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Feature Article

Batch Failure Rates in Biomanufacturing

Good Training and Investing in the Right Equipment Upfront Are Among Solutions

Eric S. Langer

Batch failures in biopharmaceutical manufacturing are a huge concern due to the cost of the lost batch, the additional work required to clean contaminated equipment, and the delays associated with the lost batch. The 5th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production identified and quantified the leading causes of batch failures based on data from 434 biopharmaceutical developers and CMOs from 32 countries.

With total failure rates around 7%, manufacturers are feeling the pinch. According to Beth Junker, Ph.D., senior director, bioprocess R&D, [Merck Research Laboratories](#), “costs of these failures are often greater than \$1–2 billion.” Dr. Junker notes that the threefold higher contamination rate in the 1,000+ L and <1,000 L facilities, coupled with the fivefold higher loss owing to operator error, suggests the need for more reliable personnel and processing at these larger scales. Some of the differences in scale are likely due to the larger and more diverse product portfolios at smaller-scale facilities.

Failure Rates

Size of production matters when evaluating batch-failure rates. For facilities 1,000 liters and larger, respondents indicated that the highest rates of failure occurred through contamination (average percentage rate 2.3%). For facilities smaller than 1,000 liters, contamination contributed a smaller percentage of failures (0.8%). For the smaller than 1,000 L facilities, the most common cause of batch failures was material failure (1.9%).

Interestingly, the report showed that total (cumulative) failure rates at both large- and small-scale facilities were within 1% of each other (7.6% vs 6.6% failure rates, respectively).

The four most significant reasons for batch failures at both 1,000+ L and <1,000 L scale facilities accounted for 80% of all failures. For the 1,000+ L scale facilities, following contamination, were operator error, equipment failure, and failure to meet specs.

For facilities smaller than 1,000 L, batch failures were due to material failure, equipment failure, product cross-contamination, and contamination. At the smaller facilities, differences associated with more diverse, smaller-scale product portfolios may have been a factor in the differences in causes of failures.

According to industry experts, the three key methods for reducing batch failure rates include implementing a risk-management program, a strong training program, and investing in the right process equipment, according to Michael Larson, manufacturing manager, [CMC ICOS Biologicals](#) risk-management program allows companies to “address potential problems before they happen,” Larson notes.

Training and Equipment

A strong training program that qualifies staff on major process steps, with annual reviews, can be critical in reducing failures. “Successful training includes explanation of the task, successful performance of the task under the trainer’s supervision, successful performance of the task under limited supervision, and a verbal or written test assessing the trainee’s understanding of the task,” Larson states.

Purchasing the right equipment may seem obvious, but according to Larson, “in my experience there have been too many failures because a company did not invest in the correct equipment because it was spooked by the cost. This has been true for everything from large systems all the way down to process hoses.”

According to Colleen Dodson, process engineer at [Biogen Idec](#), batch failures create a significant amount of additional work “to

insure that equipment and transfer lines have been cleaned of the contaminant once it has been identified.”

To combat the costs associated with batch failures she recommends implementing steam-in-place and clean-in-place initiatives, “early on in the purification process, where contamination would probably lead to disposal of the whole batch versus just a portion. Existing processes should be retrofitted with these capabilities if contamination becomes an issue.”

Dodson adds that guaranteeing that processes are automated at all feasible points can help reduce operator errors as well. In addition to automation, “ensuring that batch records are well written and streamlined, so as to not have too much unnecessary information will also reduce operator error.”

This analysis of batch-failure rates quantifies where failures are occurring. With an overall industry failure rate of around 7%, finding better solutions can be a financially responsible activity. Risk-management programs, good training, biting the bullet, and investing in the right equipment upfront, and automating as much as possible can help reduce failures.

When they do occur, initiatives including SIP, CIP, and streamlined records can moderate the effects. The 5th Annual report indicated some secondary reasons for batch failures such as equipment failure and failure to meet product specifications. These may be more difficult to manage, but with proper processes and the right equipment such errors can be minimized.

Eric S. Langer is president and managing partner at BioPlan Associates. Web: www.bioplanassociates.com. Email: elanger@bioplanassociates.com.

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