Not so long ago, a microbiologist working for a producer of non-sterile medicines had a relatively easy life – a few total viable counts on some incoming materials here, an occasional test on the water system there – all very relaxed and low key.

How life has changed! Now in some manufacturing establishments for non-sterile products, the microbiology department is as highly staffed and as busy as its counterpart in sterile manufacture, carrying extensive tests on incoming materials, intermediates, water systems, production equipment, production staff and extensive environmental monitoring. Ten years ago, seeing a settle plate in a tablet packing area would have been a cause for consternation – now it is relatively commonplace. All this leads me, as a microbiologist, to ask the questions “is all this really necessary?” and “how is it benefiting the patient?”

Our approach to microbiological control of non-sterile products should be essentially the same as to all other policies and strategies in our industry – it should be based upon an objective evaluation of RISK. Unfortunately, I believe that, in terms of microbiology, much of what we currently do, and what we are encouraged to do by the regulators, is not based on risk and does not represent good science.

As for FDA, 21CFR211.113 states a requirement for…

“Written procedures describing the systems designed to prevent objectionable microorganisms.”

which begs the question “what is an objectionable microorganism?” This is not clearly defined, but it doesn’t stop FDA from taking regulatory action; microbial contamination is a frequently cited reason for recalls in FDA-regulated markets, but it is by no means clear whether all these recalled products actually represented a health threat to patients.

In truth, we often over-estimate the risk to patient safety in our industry. Let us be clear; the majority of non-sterile medicines are administered to patients who are, by many criteria, fit and well. If patients were seriously ill, they would not be prescribed tablets, capsules, patches, etc. Thus, people suffering with headaches, muscle or joint pain, raised blood pressure, raised cholesterol, nicotine addiction and similar conditions are not especially at risk of microbiological infection. The microbiological content of their food intake is not monitored, so why should we make such a big deal out of the few grams of medicines they take each day?

Of course, many of you will counter this argument by quoting examples of non-sterile products which are administered to patients with heightened susceptibility to infection, and in these cases I fully agree that some measures need to be taken – this is the essence of RISK MANAGEMENT! However, adopting a “one size fits all” policy is unscientific, inefficient, costly and potentially dangerous in that it may dilute the effort put in to controlling those products and processes which really need it.

As part of a coherent, risk-based approach to the microbiological control of non-sterile products, we need to consider, in addition to the health status of the recipient, the potential sources of contamination as well as risk mitigating factors. Thus, we need to...
understand the risks from…
  > Formulation
  > Starting Materials
  > Water
  > Equipment
  > People
  > Process Environment

**FORMULATION**

All microorganisms require water – and lots of it – to grow. Many non-sterile formulations have very low levels of available water, either because they are dry or solid (tablets, capsules, powders, etc), they are water free (ointments), or they have formulation components which reduce the amount of water available to microorganisms (so-called humectants). It is only those products which contain substantial amounts of water (or intermediates and additives which do) which constitute a significant microbiological threat. Thus, oral liquids, topical liquids, creams, semi-solids, etc constitute a potential microbiological risk, which is why so many of these products are formulated to contain a chemical preservative agent, the efficacy of which is established during development and confirmed periodically on commercial lots.

Thus, the nature of the formulation should be considered as part of the overall microbiological risk assessment.

**STARTING MATERIALS**

As dosage form manufacture consists in the main of mixing and packaging of actives and excipients, it follows that the microbiological content of medicines is derived largely from those starting materials. Thus, it makes sense that microbiological control of starting materials should be the foundation of any control strategy for non-sterile medicines. But, here again, we should apply risk principles and take into account the type of raw materials. Synthetic excipients or actives produced by an aggressive synthetic pathway are unlikely to be contaminated with significant levels of microorganisms as the temperatures, pressures, extremes of pH, etc will have destroyed any contaminants. Only the final stages of preparation, such as crystallisation from water, represent a potential threat. Thus, microbiological monitoring of such materials lot by lot would be excessive and unnecessary. On the other hand, materials of organic or natural origin (starches, sugars, gelatine, gums, etc) are much more likely to carry a high bioburden and pose a much greater risk. Here, increased monitoring and control is warranted, and pharmacopoeial requirements reflect this.

**WATER**

Water is potentially a major source of microbiological contamination, as a poorly designed and controlled water system can contain high numbers of microorganisms, especially Gram negative organisms which may be less susceptible to the killing effect of chemical preservatives. Thus, where water is a key formulation constituent or process component, its control is of crucial importance.

**EQUIPMENT**

If kept clean and dry, process equipment is unlikely to represent a significant source of microbiological contamination to medicines. However, poor design of equipment can result in the presence of “reservoirs” of potential contamination. Thus, the extent of microbiological monitoring of process equipment may range from none to a lot, depending upon the risk factors that exist. Please understand, though, that the best way to control contamination is to remove the potential source (i.e. re-design the equipment).

**PEOPLE**

People are often cited as a major potential source of contamination to medicinal products. However, if we exclude sterile products from this discussion, I believe that when certain sensible prevention measures are
taken, microbiological risks from people are actually small. An operator would have to bathe in a liquid product to contribute a significant microbiological challenge to it! This is not to trivialise the risk from people, rather it is intended to put it into perspective. Accepted practices of good gowning, good personal hygiene and adoption of clear hygiene practices, allied with instructions to minimise direct contact with product and product contact surfaces, should be sufficient. Actual microbiological monitoring of staff should be regarded, except in exceptional circumstances, as unnecessary and potentially misleading.

**PROCESS ENVIRONMENT**

If the contribution of people to microbiological contamination of non-sterile products can be considered relatively minor, the contribution from the air is, in the most part, negligible. True, there is a GMP requirement for some liquids and inhaled products to be processed in a controlled environment so as to minimise microbiological contamination, and this is entirely justified on a risk basis, but for the vast majority of non-sterile products, the environment contributes little risk to the product and so microbiological environmental monitoring constitutes at best a luxury and at worst a waste of valuable resource.

Before instituting a microbiological environmental monitoring programme into a non-steriles facility, ask yourself a few questions…

- What am I looking for?
- Where will I monitor, how and how often?
- What is the relationship, if any, between environmental monitoring data and patient risk?
- How much is unacceptable and why?
- What is acceptable and why?

This article represents a very brief, and deliberately provocative, overview of the strengths and limitations of microbiological control strategies for non-sterile products.

**IN SUMMARY**

1. Effective microbiological control of non-sterile products is essential if we are to assure their fitness for use but the extent of that control must be based upon an objective assessment of risk.

2. Know your…
   - Products
   - Processes
   - Sources of contamination
   - Mitigating factors

3. Remember that microbiological monitoring is not the same as microbiological control.

4. Microbiological control strategies should be targeted to providing the following benefits…
   - Better knowledge and control of risk areas
   - Consistently good hygiene practices
   - Elimination of microbiological “hot spots” in processing
   - Reduced risks to patients and not just perceived regulatory compliance

5. Ensure you are adding VALUE, and not just cost.

If you cannot answer most or all of these questions, why would you wish to go ahead?