CLEAN UP YOUR ACT

Ensuring that drugs are produced in aseptic conditions is crucial for pharmaceutical companies and end users. The US FDA has marshalled industry stakeholders in an effort to clarify their cGMP expectations, explains Richard Friedman, US FDA CDER, in conversation with Jim Banks.

Profile

Richard L Friedman is team leader of guidance and policy, in the Division of Manufacturing and Product Quality at the US FDA's Center for Drug Evaluation and Research. In his position, he is responsible for interpretation and development of cGMP guidance and policy. He has been employed by the US FDA since 1990 with earlier positions as drug specialist and senior compliance officer.

Microorganisms are invisible, yet capable of great harm. Excluding them from the pharmaceutical manufacturing process is a fundamental responsibility, required to guarantee the integrity of pharma products and protect their end users.

Approaches to aseptic processing, however, have differed greatly in the industry over the years, and at times this piecemeal approach has led to large numbers of recalls and product warnings. In the US, the FDA has observed the problem over the years and has prioritised consultation on aseptic processing among its many responsibilities.

'Aseptic processing needs close monitoring,' says Richard Friedman, team leader, guidance and policy, Office of Compliance for the US FDA Center for Drug Evaluation and Research. 'No manufacturing process in the industry requires more vigilance and precise execution. It is not a forgiving process. If any one factor in process control is out of synch, then it can lead to product contamination.'

The FDA's ultimate responsibility is to protect patients, and it clearly saw manufacturing process sterility assurance as a key area to tackle in order to fulfil its aims. 'Often, it is sick people who are taking injections, so the patient populations are very much at risk,' notes Friedman. 'This just underscores the fact that there is little margin for error. The FDA realises the priority we must place on inspection and surveillance.'

In the late 1990s, aseptic processing, though always on the agenda, became a higher priority for the FDA. This was driven by a significant number of incidents in which drug companies did not meet the required standard.

'In both foreign and domestic inspections we saw a problematic trend in aseptic processing,' says Friedman. 'There was not only a growing number of serious regulatory actions, but also a marked increase in the number of product recalls due to non-sterility, including class 1 recalls, where there is serious risk of injury or death. There were also many instances where there was a lack of sterility assurance, and the manufacturer couldn't provide a minimum level of confidence in the product.'

Sensing that the industry needed a nudge, the FDA, as part of the current good manufacturing practice for the 21st-century initiative, developed new guidance for the pharmaceutical industry on aseptic processing. Two years later, its effectiveness is becoming apparent.

Clarity and flexibility

The FDA took a consultative approach to developing its 2004 guidance, which it believes has proven to be a good template for the industry. In updating its

1987 Industry Guideline on Sterile Drug Products Produced by Aseptic Processing (see box), it focused on clarifying responsibilities regarding the sterilisation of drug products, containers and closures, as well as the requirements of a high-quality environment for filling and sealing. It also looked closely at personnel qualifications, cleanroom design, process design, quality control, environmental monitoring and the review of production records. Furthermore, it encompassed the use of isolator systems.

So far, the guidance seems to have been effective in reducing the number of serious regulatory actions, though there are still some occasional sterility failures. This suggests that, for many firms, voluntary compliance works. Indeed, Friedman believes that this is the most desirable model.

> 'Many in the industry have recognised the need to modernise their operations.' Richard Friedman

'We have had an active dialogue with the industry on aseptic processing, and we find that clear guidance and good quality management systems encourage compliance,' he says. 'We still see some problems, but their frequency or magnitude may be lessened due to the FDA guidance. As an example, many in the industry have recognised the need to modernise their operations, such as increasing automation or protecting their lines with an isolator.'

One challenge in writing the guidance was to take into account new and emerging technologies, which might influence future process and facility design. For instance, rapid microbiological test methods, restricted access barrier systems, robotics and isolation technology – all mentioned in the guidance – are considered, while leaving enough flexibility to adapt to unanticipated technological advances. Furthermore, the guidance had to take into account the variation in the sophistication of existing production lines.

'Some operations were very inconsistent,' says Friedman. 'Some had design concepts from the 1950s to the 1970s, and had not made any improvements for years. We spoke to the industry about contemporary design. We looked at the latest science, so that the guidance would stand the industry in good stead for at least the next ten years.'

Positive signs

The positive response to the 2004 guidance is in no small part due to the way in which the FDA and the industry approached drafting the new guidance.

All relevant disciplines had a chance to influence the process, with engineers, microbiologists and GMP experts from around the world contributing their opinions.

This close consultation with the industry led to some 'vigorous and challenging' discussions, but the impressive degree of openness and engagement from the regulator and the industry meant these discussions were constructive. 'The industry worked closely with us towards a positive evolution of aseptic processing,' notes Friedman. 'The industry should be complimented. Its experts deserve kudos for their major contributions.'

As well as producing a robust and flexible set of guidelines for aseptic processing, the consultation also provided a positive omen for similar procedures in the future. 'The consensus building around the 2004 guidance is seen as unprecedented,' says Friedman. 'Egos were put aside and we focused on pure and pragmatic science. The FDA took on some difficult issues and resolved them. The process used to address these difficult technical issues produced excellent results, and we are happy to see other countries adopting these concepts in their aseptic guidance documents. We've taken a significant stride forward.'

The industry now has a clear working model for aseptic processing, and has shown that it can tackle fundamental issues in a collaborative way. END

VALIDATION OF ASEPTIC PROCESSING AND STERILISATION: PROCESS SIMULATIONS

To ensure the sterility of products purporting to be sterile, sterilisation, aseptic filling and closing operations must be adequately validated (§ 211.113). The goal of even the most effective sterilisation processes can be defeated if the sterilised elements of a product (the drug formulation, the container and the closure) are brought together under conditions that contaminate any of those elements.

An aseptic processing operation should be validated using a microbiological growth medium in place of the product. This process simulation, also known as a media fill, normally includes exposing the microbiological growth medium to product contact surfaces of equipment, container closure systems, critical environments, and process manipulations to closely simulate the same exposure that the product itself will undergo. The sealed containers filled with the medium are then incubated to detect microbial contamination. Results are then interpreted to assess the potential for a unit of drug product to become contaminated during actual operations (for example, start-up, sterile ingredient additions, aseptic connections, filling, closing). Environmental monitoring data from the process simulation can also provide useful information for the processing line evaluation.

Taken from the 2004 'Guide for Industry Sterile Drug Products Produced by Aseptic Processing – CGMP'. For the full version, visit: www.fda.gov.