of bias, the magnitude of the effect changes in one direction over time (dynamic) and therefore incents this time-specific category.
- Random bias (instrument, reagent, calibration, calibrator, commodities, etc.)
  In this paper, random bias is assigned to factors such as reagent lot-to-lot differences, between-instrument variability, and between-commodity lot variability.
  In the context of the timeframe for this design example, samples being assessed within one lot, instrument, or setup are consistently biased from an expected mean value due to random variation in the manufacturing of this component. This effect with reagent lots, for example, may result in elevated patient results on one lot and lower patient results on the next and therefore can be viewed as random from one lot to the next leading to the term, random bias.
  This definition of bias is useful in IVD design as design specifications control a given component within a manufacturing allowed tolerance. Process and design factors for components such as calibrator lots are manufactured to a target with a specific allowable manufacturing tolerance (bias) from this target. When completed, the allowed manufacturing variation present in this calibrator lot can have an effect of biasing the patient results tested on this lot by a specific amount. The bias should be controlled to a level allocated from the quality goal. By acknowledging this, the concept of random bias therefore aligns with the reality of manufacturing and testing capability.

2.2.2.2. Random error (imprecision). The remaining effects not accounted for in this model as systematic error are classified as random error.

A common method IVD manufacturers use to estimate the random error effect is through a standard 20-day precision study per CLSI EP05-A3 [11] where repeatability and within-laboratory (intermediate) variance are measured. Variability in sample volume, pipette error, dilution error, etc. is exhibited through within-run (repeatability), between-run, between-day variance.

A key note for all estimates of analytical error is that to reflect the impact of TAE in the clinical laboratory, it is important that the material used to assess bias and precision reflects the behavior of patient specimens and is indicative of patient results. This commutability to patient results is discussed in detail in literature [12,13].

2.2.3. Translate the quality goal into design requirements through error budgeting

Error budgeting the ATE during design input is critical to building effective design specifications and lower level component specifications. We will now discuss application of this concept to IVD system

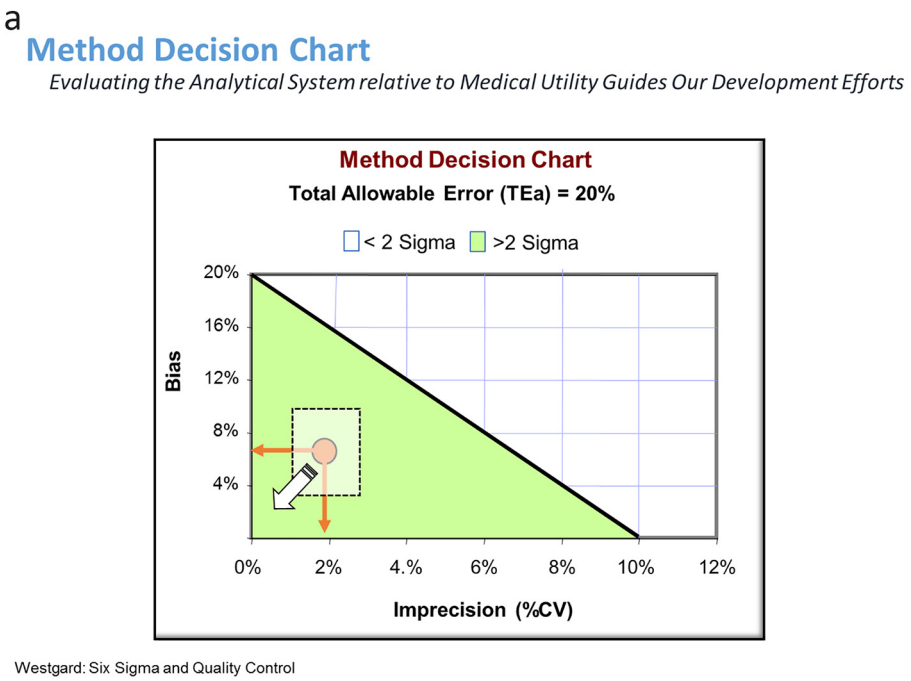

Fig. 4. (a) Assessing performance using the method decision chart. (b) Detailed performance using the method decision chart and allocated error sources. Where BIASa = allowable Bias, % CVa = allowable imprecision, and TEa = total allowable error.

design.

Basic tolerance analysis ("stack-up") method

1. Establish a total allowable error model
   One structured approach to evaluating the acceptability of actual analytical error on a system is to build on the Method Decision Chart approach presented by Westgard [10]. The method decision chart is a graphical tool that provides a practical and useful method to evaluate quality on a sigma-scale by specifying maximum acceptable combinations of random and systematic error and comparing an assay's actual performance against these limits. This is illustrated in Fig. 4 with combinations of actual bias and imprecision landing in the shaded zone being classified as having acceptable analytical performance and results above this zone having unacceptable performance. Long-term performance delivered by a manufacturer must be greater than the minimum capability (> 2 Sigma) shown in Fig. 4 to provide the laboratory a safety margin to maintain effective QC and to address expected variation in performance in the future. Desired levels of design performance approaching 6 Sigma or greater will be reviewed in the next section.
2. Plot actual performance
   The factors contributing to constant and dynamic systematic error described earlier are summed together and plotted along the Y-axis. It is important to note that in cases where "dynamic" systematic error is present this plot should be evaluated at expiration to evaluate acceptability of total error at the end of the claimed shelf-life of

the product.

3. Plot the random bias interval
   Along with the estimate of bias discussed in the previous step, a confidence bound obtained from the factors contributing to random systematic error can be added to the plot. This estimate can be obtained by summing the random bias contributions for these factors and plotting this effect as an interval around the bias estimate provided in the last step on the Y-axis. This provides an interval of expected analytical performance that might be observed over time across different reagent lots, instruments and at different labs among other factors listed in Fig. 3.
4. Plot the imprecision interval
   On the X-axis, the expected variability in the estimation of intermediate (i.e., within-laboratory) imprecision across time can also be added as an interval to the average imprecision estimate. Together with the bias dimension, this provides a zone of expected estimates of total error over the life of the product as shown in the shaded rectangle in Fig. 4.

5. Assess expected performance against total allowable error (quality goal)
   As a first pass capability assessment, the combined effect of the systematic and random error can be evaluated relative to the quality specification requirement. The point estimate along with the quality specification bound at 95% confidence for analytical error (2 sigma) are shown in Fig. 4. In this case, one can see that the analytical error for this system is expected to meet the minimum quality performance requirement over time and other factors.
6. Estimate overall capability
   The final step in this process is to assess the actual capability performance at a more granular level to more clearly define if this level of performance is acceptable. As Westgard has proposed, not only must minimum levels of quality be met, but a safety margin of performance is needed to assure quality monitoring can safely detect unexpected performance issues [10]. Therefore, levels of performance much greater than 2-sigma are necessary to meet the laboratory needs and to address the expected systematic and random error associated with, e.g., manufacturing variation, stability, and imprecision. These are reasons why every manufacturer should strive for capability approaching 6 Sigma or better whenever possible.
   The sigma value method proposed by Westgard [10] is one practical means to measure and report a product's capability to meet quality goals. This method is simple, effective and well aligned with industry standard techniques. It clearly and effectively communicates the capability to analytical performance requirements and can be used in a standardized way to effectively aggregate and visualize the performance of many products at the same time in one plot, an example of which can be seen in Westgard et al. [14]. Other techniques may be used, but the authors believe alignment around a single well defined, time-proven standard like sigma values is best. Fig. (b) shows a visual stack-up of the error sources using the method decision chart, the confidence bound around the expected performance, and finally the capability being achieved in terms of sigma value zones.
   In this example, the capability for this assay is expected to be consistently in the > 6 Sigma zone over time classifying the assay's performance as world-class as it would be extremely rare that any combination of systematic or random error of this product would produce a patient result with error that would exceed the required analytical quality goal specified in step 1. This example illustrates a performance safety margin that allows the laboratory to operate with confidence and further demonstrates why manufacturers must work to achieve base sigma level performance significantly higher than the minimum 2-sigma requirement. When reduction of the analytical error performance is warranted, this diagram can clearly identify and direct effort toward the dominant error sources. Performance can be re-evaluated on the same scale after design or process refinements are made.

As an added benefit of this process, this performance information could also be provided to a laboratory who may desire to understand the expected bounds of error for an assay or system to establish more effective laboratory management strategies.

2.2.4. Example: Designing calibrators and calibration

For IVD systems, the calibrator set is the foundation for establishing the dose-response curve and allows the laboratory to report consistent results for patient specimens under varying conditions.

2.2.4.1. Calibrator and calibration uncertainty. In situations where only one calibrator is used to calibrate a reagent or an instrument, the measure of calibrator uncertainty has direct, clear effect on the accuracy of patient results.

In many cases where a set of calibrators function together as a kit, curve fitting methods are used to generate a calibration model. In these cases, it is important to understand the error associated with sets of calibrators as they work together to estimate the expected calibrator uncertainty (i.e., as controlled by manufacturing tolerances).

In each of these cases, robustness characterization studies should also be used to understand how well these calibrations will perform under both nominal and boundary use conditions. For example, performance can be determined using fresh and thermally stressed reagent lots across multiple instruments. This understanding provides confidence in the long-term effectiveness of the calibration method under real-use conditions.

Ultimately, the use of external quality assurance services (EQAS) and other laboratory-based studies provide the most realistic estimate of total error and calibrator performance as these studies deal with the real-world issues associated with shipping, storage, use conditions and other factors that may or may not have been otherwise considered.

2.2.4.2. Design of calibrators. When estimating the impact of calibrator uncertainty on the accuracy of a patient specimen result in the laboratory, the variation of calibrator potency due to manufacturing or testing error in the working reference calibrators must be accounted for. The error allocations and design choices to support these allocations down to commercially available calibrators is shown in Fig. 5. In this figure, the manufacturer begins with the quality goal for total allowable error and allocates error allowances downwards into the details of the design as shown by the traceability arrows. These lower level components are then built to produce a product that can be verified and validated to meet its top-level design requirements.

As a more detailed example, Fig. 6 illustrates the stack-up of manufacturing error as we move from primary reference materials to materials manufactured at production scale and supplied commercially to customers.

The top portion of the diagram represents the sources of error present when creating an internal reference. In any manufacturing step, the expected level of error in the product being manufactured must be characterized. In this example, the calibrator manufacturing error is represented by the combination of the error allowed by the manufacturing acceptance limits (i.e. the LSL and USL – Lower and Upper Specification Limits) and the error in the measurement system shown by the error distribution to the right. The estimates on the expected level of constant and random bias due to calibrator manufacturing can then be quantified by combining the error associated with making a reference calibrator with the error contribution due to manufacturing calibrators relative to this reference in the bottom half of the plot.

This total stack-up of constant and random biases should be part of an assessment of expected analytical performance discussed in the previous sections of this paper.

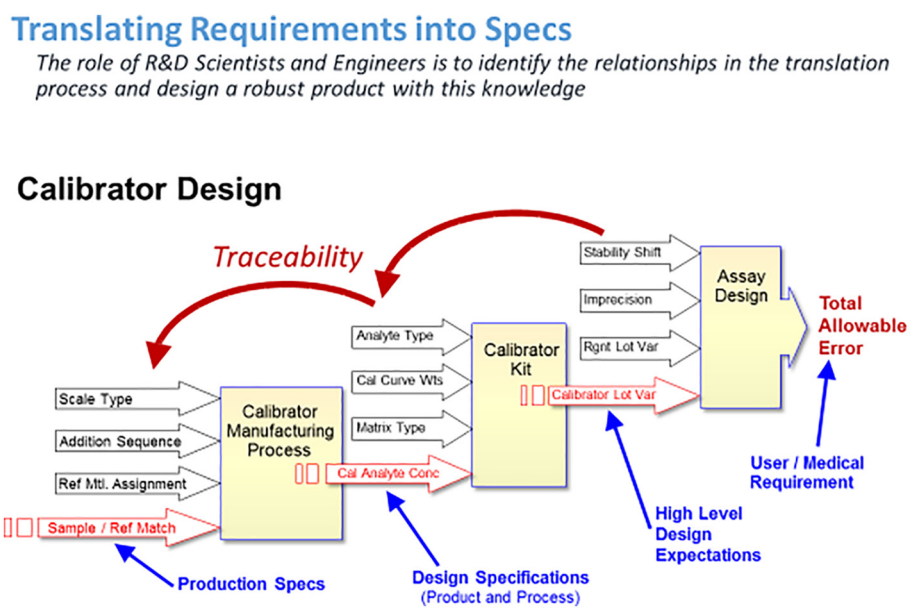

Fig. 5. Cascaded flow of error sources.

2.3. Verification and validation of analytical performance

Manufacturers can make use of both a top-down and a bottom-up approach in the design and validation of IVD systems by assessing both the lower level components against their detailed specifications and assessing the performance of the final system against customer requirements.

As previously stated, overall total error should be designed for and estimated by allocating error to the various sources of recognized bias and imprecision where expected performance can be assessed relative to requirements.

Before a new product is released to the market, manufacturers must first verify and validate the effectiveness of these design allocations under real-use conditions. This provides assurance that the IVD system operates as expected and that key sources of error that might contribute to the total analytical error of patient results have not been overlooked.

3. Results and discussion

What does this design process mean to laboratories and to patients? Most importantly, this approach leads to more accurate results for patients and a higher likelihood of improved classification of clinical outcomes and patient care. As Ferraro et al. [1] stated:

"Indeed, diagnostic accuracy is not a 'true' health outcome as this type of study answers the question 'Does the result of the laboratory test predict an outcome of interest (e.g. classification of the clinical condition)?' whereas health outcome studies ask if use of the test is associated with improved patient outcomes."

A manufacturer's role is to answer the first question as accurately as necessary, thereby helping the laboratory answer the second.

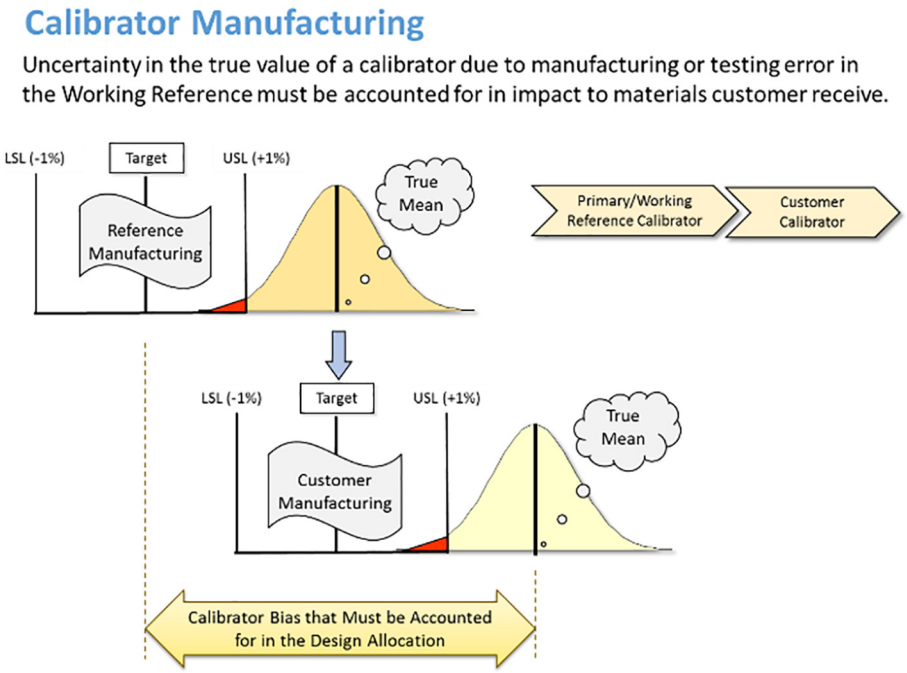

Fig. 6. Calibrator error stack-up.

While this process can be used to control analytical variation (bias and imprecision), there are still challenges present that must be faced. One of the biggest challenges for manufacturers and labs is that many analytes do not have published quality goals, and even those that are published have different specifications depending on the source. Another issue is that there are multiple ways to report error performance [5]. Lastly, many analytes are not standardized, leading to problems that have been well documented in literature [6,7]. Programs and leadership in driving harmonization of the varying methods that exist today is overdue and would be a key driver to future improvement.

Manufacturers must consider each of these factors and each manufacturer has its own way of addressing them. This means that claims for measurement uncertainty or sigma performance of an assay as reported by manufacturers may not be appropriate to compare across systems from different manufacturers because the underlying approach for estimating measurement uncertainty and total allowable error may not be consistent. This can and must be solved to make better progress in the future.

4. Conclusions

What can we, as members of the IVD industry, do to address these challenges? We can support and drive the publication of analytical quality goals for analytes that currently do not have them through focused collaboration between manufacturers, laboratories and scientific societies. We can ask ourselves if having multiple quality goal sources with conflicting requirements is necessary and seek to harmonize those goals. We can push to harmonize practices for reporting analytical error performance, thus providing greater value to laboratories, physicians and patients.

It is helpful to keep in mind that each of us, regardless of our role in the IVD industry, is at some point in our lives also a patient. To build from Dr. Smith's Essential Question, “What amount of medical harm due to analytical error is it OK to let go undetected?”, we want to know for our friends and family members, “What amount of medical harm due to analytical error is acceptable for me to let go undetected when testing is performed on my loved one?” To the authors, this question is a key motivating factor in building high quality, safe and effective products, and encourages us to challenge the industry to collaborate with us to harmonize methods for measuring and reporting analytical error.

Informed consent

This research was not performed using patients or patient volunteers, therefore informed consent was not applicable to this research.

Competing interests

None.

Declaration of interest

The authors are employees of Abbott, receive salary from Abbott and own Abbott stock. Anthony Orzechowski is an adjunct professor at Northwestern University.

Submission declaration and verification

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