News & Analγsis Interview

## Pharmaceutical BIOPROCESSING

### Pharmaceutical microbiology

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Interview conducted by Jessica Thorne, Assistant Commissioning Editor.

#### » What led you to specialize in a career of pharmaceutical microbiology?

I began my career working for the blood service; then I dabbled a little in parasitology, before moving into the pharmaceutical industry – working in a microbiology laboratory. I was fortunate to gain promotions at the same time that pharmaceutical microbiology was emerging as a discipline in its own right, out of the wing of industrial microbiology. This is a rare position in industry: to be learning as the pharmaceutical sector itself begins to appreciate the nuances of pharmaceutical microbiology.

# » As the Head of Microbiology, Bio Products Laboratory Ltd (Hertfordshire, UK), can you update us on the research you and your team are currently undertaking?

There are a number of areas that we are currently looking at. One area is with disinfectants, where we are evaluating different sporicides in an attempt to find a chemical that is effective at destroying endospores and one that is not overly harmful to different materials. We are also examining a genotypic identification system, which will revolutionize the undertaking of root cause analysis (theoretically allowing contamination to be traced from a changing room to an operator's finger plate). We have also recently looked at different methods of endotoxin detection; and we have evaluated some 'real-time' viable particle counters, which get round the 'viable but nonculturable' issue within pharmaceutical grade cleanrooms.

## » Since your career began, how has the field of pharmaceutical microbiology evolved?

The main development has been with culture, not in the microbial sense but with the way that the work role is approached. Ten years ago it was commonplace to find microbiologists who did not leave their laboratories. Now the emphasis is upon proactive pharmaceutical microbiology, where the microbiologist walks the factory floor. This is essential for formulating corrective and preventative actions in relation to contamination events; and also for assessing environmental risks before they happen.







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This tallies with another major development, which is risk assessment. Here, pharmaceutical microbiologists have borrowed heavily from food microbiology in the use of risk assessment tools such as hazard analysis and critical control points. Risk assessment has also been driven by regulators, especially with initiatives such as the International Conference of Harmonization Q9 'Quality Risk Management'. Such initiatives have expanded the range of available risk assessment tools to include techniques, such as failure modes and effects analysis, which is useful for equipment assessments (e.g., isolators).

The final development of importance is with rapid microbiological methods. These techniques are gradually gaining ground and offer advantages in terms of time-to-result, accuracy of the result, and lead to a reduction in human error.

## » A lot of your recent papers have focused on the regulatory aspects of pharmaceutical microbiology. In your opinion, how important is this work for the field of biomanufacturing?

Regulations are important to a degree. It still stands that many aspects of regulations are open to question and debate. For example, when the EU Good Manufacturing Guide (GMP) was recently updated in relation to the oversealing of parenteral products, there was considerable discussion as to what the 'supply of grade A air' meant in relation to the time of monitoring.

With other areas, the regulatory changes have been of benefit. The harmonization of the microbial limits test (between the European, US and Japanese Pharmacopeias) was, to my mind, balanced and led to a reduction in test complexity. It also reduced the amount of testing required for different markets. In relation to this, some of the initiatives being undertaken by the US Pharmacopeia Microbiology Committee have been very useful. The forthcoming bioburden chapter, for example, looks interesting, as do the new chapters pertaining to different sterilization test methods.

There are, nonetheless, many areas where there is little regulatory guidance. The most notable example is with environmental monitoring. Here, the microbiologist needs to develop the program and decide on the number of samples, times of monitoring, frequency of monitoring, types of culture media and so forth. For this, risk assessment can prove to be a useful tool.

### » From your experience, what are the advantages of using microorganisms for the manufacture of biologics?

Microorganisms offer significant advantages for the development of biologics, especially given that many biologics are produced using recombinant DNA technology. New techniques are allowing microorganisms to be better controlled, and several species have been shown to be ideal candidates for genetic manipulation. Here, recombinant *Escherichia coli*, or several yeast cultures, have proved to be the most versatile.

In particular with *E. coli*, the bacterium has proved to be a very versatile host for the production of heterologous proteins, and various protein expression systems have been developed, which allow the production of recombinant proteins in *E. coli*. Here, researchers can introduce genes into *E. coli* cells using plasmids that permit high level expression of protein, and such protein may be mass produced in industrial fermentation processes.

Microorganisms have been successfully used in the development of a range of biologics, including blood factors (e.g., recombinant factor VIII, thrombolytic agents (e.g., tissue plasminogen activators), and with hormones (e.g., insulin). One of the first useful applications of recombinant DNA technology was the manipulation of *E. coli* to produce human insulin.

#### » What are the challenges faced when producing pharmaceuticals from microorganisms compared with other cell culture systems, and how are these challenges overcome?

The main difficulty is with the nature of biologics. Drugs generally have well-defined chemical structures, and a finished drug can usually be analyzed to determine all its various components. By contrast it is difficult, and sometimes impossible, to characterize a complex biologic by testing methods available in the laboratory, and some of the components of a finished biologic may be unknown.

Another significant challenge is with the microorganisms used to produce biologics. These microbes can be sensitive to very minor changes in the manufacturing process. Small process differences can significantly affect the nature of the finished biologic and, most importantly, the way it functions in the body.

A third issue with cost. Biologics are more expensive to research, manufacture, store and deliver than pharmaceuticals. However, if the process works, then the development of such drug products can be beneficial to both patients and to the pharmaceutical organization.

#### » In a recent paper based on the comparison of different fungal agar for the environmental monitoring of pharmaceutical-grade clean rooms you reported there has been an increase in contamination of pharmaceutical products. In relation to this, what are the risks involved when using fungi for pharmaceutical bioprocessing?

This paper is part of a series of four that I have been involved with in relation to fungi. The first paper on benchmarked cleanroom microorganisms looked at patterns and trends [1,2]. The second paper looked at ways to identify fungi and evaluate the risks [3]. The third showed that many fungi found in pharmaceutical facilities have a degree of resistance to common disinfectants [4]. The fourth paper looked at strategies for environmental monitoring [5].

Fungi pose a risk to pharmaceutical bioprocessing due to the ease by which fungal spores can spread around a facility; there are also risks associated with damp environments. Some fungi are associated with poor building maintenance (e.g., *Cladosporium*); whereas other fungi, such as *Aspergillus* and *Pencillium*, are carried by people (so here a risk arises if good cleanroom gowning practices are not adhered to).

What is interesting, if one looks at US FDA drug product recalls and compares the recalls for microbiological issues during 1990s to the last decade, then recalls due to fungal contamination have increased. This is to the extent that fungi now account for approximately 21% of pharmaceutical product recalls.

If one example is required, in relation to the seriousness of fungi, then the 2012 incident at the New England compounding center is a prime example. The company was attempting to compound a sterile solution for injection for the treatment of arthritis. Due to a breakdown of GMP the starting solution became contaminated with a filamentous fungus called *Exserohilum*. The result was that over 50 people died and over 700 were infected, resulting in the most serious sterile product contamination case of all time.

#### » What do you believe needs to be done to improve regulation at pharmaceutical manufacturing facilities?

I think greater harmonization between the regulatory authorities would be a major step forwards. Testing according to different markets is time consuming and it does not often mean that the product is any safer.

The standards relating to cleanrooms require sorting out. First, there are some differences between what is contained within EU GMP in relation to particle count limits and with the ISO 14644 series of standards (which the FDA has adopted). Second, the international standard for biocontamination control – ISO 14698 – is quite out-of-date and needs revision, especially in light of the changes to the USP (chapter <1116>, relating to sterile products).

In addition, I think that there is more that can be done with risk assessment and building this into regulations. Some advances have been made with QbD approaches, and with the encouragement to use process analytical technology.

#### » What has been your career highlight to date?

That's a tough question. In terms of technology, it was interesting to be one of the first people to become involved with automated endotoxin detection systems, being among the first users of turbidimetric instruments. On the other hand, it is also interesting to be



able to evaluate some of the new rapid microbiological methods that are emerging in the marketplace.

In relation to things that I have written, a paper I wrote applying a risk-assessment approach to an isolator proved to be popular and I understand that the FDA have used it for several training courses [6]. I'm also pleased with my recent books, including the one I published this year with PDA/DHI looking at practical approaches to sterility testing.

In terms of recognition by colleagues, I was very pleased to receive the inaugural 'Excellence in Pharmaceutical Microbiology Award' from the UK and Ireland pharmaceutical microbiology society Pharmig (Hertfordshire, UK) during 2013.

### » How do you see the field of pharmaceutical microbiology progressing in the next 5–10 years?

Rapid methods are the answer. Pharmaceutical microbiology has been stuck in cul-de-sac for decades with conventional methods, and there are signs that the profession is gradually moving out of the dark ages.

Such technologies include 'real-time' particle counters, which can distinguish between inert particles and microorganisms. I think these will be used quite widely within a few years, especially when assessing aseptic filling operations. This is partly due to the fact that many of the microorganisms found within cleanroom are not capable of growing on culture media (what are often termed 'viable but nonculturable' microorganisms). Laser-scanning technologies, based on spectrophotometrics, overcome this issue.

The area that is receiving considerable investment is with sterility testing. Given that the sterility test, with a 14-day incubation, is one of the longest microbiology tests in terms of time-to-result, any technology that succeeds in reducing this time is bound to be successful. Some of these methods are growth based, such as detecting  $CO_2$  in a closed container using a fluorometric sensor. Alternate methods label microorganisms with a viability stain and can using digital fluorescent microscopy.

For the adoption of rapid methods, both the pharmacopeia and the advice from the regulators have made things considerably easier.

Connected to rapid methods, I also think that laboratories will see greater automation.

### » What words of advice would you give to someone looking to have a career in pharmaceutical microbiology?

It is important to gain a firm grounding in basic microbiology techniques. It is equally important to understand production processes. Combining these two makes for a good 'pharmaceutical' microbiologist. This knowledge can then be enriched by understanding risk assessment.

The main areas that I find new recruits to be lacking in is an understanding of the principles of sterilization and disinfection. It also seems that many undergraduate courses do not teach students very much about bacterial endotoxins.

There are some useful courses available to supplement knowledge. For example, the University of Manchester in the UK run a distance learning master's degree in pharmaceutical microbiology.

#### Disclaimer

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