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Pharmaceutical Microbiology: Current and Future Challenges

By **Tim Sandle** **Jul 25, 2017 7:00 am PDT**

It is difficult to define when the term ‘pharmaceutical microbiologist’ emerged from the collective shadows of industrial and clinical microbiology. Various decades can lay claim to the use of the term, but it was not until the 1990s that the term became properly articulated. This was following the formation of two professional groups – the Pharmaceutical Microbiology Forum in the U.S. (for which the late Scott Sutton was instrumental in its development) and the Pharmaceutical Microbiology Interest Group (Pharmig), both of which came into being around 1991.

Since these pivotal moments, the range of activities associated with pharmaceutical microbiology has extended from the laboratory and into the production environment. Today’s pharmaceutical microbiologist needs to have an understanding of engineering, regulation, the R&D process, and production workflows. The contamination control of pharmaceutical and healthcare environments and processes, together with pre-clinical drug development labs, requires a more holistic approach than simply choosing technologies and disinfectants. Today the microbiologist is expected to understand industrial processes, cleanrooms, and how to effectively evaluate microbial risks to products from people and processes.

To meet regulatory expectations, the role of the microbiologist is essential. To add to this, the input from quality assurance personnel, engineers, and process specialists is required. Whilst there is a continuing need for monitoring of the environment and conducting standardized laboratory tests, industrial pharmaceutical microbiology has moved a great deal in the past decade to embrace microbiological audits; rapid microbiological methods; conducting risk assessments, both proactive in terms of minimizing contamination and reactive, in terms of addressing microbial data deviations; and also ensuring that processes meet ‘quality by design’ principles.

Meanwhile, developments in pharmaceutical microbiology continue. To draw on two examples from 2017, the U.S. Food and Drug Administration (FDA) has made an important announcement in relation to the testing of non-sterile pharmaceuticals, and the European Medicines Agency (EMA) looks set to make an optional filter test mandatory in the forthcoming revision to Annex 1 of the EU GMP guide.

The FDA has sent an alert to pharmaceutical companies that the number of product recalls involving Burkholderia cepacia complex (BCC) remains high. Because it can be challenging to detect BCC, the FDA is calling for manufacturers of non-sterile, water-based drug products to put in place risk assessments and special tests for this group of organisms.

Burkholderia cepacia complex refers to a group of Gram-negative, non-spore forming rod-shaped bacteria composed of approximately 17 closely-related species which are grouped into nine genomovars (1). B. cepacia has emerged as a human respiratory opportunistic pathogen in individuals with weakened immune systems or chronic lung disease, especially cystic fibrosis patients, within the past 30 years. BCC bacteria exist throughout the environment, especially in soil and water environments.

The primary risk is from BCC and other water-borne opportunistic pathogens present in pharmaceutical water systems and posing a risk to products. The presence of many types of preservatives and antimicrobial agents in the product is not considered sufficient because many types of BCC are resistant to common antimicrobials (2).

New FDA guidance requires pharmaceutical manufacturers to (3):

- Establish procedures designed to prevent objectionable microorganism contamination of non-sterile drug products, such as procedures to assure adequate quality of incoming materials, sanitary design, maintenance and cleaning of equipment, production and storage time limitations, and monitoring of environmental conditions (21 CFR 211.113(a)).
- Use scientifically sound and appropriate acceptance criteria (e.g., USP Chapter <1111> Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use) and test procedures (e.g., USP <61>/<62> Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests and Tests for Specified Microorganisms, respectively) to assure that drug product components (including pharmaceutical water) and finished drug products conform to appropriate quality standards (21 CFR 211.160(b)).
- Provide appropriate drug product specifications (tests, methods, and acceptance criteria) in applications submitted to the FDA (21 CFR 314.50(d)(1) for new drug applications, or 21 CFR 314.94(a)(9) for abbreviated new drug applications). As appropriate, additional laboratory tests may be needed to determine whether products are suitable for release.
- Ensure that the methods used to test finished drug products prior to release for distribution are appropriately validated, accurate, sensitive, specific and reproducible (21 CFR 211.165).
- Test in-process materials during the production process (e.g., at commencement or completion of significant phases, or after storage for long periods), using valid in-process specifications to assure, among other things, that the drug product will meet its final specification, including criteria for absence of microbial contamination, where appropriate (21 CFR 211.110).
- Investigate any failure to meet specifications, including other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy (21 CFR 211.192), and implement appropriate corrective and follow-up actions to prevent recurrence.

These are challenging issues for pharmaceutical manufacturers, not least with developing appropriate microbiological screening.

The second example topic, equally challenging for sterile products manufactures, is with Pre-use, Post-sterilization Filter Integrity Testing (PUPSIT). This is, where not currently in place, an additional test of filters used in aseptic processing (it is common practice to assess the integrity of filters following use). Some filter users test the integrity before the filtration process and before the filter is sterilized. Established filter testing practices are the bubble point, diffusive flow or pressure hold test.

Currently EU GMP makes a recommendation for PUPSIT (4). Indications from EMA inspectors, however, suggest that in the revised version of EU GMP (expected to appear in draft form during 2017) that the test will become mandatory. The argument for PUPSIT is that during sterilization, filters can experience thermal and mechanical stresses. This may cause an alteration to the pore size of the filter which may be present at the time of use, but not present (or not detectable) at the time of testing post-use. The two things that may happen are: the pore structure can become enlarged due to the steam sterilization or a minor flaw is created. There are, however, no reported instances of this happening and the issue has triggered intense debate between industry and regulators.

Accepting that, in Europe at least, PUPSIT will be required, the task of doing so will prove challenging. Performing an integrity test of an already sterilized product filter in-line requires the filter to be wetted while also maintaining the downstream side sterile. The test gas must also be evacuated on the downstream side throughout testing maintaining sterility. The upstream side also must be protected from uncontrolled bioburden, which generally is understood as maintaining sterility of the upstream side by using sterile water for wetting and a sterilizing barrier between the integrity tester and the filter to be tested. This is not straightforward and it can be difficult to perform a PUPSIT without breaching system sterility (5). Should Annex 1 make PUPSIT mandatory, as seems likely, this will pose a major challenge for engineers, process operators and

microbiologists (who will be especially concerned about sterility assurance).

These issues crystalize why we must continue to debate and discuss topics pertaining to pharmaceutical microbiology. In this special, microbiology themed issue of the Journal of GxP Compliance some key topics and challenges facing pharmaceutical microbiology are presented.

One of the most difficult and challenging areas for the pharmaceutical microbiologist is the environmental monitoring program. While each of the elements of the program are seemingly simple it is surprising how often programs are ill-though through and therefore deficient in the eyes of regulators. In an article titled “Developing or updating your Environmental Monitoring Program”, renowned environmental monitoring expert Jeanne Moldenhauer outlines the key elements of the program and draws these together holistically. The article covers topics such as the types of samples; the process for selecting sample locations; the frequency of monitoring; and, importantly, what to do with the data. Too often environmental monitoring focuses on the ‘how to?’, in terms of sampling, with less attention paid to the analysis of data. The key signals from environmental monitoring can only be seen through trend analysis.

Sterilization and the operation of sterilizers is an area that microbiologist need to understand and to participate in the development of. However, all too often the realm of sterilizers is left to engineers. Microbiologists can participate in many ways: helping to develop cycles, selecting biological indicator types and with positioning monitoring locations. One specific area where microbiologists and engineers need to collaborate on is with deciding which loads to qualify. Where sterilizers are for multiple items it would be a very complex task to attempt to qualify each item. Instead a process of selecting worst case combinations can be undertaken, which is the theme of an article by Tim Sandle titled “Matrix approach for the qualification of a pharma facility autoclave.” In the article, methods for assessing materials on the basis of mass and complexity (such as narrow tubing) are discussed and an approach presented to allow readers to review practices in their own facility and to benchmark against.

Sterilization from a different perspective is addressed in an article by Tim Sandle titled “Sterilization of microbiological culture media.” While the sterilization of media, by steam or radiation, is well-established things can go wrong with the process and a failure to run appropriate quality control checks or to validate the process in the first place can lead to culture media that is either non-sterile or which has lost its growth promoting properties. These problems can be further exacerbated by the melting of previously sterilized media. In a ‘back to basics’ piece, Sandle presents the validation considerations for the microbiologist to take note of.

Concerns with fungi are high up on the list of topics that regulators will raise when inspecting a pharmaceutical manufacturing facility. There have been some well documented cases, as FDA recall letters show, of pharmaceutical product recalls as the result of fugal contamination. Sometimes fungal incidences can become ‘lost’ as part of the overall environmental monitoring program (where the total bacterial and fungal count is recorded). A way around this is to use a separate fungal limit. There are different ways to approach this, and Jeanne Moldenhauer presents a practical way in her article titled “Setting Limits for Mold Contamination.”

Once the data from the environmental monitoring program has been collected, together with the results of other laboratory microbiological tests, microbial identification plays a key part of the corrective and preventative action process. Understanding where contamination may have come from aids with the investigation. But how many samples to test? This questions requires a strategy, which needs to be based on the criticality of the sample (what does the sample result infer about process risk) and consideration of what will be done with the data. The approach is complicated by the methods available, such as the choice between genotypic and phenotypic methods. These issues are addressed by Tim Sandle in the article “Microbial Identification strategy for pharmaceutical microbiology.”

These articles highlight just some of the concerns and pertinent topics facing pharmaceutical microbiologists, and others interested in contamination control. Microbiologists need to be in touch with regulatory issues as well as technological changes affecting how risks are controlled (such as advancements in containment technology) and how results are gathered (the continued growth in rapid microbiological methods). These themes and challenges will be highlighted in future articles to be featured on IVT Network.

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