

# **FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness**

## **I. Background**

On November 21, 1997, President Clinton signed into law the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115). Section 127 of the Modernization Act amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 503A (21 U.S.C. 353a), which governs the application of Federal law to pharmacy compounding. Under section 503A(a) of the act, a compounded drug product is a drug product made in response to, or in anticipation of, receipt of a valid prescription order or a notation on a valid prescription order from a licensed practitioner that states the compounded product is necessary for the identified patient. Compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling (section 503A(f) of the act).

Under section 503A of the act, compounded drug products are exempt, under certain circumstances, from three key provisions of the act: (1) The adulteration provision of section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements); (2) the misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (21 U.S.C. 355) (concerning the use of drugs under investigational new drug applications (INDs) and the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).

To qualify for these statutory exemptions, a compounded drug product must satisfy several requirements. One requirement is that the drug product may only be compounded if we have not identified it, by regulation, as a drug product that "presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product" (i.e., is demonstrably difficult to compound) (section 503A(b)(3) of the act). This concept paper presents our preliminary thoughts on developing a list of products that are demonstrably difficult to compound.

## **II. Our Evaluation Method**

### **A. Early Findings**

In our evaluation of drug products for inclusion on the list of products that are demonstrably difficult to compound, we found that some products with similar characteristics (e.g., products using the same sophisticated drug delivery system) raise similar concerns for pharmacy compounding. For example, our preliminary evaluation of metered dose inhaler (MDI) products demonstrated that all MDI products, if compounded, would present the same difficulties in maintaining the safety and efficacy of the drug. We reached the same tentative conclusion regarding the compounding of all dry powder inhaler (DPI) products, transdermal delivery systems (TDSs), and sterile products that are compounded under procedures other than those described in Chapter 1206 ["Sterile Drug Products for Home Use"] of the United States Pharmacopeia (USP). Therefore, we are thinking of including both specific drug products and categories of products that are grouped by relevant factors (e.g., specific drug delivery system) in the list of drug products that are demonstrably difficult to compound. We invite comment on this approach to developing the list.

### **B. Factors We May Consider**

Section 503A of the act requires us to identify drug products that present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of the drug product. The potency, purity, and quality of a drug product may affect its safety and effectiveness. These qualities may also be affected by how the drug product is compounded.

To assess the potential effect of compounding on the potency, purity, and quality of a drug product, which affects the safety and effectiveness of the drug product, we are considering evaluating drug product or drug category candidates for inclusion on the list using the following factors.

1. Drug delivery system

- Is a sophisticated drug delivery system required to ensure dosing accuracy and/or reproducibility?
- Is the safety or efficacy of the product a concern if there is product-to-product variability?

2. Drug formulation and consistency

- Is a sophisticated formulation of the drug product required to ensure dosing accuracy and/or reproducibility?
- Because of the sophisticated formulation, is product-to-product uniformity of the drug product often difficult to achieve?
- Is the safety or efficacy of the product a concern if there is product-to-product variability?

3. Bioavailability

- Is it difficult to achieve and maintain a uniformly bioavailable dosage form?

- Is the safety or effectiveness of the product a concern if the bioavailability varies?

#### 4. Complexity of compounding

- Is the compounding of the drug product complex?
- Are there multiple, complicated or interrelated steps?
- Is there a significant potential for error in one or more of the steps that could affect drug safety or effectiveness?

#### 5. Facilities and equipment

- Are sophisticated facilities and/or equipment required to ensure proper compounding of the drug product?
- Is there a significant potential for error in the use of the facilities or equipment that could affect drug safety or effectiveness?

#### 6. Training

- Is specialized, highly technical training essential to ensure proper compounding of the drug product?

#### 7. Testing and Quality Assurance

- Is sophisticated, difficult to perform testing of the compounded drug product required to ensure potency, purity, performance characteristics, or other important characteristics prior to dispensing?
- Is there a significant potential for harm if the product is compounded without proper quality assurance procedures and end-product testing?

In developing the list of products that are demonstrably difficult to compound, we would evaluate products and categories of products in light of each factor described above. We would balance the factors, on a case-by-case basis, in deciding whether a product or category of products

is appropriate for inclusion on the list. No single one of these factors would be considered to be dispositive.

In developing this list and applying these factors, we indicate special equipment, facilities, testing, and formulations that must be used to ensure a safe drug product. It is important to keep in mind that compounded drug products are exempt from the statutory requirements noted above and undergo neither the premarket IND, NDA, or ANDA review process nor the post-approval GMP inspection process by FDA that would help ensure that these factors are adequately addressed.

### C. Comments

We request comment about the use of these factors and about any additional factors that we should consider in evaluating drug products for inclusion on the list of drug products that are demonstrably difficult to compound. We also seek comment on whether we should consider the difficulty or importance of achieving stability for a drug product in our evaluation of whether a drug product is demonstrably difficult to compound.

We are interested in learning more about the extent to which individual products are compounded and about related adverse events. Health care professionals, including compounding pharmacists, are not required to report this type of information to us. However, some adverse experiences that may be attributed to compounded products have been described in the pharmaceutical literature. We would like to know more about adverse events related to compounded products and encourage comments on this topic.

### **III. Products We are Considering Including on a List of Products That are Demonstrably Difficult to Compound**

We are considering including the following on the list of products that are demonstrably

difficult to compound.

#### A. Sterile Products Compounded Under Procedures Other Than Those Described in Chapter 1206 of the USP

Sterility is a fundamental and essential characteristic of certain drug products. All dosage forms administered parenterally, aqueous-based inhalation solutions, and ophthalmic products must be sterile (i.e., free from all living microorganisms). Other products should be sterile, for example, topical products intended to treat burn and cutaneous wounds. Freedom from microorganisms is ensured initially by subjecting the product to a valid sterilization process. The sterile product must then be packaged in a form that ensures retention of this characteristic. Sterility is absolute and should never be considered in a relative manner -- a product cannot be partially or almost sterile.

Improperly prepared sterile products have a significant potential to negatively impact the public health. Many sterile drugs are parenteral products (i.e., products that are injected into the body). Parenteral medications have special and critical requirements (e.g., to be sterile and pyrogen-free) that are not necessarily shared by drugs given through other routes of administration, primarily because: (1) Administration of parenteral drugs is invasive and bypasses the body's normal barriers to external contaminants; and (2) patients receiving parenteral therapies may be critically ill, debilitated, susceptible to infection, or in need of heightened medical care.<sup>1</sup>

The preparation of sterile products is often unavoidably complex, involving many steps

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<sup>1</sup> United States Pharmacopeia, Quality Assurance for Sterile Drug Compounding An Educational Source, 1998.

and manipulations. Each step poses an opportunity for microbial contamination.<sup>2</sup> The manipulation of a sterile drug product may contaminate it, especially when nonsterile components are used (e.g., if the product is packaged into a nonsterile syringe or vial purported to be sterile), nonsterile equipment is used, or novel, complex, or prolonged aseptic processes are employed.

Compounding sterile products from sterile components using proper techniques and equipment is generally associated with a low risk of product contamination. However, manipulating sterile components does not guarantee that a sterile product will be produced. Each time a pharmacist removes a sterile product from its original container or reconstitutes a sterile product, a risk of compromising the sterility of the product exists.<sup>3</sup> Although pharmacists are not required to verify the sterility of commercially-produced sterile drug products, pharmacists need to attempt to ensure that the products remain sterile during manipulation in the pharmacy.<sup>4</sup> At the very least, minimum standards for low-risk compounding of sterile products must be met.

The practice of compounding sterile products using nonsterile components and equipment is associated with a high risk of product contamination. Examples include compounding injectable morphine from powdered morphine sulfate and compounding total parenteral nutrient solutions from nonsterile ingredients. Another example of compounding with a high risk of product contamination is batch preparation from nonsterile materials of multiple units of a sterile product in a reservoir before filtration and distribution into sterile containers. Written policies and

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<sup>2</sup> ASHP Invitational Conference on Quality Assurance for Pharmacy Prepared Sterile Products, American Journal of Hospital Pharmacy, 48:2391-2397, 1991.

<sup>3</sup> Boylan, J. C., "Essential Elements of Quality Control," American Journal of Hospital Pharmacy, 40:1936-1939, 1983.

<sup>4</sup> Akers, M. J., G. E. Wright, and K. A. Carlson, "Sterility Testing of Antimicrobial-containing Injectable Solutions Prepared in the Pharmacy," American Journal of Hospital Pharmacy, 48:2414-2418, 1991.

procedures need to be established for each step, including the sterilization process, end product testing, and process validation.<sup>5</sup> Without specialized training, facilities, and testing, contamination is likely. At the very least, minimum standards for high-risk compounding of sterile products must be met.

As reported in the pharmaceutical literature, some pharmacies prepare injectable products from nonsterile ingredients and falsely assume that the bacteria retaining filters render the product safe.<sup>6</sup> Even if properly used, sterilizing grade filters may not consistently remove all harmful foreign substances that may be present in nonsterile ingredients.<sup>7</sup>

Incidents of patient morbidity and death from pharmacy-prepared sterile drug products have occurred. Four deaths resulted from the use of contaminated cardioplegic solution (prepared by a hospital pharmacy) in heart surgery, and severe eye infection and loss of an eye resulted from pharmacy-compounded indomethacin eye drops that were not sterile.<sup>8</sup>

A pharmacy recalled one product, DMSO for Injection,<sup>9</sup> because lab analysis found samples contaminated with microbial growth. This same firm subsequently recalled another

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<sup>5</sup> Friebe, W. R., "Control of the Aseptic Processing Environment," American Journal of Hospital Pharmacy, 40:1928-1935, 1983.

<sup>6</sup> Perrin, J., "Unsafe Activities of Compounding Pharmacists," American Journal of Health Systems Pharmacists, 52: 2827-2828, 1995.

<sup>7</sup> Id.

<sup>8</sup> Tormo, V., "Perspective on Sterile Compounding Practices and Draft Guidelines," American Journal of Hospital Pharmacy, 49:946-947, 1992.

Feinberg, J., "Compounding Sterile Products: What Is Good Pharmacy Practice?" 7:1012-1014, 1992.

<sup>9</sup> Recall D-270-6 (Class I). Recall notices are available on the Internet: go to <http://www.fda.gov/search.html> and enter the recall number.



injectable product, Glycyrrhizic 8mg/30mL vials,<sup>10</sup> because lab analysis found the product contaminated with *Aspergillus versicolor*.

Pharmaceutical manufacturers of sterile products devote substantial resources to processes for achieving and maintaining product sterility. When these manufacturers cannot achieve or maintain sterility, the consequences may be severe. In February 1999, a firm recalled injectable dental products containing lidocaine, epinephrine, and mepivacaine.<sup>11</sup> Testing revealed that the firm had released non-sterile products. Organisms cultured during testing included *Staphylococcus auricularis*, *Staphylococcus epidermis*, and *Enterococcus faecalis*. Some of these microorganisms were found in the firm's sterile filling room environmental samples. These examples represent potentially life-threatening health hazards. In addition, between the years of 1996 and 1999, 24 recalls of sterile products were made due to lack of assurance of sterility.<sup>12</sup> The risks of having a non-sterile product are greater when the manufacturing controls employed by manufacturers are not in place. In one reported study of the sterility and concentration of eye drops, 100 samples of 1% pilocarpine hydrochloride solution were evaluated.<sup>13</sup> Of the 100 samples that were evaluated, 66 were prepared by local pharmacies and 34 were prepared by

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<sup>10</sup> Recall D-062-8 (Class I). Recall notices are available on the Internet: go to <http://www.fda.gov/search.html> and enter the recall number.

<sup>11</sup> Recall D-119/122-9 (Class I). Recall notices are available on the Internet: go to <http://www.fda.gov/search.html> and enter the recall number.

<sup>12</sup> Recalls D-073-7 (Class II), D-191-7 (Class II), D-192-7 (Class II), D-193-7 (Class II), D-194-7 (Class II), D-195-7 (Class II), D-013-9 (Class II), D-014-9 (Class II), D-015-9 (Class II), D-016-9 (Class II), D-017-9 (Class II), D-169-9 (Class II), D-170-9 (Class II), D-039-7 (Class II), D-009-7 (Class II), D-197-7 (Class II), D-188-9 (Class II), D-189-9 (Class II), D-190-9 (Class II), D-191-9 (Class II), D-143-9 (Class II), D-168-9 (Class II), D-172-6 (Class II), and D-173-6 (Class II). Recall notices are available on the Internet: go to <http://www.fda.gov/search.html> and enter the recall number.

<sup>13</sup> Turco, S.J., "Sterile Dosage Forms," Ophthalmic Preparations, 1994.

pharmaceutical manufacturers for interstate commerce and dispensed by local pharmacies. Fifty-two of the 66 solutions prepared by local pharmacies were contaminated with bacteria and/or fungi, whereas 1 of 34 samples prepared by pharmaceutical manufacturers was contaminated.<sup>14</sup>

### Sterile Products -- Preliminary Analysis of Factors

#### 1. Drug delivery system

Sterile products do not usually require a sophisticated drug delivery system to ensure dosing accuracy and reproducibility. Therefore, when balanced with the other factors, the drug delivery system of sterile products does not significantly contribute to a conclusion that sterile products present demonstrable difficulties for compounding that would reasonably demonstrate an adverse effect on the safety or effectiveness of the drug.

#### 2. Drug formulation and consistency

Generally, it is not challenging to achieve consistency of sterile drug product formulation. Therefore, when balanced with the other factors, the drug formulation of sterile products does not significantly contribute to a conclusion that sterile products present demonstrable difficulties for compounding that would reasonably demonstrate an adverse effect on the safety or effectiveness of the drug.

#### 3. Bioavailability

Most sterile products are delivered directly to the site of action. Therefore, when balanced with the other factors, the bioavailability of sterile products does not significantly contribute to a conclusion that sterile products present demonstrable difficulties for compounding

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<sup>14</sup> Of note, the concentration of pilocarpine hydrochloride was also more uniform in the samples prepared by pharmaceutical manufacturers for interstate commerce; the uniformity of the solutions prepared by local pharmacies varied greatly.

that would reasonably demonstrate an adverse effect on the safety or effectiveness of the drug.

#### 4. Complexity of compounding

The preparation of sterile products is unavoidably complex, involving many steps and manipulations. Each of the steps in the compounding process poses an opportunity for microbial contamination.<sup>15</sup> Even when sterile products are used as components, pharmacy manipulation of the sterile products may potentially affect the end product's sterility, potency, pyrogenicity, and particulate matter.<sup>16</sup> Because of the requirements and nature of sterile products, they are the most difficult to prepare and the consequences of error are most severe.<sup>17</sup>

In addition to being sterile, injectable pharmaceuticals must also be free from pyrogens.<sup>18</sup> Pyrogens, or endotoxins, are high-molecular-weight compounds. Chemically, pyrogens are lipopolysaccharides. Pyrogens are by-products of microorganisms and cause a reaction (generally a fever) when introduced into humans.<sup>19</sup> Pyrogens in parenteral products typically come from one of three sources: (1) The water used as a solvent, (2) the containers, or (3) the chemicals or drugs used in the preparation of the product.<sup>20</sup>

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<sup>15</sup> ASHP Invitational Conference on Quality Assurance for Pharmacy Prepared Sterile Products, American Journal of Hospital Pharmacy, 48:2391-2397, 1991.

<sup>16</sup> Boylan, J. C., "Essential Elements of Quality Control," American Journal of Hospital Pharmacy, 40:1936-1939, 1993.

<sup>17</sup> Turco, S. J., Sterile Dosage Forms, their Preparation and Clinical Application, 4th ed., 1994.

<sup>18</sup> United States Pharmacopeia, Quality Assurance for Sterile Drug Compounding, An Educational Source, 1998.

<sup>19</sup> United States Pharmacopeia, Quality Assurance for Sterile Drug Compounding, An Educational Source, 1998.

<sup>20</sup> Turco, S. J., Sterile Dosage Forms, their Preparation and Clinical Application, 4th ed., 1994.

Sterile products must be free from particulate matter, the mobile, undissolved substances that are unintentionally present in products.<sup>21</sup> Particulate matter in a sterile product may come from: (1) The solution itself and its ingredients; (2) the production process and its variables, such as the environment, equipment, and personnel; (3) the product's packaging; or (4) the preparation of the product for administration (i.e., manipulating the product, the environment in which it is prepared).<sup>22</sup> Particulate matter in intravenous solutions may be harmful, especially to patients receiving large volumes of infusion fluids (e.g., elderly persons and cancer patients) and to hospital patients who are recumbent and have sluggish pulmonary circulation.<sup>23</sup> At least two deaths and two injuries have occurred as a result of the use of intravenous infusion of nutrient admixtures.<sup>24</sup> Autopsy reports in these cases showed the presence of calcium phosphate in blood clots in the lungs of the deceased, which may have been caused by the precipitation of calcium phosphate in the admixture.

The presence of particulate matter in sterile products produced by pharmaceutical manufacturers has led to product recalls. Between 1996 and 1999, 28 recalls (Class II and Class III) of sterile products were initiated due to the presence of foreign substances, particulate matter, or precipitate. The particulate matter in the contaminated products consisted of many substances,

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<sup>21</sup> United States Pharmacopeia, Quality Assurance for Sterile Drug Compounding, An Educational Source, 1998.

<sup>22</sup> Turco, S. J., Sterile Dosage Forms, their Preparation and Clinical Application, 4th ed., 1994.

<sup>23</sup> United States Pharmacopeia, Quality Assurance for Sterile Drug Compounding, An Educational Source, 1998.

<sup>24</sup> McKinnon, B. T., "FDA Safety Alert: Hazards of Precipitation Associated With Parenteral Nutrition," Nutrition in Clinical Practice, 11:59-65, 1996.

including glass particles, precipitates, and "charred organic flakes."<sup>25</sup> The presence of particulate matter in products intended to be sterile represents a potentially life-threatening health hazard.

For these reasons, compounding sterile products is highly complex. This factor would support the inclusion of sterile products on the list of products that are demonstrably difficult to compound.

## 5. Facilities and equipment

To maintain the essential characteristics of sterile products (i.e., sterility and freedom from particulate matter and pyrogens), the products and their components must be manipulated in a suitable environment using aseptic techniques. A product, even one with components of the best quality (e.g., a commercially manufactured sterile product), may quickly become unacceptable if it is compounded using an improper procedure or in a contaminated environment. It is important to minimize bioburden during the production process even when terminal sterilization is used.

Therefore, the production facilities and associated procedures must meet exacting standards.<sup>26</sup>

For these reasons, sophisticated facilities and equipment are required to ensure proper compounding of sterile products. This factor would support the inclusion of sterile products on the list of products that are demonstrably difficult to compound.

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<sup>25</sup> Recalls D-118-6 (Class III) D-021-8 (Class II), D-177-8 (Class II), D-178-8 (Class II), D-179-8 (Class II), D-265-7 (Class II), D-001-9 (Class II), D-156-9 (Class II), D-151-9 (Class III), D-042-9 (Class II), D-043-9 (Class III), D-099-8 (Class II), D-200-7 (Class III), D-201-7 (Class III), D-202-7 (Class III), D-203-7 (Class III), D-172-7 (Class III), D-103-7 (Class III), D-104-7 (Class III), D-105-7 (Class III), D-106-7 (Class III), D-107-7 (Class III), D-108-7 (Class III), D-109-7 (Class III), D-062-6 (Class III), D-133-6 (Class III), D-230-9 (Class III), and D-169-8 (Class II). Recall notices are available on the Internet: go to <http://www.fda.gov/search.html> and enter the recall number.

<sup>26</sup> Avis, K. E., "Parenteral Preparations," Remington's Pharmaceutical Science, 18th ed., p. 1545-1569, 1990.

## 6. Training

Studies have shown that sterile solutions can easily become contaminated during preparation and use. Studies at the University of Pennsylvania Hospital of over 1,000 units of parenteral nutritional solutions prepared by the hospital pharmacy demonstrated rates of contamination between 4 and 10 percent, depending on the efficiency of the laminar flow hood and the technique of the preparer.<sup>27</sup> The studies demonstrated that when the preparer used excellent technique, the rate of contamination was as low as 1 percent.

The maintenance of sterility should not be assumed when sterile products are compounded from sterile components in a laminar flow hood or using filtration techniques. Although a laminar flow hood provides an aseptic environment, use of the hood alone neither ensures the sterility of a product nor prevents contamination due to poor aseptic techniques.<sup>28</sup>

The processes used in pharmacies to prepare sterile products are highly personnel-intensive. The contamination of pharmacy-prepared products (e.g., intravenous admixtures and prefilled syringes) by aseptic processing most likely will be caused by personnel-associated factors. These factors may include the shedding of contaminants from people into the controlled environment, improper procedures under laminar air flow, and the use of poor aseptic technique. Therefore, pharmacy personnel involved in compounding sterile products must have sufficient knowledge, training, and experience to perform the task correctly and safely. Furthermore, a pharmacy's quality assurance program for sterile products must include requirements that personnel consistently adhere to performance standards; that performance problems be monitored, detected,

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<sup>27</sup> Turco, S. J., "Hazards Associated with Parenteral Therapy," Sterile Dosage Forms, App. 4, p. 428, 1994.

<sup>28</sup> Frieben, W. R., "Control of the Aseptic Processing Environment," American Journal of Hospital Pharmacy, 40:1928-1935, 1983.

and corrected; and that personnel undergo initial and periodic certification.<sup>29</sup>

For these reasons, specialized technical training is essential to ensure proper compounding of sterile products. This factor would support the inclusion of sterile products on the list of products that are demonstrably difficult to compound.

#### 7. Testing and Quality Assurance

As described previously, improperly prepared sterile products have a significant potential to negatively impact the public health. Quality assurance is one of the basic elements of pharmacy practice and is especially important in sterile product compounding, whether sterile products are prepared from sterile components (which requires maintaining sterility) or from nonsterile components (which requires achieving sterility). Quality assurance can be accomplished when training, testing, facilities, and equipment are properly used and monitored.

In 1996, the American Society of Health System Pharmacists (ASHP) reported on the second national survey of quality assurance activities for pharmacy-prepared sterile products. ASHP reported that there have been improvements in the preparation of sterile products in the 5 years following the first survey (in 1991). However, a closer look at the results by ASHP revealed that the appropriate level of performance has not been achieved. Particularly dismaying to ASHP were the findings that few pharmacies perform environmental sampling, end-product testing, and process validations, and often sterile products are prepared in uncontrolled environments. According to ASHP, pharmacists often express the opinion that changes in this level of performance are not needed because clinical problems occur relatively infrequently. A more accurate interpretation of the relative infrequency of clinical problems might be that

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<sup>29</sup> Levchuk, J. W., "Parenteral Products in Hospital and Home Care Pharmacy Practice," Pharmaceutical Dosage Forms: Parenteral Medications, Vol. 1, 2nd ed., p. 513-568, 1992.

contamination occurs but the extent of the problem is unknown, in part because many patients simply recover from the ill effects of contamination or the illness is not attributed to the drug. Adverse events are almost inevitable if this level of performance is maintained, especially when: (1) Products are prepared in advance and stored (as occurs with batch preparation of a product), (2) products provide good conditions for bacterial growth (as in parenteral nutrition fluids), (3) products are prepared in unclean environments, and (4) patients receiving intravenous therapy are seriously ill.<sup>30</sup>

Sterile drug products should be prepared in accordance with properly designed and validated written procedures. Validation of sterile product preparation (through either terminal sterilization or aseptic processing) involves protocols designed to demonstrate that microorganisms will be effectively destroyed, removed, or prevented from being inadvertently introduced by personnel or through preparation-related activities.

All compounded sterile products should be inspected prior to use in patients. Low-risk compounded sterile products (e.g., sterile products prepared from sterile components using proper techniques and equipment) should, at a minimum, be inspected physically and visually for cloudiness and particulate matter. High-risk compounded sterile products (e.g., sterile products prepared from nonsterile components using proper techniques and equipment) should undergo end-product sterility and pyrogen testing before they are dispensed from the pharmacy.

For these reasons, there is a significant potential for harm if sterile products are compounded without proper quality assurance procedures and end-product testing. This factor would support the inclusion of sterile products on the list of products that are demonstrably

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<sup>30</sup> Myers, C. E., "Needed: Serious Attention to Sterile Products," American Journal of Health-System Pharmacy, 53:2582, 1996.



difficult to compound.

### Sterile Products -- Preliminary Conclusion

Pharmacy compounding of sterile products is a complicated issue. As described in detail above, the preparation of sterile products is unavoidably complex. We also recognize that there is a substantial need for compounded sterile products, especially in the area of extemporaneous compounding. We believe that the concerns associated with the preparation of sterile products may be alleviated by the use of minimum standards. We evaluated guidelines for pharmacy-prepared sterile products issued by the ASHP<sup>31</sup> and USP and have tentatively concluded that Chapter 1206 of the USP, "Sterile Drug Products for Home Use," describes more comprehensive controls.

For the following reasons, sterile products compounded under procedures other than those described in Chapter 1206 of the USP appear to present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of such drug products.

- Sterility of the compounded drug product is necessary and difficult to achieve and maintain.
- The compounding of sterile products is complex.
- Sophisticated facilities and equipment are required to ensure proper compounding of sterile products.
- Specialized technical training is essential to ensure proper compounding of sterile products.

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<sup>31</sup> American Society of Health System Pharmacists, "ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products," American Journal of Health-System Pharmacy, 57:1150-69, 2000 (supersedes "Technical Assistance Bulletin on Quality Assurance for Pharmacy-Prepared Sterile Products," September 1993).

- A significant potential for harm exists if sterile products are compounded without proper quality assurance procedures and end-product testing.

We are therefore considering including sterile products compounded under procedures other than those described in Chapter 1206 of the USP on the list of products that are demonstrably difficult to compound.

Chapter 1206 of the USP describes in detail methods for preparing and dispensing sterile drug products, including processes for the validation of sterilization and aseptic processes, the quality and control of environmental conditions for aseptic operations, personnel training, aseptic techniques, finished product release testing, storage and expiration dating, quality assurance programs, and equipment and facilities (including the use of smooth, nonshedding work surfaces, laminar air flow work benches, buffer rooms, anterooms, and gowning attire).

Chapter 1206 was written by USP to describe standards for compounding products intended for home use. We tentatively find that the standards in Chapter 1206, when applied to the compounding of any sterile drug product, would reasonably ensure the potency, purity, and quality of the drug product. In May 2000, USP published an in-process revision of Chapter 1206 to include procedures for all pharmacy-prepared sterile products.<sup>32</sup> Therefore, we are considering proposing that the procedures described in Chapter 1206 be followed for the compounding of all sterile products, including sterile products that are compounded in hospital pharmacies for administration in hospitals.

Chapter 1206 of the USP describes different methods and acceptable environmentally controlled workspaces for high-risk and low-risk compounding of sterile drug products. As

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<sup>32</sup> United States Pharmacopeia, Pharmacopeial Forum, Volume 26, p. 812, 2000.

explained in Chapter 1206 of the USP, a pharmacist dispensing a sterile drug product is responsible for ensuring that the product has been prepared, labeled, controlled, stored, dispensed, and distributed properly. The dispensing pharmacist is also responsible for ensuring that the sterile product retains its quality attributes within acceptable limits through a written quality assurance program. Chapter 1206 of the USP emphasizes the quality and the control of the processes used, personnel performance, and the environmental conditions under which the processes are performed. We believe that the safety, potency, purity, efficacy, and quality of sterile drug products may be maintained if they are compounded under the procedures described in Chapter 1206 of the USP.

We seek comment on whether it would be appropriate to include on the list of drugs that are difficult to compound, sterile products that are not compounded in accordance with Chapter 1206 of the USP. We are also specifically seeking comment on requiring compliance with USP Chapter 1206 for relatively low-risk compounding (i.e., compounding sterile drug products from sterile components using proper techniques and equipment).

#### B. Transdermal Delivery Systems (TDSs)

A TDS is a self-contained, discrete dosage form that, when applied to intact skin, delivers a drug through the skin at a controlled rate to the systemic circulation.<sup>33</sup> The delivery rate is usually controlled by the skin or by a membrane contained in the delivery system.<sup>34</sup>

TDS products are complex to develop and may require the use of new technologies. Each

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<sup>33</sup> Monkhouse, D. C., A. S. Huq, "Transdermal Drug Delivery -- Problems and Promises," Drug Development and Industrial Pharmacy, 14:183-209, 1988.

<sup>34</sup> Zatz, J. L., "Fundamentals of Transdermal Controlled Drug Administration: Physicochemical Considerations," Drug Development and Industrial Pharmacy, 9:561-577, 1983.

system is formulated to meet specific biopharmaceutical and functional criteria. The materials of construction, configurations, and combination of the drug with the proper cosolvents, excipients, penetration enhancers, and membranes must be carefully selected and matched to optimize adhesive properties and drug delivery requirements. The equipment and the technology required for the manufacture of TDS products limit their preparation to properly equipped manufacturers.

The four major types of TDS products are: (1) Reservoir, which holds the active ingredient in a solution or suspension between the backing layer and a rate controlling membrane (reservoir systems consist of an adhesive overlay for proper skin adhesion); (2) matrix, which consists of a solution or suspension dispersed within a polymer or cotton pad that is in direct contact with the skin and is held to the skin by adhesive that is applied to the perimeter of the system; (3) drug-in-adhesive matrix, in which the drug is dispersed in the adhesive, providing for direct skin contact; and (4) multilaminate drug-in-adhesive matrix, in which the drug is dispersed in adhesive, but there are multiple layers of the drug that are divided by membranes between the layers.<sup>35</sup> This concept paper only discusses these four types of TDSs, and we propose to treat all four types of TDS products in the same manner.

As stated previously, a TDS delivers a drug through the skin at a controlled rate to the systemic circulation. This concept paper does not cover products that do not meet these criteria. Examples of products that are not TDSs include surgical tape containing a drug for topical use and a topical ointment used in conjunction with an occlusive dressing.

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<sup>35</sup> Ghosh, T. K., W. R. Pfister, and S. Yum, Transdermal and Topical Drug Delivery Systems, 1997.

## TDS Products -- Preliminary Analysis of Factors

### 1. Drug delivery system

In general, a TDS comprises a backing that supports a reservoir that holds the active ingredient solution together with release-controlling materials, an adhesive to hold the patch in place on the skin, and a protective peel-away cover.<sup>36</sup> Some TDS products also contain a membrane that forms the patch/skin interface and controls the rate of drug release.

The process by which a TDS is developed and manufactured is highly complex. There are no standard designs. Each product is developed individually. Manufacturers interested in developing a TDS product develop deliberate project plans that address factors such as the permeation of the active ingredient through the skin at a specific rate, the pharmacokinetic properties of the drug substance, the interaction and compatibility of the components of the system, and the surface area of the system.<sup>37</sup> Without such careful consideration in the design phase, safe and effective delivery of the drug substance cannot be ensured.

The purpose for each component of a TDS must be well defined, and all the component specifications must be well controlled. Most TDS components are critical to the proper functioning of the dosage form, and their quality specifications are unique to each product. Components cannot merely be chosen from a catalog or used off-the-shelf. Adequate TDS performance is dependent upon controlling both the quality of the customized components and a unique fabrication process. Variability in either is likely in the compounding setting and would

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<sup>36</sup> Scheindlin, S., "Nothing New Under the Sun or in Pharmacy," Pharmacy Times, 44-46, September 1994.

<sup>37</sup> Cleary, G. W., "Transdermal Drug Delivery," Cosmetics and Toiletries, 106:97-109, 1991.

translate into unacceptable variability in product quality.<sup>38</sup> The packaging of the TDS is critical for its stability, and considerable knowledge of the packaging material and equipment is needed. The container closure system for a TDS is usually a foil pouch made from multilaminates with foil, paper, and heat sealable polyethylene portions. The foil serves as a vapor barrier, and polyethylene is used for heat sealing purposes. Since TDS products may contain volatile components, it is critical that the stability of the volatile components be maintained. Quality controls such as testing for proper heat sealing and stability are required.<sup>39</sup>

For these reasons, the TDS drug delivery system is highly sophisticated and its design is essential to ensure dosing accuracy and reproducibility. This factor would support the inclusion of TDS products on the list of products that are demonstrably difficult to compound.

## 2. Drug formulation and consistency

The proper formulation of a TDS is essential for providing a suitable drug delivery rate. There have been incidents in which commercial manufacturers of TDSs have recalled products due to formulation difficulties. For example, one firm initiated a recall of its TDS product because of ingredient crystal formation, which resulted in a loss of potency.<sup>40</sup>

Not all drug substances are suitable for the transdermal route of administration. In fact, many pharmacologically active drugs have the incorrect physicochemical properties to partition

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<sup>38</sup> Van Buskirk, G. A., M. A. Gonzalez, V. P. Shah, S. Barnhardt, C. Barrett, S. Berges, et al., "Workshop Report: Scale-up of Adhesion Transdermal Drug Delivery Systems," Pharmaceutical Research, 14:846-853, 1997.

<sup>39</sup> See, for example, recall D-168-6 (Class II). The product was recalled because a packaging defect allowed the system to dry out and become lower in weight than the control system. Recall notices are available on the Internet: go to <http://www.fda.gov/search.html> and enter the recall number.

<sup>40</sup> Recall D-126-4 (Class III). Recall notices are available on the Internet: go to <http://www.fda.gov/search.html> and enter the recall number.

into the skin. A thorough understanding of the drug's physical chemistry is vitally important when selecting a drug for transdermal delivery.<sup>41</sup> Further, the therapeutic agent must be potent. Given that the size of a patch cannot (for practical purposes) exceed approximately 50 square centimeters and given that the barrier function of the skin is difficult to overcome, it is not within the capability of existing technology to deliver significantly more than 50 milligrams of drug per day by the transdermal route. Additionally, the agent must be effective when delivered slowly over a relatively long time period.<sup>42</sup> These factors limit the number of drug substances suitable for transdermal delivery and increase the risk that an unsafe or ineffective product may be compounded.

In the manufacture of TDS products, the components of the formulation, vehicle, adhesive, and penetration enhancers or surfactants must be tested and matched to each other. These components affect the release rate of the drug and the adherence of the device to the skin and, therefore, have a large impact on the design of the final product.<sup>43</sup> No universal TDS blueprint exists that can be followed to ensure an optimal product because the parameters depend on the specific pharmacologic properties of the drug, its physicochemical properties, and its clinical function.<sup>44</sup>

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<sup>41</sup> Cleary, G. W., "Transdermal Drug Delivery," Cosmetics and Toiletries, 106:97-109, 1991.

<sup>42</sup> Guy, R. H., "Current Status and Future Prospects of Transdermal Drug Delivery," Pharmaceutical Research, 13:1765-1769, 1996.

<sup>43</sup> Recalls D-308-4 (Class III), D-309-4 (Class III), and D-254-7 (Class III), all initiated due to release rate problems. Recall notices are available on the Internet: go to <http://www.fda.gov/search.html> and enter the recall number.

<sup>44</sup> Pfister, W. R., D. Hsieh, "Permeation Enhancers Compatible with Transdermal Drug Delivery Systems: Part II System Design Considerations," Pharmaceutical Technology, p. 54-55, October 1990.

Vehicle selection is also important to the performance of a TDS. Factors such as drug stability in the vehicle, the specific product use, and the site of application must be considered to produce a dosage form that will readily release the drug when placed in contact with the skin. Further, the release characteristics of the vehicle are dependent on the physicochemical properties of the specific drug substance to be delivered to the skin. A vehicle that optimally delivers one drug substance may be inappropriate for delivery of a different drug substance. The vehicle can grossly affect drug bioavailability and thus influence the clinical efficacy of the drug.<sup>45</sup>

TDS products are worn on the skin and must provide good skin contact over the total area of application to ensure adequate drug delivery. As a result, special attention is required in selecting the adhesive used in the system. TDS products are worn for extended periods and must stay firmly attached during that time. There is often direct contact between the adhesive and the drug or other excipients. This contact may alter the properties of the adhesive and/or may influence the release of drug. The adhesive type (for example, silicone rubber, acrylic copolymer, or polyisobutylene) has an effect on the solubility of the drug in the adhesive and on the diffusion coefficient of the drug within the adhesive matrix. This interaction can affect the rate and extent of drug release from the TDS.<sup>46</sup> Substituting one adhesive for another may significantly alter the performance of the system or produce localized sensitivity reactions to the new substance.

Skin irritation and sensitization must also be addressed in the development of a TDS. A skin reaction may be caused by the drug itself or by any vehicles, enhancers, adhesives, or

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<sup>45</sup> Cleary, G. W., "Transdermal Drug Delivery," Cosmetics and Toiletries, 106:97-109, 1991.

<sup>46</sup> Van Buskirk, G. A., M. A. Gonzalez, V. P. Shah, S. Barnhardt, C. Barrett, S. Berges, et al., "Workshop Report: Scale-up of Adhesion Transdermal Drug Delivery Systems," Pharmaceutical Research, 14:846-853, 1997.



polymers that are present in the system. Adding a new component can completely change skin adhesion or drug permeation and may even create toxicity.<sup>47</sup>

Another important component of a TDS product is its backing. The type of backing used in a TDS product may vary the drug delivery rate and the adhesion of the TDS to the skin. The use of an improper release liner may lead to the inability of a patient to remove the release liner from the system.<sup>48</sup>

The drug delivery rate may also change when a membrane is used without prior testing of its physical and chemical characteristics.

For these reasons, the drug formulation of a TDS product, including the interaction of all TDS components, is highly sophisticated, and the proper formulation is required to ensure dosing accuracy and reproducibility. This factor would support the inclusion of TDS products on the list of products that are demonstrably difficult to compound.

### 3. Bioavailability

The skin can be a formidable barrier to the entry of foreign agents into the body. The outermost layer of the epidermis, the stratum corneum, is the major rate limiting barrier. However, the skin does permit the passive absorption of lipophilic low molecular weight drugs in quantities that may be sufficient to cause local or systemic effects. As previously discussed, drug substances vary in their ability to partition into the skin and enter the systemic circulation. Without a thorough understanding of the physicochemical profile of the specific drug, transdermal delivery may lead to therapeutic failure or toxicity. Not all drugs adequately released by a TDS will reach the

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<sup>47</sup> Cleary, G. W., "Transdermal Drug Delivery," Cosmetics and Toiletries, 106:97-109, 1991.

<sup>48</sup> Cleary, G. W., "Transdermal Drug Delivery," Cosmetics and Toiletries, 106:97-109, 1991.

systemic circulation at the desired level.<sup>49</sup>

Skin temperature and moisture also influence the rate and extent of absorption of the drug substance delivered transdermally. If the backing material of the system is changed from nonocclusive (allowing gases and water vapor to diffuse through the structure) to occlusive (impermeable to gases and liquids), the skin temperature and moisture will be elevated.<sup>50</sup> This elevation could potentially induce increased levels of drug in the blood and toxicity in certain circumstances.<sup>51</sup>

Bioavailability is also affected by the design and formulation of the TDS. For example, use of the improper amount of penetration enhancer may lead to a lack of efficacy or toxicity.

For these reasons, reproducible bioavailability of TDS products is difficult to achieve. This factor would support the inclusion of TDS products on the list of products that are demonstrably difficult to compound.

#### 4. Complexity of compounding

TDS products are complex to develop and many complicated and interrelated steps are involved in the compounding of TDS products. As discussed above, the materials of construction, configurations, and combination of a suitable drug with the proper cosolvents, excipients, penetration enhancers, and membranes must be carefully selected and assembled to ensure effective delivery of the drug product.

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<sup>49</sup> Ghosh, T. K., A. K., Banga, "Methods of Enhancement of Transdermal Drug Delivery Part I, Physical and Biochemical Approaches," Pharmaceutical Technology, p. 72, March 1993.

<sup>50</sup> Cleary, G. W., "Transdermal Drug Delivery," Cosmetics and Toiletries, 106:97-109, 1991.

<sup>51</sup> Block, L. H., "Medicated Applications," Remington's Pharmaceutical Science, 18th ed., p. 1596-1602, 1990.

For these reasons, compounding TDS products is highly complex. This factor would support the inclusion of TDS products on the list of products that are demonstrably difficult to compound.

#### 5. Facilities and equipment

Expensive and sophisticated equipment is needed to ensure the proper compounding and testing of TDS products. The process of fabricating a TDS requires special equipment for the casting solution and for coating, drying, laminating, and pouching the products. Furthermore, the solvents used in the fabrication process require environmental controls.

Sophisticated facilities and equipment are needed to ensure proper compounding of TDS products. This factor would support the inclusion of TDS products on the list of products that are demonstratively difficult to compound.

#### 6. Training

The specific formulation requirements, the complicated and interrelated steps needed to compound a TDS product, and the sophisticated equipment involved in the assembly and testing of a TDS product necessitate personnel with specialized, technical training in production and quality assurance for TDS products. The training that is essential to ensure proper compounding of TDS products is specialized and technical and directly affects the potency, purity, and quality of the drug. This factor would support the inclusion of TDS products on the list of products that are demonstratively difficult to compound.

#### 7. Testing and Quality Assurance

In-process and end-product testing of TDS products is important to ensure that the multi-variable production process is successful. If a TDS product has not been adequately tested and evaluated clinically, the product may not be effective. Generally, adequate tests measure

content, content uniformity of the active ingredient, purity, residual solvents, residual monomers, release liner peel force, adhesion, microbial testing, release rate, and pouch integrity.

Even minimally adequate batch testing of TDS products requires expensive and sophisticated equipment. For example, to adequately measure the release rate of the system, a manufacturer would commonly use Apparatus 5 of the USP. Adequate dissolution testing involves special training for the handling of samples.

For these reasons, the testing required to ensure potency, purity, and quality of TDS products is sophisticated and difficult to perform. This factor would support the inclusion of TDS products on the list of products that are demonstrably difficult to compound.

#### TDS Products -- Preliminary Conclusion

TDS products appear to present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of such drug products for the following reasons.

- TDSs are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of TDS products is complex.
- Sophisticated facilities and equipment are needed to ensure proper compounding of TDS products.
- Specialized technical training is essential to ensure proper compounding of TDS

products.

- Sophisticated, difficult to perform testing of the compounded product is required to ensure potency, purity, and quality of the drug product prior to dispensing.

We therefore are considering including TDS products on the list of products that are demonstrably difficult to compound.

### C. Metered Dose Inhaler (MDI) Products

The MDI is one of the most complicated drug delivery systems currently marketed by the pharmaceutical industry. MDI products contain therapeutically active ingredients dissolved or suspended in a propellant, a mixture of propellants, or a mixture of solvents, propellants, and/or other excipients in compact pressurized aerosol dispensers. The aerosol dispenser consists primarily of a metal or glass container, a valve assembly, and an actuator of suitable design. An MDI product may discharge up to several hundred metered doses of one or more drug substances. Depending on the product, each actuation may contain from a few micrograms (mcg) up to milligrams (mg) of the active ingredients delivered in a volume typically between 25 and 100 microliters.

MDI products are unique with respect to formulation, container, closure, manufacturing, in-process controls, final controls, and stability. These features can affect the safety and efficacy of the product as well as the ability of the product to deliver reproducible doses to patients.<sup>52</sup>

MDI products are primarily used by patients suffering from chronic lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Individuals suffering from asthma and COPD tend to have airways that are hyper-reactive to inhalants. It is therefore critical that the

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<sup>52</sup> FDA, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation" (draft), 1998.

contents and the delivery characteristics of MDI products be carefully controlled to ensure that the product will be safe and effective. Even slight changes in the formulation, drug substance particle size, valve, or actuator can have a major effect on the aerosol delivery and potency characteristics. This effect can significantly alter the safety and effectiveness of the device. For example, a change in particle size distribution may lead to greater systemic absorption of a beta agonist drug, which can increase the amount of systemic side effects and may also decrease the local effectiveness of the drug in the lungs.

### MDI Products -- Preliminary Analysis of Factors

#### 1. Drug delivery system

Unlike most other drug products, the dosing and performance and, therefore, the safety and efficacy of a MDI product may be directly dependent on the design, reproducibility, and performance characteristics of the container closure system. In MDI products, the container closure system consists of the container, the valve and its components, the actuator, additional accessories (e.g., spacer), and protective packaging, if applicable.

*Container and valve* -- The composition of the container and coating material (if applicable) may affect the quality of an MDI product. Since inhalation aerosol formulations include organic liquids as the propellant or the vehicle (e.g., chlorofluorocarbons, hydrofluorocarbons, alcohols), potential leaching of compounds from the elastomeric and plastic components of the container closure system into the formulation is a serious safety concern. Materials that leach from the components of the container closure system (e.g., plastics, rubbers, and sealants) into the drug formulation have the potential to induce bronchospasm. Many of these materials (e.g., various rubbers) are carcinogenic compounds whose levels must be carefully limited to minimize the risk to patients who use MDI products chronically. The metering valve

must be compatible with the formulation. The valve should repeatedly dispense the aerosolized drug in discrete, accurate, small doses in the desired physical form. The performance of the valve and its compatibility with other components of the drug product must be known. For plastic components, there is the potential for drug adsorption into the plastic, swelling of the plastic, and leaching of contaminants from the plastic into the drug product. The specific valve used in each MDI drug product should be carefully selected considering the type and critical dimensions of the container, the formulation, stem diameter, stem groove dimensions, and, if applicable, the stem and body orifices of the valve.

*Actuator* -- For MDI products, the actuator generates aerosol particles, directs the dose, influences the velocity of the aerosol particles, and controls the amount of medication, the particle size distribution, and droplet size distribution of the formulation that is available to the patient. The size, shape, tolerances, and design of the actuator, actuator orifice, and the valve stem holder are critical to the function of the actuator.<sup>53</sup>

For these reasons, the drug delivery system of MDIs is highly sophisticated and is crucial to ensuring drug dosing accuracy and reproducibility. This factor would support the inclusion of MDI products on the list of products that are demonstratively difficult to compound.

## 2. Drug formulation and consistency

In an MDI, the drug formulation that is delivered to the patient is a mixture of micronized (or solubilized) drug substance in the desired physical form within a residual matrix of oily excipient material, propellant, and/or solvent. The composition of an MDI formulation and the physicochemical content of each of the formulation components are crucial in defining the overall

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<sup>53</sup> FDA, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation" (draft), 1998.

physical stability and performance characteristics of the drug. The formulation composition also has a direct effect on the degree or extent of agglomeration or suspendibility of the drug substance particles. In suspension inhalation aerosols, the drug substance can float or settle, depending on the relative densities of the drug substance and the liquid phase of the formulation. Other important properties of the drug substance may include particle size distribution, particle morphology, solvates and hydrates, clathrates, morpnic forms, amorphous forms, solubility profile, moisture or residual solvent content, microbial quality, pH profile and pKa(s), and specific rotation.

The formulation of a typical MDI product is composed mostly of propellant(s) and cosolvent(s). The type and amount of the propellant(s) and cosolvent(s) determine the internal pressure of an inhalation aerosol, a critical factor in MDI performance.

Preferential interaction of the formulation with various internal container closure system components (for example, adherence of the drug substance to the walls of the container or valve components) may contribute to a nonhomogeneous distribution of drug substance. This interaction can contribute to inconsistent dose delivery and particle size distribution.

In an MDI, the aerosolization of materials from a pressurized container is a complex and rapid sequence of events. When the contents of the metering chamber are released, the contents expand in volume and form a mixture of gas and liquid before being discharged as a jet through the opening of the actuator. Within the expanding jet, the droplets undergo a series of processes. After the drug product is aerosolized into many droplets and during the propulsion of these droplets from the actuator to the patient's airway, the drug substance particles in the droplets become progressively more concentrated because the volatile propellant components rapidly evaporate.



Due to the unique features of MDI products, an individual interested in manufacturing or compounding an MDI product would need to know a great deal of specific and detailed information about the formulation of the product. Such information would include the comprehensive characterization of the physical and chemical properties of the drug substance and parameters that are critical for reproducible drug product performance. These parameters may include specifications for control of particle size distribution and crystalline forms (e.g., shape, texture, surface) of the drug substance.

Excipients make up a significant portion of the formulation content by weight for most MDI products. As a result, the quality of the excipients has a substantial effect on the quality, potency, purity, safety, effectiveness, and stability of such drug products. The sensitive nature of the patient population warrants complete characterization and strict quality control of these excipients. Excipients that are approved for other routes of administration may be toxic when delivered directly to the airways by inhalation. Minor changes in the concentration or dose of an excipient can result in markedly different toxicologic changes when given by the inhaled route. In addition, careful control of the impurities and degradation products in the drug substance and drug formulation (i.e., propellants and surfactants) is crucial because even minute quantities of some substances can lead to bronchospasm when inhaled by sensitive individuals.<sup>54</sup>

Currently, almost all MDI products contain chlorofluorocarbons (CFCs). The manufacture and/or importation of CFCs for commercial applications other than MDIs have been banned in the United States and other developing countries under the terms of the Montreal Protocol on Substances that Deplete the Ozone Layer (September 16, 1987, S. Treaty Doc. No. 10, 100th

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<sup>54</sup> FDA, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation" (draft), 1998.

Cong., 1st sess., 26 I. L. M. 1541 (1987)) and the 1990 Clean Air Act (42 U.S.C. 601 et seq.). As a result, access to pharmaceutically pure CFCs is tightly regulated, and it may be difficult for a compounding pharmacist to obtain the appropriate pharmaceutical grade CFCs.

The development of MDIs with propellants other than CFCs has proven to be difficult and has involved large expenditures of both time and money by some of the largest pharmaceutical firms. It would be unreasonable to expect compounding pharmacies to be able to produce non-CFC MDIs without compromising the safety and efficacy of the product.

The composition of the formulation contained in MDIs and the complexity of the dosage form itself make product-to-product uniformity critical for dosing accuracy, yet difficult to achieve. The safety and efficacy of MDI products are concerns if there is product-to-product variability.

For these reasons, the drug formulation of an MDI product is highly sophisticated and its composition is crucial in defining the drug's physical stability and performance characteristics. Product-to-product uniformity is critical for dosing accuracy and is difficult to achieve. This factor would support the inclusion of MDI products on the list of products that are demonstratively difficult to compound.

### 3. Bioavailability

The compounding process can significantly affect the bioavailability of MDI products. As discussed previously, the composition of an MDI formulation and the container closure system are crucial in defining its performance characteristics. The propellant(s), cosolvent(s), and excipients of an MDI product may affect the bioavailability of the drug product.

Reproducible bioavailability of MDI products is difficult to achieve. This factor would support the inclusion of MDI products on the list of products that are demonstrably difficult to

compound.

#### 4. Complexity of compounding

There are multiple, complicated and interrelated steps with a significant potential for error in compounding MDI products. As discussed above, the MDI is one of the most complicated drug delivery systems currently marketed. The product formulation and the design and performance characteristics of the container closure system need to be carefully controlled to ensure the dosing (including the dosing characteristics), performance, stability, and bioavailability of the MDI product.

For these reasons, compounding MDI products is highly complex. This factor would support the inclusion of MDI products on the list of products that are demonstrably difficult to compound.

#### 5. Facilities and equipment

The complex nature of the formulation and the container closure system of MDI products requires that they be produced in an area with stringent environmental controls. Air cleanliness, humidity, and temperature should be regulated. Exposure to high temperature during manufacturing followed by storage at room temperature can disrupt particle size distribution<sup>55</sup> and has resulted in recalls of commercial products.

Sophisticated equipment, such as a crimper and pressure filler for propellant and a propellant pump, is required for the production of MDIs. In addition, a product filler capable of reproducing an exact fill amount from container to container is needed.

Sophisticated facilities, including an area with stringent environmental controls, and

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<sup>55</sup> FDA, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation" (draft), 1998.

sophisticated equipment are needed to ensure proper compounding of MDI products. This factor would support the inclusion of MDI products on the list of products that are demonstratively difficult to compound.

#### 6. Training

The specific formulation requirements and the special attributes of the container closure system for MDIs necessitate personnel with specialized, technical training in production and quality assurance for MDI products. This essential training directly affects the potency, purity, and quality of the drug. This factor would support the inclusion of MDI products on the list of products that are demonstrably difficult to compound.

#### 7. Testing and Quality Assurance

The following tests are necessary to assure MDI product quality.

*Particle Size Distribution* -- One form of control which is more critical for inhalation aerosols than for most other conventional drug products is aerodynamic particle size distribution of the delivered dose. In fact, MDI products have been recalled because of failure to meet particle size distribution specifications.<sup>56</sup> A change in particle size distribution may lead to greater systemic absorption of a beta agonist drug, which can increase the amount of systemic side effects and may also decrease the local effectiveness of the drug in the lungs. Particle size distribution is dependent on the formulation, the valve, and the mouthpiece of the MDI. The optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized as being in the range of 1 to 5 microns. The aerodynamic particle size distribution is influenced by

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<sup>56</sup> Recalls D-050-5 (Class II) and D-121-4 (Class I). Recall notices are available on the Internet: go to <http://www.fda.gov/search.html> and enter the recall number.

many factors, including the characteristics of the spray of the drug product, and is not solely determined by the size of the individual drug substance particles initially suspended in the formulation.

*Moisture Content* -- Testing for the presence of water in the container should be performed, particularly for suspension formulations. Water or moisture should be strictly limited to prevent changes in particle size distribution, morphic form, and other characteristics (e.g., crystal growth and aggregation).

*Leak Rate* -- The vapor pressure within the container directly influences the performance of the actuator and valve and, therefore, the delivery of the proper dose to the patient. Additionally, leakage of the propellants may concentrate the contents of the container to a point where dose content uniformity, particle size distribution, or both would be outside acceptable limits. Commercial MDI products have, in the past, been recalled due to failure to meet leak rate specifications.<sup>57</sup>

*Leachables* -- Because inhalation aerosol formulations include organic liquids as the propellant or the vehicle (e.g., CFCs, hydrofluorocarbons, alcohols), potential leaching of compounds from the elastomeric and plastic components of the container closure system into the formulation is a serious concern. Testing should be performed to identify leachables and their concentration profiles in the drug product.

*Microbial limits* -- The microbial quality of an MDI product should be controlled by appropriate tests and acceptance criteria for total aerobic count, total yeast and mold count, and freedom from certain pathogens. At a minimum, the acceptance criteria should meet the criteria

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<sup>57</sup> Recall D-064-7 (Class III). Recall notices are available on the Internet: go to <http://www.fda.gov/search.html> and enter the recall number.

proposed in the Pharmacopeial Forum.<sup>58</sup> Furthermore, appropriate testing should be performed to demonstrate that the drug product does not support the growth of microorganisms and that the microbial quality is maintained throughout the expiration period.<sup>59</sup>

Sophisticated and difficult-to-perform testing of MDI products, including particle size distribution, moisture content, leak rate, leachables, and microbial limit testing are needed to ensure potency, purity, and quality of MDI products prior to dispensing. This factor would support the inclusion of MDI products on the list of products that are demonstratively difficult to compound.

#### MDI Products -- Preliminary Conclusion

MDI products appear to present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products for the following reasons.

- Metered dose inhalers are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility, and product-to-product uniformity is critical for dosing accuracy and is usually difficult to achieve.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of MDI products is complex.

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<sup>58</sup> United States Pharmacopeia, The Pharmacopeial Forum, Vol. 22, p. 3098, 1996.

<sup>59</sup> FDA, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation" (draft), 1998.

- Sophisticated facilities and equipment are required to ensure proper compounding of the drug product.
- Specialized, technical training is essential to ensure proper compounding of the drug product.
- Sophisticated, difficult to perform testing of the compounded drug product is required to ensure potency and purity.

Therefore, we are considering including MDI products on the list of products that are demonstrably difficult to compound.

#### D. Dry Powder Inhaler Products

Dry powder inhalers (DPIs) are designed to dispense powders for inhalation. DPIs contain active ingredient(s) alone or with suitable excipient(s). A DPI may discharge up to several hundred metered doses of drug substance(s). DPIs are complex drug products that differ in many aspects from more conventional drug products. Current designs include pre-metered and device-metered DPIs, both of which can be driven by patient aspiration alone or with power assistance. Pre-metered DPIs contain previously measured doses or dose fractions in some type of units (e.g., single or multiple presentations in blisters, capsules, or other cavities) that are subsequently inserted into the device during manufacture or by the patient before use. After insertion, the dose may be inhaled directly from the pre-metered unit or it may be transferred to a chamber before being inhaled by the patient. Device-metered DPIs have an internal reservoir containing enough formulation for multiple doses that are metered by the device itself during actuation by the patient. There is a wide array of potential DPI designs, all complex in their design and function and many with characteristics unique to the particular design.

Regardless of design, the most crucial attributes of DPIs are the reproducibility of the dose

and particle size distribution. It is difficult to maintain these qualities through the expiration date and to ensure the functionality of the device during the period of patient use. The unique characteristics of DPIs must be considered in their preparation, particularly with respect to the product's formulation, container closure system, and testing.<sup>60</sup>

### DPI Products -- Preliminary Analysis of Factors

#### 1. Drug delivery system

Unlike most other drug products, the dosing and performance and, therefore, the safety and efficacy of a DPI product are directly dependent on the design, reproducibility, and performance characteristics of a DPIs container closure system.

A DPI product consists of its container and closure system (including any protective packaging) and the drug formulation. The design, composition, and quality control of the individual components of the container closure are key to maintaining the chemical and physical stability of the formulation and ensuring that the performance characteristics of the drug product (e.g., dosing, particle size distribution) are reproducible. The performance characteristics of the device and its compatibility with the formulation must be thoroughly investigated. A properly performing DPI should deliver accurate doses of the drug substance in the desired physical form through the life of the device.<sup>61</sup>

For these reasons, the drug delivery system of DPIs is highly sophisticated and is crucial to ensuring drug dosing accuracy and reproducibility. This factor would support the inclusion of DPI products on the list of products that are demonstratively difficult to compound.

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<sup>60</sup> FDA, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation" (draft), 1998.

<sup>61</sup> FDA, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation" (draft), 1998.



## 2. Drug formulation and consistency

The composition and physicochemical characteristics of the formulation and components of a DPI have a direct effect on the stability of the formulation as well as on the dosing performance of the product.

For example, a carrier may be used in a DPI as a bulking agent to enhance reproducible dose metering. The suitability of a carrier is dependent on its chemical and physical characteristics, which have a direct effect on the performance of the product (e.g., the ease of drawing-up and transporting of the formulation, energy input needed for dispersion of the active ingredient from the carrier, hygroscopicity of the formulation). Hygroscopicity (i.e., the extent to which the formulation takes up or retains moisture) may affect the particle size distribution of the emitted drug substance, the stability of the drug substance, the dose hold-up in the device, and hence the delivered dose.

Other important properties of the drug substance that relate to formulation and consistency may include particle size distribution, particle morphology, solvates and hydrates, morphic forms, amorphous forms, moisture or residual solvent content, and microbial quality.

Interaction of the formulation with various container and closure components may contribute adversely to the performance characteristics of the drug product. These interactions can contribute to inconsistent dose delivery and particle size distribution.

Due to the unique features of DPI products, an individual interested in manufacturing or compounding a DPI product would need to know a great deal of specific and detailed information about the formulation of the product. Such information would include the comprehensive characterization of the physical and chemical properties of the drug substance and parameters that are critical for reproducible drug product performance. These parameters may include

specifications for control of particle size distribution and crystalline forms (e.g., shape, texture, surface) of the drug substance.

Excipients make up a significant portion of the formulation content by weight for most DPI products. As a result, the quality of the excipients has a substantial effect on the quality, potency, purity, safety, effectiveness, and stability of such drug products. The sensitive nature of the patient population warrants complete characterization and strict quality control of these excipients. Excipients that are approved for other routes of administration may be toxic when delivered directly to the airways by inhalation. Minor changes in the concentration or amount of an excipient can result in different toxicology when given by the inhaled route. In addition, careful control of the impurities and degradation products in the drug substance and other drug formulation components (e.g., carriers) is crucial because even minute quantities of some substances can lead to bronchospasm when inhaled by sensitive individuals.<sup>62</sup>

The composition of the formulation contained in DPIs and the complexity of the dosage form itself make product-to-product uniformity critical for dosing accuracy, yet difficult to achieve. The safety and efficacy of DPI products are concerns if there is product-to-product variability.

For these reasons, the drug formulation of a DPI product is highly sophisticated and its composition is crucial in defining the drug's physical stability and performance characteristics. Product-to-product uniformity is critical for dosing accuracy and is difficult to achieve. This factor would support the inclusion of DPI products on the list of products that are demonstratively difficult to compound.

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<sup>62</sup> FDA, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation" (draft), 1998.

### 3. Bioavailability

The bioavailability and, therefore, effectiveness of a DPI can be significantly affected during compounding. As discussed above, the composition of an DPI formulation and container closure system are crucial in defining a DPI product's performance characteristics. The excipients of a DPI product may affect the performance of the drug product and, therefore, the bioavailability and effectiveness of the drug product.

For these reasons, reproducible bioavailability and, therefore, effectiveness of DPI products are difficult to achieve. This factor would support the inclusion of DPI products on the list of products that are demonstrably difficult to compound.

### 4. Complexity of compounding

There are multiple, complicated and interrelated steps with a significant potential for error in compounding DPI products. As discussed previously, the DPI is one of the most complicated drug delivery systems currently marketed. The product formulation and the design and performance characteristics of the container closure system need to be carefully controlled to ensure accurate dosing and the performance, stability, and bioavailability of the DPI product.

For these reasons, compounding DPI products is highly complex. This factor would support the inclusion of DPI products on the list of products that are demonstrably difficult to compound.

### 5. Facilities and equipment

The complex nature of the formulation and the container closure system of DPI products requires that they be produced in an area with stringent environmental controls. Air cleanliness, humidity, and temperature should be regulated. For example, exposure to humidity during the manufacturing process can disrupt particle size distribution, as can exposure to high temperature

during manufacturing, followed by storage at room temperature.

Sophisticated equipment that is specialized and custom made for each DPI is necessary to make the drug product and delivery system.

Sophisticated facilities, including an area with stringent environmental controls, and sophisticated equipment are needed to ensure proper compounding of DPI products. This factor would support the inclusion of DPI products on the list of products that are demonstratively difficult to compound.

#### 6. Training

The specific formulation requirements and the special attributes of the container closure system for DPIs necessitate personnel with specialized, technical training in production and quality assurance for DPI products. This factor would support the inclusion of DPI products on the list of products that are demonstratively difficult to compound.

#### 7. Testing and Quality Assurance

Sophisticated, difficult to perform testing of DPIs is necessary to ensure their potency, purity and performance characteristics. Performance of the following tests is recommended:

*Particle Size Distribution of Emitted Dose* -- One form of control that is more critical for inhalation powders than for most other conventional drug products is the aerodynamic particle size distribution of the delivered dose. Particle size distribution in a DPI is dependent on the formulation and the container closure system. The optimum aerodynamic particle size distribution for most inhalation products has generally been recognized as being in the range of 1 to 5 microns. The aerodynamic particle size distribution is influenced by many factors, such as the physicochemical characteristics of the drug substance, carriers (if present), environmental conditions such as humidity, and interactions among the drug substance, carrier (if present), and

delivery system. Extensive testing parameters for DPIs are necessary to maximize reproducibility and limit variability inherent to DPIs. This testing is important because there are intrinsic differences between formulations, devices, and methods of delivery of DPIs. For example, since DPI products are necessarily dry, selection of and specifications for the surfaces of the container closure system with which the formulation may come in contact may be critical in terms of drawing-up and transporting impacted formulation particles. Consideration must also be given to flow rate selection and duration. In general, varying humidity conditions may affect particle size distribution determinations, necessitating tighter control of this condition.

*Moisture Content* -- Moisture content in DPIs must be tested for and strictly limited because its inclusion may have a significant effect on characteristics such as particle size distribution, crystallinity, dose content uniformity, microbial content, and stability.

*Microbial Limits* -- The microbial quality should be controlled by appropriate tests and acceptance criteria for total aerobic count, total yeast and mold count, and freedom from designated indicator pathogens. The acceptance criteria should at a minimum meet the criteria proposed in The Pharmacopeial Forum.<sup>63</sup> Furthermore, appropriate testing should be done to show that the drug product does not support the growth of microorganisms and that microbial quality is maintained throughout the expiration period.<sup>64</sup>

Sophisticated and difficult to perform testing of DPI products, including particle size distribution, moisture content, and microbial limit testing, is needed to ensure potency, purity, and quality of DPI products prior to dispensing. This factor would support the inclusion of DPI

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<sup>63</sup> United States Pharmacopeia, The Pharmacopeial Forum, Vo. 22, p. 3098, 1996.

<sup>64</sup> FDA, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation" (draft), 1998.

products on the list of products that are demonstratively difficult to compound.

#### DPI Products -- Preliminary Conclusion

DPI products appear to present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products for the following reasons.

- Dry powder inhalers are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility, and the product-to-product uniformity that is critical for dosing accuracy is usually difficult to achieve.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of DPI products is complex.
- Sophisticated facilities and equipment are required to ensure proper compounding of the drug product.
- Specialized, technical training is essential to ensure proper compounding of the drug product.
- Sophisticated, difficult to perform testing of the compounded drug product is required to ensure potency and purity.

We therefore are considering including DPI products on the list of products that are demonstrably difficult to compound.

#### **IV. Other Products**

In time, we may add more products and categories of products to the list of drug products that are demonstrably difficult to compound. We are interested in suggestions on other products that should be included on the list.

#### **V. Contact Us**

Please submit comments on this concept paper before August 15, 2000, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. In your written comments, please refer to docket number 00N-1357.

For further information about this concept paper, contact: Andrea C. Masciale, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.