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Maximize Contamination Control by Lifecycle Assessment of Microbiological Risk

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Good decisions are derived from accurate, timely information combined with adequate knowledge related to the problem being solved. Today's pharmaceutical environment requires decisions about risk and contamination control. A mentality that incorporates a lifecycle or holistic approach to microbiological contamination control has been proven to be successful.

International Conference for Harmonisation (ICH) Q9, *Quality Risk Management* (1) has sections that are important to different professionals in a pharmaceutical business. For microbiological risk, the combination, and not independence, of all of these sections for risk assessment is crucial. A broad view and approach is the best way to assess and manage risk for microbiological control.

This lifecycle thought process fits all types of pharmaceutical areas, including sterile and non-sterile classical pharmaceuticals, biopharmaceuticals or biologics, consumer health nutraceuticals, or herbal products.

Quality professionals have a wide breadth of experience in our industry. Impact of this experience can be proven in manufacturing at commercial, clinical, or pilot scale along with quality control or quality assurance. Bringing together the perspectives from different phases of pharmaceutical development; from scale-up to commercial manufacturing, shelf-life storage, and patient use; can broaden our understanding. In each of these phases, a contamination control mindset plays a key role in developing and producing a product with reduced microbiological risk.

Drug Development

The first phase of a drug's lifecycle is drug development. The most important intent in risk determination is, of course, the patient's safety. Second is the risk to the product.

Patients depend on their products to be safe from contamination when they first, and continue, to use them. Remember, patients don't ask the question, "Is this product microbiologically safe for my child, my parent, my sibling, my significant other, or for me?" Patients inherently accept and take for granted that a drug product has already gone through scrutiny and preventive measures to ensure safety from microbial contamination. This is the foundation that risk must be built upon.

A set of three parameters are commonly used to develop our understanding of risk related to patient safety. In drug development, one must generate as much knowledge as possible that is related to these parameters. The following explanations will help define these parameters:

- **Route of Administration**: This is really how the drug will be delivered to the patient—method, mechanism, or body part in which the drug impact the most.
- **Patient Health** and **Type**: This is the real-time health of a patient receiving the drug, and this is an aspect of age, culture, and pre-disposed conditions that could be environmentally imposed.
- **Target Dose Intent**: That is the target organ, region, or breadth of exposure to the human body.

Let’s consider the first parameter, “Route of Administration.” Risk relates directly to areas of the body where preventive measures are inherent yet may be ineffective due to the administration of a drug. For instance, highest risk is assessed to parenterals; which include intravenous, intramuscular, and some subcutaneous injections; because the administration of drug bypasses the protective layers of skin and derma and penetrates directly into the bloodstream (2). Ophthalmic and otic administration is directly on or through mucosal layers.

What about topicals for wounds or abrasions? Topicals for treatment of wounds contact abraised or broken skin as well as exposed mucosal areas.

Inhaled or intranasal drugs enter directly into the lungs or cavities, where much protection is on the external portion of the body (such as the nose and mouth). Tablets and capsules go through the gastrointestinal tract and are exposed to changing pH conditions, which lead to lower risk; chances are that the normal flora of those areas are higher in levels and species diversity than what a product may inherently contain.

The second parameter, “Patient Health and Type,” sometimes contains such information that is not known except for the initial intent of the drug. This area can be problematic if sufficient information is not available at time of assessment. Ongoing assessment post-approval (i.e., post-drug approval) is strongly recommended by the author. As potential patient populations can change or expand, assessment should be re-visited.

Patients can have chronic or acute disease conditions, and if they have more than one, these can complicate the decisions. As might be expected, immune-compromised patients carry the most risk in most circumstances (3), but the question that has been posed many times is, “Should we always consider that an immune-compromised patient may be using any drug?” This could be considered either a “conservative” approach or an “overkill” approach, which may lead to unwarranted restrictions on product testing criteria. Think about it. Is the use of “all possible patient health and types” approach practical, and does it offer reasonable cost-benefit impact on patients or products? The key information is the “intended” patient population, supported by manufacturing controls to assure a consistent, high-quality product.

“Patient Type” also leads into the discussion about impact based on body prevention from contamination, maturity, or loss of maturity of preventive mechanisms of the human body (due to age) and environmental conditions that can impact preventive mechanisms of the body (4). This parameter can be very broad. For example, inherited pre-disposition can be detrimental to preventive mechanisms; thus, patients with sickle cell anemia or certain types of lymphomas may be impacted by the microbiological quality of the drugs they take.

The third parameter is the target of the drug. The intent of the drug indicates where in the body the drug target is, how the drug will be assimilated (pharmacokinetics and pharmacodynamics of a drug), and what challenges come from that particular target or region. Antimicrobials can go throughout the body and become systemic. Cancer therapy also may be broad in application or specific in target area. Dialysis impacts the flow of fluids and can impact body areas broadly (e.g., regionally).

Building Better Understanding in Other Areas

Other useful information can be used in our risk assessment. How the product is going to be used can be very helpful input. In other words, is a doctor, nurse, or physician going to administer the drug? Will the patient be self-medicating or self-administering the drug(s) as compared to being given the drug at a hospital, clinic, or doctor’s office? Is the drug a multi-dose delivery product or for single dosing? Will a multi-dose product be infused over time, implanted internally, or be dosed from a patch on the exterior of a body?

Possibly adding risk to the picture, one should determine if there will there be any compounding occurring prior to patient administration. If so, will compounding occur at a pharmacy or at a compounding “facility”? In some cases, learning from negative events can lead to better controls. Take, for example, a 2012 recall (5) from a New England drug compounding facility, where subject compounded drug preparations led to numerous deaths.

Formulation Control

Mentioned earlier was that the foremost importance of risk is patient safety. A not too distant second in importance is product quality since that also can impact patient safety. There will always be risk to the patient if product quality is not adequate. A compliance risk is also possible if there is no control over current good manufacturing practices (cGMPs) (6), and that leads to product quality issues.

Microbiological contamination can cause:

- Degradation of product: This can lead to potential lack of product efficacy.
- Growth and replication of microorganisms in product: This could lead to potential infection or opportunistic infection of patient.

Understanding the nature of the product formulation can assist in understanding the impact of contamination. Contamination is a cGMP issue. If something goes wrong or is not controlled well, it can become a health issue; thus, it could lead to inspection, possible regulatory findings, or a halt to manufacturing. One must recognize the cascade of problems if microbiological quality is not controlled well.

Contamination is also a quality issue. Determining risk and the parameters to consider are the first steps to a high-quality product. Next, to close the loop, one should discuss control (or mitigating risk). In development, keeping the end in mind, one is trying to design and develop a microbiologically robust formulation. Taking the holistic approach, which means thinking broadly in a sequential manner of how a product is developed, one wants to first understand and gain knowledge about the raw materials (i.e., the excipients, the active ingredient, and any components).

The knowledge we want to gain concerns the origin of raw materials and any inherent risks for bioburden or endotoxin. This means evaluating the input materials, identifying if they indicate potential for being a carrier of bioburden or endotoxin, and determining whether they can support proliferation of microorganisms.

Assessing origin and handling in simple terms is determining if material is from an animal or plant or if it is a mineral. If organic material is packaged in containers that lack protection from changing environmental conditions, then actual conditions of storage, transport, as well as regional environmental challenges can directly impact the quality related to microbiological content (7).

It is important to understand the process that produces the excipient or converts material into the excipient. Often, one can attain this information from the manufacturer or can seek it out from a resource such as the *Handbook of Pharmaceutical Excipients* (8).

Evaluation of the process can lead to identification of the existence or non-existence of microbiological controls and determination of if they are inherent or directly intended for purpose. Adequate sampling and testing may or may not be performed by the manufacturer. Evaluation of sampling can determine if the sampling is truly representative of the batch. The testing should be adequate for its intended purpose. Because one often depends on a supplier’s Certificate of Analysis to indicate state of control and specification compliance, integrity of testing is important.

Origin of the materials can provide key information, yet a synthetic process reduces risk of microbiological challenge. For biological actives though, origin is very critical. There are bacteriological, mammalian, and plant sources that carry risks. For any active ingredient from a biological or synthetic process, process control is a key to learning risk. Biological process control has well-developed control points. Synthetic process control is mainly the impact of chemical and physical steps that add coincidental microbiological control (e.g., pH, solvent usage, drying, high and low temperature extremes, along with any complementary processes such as milling or filtration).

Primary components that are in contact with the product are packaging and any delivery device component parts (such as valves, tubes, actuators, droppers, pumps). Secondary packaging design can also enhance protection from microbiological contamination during shelf-life and use by restricting access by contaminants. Examples of this type of design are inhalers, desiccants used with tablets or capsules, intra-nasal closures, and use of a screw-cap closure versus a flip-top cap. In summary, the basis of developing a microbiologically robust formulation (9) comes from:

- Good understanding of the raw materials used and how they are controlled.
- A formulation that has inherent antimicrobial properties (or is preserved).
- The nature of the product and route of administration are understood.
- If contaminated, understanding if the product can enhance or prevent proliferation.
- Appropriate packaging that can prevent contamination.

If one has a robust formulation, half the battle of contamination prevention has already been won.

Process Control

The other area to develop better understanding for contamination prevention is the process, including process control. The cGMPs lay the foundation for adequate conditions in a general sense. Cleanliness of a manufacturing operation includes control of air quality as well as surface cleaning and disinfection in manufacturing areas. There should be an appropriate frequency of cleaning, adequate choice and use of disinfectants, and appropriate methods of storage of equipment. Monitoring can be used to determine the frequency and efficacy of cleaning methods and materials.

There are numerous opportunities for exposure of product, from raw material dispensing and intermediate processing to the finish/fill operations; each has its own inherent challenges.

Be aware of control needed for upstream processes unless there are solid downstream controls (e.g., open versus closed vessels and transfers of intermediates from one stage to another). Just as risk determination for formulation during development is a useful activity, risk assessment for manufacturing is valuable as an evaluation of the controls and how they may impact contamination. Bioburden or bacterial endotoxin may be appropriate critical quality attributes given the nature of the process and product being assessed. Similar to hazard analysis critical control points (HACCP) terms, one would seek to identify any microbiological or bioburden control points in a process prior to the packaging of the finished product. The same approach is referred for identifying endotoxin control points in the process if the product has pyrogenic implications to the patient.

What one does with this knowledge and information that is gathered for a risk assessment is the key to its value. Multiple quality tools can be utilized to help organize the information and provide a framework for assessing risk and evaluating gaps in knowledge (10).

Supply Chain Challenges

What happens to product after it is packaged can be well choreographed or mysterious. Professionals are concerned about protection from contamination because something can happen that allows contamination to adulterate the product. One needs to think ahead of what the possibilities are for the packaged product so that quality can be designed as another preventive measure.

In a warehouse, conditions should be controlled to protect the product, but one should understand what the implications are for uncontrolled temperature and humidity relevant to microbiological challenge. The modern distribution system is usually well controlled, but that does not mean that product cannot be mishandled at some point in time; that is, how often have we seen or heard about extreme temperature conditions or breakage of glass containers? For example, the following is consistently brought to our attention:

- Unseen cracks in vials or syringes that can lead to microbiological issues
- Temperature impact on formulation that can lead to preservative ineffectiveness
- Humidity in hot climates that can lead to fungal growth inside caps or on outside of packages.

Consideration of who doses the medication was mentioned previously. This has an impact on risk. There is risk during compounding if it is not done under adequately controlled conditions based on product type. Furthermore, one does not always know precisely how adequately drugs are handled in the pharmacy and hospital environments. One can learn much by reading the package insert with a drug intended for self-medication. Packaging is a key protective measure for microbiological challenges and for maintaining shelf-life quality. Looking at the drug instructions, packaging, and expiration date can help indicate how robust they must be to minimize contamination before or after use (opening), including multi-dose packages.

The highest risk compounded drugs are sterile drugs. Some non-sterile drugs also carry a high-risk because they can become contaminated with opportunistic pathogens or strict pathogens. For any drug compounding, one should look to see what controls are in place to minimize contamination.

Determination of who oversees these controls can help verify that they exist and that they work. Being aware of what happens to a drug after the manufacturing process is completed can be an important step. A recent review and sharing of concerns by US Food and Drug Administration about the handling of sterile drugs in clinical or hospital pharmacy environments has led to more scrutiny about handling practices as well as in-use expiration dating. Current expectations by new drug review scientists

are for performing challenge studies (11).

Awareness is another strong expectation. For example, it is useful to know that some single dose parenterals could possibly be handled as if they were a multi-dose product. By having this awareness, one can build in robustness.

Again, packaging is a first-line preventive tool for microbiology. It should not be taken for granted. The type of packaging microbiologically impacts shelf-life in addition to other quality attributes. Package integrity testing can develop confidence in package integrity or seal integrity during development and transfer to commercial production. Two control aspects revolve around package integrity. One is design, and the other is verification testing. Containers and closures should have defined, verified specifications and be fit-for-purpose. Incoming component inspection and quality acceptance levels are performed to track compliance with specifications. Integrity testing of packaging should be appropriate for the package types. Testing can also occur through the lifecycle of a product to ensure integrity is consistent. Collaborating and consulting with packaging experts will enhance development of robust package integrity and help said experts understand the microbiological issues (12, 13).

Conclusion

Holistic thinking is the smartest approach to risk determination. Taking into account the lifecycle of a product from control of input materials to use of a product by the patient, broad use of information, knowledge, and common sense will make microbiological risk assessment a scientifically driven process. Good decisions come from a combination of scientific thinking and common sense.

References

1. ICH Q9, *Quality Risk Management*.
2. D.C. Singer, “Risky Business,” *Quality Progress* **44** (7), 44–53, 2011.
3. T. Sandle, “Dimorph and Filamentous Fungi,” in M.T Mascellino, *Bacterial and Mycotic Infections in Immunocompromised Hosts: Clinical and Microbiological Aspects*, OMICS Group Inc., Henderson, NV, 2013.
4. S. Sutton and L. Jimenez, “A Review of Reported Recalls Involving Microbiological Control 2004-2011 with Emphasis on FDA Considerations of ‘Objectionable Organisms’” *American Pharmaceutical Review* **15** (1), 42–57, 2012.
5. FDA Safety Notice, “Fungal meningitis outbreak,” December 12, 2012.
6. *Code of Federal Regulations,* Title 21, Food and Drugs (Government Printing Office, Washington, DC), Parts 210 and 211.
7. L. Clontz, *Microbial Limit and Bioburden Tests: Validation Approaches and Global Requirements*, CRC Press: Boca Raton, FL, 2009.
8. R.C. Rowe, et al., *Handbook of Pharmaceutical Excipients*, American Pharmacists Association and Pharmaceutical Press, 2012.
9. D. Singer, “A Strategy for Developing Robust Pharmaceutical Microbiological Control. *American Pharmaceutical Review* **15** (5), 58–65, 2012.
10. N.R. Tague, *The Quality Toolbox*, ASQ Quality Press, Milwaukee, WI, 2005.
11. J.W. Metcalf, “Microbiological Quality of Drug Products after Penetration of the Container System for Dose Preparation Prior to Patient Administration,” *American Pharmaceutical Review* **12** (1), 84–89, 2009.
12. T. Sandle, “Container Closures for Pharmaceutical Preparations: A review of Design and Test Considerations,” *BioPharm International* **25** (12), 32–36, 2012.
13. *USP* Chapter <1207> “Sterile Product Package Integrity Evaluation.”
