Innovations in Pharmaceutical Technology

The role of sterile alcohol in critical contamination control

Adams Healthcare

Increasing guidelines and regulations relating to good manufacturing practices (GMP) are a constant source of workload, and in some cases pressure, for laboratories, pharmaceutical manufacturers and hospitals throughout the world. An important move forward in ensuring the quality of materials used in areas of critical contamination control has been the introduction of regulatory standards that stipulate all disinfectants used in Grade A and B (corresponding to US Federal Standard 209E: Class 100) pharmaceutical preparation and filling areas must be sterile prior to use. Today, companies requiring effective contamination control products for use in areas where sterile products are prepared, manufactured, filled and packaged, must face the costs (actual and missed opportunity) of full compliance with such guidelines.

Until recently, these costs have been considerable - due to the fact that producing contamination control products to the standards required by GMP guidelines have had to remain an in-house operation, as there has been no alternative commercially available. A survey published in the Journal of the Parenteral Drug Association (PDA) identified alcohol as being the most widely used contamination control product. This is most likely due to its efficacy against vegetative micro-organisms, its rapid drying time and the fact that it leaves no residue. It is also known that alcohol’s efficacy is optimised at a 70 per cent dilution with water for injection (WFI) - also recognised in the same survey as being the most frequently used diluent, due to its ability to provide the highest grade of pharmaceutical water available and to effectively minimise the endotoxin risk.

However, anything less than sterile 70 per cent alcohol in WFI creates a ‘contamination control paradox’ in that the product used to control contamination can actually contribute to the risk by introducing spores or endotoxins (Figure 1). Because sterile alcohol in water for injection eliminates this risk, it is recognised by the pharmaceutical industry as the ‘gold standard’.

To this effect, manufacturers are keen to utilise this very specific combination as an effective control against the risk of contamination within their facilities and end-products. However, there are considerable drawbacks encountered when using in-house facilities for the manufacture of sterile alcohol in WFI.

In-house production

In order to ensure the sterility of the contamination control product, a number of quality control

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checks must be adhered to. Briefly, these comprise:
analysis, control, documentation and batch
numbering of all raw materials and packaging
components; audit and approval of suppliers;
pre-sterilisation of packaging; integrity testing of
all filters; filter of raw materials and finished
solution; aseptic filling; analysis of finished
product; sterility testing and endotoxin analysis of
finished product; validation of all parts of the
production process; compilation of batch
documentation; and validation of shelf-life.

These processes are key to ensuring the sterility
of the in-house prepared contamination control
product, and must be undertaken by qualified
personnel. This raises a number of issues with

regard to in-house production. Demands are made
on essential personnel and resources, as the sterile
alcohol is tested to ensure compliance with vital
quality assurance standards. In effect, it is
necessary to devote almost as many resources to the
in-house production of sterile alcohol in WFI as it
is to manufacture a high-value sterile pharmaceutical
or diagnostic product.

Companies are therefore placed in a difficult
position: if they do not make their own alcohol to
the same standard as their finished products, they
can compromise product quality, run the risk of
contamination and fail to comply with regulatory
guidelines. On the other hand, if they do, failure
to utilise space, technology and expertise on
profitable finished products can have an adverse
impact on the bottom line.

Understandably, the amount of validation and
documentation associated with such high quality
products is considerable. However, working to
expand its contamination control portfolio, Adams
Healthcare has invested in a long-term
development programme that began with the
emergence of Spiriclens® sterile isopropyl alcohol
70 per cent v/v in water for injection. Adams
worked closely with a number of key pharmaceuti-
cal manufacturers in order to develop a technical
specification that would benefit the industry as a
whole and allow, for the first time, the ability to
outsource the production of sterile alcohol in WFI.
The specification would not only ensure
consistency for manufacturers across all their
facilities, but would also meet or exceed the quali-
ity assurance achieved by their own in-house
production processes.

Spiriclens® Sterile Spray contains isopropyl
alcohol (IPA) USP 70 per cent in WFI USP/Ph
Eur in a nitrogen pressure spray. Each unit is
triple-bagged and sterile for effective entry into,
and use in, aseptic areas. Obviously, to introduce
and use a product extensively in an aseptic process,
prospective users must have total confidence in its
quality; for this reason, a number of rigorous
checks are built into the production of Spiriclens®
to ensure its sterility.

All starting materials used are of pharmaceutical
quality, meet both US and European monographs
and are sourced only from approved and audited
suppliers. Adams analyses, controls, documents
and batch numbers all raw materials and
components. However, it is the production process
that ultimately provides the confidence to
encourage potential users to outsource to this
option. Each step has been validated and
documented, and is fully traceable. Adams has a
transparent production process in that it can be
visited and audited by any manufacturing
company wishing to do so. An outline of the
production process is given below.

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Figure 2. Spiriclens® sterile spray IPA 70 per cent v/v in water for injection in
use at Nycomed Amersham.
The production process

As a crucial part of the specification, the Spiriclens® process begins with the production of WFI in a fully validated and externally audited plant. The WFI is manufactured on site and tested daily to ensure that it meets the USP and Ph Eur specifications. After testing, the WFI enters a sealed stainless steel mixing vessel where it is mixed with IPA USP, which is subject to filtration through a 0.2µ filter. (The filter is itself integrity-tested before and after use with each batch production.) To ensure quality, the mixed IPA USP 70 per cent in WFI is 0.2µ filtered, filled and sealed under class 100 laminar flow. Each can is pressurised with 0.2µ filtered nitrogen. Again, all filters are integrity tested pre- and post-batch production.

The production line is fitted with automatic pressure and weight checking equipment to ensure the rejection of any canister that does not meet the finished product specification. As a further check, bioburden analysis is performed on samples taken randomly throughout the production cycle - a vital element of the in-process quality control procedure.

After the fitting of the actuating button and cap, each canister receives ink jet code batching data to the base and is visually checked for accuracy. The final stage of the production process is the placement of an irradiation indicating dot, and the packaging of the canister within three integrally sealed bags which, once sterilised, allows it to be effectively introduced into aseptic areas. Clear and colourless, the liquid has an alcohol content of between 68 and 72 per cent by volume. It passes both the Ph Eur 1997 test for sterility and USP XXIII, addendum 8, 1998.

Spiriclens® finished product has endotoxin levels of below 0.3 EU/ml for a validated 1:30 dilution. The product is presented as a positive nitrogen pressure spray, the use of which maintains integrity and avoids the ‘backflow’ associated with trigger sprays (a potential source of contamination). The use of the pressure spray enables sterility to be maintained throughout the product’s use. Adams has validated the in-use shelf-life of Spiriclens to 28 days, at which time the contents of the canister would normally have been consumed. Sterility tests were undertaken on product used every day at predetermined intervals within a 28-day period. The results proved that sterility was maintained for the duration of product use - providing complete confidence in its application.

Terminal sterilisation

Terminal sterilisation is by gamma irradiation. The triple-bagged units are placed in a fourth bag, contained within a double-walled shipping cardboard carton. Each carton is subject to an irradiation dose of between 25 and 40KGy at a leading irradiation specialist. The irradiation process is validated to ensure a minimum dose of 25KGy is achieved during the cycle. This dose is then validated using guidelines provided by the Association for the Advancement of Medical Instrumentation, (AAMI), to ensure a sterility assurance level (SAL) of 10⁻⁶. The finished product is subject to sterility testing and endotoxin analysis to ensure compliance with the specification.

Spiriclens® is now replacing in-house facilities for the production of sterile alcohol in WFI in an increasing number of leading manufacturers of sterile pharmaceutical and parenteral imaging agents. The product has gone a long way towards turning around the issue of meeting with guidelines and regulations relating to the sterility of materials used in Grade A and B areas. Outsourcing is now an option that will enable manufacturers to comply fully with all necessary standards relating to sterilisation in a more cost-effective, more efficient way than ever before.