Case study: aseptic processing contamination

Business

A pronounced trend of sterility failures occurred at both the API site and at the customer’s laboratory. It was determined that the contamination occurred during aseptic production of the API.

IGMP Issues Although manufacturing practices at the finished dosage form site were found to be compliant, the FDA identified major IGMP issues at the API site. The design of the process did not assure adequate protection from microbial contamination, and personnel routinely performed many intensive manual manipulations that could imperil the exposed sterile product.

However, the process simulation (I. E. , media fill) program was not adequately representative of the actual manufacturing process.

Examples of process simulation deficiencies included In this case, the production system was most deficient. In addition to aseptic process design deficiencies, the process simulation validation program was inadequate. Without a sufficiently sensitive process simulation program, there was a consequent loss of a media filly’s basic benefits of promptly detecting and diagnosing an existing source of contamination.

In a strong quality system, it is essential that a sound scientific foundation (21) support reliable daily decision making. In particular, good science should pervade a pharmaceutical manufacturer’s approaches to product development, process validation, standard operating procedures (Sops) and investigations. Two of these, product development and process validation, involve studies intended to yield important information about a product or process.

In the event of a poorly conceived study, conclusions based on assumptions may lead to erroneous process design decisions, with a consequent risk to product quality.

A Compliance Policy Guide issued by FDA in March 2004 (22) stresses the importance of cantonal experimental design and continuous learning throughout the product lifestyle. Effective studies reveal the factors that have an influence on process variability. A well-conceived process simulation provides initial and periodic feedback on the state of control of the aseptic process. This information should translate to appropriate decisions throughout the product lifestyle, such as improvements in operational design and monitoring.

Outcome The firm used a microbiological inhibitory material (very high pH) as the medium for the process simulation.

The suitability of the culture medium was not evaluated (e. . , lack of data on inherent growth promotion capability of the move. 59, No. 2, March-April 2005 The API and finished parental lots found to be non-sterile were rejected. Intensive aseptic activity by personnel was considered the route of contamination.

Tater ten repeat tea sterile TTY Taluses, ten Talents prowl II cut manufacturer voluntarily recalled over 50 finished product lots due to concern that these lots were instiller.

The sterile API firm ultimately modified the process to include semi-closed process concepts as well as automation. Case Study 2: Assuring Container-

closure Integrity throughout Manufacture Distributed parental drug product was found to be contaminated with Interconnect cloacae. Testing of previously unopened vials grew this microorganism and others, including Assonants melancholia. Cultures of previously unopened vials grew E.

Cloacae. Patient blood cultures yielded E. Cloacae. It was determined that container-closure integrity of this parental product was lacking.

At least one lot was “ directly implicated” in skepticism, and other lots were thought to possibly pose this hazard. Over 25 reports of skepticism were received by FDA naming the most worrisome lot or “ unknown.

” The firm voluntarily conducted Class 1 recall (“ strong likelihood that product will cause serious adverse health consequences or death”) of more than 10 lots manufactured during the period of concern. Case Study 3: Modified 0. 2-micron Filter Design and Change Control Systems Container-closure integrity problems were identified.

A production operator dropped finished bulk pallets containing sealed glass vials that had already been through secondary packaging. When cleaning the spillage, production personnel also took the unusual step of washing the ostensibly still intact vials with potable water from a nearby sink.

Quality System Context The packaging and labeling system was most deficient in this case. Poor handling of sealed glass vials at the final packaging stage was considered the root cause of the non-sterility. The rough handling of these bulk vials resulted In suddenly Ana enameller cracks In ten vials.

Interconnect cloacae and other microorganisms apparently were introduced to the product when the firm performed the washbowl of the glass vials with potable water. FDA collected several water samples at the firm and the same organism, E. Cloacae, was isolated from the water hose and the sink.

The filter vendor issued a letter notifying customers of he filter design modification and stating that studies indicated that the change appeared to be only a minor one. A critical IGMP concept was reinforced in this case.

While it is routinely stressed that careful controls are needed when the sterile product is exposed during processing, at the essence of IGMP is the principle that every production phase through to packaging must be robust. A firm’s quality system should assure proper design, control, and maintenance of all facets of the manufacturing operation. The facilities and equipment system was most deficient in this case. The change control program within an effective quality system should accurately assess the potential for a problem due to an equipment modification and specify how the significance of the change is to be evaluated.

If product-specific studies (5) had been conducted in this case, major product loss due to equipment failure could have been avoided. Outcome The product was shipped and many Adverse Drug Events (Adds) of skepticism were reported to FDA. Several integrity failures (post-processing) followed, including some double failures of redundant filter con- 120 A filter vendor changed the geometrical design of the outer cage of a 0. 2-micron sterilizing-grade cartridge. The vendor considered the change to be a minor, aesthetic one Tanat would not affect reload TTY or restiveness AT ten Tilter.

However, for their part, the sterile drug manufacturer’s change control system was expected to assess whether the modified sterilizing-grade filter continued to be suitable for its intended use.

PDA Journal of Pharmaceutical Science and Technology figuration’s. The vendor later recalled the filters. Although the vendor conducted some studies before releasing the new filters to the market, the studies did not detect an increased rigidity of the cage that afforded inadequate expansion room to accommodate filter medium swelling during some manufacturing operations.

The lack of adequate expansion room resulted in the rupture of some filters during processing, depending on the liquid being filtered and the processing conditions. Vendor claims and conclusions should be noted.

An essential element in a firm’s quality system, however, is a change control program to adequately assess whether equipment modifications will adversely affect their unique operation. Ultimately, in this case, the affected lots were rejected by the manufacturer, and the firm returned to using the original, suitable filter design.

Case Study 4: Blow-Fill-Seal (BBS) Equipment Design and Maintenance A firm experienced both sterility and media fill failures. Stenographers melancholia was identified as a sterility failure isolate. Media fill isolates included Pseudonymous SSP. And Counteracted SSP.

The blowfly-seal (BBS) processing line had a good prior sterility history. IGMP Issues Mold plates used to form the primary product container were chilled

with cooling water. This demoralized potable water was held in a tank at low temperature prior to use.

When sampled, the cooling water yielded very high microbial counts. Leaks developed n the mold plates, allowing contaminated water to infiltrate into product, causing non-sterility. Based on this significant breach in equipment integrity, among the most relevant IGMP deviations were the unsuitable processing equipment and the lack of an adequate preventative maintenance program.

The facilities and equipment system was most deficient. The unsuitable equipment and inadequate provoke. 59, No. 2, March-April 2005 ventilate maintenance program were key factors in the product contamination. Outcome Both the sterility failure and media fill failure were attributed to contamination by cooling water. Pinhole leaks in the aseptic filling machine’s mold plates allowed cooling water to directly contaminate the product.

The exact date of problem occurrence was unknown, making the corrective and preventative action (CAP) plan more difficult. Numerous lots were rejected. The firm concluded that frequent visual inspections of BBS molds for leaks had not provided for sufficient preventative maintenance, and it implemented corrective measures including regular testing of molding equipment pressure integrity.

Case Study 5: Parental-Grade Drug Substance Pertinacity An API manufacturer produced an active ingredient hat was used to manufacture both impeccable and tablet products. The API was tested against United States Pharmacopoeia (USPS) monograph requirements. It was produced by

a multi- step process beginning with fermentation and ending with purification and isolation steps.

Downsize water was used for cleaning equipment, a dissolution step, and as a washing solvent in the final processing steps, including final purification.

Numerous adverse reactions (including serious pyrotechnic reactions) occurred in patients taking parental products produced by two different dosage form manufacturers who used the supplier’s API. The FDA identified a number of IGMP problems during an international inspection of the API manufacturer. For example, the firm used unsuitable water in final processing steps. The firm lacked an adequate change control system.

No validation was done when the firm scaled-up the process a few years earlier, although multiple significant changes to the process were implemented at that time.

There also was no equipment usage log for a spray dryer (used for multiple products) that was used in the API process. The same person signed as operator and checker for a batch step in many instances. 121 Some of the firm’s records were rewritten without explanation. The possible contributors of antitoxins and any potential capability of the process to destroy or remove indention had not been evaluated.

The inspection review of the process ultimately found that there was little or no opportunity for indention reduction in the process.

The FDA inspection also found that the firm’s composite testing of the finished API had revealed instances of batches approaching, as well as at,

the indention acceptance Limit. Major laudatory controls deviations were found, including a failure of the microbiology laboratory to perform indention controls required by the USPS Bacterial Indention Test. Water used for purification steps and final equipment rinses was not tested for total microbial counts. There was also no program to determine gram stain, or identity, of microorganisms.

The audit of the chemistry laboratory found that impurity tests for the finished API were not validated and that the high performance liquid chromatography system suitability was only conducted monthly. Although the API firm received customer complaints from finished parental manufacturers reporting numerous occurrences of adverse reactions upon administration (infusion) of the firm’s drug, the firm did not adequately identify the root cause of the product safety problem and repeatedly failed to implement an effective CAP plan.

With respect to the API vendor, multiple quality system elements were found to be highly objectionable, as detailed above. In addition, while the API manufacturer’s quality problems were clearly numerous, the materials system of the finished dosage form manufacturers also was in question. It is useful to think back in one’s experience and consider how many times raw material variability has been the origin of a product problem that led to defects, product loss, rejections, or recalls.

This writer has frequently seen inadequate raw materials named as he cause of product quality failures.

In a Complainant quality system, the materials system should provide ongoing assurance of acceptable raw material quality. A different approach to incoming lot testing, or a qualification program that better gauged supplier reliability, might have prevented use of multiple lots of the low quality drug substance (23). For example, 122 conducting an effective audit of a vendor’s facility is a dependable way to prevent a supplier from becoming the weak link in what might otherwise be a strong quality system.

Outcome/Discussion In this case, there was a fundamental failure of the API rim to adequately consider intended use of the API when designing the process. The firm also sold the API for use in nonparallel dosage forms.

The firm used the same manufacturing approach when producing lots destined for parental dosage forms as that for oral solid dosage forms. Overall, ten API Tell Ana very talented c including little assurance of process or laboratory control and unacceptable water systems and standards.

The greatest amount of bacterial indention was contributed during the final wash of crude active. Additional contribution of indention might have occurred during other steps (e. G. , cleaning), in which rinse eater with significant indention load was used to wash product contact surfaces.

When the FDA tested individual samples from discrete parts of drums of a given batch, some of these samples failed USPS Bacterial Indention specifications. Pyroxene testing, performed as part of the Joint FDA and Centers for Disease Control investigation, also yielded multiple pyrotechnic results.

In line with the data seen throughout this case study, however, some of the other samples were non-pyrotechnic. Due to the firm’s lack of process control, there was significant potential for intra-batch variation (I. E.

, drum to drum variability). The firm’s investigations ad used composite samples. Medical practitioners reported over 200 ADDS following administration of the contaminated drug. Recalls and market withdrawals by both the API and finished product manufacturers followed, due to major quality and safety concerns. The FDA placed the API firm on import detention.

The firm remained in this status for multiple years due to failure to reach minimal compliance with IGMP. The firm ceased manufacturing the API that was associated with the Adds. Several years later, under new ownership as well as new quality assurance managers, and after assistance of a consultant, the firm made numerous erections and was allowed to resume shipping other Apish. Case Study 6: Emergence of a Persistent and Problematic Environmental Contaminant A firm experienced multiple media fill failures on a specific line, with the same recurring fungal isolate common to each of them.

While not in the same proportion or frequency as the fungal microbe, some additional microorganisms were also isolated.

Environmental monitoring data did not include any past isolations of this particular organism. Following the media fill failure, the investigation required environmental sampling at various ewe locations in the aseptic processing area. The existing environmental monitoring systems did not

recover this organism before the initial media fill failure. In addition, the environmental monitoring performed during the media fill Taluses 010 not exceed any alert or Acton levels.

However, when ten Tell created an extensive environmental sampling plan as part of the investigation, it identified many instances of this microorganism on the aseptic processing equipment and in multiple locations in the room. The firm came to the conclusion that the organism was on the aseptic processing line and the problem was due to inadequate cleaning and sanitation.

Among the concerns was an area inside a machine panel, located in the critical zone, that had never been cleaned or sampled.

Following the investigation, the machine panel was considered a primary source of the spread of contamination in the class 100 (ISO 5) area and aseptic processing room. The firm fumigated the room to try to control the contamination. However, the firm later reported to the FDA that another media fill failure had occurred with the same fungus present. The firm concluded that more work had to be done to remedy the root cause and then hey would again attempt to perform three successful media fills to confirm the return to a state of control.

After further intensive efforts, the firm restored appropriate conditions for the aseptic production of a sterile drug.

This case study is consistent with what is seen in many cases: once such a contaminant becomes airborne and is allowed to proliferate unchecked, it is

not a simple task to bring the environment back under control. Case Study 7: Extensive Aseptic Interventions by Personnel Approximately 60% of the units run in a media fill were found to be microbiological contaminated. The rim implemented minor corrections to their satisfaction.

The firm then ran three further media fills. A second media fill yielded a high level of contamination. Isolates in both failures were common skin-borne microbes (e.

G. , Staphylococcus SSP.). A sterility failure had also occurred in the prior 6 months. IGMP Issues Multiple significant aseptic maneuvers were required by this small-volume parental process.

Media fill investigations indicated that these steps appeared to pose significant risk to the product. Aseptic gowning by personnel was inadequate. While the facilities and equipment system was clearly