Microbiological Quality Considerations in Non-sterile Drug Manufacturing

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2021
Pharmaceutical Quality/Microbiology
Pharmaceutical Quality/Manufacturing Standards (CGMP)

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Microbiological Quality Considerations in Non-sterile Drug Manufacturing Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist manufacturers in assuring the control of microbiological[2] quality of their non-sterile drugs (NSDs).[3] The recommendations herein apply to solid non-sterile dosage forms, as well as semi-solid, and liquid non-sterile dosage forms (e.g., topically applied creams, lotions and swabs, and oral solutions and suspensions). NSDs can be prescription or nonprescription drugs, including those marketed under approved new drug applications (NDAs) or abbreviated new drug applications (ANDAs), and nonprescription drugs without approved new drug applications which are governed by the provisions of section 505G of the FD&C Act (often referred to as over-the-counter (OTC) monograph drugs).[4] These recommendations, if followed, will also assist manufacturers in complying with the current good manufacturing practice (CGMP) requirements for finished pharmaceuticals and active pharmaceutical ingredients (APIs).[5]

This guidance discusses product development considerations, risk assessments, and certain CGMPs that are particularly relevant to microbiological control in a manufacturing operation for a NSD. It also provides recommendations to help manufacturers assess the risk of contamination of their NSDs with objectionable microorganisms in order to establish appropriate specifications and manufacturing controls that prevent such contaminations and assure the safety, quality, identity, purity, and efficacy of the NSD.[6]

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, the terms "microbiological" and "microbial" are used interchangeably.

[3] For the purposes of this guidance, non-sterile drugs (NSDs) refers to non-sterile finished dosage forms.

[4] The term 'OTC monograph drug' means a nonprescription drug without an approved new drug application which is governed by the provisions of section 505G. See FD&C Act section 744L(5).

[5] See 21 CFR parts 210 and 211, CGMP for Finished Pharmaceuticals, and FD&C Act section 501(a)(2)(B) for APIs.

[6] The term "objectionable microorganisms" as used here refers to organisms that are objectionable due to their detrimental effect on products or potential harm to patients or objectionable due to the total number of organisms. See 43 FR 45053 (Sep. 29, 1978).

For application products (i.e., NDAs, ANDAs) this guidance also explains how applicants should submit NSD controls in original submissions and report changes in microbiological specifications and testing programs to the FDA, in accordance with current Agency guidances regarding changes to an approved application.

To illustrate the importance of a microbiological risk assessment and control strategy, this guidance discusses incidents of *Burkholderia cepacia* complex (BCC) and other microorganism contamination in non-sterile dosage forms that resulted in adverse events and recalls of the drug products. The guidance describes proper prevention of and testing for BCC in aqueous dosage forms of NSDs.

The guidance describes the Agency's current thinking on microbiological contamination of topical antiseptic drugs intended for use by health care professionals in a hospital setting or other health care situations outside the hospital,[7] which are used prior to medical procedures to reduce the number of bacteria on the skin and that in some cases are not manufactured as sterile products.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA's guidance documents should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

This guidance was developed, in part, as a result of the Agency's review of FDA Adverse Event Reports (FAERs)[8] and recalls involving contamination of non-sterile dosage forms. A review of FAERs that occurred between 2014 and 2017 revealed 197 FAERs associated with intrinsic[9] microbiological or fungal contamination, and of those, 32 reported serious adverse events. Because spontaneous reports[10] in FAERs are voluntary by definition, the Agency anticipates a degree of underreporting. The actual number of incidents associated with microbiological contamination is likely significantly higher than the number of events reported.[11]

[7] Such products include health care personnel hand washes, health care personnel hand rubs, surgical hand scrubs, surgical hand rubs, and patient antiseptic skin preparations (i.e., patient preoperative and preinjection skin preparations).

[8] FDA Adverse Event Reporting System (FAERS) Latest Quarterly Data Files - https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm.

[9] *Intrinsic* means the microbial or fungal contamination originated with the manufacture, packaging, shipping, or storage of the drug, not from extrinsic sources, (e.g., consumer or health care provider use errors).

[10] For definition of *spontaneous report* see FDA's The Public's Stake In Adverse Event Reporting - https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm179586.htm.

[11] According to FDA's Question and Answers on FAERs, "FDA does not receive reports for every adverse event or medication error that occurs with a product…There are also duplicate reports where the same report was submitted by the consumer and by the sponsor [drug manufacturer]." https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/.

The review of voluntary recall actions during the same time period revealed over 50 events associated with objectionable microbiologically contaminated NSDs.[12] The recalls showed that a wide range of objectionable microorganisms were found in both aqueous and non-aqueous NSDs.[13]

The Agency is also aware of specific concerns regarding BCC and its association with contamination of aqueous-based NSDs that resulted in a number of serious adverse events, i.e., infections and deaths.[14] In May 2017, FDA released a statement[15] alerting drug manufacturers of the recent product recalls associated with the presence of BCC in NSDs. The statement also reminded drug manufacturers of their responsibilities to prevent objectionable microorganisms from adversely impacting their NSD manufacturing processes, as well as the products themselves.

Analysis of these events, combined with FDA's experience conducting microbiology assessments of non-sterile drugs for NDA and ANDA products and compliance actions, helped to inform the recommendations in this guidance.[16]

III. STATUTORY AND REGULATORY FRAMEWORK

Under section 501(a)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act),[17] a drug will be deemed adulterated if:

> "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess," or "if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health."

For finished pharmaceuticals, the CGMP regulations described in 21 CFR parts 210 and 211 address prevention of objectionable microorganisms in non-sterile drug products, bioburden specifications, and in-process testing. Specifically:

[12] See footnote 6.
[13] FDA Recalls, Market Withdrawals, & Safety Alerts - https://www.fda.gov/Safety/Recalls/default.htm.
[14] Glowicz J et al, 2018, A multistate investigation of health care–associated Burkholderia cepacia complex infections related to liquid docusate sodium contamination, January-October 2016, Am J Infection Control, Vol 46: 649-665, https://www.ajicjournal.org/article/S0196-6553(17)31287-7/fulltext.
[15] FDA advises drug manufacturers that Burkholderia cepacia complex poses a contamination risk in non-sterile, water-based drug products, May 2017, https://www.fda.gov/Drugs/DrugSafety/ucm559508.htm.
[16] CDER began chemistry, manufacturing and controls (CMC) microbiology reviews of NSD in the mid-1990s with a focus on aqueous based NSDs.
[17] See 21 U.S.C. 351(a)(2).

21 CFR 211.113(a), Control of microbiological contamination, states that appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

21 CFR 211.110(a)(6), (b), (c), Sampling and testing of in-process materials and drug product, requires (where appropriate) in-process bioburden testing and valid in-process specifications to assure the drug product meets its microbiological specifications. In-process testing shall occur during the product process, e.g., at commencement or completion of significant phases or after storage for long periods.

21 CFR 211.84(d)(4) and (6), When appropriate, components shall be microscopically examined. Each lot of a component, drug product container, or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

To assure the microbiological quality of NSDs subject to premarket approval, applicants must propose appropriate drug substance and product specifications (i.e., tests, analytical procedures, and acceptance criteria) in their submissions in accordance with 21 CFR 314.50(d)(1) [NDAs] and 21 CFR 314.94(a)(9) [ANDAs].[18]

In general, a drug with a name recognized in an official compendium must comply with the United States Pharmacopeia (USP) compendial standards for identity, strength, quality, and purity, or be deemed adulterated, misbranded, or both.[19] If USP has established a monograph for a drug, the USP monograph will identify the official tests, procedures, acceptance criteria, and other requirements. When USP monographs include a test or specification referencing "Applicable General Chapters,"[20] the applicant should ensure that their monograph product complies with the testing requirement, or it could be deemed adulterated. Some of the USP General Chapters that are more commonly referenced in drug monographs, as they apply to controlling microbiological activity in NSDs, include, for example:

- USP <60> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS TESTS FOR BURKHOLDERIA CEPACIA COMPLEX
- USP <61> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: *Microbial Enumeration Tests*
- USP <62> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: *Tests for Specified Microorganisms*

[18] For the definition of specification, see 21 CFR 314.3(b) and also ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000).

[19] FD&C Act 501(b) and 502(e)(3)(B) and (g); also 21 CFR 299.5.

[20] See USP, Conformance to Standards, 3.10, "Applicable general chapters" means general chapters numbered below 1000 or above 2000 that are made applicable to an article through reference in General Notices, a monograph, or another applicable general chapter numbered below 1000."

In addition to USP monograph requirements, further microbiological tests are often performed as part of batch release requirements as described in 21 CFR part 211.[21]

Objectionable microorganisms and bioburden in non-sterile APIs should be controlled. FDA guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016) states:

> "Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include control of impurities (e.g., organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable microorganisms should be established and met."

IV. MICROORGANISMS AND LIFECYCLE PRODUCT QUALITY

A. General — Microbiological Concerns Regarding NSDs

Prevention, control, and monitoring of the microbiological population in non-sterile drug components and drug products are necessary to minimize the risk of:

- patient exposure to significant numbers or harmful species of microorganisms, especially in immunocompromised patients[22]
- patient exposure to harmful microbial metabolites and/or toxins
- drug spoilage or degradation

The statutory and regulatory framework described in section III above, coupled with sound scientific rationale, provides the foundation for establishing a program to monitor and control the manufacturing process to prevent objectionable microorganisms from affecting the quality of a NSD.

To ensure product quality and patient safety, it is essential to limit the level and type of microorganisms in NSDs during manufacturing and over product shelf life. While a NSD is not required to be sterile, there is a threshold of microbiological content above which safety and efficacy of a given NSD may be adversely impacted.

The CGMP regulations require that components are sampled, tested, or examined prior to release by the manufacturer's quality control unit.[23] Naturally-derived components (e.g., plant or animal derived ingredients, and naturally occurring ingredients such as water) may contribute significantly to the total bioburden of the drug product and must be subjected to microbiological

[21] CGMPs are not limited to drugs marketed under approved applications. See FD&C Act section 501(a) and 21 CFR parts 210 and 211.

[22] For the purposes of this guidance, we define immunocompromised patients as those who have a weakened immune system, which may be due to trauma, surgery, illness, or chronic disease. It also includes vulnerable populations, such as infants and the elderly.

[23] See 21 CFR 211.84.

testing in accordance with established procedures.[24] For instance, water is a common component used in NSD manufacturing. However, water system control deviations can be difficult to detect due to limitations of sampling.[25] These deviations may lead to the formation of biofilms and have been shown to have a profound impact on microbial quality of an aqueous-based drug. Consequently, proper water system design and control, appropriate microbial action limits,[26] and routine water quality testing is critical to assuring that microbial levels are below established limits, and that the water is free of objectionable microorganisms.[27] Therefore, it is important for manufacturers to have a robust design for water systems, including controls designed to prevent objectionable microorganisms and procedures for monitoring, cleaning, and maintenance.[28]

Aqueous non-sterile products, which may support microbial growth during the product shelf life due to their water activity (a_w),[29] should be designed to prevent microbial proliferation of intrinsic microorganisms or those inadvertently introduced during use. While the potential for microbial growth during the manufacturing process or over storage through the shelf life can be partially mitigated by a properly designed preservative system or formulation, antimicrobial preservatives can provide a false sense of product safety regarding the presence or growth of microorganisms. Two purposes of a preservative are to counteract possible incidental microbial contamination during multiple uses of a product by a consumer and maintain microbial control over the shelf life of the product. Preservatives are not a substitute for a comprehensive approach to preventing objectionable microorganisms from contaminating NSDs, and should not be presumed to reduce in-process bioburden during manufacturing. Certain microorganisms have been found to degrade commonly used preservatives, despite the drug having previously met antimicrobial effectiveness testing acceptance criteria. Consequently, non-sterile drug manufacturers should be aware of the potential for the development of preservative resistance. This potential decrease in preservative effectiveness should be investigated (root cause analysis and corrective action to eliminate the source of contamination) in cases of objectionable microbes or an upward trend in total microbial enumeration counts. This issue is discussed as a special case study regarding *Burkholderia cepacia* complex and Aqueous Drug Products in section IV.C.3.a Microbial Considerations – Special Cases of this guidance.

In contrast, many non-sterile liquid products that are not aqueous-based, such as those containing high percentages of alcohol or other non-aqueous solvents, can potentially pose lower risk of microbial proliferation during processing, holding of in-process materials, and storage over shelf

[24] See 21 CFR 211.84(d) and 211.113(a).

[25] An effective and ongoing monitoring program is important in determining if water used to support batch manufacture continues to meet predetermined quality characteristics. For products that include water in manufacturing operations, more sensitive water sampling strategies are generally appropriate, and should include use of larger sample sizes (e.g., 100 mL) with membrane filtration.

[26] *Microbial action limits* should be established based on the risk-based impact assessment, as described in section IV.B.

[27] See 21 CFR 211.84(d).

[28] See 21 CFR 211.63, 211.67, 211.100.

[29] It is important to note that water activity is different from water content. USP <1112> defines water activity as the ratio of the vapor pressure of water in the drug, when in a completely undisturbed balance with the surrounding air media, to the vapor pressure of distilled water under identical conditions. See USP <1112> APPLICATION OF WATER ACTIVITY IN DETERMINATION TO NONSTERILE PHARMACEUTICAL PRODUCTS. In contrast, water content is the amount of moisture in the drug.

life.[30] Also, non-sterile solid drug products, such as tablets and capsules, have a low water activity that usually does not allow for microbial growth during product shelf life. However, it should be noted that although microorganisms that are present in a non-sterile drug product with low water activity will not proliferate, they can persist in non-aqueous liquids and dry products throughout the shelf life of the product. The CGMP regulations require that written procedures be established to prevent introduction of objectionable microbiological contamination in the manufacture of drug products not required to be sterile, and that a program be designed to assess the stability characteristics of drug products, including NSD.[31] Consequently, it is important to provide for appropriate microbiological control of the components (e.g., excipients and APIs) of non-sterile drug products, even if the components possess a low water activity.

Non-sterile solid drug products also can be at risk for microbial proliferation through contamination during manufacturing. For example, extended in-process hold times of aqueous solutions or slurries at various points in the manufacturing process of a solid drug product could allow for microbial proliferation exceeding the appropriate levels for such dosage forms. Consequently, procedures that establish time limits are essential to assure product quality, including control of microbiological quality, at each process step used in the manufacture of both liquid and solid NSDs to prevent objectionable microorganisms.[32]

While not exhaustive, the USP provides a widely accepted set of microbiological test methods for non-sterile drug products.[33] USP also recommends the establishment of acceptance criteria regarding total numbers of microorganisms, in addition to selected specified microorganisms in NSDs.[34] However, the USP does not provide a comprehensive list of objectionable microorganisms; therefore, firms should identify any additional controls and acceptance criteria that are necessary. The need for additional controls of objectionable microorganisms should be determined for each product. For example, the presence of BCC in aqueous non-sterile drug products may lead to both drug product degradation and patient infection. The intended patient population, drug product indication, and route of administration should be considered when establishing a microbial specification and determining if a specific microorganism is objectionable in the drug product.

B. Risk-Based Impact Assessment

The controls necessary to prevent objectionable microorganisms will depend on the risk (probability and hazard potential) of microbiological contamination in the NSD, including the characteristics of the NSD (e.g., formulation, component selection, conditions of use, and route of administration), the NSD manufacturing process, and the impact of the manufacturing environment. Well-designed and appropriately controlled manufacturing processes present fewer opportunities for introducing objectionable microorganisms and their proliferation or growth. For certain low-risk manufacturing operations (e.g., tablet manufacture), reduction in

[30] There have been recalls in alcohol based products. Refer to Appendix, Case 6.
[31] See, e.g., 21 CFR 211.113 and 211.166(a).
[32] See 21 CFR 211.111 and 211.113(a).
[33] USP <61> MICROBIAL ENUMERATION TESTS and USP <62> TESTS FOR SPECIFIED ORGANISMS.
[34] USP <1111> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: ACCEPTANCE CRITERIA FOR PHARMACEUTICAL PREPARATIONS AND SUBSTANCES FOR PHARMACEUTICAL USE.

microbiological monitoring and testing may be justified using a risk assessment (see section C below).

A risk-based impact assessment helps manufacturers identify product-specific characteristics and manufacturing process elements that are more likely to introduce bioburden or objectionable microorganisms into the NSD. Systems designed to mitigate risks based on this risk-based impact assessment are more likely to prevent objectionable microorganisms in NSDs. The elements listed below, while not an exhaustive list, should be considered in the risk management plan to reduce objectionable microorganisms, where relevant.

1. Product Specific Elements

- Dosage Form
  - Liquid products typically have a higher potential for microbial growth than other types, and semi-solids typically have a higher potential for microbial growth than solids.[35]

- Water Activity[36]
  - Water activity of non-aqueous NSDs should be low enough to inhibit microbial growth.
  - When NSDs have a higher water activity, there is higher potential for microbial growth and additional manufacturing controls may be needed.

- Proposed Use
  - Consider the patient population–the spectrum of patients that could be exposed to the drug and disease state of the most vulnerable patients taking the drug.
  - Consider the route of administration.
  - Consider the body site to which the NSD may be administered (e.g., the skin, the respiratory tract, the gastrointestinal tract, or the urinary tract), and whether the tissue may be injured or diseased, and therefore more susceptible to infection.
  - Consider the setting in which the product is used (e.g., operating room, NICU).

[35] Dosage form will dictate the type of and extent to which microbial enumeration testing should be performed on the finished product. General enumeration testing is described in USP <61> and USP <62>. For solid dosage forms, ICH *Q6A Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* includes recommendations for conditions under which "periodic or skip testing" with regard to microbial enumeration testing may be considered.

[36] USP <1112> APPLICATION OF WATER ACTIVITY DETERMINATION TO NONSTERILE PHARMACEUTICAL PRODUCTS - Reduced water activity (a_w) will greatly assist in the prevention of microbial proliferation in pharmaceutical products; the formulation, manufacturing steps, and testing of nonsterile dosage forms should reflect this parameter.

- Packaging
  - Ensure container/closure provides adequate protection from foreseeable external factors that can lead to microbial contamination (e.g., water or microbial ingress).[37]
  - Consider the appropriateness of a single-dose versus a multiple-dose container-closure when selecting the NSD packaging.[38] For certain dosage forms, a single-dose container/closure might provide superior safety with respect to preventing extrinsic microbial ingress into the finished product.

- Product Components and Composition
  - Consider selection of appropriate preservatives that assure effectiveness to prevent microbiological proliferation throughout the shelf life.
  - Assure all incoming lots of raw materials are suitable for their intended use, including acceptable microbiological quality.[39]

- Microbiological Testing–Product Specific Considerations
  - Establish appropriate microbial limits for components, in-process materials, and finished products.[40]
  - Ensure the sampling plan detects variation within a batch.[41]
  - Ensure appropriate sensitivity of methods for detecting a variety of microbes that could be in components or the finished product and that could pose a risk to patients or product stability.[42]
  - Implement appropriate action limits and test methods for water that is used as a component, including use as a processing aid.[43] Purified water, USP, that does not exceed 100 CFU/ml is recommended for use in solid oral dosage forms. More stringent microbiological quality standards may be appropriate for other dosage forms.[44]

2. Manufacturing Elements

- Manufacturing Process Steps: Certain processing steps may have a greater impact than others in either promoting or reducing bioburden.
  - Bulk storage steps, especially those that are aqueous-based in the manufacturing process, may create conditions in which microorganisms can proliferate, particularly during extended in-process holding periods (i.e., time between different unit operations). Other manufacturing steps might introduce objectionable microorganisms. Therefore, extended holding of aqueous in-process materials (e.g., coating suspensions/solutions, liquid mixtures prior to the addition of a

[37] CFR 211.94(b).
[38] USP <659> PACKAGING AND STORAGE REQUIREMENTS.
[39] See 21 CFR 211.84(d)(6).
[40] See 21 CFR 211.113(a).
[41] See 21 CFR 211.110(a).
[42] See 21 CFR 211.160(b).
[43] See 21 CFR 211.84(d)(6).
[44] USP <1231> WATER FOR PHARMACEUTICAL PURPOSES.

preservative) is not advisable. Holding time limits must be established to preserve product quality.[45]

- Inadequate equipment cleaning processes, such as extended hold times before cleaning and insufficient drying after equipment has been cleaned, may also promote microbiological contamination.
- Inadequate environmental controls, such as production areas open to a natural, uncontrolled, or insufficiently controlled environment when product or product contact surfaces are exposed may promote microbiological contamination.
- Some manufacturing steps (e.g., those that involve filtration, high temperature, extreme pH, or organic solvents) might result in an in-process material that has a reduced bioburden.

- Components: Non-sterile components can be a source of objectionable microorganisms in the manufacturing process. Appropriate specifications[46] for these components, as well as strategies for monitoring, controlling, preventing objectionable microorganisms must be established.[47] Special attention should be given to purified water[48] and naturally-derived components due to their intrinsic risk for contamination.

- Water System: Water used as a component (or as a processing aid) must be, as for any other component, of appropriate quality for its intended use in processing and in the formulation.[49,50] When water used as a component is processed in-house, the purification system must be well-designed and rigorously controlled and maintained.[51] Maintenance and control of water purification systems should include proactive replacement of parts to prevent deterioration and routine monitoring to assure the system can consistently produce water meeting its predetermined quality characteristics. The procedure for monitoring should incorporate appropriate action and alert limits and include timely sampling after key water processing steps and equipment used in the water processing and delivery system, including all points-of-use. Water used as a cleaning agent, depending on conditions of use and equipment, should be monitored to ensure it meets appropriate quality for its intended use.

- Environment: Manufacturers must ensure that facilities, equipment, and environmental conditions are adequate to ensure control of air quality for manufacture, such as preventing introduction of microbiological contaminants or bioburden that would be objectionable to the particular NSD being produced.[52]

[45] See 21 CFR 211.111.
[46] See 21 CFR 211.160(b).
[47] See 21 CFR 211.100(a), 211.113(a).
[48] USP <1231> WATER FOR PHARMACEUTICAL PURPOSES.
[49] See 21 CFR 211.80, 211.84, 211.160(b).
[50] USP <1231> WATER FOR PHARMACEUTICAL PURPOSES classifies different water quality grades to indicate relative purity and absence of microorganisms.
[51] See 21 CFR 211.63, 211.67.
[52] See 21 CFR 211.46(b), 211.56.

Manufacturers should periodically identify microorganisms present in the manufacturing facility which might lead to contamination of the NSD, and ensure that their controls effectively mitigate the impact of these microorganisms on their NSD.

- Equipment: It is important to maintain the sanitary condition of equipment by limiting bioburden through proper design (e.g., vessels, piping), maintenance, cleaning, and sanitization.

- Cleaning and Sanitizing Agents: Manufacturers must use cleaning/sanitizing agents appropriate to assure that buildings and facilities are maintained in a clean and sanitary manner, which should include ensuring that they do not harbor objectionable microorganisms.[53] Appropriate equipment cleaning is essential to prevent objectional microbiological contamination of components, containers, closures, packaging materials, and drugs.[54]

- Personnel: Manufacturers should take steps to establish and maintain appropriate practices to minimize the potential impact of personnel introducing objectionable microorganisms into the manufacturing process. They must ensure that personnel follow good hygiene practices.[55]

- In-Process Testing: Manufacturers are required to establish procedures to assure the quality of in-process materials is consistent with the finished product's established specifications, which includes evaluating whether microbial attributes are met during processing.[56]

- Microbiological Release Testing (as appropriate):
  - Total microbial content (microbiological enumeration testing)[57]
  - Specified organism testing and identification program to identify other objectionable microorganisms[58]

[53] See 21 CFR 211.56.
[54] See 21 CFR 211.56, 211.67.
[55] See 21 CFR 211.28(b).
[56] See 21 CFR 211.110(a)(6).
[57] USP <61> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: MICROBIAL ENUMERATION TESTS.
[58] USP <62> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: TESTS FOR SPECIFIED MICROORGANISMS.

C. Microbiological Concerns for Specific Dosage Forms and Special Cases

1. Solid Dosage Forms

Compared to other NSDs, solid dosage forms represent a lower microbiological risk to patients due to their low water activity. Therefore, the microbiological controls associated with their manufacture are generally not expected to be as stringent as those associated with the manufacture of other NSDs.

The microbiological quality of the finished solid dosage form is also monitored through finished product testing.[59] Microbial enumeration testing of the finished drug product can be performed by methods described in the USP for Total Aerobic Microbial Counts (TAMC), Total Combined Yeast and Mold Count (TYMC), and specified organisms, as appropriate.[60,61] If testing is performed using compendial methods, method suitability testing should be performed using the drug product. Other test methods, including rapid microbiological methods, may be used for product testing, but will require validation to demonstrate their suitability and equivalence to the compendial methods.[62]

Although the USP contains recommended acceptance criteria for microbial control, and specifies the absence of certain objectionable microorganisms,[63] manufacturers may develop alternative approaches to microbiological control, including limits/release criteria. For example, many finished solid oral dosage forms have a water activity that does not permit growth or persistence of many vegetative cells. Therefore, it is possible that water activity determination during product development, in conjunction with in-process controls designed to limit objectionable microorganisms, can serve as justification for the reduction or elimination of microbiological testing for release of certain types of solid oral finished products. If there are sufficient data to demonstrate that in-process microbiological controls are successful, finished product water activity is acceptable, and component lot bioburden test results remain consistently in control, the microbial enumeration testing of the finished product may be reduced or eliminated (see section below titled "Potentially Reducing Microbiological Release Testing for Solid Dosage Forms Based on Risk-Based Impact Assessment"). If such surrogate criteria are used in lieu of a product release test, it is important to establish and document appropriate process and facility controls, including testing of incoming component lots and controls in the manufacturing process, as these controls serve to limit the bioburden in the final product.

[59] See 21 CFR 211.165(b).
[60] USP <61> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: MICROBIAL ENUMERATION TESTS.
[61] USP <62> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: TESTS FOR SPECIFIED MICROORGANISMS.
[62] See 21 CFR 211.194(a)(2).
[63] USP <1111> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: ACCEPTANCE CRITERIA FOR PHARMACEUTICAL PREPARATIONS AND SUBSTANCES FOR PHARMACEUTICAL USE.

Potentially Reducing Microbiological Release Testing for Solid Dosage Forms Based on Risk-Based Impact Assessment

Solid dosage forms with a water activity that will not support vegetative microbial growth are excellent candidates for reduced microbial testing for product release and stability. ICH *Q6A Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* includes recommendations for conditions under which "periodic or skip testing" with regard to microbial enumeration testing may be considered. The recommendations in ICH Q6A are based on product characteristics and provide a logical approach to determining an appropriate microbiological testing schedule. To support the reduction or elimination of microbiological release testing for solid dosage forms, manufacturers should conduct a risk-based impact assessment, as recommended in section IV.B of this guidance.

Microbiological testing in a stability program may be reduced or eliminated for lower risk solid dosage forms with appropriate justification, including the manufacturer's historical experience in manufacturing the NSD, such as the amount of microbiological release and stability data, any adverse findings, and the extent of process, facility, and component bioburden controls. Note that some solid dosage forms that contain growth-supporting components, such as proteinaceous components,[64] should undergo a risk assessment to determine if they are candidates for reducing or eliminating the need for microbiological testing in stability protocols.

2. Non-Solid Dosage Forms

Typically, non-solid dosage forms (e.g., solutions, suspensions, lotions, creams, and some ointments) have higher water activity than solid dosage forms and thus a higher risk of supporting microbial growth. The capacity of non-solid dosage forms to support microbial growth is largely dependent on the water activity of the drug product components. Many contamination events have been associated with products with water activity levels that support microbial growth, and therefore we recommend that non-solid dosage form manufacturers focus on microbiological quality when evaluating the overall manufacturing process. Understanding a product's water activity throughout the manufacturing process can aid in decisions related to manufacturing, in-process holding times, and storage conditions. For products, components, and in-process materials with water activities that are known to support microbial proliferation, greater scrutiny should be placed on process controls throughout the operation. This includes in-process and finished product microbiological monitoring methods and acceptance criteria, validation of in-process holding periods,[65] and any manufacturing step that is vulnerable to microbial proliferation. For example, naturally occurring ingredients with low water activity may have high intrinsic bioburdens and require special attention. Also, the presence of objectionable microorganisms in the manufacturing steps for topical drugs has resulted in microbial contamination of such products, which typically have low water activity. Additionally, suspensions can present an additional challenge in managing objectionable microorganisms.[66] Product stability studies should take into account that suspensions may separate into different

[64] Solid oral dosage forms with certain naturally-derived active ingredients (e.g., pancreatic enzymes) and soft gelatin capsules have a higher likelihood of harboring objectionable contamination.

[65] See 21 CFR 211.111.

[66] See footnote 6.

phases, during storage and distribution, that may result in the segregation of formulation ingredients and cause an unequal distribution of preservatives. The phase with insufficient preservatives may have high water activity resulting in microbial growth.

In addition to evaluating the overall manufacturing process, it is also important to ensure that manufacturing equipment is cleaned and maintained such that water residue does not remain on equipment while it is stored, unused, or unprotected.[67] Water residue can promote microbial growth. Equipment surfaces, including those that may not contact product directly, should be dried or stored in manner that permits rapid drying as soon as possible after cleaning and sanitization.

Non-solid products with low water activities nonetheless can harbor objectionable contamination due to introduction of contamination during manufacturing or from raw materials. However, microbial proliferation during shelf-life is less common. For non-solid products with synthetic components and water activities that are well below those that are known to support microbial proliferation, less frequent microbiological testing conducted in the finished product stability program may be supportable. Batches placed in a stability testing program are typically sampled and tested at multiple time points over their labeled shelf life, including beginning and end and several interim points. To support reduced (i.e., fewer stability time points) microbiological testing of finished product lots in the stability program, a risk-based impact assessment should be performed that includes water activity data, microbiological monitoring information related to the manufacturing process, bioburden potential of the components, manufacturing history (with attention to any failures and deviations), and an understanding of the processing steps that may contribute positively or negatively to microbiological quality (see previous subsection on "Potentially Reducing Microbiological Release Testing for Solid Dosage Forms Based on Risk-Based Impact Assessment").

3. Microbiological Consideration – Special Cases

This section discusses examples of NSD product formulations and intended uses that inherently pose greater relative risk for objectionable microorganisms or bioburden to harm the patient population (e.g., administration of NSD to skin prior to medical procedures that break the skin). This example demonstrates that more rigorous identification and assessment of the bioburden in these products is critical to understand product hazard. Appropriate laboratory methods must be used, and qualified staff must review the results to determine if the product is contaminated with objectionable microorganisms.[68,69] These methods should differentiate and identify objectionable microorganisms. Such batch quality information is critical to prevent distribution of an objectionably contaminated product that poses a hazard to consumers, and to facilitate an investigation of the cause(s) to correct or prevent a quality problem.

[67] See 21 CFR 211.67.
[68] See 21 CFR 211.160(b).
[69] See 21 CFR 211.25(a).

a. Burkholderia cepacia Complex and Aqueous Drug Products

Non-sterile aqueous drug products have the potential to be contaminated with BCC organisms because of the potential for these microorganisms to be present in pharmaceutical water systems. (Refs. 2, 18, 19, 21). *Burkholderia cepacia* is now considered part of a complex of at least 17 genomovars, or closely related species (Refs. 2, 8, 14).

These organisms are opportunistic human pathogens that can cause severe life-threatening infections (Refs. 2, 14, 24). It is important that non-sterile aqueous drug products not contain BCC organisms because of their unique characteristics and the safety risk they pose. BCC strains have a well-documented ability to utilize a wide variety of substrates as energy sources, many of which are traditional preservative systems (Refs. 1-4, 12, 13). Thus, despite the presence of an otherwise adequate preservative system in a non-sterile drug product, BCC strains can survive and proliferate in a non-sterile product over its shelf life. While microbial enumeration testing for finished product release may demonstrate an acceptable level for the total aerobic microbial count, BCC can proliferate to unsafe levels by the time the product reaches the patient. In May 2016, the FDA was notified by the Centers for Disease Control and Prevention (CDC) of severe illnesses and deaths associated with BCC in patients in 13 hospitals across 9 states. This prompted the recall of a non-sterile OTC liquid stool softener due to BCC contamination (Ref. 17). In a series of cases from 2000 to 2002, involving a medical device (an ultrasound gel), intrinsic contamination by BCC led to serious blood infections after the gel was used in association with transrectal prostate biopsies (Ref. 6).

Pharmaceutical water and naturally-derived components used in the manufacturing process are the most likely sources of BCC in drug products. Therefore, a robust implementation of the CGMPs is essential to ensure product quality and patient safety, including:

- establishing a risk management program for the design and control of operations to prevent BCC contamination[70]
- using robust water systems[71]
- ensuring components meet appropriate specifications for bioburden[72]
- appropriately sanitizing and cleaning equipment,[73] and
- validated sampling procedures[74] to routinely perform in-process monitoring and finished product testing for the presence of BCC

Unless a manufacturer performs validated manufacturing steps (e.g., microbial retentive filtration of the bulk product formulation with a sterilizing filter right before filling) that render a drug product free from BCC, release testing is essential as the last in a series of controls that helps demonstrate that the non-sterile aqueous drug product is free from BCC (Ref. 7).

[70] See 21 CFR 211.100(a), 21 CFR 211.113(a).
[71] See 21 CFR 211.42(a).
[72] See 21 CFR 211.80(a), 211.84(d)(6).
[73] See 21 CFR 211.67(a).
[74] See 21 CFR 211.110(a), 21 CFR 211.165(a).

The USP provides a compendial test for BCC that became official on December 1, 2019, entitled ⟨60⟩ MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS—TESTS FOR BURKHOLDERIA CEPACIA COMPLEX. FDA recommends that manufacturers use the USP method described in this USP chapter to test drug products for the presence of BCC. If a manufacturer chooses to develop an alternative in-house method, the alternative method or procedure must be fully validated and must produce comparable results to the compendial method.[75] Additionally, any applicant choosing to develop an alternative method should be aware that test methods can be complicated by the fact that BCC are highly adaptable and variable in their ability to survive and grow in a variety of environments (Refs. 1, 8). There can be difficulties detecting and correctly identifying and classifying BCC (Refs. 1, 15) and, consideration of the diverse phenotypes exhibited by BCC members is essential for recovery method development (Ref. 3).

b. Preoperative Skin Preparation Drug Products (Topical Antiseptics)

Patient preoperative skin preparations are topical antiseptic drug products used to reduce the number of microorganisms on the skin prior to medical procedures or injections, as the skin is typically covered with microorganisms (Ref. 16). Some of these products are not manufactured as sterile products (Ref. 16). However, there have been a number of published reports of infection outbreaks associated with antiseptic products due to microbial contamination (Refs. 9, 10, 11, 21). Notably, contaminated antiseptic products made up a majority of non-sterile product recalls that occurred between 2009 and 2013. There were eight recalls due to microbial contamination of alcohol or povidone-iodine prep pads.

The product indication alone (application to a body surface that is about to be surgically compromised), as well as recent infection outbreaks and product recalls, suggest that the sterility of the product may be an important risk mitigation or have an important impact on clinical outcomes. In 2011, the FDA published a news release reminding health care professionals to check the labeling on alcohol prep pads to determine if they are sterile or non-sterile due to recent contamination events.[76] FDA recommended that only sterile pads be used for procedures requiring strict sterility measures (Ref. 19). FDA encourages manufacturers of patient pre-operative antiseptic products to explore manufacturing processes for these products that render them sterile, whether the product is under development or currently marketed. FDA welcomes questions regarding development of sterilization processes for these products, and is committed to working with applicants and other stakeholders on options for sterilization of pre-operative antiseptic products.[77]

[75] See 21 CFR 211.194(a)(2), 21 CFR 211.194(a)(6), USP <1223>.

[76] FDA Press Announcement "FDA reminds health care professionals about safe use of non-sterile alcohol prep pads," February 1, 2011, https://wayback.archive-it.org/7993/20170113073826/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm241750.htm. See also "FDA Drug Safety Communication: FDA requests label changes and single-use packaging for some over-the-counter topical antiseptic products to decrease risk of infection," November 13, 2013, https://www.fda.gov/Drugs/DrugSafety/ucm374711.htm.

[77] Requests not associated with a specific application can be sent to CDER-OPQ-Inquiries@fda.hhs.gov.

c. Transdermal Products

Traditional transdermal and topical delivery systems (collectively TDS) pose limited microbial risk when used on intact skin.[78] However, as the technology for these products continues to evolve, the potential risk to patients should be re-assessed to determine the need for additional manufacturing controls.

TDS designed with a physical mechanism to abrade or penetrate the skin increase the potential for infections, especially given that skin thickness varies across individuals, body sites, and by patient age. During development manufacturers of such TDS should consider the risks and determine whether the TDS should be manufactured as sterile or with a bioburden level below that normally seen with TDS designs that rely on chemical permeation enhancers.[79] The FDA encourages these manufacturers to contact the Agency in the early phase of planning and product development.[80]

D. Updating Approved Drug Product Specifications

FDA does not expect application holders of approved drug products to amend the product specification in cases where it is inconsistent with the recommendations discussed in this guidance. If a new supplemental application proposing a manufacturing change that may impact the risk of increased microbiological growth (e.g., new manufacturing process, relaxation of critical process parameters) is submitted, FDA assessors may request that application holders update the microbiological testing information in the product specification during assessment and before approval. Application holders may wish to consider updating a given drug product specification as recommended in this guidance. This could help to expedite approval of future supplements for other manufacturing changes.[81] Table 1 provides guidance regarding the filing category for submission of supplements that propose changes to the microbiological testing program of non-sterile drug products.

[78] Technical considerations (beyond microbiological aspects) for traditional transdermal systems are addressed in FDA's draft guidance for industry *Transdermal and Topical Delivery Systems - Product Development and Quality Considerations* (November 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[79] See FDA's guidance for industry *Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment* (June 2006).

[80] When the submission is for an NDA, contact the specific drug product's review division with questions. When the product under development is an ANDA, the Office of Pharmaceutical Quality (OPQ) and Office of Generic Drugs (OGD) may be contacted through general correspondence, controlled correspondence, or request for a Pre-ANDA Meeting, as applicable.

[81] FDA also recommends that non-application drug products consider updating drug product specifications as maintained by the pharmaceutical quality system as recommended in this guidance.

625 Table 1. Regulatory Filing Strategy for Proposed Changes to the Microbiological Testing of
626 Non-Sterile Drugs
627

Proposed Testing Change	Regulatory Filing	Related Guidance
Currently not performing microbial enumeration testing. Proposing to add testing according to USP General Chapters <61> and <62> with criteria consistent with USP General Chapter <1111>.	Annual Report	Guidance for industry on *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports*
Currently performing microbial enumeration testing with less stringent acceptance criteria than that suggested in USP General Chapter <1111>. Proposing to tighten acceptance criteria to USP recommended levels.	Annual Report	Guidance for industry on *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports*
Currently performing microbial enumeration testing. Proposing to delete microbial enumeration testing based on submission of a risk assessment. This type of proposal would only be appropriate for testing and evaluation of certain solid dosage forms with a low water activity.	Prior Approval Supplement (PAS)	Guidance for industry on *Changes to an Approved NDA or ANDA*
Currently testing according to USP General Chapters <61> and <62> with criteria consistent with USP General Chapter <1111>. Proposing to add BCC test, but currently not performing testing for BCC.	Changes Being Effected (CBE-0)	Guidance for industry on *Changes to an Approved NDA or ANDA*

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APPENDIX: Case Study Examples of Microbiological Contamination of NSD Products; Impact on Product Quality and Manufacturing Process

The following seven case studies summarize incidents of NSDs contaminated with microorganisms leading to infections, and ultimately product recalls. In each of the cases below, the manufacturer of the product initiated voluntary recall actions to mitigate the impact of the contaminated product on patients and end-users, and instituted new processes and corrective measures to prevent future microbial contamination of their product. Of particular significance are the root cause analyses and corrective/preventative strategies that manufacturers took to address microbiological contamination. These examples suggest that risk assessments should be an integral part of strategies to prevent the microbiological contamination of NSDs.

Case 1: Contamination of an oral solution with *Burkholderia cepacia* complex *(BCC)*

In 2016, an OTC product (oral liquid docusate sodium) indicated for constipation was contract manufactured for a customer who marketed the products under its own label. FDA investigated a multistate outbreak of serious *BCC* infections in 108 patients, including multiple associated patient deaths. Testing by FDA and CDC revealed that more than 10 lots of oral liquid product were contaminated with *BCC*. The *BCC* clinical isolates matched with the product isolates. The investigation also detected *BCC* in the water system used by the firm to manufacture the product. FDA and CDC identified the contract manufacturer as the source of the outbreak. The poorly designed water system (cold system; not continuously circulating), inadequate monitoring of the system, poor manufacturing controls, and inadequate microbiological testing methods all contributed to severe risks to the consumer. All lots of liquid products made by the contract manufacturer were ultimately recalled.

Case 2: Contamination of aqueous-based throat spray and liquid antacid with *Escherichia coli*

In 2014, a manufacturer of an aqueous-based, non-sterile spray to relieve throat dryness and to restore throat comfort was determined to be contaminated with *Escherichia coli (E.coli)*. The contamination was discovered when a microbial assay of the product returned results that indicated the bacterial count to be too numerous to count (TNTC). Although the root cause was not fully determined by the firm, several manufacturing practices were corrected as a result of the event, including new processes and procedures for cleaning and storage of equipment, and physical separation between used equipment and equipment that had been sanitized. Over 20,000 units of this product were distributed nationally.

A separate case of *E.coli* contamination of an antacid liquid occurred in 2013, in which over 10,000 units of the contaminated product were distributed nationally prior to completion of quality assurance testing. When the microbial assay for the product returned with *E.coli* counts greater than 3000 CFU/g, the product was immediately recalled by the manufacturer. After the manufacturer's investigation, the quality assurance procedures were updated and employee training was conducted. However, the root cause of the contamination was not determined. In this instance, there were no reported injuries or illnesses that were attributed to the contaminated product.

744
745 A review of FDA's recall database between 2012 and 2017 demonstrates that at least four other
746 separate events have occurred with non-sterile aqueous based products resulting in *E. coli*
747 contamination.
748
749 **Case 3: Contamination of moisturizing cream with *Pseudomonas* and *Staphylococcus***
750
751 In 2017, a manufacturer of a baby eczema moisturizing cream reported that their product was
752 contaminated with *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Over 15,000 units of
753 the product were distributed nationally. The microbial assay determined that the bacterial load in
754 the products was 87,500 CFU/g, despite presence of a preservative in the formulation. The root
755 cause for the microbiological contamination appeared to be a raw material of natural origin that
756 became contaminated due to improper storage at the firm, and apparently resulted in
757 microbiological growth in finished product.
758
759 Similarly, in 2015, a distributor of a liquid antacid determined that over 100,000 units of their
760 nationally distributed product was objectionably contaminated. Product contamination included
761 *Pseudomonas aeruginosa*, as well as high yeast and mold counts. The recall scope was based on
762 assessment of retention samples spanning 12 months. The root cause of the contamination
763 appeared to be related to issues in the contract manufacturing process, but the ultimate root cause
764 was not identified.
765
766 **Case 4: Excessive contamination of a non-aqueous-based cream indicated for infants**
767
768 In 2018, a zinc oxide diaper rash cream, indicated for infants, was imported by a US distributor
769 who intended to market it as an OTC product. When tested, it was found to be objectionably
770 contaminated. Although the product was not aqueous-based, and had a low intrinsic water
771 activity, it contained excessive numbers of bacteria and fungi. Samples included units with
772 several very high aerobic microbial counts including values such as 3.5 million CFU Total
773 Aerobic Microbial Count (TAMC)/mL and 27,000 CFU TAMC/mL. Many of the bacteria were
774 spore formers of the *Bacillus*, spp. Yeast and mold count levels were also very high, including
775 2700 Total Combined Yeast and Mold Count (TYMC)/mL, 39000 TYMC/mL, and 200
776 TYMC/mL. The manufacturer recalled all lots of the product and ceased shipping to the US.
777
778 **Case 5: Topical cream contaminated with *Enterobacter,* sp.**
779
780 In 2018 a manufacturer of a topical cream-based drug became aware that several lots of their
781 product were contaminated with *Enterobacter,* sp. The product was inadvertently shipped prior
782 to the completion of the microbial assay, which resulted in a microbial count that was TNTC. In
783 addition to the assay, there was an unusually strong odor not typically associated with the
784 product. After the recall was initiated, the manufacturer received customer complaints regarding
785 a strong odor from the product. The potential root cause for the microbiological contamination
786 was suspected to be improper changeover cleaning of the filling equipment. Several corrective
787 actions were taken to prevent future microbial contamination of product, including revision of
788 preventative maintenance and release testing procedures and employee re-training.
789

Case 6: Alcohol antiseptics contaminated with *Bacillus cereus*

In 2011, an alcohol-based antiseptic product was produced under poor manufacturing conditions and the product was found to be contaminated with *Bacillus*, spp., including *Bacillus cereus*. Adverse events were reported to be associated with the contaminated antiseptics. Inspection of the firm found lack of appropriate controls to prevent contamination during formulation, filling, and storage of the drug products. Equipment was also observed to be insufficiently cleaned. These deficient conditions likely contributed to the contamination events. The manufacturer issued a voluntary nationwide recall of all lots of alcohol prep pads, alcohol swabs, and alcohol swab sticks, due to confirmed and potential microbial contamination.

Case 7: Contamination of an API with *Aspergillus*, sp. and *Enterobacter*, sp.

In 2016, a manufacturer of an API that is further utilized by other manufacturers to derive oral and injectable finished pharmaceuticals became aware of customer complaints that their API contained TNTC/g levels of fungal contamination by various *Aspergillus* species. The root cause for this microbiological contamination appeared to be related to parts of the drying equipment used to dry the API. As corrective action, the API manufacturer replaced defective drying equipment ductwork to prevent trapped moisture from collecting within it, and revised existing preventive maintenance/monitoring procedures to enable a more robust control against microbiological contamination. The API manufacturer initiated a voluntary recall that impacted several API lots over the course of one year, and several manufacturers of finished drug products. There were no reported injuries or illnesses associated with the contaminated product.

In 2014, another manufacturer of a bulk cream base used to compound topical drugs recalled several lots of its bulk cream due to high counts of mold and bacteria, and specifically high counts of *Aspergillus*, sp. and *Penicillium*, sp. (among other microorganisms). The root cause of the microbial growth was insufficient manufacturing instructions that resulted in personnel adding lower amounts of preservatives than needed to ensure uniform distribution throughout each of the affected batches. When the final products were manufactured, enclosing the cream in its final container/closure resulted in the development of moisture as the product cooled. The moisture enabled mold to grow. Microbial assays of impacted lots all demonstrated mold growth, and corresponding microbial identity testing demonstrated lower preservative amounts in impacted batches. To mitigate future errors, the bulk cream manufacturer modified their manufacturing procedures and processes to ensure uniform distribution of the preservatives in each bulk cream batch.

Case 8: Fungal contamination traced to excipient

In 2001, a manufacturer recalled 45 lots of Glyburide tablets for fungal contamination. The source of the contamination was traced to a filler/binder excipient used in the formulation. A subsequent FDA Warning Letter cited the firm for not conducting an adequate investigation to determine the sources of the fungal contaminants and identify other Glyburide tablet lots manufactured which used the same excipient lots as well as the failure to appropriately sample and test the excipient. Additional investigation found that the air used in the drying process of

the excipient was contaminated with seasonal fungal spores during the chemical synthesis of excipient at the excipient manufacturing facility.

Case 9: Contamination of eletriptan hydrobromide with *Pseudomonas*, sp. and *Burkholderia*, sp.

In 2019, a firm recalled two lots of eletriptan hydrobromide because these product lots failed microbiological specifications for the potential presence of *Pseudomonas,* sp. and *Burkholderia*, sp. For the general population these risks are low, and may include temporary gastrointestinal distress without serious infection. However, for certain vulnerable patient populations (such as patients with compromised immune systems, cystic fibrosis and chronic granulomatous disease) this objectionable contamination may pose the potential for serious adverse events including life-threatening infections.