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SCAN-BRIEF

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In This Brief...

CUSTOM MANUFACTURED CONTROLS FOR THE CLINICAL LABORATORY

Options from Scantibodies Laboratory

The Need for Controls

Controls are used in all clinical laboratories to monitor the analytical process and to assure that the test reagents and systems are performing according to the specifications of the manufacturers of those test reagents and systems. The use of controls complies with the requirements of Good Laboratory Practice (GLP), the CLIA, and the various regulatory agencies overseeing the operations of clinical laboratories.

The initial question regarding controls, therefore, is no longer whether to use them, but which type to choose. The traditional option has been to select from the various off-the-shelf controls to find the one that best fits the overall needs of the laboratory. This option meets some requirements while other requirements are left unaddressed. The possibility of having a control customized to fit the individual needs of the laboratory has not been an option in the past. *SCANTIBODIES Laboratory, Inc. now offers this option.*

On the following pages is a summary of the numerous functions of controls. The first questions are: (1) What is the purpose of the required control? and (2) What design for the control would best meet those requirements? Currently, customers often have to use a control with a long list of unneeded values from superfluous methods obtained by questionable value assignment models. It is better to focus on those methods used by the lab and assign values for those methods using a statistically-valid model.

This issue of SCAN-Brief explores the option of custom control manufacture as it relates to quality (including suitability and effectiveness) and economy.

Limitations of Typical General Purpose Controls

General-purpose controls are typically "one size fits all" products. They are promoted as being functionally adequate for a great number of analytes and a large number of methods for measuring those analytes. For example, common, general-purpose controls give the illusion of functional adequacy with the impressive data sheet citation of approximately 1000 values and ranges for analytes and methods. This large number of

analytes and methods has five significant limitations, however.

- The high cost of this extensive value assignment is borne by the user who is interested in only a small fraction (perhaps fewer than 5%) of these values. Why pay for methods you do not need?
- Conversely, there may be values that the user does need from methods that are not reported on the assay sheet.
- A common method for value assignment is to give samples of the control to the "unbiased" manufacturer and let him set the ranges he deems appropriate. Since the assay manufacturer knows that his assay will be listed side by side with all of his competitors, the stage is set for him to use this exercise to his marketing advantage by presenting ranges that are "too good." That is, he is in a position to use his SOP's for discarding "aberrant" values, thereby making the assay appear more precise than the users will find it to be.
- "One lab method" for value assignment also lacks the essential statistical validity offered by a more sound multi-lab testing model.
- "One size fits all" general-purpose controls are designed with the level of an analyte set so that no major method will give a zero value. This forces the low level to be set above the minimum detectable limit of the least sensitive method cited. To restate, if the minimum detectable limit for a sensitive method is much lower than the dominant test method used, general purpose controls have to set the low level control above the limit of the dominant test's sensitivity or risk losing the users of that method as customers.

Limitations of Kit Controls

Kit controls also have significant limitations. Kit controls are most often manufactured with the same process and materials as the kit calibrators. This lack of independence makes the kit control unsuitable to monitor the integrity of the calibrator. If an instability should arise from the control/calibrator materials or process, the kit control will shift to the same degree as the kit calibrator because they are one and the same. This gives the lab a false assurance that a non-performing test is indeed functional.

Limitations of Pooled Patient Serum for Controls

The use of pooled patient serum is a common laboratory alternative to general-purpose controls, but is an alternative which poses many potential and often overlooked problems. Those problems include the following:

Disease Testing – These pools are typically made up of donors who are not individually tested for disease (HIV, HBsAg, etc.) due to the cost of testing numerous small samples and the law regarding donor consent. This is especially important given the medical state of the donor population used. The final pool cannot be tested for diseases since the available tests are licensed for single donor testing only. Since this risk is avoidable via donor-tested controls, the lab's liability is heightened.

Analyte Range – The range of analytes available is limited by the range of the samples available; therefore, very high and very low analyte levels are difficult to achieve. This is especially true for analytes where abnormal levels are limited to rare disease states and for drugs where the high levels are toxic and the low levels are sub-therapeutic. This also leads to large lot-to-lot variation.

Multiple Controls – It is necessary to use numerous controls since it is virtually impossible to find patients with the required analyte profiles. For example, one can pool samples to get specific HCG levels, but all the thyroid markers will probably be about the same. The use of multiple controls can lead to confusion in the laboratory.

Storage – In-house produced controls are almost always frozen rather than freeze dried. This means that they require the use of freezer space, which is often limited, rather than the use of the more available refrigerator space.

Consistency of Manufacture – Since typically there is no defined procedure for production of patient pool controls, the process can vary significantly, which could impact stability and consistency from vial to vial. Validation testing and documentation of process control, dispensing, stability, vial to vial homogeneity, etc. are typically not performed with pooled patient serum controls.

Cost – The use of self-manufactured controls (*continued on page 4)*

The Functions of Controls:

The following table contains a list of functions that controls accomplish (column 1) and the various types of controls required by the clinical laboratory (column 2) to achieve those functions. The frequency and the responsible party for the accomplishment of each function are also keyed as follows:

A Routinely by the clinical lab
B At the time of validation by the clinical lab or the manufacturer for the clinical lab
C By the clinical lab at the time of troubleshooting
D By an expert evaluator at time of assay evaluation (i.e., literature)
E By the manufacturer at time of new lots of reagents and stability checks
F By the survey organizers for surveys
G By the manufacturer during R&D and claims support validation

Purpose or Parameter to Assess (Frequency)	Type of Control	Notes
1. Assay Precision (A)	Precision Controls	Replicates must be run for intra-assay C.V. Means between assays must be analyzed for inter-assay C.V. One to three controls are used, possibly in connection with the Westgard Rules
2. Sample Carryover (B)	Precision Controls	Assaying the low control immediately after the high control
3. Assay Drift (A)	Precision Controls	Intra-Assay – Run controls at the beginning and end of the assay. Inter-Assay – Compare between assays
4. Reagent Deterioration (A)	Precision Controls	Confirms assay specifications
5. Technician Error (A)	Precision Controls	
6. Instrument Failure (A)	Precision Controls	
7. Inter-Lab Comparison (A)	Precision Controls	Requires a data processing system that provides comparison of values from other labs
8. Assay Range (B)	High-End Precision Controls	Determination of hook effect
9. Accuracy (A)	Accuracy Controls	Assign values using reference materials/methods or consensus values
10. Certified Reference Materials (G)	Accuracy Controls	"Higher Order Controls" certified by a reference institute
11. Disease Profile Controls (B)	Accuracy Controls	With analyte levels typical for a disease state; may be used for clinical validation of an assay
12. Specificity (D)	Accuracy Controls with specific levels of cross reactants	
13. Sample Collection (D)	Accuracy Controls as sera including SST* (serum separator tubes) and plasma with various anticoagulants	For validation of assay in connection with sample collection procedures
14. Control Deterioration (C)	Alternate set of Precision Controls or Accuracy Controls	
15. Disease Diagnosis (A)	Precision/Accuracy Controls with levels in normal range, at decision limit, and in pathological range	
16. Reagent Release (E)	Precision/Accuracy Controls and/or patient panels	For use by manufacturer
17. External Quality Assessment or Survey (F)	Precision/Accuracy Controls	
18. Assay Sensitivity (B)	Zero and/or Low Control	2 x S.D. of zero control signal = sensitivity (signal to noise dependent)
19. Linearity (B)	Set of Linearity Controls	Best to have a set of 5-10
20. Dilution (B)	Off Scale Control	Particularly important for instruments with automatic dilution
21. Safe Transport of Reagents and Easy Trouble Shooting with Reagent Manufacturer (A)	Link Controls	Manufacturer uses controls to routinely release reagents and lab uses the same controls for Internal Quality Control (IQC)

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is not as economical as it appears initially, since it requires potentially large amounts of technician time and testing to produce and validate the controls.

What Are Custom Controls?

Custom controls are those controls specifically designed and value assigned to fit the needs of an individual user. The possible areas of customization by Scantibodies include choice of matrix, analytes, number of levels (e.g., to allow use of Westgard Rules), target levels, test methods, fill size, packaging, price, form (liquid, lyophilized, frozen), lot size (from as few as 100 vials for very small applications to as many as ~50,000 vials). Large lot sizes enable the lab to use the same lot of controls for 2-3 years for long term Levey Jennings charts, etc.

Some off-the-shelf controls may not be commutable for a certain method. This means that the controls may not behave as patient samples. Therefore, a certain commutability (e.g., linearity, kinetic response, etc.) may be specified for a custom control for a specific test method.

Who is a Potential Candidate for Custom Controls?

System and Reagent Manufacturers – When a reagent manufacturer develops a new assay, a suitable control must be available for its customers to perform the QC monitoring required. There may be a control commercially available. In other cases, the manufacturer may elect to provide the control themselves. However, for unbiased monitoring, it is preferable that a "system check" control be supplied by a third party who is independent of the system and reagent manufacturer. Moreover, the expertise of assay manufacturers lies in the development of instrument and/or reagent systems and not in the area of controls manufacture. This means they are forced out of their core competencies to develop controls and perform the necessary testing to establish control performance characteristics and stability claims needed to submit for regulatory approval.

In order to comply with GLP, laboratories also require controls for validation to be used at the time of system installation and periodic revalidation. Both system and reagent manufacturers require special controls to be used during the manufacturing process and the requirements (e.g., verifying the low-end precision and sensitivity by instrument or by reagent lot) for such controls are typically different than those of commercially available controls.

The use of Scantibodies' custom controls eliminates this time and resource-consuming activity, allowing the assay manufacturer to concentrate on the development of more assays (instead of controls), thus bringing more products to market faster.

Scantibodies' custom controls provide laboratories with the confidence of independent third party assay confirmation.

Clinical Reagent Distributors – Distributors not directly connected with a control manufacturer may desire to offer custom controls to their customers. However, they are often either unable to purchase them at all, the lead times are too long, the lot sizes are too great, or the price is too high to allow them to distribute the controls. Since Scantibodies' custom controls are available in small lots, with a rapid turnaround and a low transfer price, the distributor is enabled to offer controls to its customers.

Large Reference Laboratories – Such laboratories often have special needs due to the types of testing they perform in certain areas. This results in having to use several different controls because no single control offers all of the analytes needed. In addition, the controls being used often contain analytes and assays that are not needed, but have contributed to the price the lab has paid for the product. A custom control allows the lab to design a product that best fits its individual needs, thereby reducing the number of types of controls required. A vial size of 25-50 mL is often preferable for a large lab.

Hospital Purchasing Groups – These laboratories' requirements are similar in many ways to that of the large reference laboratories. This is especially true in the area where they pay for analytes and test methods that they do not need or buy numerous controls to cover all of the analytes needed.

Survey Organizers – Unlike the previously described groups which use controls for Internal Quality Control (IQC), survey organizers provide controls for External Quality Assessment (EQA). The goal of such controls is to provide an independent outside evaluation of laboratory performance as well as to compare the performance of different instrument and reagent systems. For survey controls, it is critical that the controls have the best

demonstrated commutability between the control and patient samples. Without good commutability (i.e., biases between control and patient sample), valid comparisons between laboratories and instrument reagent systems cannot be made. To prevent participants from knowing the analyte values, the survey organizer prefers not to use commercially available controls. Therefore, the custom control is the best option for the survey organizer.

Why Should One Buy a Custom Control?

Third Party Independence – Third party controls provide confidence that the control is manufactured independently of assay reagents. The control must alert the technologist to shifts due to reagent or kit lot changes. Then the problem of a corresponding shift in patient values can be detected and the appropriate corrective actions taken before erroneous values are reported.

Most kit controls are made from the same raw materials and with the same process as the calibrators in the kits. If degradations of those materials should occur, it would happen in both the controls and the calibrators. This would result in the test appearing to be in control while it had actually shifted. In other words, kit controls are really an additional set of calibrators or "pseudo controls."

Custom controls are produced with a process and materials different from the kit calibrators. This allows the controls to effectively monitor the assay integrity.

Customization – Unlike conventional controls, custom controls are manufactured to fulfill a particular user's needs without an overall compromise to meet the needs of a wide array of users. This means that the customer gets and pays for what is needed and only what is needed. All desired analytes may be included at the needed values and the fill size, closure colors, etc. may be tailored to the individual customer's needs.

Price – Because Scantibodies is a supplier to manufacturers and a producer of its own raw materials with more than twenty years experience, the cost of custom controls can be lower than the off-the-shelf control products. This can be especially cost effective for assay manufacturers, since there is neither R&D involved to develop the controls, nor regulatory submissions to file.

Lead Time – This is especially an issue for assay manufacturers and reagent distributors who need to accommodate fluctuations in sales while maintaining minimum inventories. The typical Scantibodies' lead time for repeat orders is 60 days, with 60-90 days for new products, depending on the configuration and complexity of the product.

Pilot Option – Off-the-shelf controls allow for a sampling of an existing product. However, with customized controls, a pilot may be produced and sent for qualification and refinement so that the production lot can be changed to reflect final adjustments. Since the pilot and the main lot are produced with the same lots of materials and by the same process, assurance is obtained that the pilot lot will be representative of the main lot.

Constituent Selection – The constituent selection is broken down into four parts. The first is to define the analytes that the control must contain. Second is to define the test system/method to be used to assay each of the selected analytes. The third is to decide the number of levels required, typically two or three. There are instances where multiple levels are run periodically, while only a single level is run routinely. If the control is to be used on a single method for each analyte, the final product testing is much easier (and less expensive). The fourth is to select the target levels for each analyte for each level. The levels are set with the following objectives in mind:

- **Normal/Pathological Range –** This two level set consists of one level in the normal range and one level in the abnormal (pathological) range. This assures that the instrument/reagent system is functionally adequate to detect patients in each category.
- **Clinical Decision Point –** This single level control is set at the point where physicians decide the diagnosis of the patient and whether or not to initiate treatment of the patient. Controls at this limit assure that the test system is performing properly at the most diagnostically critical point where treatment or diagnostic decisions are made.
- **Clinical Set –** This (combination of the above levels) is a three level set with the levels in the normal range, at the decision limit and in the pathological range. This provides confirmation of the

consistent clinical predictability of the assay.

- **Test System Limits –** This set of controls challenges the low end sensitivity and the upper limit of linearity of the test system range. The idea is that if the test system is performing properly at the extremes, there is a high probability that the system will perform properly between the limits.
- **Analytical Set –** This would be a three level set with levels in the low range of the assay, at the midpoint of the assay range and in the high end of the assay range (irrespective of clinical utility). This provides confirmation of the assay performance from an analytical chemistry viewpoint. The idea is that if the analytical tool is performing, the clinical utility can be assumed.

Once the customer has defined the specifications, Scantibodies will serve as a partner and provide recommendations and comments as needed regarding the following areas:

- **Feasibility of Manufacturing –** It may be that a specified control is not feasible to manufacture because of limitations imposed by the raw materials, known cross-reactivity, interferences between analytes, test system requirements, etc.
- **Economy of Manufacturing –** This is where the analyte level or process requested results in an extraordinary cost due either to the high cost to raise the analyte up to the target level or the high cost to lower it to the target level from the endogenous level.

Scantibodies' Product Configuration

Matrix Selection – The serum matrix is tailored to the requirements of the individual control. All matrices begin with a 100% human base which minimizes problems of test comparability and commutability. Human serum products are donor tested and found non-reactive for HbsAg, anti-HBc, anti-HIV-I/II, anti-HCV, anti-HTLV-1, syphilis, and with normal levels of ALT. Serum controls are supplied in several matrix formats. The most cosmetically appealing and easy to work with is lipid stripped because of its excellent clarity and rapid reconstitution. However, there are some controls which require the presence of lipids to form part of the constituent profile or are essential to assay performance (e.g., hydrophobic steroids). The controls are also filtered through 0.2 micron filters immediately prior to filling to reduce bioburden. Certain preservatives/stabilizers may be added if needed without affecting product performance.

Pilots – Pilots may be made before the production run is manufactured. These pilots can then be evaluated by Scantibodies and/or the customer to allow for final "fine tuning" of specifications and formulation. The same lots of materials used in the pilot are used to manufacture the production lot, giving the maximum confidence that the final lot will be comparable to the pilot lot.

Regulatory Compliance - Scantibodies handles all of the regulatory issues for each of its products. This is important because it minimizes the time from inquiry to delivery of product.

Stability – Both accelerated and real time stability studies are performed according to the customer's needs in Scantibodies' multiple laboratory sites and/or in outside reference labs on each lot of controls manufactured. This assures that the control meets all of its claimed performance characteristics and that the target values have been achieved and will remain stable for the full shelf life.

Scantibodies' Packaging Configuration

Vial Type and Fill Volume – The fill volumes may range from 1 mL to 50 mL. The vials can be plastic (natural or opaque) or glass (clear or amber) depending on the product. The vials can have stoppers in various colors. The closures can be screw caps, aluminum crimp-style caps, or dropper-type vials. Where appropriate, ampules may be used.

Packaging and Documentation – The vials (with or without labels) may be supplied packed upright in shallow trays or packed in the customer's final boxes. Optional packaging services include preparation of the package insert and/or labeling. For customers who want to do their own filling, controls can be shipped in bulk form.

Testing Performed on Scantibodies' Custom Controls

Value Assignment – Since the analyte value assigned to a control is its most important aspect, Scantibodies takes great care in this activity. (*continued on page 8*)

Possible Analytes in Custom Controls

The following is a list of possible constituents in Scantibodies' controls at the time of printing. Also available are controls for alcohol and vitamins.

Serum Protein Control (Liquid)

- Albumin
- α_1-Antitrypsin
- α_2-Macroglobulin
- ASO/ASL
- Ceruloplasmin
- Complement C3
- Complement C4
- CRP
- Haptoglobin
- IgG
- IgM
- IgA
- Rheumatoid Factor (Rf)
- Transferrin

Tumor Marker Control

- AFP
- CA 125
- CA 15-3
- CA 19-9
- CA 72-4
- Calcitonin
- CEA
- CYFRA 21-1
- Ferritin
- HCG
- ß$_2$-Microglobulin
- NSE
- PAP
- Prolactin
- PSA

Therapeutic Drug Monitorings (May be combined with general chemistries.)

- Amikacin
- Carbamezepine
- Cortisol
- Digitoxin
- Digoxin
- Kanamycin
- Gentamycin
- Lidocaine
- Phenobarbital
- Phenytoin
- Primidone
- Procainamide
- Quinidine
- Theophylline
- Tobramycin
- Valproic Acid
- Vancomycin

General Chemistry

- α_1–Acid Glycoprotein
- α_1-Antitrypsin
- Acid Phosphatase
- A/G Ratio
- Albumin
- Aldolase
- Alkaline Phosphatase
- Ammonia
- Amylase
- Amylase, Pancreatic
- Apolipoprotein A-1
- Apolipoprotein B
- ASO/ASL
- Bilirubin, Direct
- Bilirubin, Indirect
- Bilirubin, Total
- Calcium
- Ceruloplasmin
- Chloride
- Cholesterol, Total
- Cholesterol, HDL
- Cholesterol, LDL
- Cholinesterase
- Complement C3
- Complement C4
- Copper
- Creatine Kinase
- Creatinine
- CRP
- Free Fatty Acid
- Fructosamine
- GGT
- Globulin
- Glucose
- GOT (AST)
- GPT (ALT)
- Haptoglobin
- IgA
- IgE
- IgG
- IgM
- Inorganic Phosphate
- Iron
- Lactate
- LAP
- LDH
- Lipase
- α_2-Macroglobulin
- magnesium
- Osmolality
- pHPotassium
- Rheumatoid Factor (Rf)
- Sodium
- Total Protein
- Transferrin
- Triglycerides
- Urea
- Uric Acid
- Zinc

Hormones

- ACTH
- Aldosterone
- Andostenedione
- Calcitonin
- C-Peptide
- CK-MB
- DHEA-S
- Estradiol
- Estriol
- Estrone
- Ferritin
- Folate
- FSH
- HCG
- ß-HCG
- 17-α-Hydroxyprogesterone
- Insulin
- LH
- ß$_2$-Microglobulin
- Myoglobin
- Osteocalcin
- PAP
- Parathyroid Hormone
- Progesterone
- Prolactin
- Somatomedin C
- T3 (Triiodothyronine)
- T4 (Thyroxine)
- TBG
- Thyroxine-Binding Capacity
- Testosterone
- Total Iron Binding Capacity
- TSH
- Vitamin B12
- 25-Hydroxyvitamin D

Infectious Diseases

- CMV Antibody
- Herpes Antibody
- Rubella Antibody
- Toxoplasmosis Antibody

Scantibodies is able to establish and carry out a statistically valid value assignment to generate an analyte, value and range reflective of what a broad base of users will find. In order to incorporate method-dependent value assignment and reference method value assignment, the value assignment process may include the following:

1. Assay at multiple Scantibodies' sites.
2. Assay at several user laboratory sites.
3. Assay by reference method with reference materials
4. Assay and assignment of "accuracy value" by a reference institute.
5. Utilization of:
   a. multiple lots of assay reagents
   b. different instruments
   c. multiple days
   d. different technicians

The experts at Scantibodies are prepared to design the model and carry out the value assignment that is most appropriate for the control.

Specification Definition Process – There are numerous choices to be made when specifying custom controls but the process is not as daunting as it appears. To make the development of specifications simple, Scantibodies has developed an External Statement of Work (ESOW) which guides the customer easily through the specifications to be developed. In addition, Scantibodies' experienced staff works closely with the customer to assure that the process goes smoothly and the customer's needs are met.

Summary

Standard controls fill certain, limited needs. However, custom controls offer benefits that are cost effective while incorporating customer needs not found in off-the-shelf controls. As one can see, there are many possibilities to be considered in the purchase of custom controls. Scantibodies has personnel who are expert in the manufacture of controls. With a simple but thorough system for collecting and organizing specifications (ESOW), the process from concept to product is straightforward and rapid. If you need custom controls, or would like to have more information, please contact Scantibodies by phone at (619) 258-9300 ; fax: 619-258-9633 ; or email: cs@scantibodies.com, for an ESOW form.

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