COMMENTARY

# In-use physicochemical and microbiological stability of biological parenteral products

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**Am J Health-Syst Pharm.** 2015; 72:396-407

Pharmaceutical scientists in the biotechnology industry have traditionally focused on achieving acceptable shelf lives of drug products in their original, unopened product unit configuration (e.g., two years stored at 2–8 °C). However, it is now clear that stability considerations extend beyond the life of the finished drug in the unopened vial. Potential users of the product who would likely prepare the ready-to-administer drug preparation include compounding facilities and centers, hospital pharmacies, physicians, and nurses. How the product will be handled by the user is extremely important in ensuring the stability, effectiveness, and safety of the product. For biological therapeutic products, a number of common preparation practices, such as reconstituting, diluting, storing, and administering a parenteral product, have the potential to result in instabilities.

Protein biopharmaceuticals are frequently prepared aseptically in a hospital pharmacy or manufactured in advance in a compounding facility or center, and the ready-to-administer preparations are likely subjected to a holding time before use. Aseptic preparation of ready-to-administer parenteral preparations by dilution, reconstitution, or infusion preparation can be done for individual patients within a hospital pharmacy, whereas bulk production of ready-to-administer preparations at compounding centers is considered manufacturing. Within this commentary, the terms compounding and manufacturing (in the context of drug preparations) are used interchangeably. Of note, the scale of production and potentially significant holding times of the compounded product require these operations follow general good manufacturing practice (GMP).

Some products require extended administration intervals, (e.g., continuous infusion for up to 24 hours or longer).[1] The active drug may not be in the original stabilizing solution during the time between storage and administration, potentially compromising the drug's stability.[2] The dilution of excipients, such as surfactants, that stabilize the protein and the use of destabilizing vehicle solutions,

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The authors acknowledge Claudius Kreyenbühl for providing valuable discussions and generating growth curves, as well as Lynne Krummen, Ph.D.; Kathy Francisssen, Ph.D.; Ines Krämer, Ph.D.; Maged Darwish, Ph.D.; John Wang, Ph.D.; Jeanne Mateffy, M.S.; Angela Lint, B.S.; Artemio Alanis, Pharm.D.; Michael Goldberg, M.D., Ph.D.; and Ping Yeh, Ph.D., for valuable discussions and John Metcalfe, Ph.D., for review of this manuscript.

The authors have declared no potential conflicts of interest.



DOI 10.2146/ajhp140098

such as dextrose solution, can result in protein instability.[3] For lyophilized products, interim storage of the reconstituted solution can also result in physical and chemical instability.[4] Contact of the drug with various surfaces can also affect stability and drug recovery, and care should be taken to ensure that in-use components such as i.v. infusion bags, lines, and filters have been previously evaluated for compatibility. Furthermore, the preparation process may introduce microbial contamination if proper aseptic techniques are not used.[5] Therefore, physicochemical and microbiological stability and recovery of the active drug after dilution or reconstitution should be evaluated during drug development to provide healthcare professionals with the necessary information about in-use stability.

The physicochemical and microbiological qualities of biological products are functions of the aseptic preparation process, conditions of interim storage, and administration procedures. Within the preparation process, key factors to maintain physicochemical stability include compatibility with the diluent or vehicle solution and compatibility with the container. Key factors for quality assurance within the aseptic compounding process include the environment (e.g., a laminar-airflow hood versus an uncontrolled environment) and the complexity of the process, such as the number of drug product units or entries into the i.v. infusion bag, as described in *United States Pharmacopeia* (*USP*) chapter 797.[6] This chapter also applies to the compounding of nonbiological products, and its mention here is intended to educate the reader on the discrete hold-time guidance that exists based on the compounding complexity, which should be considered in conjunction with physicochemical product-quality data, the patient population, and the therapeutic need.

The available literature published on each of these aspects of physicochemical and microbiological stability of biological products is discussed.

**Considerations regarding in-use stability.** In-use stability considerations and recommendations are provided by pharmaceutical manufacturers on the package insert; however, products are often used beyond these recommendations. In many cases, users perform their own physicochemical stability studies (for products after opening the package) or rely on third-party published studies, which may lack adequate and product-specific method panels and assessment criteria. Thus, some literature may provide conflicting recommendations based on incomplete analyses. In addition, there is no clear guidance on in-use stability, specifically with respect to appropriate analytic testing and acceptance criteria.

When compounding and preparing sterile, unpreserved, ready-to-administer parenteral products, care must be taken to avoid microbial contamination. Considering the number of cases of product contamination and lack of quality assurance that surfaced after the New England Compounding Center incident associated with the meningitis outbreak,[7] it became obvious that many compounding centers do not have appropriate measures in place to ensure sterility. Compounded products may be subjected to extended hold times due to the fact that medication is often compounded in bulk rather than per individual patient prescription, putting microbiological quality at risk. Many of these facilities considered themselves compounders rather than manufacturers that should follow GMP principles.

While the pharmaceutical industry can conduct microbial growth studies to help provide an understanding of a product's microbiological integrity after accidental contamination, these studies may provide limited information under specific experimental conditions, such that the data may have limited value to reduce the actual occurrence of compounded nonsterile units. Microbiological growth data should not be effectively viewed to allow or even promote compounding under nonsterile conditions.

**Aspects of physicochemical stability.** In-use stability of small-molecule drugs is well understood by pharmacists.[8] In contrast, limited information about in-use stability and compatibility of biologicals is available due to the complexity of large-molecule proteins and the advanced analytic characterization assays required to assess their unique stability issues.

In some cases, the protein or small-molecule drug may be incompatible with a particular diluent or container material. For example, certain protein biopharmaceuticals administered by i.v. infusion are compatible with 5% dextrose injection but not with 0.9% sodium chloride injection due to particulate formation. In other cases, chemical instability of the protein can occur, such as glycation in 5% dextrose injection or in sucrose-containing formulations during long-term storage.[9] Oxidation is also a concern due to the gas permeability of the i.v. infusion bag material and light-induced degradation.[10]

Protein concentration is a key indicator of product recovery, which can be challenging to measure accurately within a diluted infusion bag configuration or at a portion of the infusion device near the patient, particularly when the protein concentration is less than 0.1 mg/mL.[11] Adsorption of the drug to surfaces of the infusion bag, lines, or inline filter can lead to unacceptable product loss, decreased potency, and potential underdosing. Most first-in-human clinical trials test low doses before increasing the doses to a therapeutically effective range.[12] These initial doses of "minimum

anticipated biological effect level" are used to mitigate the risk of adverse reactions.[13] The resulting extremely low protein concentrations may be well outside of the standard range of detection for accurate measurement of the purity, content, and stability of the preparations and may only be measurable via an enzyme-linked immunosorbent assay (ELISA), colorimetric assays (e.g., Bradford assay, bicinchoninic acid assay), or absorbance spectroscopy using a variable path length (or slope spectroscopy) rather than by traditional absorbance at a fixed path length or by size-exclusion chromatography.[14,15]

Analysis of physicochemical stability during simulated administration is also warranted, given that (1) additional surfaces come into contact with the protein, (2) the drug product formulation may be diluted, including dilution of critical excipients required for protein stability, and (3) environmental stressors may be present during use.[3,16] Process-related impurities, such as leachables from the i.v. infusion bag and administration lines and silicone oil lubricant from the disposable syringes, have been reported to induce aggregation and other degradation reactions in some cases.[17,18] Glycation products potentially occurring in 5% dextrose injection are detectable by specific analytic methods, such as liquid chromatography–electrospray ionization mass spectrometry.[9] The formation of glycated protein degradants as well as reactions with leachables may be relevant for storing the compounded product over an extended period of time.

Published data on the evaluation of compatibility of specific products under simulated administration conditions need to be assessed with due diligence. Many such studies purport to show extended product stability over what is recommended by the manufacturer (Table 1) but often do not use the number and quality of assays necessary to establish the purity and stability of a protein biopharmaceutical. As noted by Sreedhara et al.,[2] these studies often lack product-specific analytic methods that monitor product impact. For instance, Kupfer et al.[23] tested the stability of alemtuzumab over 14 days at 6 °C using only size-exclusion chromatography and pH, concluding that the results of these tests established both physical and chemical stability of the antibody over the study period. Goldspiel et al.[24] followed the same methodology and reported 24-hour stability of alemtuzumab at ambient temperature and lighting. Paul et al.[25] reported the stability of diluted rituximab preparations (in polyolefin bags containing 0.9% sodium chloride injection) stored for six months at 2–8 °C based on various analytic methods and criteria but without particle analysis. Zhang et al.[26] used ELISA to determine the stability of diluted rituximab stored in glass vials and infusion bags. Bakri et al.[27] concluded that bevacizumab was stable for six months at refrigerated or freezing temperatures in a syringe based purely on ELISA, which showed a 15.9% decrease in activity over this period. The stability of infliximab in polyvinyl chloride bags stored for up to 14 days under refrigerated conditions was reported by Ikeda et al.[28] However, as widely accepted, a single analytic method is inadequate to assess the variety of degradation products that may occur with a protein product and thus cannot serve to assess overall stability.[29] It is expected that protein-based drugs can have multiple modes of degradation, each of which may require a unique assay that has been shown to be stability indicating.

There has been some recent emphasis on improving the analytic rigor of studies to support extended product stability,[30] but the acceptance criteria are often undefined, as meaningful acceptance criteria would be based on product specifications and sound product knowledge. Finally, analytic reference standards are generally unavailable to third parties. Therefore, analytic scientists other than the pharmaceutical manufacturer usually cannot reliably determine whether a result is acceptable.

Drug recovery from the infusion devices also requires investigation. The issue of absorption causing reduced drug recovery from infusion devices was thoroughly studied with insulin about 40 years ago.[31-34] The large surface area and unique materials of infusion bags and lines can lead to adsorption. As observed with interleukin-2, surface interactions can cause loss of biological activity due to conformational perturbation during simulated pump-based administration.[16] The adsorption phenomenon is especially relevant when the preparation is highly diluted, resulting in very low concentrations of the protein.[33,34] In addition, the dead volume in different administration systems needs to be accounted for to ensure accurate dosing.[35] If the volume of the infusion bag is less than 100 mL, the administration sets are to be flushed with vehicle solution after infusion. Accounting for a variable dead volume can be challenging if the administration devices are sourced separately and not packaged with the pharmaceutical product. However, flushing of the lines to ensure accurate dosing can be challenging in practice.[36] Also noteworthy is that prefilled infusion bags often contain significant variability in their fill volume. Protein concentration may be affected by this factor if the total volume is used for dilution.

Procedures for introducing diluent for reconstitution of lyophilates or withdrawal of product solution from product vials can vary widely. In general, disposable syringes and adequately sized needles are used. An additional needle may also be introduced to ensure pressure equilibration. However, due to recommendations and considerations for

small-molecule cytotoxic drugs, the prevention of occupational exposure becomes increasingly important.[37] In order to minimize accidental exposure of healthcare professionals to the active drug, solution transfer and reconstitution devices are used.[38] These devices must be carefully assessed for product compatibility and dead volume. For example, these devices have been found to pierce out rubber stopper fragments from product units (known as stopper coring), and these fragments may end up in the administered preparation unless particle filters are an integrated part of the device.[39,40]

Storage and handling of the reconstituted or diluted preparations also require consideration. The transport of any biological product, including ready-to-administer preparations, under uncontrolled conditions (e.g., with nonvalidated cooling systems or at ambient temperature) can lead to instability.[2,41] Accidental freeze–thaw cycles or extreme shaking of the bags may also affect stability. Compatibility and stability of the drug–drug admixtures can be tested by the pharmaceutical manufacturer if the analytic tools (methods, acceptance criteria, reference standards) are known and available.[42] However, because specific admixtures used clinically may not be known to and studied by the pharmaceutical manufacturer, prescribing information indicates that mixing of drugs is not advised because of the lack of data.[43] As many factors during storage, handling, and administration of the biological product can compromise its quality, safety, and efficacy, the product labeling and information (e.g., summary of product characteristics, package insert, investigator's brochure in the case of clinical drug product, training materials) should be followed.[44]

**Aspects of microbiological stability.** Microbial contamination issues associated with improper sterile compounding in the United States resulted in 29 recall notices affecting over 2000 products between October 2012 and December 2013.[45] According to the Centers for Disease Control and Prevention, the number of cases related to the fungal meningitis outbreak as of August 2013 totaled 751 across 20 states, resulting in 64 deaths to date.[7,46] These figures contributed to the call for increased oversight of sterile compounding facilities and additional microbiological studies during pharmaceutical development of the drug product.[47-50]

Overall microbiological risk is a function of the probability of microbial contamination and the impact of the potential risk to products and patients. Sterility assurance, which defines the probability of microbial contamination, is based on the compounding process (policy, procedures, and complexity of the compounding process), personnel (technique, experience, and training), and environment (laminar-airflow hood or class 5 cleanroom versus bedside). The impact on the products and patients is dependent on the compounded product solution (microbial growth potential and potential periodic verification of the sterility of a compounded batch), environment (time and temperature of interim storage and administration), and patients (immune system and acute therapeutic need).

Aseptic compounding within hospital pharmacies can be performed during batch preparation using presterilized final containers and sterile syringes or on an individual patient basis. The term *compounding* is used instead of *manufacture* in order to distinguish it from the industrial manufacture of licensed biological drug products.[6,51-53] However, in many cases, compounding is also performed during bulk production; for these operations, manufacturing considerations apply. In any case, the preparation of parenteral products for single use by dilution or reconstitution needs to ensure maintenance of sterility (absence of any viable microorganism), especially if the products are to be stored for significant periods of time at 2–8 °C or ambient temperature before administration. Even when the products are used immediately, precaution should be taken against inadvertent injection or infusion of these contaminants and endotoxins into patients.

To prevent microbiological contamination during container

Table 1.
**Comparison of In-Use Stability Recommendations From Various Sources[23-28]**

| Product | Container Type and Temperature | Maximum Recommended Storage Time | |
|---|---|---|---|
| | | Manufacturer | Other Investigators |
| Alemtuzumab | Glass bottles or polyolefin containers at room temperature | 8 hr[19] | 24 hr[23,24] |
| Bevacizumab | Disposable syringes; refrigerated or frozen | 8 hr[20] | 3–6 mo[27] |
| Infliximab | Polyvinyl chloride infusion bags at 4 °C | 3 hr to start infusion (after reconstitution and dilution)[21] | 14 days[28] |
| Rituximab | Polyvinyl chloride infusion bags at 4 °C | 24 hr[22] | 14 days[25,26] |

penetration, reconstitution, dilution, or administration, aseptic assurance measures and processes followed by the pharmaceutical industry and compliance with Good Preparation Practice should be considered. Various aseptic compounding considerations have been formulated in detail by various organizations, such as the German Society of Hospital Pharmacists, other European associations of hospital pharmacists, and the American Society of Health-System Pharmacists.[54-57] This also includes specific instructions on optimal cleaning of the laminar-airflow hood during each shift.[6] Additional guidance is provided on the following key areas:

- Quality of raw material and (primary) packaging components,
- Cleaning and disinfection,
- Equipment qualification,
- Cleanroom qualification, checks, and monitoring,
- Personnel training and qualification,
- Process validation and simulation studies (media fill),
- Documentation,
- Storage and transport, and
- Labeling.

For lyophilized products, pharmaceutical manufacturers typically do not provide the diluent for reconstituting the product, so diluents are purchased separately by the hospital pharmacy. In cases where diluents or reconstitution media other than those provided with the product are used, the compounding, sourcing, and quality of the media are of utmost importance.[58] Sterility assurance of off-the-shelf diluents or reconstitution solutions that are provided in bulk for multiple use relies on the collective aseptic practices of the compounding facility.

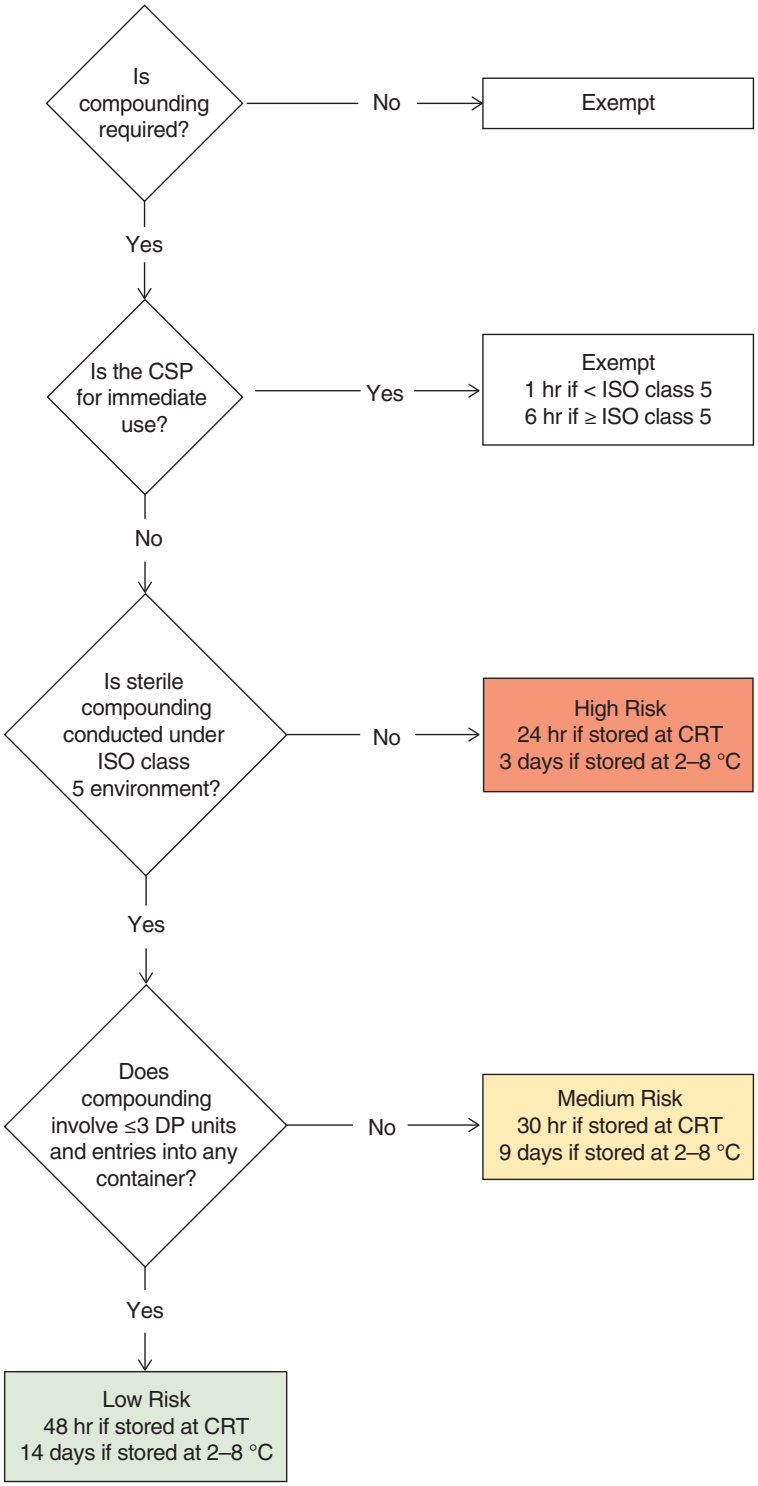
Clearly, sterility assurance during aseptic compounding is the primary means of ensuring patient safety. Although inline i.v. filters can add an additional level of assurance against microbes reaching the patient, endotoxins that pass through the filter can have deleterious effects on patients. Although specific i.v. filters, such as 0.2-µm positively charged nylon filters, have been shown to bind endotoxin[59] and have been sometimes used (e.g., for administration of total parenteral nutrition compounded from various components for pediatric use in hospital pharmacies), it is imperative to ensure the absence of contamination.

**Assessing the risk for microbiological contamination after container penetration.** To ensure patient safety, the pharmaceutical industry relies on regulatory guidance and provides instructions for product handling when compounding in hospital pharmacies or compounding centers. Product-specific risk assessments in conjunction with guidance documents[6,13] may help to create a useful decision tree. As shown in Figure 1, the *USP*-based assessment accounts for the sterile compounding environment and the number of drug product units or entries into the i.v. infusion bag.[6] Although the preparation of ready-to-administer biological products is performed within a laminar-airflow hood, access to a class 5 cleanroom can be prohibitive for certain indications, such as ophthalmic products for intraocular or intravitreal injection. Another approach would be a semiquantitative risk assessment, similar to the method of Akers and Agalloco,[60] in which many variables of the compounding environment, interim storage, and administration conditions are considered to calculate a net risk factor. The assessment provides general guidance for holding times under refrigeration and room temperature based on the risk level. The storage times specified in *USP* chapter 797[6] are to be considered guidance for reference but are insufficient to justify holding times in the absence of physicochemical quality data and product-specific microbiological risk assessment.

Regulatory agencies have recently requested that pharmaceutical manufacturers perform microbial challenge studies to assess the microbial growth potential of the compounded product. Specifically, Metcalfe[61] and Lolas and Metcalfe[62] have suggested testing the microbiological growth potential of different microorganisms in actual single-dose formulations, as "each drug formulation possesses a different potential for supporting or inhibiting microbiological growth." Historically, such growth- or inhibition-rate tests were restricted to multidose formulations to ensure antimicrobial effectiveness of the preservative within the drug product formulation.[63] On the other hand, single-use drug product formulations traditionally were not tested because they lacked a preservative. Furthermore, most compounded infusion solutions are not designed for antimicrobial effectiveness and are mostly aqueous solutions that may contain sugars or amino acids or both. Thus, microbial growth is expected in these products. Although the onset of microbial growth may vary based on the availability of a carbon source within the preparation, growth rates for individual biological products are not likely to significantly differ.[64]

An experimental strategy for assessing microbial growth potential would involve microorganisms such as those suggested in *USP* chapter 51[63] (for preservative efficacy testing) and typical skin microflora and microbes causing nosocomial infections (e.g., *Escherichia coli* and *Pseudomonas aeruginosa*).[61,62] An inoculum of fewer than 100 colony-forming units per milliliter would be introduced into the diluted product solution, and microbial levels would be assessed at multiple time points (including the intended storage duration) under suggested storage conditions. Assessment could also include testing with and without an inline i.v. filter for microbial and/

**Figure 1.** Microbiological risk assessment for compounded sterile products based on *United States Pharmacopeia* chapter 797.[6] Times within boxes indicate maximum recommended time between product compounding and use "Exempt" refers to immediate use (as defined by dosing within one hour if conditions were less than those of a class 5 cleanroom or six hours if conditions met or exceeded those of a class 5 cleanroom), in which case these products are exempt from holding-time criteria. The risk levels refer to the potential for microbial contamination based on the complexity of the compounding process and associated maximum holding times. CSP = compounded sterile product, ISO = International Organization for Standardization, CRT = controlled room temperature, DP = drug product.



or endotoxin reduction[59] if this is the administration scheme recommended by the pharmaceutical manufacturer.

There are important caveats for the interpretation of results of such studies. Because the microorganisms that cause nosocomial infections usually vary across different clinical centers, a microbiological growth study would be unable to reflect all actual-use and compounding conditions and contaminants. If a microorganism with a higher growth rate than the ones tested happened to contaminate the compounded product, holding times solely derived from the microbial challenge study would be misleading.[59,64,65] In addition, it is not feasible to distinguish different risk levels of contamination during aseptic preparation of various products at the same working session. Therefore, all products must be handled with the same diligence, and this preparation practice should be based on the products most sensitive to contamination. Growth promotion studies can help to assess microbial growth but cannot substitute for adequate aseptic procedure, which is the responsibility of the user. As an analogy, the occupational risk posed by cytotoxic products varies, but for practical reasons, all such products must be handled with the same degree of care during aseptic preparation.

In practice, typical aqueous, unpreserved, single-dose protein drug product solutions have been shown to promote microbiological growth following contamination. As an example, for an unpreserved monoclonal antibody drug product diluted in 0.9% sodium chloride injection, there was less than a 0.5-log increase in microbial counts for the organisms tested after storage at 2–8 °C (Figure 2; authors' unpublished data). At room temperature and above, an expected increase in microbial counts occurred within several hours for the microorganisms tested. *E. coli* showed the most significant growth after extended storage at 20–25 °C. Metcalfe[61] and Lolas and Metcalfe[62] suggested to include safety factors for storage beyond the intented use (per product label). However, since microbial challenge itself is a form of accelerated stress, data that establish microbiological stability for the in-use storage conditions specified in the product prescribing information should be sufficient and included in the product-specific assessment. Significant variability can exist in the reported time until the onset of microbial growth due to several factors, including the specific microorganisms tested and the carbon source from the media within the microbial stock contributing to the growth potential when added to the infusion solution. The intrinsic variability in evaluating microbial growth potential is a key consideration in the experimental design, data interpretation, and general strategy around microbial challenge studies.

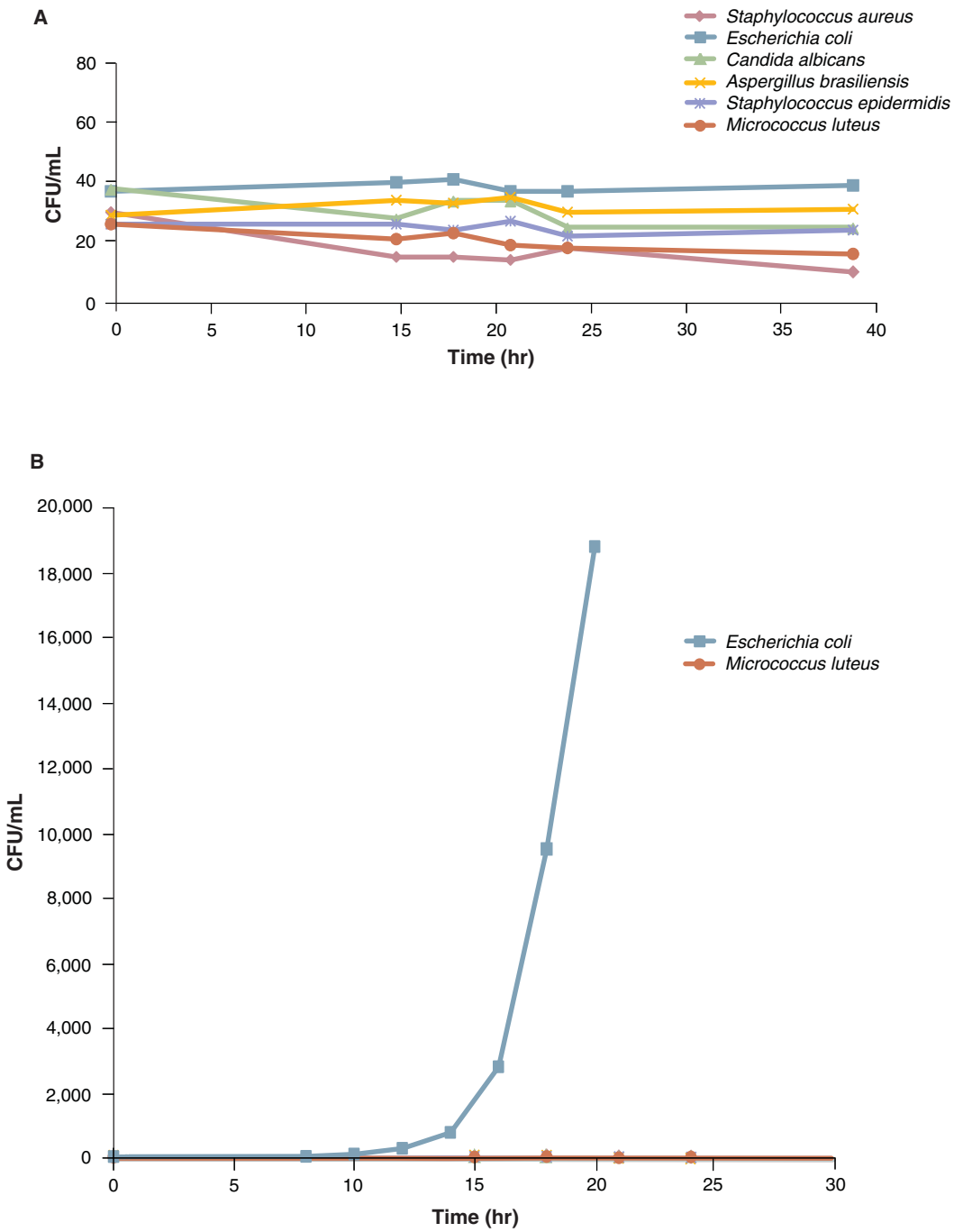
Formulation variations within the original undiluted drug product likely have only a minor impact on microbial growth after dilution into the infusion vehicle solution; hence, the microbial growth potential of each vehicle solution (0.9% sodium chloride injection or 5% dextrose injection) can be studied independently of the specific drug product. Rawal and Nahata[66] found variation in microbial viability and growth rates in infusion vehicle solutions of 5% dextrose injection, 0.9% sodium chloride injection, lactated Ringer's injection, and an amino acid solution for several microorganisms (*E. coli*, *P. aeruginosa*, *Staphylococcus aureus*, *Bacillus fragilis,* and *Candida albicans)*. In assessing the antimicrobial properties of various parenteral preparations, Karstens and Krämer[64] used both 5% dextrose injection and 0.9% sodium chloride injection as positive controls and found neither growth-promoting nor growth-reducing properties for the specific microorganisms tested (*S. aureus*, *Enterococcus faecium*, *P. aeruginosa*, and *C. albicans*). The antimicrobial effectiveness of preservatives or excipients (e.g., benzyl alcohol) in drug products needs to be tested within any diluted form of the compounded product.

The same aseptic handling considerations are applicable for parenteral formulations administered subcutaneously as those administered by i.v. injection or infusion unless ready-to-use or ready-to-administer products (those not requiring reconstitution or withdrawal of drug with a disposable syringe for administration) are used. The interim holding time and associated potential for microbial growth may vary depending on the location of the compounding process (offsite versus onsite, pharmacy versus bedside). Furthermore, the complexity of the compounding process itself should be considered. For example, the simple dispensing of a partial dose from a vial may carry a different risk than reconstituting a lyophilized drug product or pooling multiple vials for administration.

The potential impact of microbial contamination on patients should also be considered, as the clinical consequences of microbial contamination can be severe.[67] For example, microbial contamination of i.v. administered solutions can lead to endocarditis or osteomyelitis. Subcutaneous infection can manifest as phaeohyphomycosis, and contamination of ophthalmic drugs for ocular, intraocular, or intravitreal injection can lead to eye infection, keratitis, or sinusitis.[68]

Although *USP* chapter 797 attempts to capture elements of aseptic assurance (compounding complexity, environment, and procedures) and product interim storage criteria (Figure 1),[6] most risk-assessment models omit key elements, such as patient immunologic status, acute therapeutic need, and pharmacist

**Figure 2.** Microbial growth curves for a 20-mg/mL immunoglobulin G1 solution in 0.9% sodium chloride injection that was inoculated with approximately 10–100 colony-forming units (CFU) per milliliter of the indicated microorganisms followed by storage at 2–8 °C (panel A) or 20–25 °C (panel B).

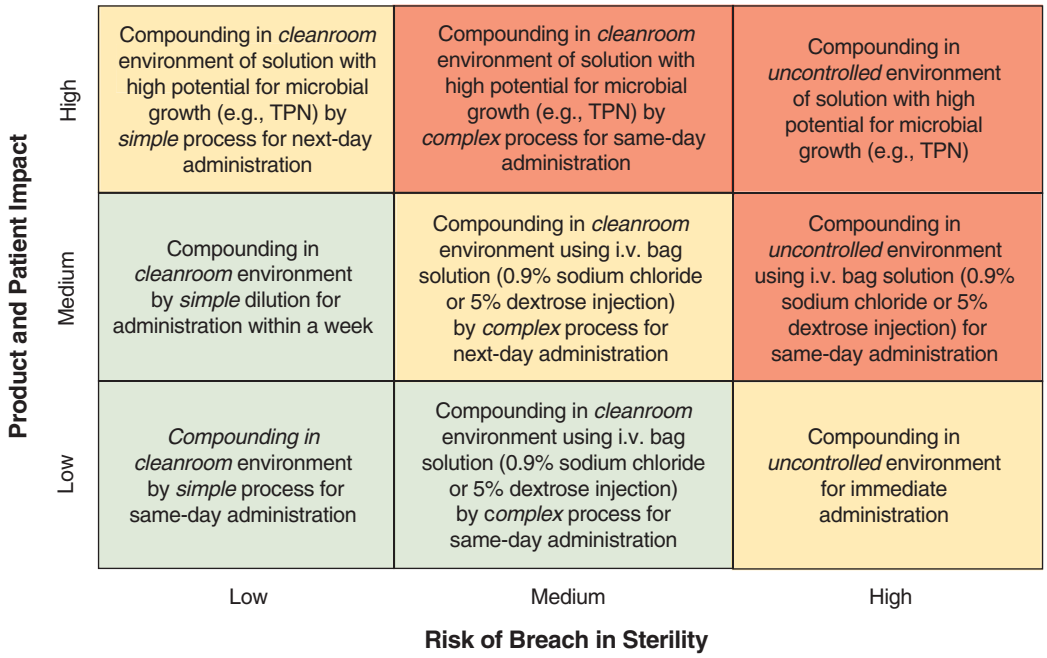


or healthcare professional training. For example, a lifesaving antitoxin injection prepared in the field has a different risk profile than a long-term home-use product. A balanced risk assessment should account for all factors that affect probability and impact. A graphic representation of these risks is shown in Figure 3, along with some general examples illustrating the relative risk of aseptic assurance and the impact on the product and patient. Thus, product-specific risk assessments with quantitative analysis of the risk and severity of impact can be helpful when defining and justifying the holding time for compounded products and associated risk-mitigation strategies for clinical and commercial biological products. Microbial challenge data alone are insufficient to provide sterility assurance and may provide a false sense of sterility based on the subset of microorganisms, which may not be representative of contamination in the field.

The factor most important for protecting patients from a microbiological point of view lies with the hospital and pharmacy personnel compounding the product. Trissel et al.[69,70] found that complex compounding procedures carry a relatively high risk of microbial contamination and that improved work practices can significantly reduce the contamination rate. Aseptic process and product handling training can be an effective tool to assess the robustness of the aseptic compounding process. Similar to human factor engineering studies for combination product development, aseptic process training may be a mechanism to conduct infield testing with trained personnel to assess the compounding risks related to the complexity of the process and the clarity of the instructions. Compounding pharmacies that prepare infusions should also perform regular mock compounding with media, a practice shown to be an effective tool to detect and measure sterility assurance. These types of exercises are required by *USP* chapter 797[6] as well as the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme in many other countries.[54-56] A 2011 nationwide survey of hospital pharmacies in the United States revealed that only 65% of respondents had *USP* chapter 797-compliant cleanrooms for compounding sterile preparations.[71]

**Key points.** In-use studies must demonstrate chemical and physical stability to justify the acceptability of the holding time and conditions of the compounded solution of a specific drug product. Per the European Agency for the Evaluation of Medicinal Products, the unpreserved product should be used immediately to minimize microbial growth,[13] and it is the responsibility of the hospital pharmacy to ensure appropriate and validated aseptic practices and suitable holding-time conditions before drug administration.

**Figure 3.** Microbiological risk associated with compounded sterile products. High risk is indicated by red, medium by yellow, and low by green. TPN = total parenteral nutrition.



The quality of aseptic compounding is highly regulated in Europe. Also, *USP* chapter 797 provides guidance on compounded sterile products based on risk factors associated with aseptic compounding,[6] but it is insufficient to justify sterile compounded product holding times in the absence of a product-specific risk assessment. Although the Food and Drug Administration (FDA) has not historically had oversight of sterile compounding facilities, which are subject to state control, the Drug Quality and Security Act, which was signed into law in November 2013, provides FDA with the authority to regulate sterile compounding facilities that register annually as outsourcing facilities.[72] In addition, guidance on pharmacy compounding is currently being drafted by FDA's Center for Drug Evaluation and Research.[73]

Hospital pharmacies and compounding centers should rely on and use physicochemical stability data from the pharmaceutical manufacturer and closely follow the instructions for use. Pharmaceutical manufacturers should provide extended practice-oriented data about the physicochemical compatibility and stability for drug preparations and in-use administration. Furthermore, aseptic compounding processes need to be ensured and validated by each compounding facility and hospital pharmacy. This includes but is not limited to equipment verification, environmental monitoring, process control (media fills), and training and certification of operators regularly to ensure patient safety.

The primary influence on aseptic outcome for single-dose products is the pharmacy's aseptic practice, whereas the potential microbial growth in a single-dose drug product formulation is a secondary factor. Microbial risk assessments based on sterility assurance (process, personnel, and environment) and the impact on the product and patient can be useful tools to identify key elements of training and drug delivery processes to ensure patient safety.

**Conclusion.** Continued dialogue among regulatory agencies, sterile compounding units, and the pharmaceutical industry is needed to ensure product quality in terms of the physicochemical stability and sterility of compounded single-dose parenteral products. In addition to established practices to ensure physicochemical stability within pharmaceutical development, the associated legislation on sterile product compounding will need to evolve to provide guidance and set standards on microbiological product quality assurance.

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