Quality Control Testing Throughout the Product Development Lifecycle

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Quality control (QC) is an essential function in the manufacturing operations of a pharmaceutical, biological, medical device or combination product. A significant portion of the QC function (department, organization) includes but is not limited to the testing of raw materials, water, components, active pharmaceutical ingredients and commercial products. Quality control testing laboratories (QC laboratories) – whether internal to the sponsor organization or in the form of an external laboratory (i.e., contract laboratory) – provide essential scientific or technical support services across the continuum of product development. This

chapter will cover such testing programs as well as describe a generic Quality Management System (QMS) that would be expected to be in place and in use for a typical QC laboratory.

Life science manufacturers (e.g., devices, diagnostics, pharmaceuticals, biologics) must comply with innumerable requirements and regulations (e.g., at local, state, national, or international government or institutional levels). For our purposes in this chapter, the term "sponsor" will be synonymous with "client" or "manufacturer". Most sponsors, as the R&D process unfolds, develop an increasing knowledge of the structure and functionality of their product candidate, namely, its physical-chemical properties, its activity and quality attributes and its expected benefit to the patient. That said, expertise in pharmaceutical development from a process standpoint sometimes does not coincide with the necessary and corresponding methodological expertise expected in the performance of QC tests that are used to assess the safety and/or efficacy of product batches. For some sponsors, even the types of tests that need to be performed (e.g., general biocompatibility, analytical chemistry) may not be fully understood because of a lack of in-house knowledge. Thus, reliance on a contract testing laboratory can be a good option, especially for startups, small and mid-sized companies. Contract QC testing laboratories are available as an alternative to and/or supplement to in-house QC laboratories. Indeed, this chapter will describe, in a hybrid manner, the operational realities in both QC contract laboratories as well as vertically integrated manufacturers. It's worth pointing out at the outset that companies that outsource their QC testing to contract laboratories remain responsible for the cGMP performance of these external laboratories. So, think of contract laboratories as an extension of the sponsor from scientific, quality and compliance perspectives.

High performing contract QC laboratories make it their business priority to understand test methods and the associated requirements and regulations to the same level of expertise as the sponsors do for the manufacturing of their products. Contract QC laboratories do not manufacture products and, instead, generate

their revenue by providing testing services as a specialized business entity. Conversely, the same QC testing efforts, if performed directly by manufacturers, are perceived differently by management, as QC is classified as an operational expense against company profits.

Contract QC laboratories are independent organizations and exist to generate objective and unbiased data of test articles (e.g., biologics, pharmaceuticals, recombinants, medical devices, diagnostics, environmental monitoring samples; utility system samples, facility substrates) to help manufacturers demonstrate the level of compliance against current good manufacturing practice (cGMP) regulations. When Investigational New Drug (IND), New Drug Application (NDA) or 510(K) regulatory submissions are made, the involvement of a contract QC laboratory can lend additional credibility to the regulatory authority in support of the marketing application. Sometimes even sponsors that have in-house QC laboratories do not have all of the resources (e.g., headcount, equipment) to meet certain corporate deadlines. Thus, contract QC laboratories can be an important (and sometimes a critical) element in the product development process as well as for post-regulatory approval, a necessary part of the supply chain (e.g., routine QC testing of products).

Because of their specialized subject matter expertise, contract QC laboratories are often used by life science sponsors to ensure the proper selection of QC tests that need to be performed, as well as to then perform those tests in accordance with cGMPs that provide the requested data/results denoting the quality attributes of test articles for sponsors. The earlier that sponsors involve QC laboratories for advice and to establish testing plans, either in support of clinical trial materials or commercial batches, the smoother the process will go once it comes time for QC testing to be performed.

There are several aspects to a high performing contract QC laboratory which can make it a preferred choice for sponsors seeking quality testing services.

- First, QC laboratories are occasionally led (and even founded) by subject matter experts connected to the actual scientific testing methodologies. Because they depend entirely on the provision of testing services to be successful from a business standpoint, contract QC laboratories typically have robust internal quality systems that are specific to laboratory testing services. This is intended to let the sponsor conclude, upfront and with a high level of confidence, that the QC test(s) will be performed correctly.

- Second, contract QC laboratories typically possess extensive experience performing the tests, understand the science behind the tests, and can further offer tests that have been or need to be validated consistent with GMP. This experience also prepares the QC laboratory to troubleshoot experimental issues should the reported results not be as anticipated.

- Third, contract QC laboratories will be expected to fully understand the quality standards that underpin the test, whether national and/or international in origin.

- Fourth, if the QC laboratory was involved (as some are) in writing the national and international standards that are referenced in the tests, they can properly guide the sponsor as to the intent of the standard, which can be difficult to interpret at times, and which can help the sponsor know what is coming down the regulatory pipeline. For example, QC laboratories involved with writing standards and guidance documents often know a year or two in advance of changes that are going to be made and can appropriately guide sponsors based on these emerging regulatory-industry trends. What this means is that the higher echelon QC laboratories are those with repositories of expert scientific thinking and influence within the industries they serve.

RESEARCH AND DEVELOPMENT PROGRAMS

QC laboratories inject value into R&D programs through collaborations with sponsors by providing insight on the testing that will need to be performed and share thoughts on potential issues to keep in mind during development. For example, there are some product types that are difficult to sterilize (e.g., complex medical device instrument trays), and with some advice earlier on in the R&D process, the sponsor can engineer product candidates (e.g., medical device, parenteral drug) to be terminally sterilized (e.g., steam, ethylene oxide, irradiation) without deleterious quality effects. In addition, in the development of antimicrobials such as antiseptics, handwashes, disinfectants and antibiotics, the QC laboratory can assist the sponsor to narrow down the field of antimicrobial candidates through customized screening tests (e.g., Killing Time; Minimum Inhibitory Concentration). These microbiological tests, for example, support research programs and save costs, through selective elimination of experimental formulations that either are not efficacious *in vitro* or otherwise have unfavorable characteristics such as a short shelf life following placement in a stability testing program.

EARLY STAGE DEVELOPMENT

When a product candidate is judged suitable for further development by the sponsor, some preliminary tests can be performed to gain a fuller understanding of the critical attributes of the molecule (or device). For example, a cytotoxicity test may need to be performed to provide some general information about the relative biocompatibility of a cardiac device. Another example is when a patient is at risk of developing a fever from contact with a parenteral drug substance. In this case, the USP <85> Bacterial Endotoxins Test may need to be performed to verify the safety of the test article. This approach provides an understanding to the manufacturer about whether the underlying manufacturing process is prone to adding the fever causing substance (i.e., endotoxin) somewhere in the process stream. For example, to potentially

determine whether, downstream, a contaminated filtration unit that was not properly cleaned in-between manufacturing runs became, in effect, an "endotoxin sink". In both examples, the QC tests referenced are inexpensive, fast and can help to reveal potential quality issues early in the development process. Stability testing may also be performed during early stage development to get an initial understanding of the stability profile of the drug candidate over time. Stability studies include evaluation at multiple temperature and humidity conditions, as well as stress testing and so-called bench-top studies to evaluate parameters such as light, motion, orientation, etc., on the stability of the test article. Because time cannot be reclaimed – a point that cannot be overemphasized given the typical duration and cost in conducting product development – it is truly important for sponsors to generate stability information relatively early in the R&D process. A contract QC laboratory, geared to provide a range of stability studies, may therefore be a useful testing complement to sponsors, especially for startups.

During early stage development, the first version of a new product's Certificate of Analysis (COA), listing the tests and acceptance criteria (also known as specifications), is often prepared. The utilization of a COA by a QC laboratory can happen in a couple of ways. Sometimes the sponsor already has a COA established and contacts a QC laboratory to determine if it can perform some or all of the designated tests and, if so, to contract with that QC laboratory. In other situations, the sponsor might request a QC laboratory to partner with it in the establishment of a COA followed by performing the stipulated tests on a defined basis. Note that the testing of articles by QC laboratories is achieved through a laboratory test system which is the composite of the test method, the laboratory equipment, a reference standard (if applicable), laboratory reagents, operating personnel, and operating facility/environment. Each of these elements of a laboratory test system should be governed by Standard Operating Procedures (SOPs) and cGMPs. QC laboratories use SOPs to standardize within their facility general procedures and testing methodologies. We think of them as training aids and require employees to demonstrate their understanding of the SOPs that they

are accountable to. QC laboratory employees are required to regularly demonstrate their review and competency of SOPs in order to be granted permission to perform specific tasks.

LATE STAGE DEVELOPMENT

As product candidates are scaled up and enter later stage development, the product contact materials (e.g., container-closure system; packaging) and manufacturing process should be well characterized and well controlled. This is the stage where much of the required QC testing is performed in preparation for selection of the final product candidate and associated regulatory submission. Sponsors that work with the QC laboratory in the earliest stages of development gain the greatest advantage by this late stage development phase. If QC testing agreements are already in place with a contract QC laboratory, for example, and if the required tests have already been performed by the QC laboratory during the earlier stages of development, it should facilitate (and confirm) both the selection of tests that need to be performed as well as delineate how the tests are to be qualified, validated or verified (if compendial in nature) during late stage development (i.e., when a product candidate is entering a pivotal clinical trial). Also, the QC laboratory can help the sponsor understand well in advance what the testing regimen is likely to be so that it can appropriately plan and budget for the contract QC laboratory services. Stability programs continue unabated during the drug development process.

COMMERCIAL TESTING

The relationship and division of responsibilities is often codified in a written Quality Agreement between the sponsor and QC laboratory. The primary role a QC laboratory can play when an FDA-approved product enters commerce is that of performing routine tests quickly and properly to enable the manufacturer (following its own quality assurance review process of the QC results) to disposition product without delay in compliance with all

relevant regulatory requirements and industry practices. If the QC laboratory is contracted by the sponsor to perform the QC testing, there should be clear lines of communication between the parties in facilitating the batch disposition process. The goal is for the QC laboratory to initiate the testing process on the day of sample receipt on behalf of the sponsor, who expects cost-effective, timely and accurate testing services. While these client demands represent the gold standard expectation for QC laboratories, it can be a difficult paradigm to achieve! The better QC laboratories are those that are highly specialized businesses to effectuate challenging sponsor expectations. Post regulatory approval, to understand the impact of sponsor-directed changes (e.g., new manufacturing facility, scaled-up manufacturing process, new container-closure system), the use of validated QC tests are crucial scientific tools to assess the impact and risk of the change(s) on the quality attributes of the product as referenced in the predicate COA on file.

When QC test results are not what is expected (i.e., they are "discrepant"), a well vetted SOP should be in place to first, quickly determine if there is a laboratory assignable cause and, if not, to assist the sponsor in troubleshooting its manufacturing processes to help investigate and hopefully remedy the underlying quality issue. A typical example is in performing bacterial endotoxins testing (BET) for products that require a non-pyrogenic label claim. This test should be performed throughout the manufacturing process as well as on the final product. A discrepant BET result from any stage of the process should trigger a hold on the product while the QC laboratory performs its internal investigation on the test method and while the manufacturer investigates, for example, its water systems and suppliers for potential sources of endotoxin. A QC laboratory with extensive experience in BET can quickly review its internal data and, if necessary, conduct additional investigative testing or a new round of expanded testing (per a QA-approved retesting protocol) to verify whether the original discrepant result was confirmed. It can also work with the manufacturer and, with an understanding of the raw materials and even the manufacturing process, provide useful insights regarding what could have caused the discrepant result.

SELECTING A CONTRACT TESTING ORGANIZATION

It is our experience that the primary reason a manufacturer selects a contract QC laboratory is because it trusts that the QC laboratory will perform the testing to achieve the business objective. The work product is fully documented, and the data/results are accurate and verifiable. A consistent record of strict regulatory compliance is highly relevant because significant sponsor resources (and brand reputation) are at stake. There is a great dependency by the sponsor that the QC results produced by the QC laboratory will possess sufficient technical, scientific and documentation rigor, and that these results will stand up to thorough regulatory review (e.g., that the claims made by the manufacturer are, in part, supported by the QC laboratory). The evaluation and approval of suppliers is generally prescribed by regulations, and this evaluation should include a review of the QMS and compliance track record. QC laboratories are often considered to be high risk suppliers, since they provide critical data to the sponsor or regulatory authority about product safety. While raw materials and finished product batches, for example, are routinely verified through QC testing on a lot to lot basis, the generated reportable results are reliant on a well-functioning QMS.

As is the case with all cGMP suppliers, there are several aspects in selecting a QC laboratory. The obvious aspects are simple, such as verifying that certifications and/or accreditations are in place and obtaining an initial understanding for the breadth of service offerings. Certifications and accreditations (they are different terms as will be explained) require a substantial investment in time and resources by QC laboratories. Contract QC laboratories which are serious about demonstrating their commitment to quality should strongly consider certifying with objective and independent evidence their receipt and attainment of the highest QC laboratory standards. For example, a common approach for QC laboratory selection is to identify International Organization for Standardization (ISO) 17025 accredited laboratories (ISO, 2017a). ISO 17025, General Requirements for the Competency of Testing and

Calibration Laboratories, is aligned with ISO 9001, Quality Management Systems (ISO, 2015), and ISO 13485, Medical Devices – Quality Management Systems: Requirements for Regulatory Purposes (ISO, 2016). However, ISO 17025 also specifically addresses QMS requirements and aligns well with many GMP requirements (e.g., validation, calibration, management review). Determine whether the QC laboratory is accredited and, if so, whether the services being requested are listed within the scope of accreditation. Accreditation to ISO 17025 does not automatically imply recognition of every test performed by that laboratory; instead, each test is applied for and accredited separately. The term "accreditation" implies a formal program that is recognized by ISO, as opposed to the term "certification", which is not officially recognized by ISO.

Beyond ISO 17025 accreditation, FDA provides requirements for various aspects of laboratory controls in 21 CFR, Parts 211.22, 211.84, 211.160, and 820.50. From an international perspective, the International Chapter on Harmonization (ICH) Q10, Pharmaceutical Quality System (ICH, 2008), provides information on supplier identification and qualification of outsourced activities. The use of a Quality Agreement is common in industry to incorporate or to cross-reference quality requirements (e.g., change management) into the contract QC laboratory's QMS.

The selection of a QC laboratory with a substantial breadth of test offerings can optimize sponsor resources. The more laboratories that are involved in performing assorted QC tests listed in the COA, the more complex the management of these external laboratories can be from a management oversight standpoint. For example, a single QC laboratory performing both sterility and endotoxin testing, as opposed to two distinct laboratories taking on those responsibilities, is a more efficient path to follow because only one laboratory qualification audit need be performed as opposed to two audits. Additionally, if multiple QC laboratories are being used, the manufacturer must spend additional time performing audits as well as coordinating and ensuring application integrity in regulatory submissions.

When selecting a contract QC laboratory, sponsors are strongly advised to evaluate the laboratory's scientific expertise, QMS and company culture. QC laboratories represent unique cultural environments in that they are different than sponsor R&D laboratories. QC laboratories operate with alacrity; R&D laboratories, often less so. Sponsors are encouraged to spend time interviewing the QC laboratory's scientists involved in performing the testing, and to discuss topics with the company's scientific leaders (e.g., scientific interpretation of results, industry participation in developing standards and guidance documents). The better contract QC laboratories are those that can additionally speak to the scientific intent behind the standards and guidance documents, not just recite and perform what is written on the pages of a test method. The last aspect of selecting a QC laboratory involves ensuring that it has the necessary internal procedures and that it appropriately supports the testing that is needed. The QC laboratory's QMS requires the existence and use of SOPs that are kept up to date. Refer to Tables 1 and 2 below.

Table 1 Recommended criteria for selecting a contract QC laboratory

Item	Selection criteria
1	Objective metrics of performance such as employee error rate and trend, compliance with schedule
2	Geographic location – there is a client benefit to having ready access and to be close to the laboratory, especially for meetings to discuss technical matters
3	Breadth of services and/or possession of intellectual property to allow specialized services not widely available
4	Global reach – large companies have geographically spread manufacturing operations
5	Accreditation to appropriate standard by internationally recognized accreditation body
6	References
7	Cost

The following is a partial list of recommended SOPs that should be in place and in use in a contract QC laboratory, with a short summary of each.

Table 2 Critical SOPs expected in a QC laboratory QMS – for illustration purposes only

Topic	Description
Investigation and management of discrepant QC results	The QC laboratory must have a robust process for the handling and disposition of discrepant results (i.e., atypical and out-of-specification) as well as possible laboratory errors. The system should ensure that all physical, chemical, microbiological and biological laboratory-generated OOS results are promptly and systematically investigated and documented. The SOP should describe a standardized investigation procedure and should seek to identify the underlying root cause(s) of the discrepant result and specify the appropriate corrective action(s). Corrective actions should be monitored to assess their effectiveness in redressing the underlying cause of the discrepant result.
Test methods development/ validation/transfer	The QC laboratory must have a robust process for methods development, validation and transfer. Specifically, the SOP addresses items such as generation of a validation or transfer protocol, acceptance criteria, responsibilities, samples to be tested, and documentation of a validation or transfer report. A change control process should also be included to assess the impact on completed validations when methodological changes are required.
Management and inventory control of laboratory reference standards and reagents	The QC laboratory must have a robust SOP for the handling of reference standards (e.g., MHRA (2007) and 21 CFR 211.194(c)) and reagents. Reference standards play a key role in ensuring the empirical validity of data generated from samples of raw materials, intermediates, final bulk, and finished products. The SOP should provide instructions for the procurement, receipt, storage, inventory control and use of reference standards and reagents. The SOP should apply to both purchased and internally produced reference standards as well as chemical and biological reference standards, as applicable.

Topic	Description
Laboratory sample management	This SOP governs how samples (test articles) will be handled during receipt, logging in, storage, staging, testing, and disposal in the laboratory (e.g., MHRA (2007) and 21 CFR 211.82) that speak to sample management in general. Traceability is a key aspect of good laboratory practices. The SOP should safeguard and track the chain of custody of all laboratory samples.
Sample labeling	This SOP governs the requirements for completeness of sample, reagent, sample preparation and reagent preparation labeling. The SOP should detail the necessary information to be contained on sample labels including expiry, safety information and storage temperatures (e.g., MHRA (2007) and 21 CFR 211.194(a)(1)).
Rounding of data and reporting of significant figures	This SOP governs the principles for the rounding of laboratory data and results and specifies the requirements regarding the number of significant figures to which laboratory data and results are reported and define rules to be used for reporting of significant figures.
Notebook/worksheet management and documentation practices	This SOP governs laboratory notebooks and worksheets (e.g., MHRA (2007) and 21 CFR 211.19414) that address recording of results and laboratory documentation. The SOP should detail the issuance, use, control, laboratory retention, and archiving of laboratory notebooks/worksheets that record laboratory data. The system should also define good documentation practices in the laboratory, covering items such as signatures/initials of reviewers, date of review, use of ink only, legibility, clarity and completeness, and recording on pre-numbered pages in bound logbooks.
Calibration and preventative maintenance for GMP laboratory instruments	This formal system (which may be in the form of all-encompassing SOPs or instrument-specific SOPs) governs the qualification requirements of all GMP laboratory instruments and equipment, as well as their calibration and preventative maintenance requirements (e.g., 21 CFR 211.160 (b)(4)) that speak to equipment calibration.

Topic	Description
Laboratory training	This SOP governs laboratory training requirements (e.g., 21 CFR 211.25(a))17 that speak to personnel qualifications. The SOP should include guidance concerning various training elements that should be a part of each testing laboratory (e.g., cGMP training, compulsory training (such as new employee orientation), on-the-job training (OJT), SOP training, safety training, other/external training). Requirements for competency-based training programs, clearly defined roles and responsibilities for managers and trainers, and adequate training documentation should also be included.
Internal audits	This SOP governs the status of laboratory quality systems and GMPs of audited laboratories. Specifically, the SOP seeks to assess whether laboratory operations are being conducted in accordance with relevant SOPs, cGMPs, applicable regulatory requirements, and industry standards. The SOP should specify the requirements for documenting, classifying, and correcting findings/observations.

Typically, once a QC laboratory has been selected by a sponsor, an inquiry is made about the availability of that laboratory to perform anticipated testing projections as well as for cost estimates. In many cases, the qualification and business development cycle between a sponsor and the contract QC laboratory is lengthy because it involves stakeholders in regulatory affairs, quality, manufacturing operations and procurement. Often many documents are executed that make explicit the understanding of the parties such as master service agreements, quality agreements, and confidentiality agreements. Refer to Table 3 created by Daniel Prince, Gibraltar Laboratories Inc. for data on the types and incidence of promulgated agreements in place at a contract QC laboratory. The necessity for these agreements is the sponsor's decision. The diverse data pattern is reflective of the broad and varied universe of companies that need contract testing services. Confidentiality agreements are the most commonly requested agreement followed by quality agreements. Once a QC laboratory has been selected, it is subject to follow-up inspections by the sponsor (whether planned or perhaps "for-cause") to ascertain if the initial selection criteria are all still being consistently met.

Table 3 Types and frequency of contract test laboratory and sponsor agreements at an example QC laboratory – for illustration purposes only

Agreement type	2019	2018	2017	2016	2015	2014
No agreement/ contract	51.0%	50.4%	41.9%	34.0%	38.0%	30.0%
Only confidentiality	11.3%	13.1%	14.6%	8.2%	9.0%	12.2%
Quality and confidentiality	15.0%	10.4%	12.7%	22.6%	18.5%	21.8%
Only master services	11.1%	11.2%	12.0%	13.5%	12.5%	13.4%
Master and confidentiality	1.0%	1.7%	4.7%	2.3%	1.5%	2.4%
Only quality	7.5%	9.6%	9.0%	13.3%	13.2%	9.6%
Master and quality	1.7%	2.1%	1.6%	1.8%	3.3%	3.7%
All types	1.4%	1.5%	3.5%	4.3%	4.0%	6.9%

DESIGNING QC TESTING PROGRAMS

There are different ways that regulatory requirements play a role in designing a QC test program. Sometimes the regulations are very specific regarding tests that must be performed or approaches that must be followed. For example, parenteral QC testing always includes testing for sterility, particulate matter, endotoxin and package integrity. In these cases, the QC laboratory can assist the sponsor in identifying the applicable regulations and the approach to use when designing the test program. Another example is when a finished product is marketed as "sterile". This means that an aseptic

or terminal sterilization process must be selected, and a validation of that process carried out in accordance with regulatory requirements and/or industry practices. A regulatory tenet is that terminal sterilization must be employed whenever possible to statistically define the probability that a given product batch is sterile. The standard for medical devices and pharmaceuticals is a sterility assurance level (or probability of a non-sterile unit) of less than one in one million or 10^{-6}. There are always some decisions to be made in carrying out sterilization validations, but the general steps are well characterized and spelled out in the industrial standards (e.g., AAMI (2011), ISO (2017b), EN (2001)) that are generally recognized by regulatory authorities such as FDA or US EPA.

Sometimes the regulations are not as specific but only provide an endpoint that must be reached. In this case, the QC laboratory can be helpful in providing an understanding of the various potential approaches to reaching the endpoint for the specific product in question. Regarding endotoxin testing for some product types (e.g., parenterals) the approach to testing is straightforward in that every batch must be tested (e.g., endotoxin levels). For implanted products it is not expected that every batch be tested because there is not as direct of a link between endotoxin contamination and its appearance in the bloodstream or lymphatic system as would expected to be the case for injectable products. Instead, a statistically based sampling plan is a rational approach for assessing quality compliance. If discrepant results are observed, the sampling-testing frequency is increased as part of a QA-approved retesting plan.

Compendial requirements tend to be straightforward. For example, the United States Pharmacopeia (USP) (*www.usp.org*) provides many compendial requirements that detail the exact tests to be performed and the corresponding acceptance criteria. The USP is provided as a combination with the National Formulary (NF) as the USP-NF. If a drug ingredient or drug product has a corresponding USP quality standard, the manufacturer must conform to the USP requirements to use the designation "USP" or "NF" on its labeling. If the product is labeled with USP-NF but does

not satisfy the compendial requirements for strength, quality or purity, it is considered adulterated. USP also sets standards for dietary supplements and food ingredients. USP cannot enforce its standards, but they are enforced by FDA and other government authorities. For example, if USP sterile water for injection (WFI) is intended to be part of a finished product, the USP monograph for sterile WFI specifies that the following tests be completed, with the corresponding acceptance criteria:

- Oxidizable substances test of 100 mL; the pink color does not completely disappear.
- Total Organic Carbon, meets the requirements for USP Sterile Water <643>.
- Water Conductivity, meets the requirements for USP Sterile Water <645>.
- Particulate Matter in Injections, meets the requirements for USP <788>.
- Sterility Tests, meets the requirements of USP <71>.
- Bacterial Endotoxins Test, USP <85>, less than 0.25 USP endotoxin unit/mL

There are other important compendia issued around the world, prominently including Europe (EP) (*www.edqm.eu/en/european-pharmacopoeia-ph-eur-9th-edition*), Britain (BP) (*www.pharmacopoeia.com*, Japan (JP) (*www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0019.html*) and China (Chap) *(www.usp.org/products/chinese-pharmacopoeia*). In some cases, test monographs have been harmonized amongst several of these compendial organizations (USP, EP, JP), as shown below:

- USP <1> Extractable Volume.
- USP <61> Microbial Enumeration.

- USP <62> Tests for Specified Microorganism.
- USP <71> Sterility Test.
- USP <85> Bacterial Endotoxins.
- USP <281> Residue on Ignition.
- USP <701> Disintegration.
- USP <711> Dissolution.
- USP <788> Particulate Contamination.
- USP <905> Uniformity of Content/Mass.
- USP <1061> Color (Instrumental Method).
- USP <1111> Limits for Non-Sterile Products.

The QC laboratory's regulatory affairs department (or equivalent) tracks global compendial updates and correspondingly revises their QMS. Changes that impact sponsor test articles should be promptly conveyed to the sponsor. There are additional compendial requirements relating, for example, to packaging, storage and labeling. Note that USP chapters that are marked as lower than <1000> are binding from an FDA compliance perspective whereas chapters that are marked over <1000> are so-called "Informational Chapters". The pharmaceutical industry tends to be conservative and will often implement informational chapters into their respective testing plans given the importance that FDA places in the USP, and in sponsors authoritatively proving the quality attributes of all of their products in commerce on a lot-lot basis.

In addition to regulatory and/or compendial requirements, there are also industry practices which represent *de facto* ways of maintaining cGMP compliance. This is perhaps the time where involving a contract QC laboratory can be of great value to sponsors. Industry practice is typically not described in standards or regulations *per se*. In the life science environment in which innovation in science, technology, methods, etc., are rapidly evolving, the "official" rules can take years to appear in a regulation

or compendium, and thus to accurately reflect, *post hoc*, what has actually been taking place in industry. This is what the "c" in cGMP is meant to signify; namely, that the FDA expects a manufacturer to comply with industry norms (as they evolve). So, the contract QC laboratories active in their respective industry areas are better positioned to provide additional methodological and compliance value to their clientele. The QC laboratories that are active in their industries are generally easier to distinguish due to their involvement in standards-writing bodies, speaking at conferences and/or providing webinars on topics ranging from biocompatibility to rapid microbiology methods. When there are not yet specific regulatory or compendial requirements to reference (e.g., gene therapy testing), regulatory bodies expect manufacturers to select appropriate guidance and/or requirements from related industries. Sometimes sponsors establish requirements that are outside of or in addition to what is required by regulatory bodies, compendia, or industry practice. These other requirements are sometimes associated with label or marketing claims that are desired by the sponsor. These requirements can be specific to a product and/or related to its functionality.

TEST METHOD QUALIFICATION VS. TEST METHOD VALIDATION

Test methods used for release testing purposes must first be validated or verified (if compendial in origin). In fact, precisely when to validate a QC test method is a matter of spirited debate amongst cGMP colleagues. Safety methods such as sterility and endotoxin should be validated and deployed on clinical trial materials prior to administration into human subjects. Analytical methods should also be validated during the clinical development process but are typically qualified earlier in the clinical development process. Methods may need to be re-qualified or even re-validated as a manufacturing process is scaled up or if there are major changes to the manufacturing facility or manufacturing process. See Table 4.

Table 4 Test qualification versus test validation

Test qualification	Test validation
• Determining whether a test is suitable for its intended purpose • There are limited pre-determined performance criteria	• Assuring the test is suitable for its intended purpose on a routine basis • Often performed such that the data are applicable to a wide range of product types • Pre-defined test performance criteria exist

TEST METHOD QUALIFICATION

Test method qualification studies identify/refine method quality attributes such as specificity, linearity, accuracy, precision, robustness, stability etc., where applicable. The qualification process is intended to evaluate each of these attributes individually, and to understand the upper and lower limits of variables such as temperature, concentration, contact time, expiry dates on these quality attributes. The knowledge obtained from test method qualification is used to limit the number of variables to be studied during the ensuing test method validation exercise and should provide a sufficient foundation for the development of a scientifically sound validation protocol. Test method qualification is an iterative, development-driven process intended to demonstrate objective performance of quality attributes against predefined specifications. The outcome is either that the method is determined to be suitable or it is rejected for the intended test article application.

It is appropriate to address the difference between compendial versus non-compendial methods. Compendial methods, such as those defined in the pharmacopeia (e.g., USP, EP, JP), require minimal qualification because substantial work, often in the form of round-robin testing, has already been performed by industry in the creation and publishing of the compendial method in the first place. For these methods the qualification process might simply be

a paper justification that the method, as described in the pharmacopeia, is completely applicable to the test article (e.g., drug product) in question.

TEST METHOD VERIFICATION

The pharmaceutical industry has extremely robust programs to ensure test methods are accurate and reliable. In addition to the qualification program described above the QC laboratory must also perform method verification and/or method validation. Refer to USP <1225>, Validation of Compendial Procedures (*www.usp.org*), and to USP <1226>, Verification of Compendial Procedures (*www.usp.org*). The verification process for compendial test procedures is the assessment of whether the procedure can be used for its intended purpose, under the actual conditions of use for a specified test article. Verification testing is performed to determine whether the compendial procedure will perform suitably as intended inside the QC laboratory. If not, an alternate test method or approach to the compendial method is indicated. A common example for this is in application of USP <71>, Sterility Tests (*www.usp.org*), to a product. In this case the aspect of the test that must be verified (i.e., absence of Bacteriostasis and Fungistasis) is spelled out for the user and is called method suitability and the process for performing method suitability is well described in USP <71>. A passing method suitability test means that the test can be applied to product, under the conditions used in the method suitability test. All other aspects of the sterility test have previously been qualified, which results in minimum work to be performed by the user. This is the benefit of selecting a compendial method for testing, which obviously makes it the approach of choice whenever possible.

Verification requirements should be based on an assessment of the complexity of both the procedure and the test article to which the procedure is applied. Only those characteristics that are appropriate for the verification of the procedure need to be evaluated. The degree and extent of the verification process may depend on the level of training and experience of the user, on the

type of procedure and its associated equipment or instrumentation, on the specific procedural steps, and on which test article(s) is being tested. Verification of a test on a drug product should include an assessment of elements such as the recovery of impurities and drug substances from the drug product matrix, as well as the suitability of chromatographic conditions and columns, the appropriateness of detector signal responses, etc.

An assessment of specificity is a key parameter in verifying whether a compendial procedure is suitable for use in assaying drug substances and drug products. For instance, acceptable specificity for a chromatographic method may be verified by conformance with system suitability resolution requirements (if specified in the procedure). However, drug substances from different suppliers may have different impurity profiles that are not addressed by the compendial test procedure. Similarly, the excipients in a drug product can vary widely among manufacturers and may have the potential to directly interfere with the procedure or cause the formation of impurities that are not addressed by the compendial procedure. In addition, drug products containing different excipients, antioxidants, buffers, or container extractives may affect the recovery of the drug substance from the test matrix. In these cases, a more thorough assessment of the matrix effects may be required to demonstrate suitability of the procedure for the drug substance or drug product. Other analytical performance characteristics such as limit of detection (LOD), limit of quantitation (LOQ) and precision when assessing the level of impurities, for example, may be useful when demonstrating the relative suitability of the compendial procedure under actual conditions of laboratory use.

TEST METHOD VALIDATION

Test method validation is the process by which it is established, through laboratory studies, that the performance characteristics of the test consistently meet the requirements for the intended QC applications. Typical test performance characteristics that should be considered in method validations are listed below:

- Accuracy.
- Precision.
- Specificity.
- Detection limit.
- Quantitation limit.
- Linearity.
- Range.
- Robustness.

These are the same quality attributes that are initially evaluated during method qualification exercises. They are defined in USP <1225>. The description of the analytical procedure should define what the test results for the procedure are. As noted in ISO 5725-1 (ISO, 1994) and ISO 3534-1 (ISO, 2006), a "test result" is:

> "The value of a characteristic obtained by carrying out a specified test method. The test method should specify that one or several individual measurements be made, and their average, or another appropriate function (such as the median or the standard deviation), be reported as the test result. It may also require standard corrections to be applied, such as correction of gas volumes to standard temperature and pressure. Thus, a test result can be a result calculated from several observed values. In the simple case, the test result is the observed value itself."

A test "final" result, in the opinion of the QC laboratory, is the final, reportable value that would be compared to the acceptance criteria (specification).

TEST ARTICLE CATEGORIES

What follows (Table 5) is a description of the types of test articles that are routinely tested by QC laboratories. In some cases, test articles may need to be tested on a routine basis such as drugs whereas in the case of medical devices, this may not necessarily be

the case. In some instances, the test article is in support of validating a manufacturing facility or manufacturing process. In all cases, the testing of this range of test articles helps to establish a contemporaneous documented record of scientific information associated with product development programs. Table 6 separately describes ISO particulate cleanliness levels.

Table 5 Types of test articles tested in QC laboratories (partial list)

Test article	Description
Pharmaceuticals (drugs)	The pharmaceutical industry has always performed extensive QC testing compared to other product categories. Not only is the final product tested, but also water, excipients, raw materials, active pharmaceutical ingredients, process samples, etc. There are four primary aspects of drugs – identity, strength, quality and purity – and each of them is usually tested on individual components of a finished product as well as on the finished product itself. In addition to the tests performed on the finished product and components, since many pharmaceutical products are aseptically processed, characterizing the manufacturing environment is critical and usually also requires significant testing for particulates, process simulations, etc.
Biologics	Biologics test articles include cells, culture supernatant, mycoplasma, protein, DNA, and RNA. These test articles are typically tested on a lot to lot basis. The FDA will typically perform independent confirmatory testing of licensed biologics prior to the sponsor releasing batches to market.
Medical devices	With most medical devices the materials used are not absorbed by the patient, so characterization of materials initially and routinely is less critical. It is rare to perform testing on plastic and metal raw materials and components, with the exception of initial and/or occasional bioburden and endotoxin testing as part of supplier qualification and periodic evaluation. Biocompatibility testing, usually on finished products, is a requirement but usually only performed initially and then as part of change management. Thus, the bulk of QC testing performed on medical devices is on finished products and often at a decreased frequency compared to pharmaceutical products. Since most medical devices are terminally sterilized, QC testing is more related to sterilization practices than purity and functionality of the product. This results in testing being performed on a monthly or quarterly basis rather than on every batch of product. The primary exception to this is for products that require a non-pyrogenic label claim; in these instances, samples from every production batch are usually tested for BET.

Test article	Description
In vitro diagnostics	*In vitro* diagnostics (IVDs) have relatively relaxed QC testing needs because they usually (i) do not contact compromised tissue of patients and (ii) only contain samples from the patient for storage, shipping or testing purposes. This means that the regulatory scrutiny is reduced with testing more related to not contaminating the patient sample rather than contaminating or causing harm to the patient. Simple tests such as bioburden are most common, though infrequently performed. There is one type of test that is often performed on IVDs that are usually not performed on other product types: DNase and RNase. Some IVD products are intended for DNA/RNA evaluation, so the presence of something that would cleave DNA or RNA would be problematic from a quality standpoint.
Utility systems (water)	The QC laboratory also tests materials used in the manufacturing process as well as the manufacturing environment. For example, water is frequently used as an ingredient, cleaning agent and solvent. Depending upon its usage it might also need to be certified to meet USP requirements such as Purified Water, Water for Injection, Water for Irrigation, and possibly Sterile Water. Also, regardless of the initial purity of any water used in product or processing, if it is handled or stored improperly it can become adulterated with microbial growth. Thus, having rigorous control over any water-related process is critical and it usually requires routine testing and trending of the data to demonstrate continued control.
Utility systems (compressed gas)	Compressed gas is used in analytical applications such as analysis by liquid chromatography, gas chromatography, atomic absorption, as well as to supply CO_2 to tissue culture incubators. Contaminants in compressed gas will interfere with data interpretation and must be avoided. It is a special technique to aseptically obtain samples of the gas and then perform the appropriate analysis. Nitrogen gas, for example, is tested for identity, limit of oxygen and microbial content.
Cleanroom air (particulates)	Air quality is a critical control parameter. Particulate matter suspended in the air must be prevented from contaminating the process or final product. Specialized air samplers are used to regularly collect large volumes of air. The data are collected and trended as part of the environmental monitoring program. Alert and action levels are established to assure that the manufacturing environment is operating as expected and, in the event that the data indicate otherwise, management can proactively investigate. The quality attribute established depends on the criticality of the specific location being sampled. Three basic analyses are performed, and the levels or limits used are shown in Table 6. Note: these recommendations are specific to an aseptic process and thus might not be applicable to all situations. Sponsors are responsible to establish appropriate environmental alert levels and action levels.

Test article	Description
Validation	Validation samples include, for example, process simulation trials for parenterals, cleaning validation studies (swabs; rinses); antimicrobial agents for contamination control in the manufacturing facility, and sterilization validation.
Antimicrobial	The capacity of a material, formulation, ingredient or product to kill microorganisms or to prevent their growth by causing physical damage and or interference with the microorganism's essential metabolic activities, e.g. antibiotics, antiseptics and disinfectants must be known. Further, all microorganisms require that water be available in the cell to be vital. Materials, products etc. with very low water activities are by definition antimicrobial because every microorganism has a limiting water activity value below which it cannot grow. For all microbes, cell division will not occur at a water activity (aw) at 0.60 or lower (Stevenson et al., 2015).

Table 6 Environmental monitoring alert and action levels (USP <1116>)

	ISO 5 [Grade A] LFHs and BSC				ISO 6 [Grade B] Sterile Packing			
	Alert level		Action level		Alert level		Action level	
	≥0.3µm	≥0.5µm	≥0.3µm	≥0.5µm	≥0.5µm	≥5.0µm	≥0.5µm	≥5.0µm
Non-viable particulate/m^3	5,000	1,760	10,200	3,520	17,600	150	35,200	290
Viable air CFU/m^3	N/A		≥1		>5		>7	
Contact and settling plates	N/A		≥1		>2		>3	
Personnel gown	N/A				>2		>3	
Personnel gloves	N/A		≥1		N/A			

Airborne non-viable particulate matter

	ISO 7 [Grade C] Pass through, cleaning, packing, sterilization, utility room, and quarantine areas				ISO 8 [Grade D] Air locks			
	Alert level		Action level		Alert level		Action level	
	≥0.5µm	≥5.0µm	≥0.5µm	≥5.0µm	≥0.5µm	≥5.0µm	≥0.5µm	≥5.0µm
Non-viable particulate/m^3	176,000	2,000	352,000	2,900	352,000	20,000	3,520,000	29,000
Viable air CFU/m^3	>50		>100		>100		>200	
Contact plates	>15		>25		>25		>50	

SPECIALIZED VALIDATION TESTING

A sound cleaning and sanitization program is needed for controlled environments used in the manufacture of pharmacopeial articles to prevent the microbial contamination of these articles. Refer to USP <1072>, Disinfectants and Antiseptics (*www.usp.org*). Sterile drug products may be contaminated via their pharmaceutical ingredients, process water, packaging components, manufacturing environment, processing equipment, and/or manufacturing operators. cGMPs emphasize the size, design, construction, and location of buildings, materials, and the appropriate material flow to facilitate cleaning, maintenance, and proper operations in the manufacture of drug products.

Antimicrobial agents are an important tool in microbial control and patient safety. However, when disinfectants are used in a manufacturing environment, care should be taken to prevent the drug product from becoming contaminated with chemical disinfectants because of the inherent toxicity of the disinfectants.

The requirements for aseptic processing include readily cleanable floors, walls, and ceilings that have smooth and nonporous surfaces; particulate, temperature, and humidity controls; and cleaning and disinfecting procedures to produce and maintain aseptic conditions. The cleaning and sanitization program should achieve specified cleanliness standards, control microbial contamination of products, and be designed to prevent the chemical contamination of pharmaceutical ingredients, product-contact surfaces and/or equipment, packaging materials, and ultimately the drug products. Generally, there should be a step to ensure that residual disinfectants and sterilants do not remain on product-contacting surfaces by implementing a residual removal process, such as an isopropyl alcohol (IPA) wipe of the surface after the disinfectant has dried. The effectiveness of the residual removal process should be demonstrated, usually by an analytical chemistry method to determine the presence and relative quantities of the residual disinfectant or sterilant.

In addition to disinfectants, antiseptics are used to decontaminate human skin and may be used by personnel prior to entering the manufacturing area. Chemical sterilants may be used to sterilize surfaces in manufacturing and sterility testing areas. Furthermore, sterilants (e.g., propylene oxide, glutaraldehyde, peracetic acid) may be used for the sterilization of pharmacopeial articles (e.g., tissues, inanimate surfaces). UV irradiation may be used as part of an inline water purification system. USP <1072> discusses the:

- Selection of suitable chemical disinfectants and antiseptics.
- Demonstration of their bactericidal, fungicidal, and sporicidal efficacy.
- Application of disinfectants in the sterile pharmaceutical manufacturing area.
- Regulation and safety considerations.

The specifications described in the EPA guidance involves sophisticated and specialized microbiological testing to substantiate the efficacy of the agent. Refer to US Environmental Protection Agency, Series 810 – Product Performance Test Guidelines, Group B – Antimicrobial Efficacy Test Guidelines (*www.epa.gov*). Antimicrobial testing represents a case where a specialized QC laboratory partners with a pharmaceutical manufacturer to ensure that the appropriate experimental design is being deployed (e.g., selection of microbial strains; substrates; testing conditions).

THE LIFECYCLE OF CONTRACTED TESTING SERVICES

Having a good relationship with the QC laboratory can be invaluable as a product candidate transitions from concept, through R&D to full-scale production and release of product, a process that will typically last several years. In essence, a QC laboratory should feel like an extension of the manufacturer, rather than a third party that has little to do with the day-to-day business. A healthy relationship with the QC laboratory includes regular contact and discussions where each party contributes regarding the types of tests to be performed, how they are to be performed on the test article, and the proper interpretation of results. This partnership is suggested to commence during the earlier stages of product development. When a QC laboratory is seen as merely a supplier that performs tests and is treated as such, the manufacturer can be missing out on important scientific perspectives regarding the testing strategy, and likewise the QC laboratory can be missing out on information regarding the product that can influence either how the test should ideally be performed or how the data should be interpreted. From a QC laboratory perspective, it should be straightforward to execute test programs on behalf of their clients. This ideal state is predicated on mutual respect, a clear understanding of roles and excellent communications between the QC laboratory and the sponsor.

THE FUTURE OF QC LABORATORIES

Some large manufacturers expend significant time and energy in maintaining internal capabilities and expertise. For these manufacturers there may be an infrequent need for contract QC laboratories. However, it is becoming more common for manufacturers, especially small and mid-sized companies, to place their primary internal focus on product development and manufacturing, and to use external companies for specialization on other topics such as QC testing. As a result, many QC laboratories are attempting to fill that sponsor knowledge gap by developing and maintaining internal expertise related to the testing they perform for the industries they serve. This means that the future of contract QC laboratories is increasingly bright but also increasingly evolving due to the trend, for example, by drug manufacturers in performing in-line testing of selected test articles for QC evaluation purposes and industry consolidation. That said, QC laboratories with an established reputation for scientific competency as well as a successful track record as a specialized life science-related operations business with global reach will continue to be in demand by a wide range of sponsors requesting such services in support of their product development programs. Further, as pressures mount for price control of pharmaceuticals, manufacturers are expected in response to outsource testing and concentrate their resources on their core competencies.

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Building Value into Biotechnology Development and Manufacturing

The magnitude of knowledge and experience required to have a meaningful impact on biotechnology product approvals and market success is monumental. For the first time, three expertly crafted chapters are reprinted from *Biotechnology From Idea to Market*, edited by Fred Mermelstein, Richard Prince and Carl Novina and offered electronically. These detailed advisories are written to provide guidance. Here is what Phillip A. Sharp, Ph.D and Nobel Laureate says about this text in his Foreword: "For anyone who wants to excel in biotechnology, this book presents a wonderful guide."

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Author: David L. Rosen

Manufacturing Biopharmaceuticals
From Start-Up to Commercialization
Authors: Joseph Waggett and Laura Grayson Roselli

Quality Control Testing Throughout the Product Development Lifecycle
Authors: Daniel Prince, Martell Winters and Richard Prince

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