The parenteral drug industry has grown in recent years with the development of new treatments and formulations to treat a wide range of acute and chronic conditions. In tandem with this growth has been the increasing sophistication of the packaging, including prefilled syringes and disposable injection devices. The market has moved in this direction for a number of reasons, including ease of drug administration, additional security, lower contamination risk and ease of use for non-healthcare professionals.  

Prefilled syringes have actually been around for more than two decades. The European market for prefilled syringes is relatively more mature compared with the US market. However, the market for prefilled syringes has seen healthy growth as the pharmaceutical industry has grown and become more sophisticated. Amongst the major challenges for manufacturers, is the problem of interaction of prefilled syringes with the drug, which causes concerns regarding stability. Manufacturers need to eliminate the interaction between drugs, packaging and sterilisation technologies, and processing and quality assurance control are therefore vitally important. 2

With recent developments in advanced drug delivery systems, manufacturers and contract sterilisation providers are now required to work more closely together than ever before to find a satisfactory sterilisation option for these devices. A new generation of prefilled syringes offer a unique challenge to all parties as the regulatory environment requires that they conform to both pharmaceutical and medical device standards for sterility assurance. The contract sterilisation industry has been able in most cases to adapt its processes to handle current requirements through the use of microbiological control and new sterilisation techniques such as Electron Beam. However, going forward, regulatory changes are being looked at to make the process more adaptive.

As the prefilled syringes industry has grown and matured, so too have sterilisation techniques adapted to keep pace with innovation in syringe design and production process, and with new regulations. In this article, Jenni Hollinsworth, of Isotron (the Sterilisation Services division of Synergy Health), describes the various sterilisation options available, recent trends and developments, and the implications of current and forthcoming regulations.

**CHALLENGES AND KEY CONSIDERATIONS FOR THE STERILISATION OF PREFILLED SYRINGES**

"THE RISK OF INFECTION FROM THE DEVICE PLUS THE CLEARLY DEFINED REQUIREMENT FOR TERMINAL STERILISATION OF DEVICES HAS MEANT THAT REGULATORY BODIES AND MANUFACTURERS ARE INCREASINGLY LOOKING FOR WAYS TO STERILISE THEIR COMBINATION DEVICES TERMINALLY."

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CHALLENGES FOR DRUG DELIVERY SYSTEMS

Medical device manufacturers do not have the same challenges as their pharmaceutical counterparts, as devices are normally manufactured using plastics, metals or other materials that are easily adapted to terminal sterilisation. Sterility assurance is obviously still critical for this market and standards have been developed and unified over the last 30 years, which clearly outline how conformance to medical device sterilisation standards can be undertaken.

The latest version of ISO 11137: 2006, “Sterilisation of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilisation process for medical devices”, defines the requirement to conform to a sterility assurance level (SAL) of $10^{-3}$ using irradiation as well as the microbiological tests required to achieve this.

The development of the drug delivery systems for complex diseases offers challenges to manufacturers about how to conform to both approaches. Whilst pharmaceutical manufacturers can follow either path, the risk of infection from the device plus the clearly defined requirement for terminal sterilisation of devices has meant that regulatory bodies and manufacturers are increasingly looking for ways to sterilise their combination devices terminally.

A number of approaches have been developed over the last 10 years by manufacturers and their sterilisation providers to find ways of sterilising the devices whilst not adversely affecting efficacy. These include:

- Electron Beam processing.
- Reduced irradiation dose (exposure) due to clean manufacturing.
- Temperature control and inert atmospheres.

DIFFERENT STERILISATION OPTIONS

The pharmaceutical approach to understanding microbiological risk through Quality Risk Management (QRM), using ultra-clean and consistent processes has stood the test of time whilst avoiding the need for terminal sterilisation. This approach has developed largely due to the issues associated with using the main industrial sterilisation techniques of Gamma irradiation and Ethylene Oxide gas.

These high-energy processes involve free-radical production which has always caused problems with the efficacy of the drug. In the case of Ethylene Oxide, the addition of heat and steam and residual safety concerns has made this technique non-viable. However, terminal sterilisation using Gamma radiation has remained an option for pharmaceutical manufacturers and is used in some cases.

Electron Beam Processing

Over the last 20 years, the developments of 10 MeV sterilisation beams (which are commercially viable and used by a large proportion of the medical device industry) have created new options for pharmaceutical manufacturers. Time is the main advantage of this technique as the sterilisation dose can be applied in a matter of minutes, as opposed to the hours needed for Gamma irradiation. This reduction in exposure time directly correlates to a reduction in free radical generation and the negative effects that this causes to drugs and medical plastics.

The use of Electron Beam for drug-eluting stents has been common for many years. In addition the use of shielding, thin product target areas (pizza box shapes) and orientation of products to the beam have allowed maximum doses to be controlled to relatively low levels of around 40 kGy.

Reduction in Irradiation Dose

Historically, contract irradiation plants have processed medical devices at dose ranges in the region of 25–40 kGy in line with medical device requirements set out by the industry and the Association for the Advancement of Medical Instrumentation (AAMI) (www.aami.org) in the 1970s.

The development of ISO 11137 over the last 15 years (which outlines the requirement to undertake microbiological testing) has, however, opened the door for a reduction in processing doses. This standard allows devices with low bioburden to be sterilised by minimum processing doses of 15 kGy, or even lower in some cases, and through regular auditing of bioburden. As such the efficacy of the sterilisation dose can be maintained whilst conforming to the standard.

Temperature Control and Inert Atmospheres

Even a 5-10% increase in temperature seen during Gamma and Electron Beam processing can cause degradation in some cases, so this needs to be checked during validation of the process. However, it has been proven that keeping the product at a reduced temperature through the use of dry ice prior to and during irradiation (Gamma only), helps to protect the drugs from the effects of free radicals and dampens the chemical reactions these cause in the drugs.

A major negative effect of the Gamma and Electron beam sterilisation technique is the production of the highly reactive compound, ozone, which occurs through the ionisation of air. The use of sealed packaging filled with inert gases, such as nitrogen, stops or severely reduces the production of ozone in the proximity of the drug and reduces the potential damage to efficacy even at doses of 25 kGy using Gamma.

A consideration with both temperature control and inert atmosphere approaches is control of packaging and shipping, cost of manufacturing, and the ability of the sterilisation provider to handle either low-temperature products or the risk of handling pressurised containers.

The methods outlined above have allowed combination devices to be manufactured and sterilised routinely for many years. However, the expected large increase of these products over the next 20 years, along with the complexity of drugs and devices, has meant that manufacturers and contract sterilisers are looking for a new regulatory route to make terminal sterilisation easier to achieve.

KEY CONSIDERATIONS

It is important that the manufacturer gets input from the contract steriliser at an early stage of development to ensure that the prefilled syringes can be sterilised using an appropriate technique.

Other areas for more detailed consideration are:

- Drug stability with chosen sterilisation technique.
- Development trials to establish processing parameters and product limitations.
- Packaging configuration – orientation during sterilisation.
- Temperature sensitivity and transportation requirements.
- Timelines between manufacturing, sterilisation and delivery to market.
- Regulatory compliance: UK MHRA, US FDA and other notified bodies.

FUTURE REGULATORY CHANGES

A major discussion within the industry relates to the fact that SALs (security assurance levels) of $10^{-3}$ or $10^{-4}$ are commonplace for vaccines and other pharmaceuticals produced by aseptic processing. This has therefore opened up a potential for the industry to select the appropriate SAL for a healthcare product scientifically, rather than taking the arbitrary $10^{-6}$ currently used by the medical device industry. This SAL of $10^{-6}$ is seen as overkill in some cases rather than a level required for safe use.

The subject of drug device systems continues to be an area of interest for all related industries. The International Irradiation Association (iiA) (www.iiaglobal.org) sponsored three workshops on drug combination devices held in San Diego.
CA, US, in December 2006, in Washington DC, US, in June 2007 and in London, UK, in 2008. These workshops brought together experts in the field of medical device manufacturing, sterilisation, drug development and regulatory approval to review the technical and process challenges associated with drug-device combination products, many of which are outlined earlier in this article.

CONCLUSION

The development of drug delivery systems which require terminal sterilisation has meant that the contract sterilisation industry has needed to develop ways of processing drugs through tight control of dose, bioburden, irradiation source and packaging, whilst not adversely affecting the efficacy of the drug. These techniques allow manufacturers to routinely sterilise drug delivery systems.

With a detailed understanding of all medical device and pharmaceutical sterilisation requirements, from design to regulatory compliance, Isotron offers support and guidance to a diverse range of medical device manufacturers. Combined with an appreciation of the importance of sterilisation services to your business, Isotron endeavours to operate as an extension of your organisation, enabling you to offer a regulatory compliant and cost effective product to the market.

ABOUT THE COMPANY:

With more than 30 years’ experience, Isotron is the partner of choice for providing sterilisation solutions, validations and support services to the medical devices industry, including the prefilled syringes industry (Figure 1). Through a network of 19 sites (Figure 2) in nine countries across Europe, Asia and South Africa, Isotron operates the three principal sterilisation technologies of Gamma, Electron Beam and Ethylene Oxide. A schematic of the Electron Beam processing plant at Daventry, UK is shown in Figure 3.

In addition to the core technologies, Isotron also operates a network of laboratories to satisfy the microbiological needs of the industry. With a solid foundation of technical expertise and involvement with standard development and industry working groups, Isotron is uniquely positioned to provide an experts’ insight into sterilisation technologies.

REFERENCES: