Effective bioburden control is of strategic importance to the industry and is becoming the subject of growing FDA scrutiny. In the absence of agreed industry best practice, the BPOG DS Bioburden team is pioneering a clear industry position. In the summer of this year, the group will publish a White Paper that defines a best practice model for microbiological monitoring and how to respond if bacteria are recovered.

Microbiology and the control of bioburden are especially important for biopharmaceutical products, particularly as the processes involve nutrient-rich materials that can sustain microbial growth. Manufacturers, however, face a particular challenge as Diane Hardy, QA Senior Director and Chief Microbiologist at Regeneron Pharmaceuticals explains: “Bioburden control is a very hot topic when regulatory agencies inspect manufacturing facility. The lack of adequate bioburden control can lead to product recalls and plant shutdowns. That is why bioburden control is becoming a critical issue for the industry and why 17 BPOG member companies are working to establish and promote industry best practices in microbiological monitoring and response.”
The paper, Microbiological Monitoring for Biological Drug Substance Manufacturing – An Industry Perspective, focuses on microbial control of bulk drug substance manufacturing, up to the filling of the final bulk container. It is due to be published in the summer and addresses issues such as:

**Sampling and Testing**
- the absence of industry standards can lead to considerable discussion when regulators visit, inevitably inviting comparison with approaches adopted by other companies. The White Paper will provide recommended bioburden and endotoxin monitoring points across manufacturing process steps. The team believes that these recommendations will be welcomed by biotech manufacturers and regulators alike.

**Alert and Action Levels**
- again, there is no consistency within the industry when setting alert and action levels. The seventeen companies participating in this work stream, a very representative industry cross section, have benchmarked their own approaches. Given the number of variables, it has not been possible to identify definitive numbers, but a recommended approach to setting levels will be included in the paper.

**Bioburden Excursions & Response**
- extending the discussion on alert and action levels, the paper will provide an industry consensus of appropriate responses to excursions. In other words, how best to respond if bacteria are found in samples.

**Objectionable Organisms**
- to different degrees, regulators have adopted a concept taken from the food industry, where companies are required to compile a list of ‘objectionable organisms’. The idea is that, if any organism on the list is recovered in samples, then a full investigation to assess product impact is required.

“The general concept of objectionable organisms in biological drug manufacturing is a contentious subject,” says Diane Hardy. “This is because regulatory agencies have given a number of companies 483 observations for not having a List of Objectionable Organisms when many of these companies believe having a list does not apply to them.”

Regulatory agencies also have mixed views, with some expecting individual responses to each organism, and others, when inspecting a site, specifically asking for a list of objectionable organisms.

The Bioburden team believes that objectionable organism lists can lead to tunnel vision. The consensus amongst the team is that the industry needs to move away from lists, towards a risk assessment approach. One example of a risk assessment model (also called ‘Patient Safety Assessment Tools’) will be included in the paper.

The White Paper, then, presents recommendations for sampling, testing and setting alert and action levels – together with a discussion around best practice when there are excursions. After publication, the next phase planned by the BPOG team is to present the White Paper at industry conferences and to begin engaging with the regulators.

“We hope the article will promote dialogue within the industry and with the regulatory agencies,” says Diane.

**Bioburden Control Strategy**
Looking ahead, the team has also started work on a ‘Bioburden Control Strategy Framework’ to share and develop best practice in bioburden control. The framework catalogues all the key elements to be considered in a bioburden control strategy. These elements, or modules, include gowning, raw materials, transfer of materials between areas, and the flow of personnel within a facility, etc.

The plan is for the team to assign a criticality score to each element, and then share and develop best practice as a set of modules, starting with the most critical. Like the White Paper, this document will have huge significance for the industry. It is primarily intended to benefit biotech manufacturers as a best practice model, but may also be instrumental in promoting dialogue and interactions with regulatory authorities. The fact that it is being created jointly by 17 key companies within the industry will ensure that it provides a true industry stance with significant credibility.

“I believe the Bioburden Control Framework Strategy is an exceptionally important initiative for the industry, and one that the team is uniquely positioned to address. Over the last three to five years, there has been increased regulatory focus around the topics of bioburden and contamination control. The industry is being propelled down a path where fill-finish plants for non-sterile drug substances are expected to operate very closely akin to manufacturers of sterile finished products. The FDA has been reinforcing this view at industry forums, promoting the concept of an almost holistic approach to bioburden control throughout the entire process.

“The single most important outcome from the BPOG initiative will be clearer thinking around how to appropriately interpret the regulations associated with a sterile facility in the context of a non-sterile API plant. It is crucial to do this collectively, and BPOG is the perfect environment to develop this industry perspective. By default, the more companies that adopt a common industry framework, the more the inspectors are exposed to it, the more it will be accepted as current Good Manufacturing Practice.”

David Philips
Senior Director of Quality Control
Shire