

Successful Use of a Contract Microbiology Laboratory

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"Microbiology Topics" discusses various topics in microbiology of practical use in validation and compliance. We intend this column to be a useful resource for daily work applications.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please send your comments and suggestions to column coordinator Scott Sutton at scott.sutton@microbiol.org or journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

The following key points are discussed:

- The client organization is responsible for their product and by good manufacturing practice (GMP) responsible for all data and analysis that contribute to the decision to release a batch of product to the marketplace. Contract lab reports must provide sufficient information to meet regulatory expectations.
- Regulatory agencies are increasingly attentive to the relationship between the product's owner and any contract facility used in the manufacture and testing of finished product for release. Unwanted regulatory attention can be drawn to products if the contract laboratory is involved in enforcement activity, even if the original regulatory issue had nothing to do with the products.
- As concerns over safety of various product types become more prevalent, regulatory attention is expanding beyond pharmaceuticals, devices, over-the-counter, and other traditional areas to encompass personal products, soaps, and toiletries.
- Several recommendations are provided to increase the likelihood of a successful contractor-client relationship. Most important of these include technically competent review of the lab and the reports received.
- There are several documents available to assist in the determination of the contract laboratory's suitability for pharmaceutical work. These include 21 CFR 211 (211.22, 211.165, 211.176, and 211.194), International Organization on Standardization's ISO 17025, *United States Pharmacopeia* chapter <1117> and Pharmaceutical Inspection

Convention and Pharmaceutical Inspection Cooperation Scheme's *Aide Memoire to Inspection of Pharmaceutical Quality Control Laboratories*.

INTRODUCTION

This article discusses the qualification of a contract microbiology testing lab in the good manufacturing practice (GMP) environment. The quality of work performed by the contract lab is a critical consideration in today's market, as many companies are outsourcing technical testing activities and reducing in-house capabilities in an effort to control costs. In addition, as the pool of in-house subject matter experts (SMEs) is reduced through layoffs, transfers, or attrition, the remaining technical experts must learn to become more efficient. Relying on outside expertise is one way to do this.

The manufacturer of record is held responsible for the quality of the medicines released to the US market under the company's name. This is irrespective of the location and corporate structure of the individual entities that might have actually manufactured the finished dosage form, tested the product for release, or stored and distributed it to market. In other words, if you operate a "virtual" company that is actually composed of four or five people who supervise product acquisition, contract manufacturing, contract testing, contract distribution, etc., the corporate entity is responsible. The contractors might also carry some burden, but the product belongs to the manufacturer of record. This use of services on a contract basis is becoming more critical as downsizing becomes more intense and "virtual" companies more prevalent. There are already many small and mid-sized pharmaceutical, over-the-counter (OTC), medical device, and personal products companies that are completely dependent on contract services for all microbiology testing. While many of these companies would never consider being restricted to a sole supplier for a process raw material, they are willingly dependent on a single vendor for all microbiology-related quality functions. Beyond this, the facilities will frequently not maintain a microbiology SME on staff but rely on the contract lab to determine the

appropriate tests, design the tests, perform the testing, and interpret the results for them.

The trend for a manufacturer to become dependent on a single test lab will not change as there are excellent business reasons to consolidate all testing volume to a single, traceable location. How can the client be assured that the lab is qualified for the GMP market, rather than, for example, the food or clinical markets? This is not an easy task, especially as the company may not have any in-house expertise in microbiology. How can you tell a "good" lab from a "bad" lab in terms of testing for (non-food) regulated industries? Fortunately there are guidance and informational resources available. These same documents provide an invaluable resource for the contract lab to prepare for customer audits.

RECOMMENDATIONS FOR A SUCCESSFUL CONTRACT LAB EXPERIENCE

There are a variety of guidance documents that we will review to assist in this qualification effort. However, in my experience as a consultant I have noticed several common problems in the contract lab-client relationship that should be addressed. A good review of these issues is provided in a pair of articles by Nims and Meyers (1, 2). In addition, I would also urge the following principles as guidance to a successful relationship.

Never Trust a Stranger With Your Money

Several warning letters have been issued by the US Food and Drug Administration on the topic of use of contract labs. It has become an unfortunate practice for many manufacturing facilities to use contract labs as they would internal quality control (QC) microbiology labs, except without the quality control measures in place. While it is tempting to rely on the contract lab's quality assurance unit (QAU), the responsibility for the quality of the data never leaves the client. If the quality of the data from that lab is called into question, it is the manufacturing company's products and reputation that will suffer. Always qualify the lab and perform ongoing, full data reviews of all the contractor's work as it is completed.

Bring Along Someone Who Knows What is Going On

Auditing a contract lab is a technical exercise as well as a quality activity. This article describes different regulatory guidance documents that will help in pointing out the important aspects of the microbiology lab, but this is no substitution for having a subject matter expert along for the audit. The technical audit is at least as important as the GMP audit. It is best by far to have a balanced audit team. An expert in another technical discipline does not have the appropriate background to serve as a subject matter expert in an unfamiliar area.

There Ain't No Such Thing as a Free Lunch

While on site at the contract lab, it will be tempting to develop friendships with your opposite function at the site, especially if the audit goes for several days. This natural tendency is not a bad thing, but it must not be allowed to influence the audit findings. Be careful about accepting lunch dates or other friendly overtures that might compromise your judgment and affect your eventual audit report. Everyone has to eat lunch, but be aware of the need to maintain strict objectivity.

It will be important to develop a relationship with the lab and its contact person or people, but working with a contractor who is a friend makes it more difficult to fire the lab, make demands of them, or to come down on them when needed. Do not let personal feelings cause you to compromise your responsibility to your company.

Don't Try to Fix a Computer With a Hammer

There are many different types of microbiology labs. Some specialize in environmental microbiological testing (i.e., toxic waste, not aseptic clean rooms), agricultural microbiology labs, food labs, etc. While they may try to make the argument that microbiology is all the same (it is, pretty much), they will not have the systems in place to handle medical device regulations or pharmaceutical GMPs. If they argue that it doesn't matter, all indecision should be resolved and you should immediately leave. Their science might be excellent, but you will be responsible for the quality of the work. If the documenta-

tion will not pass inspection, it is of limited use in a recall investigation. The microbiology lab is a tool—use the correct one.

Trust, But Verify

Once the lab is in place, a prudent QAU will subject the test reports to the same level of scrutiny that the group would extend to internal reports. This means having someone expert in the subject matter review the report for completeness of data, GMP compliance, and correctness of technical interpretation. It is critically important to remember that this is your product and your data. In the end, it really doesn't matter what the contract lab's policy is on quality review. It is your policy that will be the basis of any enforcement action, and if the lab is not up to your standards, it is your quality system that will be found at fault.

Never Test the Temperature of the Swimming Pool with Both Feet

The microbiology contract lab may become a critical asset. You would never allow a critical process step to be dependent on a sole supplier, but many companies will only qualify one contract lab to provide testing. This makes sense if the lab does not change and can always accept samples in a timely fashion. It will not make sense if the lab itself transfers ownership or if it becomes very popular. A laboratory will be loathe to turn business away—they will be motivated to accept all incoming work and may hire "temps" to perform your studies or try to cram too much work into the work day in times of excess testing. Always have at least two labs qualified, and know how they track labor resources.

If It Isn't Written Down, It Didn't Happen

Many contract labs send out reports that are woefully inadequate. 21 CFR 211.194 (3) clearly states the minimum expectations for laboratory records, and these requirements are further discussed and developed for the microbiology lab in the current version of *United States Pharmacopeia (USP)* chapter <1117> (4). Despite these clear expectations, many labs prepare reports that are little more than

an executive summary of the test method and the results. This might be appropriate for a certificate of analysis but not a lab report. Given the status of the contract lab as an extension of the company's QC unit, lab reports are subject to the same QAU review requirements as any other testing conducted in support of product release. Insist that all relevant lab records are provided—at a minimum this proactive documentation should allow confirmation of all critical aspects of the test, and confirmation of all calculations (i.e., rounding, averaging, \log_{10} unit manipulations, most probable number, etc.). There are contract labs out there that provide complete GMP documentation. They will most likely be more expensive than the low end of the field.

"Our People are the Best!"

Team spirit is a wonderful thing—numbers are better. Learn how the contract facility tracks resources and determine if you agree that this is a suitable measure. A starting point might be the current USP <1117> (4) discussion on laboratory resources that urges trending of three aspects of lab resource adequacy. The first is the amount of time the sample, once received, remains in queue before the initiation of the test. The second measure is the amount of time between the final bench work performed on the test and the release of the report. The final is the number of investigations performed on tests. Increases in these metrics might indicate a laboratory that is insufficiently resourced either in number of people, availability of other resources, or adequacy of lab leadership. These measures should be available during the audit and can be invaluable in determining how the lab plans to meet your testing needs.

"Our Lab is the Best Because We Operate Under GLP, Not Just GMP"

This type of statement from the sales department of the contract facility should raise concerns. The first is that this openly stated belief strongly suggests that the facility is not familiar with pharmaceutical requirements. The 21 CFR 210 and 211 requirements clearly call for GMP studies (5, 6) as Kuwa-

hara's (7) review article discusses (as does 21 CFR 820 for devices). Secondly, philosophy like this might indicate that the facility does not keep up with changes in regulatory expectations. The "superiority" of good laboratory practices (GLPs) over the perceived difficulty and cost of GMPs was a popular position years ago that has been largely supplanted with the current thinking based on revisions of the CFR and of regulatory expectations. Make sure that you pay particular attention to the "quality" side of the audit if the microbiology lab is proud of their GLP compliance.

"What We Have Here is a Failure to Communicate"

Making sure that all instructions and procedures are clearly documented is critical for both parties. The emphasis on this point is one of the particular strengths of International Organization on Standardization (ISO) 17025 certification. From the client side, it prevents the lab from performing tests that are not reviewed by the client, on material that is inappropriate to test. From the contract lab side, positive documentation of test requests provides the evidence that the specific test was contracted for that specific material (even if priorities have changed for the client). Phone call communication is excellent for maintaining the personal rapport so important to the successful business relationship, but the record of the exchange is dependent on the party's memories. It should be part of the base contract that only work authorized in writing can be initiated and that work can only be halted by authorization in writing. This agreement avoids potentially acrimonious misunderstandings later.

"You Don't Call, You Don't Write, We Don't See You in Years"

Maintaining a contract lab relationship is an ongoing process. Laboratories change owners, especially in this time of economic flux (8). The lab should be physically audited on a regular basis with an eye to the technical execution of their tasks as well as the "quality" concerns. This is especially true for the microbiology lab, as it is frequently a target of the new corporate bean counters in an acquisition. Set

up an audit schedule for lab recertification that includes regular, full technical, and quality evaluation. "Phone audits" or "survey audits" are not sufficient.

REGULATORY DOCUMENTS OF USE

Compliance personnel should reference regulatory and reference documents in dealing with contract microbiology testing laboratories. The following are useful documents:

- 21 CFR 211
- ISO 17025
- USP <1117>
- PIC/S Aide Memoire to Inspection of Pharmaceutical Quality Control Laboratories
- FDA Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories.

21 CFR 211

The first place to look for regulatory expectations is 21 CFR, Section 211.22(a) states:

"There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company."

Because this approval or rejection is one of the fundamental purposes of the QC microbiology lab (either in-house or contracted out), it is clear that the manufacturer's QAU is responsible for the quality of those data. This includes, of course, not only finished product but also raw materials and components (see 21 CFR 211.84) and in-process bioburden (9).

The majority of laboratory guidance is provided in 21 CFR 211 Subpart I-Laboratory Controls (211.160-211.176). Initially, there is a requirement that,

"...establishment of any specifications, standards, sampling plans, test procedures, or

other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit."

If there is no microbiology group in the client's organization, where does this leave the drafting of specifications? The client must assume this responsibility, but the design of the test is a shared obligation with the client holding the whip hand.

A recent situation I heard of included a ridiculously weak sterility test (1 unit, 1 medium/incubation condition). The lab came in for some heat (as they definitely knew better) until they pulled out a pair of memos from the file. The first memo contained a formal notification to the client that the sterility test as designed was unsuitable. The second memo was from the client telling the lab that the client wanted the test done in a particular way and that is what they were being paid for—the lab was to do as they were told. This pair of memos shifted the role of the microbiology lab from a consultant, an "expert" who had responsibility to guide the client, to the role of a contractor who was doing as the client instructed. There is a lesson in this story for both the client and the testing lab.

21 CFR 211.165 addresses testing and release. The following is a particularly interesting section that discusses accuracy, sensitivity, etc.:

"(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a)(2)."

We have always pretended that this does not really apply to microbiology, but we will be discussing ISO 17025 where it is becoming clear that this willful avoidance is drawing to a close. The use of USP compendial tests may allow some leeway here (10), but this only works if the test is performed exactly as described by USP or other cited refer-

ence. How many labs perform the test in precisely the same manner or have validated deviations from the compendial text?

The records for the testing are of critical importance in determining if the test was done correctly, and the lab can find a good deal of guidance in the CFR. 21 CFR 211.194 describes minimal records for all tests. The microbiology lab should add proactive documentation for all measurements that may have a significant effect on the outcome of the test. For example, if using pour plates and the method specifies that the agar temperature be 45-48°C (to prevent solidification if too cool, or thermal injury to the cells if the molten agar was too hot), does the data sheet provide a means to record this critical test parameter, and how do you monitor it? Standard records listing in 211.194 include the following:

- Description of sample
- Statement of method used—validation of test and demonstration of method suitability
- Weight or measure of sample
- Complete record of all data derived during the test
- Record of all calculations performed during the test
- Statement of the test results and how they compare with expectations
- Initials or signatures of all personnel involved with the test
- Initials or signature of a reviewer (competent to recognize errors)
- Complete records of any modifications to the test method
- Complete records of any testing/standardization of standards, reagents, etc.
- Complete records of equipment calibration/maintenance
- Complete records of stability testing.

This is a basic list that is expanded in *USP* chapter <1117>. The "responsible party" is to maintain documentation of all raw data. Several contract facilities are now charging extra for this "service" of providing the client's data to the client. The form and extent of information provided in the test

reports should be established early in the relationship (preferably before going to the expense of the qualifying audit).

ISO 17025

In many respects, ISO 17025 accreditation is a complement of the GMPs. Where the GMP grew out of responses to problems (11) and regulations meant to prevent further problems, the ISO 17025 was created out of whole cloth to provide a framework for a laboratory's quality system. Now, while it is certainly true that a quality system without science is pretty useless to a lab (doesn't really matter what you do, just so that you document it well), science without a quality system resembles a university lab—great stuff going on (maybe) but record keeping that would make it impossible to adequately describe the work performed if the researcher left. Both competent science and a solid quality system are required for our field, and ISO 17025 accreditation provides strong guidance for the lab "quality" aspect.

The thrust of ISO 17025 is to develop a complete laboratory system that drives the lab's quality management system to completeness, while requiring identification of specific technical requirements for that lab that must be met. I know many readers are skeptical of another quality document to allow ISO certification of labs, but bear in mind that FDA microbiology labs, Health Canada microbiology labs, and many governmental labs in Western Europe and the Pan-Asia region are accredited to this standard (12). It is a reasonable position to expect a contract-testing lab to be ISO 17025 accredited.

ISO 17025 provides much more detail in some areas where the documents overlap than is present in the GMPs. Some of these areas include test result reporting, measurement of uncertainty of test results (a sincerely frightening idea for microbiology once we become serious about it), and significant detail on what exactly is meant by "proficiency."

The strength of the program comes with the actual accreditation. This involves inspection and testing against the standards by a neutral third party. While this is, undoubtedly, a nerve-racking experience (es-

pecially the first time) accreditation provides a concrete and objective demonstration of the lab's caliber. The requirements are along the following topics:

- **Management requirements**
 - **Organization.** A clear description and operation of the laboratory organization, both as an entity and as part of a larger organization (if appropriate). Demonstration of impartiality is also expected.
 - **Quality system.** Requirements for a written quality manual are detailed, its components described and a requirement that all in the lab are familiar with it.
 - **Document control.** The lab must maintain control over "quality" documents in terms of approval and issue, changes, revision control, etc.
 - **Review of requests, tenders, and contracts.** These requirements are to ensure the sales force does not oversell the lab's capacities, does everyone understand what the client wants and if it is possible?
 - **Subcontracting of tests and calibrations.** This section deals with what happens if some work needs to be subcontracted and requires the customer to be informed. The lab remains responsible for the subcontractor's performance. These subcontractors shall also be certified ISO 17025.
 - **Purchasing services and supplies.** The lab keeps records, approves vendors, and employs a quarantine/release system for incoming materials to ensure nothing is used until released.
 - **Service to the client.** The lab is to provide good service and communicate with the client.
 - **Complaints.** The lab is to have a complaint resolution policy. These and the corrective actions are to be trended.
 - **Control of nonconforming testing or calibration work.** The lab has procedures in place for work that does not conform to its own procedures or the client requirements. Corrective action is implemented.
 - **Corrective action.** This section is fairly large with discussions of cause analysis, implementation and monitoring of corrective actions, and finally a determination of additional audits.
- **Preventive action.** The lab is to have a program in place to look for needed improvements and potential problems to be corrected. This information might come from a robust program of trend analysis.
- **Control of records.** This section describes the need for procedures for control (e.g., identification, collection, indexing, access, filing, storage, maintenance, and disposal) of quality and technical records. This section also provides basic data recording information.
- **Internal audits.** The lab is required to have complete internal audits, generally on an annual cycle.
- **Management reviews.** ISO 17025 also requires periodic, scheduled management reviews that cover the quality program and consider audit reports (i.e., internal, client, and external body), corrective and preventative actions, proficiency test results, changes in volume or type of work, client feedback, complaints, resources, QC activities and staff training.
- **Technical requirements**
 - **General.**
 - **Personnel.** The standard requires the workers to have training, education, experience, and proficiency suitable to their job function (also see discussion of USP <1117>). There will be a formalized method to determine if a technician is qualified for a particular activity and how to determine what training is required. Any temporary workers will operate under this system. There will be job descriptions for technical and key support people.
 - **Accommodation and environmental conditions.** The laboratory will have appropriate facilities in terms of the following:
 - ♦ Lighting
 - ♦ Environmental conditions (monitored and appropriate)
 - ♦ Sufficient separation between incompatible ("clean" and "dirty") activities
 - ♦ Controlled access to the lab
 - ♦ Measures of good housekeeping will be collected.

- Test and calibration methods and method validation. The lab must use appropriate methods and be able to cite the relevant reference for the method using appropriate, calibrated equipment. There is guidance on how to select these methods.
- Equipment. The lab must have sufficient equipment of appropriate accuracy to perform the work. This equipment must be on a calibrated condition and operated by qualified and trained personnel. Records of all activities shall be kept.
- Measurement traceability. This section deals specifically with activities associated with calibration, testing, and reference standards and the expectations associated with these activities.
- Sampling. The laboratory is expected to have sampling plans for testing and calibration, and these are to be in a defined procedure.
- Handling of test and calibration items. The lab is expected to have procedures for the transportation, receipt, handling, protection, storage, retention of test and calibration items, along with the identification of these items to prevent confusion. There shall also be procedures to accept items for testing and to stable storage.
- Assuring the quality of test and calibration results. The lab shall have QC procedures for monitoring the validity of test results and calibrations, and these results shall be in a format to allow detection of trends.
- Reporting the results. The results shall be reported accurately, clearly, unambiguously, and objectively and include all information requested by the client and necessary for the interpretation of the test or calibration results. If relevant, deviations shall be reported. If opinions are included, the lab will document the basis on which the opinions and interpretations are made.

USP <1117>

Another regulatory document specifically aimed at laboratory operations is the USP informational chapter <1117> Microbiological Best Laboratory Practices. The USP chapter is organized on operational lines, with different sections devoted to the following:

- Media preparation and quality control
 - Preparation
 - Storage
 - QC testing
- Maintenance of microbiological cultures
- Laboratory equipment
- Laboratory layout and operations
- Sample handling
- Microbiological media incubation times
- Training of personnel
- Laboratory resources
- Documentation
- Maintenance of laboratory records
- Interpretation of assay results.

This chapter was significantly changed in the 2010 revision (4) and included completely new sections on sample handling, media incubation times, and laboratory resources. In addition, all other sections were modified, with major changes in the sections devoted to equipment, training, and media. This informational chapter was written to be a tutorial but can be easily converted to an audit checklist for ease of audit review. Familiarity with this chapter should be an essential part of preparation for the audit of the contract lab facility by all members of the audit team.

PIC/S Aide Memoire to Inspection of Pharmaceutical Quality Control Laboratories

PIC/S is the acronym for both the "Pharmaceutical Inspection Convention" and the "Pharmaceutical Inspection Co-operation Scheme." There are approximately 30 cooperative national regulatory bodies in PIC/S, which exists "to lead the international development, implementation, and maintenance of harmonized good manufacturing practice (GMP) standards and quality systems of inspectorates in the field of medicinal products" (13).

The PIC/S *Aide Memoire to Inspection of Pharmaceutical Quality Control Laboratories* is designed to be an international aid in training inspectors and in preparing for an audit visit. As such it is an excellent preparatory document for looking to an audit of a contract lab. The first sections involve general considerations in a laboratory audit, followed by two

appendices—one for analytical chemistry labs and the other for microbiology labs with issues specific to each. The document describes its purpose as follows:

"Inspections of sites involved in testing of medicinal products should be more and more specific, thorough and conducted under normal working environment. These inspections may include a complete assessment of laboratory's conformance with the code of GMP or they may be limited to specific methodology or aspects of the laboratory. Inspection process of a laboratory involves the assessment of laboratory functions in full operation. Consequently, PIC/S has developed the Aide Memoires, which can be considered a good tool for enhancing the understanding and performance of inspectors. The purpose of this document is to provide guidance for GMP inspectors to assist in training and preparing for inspections" (14).

The full document is available on the PIC/S web site (<http://www.picscheme.org>). The document outline is provided as follows:

- Quality Assurance System
 - General
 - Ensuring Suppliers Quality
 - Self Inspection
 - Change Control
 - Trending
 - Risk Management
- Documentation System
 - General Information
 - Laboratory Documentation
 - Data Traceability
 - Electronic Documentation/Computerized Systems
- Personnel
 - General
 - Training
- Premises and Equipment
 - Premises
 - Equipment
 - Equipment Validation
 - Cleaning/Sanitization
 - Maintenance

- Materials and Supplies
 - Materials
 - Water/Water Systems
- Sampling and Samples
 - Sampling
 - Samples
 - Personnel for Sampling
- Testing
 - Testing General
 - Testing of Raw Materials
 - In Process Controls (IPC)
 - Testing of Intermediates
 - Testing of Final Products
 - Stability Testing
 - Validation of Test Methods
- Results and Release of Test Results
 - Handling of Test Results
 - Failures—Out-of-Specification Test Results (OOS)
 - Failures—Re-testing and Re-sampling
 - Test Results Release/Analytical Reports/Certification
- Supplement No.1: GMP Inspection in Chemical and Physical-chemical Laboratories
- Supplement No.2: GMP Inspection in Microbiological Laboratories.

FDA Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories

The FDA *Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories* is an older document, but one that is still relevant and in current use in training inspectors. The document is particularly useful in describing how the Office of Regulatory Affairs inspector might look at the lab upon arrival, and how she might go about searching for issues. It is of special interest to review the methods used for evaluation of different activities.

In brief, the guide instructs inspectors on audit attention to the following:

- Microbiological testing of non-sterile products. At first look this seems to be a dated discussion of the dangers of over-reliance on the USP microbial limits tests as a product release test and the need to ensure that all "objectionable organisms" are

accounted for in the quality system. However, a quick review of recent recalls will immediately convince an observer that this remains a valid concern.

- Facilities, equipment, and media. The inspector is instructed to review plates and tubes of media against log book entries, to review autoclave records and other documents to confirm accuracy of the records against what can be physically confirmed.
- Sterility testing. The discussion of sterility testing provides several "tips" to the inspector on how to evaluate the sterility test facility and records. While parts are dated (seven days of incubation is no longer allowed, for example), as a whole this section holds up well.
- Methodology and validation of test procedures. Inspectors are instructed to determine the source of the methods used—if not from USP, then where? If from USP or another recognized standards organization, does the lab method meet the requirements of that original method? In addition, does the lab have evidence that the method is suitable for use with the product (i.e., validation, method suitability)?
- Data storage. Lab notebooks, log books, whatever is in use should be sufficient to allow the inspector to confirm that the test was performed in compliance with the method, that the data were analyzed correctly (e.g., plate counts in countable range, averages, and log unit manipulations performed correctly, etc.), and the conclusions are supported by the data.
- Management review. FDA is concerned about scientific and technical qualifications in microbiology. The inspector is to assure himself that the data were reviewed by someone with demonstrated competency in microbiology.
- Contract testing laboratories. The inspector is instructed to review correspondence between the manufacturer and the contract lab to ensure that necessary tests are conducted, and that all testing expected in a GMP environment was performed. The contract lab reports should be evaluated as many labs will provide incomplete results. Finally,

the inspector should confirm the presence of appropriate method suitability tests.

SUMMARY

There are a wide range of microbiology testing labs on the market, and all of them are anxious for your business. As the GMP manufacturer, you are responsible for the work performed by the lab on your product and for your decisions based on that work. This will not be a problem if there is never a problem. However, if one of your products becomes involved in a dispute on the market or with FDA, the quality of the microbiology work involved in release of that product could become very important indeed. If the work is poor, or not able to pass a GMP-style audit, the testing lab will probably express regret for the inconvenience, but you may be faced with recall or legal action.

This article has provided some pointers for qualifying a microbiological laboratory for GMP work. It is not intended to be a comprehensive review but rather provide direction on where to look for more complete information. The audit team should include at least one individual with education and experience in microbiology who can serve as a subject matter expert to the rest of the team.

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8 Miller, J., "Contract Organizations Are the Sell of the Season," *Pharm Technology*, 33(4):82 - 83, 2009.

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10 FDA, 21 CFR 211.194 Laboratory Records (a)(2). "A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods, or in other recognized standard references or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice) The suitability of all testing methods used shall be verified under actual conditions of use."

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ARTICLE ACRONYM LISTING

- FDA** US Food and Drug Administration
- GLP** Good Laboratory Practice
- GMP** Good Manufacturing Practice
- IPC** In-Process Controls
- ISO** International Organization for Standardization
- OOS** Out of Specification
- OTC** Over the Counter
- PIC/S** Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
- QAU** Quality Control Unit
- QC** Quality Control
- SME** Subject Matter Expert
- USP** United States Pharmacopeia

ABOUT THE AUTHOR

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