

Cross-Contamination in Drug Manufacturing: The Regulatory Trends



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Cross-contamination among production lines is an important issue in drug manufacturing, because it can put both patients and workers at risk of adverse health effects. As the global therapeutics markets grow and drugs become increasingly more potent, authorities in the U.S., Europe and elsewhere are tightening regulations to increase safety and control exposure.

Cross-contamination 101

Therapeutics, whether simple tablets or a complex combination of drugs and devices, are generally manufactured in large production plants, run either by originator companies or CMOs (contract manufacturing organizations). To keep costs low and manufacturing efficient, production lines for a range of different active pharmaceutical ingredients (APIs) are often run in parallel.

While this is cost effective, it increases the risk of cross-contamination, where active ingredients from one line can be carried across to the other--through the air, on workers' clothing, or via contaminated equipment. This can place both workers and patients at risk.

If certain sensitizing compounds, such as penicillins and beta-lactam antibiotics, make their way into drug production, they can trigger allergic reactions, even at low levels. The risks range from the inconvenient (hives, a rash, or itchy eyes) to dangerous immune responses, including full-blown anaphylactic reactions, which may be fatal.

Contamination from potentially harmful drugs such as

steroids, hormones, cytotoxics, radiopharmaceuticals, and highly potent active pharmaceutical ingredients (HPAPIs) can cause side effects in workers, especially those who are exposed to them over long periods, and have the potential to place patients at risk as well.



“The contract manufacturing business can be uneven, with potential for times of underutilization. This has been smoothed out and managed through consolidation and increasing the scale of operations.”

DAVID POWELL, COMMERCIAL DIRECTOR, EUROPE AND ASIAPAC, HOSPIRA ONE 2 ONE

What are the regulators doing?

Regulatory authorities across the world have created rules and guidelines as part of good manufacturing practice (GMP) to prevent cross-contamination and in order to protect patients and workers. As these directives continuously evolve, manufacturing technologies change and improve as drugs become more specialized or potent.

While recommendations differ from country to country, the broad trend has been to segregate the manufacturing of specific types of products. “The FDA has been moving towards keeping the manufacturing of penicillin and non-penicillin-based drugs separate over the last 40 years,” says Jim Agalloco, a consultant with Agalloco & Associates in Belle Mead, N.J. However, this separation hasn't always been entirely complete. For example, two



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manufacturing areas may be in separate rooms, but the personnel could share washrooms, locker rooms, meeting rooms and lunchrooms, and the lines may be serviced by the same mechanics.”

The industry is now moving towards much stricter separation. For example, in 1996, the FDA proposed extending its existing guidelines for the separation of manufacturing beyond penicillin to cover cephalosporins and other antibiotics.¹ In April 2013, the FDA put in place further guidelines, requiring penicillin products to be manufactured separately from other drugs, including non-penicillin beta-lactam antibiotics.^{2,3} This latest cGMP framework,⁴ aimed at manufacturers of finished pharmaceuticals and APIs, including repackagers, is similar to the guidelines for penicillins, and includes the following requirements:

- Facility design should ensure that manufacture, processing, and packing of any of the five classes of sensitizing non-penicillin beta lactams (for example cephalosporins) are isolated from those used for other drug products for human use, in order to prevent contamination among different non-penicillin beta lactams, as well as contamination of any other products by non-penicillin beta lactams.
- The air handling systems for non-penicillin beta lactams must be separate from those used for other drugs for human use.
- Manufacturing facilities specific to individual classes of non-penicillin beta lactams do not need separate

facilities and air handling systems, and individual products can be kept separate through production campaigning and cleaning protocols.

- If there is a possibility of exposure to cross contamination, non-penicillin drug products must be tested. If detectable levels of penicillin are found, the products cannot be marketed.

The European Medicines Agency (EMA) has created similar draft updates to its GMP regulations,⁵ stating:

“In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. from live microorganisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working [manufacturing in the same location but separated by time] in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.”



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Some in the pharma industry regard cross-contamination guidelines as confusing and unclear, and are taking a cautious route, seeking to manufacture all of these types of compounds in separate facilities.

“The list is expanding, and even when things aren’t written into guidelines, people are using it as a way to make decisions about manufacturing,” says Dave Powell, Commercial Director, Europe and AsiaPac at Hospira One 2 One. “The draft and published guidelines, and even the anticipation of what might come up next, all have an impact.”



“Other drugs that may be toxic or allergenic need to be manufactured separately for clinical trials. However, these may turn out not to be as toxic as expected, and can go back into ‘mainstream’ manufacturing at the commercial stage.”

JIM AGALLOCO, PRESIDENT, AGALLOCO & ASSOCIATES

Following this type of feedback, the EMA held a workshop in September 2013 to discuss its draft toxicological assessment guidance and GMP updates. At the workshop, the EMA agreed to clarify things further, saying that the toxicological assessment would clarify limits, and the updates would look at how these were applied. For example, confirming which products need to be manufactured in separate facilities.⁶

The impact on the industry

The requirement to manufacture more and more drugs separately will increase both the complexity of the manufacturing process and the overall cost. And it’s coming at a time when the biopharma and CMO industry is moving towards consolidation, in the hopes of making the most of limited resources by managing plants that can manufacture a wide range of different drugs and drug types.

“The contract manufacturing business can be uneven, with potential for times of underutilization. This has been smoothed out and managed through consolidation and increasing the scale of operations,” says Powell. “This drive towards specialization because of segregation undoes some of the benefits of scale, making the business more challenging, especially for midsize CMOs.”

There will also be an impact on staffing logistics. “People who crossover between lines, such as mechanics or supervisors, or those who have to meet up with colleagues for project discussions, or even for lunch, will need to change clothes completely,” Agalloco says. “This increases time away from the manufacturing line, and adds costs such as laundry or disposable protective clothing.”

These increases in complexity and cost could have a number of ancillary effects. Building separate lines for individual drugs is expensive, so the impact will be particularly strong on products with tight margins, such as over-the-counter drugs, generics, and some medicines



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aimed at small patient populations. “We are starting to see a rise in CMOs that specialize in particular drug types, such as cephalosporins. However, this is ‘big bucket’ manufacturing--there will still be issues with smaller products,” says Agalloco.

Tightening manufacturing regulations could also affect innovation by increasing the cost of producing clinical trial material, particularly for research-stage companies looking to develop drug combinations that cross over among areas affected by the guidelines.

“Known cytotoxics and cephalosporin-based drugs for clinical trials will have to be manufactured separately,” Agalloco says. “Other drugs that may be toxic or allergenic need to be manufactured separately for clinical trials. However, these may turn out not to be as toxic as expected, and can go back into ‘mainstream’ manufacturing at the commercial stage.”

The challenges could make investors less willing to fund early-stage products, unless they can be persuaded that the payoff will be worth the added investment required to meet manufacturing challenges. “Investors are much more wary at the moment, and are likely to scrutinize the manufacturing process, even with products that are still in early clinical development,” Powell says.

Finding a solution

There are a number of possible approaches the pharma and CMO industries can take to deal with the tightening regulations in drug manufacturing. This includes networking and forming more informal partnerships.

For example, rather than turning customers away when products don’t fit into a CMO’s manufacturing profile or skill set, the company could recommend certain allied specialist CMOs that focus on specific manufacturing challenges, such as controlled substances requiring DEA licenses. CMOs, particularly larger ones, could also create formal partnerships by merging with specialist CMOs, making it possible to provide a full-service offering at a number of different locations.

Originator companies might consider investing in manufacturing facilities again, rather than relying on outsourcing. During slow periods, they could hire out any capacity that’s not being used. One company pursuing this approach is GlaxoSmithKline, which has in-house specialist contract manufacturing services for cephalosporins and penicillins in Mexico, the U.K., France, Italy, and China. Pharma companies could also form consortia to buy out or build specialist facilities for collaborative in-house use.

The specialization of the industry potentially opens up opportunities for smaller CMOs that are willing to take the risk of focusing on products such as cephalosporins or penicillins. According to Powell, “Innovation of products that require very specific skills and manufacturing conditions, such as antibody-drug conjugates (products that combine cytotoxics and biologic)s, is also driving segmentation.”

As categories get narrower and narrower and manufacturing becomes more specialized, however, the potential market gets smaller. If the industry is left with


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only one or two players in certain areas, customers will have fewer choices. And if CMOs are able to operate at a premium, it will drive up costs and even extend timelines. It could also leave customers vulnerable if there are hold-ups or problems in production, or quality or compliance issues, as there may be no redundancy built into the system. To combat the rising costs, pharma companies may reach out to low-cost manufacturing regions such as India, China, Latin America, and Eastern Europe.



“A worker could be exposed to microscopic levels over 7 hours and 52 minutes of his or her day. However, for 8 minutes, during equipment breakdown, the levels spike.”

CHRIS ROMBACH, BIOPHARMA MARKET MANAGER, ILC DOVER

An alternative solution: The risk-based approach

The segregated approach to manufacturing focuses on taking as much potential risk as possible out of the system. But as more complex drugs are added to the equation, manufacturing will become more difficult and costly. “The drivers are protecting workers from toxic drugs and protecting patients from cross-contamination. Allergies to penicillins can be dangerous and life threatening, but where do we draw the line?” Agalloco says. “Is any risk ever acceptable? Or is it ever realistic to expect to eliminate all risk?”

An alternative solution is to focus on acceptable levels of risk, which will vary from product to product, and then create risk-reduction strategies around them. This type of approach needs to consider both the short- and long-term effects of exposure, especially if the process has the potential to lead to spikes in contaminants.

“A worker could be exposed to microscopic levels over 7 hours and 52 minutes of his or her day. However, for 8 minutes, during equipment breakdown, the levels spike,” says Chris Rombach, biopharma market manager at ILC Dover, a U.S. company focusing on packaging and processing solutions. “This means that while the all-day limit is not exceeded, the short-term limit is. This is why it’s important to look at both.”

The Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP), developed by the International Society for Pharmaceutical Engineering (ISPE) and based on ICH Q9 Quality Risk Management, is a risk-based approach designed to manage cross-contamination risk, while balancing product and operator safety. This approach uses risk-assessment protocols to calculate health-based acceptable daily exposure (ADE) figures, which are then used to calculate the maximum levels of cross-contaminants that can be allowed in finished products. These calculations are based on animal and human toxicological and clinical data.⁷ The FDA has been involved in the development of the Baseline Guide, published in 2010.¹

The EMA issued draft guidance in December 2012 that looked at permitted daily exposure (PDE) and threshold



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of toxicological concern (TTC) based on toxicological and pharmacological clinical and non-clinical data. In a health-based approach, PDE represents a level of a specific compound that would be unlikely to cause harm if an individual were exposed to it daily for life.^{8,9}

These approaches may eliminate the need for dedicated plants, potentially holding down costs and maintaining flexibility for multiproduct plants. Ideally, the approach needs to be harmonized across the major global regulatory authorities, but basing the reduction of cross-contamination on PDE or ADE figures could be a real opportunity for CMOs, which have many years of expertise of working within multiproduct manufacturing environments. “It is possible to create a containment system that makes mixed manufacturing less of a risk,” Rombach says. “The solution would be a well-characterized and well-defined process, including management of product handling and containment.”

To manage risk-based manufacturing, suppliers are developing new products for both traditional and single-use processes, including adapting single-use technologies for use in traditional pharmaceutical manufacturing. “This could drive single-use products into small molecule manufacturing, as a way to reduce costs associated with cleaning and post-cleaning validation. Single-use technologies can be retrofitted into existing facilities,” Rombach says.

The future of cross-contamination

Cross contamination is and will continue to be a major issue for drug manufacturing. There are several potential solutions, from working with niche manufacturing companies to changing the regulations. To benefit both the patients and the workers, the long-term solution is likely to be a collaborative one, with input from all parties. “We need to have a dialogue between the people who work on the manufacturing lines, the designers and the regulatory authorities,” Agalloco says. ■

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