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What is a Compounding Pharmacist?

The heritage of pharmacy has centered on providing individualized pharmaceutical preparations for patients. Pharmacists are the only health professionals possessing the knowledge and skill required to compound medications to meet individual patient needs.

Compounding pharmacy has seen unprecedented growth in recent years. This is attributed to (1) limited dosage forms and strengths available from manufacturers; (2) hospital pharmacy intravenous (IV) and Total Parenteral Nutrition (TPN) programs; (3) home healthcare growth; (4) hospice growth; (5) unavailable drugs (discontinued drugs, drug shortages); (6) orphan drugs; (7) new therapeutic approaches with unavailable drug products; (8) special patient populations (pediatrics, geriatrics, bioidentical hormone replacement therapy, pain management, oncology, dental, environmentally/cosmetic sensitive, sports, veterinary); and others. It is virtually impossible for pharmaceutical manufacturers to accommodate the needs of all patients and that is why compounding is vital to health care today.

Compounding (sterile and/or nonsterile) occurs in over 75% of independent pharmacies, almost all hospital pharmacies, many chain store pharmacies, nuclear pharmacies, mail order pharmacies, pharmaceutical industry (investigational drug study compounding), governmental pharmacies (e.g., military, Veteran Administration, USPHS), home infusion pharmacies, specialty pharmacies, veterinary hospitals and pharmacies, nutritional pharmacies, physician offices, oncology pharmacies and clinics, regional “compounders,” close door pharmacies, and large-scale compounders with interstate distribution.

Specifically, compounding pharmacists (1) meet patient’s individual needs for their customized medications; (2) enhance patient compliance (taste, size, appearance, dosage forms); (3) provide medications not commercially manufactured; (4) provide medications in short supply or not available; (5) provide medications in different strengths if not available; (6) provide discontinued medications; (7) provide specialized medications for use in physician’s offices and clinics; (8) make tablets/capsules easier to swallow for a child or elderly patient; (9) provide medications in alternative dosage forms (topicals, transdermals) for patients; (10) provide medications for animals as well as for humans; (11) work with hormone replacement therapy and pain patients to obtain optimum results; (12) combine several medications in one preparation (e.g., IV admixtures, TPN solutions); (13) provide cancer “cocktails” for chemotherapy; (14) provide radioactive agents; (15) monitor drug therapy; (16) work hand-in-hand with physicians and other healthcare practitioners; and (17) often work on the “cutting edge” of new therapies.

The overall/general responsibilities of a compounding pharmacist include aspects associated with (1) the proper formulation of a preparation that is safe and effective; (2) determining the complexity of each preparation; (3) consultations with healthcare professionals; (4) the compounding process (methods, techniques, procedures, measuring, weighing); (5) compounding facilities (environmental quality and maintenance); (6) compounding equipment (e.g., acquisition, certification, maintenance, calibration); (7) cleaning and disinfecting; (8) component selection (e.g., active pharmaceutical ingredient, excipients, quality standards); (9) component handling (nonhazardous and hazardous); (10) component storage (e.g., temperature, humidity); (11) stability and beyond-use date assignment; (12) packaging, repackaging, and drug preparation containers; (13) labeling; (14) final preparation release checks; (15) final preparation handling and storage; (16) shipping and delivery; (17) compounding documentation; (18) quality control/assurance and continuous quality monitoring; (19) correction of any deficiencies; (20) testing (in-house and outsourced; physical, chemical and microbiological); (21) patient counseling, monitoring, complaints, and adverse-event reporting; (22) training, retraining, and assessment; (23) patient knowledge (human and/or veterinary); (24) patient or caregiver education and training; (25) personnel cleanliness and garb; (26) continuing education; (27) meeting ever-changing state board of pharmacy requirements; and many, many, many others too numerous to list.

A compounding pharmacist addresses the needs of all patients upon receipt of a prescription or medication order from a qualified-licensed healthcare practitioner. The relationship has been in effect from the early days of the medicine man, apothecary, druggist, and, today, the pharmacist. Also, prescribers and pharmacists work together to develop new or alternative dosage forms to meet the needs of patients to relieve their suffering and, in many cases, to save their lives. Many pharmacists are involved in clinical studies either by compounding the medications or working with investigators in conducting the clinical trials. Compounding pharmacists work with equipment companies in the development of new equipment for compounding and for drug administration using new devices. Yes, it is all in a day’s work for a compounding pharmacist; there are many ways that compounding pharmacists are on the “cutting edge” of pharmacotherapy today!

Loyd V. Allen, Jr., PhD, RPh
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Robotized Compounding of Oncology Drugs in a Hospital Pharmacy

Elisabetta Palma, PhD, MSN, RN
Celestino Bufarini, PharmD

ABSTRACT  In 2005, the Pharmacy Department of the University Hospital of Ancona began collaboration with the engineers of the Loccioni group in order to realize a fully automated system for the preparation of cytostatic drugs, which could be safe for both healthcare workers and patients. At present, the cytotoxic laboratory of Ancona is equipped with two robots and one Class II biological-safety cabinet. The introduction of the robots in the cytotoxic laboratory has increased both efficiency and safety of the working process. The drug-preparation process begins when the pharmacist confirms the medical prescription (exact posology, modalities of reconstitution), and starts the preparation cycle. The sterility of the preparations is monthly tested in collaboration to the local microbiology laboratory. All preparations' results were germ-free even after storage at room temperature for two weeks. The dose accuracy is verified by visual and gravimetric independent systems. Drug concentration errors exceeding the limit of 10% fixed by the Italian Pharmacopeia were found only in 1.1% of the preparations. The average dose error was 0.8% (standard deviation 1.7%).
SAFETY IN CANCER DRUG COMPOUNDING

The process of compounding and administration of oncology drugs may threaten the wellness of healthcare workers because of accidental exposure (via inhalation, ingestion, or injection), and percutaneous absorption during compounding or administration.\(^1,2\) On the other hand, the patient may suffer the risk of medication errors (MEs) that may occur because of faults in product identification, dose calculation, dose measurement, and drug-preparation labeling.\(^3\)

In order to reduce the risk of accidental exposure, the Italian laws recommend that the oncology drugs are prepared inside isolated and centralized cytotoxic laboratories by operators (pharmacists, nurses, or pharmacy technicians) with a specialized training and proven skills, similar to other countries.\(^4\) It is mandatory to wear personal protective attire in order to reduce the risk of contamination during the preparation. In fact, the drug may be spilled or dispersed (aerosols), even when using proper preparation techniques. The risk of personnel exposure may be furthermore reduced by using closed system transfer devices (CSTDs).\(^5\) The use of a Class II biological-safety cabinet (BSC) for the preparation of intravenous (IV) cancer drugs cannot prevent the risk of environmental contaminations,\(^6,8\) and traces of cancer drugs have been detected in healthcare workers’ urine samples.\(^9\)

As for the risk of MEs, any mistakes occurring within the process of drug preparation (i.e., misplaced decimal points) may have dramatic consequences for the patient.\(^10\) The risk arises when the operator who prepares drugs is tired (i.e., excessive workload) or his/her attention is diverted.\(^11\) A ME may occur during the compounding process because of incomplete and/or poorly written prescriptions, distraction, interruption, and intense workloads.\(^12\) The final preparation can be incorrect because of incorrect strength, wrong drug, or incorrect labeling.\(^13,14\)

Robotization of the cancer drug preparation process can reduce both the risk of accidental exposure and of MEs. The robots require a complete, double-checked prescription, are not affected by distractions, and do not suffer if the workload increases.

ORGANIZATION OF OUR CYTOTOXIC LABORATORY

The University Hospital of Ancona is the most important hospital on the Adriatic coast of Central Italy. Its Pharmacy Department has a dedicated cytotoxic laboratory so the preparation of all chemotherapy (about 20000 to 22000 oncologic preparation per year) is centralized.\(^15\)

As required by Italian law, the entire cytotoxic laboratory is provided with a negative air pressure system and several air filters. The laboratory is divided from the rest of the pharmacy by a cleanroom with two doors (one internal towards the laboratory and the other external towards the pharmacy).

The internal door can be opened only if the external door is closed and vice-versa. Before entering, the operators wash their hands and dress themselves with personal protective attire (i.e., non-woven fabric gowns, disposable overshoes, surgical masks).

The oncologists send the requests for a patient’s treatment plan to the pharmacists via specific software which is connected with the cytotoxic laboratory. The prescription is valid only if all the mandatory fields of the electronic paper are filled. Every medical prescription is checked by a pharmacist. If the prescription is confirmed, the information about the medical order is transferred to the robot.

THE ROBOT COMES INTO ACTION

The robot recognizes the identified drugs, diluents, and containers using a combination
Robotized Compounding

of barcode scanning and digital imaging. The compounding process is performed by the robot using a six-axis robotic arm and all drug measurements are performed and verified by three independent systems, as shown below:

1. Encoders on the syringe-driving mechanism
2. Laser-guided syringe plunger positioning
3. Pre- and post-weight comparison on a precision scale (using density, sometimes referred to as “specific gravity”) to ensure dose accuracy

Each preparation (bag or elastomer) is weighed before and after the compounding process. The robotic program provides controls and calculations based on density (“specific gravity”) and volume. The robot also manages partial vials that may remain after doses are compounded. It tracks beyond-use dating according to hospital-selected guidelines. If a subsequent dose is requested and can be compounded from an existing partial vial, the robot will do so without asking for additional product, thus reducing the amount of dangerous, polluting waste.

Implications of Automated System’s Positive Effect on Practice:

- Risk reduction of medication errors during the preparation cycle
- Reduction of training time for students and nurses
- Reduction of contamination risk (environment and workers)

The robot can handle elastomeric infusion pumps, vials up to 100 mL of volume, infusion bags up to 1000 mL of volume, and syringes of 5, 20, and 50 mL of volume. The robots can prepare a solution in a syringe in 100 seconds and in an IV bag in 145 seconds.

The quality of each preparation is checked by the robot itself via a volumetric and a gravimetric control. This process is time consuming, and the robot shows a mean length of the compounding process of the robot that is longer when compared to the operator, as observed in other studies. The length (in seconds) of the preparations is recorded by the robot itself, while the operator’s speed was checked by a chronometer. All operators were aware of this control, and that fact may have affected their performance. The time necessary to the solution of powders (cyclophosphamide and gemcitabine) was not considered. These differences are particularly evident with the preparation of cetuximab, gemcitabin, and cisplatin (Figure 1). The prescribed amount of these drugs per patient is generally more than 50 mL, therefore, the robot has to repeat (possibly several times) the process of aspiration in syringe, injection into the IV bag, and volumetric/gravimetric control. On the other hand, confusion among cytostatics is not possible because the robot checks each vial before the preparation. Despite the efficiency of the robot, it is possible that the system blokes during the preparation phase because of an incorrect closure of
the mechanical pliers, or the presence of air inside the syringe. The robot equalizes the internal pressure of the vials during the process of compounding, so spills or sprays of drug do not occur.

**QUALITY CONTROLS**

In regard to the quality control performed by the robot, only 16 preparations (1.1%) on a sample of 1509 presented an error of drug concentration exceeding the limit of 10%

![Figure 1](image-url) Figure 1 shows the differences in the mean time preparation and compounding of cancer drugs. The blue line refers to manual handling and the gray line refers to the robot. In general, the operator has a shorter mean time for a single preparation when compared to the robot.

**FIGURE 1. Mean time preparation: Operator vs. robot.**

- 820.5
- 700
- 600
- 500
- 400
- 300
- 200
- 100
- 0
- -1
- -0.5
- 0
- 0.5
- 1
- 1.5
- 2
- 2.5
- 3
- 3.5

**Seconds**

- Cetuximab
- Docetaxel
- Carboplatin (CDDP)
- Cyclophosphamide
- Cisplatin
- Gemcitabin (Gem)
- Fluorouracil (5FU)

- Mean time preparation manual handling
- Mean time preparation robot

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fixed by the Italian Pharmacopeia. Similar results have been reported by Yaniv et al,\textsuperscript{17} and the corrections were carried out by an operator using the BSC. The average dose error was 0.8\% with a standard deviation of 1.7\%, outlining a high accuracy and a good precision of the dosing system (Figure 2).

After preparation, the drugs are distributed as unitary doses to the requesting oncology wards. Similarly, the information about the scheme of therapy (administration instructions) is sent to the ward’s database in order to avoid errors.\textsuperscript{14} The bags containing the unitary doses of cytotoxic drugs and the related administration instructions have a double labelling with a barcode, so it is possible to verify which cytostatic is in which bag or syringe and to which patient it belongs.

The robot, called “APOTECA chemo” (Figure 3), is produced by Loccioni (Italy).

The software of APOTECA chemo interfaces with the hospital pharmacy system. The drug-preparation process begins when the pharmacist confirms the medical prescription (exact posology, modalities of reconstitution), and starts the preparation cycle. The nurse pre-labels the final dose container, and the proper drugs, compounding supplies, and final containers are then inserted into the robot’s loading area. APOTECA chemo is able to use several final containers, including multiple syringe sizes, multiple bag sizes, and elastomeric containers. In the robot’s software, the data about product identification and preparation instructions are already loaded, ensuring accurate results.

The robot’s internal surfaces are sanitized on a regular basis. It has been demonstrated that surface contaminations are possible when using a BSC.\textsuperscript{18} To test surface contamination of the bags and the loading/
Figure 3 shows the front board of the robot. In particular, we have signaled the air treatment zones (level 1 and 2 Hepa filters), the compounding zone, the load-unload zone (vials and bags of drugs), the human friendly interface with a touch-screen and the waste bin.

Monitoring by weight. When the container is almost at its limit, the robot seals the container with a glue-on lid and alerts the operator. The sterility of the preparation chamber is guaranteed by five HEPA filters. In addition, the “air curtains” between the chambers preclude the passage of contamination from one area to the next. The intent is to protect the operator working in the loading/unloading area from the contaminants that may be present in the compounding chamber.

The chambers, made of stainless steel, are cleanable with antimicrobial solutions and decontamination solutions typically used to clean BSCs. When the robot is not in use, the chambers are enlightened with ultraviolet lamps.

CONCLUSION

At the beginning of the collaboration with Loccioni, in September 2007, the robot of the first generation only managed five active ingredients, and was very slow. At the present time, APOTECA chemo is a robot of the third generation. The mean preparation time was halved from the beginning for fluorouracil bag (from 303 to 156 seconds), methotrexate (from 276 to 127 seconds), and epirubicin.
bag (from 565 to 253 seconds). Currently, about 95% of all preparations are robotized; APOTECA chemo handles 56 oncology molecules, which correspond to more than 160 different vials; and the production rate passed from 3,400 (2008) to 19,000 preparations (2011). The cytotoxic laboratory is also a low-bacterial load zone. Before entering the laboratory, in the cleanroom, the operators wash their hands and dress themselves with non-woven fabric gowns, disposable overshoes, and surgical masks. The sterile bags used as the final container of the preparations are double bagged. The sterility of the preparations has also been tested in collaboration to the local microbiology laboratory. Random microbiological tests are monthly performed on samples taken from the process of drug compounding. At the time this article was written, all the examined preparations appeared uncontaminated, even after being stored at room temperature for two weeks.

ACKNOWLEDGMENT

The authors express their appreciation to the engineers of Loccioni group for their support (queries to system databases and data analysis).

REFERENCES


Address correspondence to Elisabetta Palma, PhD, MSN, RN, City Hospital of Senigallia, Via B. Cellini, I-60019, Senigallia (AN), Italy or Str. Bettolelle-Filetto, 81/c I-60019, Senigallia (AN), Italy. E-mail: elisabetlapalma@yahoo.it
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TO COMPOUND OR NOT TO COMPOUND:

A Veterinary Transdermal Discussion

Abstract

Administering chronic medications to feline patients without the daily battle of oral and injectable medications is the holy grail of veterinary pharmacotherapy. For some medications, the transdermal route may be the solution. However, there are many considerations for determining if a medication will be safe for the patient and caregiver as well as effective when administered transdermally. A comprehensive checklist to assess the appropriateness of transdermal therapy is provided.

Transdermal application is a convenient way to administer medications to animals (especially feline patients) that may not be the most compliant patients. Very few medications are commercially available in transdermal dosage forms. However, compounding pharmacists are able to turn any medication into a transdermally applied product, right? Not necessarily. While the idea of being able to use only transdermal medications for difficult animals is appealing, there are many medications that are not suited for transdermal application for a variety of reasons. Some of these reasons are discussed in the sections that follow. For a complete checklist to determine suitability for transdermal administration, refer to the Table included.

Caregiver Safety

Needless to say, when administering medications to veterinary patients, a caregiver will always be involved. The caregiver should be counseled on appropriate administration techniques to decrease chances of them coming into contact with the medication. However, even with appropriate counseling, there is still a possibility of human error resulting in the person coming into contact with the medication. If a medica-
Medications that have a narrow therapeutic index, such as warfarin and digoxin, can be dangerous if given transdermally. The narrow therapeutic index increases the risk of reaching toxic levels due to the unpredictable absorption via the transdermal route.

**Patient Safety**

Patient safety is always a priority. However, it is easy to overlook the fact that a medication that is safe systemically may not be safe transdermally. If a medication is cytotoxic (e.g., chlorambucil), photosensitizing (e.g., doxycycline, enrofloxacin), or considered a contact irritant (e.g., clopidogrel, fluoxetine) in the Material Safety Data Sheet, it will likely have adverse effects on the skin when administered transdermally.

The therapeutic index of the medication also needs to be taken into account. How much of a medication is absorbed transdermally varies by medication and is often unknown. Medications that have a narrow therapeutic index, such as warfarin and digoxin, can be dangerous if given transdermally. The narrow therapeutic index increases the risk of reaching toxic levels due to the unpredictable absorption via the transdermal route.

**Ability of the Medication to Cross the Skin**

If the medication is not able to cross the skin and be absorbed, it will not be effective. There are a variety of penetration enhancers to increase the likelihood that a medication will be absorbed. However, if the medication is a large molecule (molecular weight greater than 800) or purely hydrophilic or purely lipophilic, it will have a difficult time being absorbed despite use of a penetration enhancer.

**Effectiveness of the Medication in a Transdermal Formulation**

Not all medications will produce the desired effects when administered transdermally. A number of areas need to be considered, including the intended use of the medication, desired effect, and pharmacokinetic factors such as metabolism. If the medication is being metabolized or exerting its effects in the gastrointestinal (GI) tract, then it should not be used transdermally. Medications will never reach the interior of the GI lumen; however, medications that are metabolized by the liver will eventually pass through hepatic vessels for metabolism even when administered transdermally.

---

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### TABLE. Checklist for Determining Suitability of a Medication for Transdermal Administration.

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caregiver Safety</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the medication toxic to humans?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If yes, do not compound due to risk to caregiver.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could this medication adversely affect a condition of the caregiver?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If yes, determine if someone else is able to administer the medication, or consider not compounding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the caregiver allergic to this medication?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If yes, determine if someone else is able to administer the medication, or consider not compounding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could this medication cause a positive drug test for the caregiver?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If yes, determine if this is a concern for the caregiver.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Patient Safety**<sup>2,3</sup> |
| Is this a cytotoxic medication? |
| • If yes, do not compound because the medication is likely to cause damage to the ear and to the caregiver if absorbed. |
| Is this medication a contact irritant based on information in the MSDS or previous use information? |
| • If yes, do not compound because the medication is likely to cause damage to the ear. |
| Is this medication photosensitizing? |
| • If yes, do not compound because the medication is likely to cause damage to the ear. |

*Note: Even indoor cats are at risk from lying in sunny windows.*

| **Ability of the Medication to Cross the Skin** |
| Does this medication have a molecular weight greater than 800? |
| • If yes, this medication will likely be too large to cross the skin well. |

*Note: A molecular weight less than 400 is ideal.*

| **Effectiveness of Medication in a Transdermal Formulation**<sup>3</sup> |
| Is this medication purely hydrophilic or purely lipophilic? |
| • If yes, this medication will likely not cross the skin well. |

*Note: Larger doses.*

| Is the dosage of this medication greater than 25 mg? |
| • If yes, do not compound because the surface area of the feline pinna will limit absorption of larger doses. |
| Is this an antibiotic? |
| • If yes, do not compound due to increased resistance because blood levels of transdermal formulations will be sub-therapeutic for longer periods after application than with oral formulations. |

| Does this medication exert its effects in the GI tract? |
| • If yes, do not compound because transdermal medications do not reach the GI lumen in significant concentrations. |
| Is this medication a prodrug metabolized by gut enzymes? |
| • If yes, do not compound because transdermal medications do not reach the GI tract where gut metabolism occurs. |

| Has this medication been shown to have unpredictable effectiveness for this use in oral or intravenous dosage forms? |
| • If yes, consider a trial of the medication by oral or intravenous route to ensure the medication will work in the specific patient. |

The length of time for transdermal medications to reach effective concentrations is longer than when the medication is orally administered. This prevents some medications from being transdermal candidates, such as antibiotics and medications whose effects are needed quickly. Antibiotics should not be used transdermally due to suboptimal initial concentrations leading to resistance. It is unlikely that more than 25 mg of a medication will be absorbed in a feline patient due to the limited surface area of the feline pinna. Therefore, medications requiring dosages greater than 25 mg are not good transdermal candidates. Diagnostic agents should also not be administered transdermally due to unpredictable blood levels when this route is used.<sup>8</sup>

### Monitoring, Follow-up, and Caregiver Education

While these are often not reasons why a medication shouldn’t be compounded, they are important to consider when preparing a transdermal medication. There should be a plan in place to monitor for safety and efficacy. Since transdermal medications are much less predictable than oral or intravenous medications, this monitoring plan should employ a variety of methods such as blood levels, clinical signs of efficacy and toxicity, and therapeutic markers such as T4 and blood glucose levels.<sup>1</sup>

Caregiver education is the final step that takes us back to caregiver safety. It is important for the compounding pharmacist to have a plan to counsel the caregiver on appropriate administration. The caregiver should be counseled to use warm water to clean the skin where the medication will...
TABLE CONTINUED. Checklist for Determining Suitability of a Medication for Transdermal Administration.

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this being used as a diagnostic agent?</td>
<td>• If yes, do not compound because blood levels of transdermal medications are not predictable and may not reach expected concentrations at the target receptor.</td>
<td></td>
</tr>
<tr>
<td>Is there a lack of studies showing transdermal effectiveness?</td>
<td>• If yes, consider risk versus benefit.</td>
<td></td>
</tr>
<tr>
<td>Is a therapeutic response to this medication needed quickly?</td>
<td>• If yes, do not compound because transdermal formulations take much longer to reach effective concentrations than oral formulations.</td>
<td></td>
</tr>
<tr>
<td>Is this the first attempted dosage route for this patient?</td>
<td>• If yes, oral route should be tried first. In the absence of evidence for safety and efficacy the transdermal route should be a last resort.</td>
<td></td>
</tr>
</tbody>
</table>

Monitoring, Follow-up, and Caregiver Education

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>CRITERIA</th>
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</thead>
<tbody>
<tr>
<td>Is there a need to develop a protocol to monitor for efficacy and toxicity?</td>
<td>• If yes, confirm a plan with the veterinarian to monitor therapy.</td>
<td></td>
</tr>
<tr>
<td>Is there a need to develop a comprehensive plan to counsel the caregiver regarding appropriate administration?</td>
<td>• If yes, plan to counsel the caregiver on administration of the medication to decrease exposure to them and increase effectiveness for the patient.</td>
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GI = gastrointestinal; MSDS = Material Safety Data Sheet

Conclusion

Compounding pharmacists are a great resource to veterinarians for creating a variety of dosage forms and flavors. The transdermal route is an enticing option for veterinarians to offer their clients when administering medications to a beloved pet becomes a challenge. However, it is the professional obligation of pharmacists to not just compound the prescribed medication, but to make sure that the medication prescribed is appropriate to use transdermally.

References


Address correspondence to Lauren R. Eichstadt, PharmD Candidate 2015, University of Findlay, College of Pharmacy, Findlay, OH 45840. E-mail: eichstadtl@findlay.edu

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Autologous Serum Eye Drops for Severe Dry Eye Syndrome in a Patient with Chronic Graft-Versus-Host Disease: A Case Report

Bill Mixon, RPh
Jan Mixon, RN
Edward K. Isbey III, MD, FAAO
Shari Sprinkle

Graft-versus-host disease (GVHD) is a complication in recipients of an allogeneic hematopoietic transplant and a cause of morbidity and mortality in those patients. Many patients with GVHD experience dry eye syndrome (keratoconjunctivitis sicca), a disorder in which a paucity or poor quality of tears causes multiple persistent symptoms that can include extreme unremitting ocular pain and discomfort as well as diminished vision. Individuals with dry eye syndrome that is unresponsive to therapy are often restricted in their activities and experience a greatly diminished quality of life. In many such patients, commercially available treatments fail to reduce the severity of ocular discomfort to a tolerable level. For those individuals, compounded autologous serum eye drops may be very effective in relieving the signs and symptoms of dry eye.

In this report, we present the case of a 49-year-old woman who used autologous serum eye drops to relieve severe dry eye syndrome associated with chronic GVHD that developed after an allogeneic hematopoietic stem cell transplant to treat acute myelogenous leukemia (AML). Recommendations for counseling patients in the use of that preparation and a formulation for autologous serum eye drops are included in this article, and the patient, a coauthor of this report (S. S.), presents her perspective on her response to therapy.

GVHD AND DRY EYE SYNDROME: AN OVERVIEW

GVHD is manifested as two distinct but interrelated syndromes: acute and chronic.1 Acute GVHD, which usually develops during the first 100 days after stem cell transplant, is caused by the reactivity of mature donor T lymphocytes in the graft against disparate histocompatibility antigens of the transplant recipient.1 That form of GVHD targets the skin, gastrointestinal tract, and liver, although the hematopoietic and immune systems are also affected.1 Chronic GVHD, which is a syndrome of disordered immune regulation, affects 25% to 60% of recipients of an allo-
Ocular involvement, which in our experience may develop in 60% to 90% of patients with chronic GVHD, is characterized by sicca syndrome, which includes dry eye syndrome, a disorder of the ocular surface that can significantly and negatively affect the patient’s quality of life. Dry eye syndrome, which causes photophobia; ocular sensations of stinging, burning, or a foreign-body presence; blurred vision; and eye pain, can alter the cellular and molecular structure or function of portions of the ocular surface system, increase ocular vulnerability to desiccation and damage to the epithelium, and establish a cycle of increasing inflammation and further damage to the eye. If dry eye syndrome persists and its severity increases, the level of ocular discomfort can become unbearable. Patients thus afflicted are also likely to experience profound depression and anxiety as their eye disease progresses and their independence and quality of life diminish.

The clinical experience of compounding pharmacists has shown that for many patients, commercially manufactured eye drops, ocular lubricants, and similar therapies cannot adequately relieve the discomfort of severe dry eye. For those individuals, compounded autologous eye drops can be very effective. Studies in the literature support that finding, as does the following patient profile.

**CASE REPORT**

In May 2014, a 49-year-old white woman (S. S.) was referred by her ophthalmologist (E. I.) to The Compounding Pharmacy in Hickory, North Carolina, to obtain autologous serum eye drops. That preparation was prescribed to relieve the symptoms of severe disabling refractory dry eye syndrome associated with chronic GVHD, which developed after an allogeneic hematopoietic transplant to treat AML. A certified phlebotomist in The Compounding Pharmacy used standard red-top BD Vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, New Jersey) to obtain six 10-mL tubes of that patient’s whole blood. From that sample, a batch of sterile autologous serum 25% eye drops (thirty 3-mL sterile droptainers) was prepared and dispensed after S. S. had been counseled about the use, storage, and stability of that preparation. S. S. was instructed to apply 1 eye drop to each affected eye every 30 to 60 minutes around the clock as needed but at least 8 times daily. She was advised that no special equipment (e.g., gloves to be worn during application of the eye drops) was necessary for treatment but that she might need assistance with placing the eye drops in her eyes. Before the preparation was dispensed, S. S. was also instructed to:

1. Store the droptainers containing the preparation in the freezer and ensure that they remained frozen until use.
2. Thaw, overnight in the refrigerator, the droptainer to be used the next day.
3. Keep that thawed droptainer cold to the greatest extent possible.
4. Discard any remaining preparation 24 hours after its droptainer had been opened.

At the time of this writing (approximately 8 weeks after the initiation of treatment), S. S. has experienced only benefits and no adverse effects from the use of her compounded autologous eye drops. That preparation has reduced her ocular pain to a tolerable level, diminished photophobia, and improved the acuity of her vision. To date, no changes to the formulation or its instructions for use have been made, and S. S. has refilled her prescription for autologous eye drops twice.

**COMMENTS FROM THE COMPOUNDING PHARMACIST**

**BILL MIXON, RPH**

The Compounding Pharmacy

Hickory, North Carolina

Autologous serum eye drops are available only as a compounded sterile preparation that, in our experience of more than a decade, has produced no adverse effects and only benefits for patients with severe dry eye disease. Compounding pharmacists who consider offering this treatment should consider the following factors:

**Preparation of Autologous Eye Drops**

Autologous serum eye drops can be prepared only under aseptic conditions and by combining the patient’s own properly prepared serum with a diluent such as sterile saline solution. Sterile autologous eye drops are prepared from whole blood and thus require handling blood and blood products. Special training in universal precautions for staff who compound autologous eye drops is mandatory, and other requirements also apply. According to the Occupational Safety and Health Administration, the Centers for Disease Control and Prevention recommends standard precautions for the care of all patients, regardless of their diagnosis or presumed infection status. Those standard precautions apply to blood; all body fluids, secretions, and excretions (except sweat), regardless of whether or not they contain visible blood; nonintact skin; and mucus membranes. They are designed to reduce the risk of transmission of microorganisms from both recognized and unrecognized sources of infection in hospitals, and they include handwashing and the wearing of personal protective equipment such as gloves, gowns, and/or masks when touching or exposure to patients’ body fluids is anticipated.
Compounding Autologous Serum Eye Drops

**Rx**

**AUTOLOGOUS EYE DROPS, 25% SOLUTION**

*For a 1-month supply*

<table>
<thead>
<tr>
<th>Item</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red-top BD Vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, New Jersey) containing ~60 mL of whole blood serum, autologous</td>
<td>25 mL</td>
</tr>
<tr>
<td>0.9% Sodium chloride injection</td>
<td>75 mL</td>
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</tbody>
</table>

**EQUIPMENT**

- One 0.2-micron low-protein–binding syringe filter
- Sterile droptainers (3-mL each)
- One filter straw
- Two 60-mL syringes
- One 10-mL syringe
- One 18-gauge needle

*Note: The number of droptainers needed varies per batch of autologous eye drops. Each droptainer is usually filled to contain ~2 mL of autologous eye drops.*

**METHOD OF PREPARATION**

*Note: Autologous eye drops are a blood product. All transfers, during which proper personal protective equipment must be worn, must be performed in a biological safety cabinet.*

1. Allow the whole blood to clot for 2 hours before centrifugation at 3000g for 15 minutes.
2. After donning personal protective equipment, including sterile gloves, assemble all necessary supplies under the laminar airflow hood.
3. Centrifuge the Vacutainers containing the clotted whole blood for 15 minutes to separate the cellular components from the serum.
4. Carefully uncap all droptainers within the laminar airflow hood.
5. Assemble the syringes (a 60-mL syringe with a filter straw, a 60-mL syringe with a needle, and a 10-mL syringe with a filter and a Luer-to-slip tip connector).
6. Use gauze to carefully open all containers of blood/serum. *Note: Use the tube rack to keep open tubes of centrifuged blood upright.*
7. Use the 60-mL syringe with the filter straw attached to withdraw the amount of serum necessary to make the prescribed amount of diluted serum. *Note: Be careful to avoid withdrawing the red blood cells, which are not harmful but impart a pink hue to the solution.*
8. Carefully recap all Vacutainer tubes.
9. Use the 60-mL syringe with the needle to withdraw an appropriate amount of sodium chloride injection. Remove the needle and replace it with the sterile Luer-to-Luer connector. Connect the syringe containing the sodium chloride injection and the syringe containing the autologous serum by using the Luer-to-Luer connector and carefully mix the contents of each syringe via the syringe-to-syringe method.
10. After a homogenous solution of serum and sodium chloride injection has been obtained, disconnect the syringes.
11. Attach a low-protein–binding filter to the 60-mL syringe that contains the diluted serum. Then attach the 10-mL syringe to the filter.
12. Sterilize the diluted autologous serum by forcing the solution from the 60-mL syringe through the filter into the 10-mL syringe in multiple steps until all diluted serum has been filtered.
13. Place 2 mL of the sterilized autologous serum solution in each sterile droptainer. *Note: The amount of diluted serum dispensed per droptainer may vary according to the patient's use of this preparation.*
14. Tightly replace the cap on the droptainer.
15. Dispose of all biohazardous waste in an appropriately labeled container.
16. Label each droptainer with a strip label.
17. Dispense the droptainers in an amber-colored reclosable plastic bag with a prescription label attached.

**PACKAGING**

Package this preparation in sterile 3-mL droptainers. Dispense the filled droptainers in amber-colored reclosable bags because vitamin A is light sensitive, and the drops contain vitamin A.

**LABELING**

Store the droptainers in the freezer, except for the current day’s supply. Keep “today’s supply” cold to the extent possible. Thaw each droptainer by rolling it between your hands. Discard each opened droptainer after 24 hours of use.

**STABILITY**

A beyond-use date of 30 days may be assigned for the drops that remain frozen until use.

**USE**

For the treatment of severe dry eye syndrome.
The patient for whom autologous eye drops are prescribed must find a laboratory in which standard venipuncture technique is used to draw 50 mL to 70 mL of whole blood, which should be allowed to clot. That blood must then be centrifuged for 20 minutes at 3000g, after which the serum must be decanted under aseptic conditions and transferred to suitable containers for transport to the pharmacy that prepares the eye drops. If shipment is required, the serum must be shipped frozen on dry ice, and it must remain frozen until it is delivered to the pharmacy in which the drops will be prepared.

At The Compounding Pharmacy, our registered nurse (J. M.) or a pharmacy technician who is a certified phlebotomist obtains the patient’s blood on site and stores it appropriately before the compounded preparation is made. We have found that providing phlebotomy services in the pharmacy in which the eye drops are prepared is a great convenience for patients and enables better control of the entire procedure. Autologous eye drops are prepared from serum, which is the part of whole blood that remains after the clotting process and after centrifugation (which removes the cellular components of whole blood). When an offsite laboratory obtains blood for the preparation of autologous eye drops, that facility must allow the blood to clot, centrifuge it, and then aseptically remove the serum. The serum must then be packaged in sterile containers and frozen before its delivery either by the patient or by shipment via a commercial carrier to the pharmacy that will prepare the eye drops. Each of those steps provides an opportunity for contamination or spoilage of the serum to occur.

**Administration of Autologous Eye Drops**

One to two drops should be applied to the affected eyes at least 8 times a day (around the clock, if necessary).

**Ensuring Effectiveness**

We indicate a 24-hour beyond-use date for nonfrozen autologous eye drops because credible research has shown that both time and temperature affect the stability of growth factor peptides in that preparation. We advise each patient to keep thawed drops as cold as possible without refreezing them, and we emphasize that complying with that instruction is very important. In our experience, effective treatment requires frequent use of the drops, and applying that preparation every 1 to 2 hours or even more often is necessary to ensure an appropriate response to therapy. As the patient’s eyes heal, less frequent use may provide adequate and continuing benefit.

**Typical Outcome of Treatment**

Most patients have indicated that treatment with autologous serum eye drops greatly and persistently relieves their dry eye symptoms, and they report no adverse effects from that therapy. However, each patient must be strongly cautioned that eye infection can result if eye drops are used 24 hours after their droptainer was opened or if the recommended precautions for storage are not followed.

**Special Considerations**

I do not believe that testing a patient for bloodborne pathogens is necessary before preparing autologous serum eye drops. The concept of universal precautions for handling blood or blood products assumes that every patient is infected with a bloodborne pathogen, which of course is not the case. In my opinion, such testing increases the cost of therapy, delays treatment, and would be redundant, wasteful, and potentially embarrassing for the patient.

**Summary of this Case**

For the patient described in this report, autologous serum eye drops have proven to be an effective therapy that does not produce adverse effects, and the use of that preparation is included in her therapeutic regimen.

**COMMENTS FROM THE PRESCRIBING OPHTHALMOLOGIST**

EDWARD K. ISBEY III, MD, FAAO
Asheville Eye Associates, PLLC, Asheville, North Carolina

Dry eye syndrome, which is usually classified as mild, moderate, or severe according to the signs and symptoms it produces, is characterized by blurred vision and ocular itching, soreness, discomfort,
burning, and/or a foreign-body sensation. The severe form of dry eye disease often afflicts individuals with GVHD, a disorder that produces protean systemic adverse effects and includes among its target organs the lacrimal gland, conjunctiva, and cornea. When inadequately treated, severe dry eye syndrome can result in a decrease in vision, increased mucoid discharge, corneal epithelial defects, and even ulceration of the cornea in more severe cases. Those more severe adverse effects can cause increased eye pain and (possibly) permanent blindness. Patients so afflicted also frequently experience depression because their activities of daily living are restricted, as is their independence. The combination of the physical and psychological effects of severe dry eye can be devastating.

**S. S.: Presentation, Treatment, and Response to Therapy**

When S. S. came to me for treatment in April 2014, she complained of blurred vision, severe dryness, severe photophobia, and a foreign-body sensation in both eyes. Physical examination revealed marked punctate keratopathy over the entire corneal and conjunctival surfaces in both eyes. She also had a visually significant cataract in each eye. S. S. was diagnosed as having severe dry eye syndrome associated with chronic GVHD. Prior treatment for her ocular symptoms consisted of the application of commercially manufactured artificial tears and gel lubricants, the surgical insertion of punctal plugs, and a trial of cyclosporine ophthalmic emulsion (Restasis; Allergan, Inc., Irvine, California). None of those treatments adequately relieved her eye discomfort.

Because of the positive response to autologous serum eye drops demonstrated by other patients treated in my practice and after a thorough review of the literature, I prescribed that therapy for S. S. Autologous serum eye drops contain a large variety of growth factors, fibronectin, and vitamin A, all of which help decrease inflammation on the ocular surface. Because they are prepared from the patient’s own blood, those drops are not artificial, and they are formulated without preservatives. In contrast, commercially available products designed to treat severe dry eye may contain ingredients, such as preservatives, that can increase the symptoms of that disorder in some patients.

I recommended that S. S. follow a regimen of applying, to both eyes, autologous eye drops every 30 to 60 minutes and commercially available preservative-free artificial tears every 4 to 6 hours throughout the day in addition to an ocular gel lubricant at bedtime. At the time of her first follow-up examination, she reported an improvement in her dry eye symptoms, including significantly reduced eye pain, decreased photophobia, and slightly improved vision. Clinical examination revealed a significant improvement in ocular dryness and in the appearance of the ocular surface (most notably a better tear film and reduced punctate keratopathy) in both eyes. That response to treatment was, in my experience, unusually rapid. As a result of the continued improvement of her ocular surface, S. S. has been deemed a candidate for small-incision cataract surgery. Her treatment for GVHD and AML remains ongoing. It is my hope she will also continue to benefit from the use of autologous eye drops.

**Caveats and Cautions**

Although autologous eye drops can be very helpful in relieving the symptoms of severe dry eye disease, some drawbacks and potential complications are associated with that therapy. Because autologous serum contains no preservative, there is a potential risk of inducing an eye infection via microbial contamination of the drops or bottle. Also, it is possible that a deposit of immunoglobulins in the cornea could occur when a higher concentration of autologous serum is used. For those reasons, patients for whom such drops are prescribed should be informed, before the initiation of therapy, about the signs and symptoms of intol-
erance to that treatment (e.g., ocular redness, worsening vision, eye pain), any of which could indicate a possible eye infection, a sterile ulceration of the eye, or the worsening of dry eye syndrome. All patients treated with autologous eye drops must be reevaluated by their ophthalmologist 1 to 2 weeks after the initiation of therapy. Patients with severe dry eyes must always be monitored more frequently than are patients with less severe ocular surface disease. In my somewhat limited experience, no adverse sequelae have resulted from long-term treatment with autologous serum eye drops.

It is important to remember that autologous serum eye drops should be compounded only by staff experienced in the formulation and dispensing of sterile preparations at a pharmacy that complies with the most stringent regulations and requirements for sterile compounding.

Summary

In my opinion, the rapid improvement in the severe dry eye disease associated with chronic GVHD in the patient (S. S.) described in this report could be attributed only to treatment with autologous serum eye drops. Since the initiation of that therapy, no other agent has been added to her ocular care regimen, and her treatment for GVHD and AML has not been altered. To date, the corneal surface of both eyes has improved at least 50% from its pretreatment condition. That healing has enabled more accurate measurement of the corneal curvature (an essential factor in planning for cataract surgery). I recommended that the dry eye disease of this patient be reevaluated every 4 weeks and that small-incision cataract surgery be scheduled to remove her bilateral cataracts. S. S. has complied with those recommendations and is currently scheduled to undergo bilateral cataract surgery.

THE PATIENT’S PERSPECTIVE

SHARI SPRINKLE
Candler, North Carolina

I was diagnosed with AML in March 2006, when I was 41 years old. I underwent a regimen of induction and chemotherapy, and my leukemia went into remission until 2009, when I began to feel unwell and my platelet count began to vary above and below the normal range. I...
was then diagnosed as having myelodysplasia syndrome, which was a precursor to the recurrence of leukemia. I underwent another course of chemotherapy for AML, but remission did not occur. In late 2009, my local physician stated that he could offer no more options for my treatment and suggested that I contact specialists at Duke University Medical Center in Durham, North Carolina, about my eligibility for participation in a clinical trial for patients with AML. I was subsequently accepted into an appropriate trial there, where I received the “trial drug” for 8 weeks and was then admitted to the hospital for a week to undergo radiation therapy and chemotherapy, both of which produced severe adverse effects. In July 2010, when my response to those treatments was sufficient, I received a stem cell transplant from a nonrelated donor. In late autumn of that year, I returned home from Durham to Candler, North Carolina, and felt well until approximately 6 to 8 months after I received my stem cell transplant, when I noticed a rash on my legs and began to experience ocular discomfort (my eyes became dry and itchy, and I felt as if there were sand in both eyes).

My eye discomfort progressively worsened, and I was diagnosed as having chronic GVHD, which is often associated with the development of dry eye syndrome as well as a host of other disorders. To treat my eye discomfort, my ophthalmologist at that time prescribed cyclosporine ophthalmic emulsion (Restasis), which I was not able to tolerate because it burned like a hot poker in my eyes, and Systane Ultra Lubricant Eye Drops (Novartis, Basel, Switzerland), but that product was not effective. My eye discomfort continued to increase.

Both eyes eventually became very painful day and night and were also very sensitive to light, and the vision in first my left eye and then my right eye became blurry. Those symptoms slowly progressed in intensity until about 8 weeks before the time of this writing. I was carried in the patient’s pocket because body heat will increase the ambient temperature around that preparation. Also, autologous eye drops should never be left in a hot car.

- Suggesting that patients who need to use their eye drops during the work day or while traveling place a day’s supply of frozen droptainers in a medicine bottle. Then, rubber bands can be used to secure partially thawed cold packs around the medicine bottle, which can be placed into the freezer until the cold packs have frozen completely. The medicine bottle wrapped with frozen cold packs can then be placed into a fanny-pack lined with heavy-duty bubble wrap and stored there for 8 or 9 hours.
- Encouraging patients who are traveling to take only the number of frozen droptainers they will need during their trip. If dry ice is in the cooler that carries the eye drops, patients who travel by air must disclose to their airline carrier how much dry ice is in that cooler. As an alternative, patients who travel in any conveyance can load a cooler with as many freezer bricks as possible and then slide the required number of droptainers between those bricks. At the time of arrival, the droptainers can be unpacked and stored in a freezer. Patients staying in a hotel should request a portable freezer in their room for the duration of their stay.
- Ensuring that if autologous eye drops must be shipped, they arrive during the work week and not on a weekend or a holiday.
- Following up with each patient 2 to 4 weeks after the initiation of therapy to ensure that treatment with autologous eye drops is effective; to determine how, when, and how often the drops are being applied; to confirm that each droptainer (regardless of whether it is empty) is discarded 24 hours after it was opened; and to determine whether the patient’s physician should be contacted to adjust the original prescription. Asking how much unused medication is left in each vial immediately before it is discarded is also important, as is encouraging the patient to discuss any concerns or difficulty with treatment.
- Assessing compliance by asking the patient how many droptainers of his or her eye drops remain at a given point and comparing the number of remaining droptainers to the number of days since that patient last obtained his or her autologous eye drops.

Note: It has been our experience at The Compounding Pharmacy that autologous eye drops cannot be instilled into the eye too often, and that the more often those drops are applied, the more rapid the positive response to treatment.
then spending most of each day lying in bed with a cold washcloth over both eyes in an attempt to relieve my ocular pain. I could not go outside during the day because daylight hurt my eyes. I often wanted to cry because my eyes were so painful, but I was not able to shed tears. At that point, I was examined by my new ophthalmologist (E. I.), who diagnosed cataracts and severe dry eye syndrome in both eyes. He prescribed moxifloxacin hydrochloride ophthalmic solution (Vigamox; Novartis) and Refresh eye drops and gel (Allergan, Inc.), but neither was effective. In addition, my dry eye disease rendered impossible the corneal “mapping” necessary for cataract surgery.

I tried to keep my eyes closed as much as possible throughout the day, but that did not relieve my ocular pain, which remained severe and unrelenting, so I began to explore all treatment options available to me. I investigated scleral contact lenses designed to keep dry eyes moist, but their cost was almost $8000, and my insurance company denied coverage for that option. My ophthalmologist (E. I.) and my oncologist then recommended treatment with autologous eye drops, and I was referred to The Compounding Pharmacy in Hickory, North Carolina, to obtain that preparation. The staff there provided excellent support for and instruction about using those drops, which I began to apply as soon as I returned home. My eyes felt better immediately, and the drops did not burn; they were very soothing. Two days after I began treatment with autologous eye drops, my eye pain had resolved from a score of 10 (where 10 represents the worst possible pain) to a score of 1 or 2, and I was better able to open both my eyes.

At the time of this writing, I have used those eye drops for about 8 weeks. Some days I apply them more often; other days, less frequently, according to the level of my eye discomfort. I was recently reevaluated by my ophthalmologist (E. I.), who stated after examining my eyes that the improvement in my dry eye syndrome was “amazing.” I have renewed my prescription twice since those drops were first prescribed, and I have experienced only benefits from that treatment: an 80% reduction in eye pain; less ocular sensitivity to light, although bright light still causes me some discomfort; and reduced foreign-body sensation in both eyes. After my treatment with autologous eye drops began, the onset of relief from those symptoms was very rapid and has not diminished, and I am now able to keep both eyes open at the same time. For me, that therapy has had another benefit: It has improved my corneal condition enough to permit my undergoing cataract surgery, which is scheduled in the very near future.

My insurance plan does not cover the cost of autologous eye drops, but to me, they are worth the investment, and I intend to keep using them for as long as I can afford them. That preparation does what it is supposed to do, and I advise patients with severe dry eye syndrome to try it before they opt for a more expensive alternative.

CONCLUSION

This case report confirms that when other therapies have failed, innovative treatments such as autologous eye drops often benefit patients with severe dry eye disease (including that caused by GVHD) or other disorders of the ocular surface such as neurotrophic corneal ulcers or persistent epithelial defects. In such cases, a customized ocular medication prepared without preservatives and artificial ingredients may provide the safest and most effective treatment.

ACKNOWLEDGMENT

The International Journal of Pharmaceutical Compounding appreciates the contribution of Jane Vail, St. Louis, Missouri, in the authoring of this article.

REFERENCES


Address correspondence to Jane Vail at: janevail@sbcglobal.net
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Final Guidance for Pharmacy Compounding of Human Drug Products Under Section 503A

Cynthia E. Blankenship, Esq.

On July 2, 2014, the U.S. Food and Drug Administrative (FDA) released several documents in the form of guidance to compounding pharmacists including Final Guidance for Pharmacy Compounding of Human Drug Products Under Section 503A of the Food, Drug and Cosmetic Act. Please note that this final guidance only addresses human drug compounding by 503A pharmacies.

Like all guidance issued by the FDA, this final guidance offers only insight into the FDA’s current thinking with regard to enforcement of section 503A. Many provisions within 503A will require further rulemaking and/or consultation with the Pharmacy Compounding Advisory Committee (Advisory Committee) in order to fully implement 503A. Thus, there are many questions regarding procedure as well as content that this guidance leaves unanswered.

Regarding the content of the final guidance, despite the International Academy of Compounding Pharmacists (IACP) submitting extensive comments on the draft guidance, IACP was disappointed to see very little altered in the final guidance and still much left unanswered especially in terms of office use and repackaging. The final guidance reinstates the provisions found within 503A but leaves many questions unanswered including:

1. THE DO NOT COMPOUND LIST BECAUSE A DRUG PRODUCT HAS BEEN WITHDRAWN OR REMOVED FROM THE MARKET.

   The FDA has issued a separate proposed rule that would add 25 drug products that may not be compounded to this list and modify the description of one drug product to add an exception. Regarding the process for updating this list and method of compliance, the final guidance only states, “FDA intends to update this list periodically, and expects compounders to comply with the list as it currently exists and with any final updates.”

   Thus, questions remaining include the process and timeframe that the FDA will update this list, what burden compounding pharmacists have in checking the list, and what input the Advisory Committee will have as required by language within section 503A.

2. BULK DRUG SUBSTANCES LIST (FOR 503A AND 503B).

   For 503A pharmacies, bulk drug substances can be used that do not have an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph and are not components of FDA-approved drugs where the bulk drug substances appear on a list developed by the FDA with input from the Advisory Committee. The FDA issued additional guidance that reopened the period for nominating bulk drug substances that can be used by 503A pharmacies. Despite IACP submitting over 2400 bulk drug substances, the FDA states within the revised request that all previously submitted nominations will not be considered and each bulk drug nomination must be resubmitted with additional information. The final guidance makes clear, “until a bulk drug substances list is published in the Federal Register as a final rule, human drug products should be compounded using only bulk drug substances that are components of drugs approved under section 505 of the FD&C Act or are the subject of USP or NF monographs.”
Therefore, many questions remain as to the timeframe that the FDA intends to issue a final list of bulk drug substances that may be used by 503A pharmacies and the process for developing this list as to whether the Advisory Committee will have any input as required under the language within Section 503A.

3. DEMONSTRABLE DIFFICULTIES FOR COMPOUNDING LIST.

The FDA previously requested nominations for drugs that should be included on a do not compound list because of demonstrable difficulties. While IACP did not submit nominations for the list, IACP did submit comments regarding concerns that IACP has in this process turned into a way for drug manufacturers and the FDA to include any drugs on this list without demonstrating an actual adverse effect on the safety or effectiveness of the drug product. The final guidance makes clear that this list cannot be enforced until the FDA promulgates an implementation regulation.

There is no mention within the final guidance as to the role of the Advisory Committee as required by Section 503A, thus raising questions as to how the FDA intends to engage the Advisory Committee and what input the Advisory Committee will have.

4. MEMORANDUM OF UNDERSTANDING BETWEEN THE FDA AND THE STATES.

The final guidance offers no additional information regarding the timeframe of the Memorandum of Understanding (MOU) or the content. The FDA restates within the final guidance that States will have the opportunity to enter into an MOU in a specific timeframe and if a State chooses not to do so, the FDA will begin enforcing the limit of 5% of the total prescription orders dispensed or distributed by the individual or firm in interstate commerce.

Since the FDA did not provide any additional information regarding the MOU within this final guidance, a multitude of questions still remain as to when the draft MOU will be made available; the process and opportunity to comment, if any, that stakeholders will have; the amount that a pharmacy will be able to distribute within interstate commerce should their State enter into the MOU; whether the MOU will impact distribution as opposed to also impacting dispensing despite the fact that the actual language within 503A only references distribution; and the timeframe that States will have in order to decide on a State level whether to enter into the MOU.

5. OFFICE USE AND REPACKAGING.

The FDA did not provide any additional guidance on office-use compounding or repackaging despite multiple attempts by Congress to encourage the Agency to do so. The FDA did reinstate the language regarding the requirement that a drug be compounded for an identified individual patient based on the receipt of a valid prescription order but provided nothing else in terms of whether office use and repackaging will be allowed under 503A.

IACP had strong concerns that the FDA would choose not to offer further guidance on these issues and thus sought Congressional letters from Reps. Bilirakis, Griffith, DeGette, and Green to the FDA asking for further guidance on a host of issues including office use and repackaging. IACP was able to help in collecting a combined 45 signatures of Representatives for these letters, and Congress is now awaiting further guidance from the FDA as to the Agency’s intent on enforcement of office use and repackaging under 503A.

6. THE FDA’S RELATIONSHIP WITH STATES.

The FDA provides little information as to how the Agency intends to work with State Boards of Pharmacy. The final guidance only states the following:

FDA expects state boards of pharmacy to continue their oversight and regulation of the practice of pharmacy, including pharmacy compounding. FDA also intends to continue to cooperate with state authorities to address pharmacy activities that may be violative of the FD&C Act, including section 503A. FDA’s enforcement approach with respect to such violations is described in section IV.C.

Partnership for Personalized Prescriptions Brings Together Compounding Advocates!

IACP’s compounding advocacy society, Partnership for Personalized Prescriptions (P3), www.PrescriptionPartnership.com, brings together more than 150,000 patients and practitioners, providing them with a forum to share their support and passion for compounding. Importantly, P3 members are provided with the tools to advocate on their own behalf. P3 also provides an ongoing educational resource for those interested in pharmacy compounding and its value for patients and the practitioners who serve them. A compounding pharmacist locator service is provided so that patients, physicians, veterinarians, and nurses can conveniently find compounders in their area.

Pat Stephens, PharmD, IACP President, says:

IACP has a rich heritage that began with the advocacy program, Patients and Professionals for Customized Care (P2C2). With the creation of P3, which will rebrand our original advocacy efforts, we are expanding our educational, testimonial, and advocating tools to provide a strong platform to help raise compounding awareness as well as restore the reputation of our profession.

Encourage your patients, practitioners, and your fellow pharmacist colleagues to join Partnership for Personalized Prescriptions! Together, we can work to ensure continued access to personalized medications.

Resource


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Health Care in Belarus in the 19th and 20th Centuries

Evgenii Mikhailovich Tishchenko, MD, PhD

ABSTRACT  Belarus became a Soviet Socialist Republic in the USSR in 1921. Belarus is now an independent country between Poland and Lithuania and Russia. The pharmacy sector of Belarus improved in fits and starts from 1921 to the present but serious quantitative and qualitative problems were evident until the 21st century. A number of factors caused this situation. The Soviet Republic of Belarus started with handicaps. The area, comprised of several provinces of western Russia, had no pharmaceutical factories during the imperial period and, while pharmacies were of high quality in the cities all over the Russian Empire—including Minsk, which became the capital of Belarus—pharmacies were sparse and primitive in rural areas and Belarus was basically rural. Belarus was devastated by wars—World War I, the Russian-Polish war of 1920-21, and of course, by World War II. The Bolshevik policy of nationalizing private pharmacies adversely affected dispensing between 1918 and 1921. Dispensing improved during the New Economic Policy of 1921 to 1927 with re-introduction of private enterprise and the establishment of BelMedTorg and the Mogilev Experimental Station of Medicinal Plants. The number of pharmacies and medical facilities increased during the 1930s and again after World War II. However, utopian plans to provide free or low-cost medicines to all citizens never came to fruition. Inadequate amounts of state-of-the-art and even basic medicines persisted through the 1990s. The number of pharmacists also was inadequate and their education and training was on a low level. Because of shortages, citizens of Belarus often self-medicated with medicinal plants. The transition to a market economy in the 1990s made medicines expensive for citizens but opened the door to greater interaction with Western pharmaceutical practices and physical improvements in pharmacies and pharmaceutical production.

Evgenii Mikhailovich Tishchenko is a professor at State Medical University, Grodno, Belarus.
At the beginning of the 1920s, Belarus was in turmoil. Lenin’s Bolsheviks, who had taken over the Russian government in the fall of 1917, were waging a civil war against a plethora of opponents. These opponents included liberals, who had toppled the tsarist government in February/March of that year; army officers who wished to continue the war against Germany in contrast to Lenin’s call for peace; nobles and businessmen, who were wary of the Bolsheviks’ economic policies; nationalists advocating the independence of Finland, Estonia, Latvia, Lithuania, Ukraine, Georgia, etc.; and other socialists, who wanted a coalition government, which Lenin refused. In addition, the Bolsheviks were locked in a struggle with Poland over the territory of Belarus and western Ukraine. Both territories were claimed by newly independent Poland since they had been parts of Lithuania-Poland since the 15th century through the second half of the 18th century when Russia seized them in the partitions of Lithuania-Poland. The tumult of this period, called the era of War Communism, was accentuated because old institutions were being uprooted and replaced with new ones that were both utopian and bureaucratic. Change affected the pharmaceutical sector in the eastern part of Belarus, which was attached to Russia in March 1921 by the Peace of Moscow that ended the Polish–Russian war. Western Belarus as well as western Ukraine around L’vov/L’viv would remain under Polish control until 1939/1940 when Stalin would annex this area to the Soviet Union, following the Ribbentrop-Molotov Pact.

Private pharmacies operated in western Belarus and Western Ukraine until 1939. In the eastern part of Belarus, on the other hand, the pharmaceutical sector was reorganized during the civil war of 1917/1918–1921, as was the pharmaceutical sector throughout the rest of Soviet Russia. At the beginning of the civil war in 1917/1918, municipalities and workers, under the influence of Menshevik theories, began seizing private pharmacies. The Bolsheviks soon put a stop to these activities that it termed chaotic and began issuing orders for nationalization to bring the pharmaceutical sector under control of the national government. The new Soviet government established local administrations of health care, with subdivisions called pododol’stvo, including pharmacy pododol’stvo. A state monopoly was established over the pharmaceutical market. Private pharmacies and pharmaceutical warehouses were nationalized. The instability resulting from these changes was, unfortunately, not assuaged by funding and directives from Moscow, the new Bolshevik capital of Russia. For example, during the second half of 1919, the Gomel pharmacy pododol’stvo received only one directive from the center. Thus, through local efforts and on the basis of local resources, a pharmacy laboratory was established in Gomel province and in 1919 and in 1920 a chemical-pharmaceutical lab and medical-technical workshops were established and medicines and supplies were purchased on the private market—which still existed on a small scale. Nevertheless, free pharmaceutical service for the populace—mandated by Moscow—could not be implemented nor were clinics and medical institutions regularly supplied.

In 1921, the Soviet Union instituted the New Economic Policy (NEP). The Bolsheviks had won the civil war. They now controlled territory approximating the previous Russian Empire. However, the economy was in shambles. The crisscrossing of armies though Belarus and attempts to collectivize had ruined agriculture, including the growing and processing of medicinal herbs. In the summer of 1921, famine racked various areas of the nascent Soviet Union. The one-hundred or so pharmaceutical factories that had existed in Imperial times were in ruins. Some 11 and a half million citizens—mostly civilians—died during the civil war and famine, some from fighting and atrocities, others from starvation and disease. Uprisings of workers and peasants opposed to Bolshevik policies had erupted during the war; in March 1921, a major upheaval occurred at the Kronstadt naval base in the Gulf of Finland. The base, near Petrograd, was a former Bolshevik stronghold. Sailors, workers, and general inhabitants of Kronstadt Island called for democracy and loosening up economic strictures. Although Lenin had contemplated relaxing economic regulations prior to the uprising, the Kronstadt Rebellion precipitated major economic changes. The political system did not become more democratic; it continued to be dominated by Lenin’s Party, known as the Communist Party of the Soviet Union (Bolshevik). However, the Soviet government implemented changes in the economy, including in the pharmaceutical sector. During the period of the NEP, which began in 1921 and lasted until 1927, attempts to collectivize agri-
Compounding in Belarus

By 1928, there were 158 pharmacies in an enlarged Belarus. Forty-one of which were located in hospitals and clinics. Only 7% of pharmacy workers had a pharmacy education.
with the exception of a factory to process medicinal plants, which was organized in 1915 during World War I. This situation was rectified in the Soviet period. In October 1922 in addition to organizing pharmacy podotdels or subsections, Narkomzdrav of Belarus restructured the administration and supply of pharmacies, instituting a self-financed institution known as “BelMedTorg.” On February 11, 1924, Sovnarkom (the Council of People’s Commissars or government of) Belarus published a decree that removed the property of the Chief Pharmacy Administration (Aptekoupravlenie) from the jurisdiction of the Commissariat of Health. On July 22 1925, the Commissariat of Health approved a resolution dealing with the pharmacy administrations in the districts of the Belorussian Republic. During the 1920s, BelMedTorg enlarged trade in pharmaceuticals, lessened tariff increases, and widened the assortment of pharmaceuticals. In 1923, there were 683 kinds of pharmaceuticals; by 1924 there were 781. In 1924, work was renewed in the Mogilev Experimental Station of Medicinal Plants that had been established in 1915. In 1925, BelMedTorg bought equipment in the U.S. and began planning a chemical-pharmaceutical factory, which opened in 1929 and was located in Minsk, for the processing of pharmaceuticals from raw materials native to Belarus. In 1927, a scientific pharmaceutical society was organized. In the same year, the Medical Technicium in Mogilev opened a Pharmaceutical Department.

THE 1930s

During the 1930s, in-patient medical help in Belorussia progressed due to the opening of a hospital that was not so much newly built as occupying space in renovated buildings formerly used for other purposes. For example, 40-bed units were established in the districts, and, in 1941, a new provincial type of hospital was established in Gomel oblast’ (The territorial division “oblast’” replaced the provinces of Imperial Russia; they were smaller in size than the provinces.). Unfortunately, while there was physical progress, the quality of medical care lagged. Sanitary-epidemiological requirements were not observed in the hospitals. The water supply was not clean, there were insufficient medicines, instruments, towels and bed linens, and food for the patients—even bread—was lacking.

Moreover, notwithstanding the growth of the pharmacy network, there also were problems with dispensing. In 1939, there were:
Recipes from Medicinal Plants used in Belarus

**Rx**

**ZELENIN FOR CARDIAC SYMPTOMS**

*For 25 mL*

- Tincture Convallariae: 10 mL
- Tincture Valerian: 10 mL
- Tincture Belladonna: 5 mL
- Menthol: 0.2 g

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the menthol in the belladonna tincture and combine with other tinctures.

**LABELING**

Administer 25 drops internally, 3 times per 24 hours.

---

**VOTCHAL DROPS FOR HEART (DIGITALIS SUBSTITUTE)**

*For 23 mL*

- Tincture Convallariae: 10 mL
- Tincture Valerian: 10 mL
- Nitroglycerin (solution) 1%: 1 mL
- Validoli: 2 mL

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Combine all ingredients.

**LABELING**

Administer 10 to 15 drops 3 to 4 times per 24 hours.

---

**Rx**

**CARDIAC REMEDY**

*For 180 mL*

- Infusion of Adonidis vernalis: 6 g
- Sodium bromide: 6 g
- Codeine phosphate: 180 mg
- Water: qs 180 mL

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Combine all ingredients.
4. Bring to 180 mL volume.

**LABELING**

Administer 15-mL orally 3 times per 24 hours.

**Rx**

**COUGH OR PAIN**

*For 180 mL*

- Thermopsis herb: 0.6 g
- Sodium bicarbonate: 6 g
- Codeine phosphate: 180 mg
- Infusion of Thermopsis: qs 180 mL

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the pepsin in 80-mL distilled water.
4. Add hydrochloric acid.
5. Bring to volume with distilled water.

**LABELING**

Administer 15 mL to 30 mL orally 3 times a day with meals.

---

- 299 pharmacies
- 218 pharmacy “points”
- 7 pharmaceutical warehouses
- 2 pharmacy bases
- 7 control-analytical laboratories
- 2 laboratories for galenical preparations
- 1 chemical-pharmaceutical factory

However, 13% of the subdistricts (raions) of oblasts had only one pharmacy and 27% of the subdistricts had only one pharmacy “point.” In rural areas, one pharmacy served 27,420 inhabitants. Pharmacies were established in buildings previously used for other purposes. Only twelve new pharmacy buildings were built in 1939. The number of trained personnel was inadequate. In 1939, there were only 400 pharmacists working in Belarus. Also, medicines, bandages, and medical items were not always available.

The Plan for Dispensing was fulfilled only 91% in 1939. And, in 1940, only 34 medical institutions in the eastern oblasts of Belarus (as distinct from the western parts acquired from Poland in that year as a result of the Ribbentrop-Molotov Treaty) had pharmacies.

**WORLD WAR II**

The pharmacy situation worsened following the German invasion and occupation of...
Belarus between 1941 and 1944. Of the pharmacies and pharmacy “points,” 85% were destroyed. Thus, in 1942-1943—whereas there were 20 pharmacies before the war—only two pharmacies operated; one pharmacy served 65,000 inhabitants in both urban and rural areas, and the pharmaceutical warehouse received medicines from Minsk only once.

According to a decree (Prikaz) of the Minsk Gebitkommissar, from December 10, 1941, prices for medicines were to rise 200%. However, in 1942, pharmacies in Minsk district (okrug) did not have exact regulations regarding sales’ prices. As a result, prices for medicines rose still further. The cost of similar medicinal articles, though, varied from district to district. Thus, in the Uzdensk Financial department, prices were higher by 270%. And, in 1943 in Mogilev district, the extra charge for the cost of medicines was 350%. At the same time in the bazaars, some severely deficit medical preparations sold for still higher prices. For example, in Nesvizh a flacon of anti-diphtherial serum cost 5,000 rubles. It must be noted that access to medicines was established not only by pricing but by administrative measures. Thus, from April 7, 1942, pharmacies in Minsk district were forbidden to prepare and dispense medicines containing oil and glycerin. And, in 1943, only half the doctors in Mogilev had permission to write prescriptions.

The Soviet Army was on the offensive by 1944. Heroic Socialist-Realist paintings in the Art Museum in Minsk depict the liberation of Minsk from the Germans. Soviet movement westward impacted the pharmacy situation in Belarus. During the first half of the year, Narkomzdrav and the Chief Pharmacy Administration of Belorussia began to take measures to deliver medicines and sanitary and household products throughout the Republic. In 1944, they acquired 56 million rubles worth of medical items from Russia, the largest republic in the Soviet Union. And, the work of producing medicines in Belarus also was about to begin again.

On November 5, 1944, the government of Belarus approved a resolution “About the Restoration of Chemical-Pharmaceutical Factories” and on January 6, 1945, the government passed another resolution “About the Organization of Manufactured [Packaged] Medicines and Biological Treatment Preparations in the Republic of Belarus.” At the end of 1945, land amounting to 612 hectares in Zheludok district (raion) of Grodno oblast’ was put under the jurisdiction of the All Union Trust of Medicinal Plants for the purpose of organizing specialized state-farms focused on growing medicinal plants. In order to bring pharmaceutical help closer to the populace, movable and stationary pharmacy points were established. By 1945, the number of pharmacies had reached 73.4% of prewar levels. Moreover, combined control-analytical and galenical laboratories operated.

In November 1943, along with forty-three other countries, representatives from the Soviet Union met in Washington and signed an agreement about the establishment of the Union Nations [UN] Relief and Rehabilitation Administration (UNRRA). On December 18, 1945, this UN organization signed an agreement with Ukraine and Belarus according to which the UNRRA would attempt, within the limits of its resources, to acquire items amounting to 61 million American dollars for Belarus and 189 million dollars for Ukraine. Belarus estimated that Fascist occupation in Belarus had caused damage amounting to 75 million rubles or 15 million dollars (in terms of 1941 prices). In the autumn of 1944, a delegation from the American Red Cross came to Minsk and viewed destruction as well as the large scale of reconstruction work.

Some fifteen representatives of UNRRA, including Americans R. Skandret, R. Fries, and T. Waller, worked in Belarus about a year. They shot a film documenting the destruction of clinics, university cities, and orphanages No. 7 and 8 in Minsk.

Through UNRRA, Belarus received equipment, tractors, steam engines, instruments, raw materials, seeds, clothes—all items of primary necessity. The amount of food products alone that were received was in excess of 100 thousand tons. The head of the administration of orphanages in the Ministry of Education of the Belorussian SSR stated on May 23, 1946, that “It was necessary to acknowledge the important role of UNRRA in helping children in orphanages. Food products that had arrived since January had greatly helped improve the children’s health. As a result of the juice, jam, milk, and other products fed to the children, they literally “grew before our eyes.” During the first quarter of 1946, it was planned to unload industrial equipment in the amount of 56 million American dollars, but actually only 15.4% of this project was completed. During this period in Belarus, only 2.3% of the plan for fats and only 11.3% of the plan for grain products were achieved.

In addition to the aforementioned aid, the UNRRA’s help in reestablishing health care must be noted, and it is especially necessary to note shipments of medicines. The UNRRA helped restore the pharmaceutical factory in Minsk, which was organizing the production of penicillin. The factory received equipment in 1946, and Belorussian specialists were sent to Canada for training. From December 1945 to June 1947, UNRRA spent 18.9% of its income from trade on health care.

From 1953 to 1955, necessary medicinal items like glucose, sodium chloride, bromide soda, and bandaging materials like cotton and gauze

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**Rx**

**PEPSIN SOLUTION FOR GASTRITIS**

*For 200 mL*

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pepsin</td>
<td>2 g</td>
</tr>
<tr>
<td>Hydrochloric acid solution, dilute</td>
<td>5 mL</td>
</tr>
<tr>
<td>Distilled water</td>
<td>qs 200 mL</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the pepsin in 80-ml distilled water.
4. Add hydrochloric acid.
5. Bring to volume with distilled water.

**LABELING**

Administer 15 mL to 30 mL orally 3 times a day with meals.
were often absent from pharmacies. And, in the Dobrushsk and Zhitovitsk district (raion) hospitals, butter was not available for the patients.

Many changes occurred in pharmacy service and subordination from the end of the 1950s into the 1970s. In 1958, a unified pharmacy and sanitary-economic-supply service was established. In 1964, however, the administration MedTekhnika was again organized in the Republic of Belarus. During the period from 1964-1972, pharmacy administrations were immediately subordinated to oblast’ health departments. In 1972, they were given the status of independent institutions, a subsection of the oblast’ executive authorities and, in 1988, scientific production units “Farmatsiia and MedTekhnika” were formed.

The pharmaceutical industry of Belarus expanded. An endocrine factory was established in 1959, and the pharmaceutical factory Borisov was established in 1964. In 1968, there was created a chief state enterprise “MedTekhnoCenter” for reforming medical education.

For the purpose of improving medical health to rural dwellers (collective farmers), there was created in 1963 a central regional (raion) pharmacy. In 1966, a request-information service about the availability and assortment of medicinal preparations was established. And, in the 1970s, an automated system for stock-taking of medicines was introduced.

Data presented in the Table included with this article illustrates that the number of pharmacies increased—although the pharmacy points with their more rudimentary offerings remained stable. However, in connection with the fact that in the 1980s hospital pharmacies were transferred from a system of receiving direct subsidies from the Belarus Republic budget to a system of self-financing (khozraschet), stocks of medicines in pharmacies declined. The guarantees for pharmacy personnel rose.

Access to pharmacies improved:

- In 1964, 1 pharmacy served 10.7 thousand of the population
- In 1970, 1 pharmacy served 9.6 thousand
- In 1977, 1 pharmacy served 9.4 thousand
- In 1988, 1 pharmacy served 9.2 thousand

Pharmacies basically were converted into institutions for selling prepared medicines rather than compounding medicines. The percentage of sales of prepared medicines in comparison to all medicines sold rose from 15.6% in 1945, to 39.4% in 1960, to 77.5% in 1969.

But, despite gains, there were essential problems in the organization of pharmacy service. Only 12.9% of pharmacies were open seven days per week. Only 51.9% of the pharmacies had their demands fulfilled by the local warehouse. Pharmacies had insufficient medicines. Only in 1993 were requests for medical preparations adequately fulfilled.

Also, at the first congress of doctors organized by the Health Ministry of Belarus in 1998, it was stated that 75% of medical institutions were constructed before 1970—and 36% of those medical institutions had been built before 1941. Forty-five percent of health facilities were placed in retro-fitted quarters; 50% did not meet sanitary-technical norms; 37% of hospitals did not have hot water supplies; 39% did not have sewerage!

Further, medical equipment was used for longer than the period of time stipulated, and renovation of it was not satisfactory. Moreover, introduction of new technology was expensive. In 1966, for example, 56% of medical equipment had been in use longer than 10 years, while 7% of equipment was not being used—50% had been entirely written off and 25% required repair. In 1996, only 50% of biomedical analyses were completed. In 1999, 37% of ultrasound apparatus had been in service for more than 10 years, and 30% of endoscopes were in a useless condition.
THE 1990s: TURN TO A MARKET SYSTEM

In the 1990s, as official documents testify, demands for medicines were still not satisfied as a result of a lack of hard currency available for their purchase. In 2000, indebtedness for medicines rose 2.7 times, while indebtedness for medicines purchased with hard currency contracted 3 times. Up to 70% of all expenditures for medicines were made in hospitals and for free-of-charge prescriptions.

TRANSLATOR’S NOTE

During the 1990s, there was a severe shortage of heart medicines, glucose, preparations, antibiotics, and even aspirin in countries of the former Soviet Union. Travelers to the former republics of the Soviet Union—now independent countries—could witness the buying and selling of medicines at bazaars and on the street. Meanwhile, travelers were asked to share or sell any medicines they might have brought with them. Additionally, frequent travelers to the now-defunct Soviet Union—like scholars given access to formerly off-limit sections of libraries or newly opened archives—were begged to bring supplies of crucial medicines with them on their next visit. For example, librarians in the Medical Library in St. Petersburg asked me for aspirin and a famous historian at St. Petersburg University asked me to bring diabetes and asthma preparations for his wife who subsequently died. Feminine hygiene products and baby diapers also were lacking. I carted a huge bag of baby diapers to friends with a newborn in the early 1990s.

Materials from the 1990s depict a wide range of changes in the pharmacy sector of Belarus, resulting from the move to a market economy during that period, as shown below.

FIRST CHANGE

The transfer of pharmacies from state ownership to commercial firms. This was done through the Resolution of the Council of Ministers of the Republic of Belarus, No. 476, issued July 31, 1992. In 1999, pharmacies that did not belong to the state amounted to only 16%; there were more pharmacy kiosks in the non-state sector—63%. These private pharmacies and pharmacy kiosks did not prepare medicines according to prescriptions but sold only pre-packaged medicines.

SECOND CHANGE

Departments of sales’ credit were opened in pharmacies between 1994 and 1996. Also, slightly earlier in 1992, phyto departments or departments of health supplements based on medicinal plants were opened in pharmacies.

THIRD CHANGE

Self-financed (khozraschet) hospital pharmacies were transferred to sanatoria (health resorts). This action was in accordance with an Order (Prikaz) of the Ministry of Health of the Republic of Belarus No. 96, issued July 21, 1995.

FOURTH CHANGE

The 1990s saw the organization of small-scale, over-the-counter trade.

FIFTH CHANGE

The number of pharmacists in state pharmacies declined; pharmacists gravitated to the private sector because the pay was higher. In 1991, there were 9608 pharmacists and 3440 provizors—pharmacists with graduate degrees. In 1999, the number of pharmacists had dwindled to 7780; the number of provizors to 3083.

SEVENTH CHANGE

There was a specialized exhibit by international producers of medical apparatus and medicines, the first of which was held in 1994. Gradually, beginning in 1997, imports of medicines—particularly those most crucial—increased, at the expense of domestically produced medicines. In 2000 in Belarus, production of medicines and medical apparatus was begun at the state enterprise “Belofarm”—an amalgamation of five factories and four enterprises having various kinds of ownership. This conglomerate sold 381 different types of medicines; 10 times more than were sold in 1994 but 3 times less than required by the number of citizens registered in the republic. As a result, only 30% of the needs of the population and treatment-prophylactic institutions were satisfied.

There were specialized exhibits by international producers of medical apparatus and medicines, the first of which was held in 1994. Gradually, beginning in 1997, imports of medicines—particularly those most crucial—increased, at the expense of domestically produced medicines. In 2000 in Belarus, production of medicines and medical apparatus was begun at the state enterprise “Belofarm”—an amalgamation of five factories and four enterprises having various kinds of ownership. This conglomerate sold 381 different types of medicines; 10 times more than were sold in 1994 but 3 times less than required by the number of citizens registered in the republic. As a result, only 30% of the needs of the population and treatment-prophylactic institutions were satisfied.

There was an increase in the number of Belorussian enterprises producing medical apparatus and equipment—a hopeful sign. In 1994, there were 40 indigenous pharmaceutical enterprises; in 1999 there were 100. For example:

- Basic production of dialysis equipment was begun in 1992
- Apparatus for laser coagulation was begun in 1995
- Various kinds of syringes began to be produced in 1997
- A system of computerized x-ray graphics was begun in 1999

All these projects were funded by the government of Belarus. In 1997, a Republican Center of...

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### TABLE. The Belorussian Pharmacy Network and Pharmacy Staffs from 1960 to 1990.

<table>
<thead>
<tr>
<th>YEARS</th>
<th>PHARMACIES</th>
<th>OF THESE, THE NUMBER IN TREATMENT INSTITUTIONS</th>
<th>PHARMACY POINTS</th>
<th>THE NUMBER OF PHARMACISTS AND PROVIZORS IN 10,000 OF THE POPULATION</th>
<th>IN THIS NUMBER THE NUMBER OF PROVIZORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>782</td>
<td>74</td>
<td>2566</td>
<td>3.9</td>
<td>0.7</td>
</tr>
<tr>
<td>1970</td>
<td>1124</td>
<td>175</td>
<td>3196</td>
<td>5.9</td>
<td>1.7</td>
</tr>
<tr>
<td>1980</td>
<td>1192</td>
<td>131</td>
<td>3026</td>
<td>7.9</td>
<td>2.5</td>
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<tr>
<td>1990</td>
<td>1217</td>
<td>30</td>
<td>3196</td>
<td>9.2</td>
<td>3.2</td>
</tr>
</tbody>
</table>

*Provizors were a level of pharmacists that also existed in Imperial Russia. They had a higher education than pharmacists.*

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Health Expertise and Research was created for the purpose of administering medicinal substances, medicinal apparatus, licensing and inspection, hygiene regulations, and registration. The Proposal about Purchasing Wares, Work and Service in the Medical Health System of the Republic of Belarus Funded by Budget Monies on the Basis of Tenders [that is, on the basis of Bids]—a Resolution of the Council of Ministers, No. 1661, October 29, 1998, and the State Program of Encouraging the growth of the Pharmaceutical Industry—a Resolution of the Council of Ministers of Belarus, No. 421, March 25, 1999, were implemented. Thus, there was expectation at the beginning of the 21st century that medical and pharmaceutical care would continue to progress in the republic of Belarus.

**TRANSLATOR’S NOTE**

The Ministry of Industry and Trade of the Russian Federation admitted in October 2009 that Russia received approximately 70% of state-of-the-art pharmaceuticals from abroad and was attempting to remedy that situation during the next decade. The Internet testifies to the fact that the indigenous Russian pharmaceutical industry is, indeed, improving.

Belarus is an independent country. But it must be noted that the provinces that comprised Belarus in Imperial Russia—although rich in famous artists—were bereft of pharmaceutical factories despite the fact that Russian Poland contained major, world-class pharmaceutical factories as did major Russian and Ukrainian cities. Thus, Belarus started out as a pharmaceutically challenged republic of the Soviet Union in the 1920s. When my husband and I attended a Conference on the History of Pharmacy at the State Medical University of Grodno in October 2012—also visiting Minsk and Vitebsk—we witnessed economic progress and commitment to bringing health care and the pharmaceutical sector up to Western European standards. All visitors to the Republic of Belarus must purchase medical insurance at the airport upon entering the country. The medical insurance that my husband and I purchased on our visit to the History of Pharmacy Conference at the Medical University of Grodno was affordable—the equivalent of 7 American dollars per person for a week. The departments at the Medical University of Grodno were fully computerized. Dr. Evgenii Tishchenko, our host and author of this article, took my husband and me to a clinic in a suburb of Grodno. The clinic was under the direction of his colleague and offered urgent care and basic maternity and natal care. It was clean, had basic equipment, and the staff appeared professional and caring. We also visited an elegant sanatorium that practices holistic and preventive medicine. Equipment there was state of the art; the staff was comprised of pharmaceutical and medical professionals. During our 2012 visit to Belarus, we also interacted with a colleague, pharmacist, and lecturer in the History of Pharmacy at the Medical University of Vitebsk, Tatiana Pritishche. She averred that she had received excellent treatment for removal of a non-malignant brain tumor the previous spring. She indeed appeared to be recovering very well.
ACKNOWLEDGMENT

The authors appreciate Mary Schaeffer Conroy, Emeritus Professor, Russian History, University of Colorado at Denver, Denver, Colorado, for her editing of this article as well as her notes of translation provided herein.

SOURCES

(Archives Containing Materials Researched by the Author)
National Historical Archive of Belarus (NIAB)
National Historical Archive of the Republic of Belarus in Grodno (NIA RB in Grodno)
National Archive of the Republic of Belarus (NA RB) in Grodno
Belorussian State Archive (BGA) of Film and Photo Documentaries
State Archive (GA) of Brest Oblast'
State Archive (GA) of Vitebsk Oblast'
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Archives of the Belorussian State Museum of History of the Great Fatherland War (A BelGosMuzeia IVOV)
Archives of the Ministry of Health of the Republic of Belarus (A MZ RB)
State Archive of the Russian Federation (GA RF)
Archive of the Military Medical Museum of the Ministry of Defense of the Russian Federation (A VMM MO RF)
Central State Archive of Lithuania (Ts GA Litvii)
Archive of New Businesses (AND) in Warsaw: Fond of the Ministry of Health and Social Security (f. MZSO)

RESOURCES

Khaziev RA. Budni zazerkal’ia sotsialisticheskoi ekonomiki khrushchevskikh vremen. Translated as: Work Day Experiences of the Socialist Economy—or Stealing from the Socialist Factory—during Khrushchev’s Administration. Istoriia [History] publication of Bashkir State University; 874–881.

Address correspondence to Mary Schaeffer Conroy. E-mail: maryesconroy@earthlink.net

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Compounding Practices
in a Portuguese Community Pharmacy

ABSTRACT
All Portuguese community pharmacies have a compounding laboratory and minimum equipment for the preparation of nonsterile (traditional) compounded medicines, but a few community pharmacies specialize in compounding. At Farmácia Lordelo, the most frequently dispensed compounded medicines are oral liquids for pediatrics and multi-drug, semi-solid preparations for dermatology patients. The majority of the compounded medicines is prepared in accordance with the national galenic formulary and standardized monographs, in order to guarantee the quality and safety of the compounded medicines dispensed.

Maria Reis, PharmD
Maria Carvalho, PharmD,
MRPharmS, PhD
Ângelo Rodrigues

The authors are affiliated with Farmácia Lordelo, Vila Real, Portugal, in the following capacities: Maria Reis, Pharmacy Director; Maria Carvalho, Consultant Pharmacist; Ângelo Rodrigues, Pharmacy Technician.

COMPounding IN portuGAL
Pharmaceutical compounding in hospital and community pharmacy is currently a common practice in Portugal. Nonsterile compounding occurs in both settings, whereas sterile compounding is almost always restricted to hospital pharmacy. Compounded medicines have always been prepared and dispensed in Portugal, but, since the foundation of a compounding-specialist centre (CETMED - Centro Tecnológico do Medicamento) back in 1999, pharmaceutical compounding began a process of reformulation and modernization. More initiatives have occurred subsequently, which have contributed to the promotion of compounding in Portugal, such as the publication of a contemporary national galenic formulary and the approval of up-to-date compounding legislation. Portuguese pharmacists no longer consider compounding an activity of the past but, instead, an opportunity for the future, and compounded medicines are now recognized as a valuable therapeutic option in Portugal. Currently, all Portuguese community pharmacies have a compounding laboratory and minimum equipment for the preparation of nonsterile (traditional) compounded medicines. A few community pharmacies have specialized in compounding and, therefore, have large laboratories and high-tech equipment for the preparation of both traditional and innovative dosage forms.

PoRTUgese LEGISLATION
In Portugal, compounded medicines correspond to medicamentos manipulados and include any fórmula magistral (magistral formula) or preparado oficinal (officinal preparation) prepared and dispensed under the responsibility of a pharmacist, who must assure their quality by following the Good Compounding Practices (GCP) established by law. A magistral formula is a medicine prepared in a hospital or community pharmacy according to a doctor’s prescription that specifies the patient for whom the medicine is intended. An officinal preparation is a medicine prepared according to the indications of a compendium, a pharmacopoeia or a formulary, in a hospital or community pharmacy, and is intended to be directly dispensed to the patients assisted by that pharmacy. GCP guidelines are constituted by a set of eight norms, as follows:
Compounding in Portugal

1. Personnel
2. Facilities and equipment
3. Documentation
4. Raw-materials
5. Packaging materials
6. Compounding
7. Quality control (QC)
8. Labelling

In Portugal, QC must be performed for all compounded medicines prepared, and the QC tests are specified by law. The verification of organoleptic characteristics, final weight/volume, pH (solutions), and uniformity of weight (solids) are some of the tests specified in the Portuguese GCP.

All substances included in compounded medicines must be part of the Portuguese Pharmacopoeia, or another scientific compendium, and must not be included in the negative list of substances that cannot be used in the prescription and preparation of compounded medicines. This negative list determines that, in Portugal, the following substances cannot be used in compounding:

- Animal organ extracts
- Active substances (for internal use) in a dosage higher than that authorized for proprietary medicines
- Active substances included in medicines that were suspended or repealed
- A set of active substances, including:
  - Clobenzorex (and other anorectics)
  - Levothyroxine (and similar substances)
  - Fluoxetine and other substances

Although compounding-only pharmacies are not found in Portugal, every community pharmacy must have a compounding laboratory with minimum dimensions that are specified by law. Moreover, there is a list of the minimum compounding equipment that is required in a pharmacy, for example, glass and porcelain mortars; balance (capable of weighing milligram quantities); and measuring cylinders and pipettes.

### PORTUGUESE GALENIC FORMULARY

The Formulário Galénico Português (FGP) is the national reference for compounding in Portugal, edited by the national association of pharmacies—Associação Nacional das Farmácias (ANF). It was first published in 2001, with the purpose of contributing to the quality of the compounded medicines prepared and dispensed in the Portuguese pharmacies; and also to contribute to the standardization of compounding in Portugal. The FGP was developed based on a comparative study of formularies from selected European countries, Switzerland, Norway, and also the U.S. A second and much larger edition of the FGP was published in 2005, including a total of 133 monographs for (liquid and semi-solid) compounded medicines, current legislation relevant for compounding, technical information and recommendations, and also standard operating procedures. Monographs for compounded medicines are very comprehensive, including a total of 15 different sections (for most medicines):

1. Formula
2. Method of preparation (manual and mechanical)
3. Description of the medicine
4. Packaging
5. Labeling
6. QC
7. Beyond-use-date and storage conditions
8. Clarifications
9. Therapeutic indications
10. Administration and usual dosages
11. Secondary effects
12. Precautions and contra-indications
13. Interactions
14. Intoxication symptoms and treatment
15. Bibliography

All monographs are complemented with the respective work sheets. An example of a FGP monograph is shown in Figure 1 (avail-
able at www.IJPC.com/webcontent or scanning page 392 with the Actable app (directions on page 391). Only pages 1 and 2 of the monotograph are shown in Figure 1.

A particularly valuable contribution to the standardization of compounding practices in Portugal was the Master’s Thesis project by Pinto.\textsuperscript{13} The researcher developed a universal vehicle for the easy and rapid preparation of oral suspensions with assured quality and appropriate characteristics for oral administration. The monograph for this vehicle was included in the FGP, and it was the basis for the development of further monographs for oral suspensions, containing different active substances, which were also included in the FGP.

The current third edition of the FGP was published in 2007 and is very different from the previous editions; it is focused on pediatrics and includes a total of 98 monographs for compounded medicines, exclusively oral liquids (solutions and suspensions).\textsuperscript{\textsuperscript{2,3,14}}

**PRACTICES IN A COMMUNITY PHARMACY**

Farmácia Lordelo, a Portuguese community pharmacy located in the North of Portugal, has specialized in the art and science of preparing compounded medicines. A photograph of Farmácia Lordelo is shown on the first page of this article. Although not compounding only, this practice represents one of the most important activities of the pharmacy. From a long tradition to a modern practice, Farmácia Lordelo is proud of providing a unique service to unique patients.

The compounded medicines dispensed by Farmácia Lordelo in 2012 were systematically reviewed and analyzed. Compounding records identify the medicines dispensed more accurately than the respective prescriptions\textsuperscript{15} and, therefore, full records were analyzed for each compounded medicine dispensed in 2012. Data regarding both the medicine and the patient were collected, as follows:

- Name of the active substance(s)
- Strength(s)
- Dosage form
- Quantity and number of times dispensed
- Use of proprietary medicines or raw materials in bulk
- FGP, standardized or non-standardized monograph
- Age and sex of the patient

The active substances dispensed were grouped according to the respective therapeutic classification,\textsuperscript{16} giving a total of 132 different active substances and 27 therapeutic groups. Dermatological drugs and sunscreens was the group with the greatest number of different active substances (\(n=17\)), followed by supplementary drugs and other substances (\(n=15\)) and nutritional agents and vitamins (\(n=12\)). The other substances mentioned in the previous sentence is a therapeutic group which includes monographs for drugs which are not easily classified, new drugs whose place in therapy is not year clear, and drugs no longer used clinically but still of interest; it also includes herbal medicines.\textsuperscript{16} With reference to the official list of active substances with a narrow therapeutic index (NTI) by ANVISA,\textsuperscript{17} only 2 NTI drugs were dispensed, as follows: 1) clindamycin and 2) minoxidil. The majority of the compounded medicines dispensed included just one active substance (single-drug) and only 19.5\% included combinations of active substances (multi-drug preparations). Apart from compounded medicines including active substances, placebo capsules were also dispensed to one elderly patient by special request. Proprietary medicines were used in the preparation of 10.5\% of all compounded medicines, either by indication of the doctor (common practice in dermatology) or by lack of raw materials in bulk. The use of proprietary medicines in compounding is convenient, as it is not always easy to access the respective raw materials, and in reasonable small quantities, from the current suppliers. However, proprietary medicines not only include the required active substance(s) but also a number of excipients that may compromise the resulting compounded medicines; therefore, raw materials in bulk are preferable in the preparation of compounded medicines.\textsuperscript{3}

The top-frequently dispensed compounded medicines corresponded to liquid dosage forms (32.5\%), namely (in decreasing order) suspensions, solutions, syrups, and foams. The volumes dispensed ranged from 25 mL up to 1000 mL per individual container. The top 10 oral liquid compounded medicines dispensed are displayed in Table 1. The majority of these oral liquids have a corresponding monograph in the FGP.\textsuperscript{12}

- Trimethoprim 1\%, omeprazole 0.2\%, and nitrofurantoin 0.5\% represented the top 3 oral liquids, which accounted for 48.2\% of all oral liquids dispensed. None of these active substances are commercially available in Portugal as oral liquids and, therefore, these are commonly prepared extemporaneously for pediatric patients. An example of a Portuguese electronic prescription for trimethoprim 1\% is displayed in Figure 2 (available at www.IJPC.com/webcontent or scanning page 392 with the Actable app [directions on page 391]). The most popular vehicle for the preparation of oral solutions and suspensions was the FGP B.12, which includes simple syrup and methylcellulose gel (Table 2). Phenobarbital oral suspension 1\% (Figure 1) is an example of a FGP monograph which includes this oral vehicle. The most frequently dispensed non-oral liquid compounded medicine was boric acid, saturated alcoholic solution (FGP A.III.1), for the topical treatment of external otitis. Minoxidil 5\%, for the treatment of alopecia, was the most frequently dispensed foam.

Semi-solid preparations were the next most frequently dispensed dosage forms and included (in decreasing order) creams, ointments,
TABLE 2. Vehicle for the Preparation of Oral Solutions and Suspensions (Formulário Galénico Português B.12).

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple syrup (FGP B.7)</td>
<td>300 mL</td>
</tr>
<tr>
<td>Banana essence, aqueous solution 10% (FGP B.9)</td>
<td>10 mL</td>
</tr>
<tr>
<td>Concentrated parabens (FGP B.8)</td>
<td>3 g</td>
</tr>
<tr>
<td>Methylcellulose, gel 1% (FGP B.11)</td>
<td>up to 1000 mL</td>
</tr>
</tbody>
</table>

FGP = Formulário Galénico Português

lotions, and gels. Creams and gels containing hydroquinone, alone or in combination, accounted for 35.2% of all topical preparations dispensed. Hydroquinone is commonly combined with glycolic acid, and kojic acid and/or tretinoin for the treatment of hyperpigmentation disorders. The next most frequently dispensed semi-solids were salicylic acid preparations, including salicylic acid in variable dosage strengths, alone or in combination with corticosteroids. The FGP includes a monograph for a concentrated (50%) salicylic acid ointment (FGP B.1), which was used in the preparation of the majority of the salicylic acid preparations dispensed. Minoxidil 2% and 5%, for the treatment of alopecia, were the most frequently dispensed lotions and the formulas commonly prescribed included purified water, alcohol, and propylene glycol and/or glycerol in variable strengths. The electronic mortar and pestle (Unguator) is the equipment of choice at Farmácia Lordelo for the preparation of the majority of semi-solid preparations.

Solid preparations were also dispensed, namely capsules and powders (mainly sachets), in variable quantities and dosage strengths. Gelatin capsules represented 93% of all solids dispensed, and the most frequently dispensed active substance was sodium bicarbonate (500 mg and 1000 mg), which accounted for 37% of all capsules dispensed. The Jaansun 100 and 300 capsule machines are the equipment of choice at Farmácia Lordelo for the preparation of 100 and 300 capsules, respectively. Sulfadiazine (150 mg to 500 mg) and folinic acid (5 mg and 10 mg), commonly prescribed in combination for pediatric patients, were the most frequently dispensed sachets. Sulfadiazine (capsules and sachets) corresponded to the widest variety of strengths dispensed (n=7). Multidose powders were also dispensed, mainly topical preparations for hyperhidrosis including boric acid, starch, calcium carbonate, and purified talc.

A total of 72.6% of all compounded medicines dispensed have been studied by Farmácia Lordelo and standardized in individual monographs, which include references for the preparation, quality control, labeling, and beyond-use-date of each medicine. Overall, the most frequently dispensed compounded medicines were for pediatric patients (44% boys vs 56% girls) because of the need for individual strengths and dosage forms; and for dermatology patients because of the need for special combinations. Compounding for medicine’s shortages and discontinued medicines was particularly important in 2012, considering the increasing disruptions in the medicines supply chain (e.g., Alli, Quadriderme, Tarmel).20

CONCLUSION

In Portugal, pharmaceutical compounding represents an invaluable therapeutic alternative that meets the need of individual patients, which cannot be met by the pharmaceutical industry, and is increasingly important in today’s healthcare provision. Although compounding-only pharmacies are not found in Portugal, a few community pharmacies have specialized in the art and science of compounding. At Farmácia Lordelo, the most frequently dispensed compounded medicines were oral liquids for pediatric patients and multi-drug semi-solid preparations for dermatology patients. The majority of the compounded medicines is prepared in accordance to the FGP and standardized monographs, in order to guarantee the quality and safety of the compounded medicines dispensed.

REFERENCES


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Certification of Sterile Equipment and Facilities: WHAT PHARMACISTS NEED TO KNOW

Amanda Lanze, PharmD
Shara Rudner, RPh, FIACP, FACA

ABSTRACT
Although it is common knowledge that all sterile compounding pharmacies must have their equipment and facilities certified and calibrated every six months, it is not as clear what is expected of pharmacists. There is currently a disconnect between the certification companies and the pharmacists. As pharmacists, we look to the certification companies as the experts and rely upon them accordingly. The certification companies look upon the pharmacy to know which testing is required. It is the role of the pharmacist to know which tests are necessary and how they are to be interpreted correctly. The end goal of certification testing is to prove that the standards listed in United States Pharmacopeia Chapter <797> are met. Testing requirements can vary from state to state. A few of the most commonly required sterile certification and calibration tests will be discussed in this article.

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION CLASSIFICATIONS/DEFINITIONS

International Organization for Standardization (ISO) classification is required for the ante-room, buffer room, and all sterile hoods. The ante-room must be certified as ISO Class 8 air quality conditions or better. The definition of ISO Class 8 air quality conditions is the condition in which the air particle count is no greater than a total of 3,520,000 particles of 0.5 micrometers and larger per cubic meter of air (100,000 particles per cubic foot) that is supplied by high-efficiency particulate air (HEPA) or HEPA-filtered air. The buffer room must be certified as ISO Class 7 air quality conditions or better. The definition of ISO Class 7 air quality conditions is the condition in which the air particle count is no greater than a total of 1,760,000 particles of 0.5 micrometers and larger per cubic meter of air (50,000 particles per cubic foot) that is supplied by high-efficiency particulate air (HEPA) or HEPA-filtered air.

The authors are affiliated with Belvidere Labs, a Restore Health Company, Highland Park, New Jersey.

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ity conditions is the condition in which the air particle count is no greater than a total of 352,000 particles of 0.5 micrometers and larger per cubic meter of air (10,000 particles per cubic foot) that is supplied by HEPA or HEPA-filtered air. The sterile hood must be certified as ISO Class 5 air quality conditions or better. The definition of ISO Class 5 air quality conditions is the condition in which the air particle count is no greater than a total of 3,520 particles of 0.5 micrometers and larger per cubic meter of air (100 particles per cubic foot) that is supplied by HEPA or HEPA-filtered air.¹

These tests must be performed under dynamic operating conditions. Dynamic operating conditions will best reflect the ISO class present during typical compounding operations. It is the pharmacist’s responsibility to make sure the dynamic conditions simulated during testing best reflect the compounding activities of the pharmacy and either the words “dynamic” or “operational” are noted on the particle count report, not “static” to reflect the correct conditions. The particle size tested must be stated. The report should have documentation of the location and number of sites tested for each ISO class. The target and actual ISO classification, along with the requirements, should be listed on the report for each area.

**AIR CHANGES PER HOUR**

Air changes per hour (ACPH) are another important factor that affects the function of a cleanroom. ACPH are conducted for ISO Classes 7 and 8 to measure the turbulent airflow. The more ACPH, the more often outside filtered air replaces the existing air in the room. This helps keep the room as clean as possible. Each ISO class will require a different number of changes, with the stricter the classification the higher the number of changes required. The measurement of airflow volume is preferable to the measurement of airflow velocity and is a more representative test of the final filter air supply.² The certification technician will need to have this information recorded in the report, along with the required limits for the desired ISO class. The pharmacist must then review the report to confirm the readings are within limit.

**EQUIPMENT TESTING**

When having a sterile hood certified, there are multiple tests that need to be performed to ensure the equipment is functioning properly. The technician will check that the HEPA filter is cleaning the air appropriately by performing a HEPA filter leak test. All HEPA filters shall be leak tested at every certification with an aerosol challenge.
and a photometer. If any leaks are detected, the pharmacist should ask the technician to repair the leak. The test should then be repeated to ensure the leak has been fixed properly. The fixed leak and the second testing results must both be documented on the final report.

ISO Class 5 sterile hoods rely on unidirectional, or laminar, airflow. Laminar airflow means that filtered air is uniformly supplied in one direction, at a fixed velocity and in parallel streams. To determine if the airflow is truly laminar in nature, an airflow smoke pattern will be performed. A glycol-based fog generator is preferred over water-based fog generators such as CO₂ and liquid nitrogen. A water-based fog generator is heavier than air and does not always provide for an accurate representation of the actual air patterns. The pharmacist should ask the technician for recommendations to reduce turbulence, if any is noted. This may be as simple as rearranging the equipment placement in the hood. If any changes are made, the test should be performed again and documented. Airflow velocity will be tested within the sterile hood. Airflow velocities are typically set to a range of 80 to 100 fpm, but the actual range is best established by the device manufacturer and maintained at that range by the certifier. The actual value must be stated along with a pass or fail notification. If the airflow velocity is not within range, the pharmacist must ask the technician to adjust the speed control and perform the test again. Both the adjustment and the re-test must be recorded.

**REFERENCES**


Address correspondence to Shara Rudner, RPh, FIACP, FACA, Belvidere Labs, a Restore Health Company, Director, National Clinical Trials Group, 440A Raritan Avenue, Highland Park, NJ 08904. E-mail: srudner@restorehc.com

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**CERTIFICATION TEST REPORTS**

All certification test reports must contain some basic information:

- Name and address of the testing organization
- Date on which the test was performed
- Clear identification of the physical location of the cleanroom or clean zone tested
- Specific designations for coordinates of all sampling locations
- Details of the test method used, with any special conditions relating to the test or departures from the test method
- Identification of any testing equipment used

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**CONCLUSION**

In conclusion, it is critical for pharmacists and certifiers to work together to clearly identify the tests that will be performed and how to interpret these tests once completed. Upon an outside inspection, a pharmacist, or their representative, must be able to correctly review their records to determine which tests have been completed. The pharmacist must understand why these tests were performed and how to correctly interpret the results in the end reports. In the end, it is up to the pharmacist to take responsibility of becoming knowledgeable about calibration and certification of their sterile facility to best increase the quality of the compounds and decrease the risk to patients.
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BASICS OF COMPOUNDING:

Tips and Hints, Part 5: Facilities and Equipment

It is not uncommon for tips that improve compounding practice to become an actual part of a Standard Operating Procedure (SOP), and this is how it should be. SOPs are constantly evolving and any change resulting in better practices should be incorporated into the facility’s SOPs. In this issue of the International Journal of Pharmaceutical Compounding, we will discuss some tips and hints that cover compounding facilities and equipment—both nonsterile and sterile.


TIPS ON THE COMPOUNDING FACILITY (GENERAL AND ASEPTIC)

GENERAL FACILITY

• Use a facility-design consultant with experience in the type of compounding planned for the facility (e.g., nonsterile, sterile).
• It is okay, and oftentimes beneficial, to use local contractors with appropriate experience for the project.
• Plan for expansion—do not limit growth.
• Be aware of immediate surroundings (buildings, businesses) when planning a new facility or remodeling a previous facility.
• Be aware of prevailing winds for outlet exhaust planning.
• Be aware of sun location throughout the day and potential temperature/heating effects—try to minimize use of shades and blinds as they tend to collect dust, etc.
• Air movement where chemicals are stored should be toward the exterior of the building and externally exhausted, if appropriate and feasible.
• Small barriers across the door threshold can minimize the escape of any spilled liquids into other parts of the pharmacy. The barrier can be sloped up and down for moving carts over it smoothly.
• Plan for adequate lighting; this is very important.
• Use smooth, rounded corners on cabinet work and in the room along with coving at the wall-ceiling and wall-floor junctures to minimize the chance of contamination throughout the compounding facility.
• Purified Water USP can be obtained by distillation, reverse osmosis, ion-exchange, deionization, filtration, or other suitable process that has been validated. When used in aseptic compounding, it is prepared by either distillation or reverse osmosis.
• Closets or lockers in a separate room(s) should be provided for coats, personal items, jewelry, and clothes/uniform changes as needed.
• Allow sufficient space for housekeeping and maintenance work, especially for storage of disposables.
• Use of disposables by housekeeping personnel can save time and enhance efficiency.
• Keep access to maintenance activities out of the compounding work areas as much as possible.
• Exhaust tubing should have smooth internal surfaces to minimize settling of particles that may be “blown-back” into the room. Smooth surfaces allow the particles to be exhausted more efficiently.
• If possible, place dust-collecting filters, containers, and motors in a room outside the pharmacy so changes of bags, etc. can occur without the potential of getting dust contamination inside the pharmacy.
• Install additional computer and audio/visual communication cables to allow for changes and upgrades in the future.
• Use large glass windows in the compounding area so patients can see the activities of compounding personnel.
• Install sufficient alarms for monitoring temperatures, air flow, etc. of the facility and equipment to warn of any difficulty.
• Install remote computer access so the facility can be monitored offsite as needed.
• Use large glass windows in the compounding area so patients can see the activities of compounding personnel.
• Install a lab-grade dishwasher with attached purified water input.
• Install pass-through windows as appropriate to minimize traffic into and out of the compounding facility.
• Arrange work flow such that finished preparations and raw materials and components do not cross or intermix during processing.

A SEPTIC FACILITY
• Limit access to the ante and buffer areas to necessary personnel. This saves cleanup time, minimizes the chance for contamination, minimizes errors, and enhances efficiency.
• Do not place rubber mats on the floor in the area where aseptic compounding is being performed.
• Remove items from cardboard/fiberboard cartons and wipe down with isopropyl alcohol (IPA) prior to bringing into the ante-room. Only bring smooth, nonshedding cardboard into the ante-room. Inside the ante-room, remove items and wipe down with sterile IPA while transferring to a clean, sanitized cart, tray, or other conveyance system for transport into the buffer area.
• Keep limited supplies of frequently used items on wire shelving in the buffer room.
• Use sufficient carts so that it is not necessary to move them between different clean area levels. The time saved in cleaning will cover the costs.
• No markers or marker boards should be in the cleanroom areas; the markers leave a particulate residue.
• During compounding, place vials, ampules, etc. in the hood parallel to the HEPA filter or back wall so no item can block or interrupt the airflow from the HEPA filter as it washes over the vials/ampules, etc.
• Upon completion of each individual preparation, clean the area and remove all nonessential supplies for the next preparation.

TIPS ON THE PHARMACY’S EQUIPMENT: COMPOUNDING
• Set up a separate file folder for each piece of equipment. This file will include all paperwork, repair information, warranty information, calibration information, etc.
• If operator manuals are missing, they are usually available online for easy downloading.
• Sometimes it is appropriate to obtain unique pieces of equipment at gourmet cooking stores.
• Obtain multiple balances, capsule machines, etc. to allow for faster throughput of compounding. A lot of time may be wasted waiting on something to become available or to dry after being washed.
• As appropriate, wash equipment in an appropriate dishwasher.
• Equipment with crevices, etc. (e.g., capsule machines) should be thoroughly disassembled, washed, and dried to prevent contamination.
• Set up a routine maintenance schedule for all equipment.
• Set up a calibration schedule for all equipment.
Basics

• Use dust covers as appropriate for compounding equipment in the nonsterile compounding area.
• If appropriate and necessary compounding equipment for a specific preparation is not available, do not compound the preparation.
• If a piece of equipment is broken, in disrepair, or malfunctioning, do not use it.
• If biological materials are utilized (e.g., human blood products), appropriate precautions must be observed as well as a biological hazard disposal method in place.
• Pipets and micropipets are accurate and can save a lot of compounding time, minimizing the need to prepare dilutions or aliquots.
• Disposable pipets and micropipets diminish the need to clean soiled pipets.
• It may be beneficial to prepare laminated instructions or calibration information and attach it to or nearby certain pieces of equipment.
• Replace a “water bath” with a “sand bath” or “glass bead” bath. Sand or glass beads can be filled into the chamber and maintained at a constant temperature. Items can be pushed into the sand and will stand on their own. This can be used in the sand bath for a long time and cleanup is minimal.
• To break foam in a preparation, spray with alcohol, silicone, carbon dioxide, or 0.9% sodium chloride solution, depending upon the preparation.

• Coffee grinder mills work great for fast particle size reduction and for pulverizing tablets, etc.
• Variable volume pipets (micro as well as macro), though expensive, are very convenient and accurate and will save time.
• An infrared thermometer (digital) is quick and accurate. Over time, they will pay for themselves.
• Bottle-top dispensers save time and are accurate for dispensing quantities over and over again.
• Consider an orbital mixer or regular laboratory shaker for time savings. Place the ingredients in the container, place in the shaker, set the timer, and do other activities.
• Drawer organizers can actually save time as items are arranged properly and easy to find.
• Kimwipes or tissue holders mounted on the wall or shelf provide easy access and time savings.
• Glass disposal boxes are safe and minimize time required for destruction of broken glassware, etc.
• Calibrate your hot plate and check it regularly.
• Chopsticks (hard plastic) work nicely for smoothing the tops of troches, suppositories, etc.

TIPS ON THE PHARMACY’S EQUIPMENT: QUALITY TESTING (SAMPLING; TESTING)

SAMPLING
• Nondestructive testing (pH measurements, physical observations, weights, volumes) do not use up the preparation. Do these tests first, followed by destructive testing, if required.
• Destructive testing (sending samples to a lab, sterility testing, endotoxin testing, chromatographic testing, etc.) results in a loss of the

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Coffee grinder mills work great for fast particle size reduction and for pulverizing tablets, etc.
sample. Appropriate excess preparation should be prepared to allow for destructive testing.

- Sampling for testing should be representative of the entire compounded preparation.
- Sample handling is important to obtain valid test results. The sample should not be allowed to evaporate or change in any way. It should be sealed to prevent absorption of carbon dioxide from the air resulting in a decrease in pH.
- Split sampling is a good practice. One can be sent to the laboratory and another retained in the pharmacy (for confirmatory testing if needed).
- Split sampling and sending to two different laboratories assists in confirming the performance of the laboratories.
- Do not ship samples out on Friday, as they will set over the weekend during transit. Use overnight delivery and ship Monday through Thursday for next day delivery.

**TESTING**

- Purchase new equipment warranted by the manufacturer.
- If using an instrument daily, leave it on and ready. Otherwise, a calibration process may be needed.
- Some instruments are temperature sensitive and varying results may be obtained with temperature fluctuations.
- Critical equipment should be protected with an Uninterruptible Power Supply (UPS).
- Rinse all glassware involved in sampling and testing with Purified Water USP. (If sterility is involved, use Sterile Water for Injection USP.)
- If outsourcing testing, confirm that the laboratory uses appropriate controls, reference standards, validated methods, etc.
- When cleaning glassware and equipment used in testing, use an appropriate laboratory detergent followed by rinsing with Purified Water USP.
- If glassware must be totally dry and has just been washed, it can be rinsed with acetone or absolute alcohol, which dries rapidly and does not leave a residue.
- In-house testing now includes, weight, volume, physical observations, pH, density, refractive index, sterility, and endotoxin testing.
- Start with a few simple test procedures and gradually increase the number and complexity as new equipment can be purchased and training obtained.
- Develop a long-lasting relationship with a quality laboratory. Your results will be retained and can be easily compared as desired over time.
- Keep a running tally of test results so any trends can be easily observed.
- If any change occurs, the change may be related to a change in ingredients, equipment, procedures, etc.
- Out-of-specification results can usually be traced to personnel or equipment failures.
- An analytical method should be selected that provides the results needed for documentation.
- Intravenous admixtures may be routinely outside the +/-10% variation because of the way they are prepared. (Possible addition of an entire vial of additive to a bag that may contain about 6% overfill of the vehicle.) However, the entire bag or bottle is generally administered so the patient actually receives the desired quantity of drug.

**CONCLUSION**

Shortcuts, tips, hints, new techniques, etc. can help make every compounding’s job easier and enhance patient care. Keep a list of these tips and hints and add to them as new techniques are developed. Also, incorporate selected ones into your pharmacy’s SOPs as appropriate.

Address correspondence to Dr. Loyd V. Allen, Jr., International Journal of Pharmaceutical Compounding, 122 North Bryant Avenue, Edmond, OK 73034. E-mail: lallen@ijpc.com

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Tips on Dealing with a Healthcare Practitioner’s No-rep Policy

Renee Moore, MBA, CPhT

I have had a lot of marketers and pharmacists ask me for suggestions on how to get in to see a healthcare practitioner when the receptionist advises them that they don’t see pharmaceutical reps. Now, I know your first inclination is to tell the receptionist, “Well I’m not a pharmaceutical rep. I work with ABC Compound Pharmacy and I’m different.” Deep down inside you probably feel that is the right thing to say in hopes that the receptionist will say “Oh, I didn’t know that. Come on back.” However, in reality, the receptionist is probably saying, “We don’t want salespeople in here.” That reality check really stings a little bit—right? But in their eyes, even if you have a PharmD, at that moment, you are a salesperson to them. You’re interrupting the physician’s day and the flow of their scheduled appointments in order to come in and talk about your pharmacy. I know it’s a little hard to admit, but that’s just...well...true! Some of the physicians may be trying to say, “We don’t want to see anyone!” How do you get around that? What should you do when the physician/physician’s receptionist say they just don’t see reps? The following four tips are provided to help you market a physician’s office that has a no-rep policy.

TIP ONE: ASK THEM WHY THEY HAVE A NO-REP POLICY

Assuming they answer the question, asking them why they have this policy would certainly shed light on why a particular healthcare provider has implemented this policy. Before visiting physicians, however, consider some of the excuses/ reasons that you might receive and be prepared. Is it because they had someone that was rude? Was someone flirting with the office staff? Did they take up too much time? Once you find out what it is, you will be more prepared to render a response. One suggested explanation is “Well, actually, I’m with XYZ Pharmacy. I’m not a pharmaceutical drug rep, and I’m actually here to find out more about your practice and how our pharmacy can collaborate and work together with your patients to make them feel better.” That way, you at least know what the situation is plus you can work with their rules in their efforts to maintain order in their office.

TIP TWO: MEET WITH THE OFFICE MANAGER

Now, I know this isn’t the same as meeting with the physician but sometimes meeting with the office manager can be better. They are usually close to the physician, and they have a better chance of getting you a meeting with the physician or may be able to relay your message to them; this can help you tremendously. If you meet with the office manager and are able to convince them that you are providing a unique service, that may help you get in to see the doctor and make the process much smoother. In other words, let the physician’s office manager handle the introductions.

TIP THREE: EXTEND YOUR APPRECIATION FOR ANY COMPOUNDS THE PHYSICIAN HAS PRESCRIBED AND YOU HAVE FILLED

If you have filled prescriptions for compounded medications that a particular physician has written, personally go to the physician’s office and in some manner extend your appreciation. Maybe take them a card and/or cookies or cupcakes because most people don’t turn away sweets and nice gifts. These are some suggestions that can give you an opportunity to get in to see them. If you are a new compounder and, therefore, don’t have anything for which to thank them, it is still a good suggestion to go by with those goodies in a leisurely “good neighbor” manner. Introduce them to your new pharmacy and let them know that you just wanted to come out and meet the healthcare practitioners in the area. Also, let the office know that you are perfectly willing and interested in sitting down and conversing with the physician and/or office manager about how you can help their patients.

TIP FOUR: CONSIDER VISITING WITH THE PHYSICIAN DURING OFF HOURS

I like to do after-lunch desserts. I would go by their office with some desserts such as ice cream sundaes, cookies, or homemade peach mango cobbler. It’s a nice time to visit and perhaps get in to see the healthcare practitioner because around that 2 to 4 o’clock PM timeframe there is a lull where everybody is kind of looking for a pick me up. These four tips arm you with some ideas on working with offices and healthcare practitioners who have a no-rep policy. Try them—you’ve got nothing to lose and EVERYTHING TO GAIN!

Address correspondence to Renee Moore, MBA, CPhT, Much Moore Marketing, LLC, Temple Hills, MD 20748. E-mail: renee@compoundpharmacymarketing.com

Renee Moore is the owner/operator of Much Moore Marketing, LLC, located in Temple Hills, Maryland.
CM is a 47-year-old male patient who is 6’1” tall and weighs 248 pounds.

A. What is the ideal body weight (IBW) for this patient in kilograms and pounds?

The following equations can be used to calculate IBW for a male patient:

IBW (kg) = 50 + 2.3 × each inch over 5 feet

IBW (lb) = 110 + 5 × each inch over 5 feet

IBW (kg) = 50 + 2.3(13) = 79.9 kg

IBW (lb) = 110 + 5(13) = 175 lbs

B. Calculate the body mass index (BMI) for this patient.

The following equation can be used to calculate BMI:

BMI = Weight (kg)/[Height (m)]^2

Weight = 248 lbs × 1 kg/2.2 lbs = 112.73 kg

Height = 6’1” = 73 in × 2.54 cm/in = 185.42 cm × 1 m/100 cm = 1.85 m

BMI = 112.73 kg/(1.85 m)^2 = 32.79 kg/m^2

C. A BMI of 30 kg/m^2 is considered obese; therefore, this patient might be subject to higher health insurance premiums. How many pounds would this patient need to lose to reach a BMI of 29.9 kg/m^2 and be considered “overweight”?

29.9 kg/m^2 = Weight (kg)/(1.85 m)^2

Weight = 102.798 kg × 2.2 lb/kg = 226.16 lbs

248 lbs – 226.16 lbs = 21.84 lbs

The patient would have to lose at least 21.84 pounds to be considered overweight rather than obese.

D. In some weight-based dose calculations, the weight for an obese patient is adjusted using the following formula:

Adjusted body weight = [(ABW - IBW) × 0.25] + IBW

where ABW is the actual body weight of the patient

What would be the adjusted body weight for this patient in kilograms?

Adjusted body weight = [(112.73 kg - 79.9 kg) × 0.25] + 79.9 kg = (32.83 kg × 0.25) + 79.9 kg = 88.11 kg

A patient is receiving 500 mL of 2.5% w/v dextrose and 0.45% w/v sodium chloride solution intravenously at a rate of 50 mL/hr.

A. How many milliequivalents of sodium would the patient receive per day from this infusion if administered continuously? [NaCl, MW 58.5]

0.45 g/100 mL × 50 mL/hr × 24 hr/day = 5.4 g/day

5.4 g/day × 1000 mg/g × 1 mEq/58.5 mg = 92.31 mEq/day

B. This patient is found to be hypokalemic; therefore, 40 mEq of potassium will be added to each additional container of fluids. How much of a 14.9% w/v potassium chloride solution should be added? [KCl, MW 74.5]

40 mEq × 74.5 mg/mEq × 1 g/1000 mg × 100 mL/14.9 g = 20 mL

C. What is the osmolarity of the intravenous fluid solution containing potassium chloride? (Assume complete dissociation and that volumes are additive; dextrose, MW = 180)

Total volume = 500 mL + 20 mL = 520 mL

KCl:

40 mEq × 74.5 mg/mEq × 2 mOsmol/74.5 mg = 80 mOsmol

80 mOsmol/520 mL × 1000 mL/L = 153.85 mOsmol/L

Dextrose:

2.5 g/100 mL × 1000 mL × 1000 mg/g = 25,000 mg

25,000 mg × 1 mOsmol/180 mg = 138.89 mOsmol

138.89 mOsmol/520 mL × 1000 mL/L = 267.09 mOsmol/L

NaCl:

0.45 g/100 mL × 1000 mL × 1000 mg/g = 4500 mg

4500 mg × 2 mOsmol/58.5 mg = 153.85 mOsmol

153.85 mOsmol/520 mL × 1000 mL/L = 295.86 mOsmol/L

Total osmolarity = 716.798 mOsmol/L

Reference


Address correspondence to Shelly J. Stockton, BS Pharm, PhD, RPh, College of Pharmacy, Southwestern Oklahoma State University, 100 Campus Drive, Weatherford, OK 73096.
**AZITHROMYCIN 100-MG/ML INJECTION**

**Rx**

For 100 mL

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin (as the dihydrate)</td>
<td>10 g</td>
</tr>
<tr>
<td>Citric acid</td>
<td>8.28 g</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>qs pH 6.4 to 6.6</td>
</tr>
<tr>
<td>Sterile water for injection</td>
<td>qs 100 mL</td>
</tr>
</tbody>
</table>

Note: This formulation should be prepared according to strict aseptic compounding technique in a laminar airflow hood in a cleanroom or via isolation barrier technology by a compounding pharmacist who is validated in aseptic compounding. This is a high-risk preparation.

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the azithromycin and citric acid in about 95 mL of sterile water for injection.
4. Adjust the pH with sodium hydroxide to pH 6.4 to 6.6.
5. Add sufficient sterile water for injection to final volume and mix well.
6. Sterile filter into appropriate sterile containers.
7. Package and label.

**PACKAGING**

Package in tight, light-resistant containers.

**LABELING**

Keep out of reach of children. Use only as directed.

**STABILITY**

Check the current edition of the United States Pharmacopeia for the appropriate beyond-use date for this compounded preparation.

**USE**

Azithromycin injection is indicated in the treatment of patients with infections caused by susceptible microorganisms.

**QUALITY CONTROL**

Quality-control assessment can include weight/volume, physical observation, pH, specific gravity, osmolality, assay, color, clarity, particulate matter, sterility, and pyrogenicity.

**DISCUSSION**

Azithromycin ($C_{38}H_{72}N_{2}O_{12}$, MW 748.98 (anhydrous), Zithromax, Zmax, Azasite) occurs as a white or almost white powder that is freely soluble in anhydrous ethanol and practically insoluble in water. It is anhydrous or contains one or two molecules of water of hydration. It contains the equivalent of NLT 945 mcg and NMT 1030 mcg of azithromycin ($C_{38}H_{72}N_{2}O_{12}$) per mg, calculated on the anhydrous basis. The anhydrous contains NMT 2.0% water, the dihydrate 4.0% to 5.0% water, and the monohydrate contains 1.8% to 4.0%, except that it may be 4.0% to 5.0%. It should be labeled to indicate whether it is anhydrous, monohydrate, or the dihydrate. Azithromycin for Injection is a sterile, dry mixture of azithromycin and a suitable stabilizing agent. It contains NLT 90.0% and NMT 110.0% of the labeled amount of azithromycin ($C_{38}H_{72}N_{2}O_{12}$). It contains NMT 0.7 USP endotoxin units/mg of azithromycin. The pH of the constituted solution is 6.4 to 6.8.

Citric acid ($C_{6}H_{8}O_{7}$, MW 192.12, citric acid monohydrate) occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder that is odorless and has a strong, tart, acidic taste. The hydrated form may contain up to 8.8% water, and the pH of a 1% w/v aqueous solution is about 2.2. Its density is 1.542 g/mL.

Sodium hydroxide (NaOH, MW 40.00, caustic soda, soda lye) occurs as dry, very deliquescent, white or almost white sticks, pellets, or fused masses which are hard and brittle. It is strongly alkaline and corrosive and rapidly absorbs moisture and carbon dioxide when it is exposed to air. It is soluble 1 g in 1 mL of water and is freely soluble in alcohol. A 0.01% solution in water has a pH of not less than 11.0.

Sterile water for injection is water for injection that has been sterilized and suitably packaged; it contains no added substances. Water for injection is water purified by distillation or by reverse osmosis and contains no added substances. Water has a specific gravity of 0.9971 at room temperature, a melting point at 0°C and a boiling point at 100°C. It is miscible with most polar solvents and is chemically stable in all physical states (ice, liquid, steam).

**REFERENCES**

BACITRACIN TOPICAL OINTMENT

<table>
<thead>
<tr>
<th>Rx</th>
<th>For 100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacitracin</td>
<td>50,000 Units</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>5 mL</td>
</tr>
<tr>
<td>White petrolatum</td>
<td>qs 100 g</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Mix the bacitracin with the mineral oil to form a smooth paste.  
   *Note: The quantity of mineral oil can be adjusted if desired.*
4. Incorporate the white petrolatum geometrically and mix until uniform.
5. Package and label.

**PACKAGING**
Package in tight, light-resistant containers.¹

**LABELING**
Keep out of reach of children. Use only as directed.

**STABILITY**
Check the current edition of the United States Pharmacopeia for the appropriate beyond-use date for this compounded preparation.

**USE**
Bacitracin ointment is indicated in the treatment of superficial infections caused by susceptible microorganisms.

**QUALITY CONTROL**
Quality-control assessment can include theoretical weight compared to actual weight, pH, specific gravity, active drug assay, color, texture-surface, texture-spatula spread, appearance, feel, rheological properties, and physical observations.²

**DISCUSSION**

**Bacitracin** is a mixture of polypeptides produced by the growth of an organism of the licheniformis group of *Bacillus subtilis* (Fam. Bacillaceae), the main components being bacitracins A, B₁, B₂, and B₃. It occurs as a white to pale buff powder that is odorless or has a slight odor. It is hygroscopic, and its solutions deteriorate rapidly at room temperature. It is precipitated from its solutions and is inactivated by salts of many of the heavy metals. It is miscible with volatile and fixed oils, with the exception of castor oil. To promote miscibility/solubilization, a small amount of a suitable surfactant can be added. When exposed to heat and light, it undergoes oxidation with the formation of peroxides and ultimately involving an autocatalytic process. Stabilizers, such as butylated hydroxyanisole, butylated hydroxytoluene, and alpha-tocopherol can be used as antioxidants to retard the oxidative process. Mineral oil can be sterilized by dry heat and should be stored in an airtight container, protected from light in a cool place. It is incompatible with strong oxidizing agents.³

**Mineral oil** is a transparent, colorless, viscous liquid that is practically tasteless and odorless when cold; when warm, it has a faint odor. It is used as an emollient, solvent, lubricant, therapeutic agent, and oleaginous vehicle. It has a specific gravity of 0.818 to 0.880. It is insoluble in water or alcohol. It is miscible with volatile and fixed oils, with the exception of castor oil. To promote miscibility/solubilization, a small amount of a suitable surfactant can be added. When exposed to heat and light, it undergoes oxidation with the formation of peroxides and ultimately involving an autocatalytic process. Stabilizers, such as butylated hydroxyanisole, butylated hydroxytoluene, and alpha-tocopherol can be used as antioxidants to retard the oxidative process. Mineral oil can be sterilized by dry heat and should be stored in an airtight container, protected from light in a cool place. It is incompatible with strong oxidizing agents.⁴

**White petrolatum** (white petroleum jelly, white soft paraffin) is a white-colored, translucent, soft unctuous mass that is inert, odorless, and tasteless. It is a mixture of semisolid saturated hydrocarbons obtained from petroleum. It is used primarily in topical pharmaceutical formulations in emollient creams (10% to 30% concentration), topical emulsions (4% to 25% concentration), and topical ointments (up to 100% concentration). It has a specific gravity of about 0.815 to 0.880 and melts in a range between 38°C to 60°C. It is practically insoluble in ethanol, glycerin, and water, but is soluble in chloroform and most fixed and volatile oils. It is stable, but, upon exposure to light, it may discolor due to oxidation of some impurities in the product. This oxidation can be minimized by the addition of a suitable antioxidant, such as butylated hydroxyanisole, butylated hydroxytoluene, or alpha-tocopherol. Heating above its melting range (about 70°C) for extended times should be avoided, but it can be sterilized by dry heat.⁵

**REFERENCES**

DEXPANTHENOL 250-MG/ML INJECTION

**Rx**

For 100 mL

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextopanthenol</td>
<td>25 g</td>
<td></td>
</tr>
<tr>
<td>Sodium citrate and/or citric acid</td>
<td>q5</td>
<td>pH 4 to 7</td>
</tr>
<tr>
<td>Sterile Water for Injection</td>
<td>q5</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

**Note:** This formulation should be prepared according to strict aseptic compounding technique in a laminar airflow hood in a cleanroom or via isolation barrier technology by a compounding pharmacist who is validated in aseptic compounding. This is a high-risk preparation.

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the dextopanthenol in about 85 mL of sterile water for injection.
4. Add either sodium citrate and/or citric acid to a pH of 4 to 7.
5. Add sufficient sterile water for injection to final volume and mix well.
6. Sterile filter into appropriate sterile containers.
7. Package and label.

**PACKAGING**

Package in tight, light-resistant containers.1

**LABELING**

Keep out of reach of children. Use only as directed.

**STABILITY**

Check the current edition of the *United States Pharmacopeia* for the appropriate beyond-use date for this compounded preparation.

**USE**

Dexpanthenol injection is used prophylactically immediately after major abdominal surgery to minimize the possibility of paralytic ileus and in the management of intestinal atony causing abdominal distention, postoperative or postpartum retention of flatus, or postoperative delay in resumption of intestinal motility and paralytic ileus.

**QUALITY CONTROL**

Quality-control assessment can include weight/volume, physical observation, pH, specific gravity, osmolality, assay, color, clarity, particulate matter, sterility, and pyrogenicity.2,3

**DISCUSSION**

Dexpanthenol (C19H19NO4, MW 205.25) occurs as a clear, viscous, somewhat hygroscopic liquid, having a slight characteristic odor. It is freely soluble in water, alcohol, and propylene glycol and slightly soluble in glycerin. Some crystallization may occur upon standing. It should be stored in air-tight containers. It has been used topically in 2% to 5% concentrations in the treatment of various minor skin disorders.4

Sodium citrate (C6H7NaO7, MW 258.07, anhydrous; dihydrate, MW 294.10, trisodium citrate) occurs as colorless crystals or as a white, crystalline powder. The hydrous form is freely soluble in water (1 g in 1.5 mL) and very soluble in boiling water (1 g in 0.6 mL); it is insoluble in alcohol. A 0.02% w/v aqueous solution is iso-osmotic with serum. It is a stable material and can be sterilized by autoclaving.1,5

Citric acid (C6H8O7.H2O, citric acid monohydrate) occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder that is odorless and has a strong, tart, acidic taste. The hydrated form may contain up to 8.8% water, and the pH of a 1% w/v aqueous solution is about 2.2. Its density is 1.542 g/mL. The hydrated form will effloresce, and the anhydrous form will be hygroscopic, depending upon the humidity in the air. If stored in air that is too dry, it may lose its water if the temperature reaches about 40°C. Its melting point is about 100°C, but it softens at about 75°C. One gram is soluble in less than 1 mL of water and 1.5 mL of ethanol.6

Sterile water for injection is water for injection that has been sterilized and suitably packaged; it contains no added substances. Water for injection is water purified by distillation or by reverse osmosis and contains no added substances. Note that water for injection is not prepared by an ion exchange process. Water has a specific gravity of 0.9971 at room temperature, a melting point at 0°C, and a boiling point at 100°C. It is miscible with most polar solvents and is chemically stable in all physical states (ice, liquid, steam).7

**REFERENCES**

EPHEDRINE SULFATE 50-MG/ML INJECTION

RX
For 100 mL
Ephedrine sulfate 5 g
Sterile water for injection qs 100 mL

Note: This formulation should be prepared according to strict aseptic compounding technique in a laminar airflow hood in a cleanroom or via isolation barrier technology by a compounding pharmacist who is validated in aseptic compounding. This is a high-risk preparation.

METHOD OF PREPARATION
1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the ephedrine sulfate in sufficient sterile water for injection to final volume.
4. Sterile filter into appropriate sterile containers.
5. Package and label.

PACKAGING
Package in tight, light-resistant containers.1

LABELING
Keep out of reach of children. Use only as directed.

STABILITY
Check the current edition of the United States Pharmacopeia for the appropriate beyond-use date for this compounded preparation.

USE
Ephedrine sulfate injection is indicated in the treatment of allergic disorders, such as bronchial asthma; it has long been used as a pressor agent and is indicated as a central nervous system (CNS) stimulant in narcolepsy and depressive states; it is also used in myasthenia gravis.

QUALITY CONTROL
Quality-control assessment can include weight/volume, physical observation, pH, specific gravity, osmolality, assay, color, clarity, particulate matter, sterility, and pyrogenicity.2,3

DISCUSSION
Ephedrine sulfate \( \left[ \left( C_{10}H_{15}NO \right)_{2}H_2SO_4 \right] \) MW 428.54 occurs as a fine, white, odorless crystals or powder. It darkens upon exposure to light. It is freely soluble in water (1 g in about 1.3 mL) and sparingly soluble in alcohol (1 g in about 90 mL). First isolated in 1887 from the Chinese herb, ma huang, it is structurally related to epinephrine. It is used for its CNS stimulatory actions.4,5

Ephedrine Sulfate Injection USP is a sterile solution of ephedrine sulfate in water for injection. It contains NLT 95.0% and NMT 105.0% of the labeled amount of \( \left( C_{10}H_{15}NO \right)_{2}H_2SO_4 \). It contains not more than 1.7 USP endotoxin units per mg of ephedrine sulfate and has a pH between 4.5 and 7.0.1

Sterile water for injection is water for injection that has been sterilized and suitably packaged; it contains no added substances. Water for injection is water purified by distillation or by reverse osmosis and contains no added substances. Note that water for injection is not prepared by an ion exchange process. Water is used to describe potable water from a public water supply that is suitable for drinking and is the beginning point of the official waters. It is a clear, colorless, odorless, and tasteless liquid. Purified water is water that is obtained by distillation, ion exchange, reverse osmosis, or some other suitable process. Water has a specific gravity of 0.9971 at room temperature, a melting point at 0°C and a boiling point at 100°C. It is miscible with most polar solvents and is chemically stable in all physical states (ice, liquid, steam).6

REFERENCES
### Fluorescein 100-Mg/ML Injection

<table>
<thead>
<tr>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescein</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
</tr>
<tr>
<td>Sterile water for injection</td>
</tr>
</tbody>
</table>

Note: This formulation should be prepared according to strict aseptic compounding technique in a laminar airflow hood in a cleanroom or via isolation barrier technology by a compounding pharmacist who is validated in aseptic compounding. This is a high-risk preparation.

**Method of Preparation**
1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Add the fluorescein to about 90 mL of sterile water for injection.
4. Add sodium hydroxide to obtain a pH in the range of 8.0 to 9.8 and a clear solution is obtained.
5. Add sufficient sterile water for injection to final volume and mix well.
6. Sterile filter into appropriate sterile containers.
7. Package and label.

**Packaging**
Package in tight, light-resistant containers.

**Labeling**
Keep out of reach of children. Use only as directed.

**Stability**
Check the current edition of the *United States Pharmacopeia* for the appropriate beyond-use date for this compounded preparation.

**Use**
Fluorescein injection is indicated in diagnostic fluorescein angiography or angiography of the retina and iris vasculature.

**Quality Control**
Quality-control assessment can include weight/volume, physical observation, pH, specific gravity, osmolality, assay, color, clarity, particulate matter, sterility, and pyrogenicity.

**Discussion**
Fluorescein (C₁₀H₁₂O₅, MW 332.31; Fluorescite) occurs as a yellowish-red to red, odorless powder that is soluble in dilute alkali hydroxides and is insoluble in water. It contains NLT 97.0% and NMT 102.0% of C₁₀H₁₂O₅ calculated on the anhydrous basis. It contains NMT 1.0% water. Fluorescein sodium (C₁₀H₁₀Na₂O₅, MW 376.27; Fluoresceit, Funduscein) contains NLT 90.0% and NMT 102.0% of C₁₀H₁₀Na₂O₅ calculated on the anhydrous basis. It occurs as an orange-red, hygroscopic, odorless powder that is freely soluble in water and sparingly soluble in alcohol. Fluorescein Injection is a sterile solution, in Water for Injection, of Fluorescein prepared with the aid of sodium hydroxide. It contains the equivalent of NLT 90.0% and NMT 110.0% of the labeled amount of fluorescein sodium (C₂₀H₁₀Na₂O₅). It may contain sodium bicarbonate. It has a pH between 8.0 and 9.8.

Sodium hydroxide (NaOH, MW 40.00, caustic soda, soda lye) occurs as dry, very deliquescent, white or almost white sticks, pellets, or fused masses which are hard and brittle. It is strongly alkaline and corrosive and rapidly absorbs moisture and carbon dioxide when it is exposed to air. It is soluble 1 g in 1 mL of water and is freely soluble in alcohol. A 0.01% solution in water has a pH of NLT 11.0. It should be stored in air-tight, non-metallic containers.

Sterile water for injection is water for injection that has been sterilized and suitably packaged; it contains no added substances. Water for injection is water purified by distillation or by reverse osmosis and contains no added substances. Note that water for injection is not prepared by an ion exchange process. Water is used to describe potable water from a public water supply that is suitable for drinking and is the beginning point of the official waters. It is a clear, colorless, odorless, and tasteless liquid. Purified water is water that is obtained by distillation, ion exchange, reverse osmosis, or some other suitable process. Water has a specific gravity of 0.9971 at room temperature, a melting point at 0°C and a boiling point at 100°C. It is miscible with most polar solvents and is chemically stable in all physical states (ice, liquid, steam).

**References**
**INDOCYANINE GREEN 2.5-MG/ML INJECTION**

**Rx**

*For 100 mL*

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indocyanine</td>
<td>250 mg</td>
</tr>
<tr>
<td>Sodium iodide</td>
<td>up to 5 g</td>
</tr>
<tr>
<td>Sterile water for injection</td>
<td>qs</td>
</tr>
</tbody>
</table>

Sterile water for injection qs 100 mL

**Note:** This formulation should be prepared according to strict aseptic compounding technique in a laminar airflow hood in a cleanroom or via isolation barrier technology by a compounding pharmacist who is validated in aseptic compounding. This is a high-risk preparation.

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the indocyanine in about 95 mL of sterile water for injection.
4. Add up to 5 g of sodium iodide and confirm a clear solution.
5. Add sufficient sterile water for injection to final volume and mix well.
6. Sterile filter into appropriate sterile containers.
7. Package and label.

**PACKAGING**

Package in tight, light-resistant containers.¹

**LABELING**

Keep out of reach of children. Use only as directed.

**STABILITY**

Check the current edition of the United States Pharmacopeia for the appropriate beyond-use date for this compounded preparation.

**USE**

Indocyanine green injection is indicated for determining cardiac output, hepatic function and liver blood flow and for ophthalmic angiography.

**QUALITY CONTROL**

Quality-control assessment can include weight/volume, physical observation, pH, specific gravity, osmolality, assay, color, clarity, particulate matter, sterility, and pyrogenicity.² ³

**DISCUSSION**

**Indocyanine Green** ($C_{43}H_{47}N_2NaO_6S_2$, MW 774.96, IC-Green) occurs as an olive-brown, dark green, blue-green, dark blue, or black powder. It is odorless or has a slight odor. Its solutions are deep emerald-green in color. The pH of a 1 in 200 aqueous solution is about 6. Its aqueous solutions are stable for about 8 hours. It is soluble in water and in methanol and practically insoluble in most other organic solvents. It contains NLT 89.0% and NMT 100.0% of $C_{43}H_{47}N_2NaO_6S_2$, calculated on the dried basis. It contains NMT 5.0% of sodium iodide, calculated on the dried basis. Indocyanine Green for Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of $C_{43}H_{47}N_2NaO_6S_2$. It contains

NMT 7.1 USP endotoxin units per mg of indocyanine green. The pH of a 1 in 200 solution is between 5.5 and 7.5.¹

**Sodium iodide** (NaI, MW 149.89) contains NLT 99.0% and NMT 101.5% of NaI, calculated on the anhydrous basis. It occurs as colorless, odorless, crystals, or white, crystalline powder. It is deliquescent in moist air, and develops a brown tint upon decomposition. It is very soluble in water, freely soluble in alcohol and in glycerin. It should be preserved in tight containers.¹

**Sterile water for injection** is water for injection that has been sterilized and suitably packaged; it contains no added substances. Water for injection is water purified by distillation or by reverse osmosis and contains no added substances. Note that water for injection is not prepared by an ion exchange process. Water is used to describe potable water from a public water supply that is suitable for drinking and is the beginning point of the official waters. It is a clear, colorless, odorless, and tasteless liquid. Purified water is water that is obtained by distillation, ion exchange, reverse osmosis, or some other suitable process. Water has a specific gravity of 0.9971 at room temperature, a melting point at 0ºC, and a boiling point at 100ºC. It is miscible with most polar solvents and is chemically stable in all physical states (ice, liquid, steam).³

**REFERENCES**

**PHENYLEPHRINE HYDROCHLORIDE 2.5%-OPHTHALMIC SOLUTION**

<table>
<thead>
<tr>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For 100 mL</strong></td>
</tr>
<tr>
<td>Phenylephrine hydrochloride</td>
</tr>
<tr>
<td>Dibasic sodium phosphate, dihydrate</td>
</tr>
<tr>
<td>Monobasic sodium phosphate, dihydrate</td>
</tr>
<tr>
<td>Boric acid</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
</tr>
<tr>
<td>Sterile water for injection</td>
</tr>
</tbody>
</table>

Note: This formulation should be prepared according to strict aseptic compounding technique in a laminar airflow hood in a cleanroom or via isolation barrier technology by a compounding pharmacist who is validated in aseptic compounding. This is a high-risk preparation.

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and measure each ingredient accurately.
3. Dissolve the four powders in about 95 mL of sterile water for injection.
4. Add the benzalkonium chloride and mix well.
5. Add sufficient sterile water for injection to final volume and mix well.
6. Sterile filter into appropriate sterile ophthalmic containers.
7. Package and label.

**PACKAGING**

Package in tight, light-resistant containers.1

**LABELING**

Keep out of reach of children. Use only as directed.

**STABILITY**

Check the current edition of the United States Pharmacopeia for the appropriate beyond-use date for this compounded preparation.

**USE**

Phenylephrine hydrochloride ophthalmic solution is used as a decongestant and vasoconstrictor and for pupil dilation in uveitis (posterior synechiae). It is also used in wide angle glaucoma, prior to surgery, refraction, ophthalmoscopic examination, and diagnostic procedures.

**QUALITY CONTROL**

Quality-control assessment can include weight/volume, pH, specific gravity, osmolality, assay, color, clarity, particulate matter, and sterility.2,3

**DISCUSSION**

Phenylephrine hydrochloride (C9H13NO2·HCl, MW 203.67, Neo-Synephrine) occurs as white or practically white, odorless crystals with a bitter taste; it is freely soluble in water and in alcohol.1 Phenylephrine Hydrochloride Ophthalmic Solution USP is a sterile aqueous solution of phenylephrine hydrochloride. It contains NLT 90.0% and NMT 115.0% of the labeled amount of phenylephrine hydrochloride. It may contain a suitable antimicrobial agent and buffer and may contain suitable antioxidants. It has a pH between 4.0 and 7.5 for buffered ophthalmic solution and between 3.0 and 4.5 for unbuffered ophthalmic solution.1

**Sodium phosphate, dibasic** is available in an anhydrous form (MW 141.96), dihydrate (MW 177.98), heptahydrate (MW 268.03), and as a dodecahydrate (MW 358.08). It is used as a buffering agent and as a sequestering agent. It is very soluble in water (anhydrous, 1 in 8: hepta-hydrate, 1 in 4: dodecahydrate, 1 in 3) but practically insoluble in ethanol. Its aqueous solutions are stable and can be autoclaved.1

**Sodium phosphate, monobasic** is available in an anhydrous form (MW 119.98), monohydrate form (MW 137.99), and as a dihydrate (MW 156.01). It is used as a buffering agent, emulsifying agent, and as a sequestering agent. The anhydrous form is available as a white crystalline powder or granules and the hydrated forms are odorless, colorless or white-colored, slightly deliquescent crystals. It is soluble 1 g in 1 mL of water but only very slightly soluble in 95% ethanol. Aqueous solutions of it are stable and can be autoclaved.1

**Boric acid** (MW 61.83) occurs as colorless scales, crystals, or as a white powder that is slightly unctuous to the touch. It is soluble in water (1 g in 18 mL), alcohol (1 g in 18 mL), and glycerin (1 g in 4 mL).6

**Benzalkonium chloride** is a bactericidal antimicrobial agent commonly used as a preservative in many ophthalmic, otic, nasal, and parenteral formulations. It occurs as a white or yellowish-white amorphous powder, a thick gel, or gelatinous pieces/flakes with a characteristic mild, aromatic odor, soapy touch and very bitter taste. It is very soluble in water, alcohol, and acetone.7

**REFERENCES**

For 100 mL

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfamethoxazole</td>
<td>4 g</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>800 mg</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.26 mL</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>100 mg</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>100 mg</td>
</tr>
<tr>
<td>Carboxymethylcellulose sodium</td>
<td>500 mg</td>
</tr>
<tr>
<td>Citric acid</td>
<td>500 mg</td>
</tr>
<tr>
<td>Flavor</td>
<td>qs</td>
</tr>
<tr>
<td>Glycerin</td>
<td>10 mL</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>1 g</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>2 g</td>
</tr>
<tr>
<td>Saccharin sodium</td>
<td>50 mg</td>
</tr>
<tr>
<td>Sorbitol solution</td>
<td>60 mL</td>
</tr>
<tr>
<td>Purified water</td>
<td>qs 100 mL</td>
</tr>
</tbody>
</table>

**DISCUSSION**

**Sulfamethoxazole** (C10H11N3O3S, MW 253.28, Gantanol) occurs as a white to off-white, practically odorless, crystalline powder that is freely soluble in acetone and practically insoluble in water. It contains NLT 99.0% and NMT 101.0% of sulfamethoxazole, calculated on the dried basis. It melts at 168°C to 172°C and contains NMT 0.5% water.1 Sulfamethoxazole and Trimethoprim Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amounts of sulfamethoxazole and trimethoprim. The pH of the preparation is 5.0 to 6.5, and it contains NMT 0.5% of alcohol.1

**Trimethoprim** (C14H18N4O3, MW 290.32, Proloprim, Trimex) occurs as a white to cream-colored, odorless crystals, or crystalline powder. It is slightly soluble in alcohol and in acetone and very slightly soluble in water. It melts between 199°C and 203°C and contains NMT 0.5% water.1

**Methylparaben** (C7H6O3, methyl hydroxybenzoate, methyl parahydroxybenzoate) is available as colorless crystals or as a white, crystalline powder that is odorless, or almost odorless, and has a slight burning taste. One gram is soluble in 400 mL of water, 3 mL of 95% ethanol, 60 mL glycerin, 200 mL peanut oil, and 5 mL propylene glycol.3

**Sodium benzoate** (C7H5NaO2, MW 144.11) occurs as a white granular or crystalline, slightly hygroscopic powder. It is generally odorless and has an unpleasant sweet and salty taste. It is soluble 1 g in 1.8 mL of water and 75 mL of 95% ethanol.4

**Carboxymethylcellulose sodium** (carmellose sodium) occurs as a white to cream-colored, hygroscopic powder or granules. It is easily dispersed in water to form colloidal solutions; it is insoluble in alcohol.5

**Citric acid** (C6H8O7.H2O, MW 210.14, citric acid monohydrate,) occurs as colorless or translucent crystals, or as a white, crystalline powder that is odorless, or almost odorless, and has a strong, tart, acidic taste. One gram is soluble in less than 1 mL of water and 1.5 mL of ethanol.6

**Microcrystalline cellulose** [(C6H10O5)n where n = 220, MW 36,000] occurs as a white, odorless, tasteless, crystalline powder that is composed of porous particles. It is practically insoluble in water, dilute acids, and most organic solvents but is slightly soluble in 5% w/v sodium hydroxide solution.7

**Polysorbate 80** (C64H124O26, MWE 1310, Tween 80, polyoxyethylene 20 sorbitan monooleate) occurs as a yellow oily liquid with a characteristic odor and a warm, somewhat bitter taste.8

**Saccharin sodium** (soluble saccharin, Sucaryl, Sweeta-with sorbitol) is an intense sweetening agent with a molecular weight of 205 for the anhydrous form. It is a white, odorless, or faintly aromatic, efflorescent, crystalline powder with an intensely sweet taste and a metallic aftertaste. One gram is soluble in about 1.2 mL water, 50 mL of 95% ethanol and 3.5 mL propylene glycol.9

**REFERENCES**

References available upon request.
**SUMATRIPTAN SUCCINATE 12-MG/ML INJECTION**

**Rx**

For 100 mL

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan (as the succinate)</td>
<td>1.2 g</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>700 mg</td>
</tr>
<tr>
<td>Sterile water for injection</td>
<td>qs 100 mL</td>
</tr>
</tbody>
</table>

Note: This formulation should be prepared according to strict aseptic compounding technique in a laminar airflow hood in a cleanroom or via isolation barrier technology by a compounding pharmacist who is validated in aseptic compounding. This is a high-risk preparation.

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the sumatriptan and sodium chloride in sufficient sterile water for injection to final volume and mix well.
4. Sterile filter into appropriate sterile containers.
5. Package and label.

**PACKAGING**

Package in tight, light-resistant containers.¹

**LABELING**

Keep out of reach of children. Use only as directed.

**STABILITY**

Check the current edition of the *United States Pharmacopeia* for the appropriate beyond-use date for this compounded preparation.

**USE**

Sumatriptan succinate injection is used in the treatment of migraine.

**QUALITY CONTROL**

Quality-control assessment can include weight/volume, physical observation, pH, specific gravity, osmolality, assay, color, clarity, particulate matter, sterility, and pyrogenicity.²³

**DISCUSSION**

**Sumatriptan succinate** (C₁₄H₂₁N₃O₅SC₄H₆O₄, MW 413.49, Imitrex) contains NLT 98.0% and NMT 101.0% of sumatriptan (C₁₄H₂₃N₃O₅S), calculated on the anhydrous and solvent-free basis. It occurs as a white or almost white powder that is freely soluble in water. It contains NMT 1.0% water. It should be preserved in tight, light-resistant containers and protected from freezing; it should be stored below 30°C.

**Sumatriptan Injection** is a sterile solution of sumatriptan succinate in water for injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of sumatriptan (C₁₄H₂₃N₃O₅S). It has an osmolality of 270 to 330 mOsmol/kg and contains NMT 29.2 USP endotoxin units/mg of sumatriptan. It is preserved in single-dose containers, preferably of Type I glass and stored between 2°C and 30°C protected from light.¹

**Sodium chloride** (NaCl, MW 58.44) is available as a white crystalline powder or as colorless crystals. It has a saline taste and is used in a variety of parenteral and nonparenteral pharmaceutical formulations. In parenteral, ophthalmic, and nasal preparations, it is used to prepare isotonic solutions. It is also used as a capsule diluent, lubricant, to control drug release from some microcapsules, to control micelle size, and to adjust the viscosity of some polymer dispersions by altering the ionic character of the formulation. The pH of a saturated solution is in the range of 6.7 to 7.3, and it is soluble in water (1 g in 2.8 mL), glycerin (1 g in 10 mL), and 95% ethanol (1 g in 250 mL). A 0.9% w/v aqueous solution is iso-osmotic with serum, and its solutions are stable. Its solutions are corrosive to iron and will react to form precipitates with silver, lead, and mercury salts. Chlorine can be liberated in the presence of strong oxidizing agents from its acidified solutions. It can also decrease the solubility of methylparaben in aqueous solution.⁴

**Sterile water for injection** is water for injection that has been sterilized and suitably packaged; it contains no added substances. Water for injection is water purified by distillation or by reverse osmosis and contains no added substances. Note that water for injection is not prepared by an ion exchange process. Water is used to describe potable water from a public water supply that is suitable for drinking and is the beginning point of the official waters. It is a clear, colorless, odorless, and tasteless liquid. Purified water is water that is obtained by distillation, ion exchange, reverse osmosis, or some other suitable process. Water has a specific gravity of 0.9971 at room temperature, a melting point at 0°C and a boiling point at 100°C. It is miscible with most polar solvents and is chemically stable in all physical states (ice, liquid, steam).⁵

**REFERENCES**

TRANEXAMIC ACID 100-MG/ML INJECTION

Rx
For 100 mL

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tranexamic acid</td>
<td>10 g</td>
</tr>
<tr>
<td>Sterile water for injection</td>
<td>qs 100 mL</td>
</tr>
</tbody>
</table>

Note: This formulation should be prepared according to strict aseptic compounding technique in a laminar airflow hood in a cleanroom or via isolation barrier technology by a compounding pharmacist who is validated in aseptic compounding. This is a high-risk preparation.

METHOD OF PREPARATION
1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the tranexamic acid in sufficient sterile water for injection to final volume and mix well.
4. Sterile filter into appropriate sterile containers.
5. Package and label.

PACKAGING
Package in tight, light-resistant containers.¹

LABELING
Keep out of reach of children. Use only as directed.

STABILITY
Check the current edition of the United States Pharmacopeia for the appropriate beyond-use date for this compounded preparation.

USE
Tranexamic acid injection is indicated in patients with hemophilia for short-term use to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.

QUALITY CONTROL
Quality-control assessment can include weight/volume, physical observation, pH, specific gravity, osmolality, assay, color, clarity, particulate matter, sterility, and pyrogenicity.²,³

DISCUSSION
Tranexamic acid (C₈H₁₅NO₂, MW 157.21, Cyklokapron) contains NLT 99.0% and NMT 101.0% of C₈H₁₅NO₂, calculated on the dried basis. It occurs as a white, crystalline powder that is freely soluble in water and in glacial acetic acid; it is practically insoluble in acetone and in alcohol. It contains NMT 0.5% water; it should be preserved in tight containers. Tranexamic acid injection has a pH from 6.5 to 8.0.¹

Sterile water for injection is water for injection that has been sterilized and suitably packaged; it contains no added substances. Water for injection is water purified by distillation or by reverse osmosis and contains no added substances. Note that water for injection is not prepared by an ion exchange process. Water is used to describe potable water from a public water supply that is suitable for drinking and is the beginning point of the official waters. It is a clear, colorless, odorless, and tasteless liquid. Purified water is water that is obtained by distillation, ion exchange, reverse osmosis, or some other suitable process. Water has a specific gravity of 0.9971 at room temperature, a melting point at 0°C and a boiling point at 100°C. It is miscible with most polar solvents and is chemically stable in all physical states (ice, liquid, steam).⁴

REFERENCES
Stability and In Vitro Toxicity of an Infliximab Eye Drop Formulation

ABSTRACT
The purpose of this study was to develop a novel 10-mg/mL infliximab eye drop, to characterize its physical and biological stability under recommended storage conditions, and to assess the formulation’s toxicity to ocular surface epithelium in vitro. Infliximab (10 mg/mL) was reconstituted using equal volumes of sterile water and 1% carboxymethylcellulose artificial tears. Aliquots were stored in either a 4°C refrigerator or -20°C freezer for up to 45 days. Physical stability was assessed through monitoring the solution’s appearance, pH, ultraviolet-visible-near infrared absorbance and scattering, as well as protein gel electrophoresis. Biological stability was assayed through binding to tumor necrosis factor-alpha using an enzyme-linked immunosorbent assay. In vitro cytotoxicity to human corneal-limbal epithelial cells was examined following a 4-hour exposure to the study drug. Refrigerated and frozen infliximab eye drops remained clear and colorless for the duration of study. The formulation’s pH (7.0) was comparable to that of the artificial tear vehicle alone. Low levels of ultraviolet-visible-near infrared light absorbance and scattering established the lack of protein precipitate after refrigeration or freezing. Protein gel electrophoresis performed under reducing conditions revealed the presence of two main protein bands of approximately 50 kDa and 25 kDa, representing immunoglobulin G heavy and light chains. The migration pattern of the proteins did not change under the different storage conditions and between day 10 and 45 after formulation. Infliximab binding to tumor necrosis factor-alpha remained stable for up to 45 days, with conservation of 101% and 102% of its initial binding activity when refrigerated or frozen, respectively. In vitro human corneal-limbal epithelial cultures showed no increase in cytotoxicity with infliximab treatment when compared to vehicle and culture media controls (P > 0.05). Infliximab can be formulated as an eye drop and remains stable when stored in accordance with current regulations regarding compounded eye drops. The demonstrated physical and biological stability as well as in vitro innocuity of this infliximab eye drop formulation may facilitate future clinical investigation targeting tumor necrosis factor-alpha as a modulator of various ocular surface diseases.

INTRODUCTION
Infliximab (Remicade; Janssen Biologics BV, Leiden, The Netherlands) is a chimeric human-mouse monoclonal immunoglobulin G (IgG) antibody against tumor necrosis factor alpha (TNF-α). Infliximab binds to the E-F loop of TNF-α and, by overlapping with the TNF-α receptor (TNFR)-binding site, blocks the biological function of this cytokine. As a biologic immunomodulator, infliximab is indicated for the treatment of severe systemic inflammatory diseases including rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease, ulcerative colitis, psoriatic arthritis, and plaque psoriasis. In addition, there is extensive clinical experience with the use of infliximab in uveitis. Systemic administration of infliximab has also been reported to stabilize corneal melting in patients with auto-immune diseases (rheumatoid arthritis, Crohn’s disease, peripheral ulcerative keratitis) that were recalcitrant to other treatment modalities. Our interest in infliximab stems from our clinical experience with this drug in a few patients with rheumatoid arthritis or Stevens-Johnson syndrome and KPro-related sterile keratolysis. Over the years, infliximab was administered intravenously to several hopeless cases of post-KPro melt. The effect of these infusions was dramatic, halting inflammation as well as the melting process.

TNF-α is a pleotropic cytokine that has been identified as a therapeutic target in several ocular diseases. For example, topical formulations of infliximab have been studied in both mouse and rabbit models of ocular surface disease such as chemical burn, dry eye, and corneal neovascularization. These animal studies support the safety and efficacy of topical infliximab in inflammatory pathology. To date however, the topical use of infliximab in human subjects has not been reported; the logistics of preparing, dispensing, and storing the eye drop for human studies is much more complex. Indeed, as a...
compounded sterile preparation, the topical infliximab formulation must comply with United States Pharmacopoeia (USP) <787> regulations. For such moderate risk eye drop preparations, these regulations specify a storage limit of nine days after formulation when refrigerated and of 45 days when frozen. As the stability of reconstituted infliximab solution following freeze-thaw has not been previously reported, the aim of this study was to analyze the physical and biological stability of infliximab when stored at -20°C for up to 45 days. In addition, the toxicity of the refrigerated and frozen formulation was evaluated in vitro using a human corneal-limbal epithelial (HCLE) cell line.

MATERIALS AND METHODS

Infliximab Formulation and Storage

A vial of sterile lyophilized infliximab powder (Lot DDM30015P1) was obtained from Janssen Biologics. As described by the manufacturer, such vials contain 100 mg of infliximab; 500 mg of sucrose; 0.5 mg of polysorbate 80; 2.2 mg of monobasic sodium phosphate, monohydrate; and 6.1 mg of dibasic sodium phosphate, dehydrate. The supplied powder does not contain preservatives.

All compounding steps were performed in a sterile hood using aseptic technique. To dissolve the infliximab powder, 5 mL of sterile water, for injection (Lot 28469DK; Hospira) without preservative, was injected into the manufacturer-provided vial, directing the stream of water toward the vial’s glass wall. The vial was gently swirled to dissolve the lyophilized powder and allowed to stand for five minutes. Following this step, 5 mL of Refresh Liquigel (Lot 80694; Allergan, Irvine, California) was also injected into the diluted infliximab vial. As 100 mg of infliximab are dissolved in a total 10 mL of fluid, the final concentration was 10 mg/mL or 1%. The infliximab 10-mg/mL solution was aliquoted into 10-mL × 1-mL eye drop bottles. Half of the bottles were kept in a 4°C refrigerator, and the others were stored in a -20°C freezer. Similarly, a 50:50 mixture of sterile water and Refresh Liquigel artificial tears was aliquoted into 10-mL × 1-mL eye drop bottles to be used as a vehicle control. Refresh Liquigel contains 1% carboxymethylcellulose sodium, boric acid, calcium chloride, magnesium chloride, potassium chloride, purified water, PURITE (stabilized oxychloro complex), sodium borate, and sodium chloride. Its pH ranges from 7.0 to 7.4. PURITE is a safe and gentle preservative that breaks down into sodium, chloride, oxygen, and water on the ocular surface. The Refresh Liquigel vehicle bottles were either refrigerated or frozen under the same conditions as the infliximab 10-mg/mL solution.

Physical Stability

The solution’s appearance, pH, ultraviolet-visible-near infrared (UV-vis-NIR) absorbance and scattering spectra as well as protein migration pattern on gel electrophoresis were monitored over time to evaluate the physical stability of the infliximab eye drop. Frozen aliquots of infliximab and vehicle were thawed on the day of analysis. Gross appearance of the infliximab solution was assessed through visual observation and digital photography. Because of the small volumes available for testing, pH analysis was performed using pH paper strips. Analysis of pH was performed on days 9, 27, and 45 after compounding. Two types of pH indicator papers were used for this purpose (Whatman pH indicator papers, Dassel, Germany and ColorpHast pH-indicator strips, EMD Chemicals Gibbstown, New Jersey).

Light absorbance and scattering were used to quantitatively assess the formation of microscopic particles in solution on days 1, 9, and 45 after compounding. Infliximab 10 mg/mL (200 mcL) was mixed with 350 mcL of Refresh Liquigel and 350 mcL deionized water and placed in a 1-cm pathlength quartz cuvette. The UV-vis-NIR absorbance spectra (250 to 1100 nm) was measured using a HP Agilent 8452 diode-array spectrophotometer (Hewlett-Packard, Andover, Massachusetts). Light scattering was used as complementary measurement of protein precipitation. Light scattering data was acquired using a standard fluorimeter (QuantaMaster 300, Photon Technology International, Birmingham, New Jersey) with 540 nm excitation and detection of scattered light at a 90° angle. After completing the measurements using the clear infliximab solution, the cuvette was then heated at 100°C for 10 seconds, leading to protein precipitation and increased cloudiness of the solution. Absorbance and scattering measurements were repeated using this heated solution to act as a positive control. Deionized water was used as a negative control.

Protein gel electrophoresis was performed on days 10 and 45 after compounding. Samples were prepared using reducing 2x Laemmli sample buffer (Bio-Rad, Hercules, California) with β-mercaptoethanol. Samples of refrigerated and frozen infliximab were loaded at 1.25 mcg of infliximab per well and run on a Bio-Rad Mini-PROTEAN TGX 4% to 20% gradient polyacrylamide gel. The gel was stained with GelCode Blue stain reagent (ThermoScientific, Rockford, Illinois) following the manufacturer’s recommendations.

Biological Stability

Biological stability was assessed through quantification of infliximab binding to its target, TNF-α, at 0, 9, and 45 days after compounding. A modified commercial sandwich ELISA assay (Quantikine ELISA Human TNF-α Immunoassay, R&D Systems, Minneapolis, Minnesota) was employed as previously described. This assay is validated for TNF-α concentrations between 15.6 pg/mL and 1,000 pg/mL, a range over which optical density varies linearly with concentration. Briefly, both the refrigerated and frozen infliximab 10-mg/mL solutions were serially diluted to the following concentrations: 4000 ng/mL, 40 ng/mL, and 0.4 ng/mL. Each of these infliximab concentrations was mixed with an equal volume of a known concentration of TNF-α (250 pg/mL). The final concentration of infliximab was thus 2000 ng/mL, 20 ng/mL, or 0.2 ng/mL while the final concentration of TNF-α was 125 pg/mL. Calculation of the stoichiometric ratio between infliximab and TNF-α revealed an excess of infliximab molecules in solution for the three highest concentrations of infliximab assayed. The stoichiometric ratios were 1880:1 (4000 ng/mL infliximab: 250 pg/mL TNF-α) and 35:1 (20 ng/mL infliximab: 125 pg/mL TNF-α).
TNF-α), 18.8:1 (40 ng/mL), and 0.188:1 (0.4 ng/mL).

The infliximab and TNF-α combination was incubated at room temperature for one hour to allow for antibody-antigen binding. The subsequent steps of the assay were performed in accordance with the ELISA immunoassay manufacturer’s recommendations. A standard curve using TNF-α concentrations between 0 pg/mL to 250 pg/mL was prepared with each assay. The refrigerated and frozen infliximab dilutions that had previously been allowed to react with TNF-α were loaded in triplicate (200 mcL per well). The optical density (OD) of each well was measured immediately after stopping the reaction using wavelengths of 450 nm and 540 nm. The readings at 540 nm were subtracted from those at 450 nm to correct for optical imperfections.

The OD reading correlates directly with the amount of free TNF-α in solution. Free-TNF-α is able to bind to the ELISA microplate. However, TNF-α captured by infliximab will not bind to the microplate antibody and will, instead, be removed during the wash steps of the assay. The amount of free TNF-α in pg/mL was calculated from the standard curve. The original amount of TNF-α allowed to react with infliximab was calculated using the standard curve and 125 pg/mL standards. The biological activity of infliximab was determined as the fraction of TNF-α that was bound by infliximab (measured 125 pg/mL vehicle control minus measured free TNF-α) over the original amount of TNF-α allowed to react with infliximab (vehicle control containing 125 pg/mL of infliximab).

Cytotoxicity

The cytotoxicity of the infliximab eye drop was assessed in vitro using an immortalized human corneal-limbal epithelial (HCLE) cell line.16 Cells cultured to pre-confluence were used to model cytotoxicity to immature or injured epithelium. Confluent and stratified cultures were used to model cytotoxicity to an intact, stratified epithelial barrier. Pre-confluent HCLE cells were plated in 12-well plates at a density of 1 × 10⁴ cells/cm² and incubated for 48 hours in a 37°C-humidified, 5%-CO₂ atmosphere. Confluent cells were plated at a density of 2.5 × 10⁴ cells/cm². After reaching confluence, the cell culture medium was supplemented with 10% calf serum and epidermal growth factor to allow for stratification over the subsequent 3 days of culture.

The infliximab solution was diluted 1:50 in unsupplemented cell culture medium (DMEM/F12, Cellgro, MediaTech, Manassas, Virginia) yielding a final infliximab concentration of 200 mcg/mL. The infliximab solution had been compounded 60 days prior and kept either refrigerated at 4°C or frozen at -20°C until the day of the exposure. Vehicle, diluted 1:50 in DMEM/F12 and DMEM/F12 alone, were used as negative controls. All cultures and assays were conducted in triplicate.

For the cytotoxicity assay, an aliquot of cell culture supernatant was collected from each well at the following time intervals: 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours. Total cell numbers were determined after the 4-hour exposure using a terminal cell proliferation assay. For this purpose, the CytoTox 96 Nonradioactive Cytotoxicity Assay and the CellTiter 96 AQueous One Solution Cell Proliferation Assay (Cell Titer; Promega, Madison, Wisconsin) were used as previously described.17 The cell number from the cytotoxicity assay quantifies the amount of dead cells that have lysed and released lactate dehydrogenase (LDH) into the cell culture supernatant. The Cell Titer assay yields the number of viable cells in culture at the 4-hour (terminal) time point. Cell culture photography was performed serially after 2-, 3-, and 4-hour exposures to monitor for cytopathic effects.

OD readings from both the cytotoxicity and Cell Titer assays were converted into cell numbers following determination of a standard curve. The linear equation for the cytotoxicity standard curve was X= (OD – 0.10945)/3.72406 × 10⁻⁵ where X is the number of cells and OD is the optical density reading at 490 nm (R² = 0.9952, valid for X = 0 to 10⁶ cells). Similarly, the linear fit for Cell Titer was X = (OD – 0.0856)/2.93628 × 10⁻⁶ (R² = 0.9777, valid for 0 to 300 000 cells).

Data Analysis and Statistics

The biological activity of refrigerated and frozen infliximab was compared at each of the 0-, 9-, and 45-day time points. To determine if biological activity decreases over time, the amount of TNF-α inhibition was compared for each of the storage conditions (0 versus 9 versus 45 days for refrigerated infliximab and 9 versus 45 days for frozen infliximab).

Cytotoxicity was compared between treatments at each time point (15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours). As well, time points were compared within each treatment to assess for increasing cytotoxicity over time. The total number of viable cells after a 4-hour exposure was examined for each treatment. To account for potential differences in cell number between wells, cytotoxicity data was reported as the number of dead cells over the amount of total cells (dead + viable) at the 4-hour time point.

The nonparametric Kruskal-Wallis test was used in all cases. To account for the possibility of errors in inference for multiple comparisons, Dunn’s multiple comparisons test was performed for each pair of the testing conditions if the P-value calculated by Kruskal-Wallis was below 0.05. Statistical analysis was performed using Instat 3.10 statistical software (GraphPad Software, San Diego, California). Statistical significance was determined when the 2-tailed P-value exceeded 0.05.

RESULTS

Physical Stability

The infliximab 10-mg/mL eye drop solution was colorless and transparent on the day of compounding. These physical properties were maintained when refrigerated at 4°C or frozen at -20°C for 45 days after compounding (Figure 1).

The pH of the infliximab solution and the vehicle was 6.9 when using the Whatman pH paper strips and 7.0 when using the ColopHast pH indicator strips. This pH was maintained at days 9, 27, and 45 after compounding. There was no difference in pH between the refrigerated or frozen infliximab and vehicle.
The UV-vis-NIR absorbance and scattering spectra of infliximab stored at 4°C for 1 and 9 days as well as infliximab stored at -20°C for 45 days were superposable. As such, only the spectra obtained at day 45 are shown in Figure 2. Infliximab showed an absorbance peak around 250 nm, relating to the typical absorbance of protein at this wavelength range (Figure 2A). The remaining spectra showed negligible baseline absorption, indicating that all visible light gets through the infliximab sample. There was a marked increase in the absorbance of the heated infliximab sample. This increased absorbance is due to the presence of protein precipitates caused by the heat denaturation of infliximab; it served as a control for the validity of this assay as a test for stability (Figure 2C). Similarly, there was minimal scattering of light by the refrigerated or frozen infliximab solution but scattering increased significantly after the sample was heated to 100°C (Figure 2B).

The protein gel electrophoresis band pattern was similar for refrigerated and frozen infliximab at days 10 and 45 after formulation. Staining revealed two main bands at approximately 50 kDa and 25 kDa size, which is typical of IgG. There was an additional faint band between the 100-kDa and 75-kDa molecular weight markers, as well as one slightly upstream to the 25 kDa band (Figure 3).

B. The scatter of visible light (540 nm) at 90 degrees from the incident beam is shown. The infliximab eye drop reveals a low level of scattering, while a marked increase is seen after heating.

C. Color photograph showing increased cloudiness and opacity of the boiled infliximab positive control. The same experiment was performed using refrigerated infliximab eye drop at 1 and 9 days after formulation. Both UV-vis-NIR and scattering spectra were superposable to those presented here.
FIGURE 3. Protein gel electrophoresis of the infliximab eye drop after 10 and 45 days of refrigeration (R) or freezing (F). The two main bands, at approximately 50 kDa and 25 kDa size, are typical of human immunoglobulin G heavy and light chains, respectively. The faint bands of higher molecular weight may represent the different migration patterns for the major glycoforms of infliximab.

Biological Stability

The binding stability of infliximab to TNF-α following refrigeration or freezing for up to 45 days was monitored using a modified sandwich ELISA assay. Infliximab-bound TNF-α forms a stable complex that does not bind to the antibody-coated ELISA microplate. Consequently, the assay quantifies the amount of free TNF-α (TNF-α not bound by infliximab). The biological activity of infliximab can therefore be calculated as the decrease in TNF-α measured by the assay in relation to the known amount of TNF-α initially participating in the reaction with infliximab.

Figure 4 demonstrates the biological stability data of refrigerated and frozen infliximab at 0, 9, and 45 days after compounding. In addition, the Table provides assessment of TNF-α binding activity using the 4000 ng/mL concentration of infliximab. This concentration was chosen for analysis because of the lower risk of dilution error. As shown in the Table, the percentage of TNF-α inhibited by refrigerated infliximab (4000 ng/mL) was 82% on day 0, 75% on day 9, and 82% on day 45 (P > 0.05). TNF-α inhibition by frozen infliximab (4000 ng/mL) was 73% at day 9 and 83% on day 45 (P > 0.05). Therefore, there was no loss of TNF-α inhibition over time for either storage condition. In addition, there was no statistically significant difference in TNF-α inhibition between refrigerated and frozen infliximab for each of the 9- and 45-day time points (P > 0.05).

Similar results were obtained with analysis of the 0.4-ng/mL and 40-ng/mL infliximab concentrations. On average, 8% (range 0% to 11%) and 49% (range 42% to 65%) of TNF-α was inhibited using infliximab 0.4 ng/mL and 40 ng/mL, respectively. As before, there was no statistical difference between the different time points and conservation temperature (refrigerated versus frozen) for these dilutions.

Cytotoxicity

There was no significant difference in cytotoxicity for the different treatments (DMEM/F12, vehicle, refrigerated infliximab or frozen...
infliximab) for either pre-confluent or confluent and stratified HCLE cells (Figure 5A and 5B). Further, there was no significant increase in cytotoxicity over time for pre-confluent cells exposed to any treatment. While Figure 5B illustrates a potential increase in cytotoxicity over time for confluent cells, this difference was not statistically significant. Normal desquamation of apical stratified cells from the cultures may be responsible for this apparent increase in cell death. As seen in Figure 5C, there were only minimal differences in the total viable cell number after 4 hours of treatment (P = 0.35 and P = 0.58, for pre-and post-confluent cells, respectively). Dead cells represented 1.8% +/- 2.0% (DME/F12) to 5.3% +/- 0.7% (frozen infliximab) of total pre-confluent cells (P > 0.05) and 15.8% +/- 1.8% (DME/F12) to 24.4% +/- 2.4% (frozen infliximab) of total confluent cells (P > 0.05) (Figure 5D). Light microscopy of pre-confluent and confluent, stratified cell cultures did not detect any cytopathologic effect of infliximab when compared to controls (Figure 6).

**DISCUSSION**

We describe the formulation of a novel infliximab (10-mg/mL) eye drop and demonstrate that it is physically and biologically stable when prepared and stored under current federal regulations (USP <797>) that specify a storage limit of 9 days when refrigerated and of 45 days when frozen. Further, we establish that the infliximab eye drop is non-toxic to cultured ocular surface epithelium when compared to cell culture media and vehicle controls.

Demonstration of a stable and non-toxic infliximab eye drop is relevant, as there is increasing interest in TNF-α as a therapeutic target for several ocular surface diseases. Indeed, several case reports support the use of intravenous infliximab to stab-

| Table. Biological Stability of Topical Infliximab Formulation When Refrigerated or Frozen for 45 Days. |
|---------------------------------|----------|----------|--------|----------|----------|--------|
| Variable| Storage Time (Days) | 0 | 9 | 45 | 0 | 9 | 45 |
| Measured TNF-α concentration, mean +/- SD (pg/mL)| Refrigerated | 25 +/- 3 | 34 +/- 0.3 | 36 +/- 5 | 26 +/- 10 | 25 +/- 2 | >0.05 |
| TNF-α consumed, mean +/- SD (pg/mL)| Refrigerated | 111 +/- 3 | 101 +/- 0.3 | 99 +/- 5 | 124 +/- 10 | 125 +/- 2 | >0.05 |
| Percentage of TNF-α consumed by reaction with infliximab| Refrigerated | 82 +/- 2 | 75 +/- 0.2 | 73 +/- 4 | 82 +/- 6 | 83 +/- 2 | >0.05 |
| Percentage of initial infliximab activity remaining| Refrigerated | 100 | 92 | 90 | 101 | 102 |

*Means and SDs calculated from triplicate assays; ‡Dunn’s multiple comparisons test; †The consumption of TNF-α was calculated by subtracting the TNF-α concentration measured in the vehicle control (containing 125 pg/mL of TNF-α) from the TNF-α concentration of samples where TNF-α 125 pg/mL was reacted with infliximab; ‡The percentage of TNF-α consumed by infliximab was calculated by dividing the amount of TNF-α consumed by the TNF-α concentration in the vehicle control; ‡The percentage of initial infliximab activity remaining was calculated by dividing the percentage of TNF-α consumed by the percentage of TNF-α consumed at baseline (day 0, 82%).

Note: TNF-α consumption by infliximab and thus the integrity of antibody-antigen binding was quantified using a validated enzyme-linked immunosorbent assay. SD = standard deviation; TNF-α = tumor necrosis factor alpha.
FIGURE 5. *In vitro* cytotoxicity and cell number of human corneal-limbal epithelial (HCLE) cells exposed to refrigerated or frozen infliximab 200 mcg/mL, vehicle or culture medium (DMEM/F12). A) Cytotoxicity, represented the number of dead cells, to pre-confluent cells exposed to each treatment for 15 and 30 minutes, as well as 1, 2, 3, and 4 hours. There was no increase in cytotoxicity over time except for (1) the DMEM exposure comparing 15 minutes to 3 hours. Asterisks (*) indicate statistically significant differences in cytotoxicity between DMEM and frozen infliximab at 15 minutes, 1, 2, and 3 hours but not at other time points. B) Cytotoxicity to confluent cells under the same exposures as in A). The apparent increase in cytotoxicity over time was not statistically significant except for (2) the refrigerated infliximab exposure comparing 30 minutes to 4 hours. The asterisk indicates a statistically significant difference in cytotoxicity between DMEM and frozen infliximab at 30 minutes only. These statistically significant differences are not consistent with other time points measured.

C) Cell number of pre-confluent and confluent, stratified HCLE cells following 4-hour exposure to each treatment.

D) Cytotoxicity after 4-hour exposure relative to total cell count (dead + viable cells) demonstrating no significant increase of cytotoxicity after exposure to vehicle, refrigerated or frozen infliximab when compared to standard cell culture medium.
Several weeks, our study is the first to demonstrate the stability of infliximab in an eye drop formulation following freeze-thaw. We further characterized the eye drop formulation's physical and biological stability. Gross appearance, pH, UV-vis-NIR absorbance and scattering, protein gel electrophoresis, as well as TNF-α binding remained stable after refrigeration or freezing for up to 45 days. In vitro cytotoxicity did not differ significantly from that of standard HCLE cell culture media nor from the eye drop's artificial tear vehicle. The importance of this demonstration lies in the current legislation regarding compounded drugs and eye drops. To be practical and cost-effective, prolonged refrigeration and freezing of drug formulations will be required to proceed with human studies using infliximab eye drops. Indeed, while the animal studies presented above suggest a benefit of topical infliximab eye drops, only human studies will establish the exact role of TNF-α modulation in the treatment of ocular surface diseases.

Notably, dry eye disease has been associated with elevated levels of TNF-α in tears. In vitro studies have shown that TNF-α induces ectodomain release of the membrane-associated mucins MUC1 and MUC16, which may lead to increased tear film instability, earlier break up time, and impaired ocular surface barrier function. TNF-α is also a potent inducer of matrix metallo-proteinases (MMP), which lead to corneal matrix degradation, ulceration, and melting. Inhibition of MMPs may explain the remarkable effect of intravenous infliximab in meloxic corneal disorders such as PUK. In the cornea, TNF-α recruits and mobilizes antigen presenting Langerhans cells at the limbus and induces their migration into the central cornea. As such, TNF-α inhibition may have an important role in mediating corneal allograft rejection.

The topical administration of infliximab for such diseases may have several advantages. First, an eye drop delivers high concentrations of the medication locally while exposing the patient to significantly lower doses. Punctal occlusion may decrease systemic absorption, further reducing the risk of systemic adverse events such as oppor-

**FIGURE 6. Confluent and pre-confluent cell culture photographs (10X) demonstrating the similar cellular morphology following a 4-hour exposure to DMEM, vehicle, refrigerated infliximab or frozen infliximab.**
tunistic infections and malignancy. Also, the topical administration of infliximab, in contrast to intravenous administration, does not require prolonged infusions in a hospital setting and spares the patient from the risk of infusion reactions.

**CONCLUSION**

In conclusion, we describe the formulation of a stable and non-toxic infliximab eye drop. Investigations using topical infliximab in animal models also suggest that topical administration is safe and effective for several ocular surface diseases. However, well-designed human-subject research is needed to substantiate these preliminary findings.

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**REFERENCES**


Address correspondence to Dr. Marie-Claude Robert, Massachusetts Eye and Ear Infirmary, Department of Ophthalmology, Harvard Medical School, 243 Charles St., Boston, MA. E-mail: Marie-Claude_Robert@MEEI.harvard.edu
Physicochemical and Microbiological Stabilities of Hydrocortisone in InOrpha Suspending Agent Studied Under Various Conditions

Philippe Bourget, PharmD, PhD
Alexandre Amin, PharmD
Fabrice Vidal
Manon Pieyre
El Oumar Dosso
Raphaëlle Beauvais
Richard Loeuillet

INTRODUCTION
Hydrocortisone, also known as cortisol, is the main endogenous steroid and more specifically a glucocorticoid hormone secreted by the zona fascicula of the adrenal cortex; it is notably released in response to stress. Naturally, its primary functions are to increase blood sugar via the liver gluconeogenesis; suppress the immune system; and provide aid in fat, protein, and carbohydrate metabolism: it also decreases bone formation. Naturally occurring glucocorticoids (i.e., hydrocortisone and cortisone), which also have salt-retaining properties, are mainly used as replacement therapy in adrenocortical deficiency states. In pediatric practice, posology ranges from 10 to 20 mg/m² per day, divided in three doses, for the purpose of mimicking the nycthemeral cycle. Hydrocortisone is marketed in France in tablet form that contains 10 mg of the active ingredient. This galenic formulation is not suitable for pediatric use, and often requires a grinding operation or a dose fractionation to facilitate administration. To overcome this difficulty, the objective of this study was to develop and evaluate the physicochemical and microbiological stabilities of hydrocortisone in a sugar-free, alcohol-free, and paraben-free InOrpha suspending agent. The studied samples were formulated into a 2-mg/mL suspension and stored in glass bottles at two temperature conditions, between 2°C to 8°C and at room temperature. Two series of twelve samples were tested for physicochemical stability using high-performance liquid chromatography as well as for a microbiological status for 28 days (daily opening of the bottles from day 0 of compounding) and for 56 days (first opening at day 28 from compounding and daily opening for 28 consecutive days). The high-performance liquid chromatography method developed is linear, accurate, precise, and robust. On the other hand, a forced degradation study has demonstrated the selectivity and specificity of the method validated as stability indicating. In both storage conditions, high-performance liquid chromatography analysis showed that tested samples had concentrations ranging within 90% to 110% of the initial concentration for 28 consecutive days upon daily bottle opening and, for a maximum of 42 days with a first opening at day 28 from the compounding time. Microbiological status remained stable throughout the course of the study. Based on the data collected, the study led to the development of a new galenic formulation of hydrocortisone suitable for pediatric use which can be safely stored under refrigerated conditions or at room temperature for a maximum of 42 consecutive days.

ABSTRACT
Hydrocortisone is principally used as replacement therapy in adrenocortical deficiency states. In pediatric practice, posology ranges from 10 to 20 mg/m² per day, divided in three doses, for the purpose of mimicking the nycthemeral cycle. Hydrocortisone is marketed in France in tablet form that contains 10 mg of the active ingredient. This galenic formulation is not suitable for pediatric use, and often requires a grinding operation or a dose fractionation to facilitate administration. To overcome this difficulty, the objective of this study was to develop and evaluate the physicochemical and microbiological stabilities of hydrocortisone in a sugar-free, alcohol-free, and paraben-free InOrpha suspending agent. The studied samples were formulated into a 2-mg/mL suspension and stored in glass bottles at two temperature conditions, between 2°C to 8°C and at room temperature. Two series of twelve samples were tested for physicochemical stability using high-performance liquid chromatography as well as for a microbiological status for 28 days (daily opening of the bottles from day 0 of compounding) and for 56 days (first opening at day 28 from compounding and daily opening for 28 consecutive days). The high-performance liquid chromatography method developed is linear, accurate, precise, and robust. On the other hand, a forced degradation study has demonstrated the selectivity and specificity of the method validated as stability indicating. In both storage conditions, high-performance liquid chromatography analysis showed that tested samples had concentrations ranging within 90% to 110% of the initial concentration for 28 consecutive days upon daily bottle opening and, for a maximum of 42 days with a first opening at day 28 from the compounding time. Microbiological status remained stable throughout the course of the study. Based on the data collected, the study led to the development of a new galenic formulation of hydrocortisone suitable for pediatric use which can be safely stored under refrigerated conditions or at room temperature for a maximum of 42 consecutive days.

The authors’ affiliations are as follows: Philippe Bourget, Alexandre Amin, Fabrice Vidal, Manon Pieyre, El Oumar Dosso, and Richard Loeuillet, Clinical Pharmacy Department, University Hospital Necker-Enfants Malades (AP-HP), Paris, France; Raphaëlle Beauvais, Hygiene Department, University Hospital Necker-Enfants Malades (AP-HP), Paris, France.

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The purposes of this study were to develop and study in various conditions the physicochemical and microbiological stabilities of an oral suspension of hydrocortisone in a suspending agent flavored with caramel, suitable for pediatric use.

Initially, we considered: 1) an assessment of the needs expressed by the clinical services of our institution and 2) a retrospective analysis of hydrocortisone use for pediatrics across 18 months of prescriptions via our local online computerized prescription software (Phedra, AP-HP institutional software). Thus, 64 prescriptions were analyzed between January 2012 and June 2013; they revealed a population of children aged between 7 days to 13 years, receiving a mean dose of 9 mg of hydrocortisone per day of treatment divided into three oral intakes of 3 mg. This preliminary step allowed optimization of usable volumes of suspension for administration at the fixed concentration of 2 mg of hydrocortisone per mL.

Stability was assessed using the percentage of recovery of hydrocortisone concentration. Further, pH and microbiological studies were performed in 24 glass bottles of 60 mL according United States Pharmacopeia (USP) conditions (i.e., refrigerated storage [2°C to 8°C] and at room temperature) at varying time points using the following two main procedures in order to evaluate stability under real conditions of use:

1. Throughout a 28-day period, with a daily opening of 12 to 24 bottles from day 0 of the compounding time
2. Throughout a 56-day period, with a first opening at day 28 from the compounding time and a daily opening for the remaining 28 days

MATERIALS AND METHODS

Chemicals Reagents

Hydrocortisone powder (Lot 11260306, Molecular formula: C21H30O5, Molecular weight: 362.4599) and InOrpha suspending agent (Lot NK30) were of pharmaceutical quality, and kindly provided by Inresa (Bartenheim, France). Methanol (Lot 13H010500) of high-performance liquid chromatography (HPLC)-grade quality, was supplied by VWR Prolabo (Fontenay-Sous-Bois, France). Potassium phosphate monobasic (Lot BCBD9656V, KH2PO4) and sodium hydroxide (Lot 32206A01, NaOH) were of analytical-grade quality and purchased from Sigma-Aldrich (St-Quentin Fallavier, France).

Equipment and Chromatographic Conditions

The pH measurements were performed on a SevenGo pH meter (Mettler-Toledo, Scherzenbach, Switzerland). Chromatographic separation was performed on a Dionex Ultimate 3000 series liquid chromatographic system equipped with a quaternary pump, a variable UV/visible detector, and an autosampler (Dionex, Voisins le Bretonneux, France). Chromatographic separation was performed with a Pursuit 5 (250 mm × 4.6 mm, dp = 5 mc m) C18 column (Agilent Technologies, Les Ulis, France). The mobile phase consisted of a mixture of potassium phosphate buffer (30 mmol/L) adjusted to pH 6.0 with NaOH (0.1N) and methanol (70:30, v/v) and was delivered at a rate of 0.8 mL per min. The mobile phase was filtered through a 0.45-mcm membrane (Millipore, Molsheim, France) and degassed prior to use. Detection was performed at 246 nm. The injection volume was 20 mcL with a run time of 10 minutes. Data were recorded. Dionex Chromelene (version 6.80) software was used for both data collection and processing.

Sample Pre-treatment for High-performance Liquid Chromatography Quantification

Of the previously agitated suspension sample, 100 mcL, as well as 4,900 mcL of the mobile phase, were successively added to a glass test tube that was approximately 8 mL in capacity. The tube was capped using a polypropylene stopper, and the mixture was vigorously shaken for 30 seconds using vortex-mixing. Then, 200 mcL of the diluted solution, at the theoretical concentration of 40 mcg of hydrocortisone per mL, was pipetted into a glass autoinjector vial with an insert. Finally, the vial was capped, and 20 mcL of the mixture was injected onto the column.

Validation Protocol and Forced Degradation Studies

Analytical validation of the method was conducted in accordance with the recommendations of the Commission of the French Society of Pharmaceutical Science and Technology (SFSTP, 2003). This guide provides a consensus on the various existing international standards (e.g., the International Conference on Harmonization: Validation of Analytical Procedures Q2 (R1)).

Calculation of the validation parameters were based on six measurements per day for three consecutive days of three levels of quality control (30, 40, and 50 mcg of hydrocortisone per mL), and were performed using the e.noval (version 3.0) software (Arlenda, Liège, Belgium). In addition, hydrocortisone samples were stressed under a variety of circumstances, and then assayed with the aim of determining the specificity of the HPLC method with regard to any possible degradation products (DP) that may appear during the storage of an oral suspension, keeping in mind that the stability-indicating criterion of an HPLC method must be demonstrated via degradation of samples under various conditions. In practice, the experimental conditions must be aggressive enough to produce primary DP, but should not destroy entirely the drug; an ideal situation is to degrade 20% to 30% of the drug to obtain DP clearly separated from the intact drug. A stepwise approach was applied on two diluted suspensions (i.e., 30 mcg and 50 mcg of hydrocortisone per mL) at various time measurements, under the following physicochemical stressing conditions:

1. Acido-basic exposure (i.e., HCl [0.1M] and NaOH [0.1N])
2. Temperature, starting at 50°C and increased by 10°C steps until 100°C
3. Oxidative exposure (i.e., H2O2 at 3%)

Time under each stressor was 2, 4, 8, and 12 hours, and was compared to a controlled and
unstressed standard. Any extraneous peak found was labeled; in accordance with USP specifications, the resolution parameter was systematically determined between DP and the intact fraction of hydrocortisone.

The full separation was accepted for a resolution parameter equal or superior to 1.5. Purity calculations were also performed using Dionex Chromeleon software (version 6.80) on the hydrocortisone peak using the control; obviously, unstressed standard was used as a reference.

**Preparation of Hydrocortisone Suspension Samples**

The hydrocortisone suspension was prepared into a clean mortar, by adding 1,440 mL of InOrpha by means of a volumetric pipette, and 2.88 g of hydrocortisone powder. After homogenization, the suspension was equally distributed into 24 60-mL glass bottles. Twelve suspension samples were stored either under USP refrigerated storage conditions or at room temperature conditions for the duration of the study.

**Stability Study**

The 24 samples of hydrocortisone suspended in InOrpha at the theoretical concentration of 2 mg per mL were submitted for physicochemical and microbiological stability studies. Samples were packaged in tinted glass bottles and stored under two temperature conditions (n=12/24 bottles for each required condition); either at USP controlled refrigerated temperature (2°C to 8°C) using a digitally controlled laboratory refrigerator from Facis (Bonneuil Sur Marne, France), or at room temperature. In order to evaluate stability under real conditions of use, the stability of the mixture was assessed via two procedures for each of the following storage conditions:

1. Throughout a 28-day period, with a daily opening of 12/24 bottles from day 0 of the compounding time
2. Throughout a 56-day period, with a first opening of 12/24 bottles at day 28 from the compounding time and a daily opening for the 28 remaining days

**RESULTS**

The physicochemical stabilities in InOrpha suspending agent (i.e., concentrations of hydrocortisone and pH measurements performed at room temperature and under refrigerated conditions) are highlighted in Tables 1 and 2, respectively. Value of 1.88 mg per mL (mean value, measured from 12/24 bottles) was set as the initial concentration of hydrocortisone (measured at day 0 [i.e., compounding time]) for the group, with a daily opening from day 0 of the compounding time; all subsequent measurements were compared to this nominal value. The same value of 1.88 mg of hydrocortisone per mL (mean value, measured from 12/24 bottles) was set as the initial concentration (measured at day 0 [i.e., compounding time]) for the group with a first opening from the 28th day of the compounding time; all subsequent time points until day 56 were compared to this reference value. Figures 1 and 2 show the mean profiles of changes in the concentration of hydrocortisone in suspension vs. time. In both storage conditions, concentration of the drug remains within the specification bounds (i.e., [90%<hydrocortisone]<110%), throughout 28 days with a daily opening from day 0 of the compounding time and throughout 42 days with a first opening at day 28 from the compounding time. The microbiological stability of hydrocortisone in InOrpha suspending agent, at room temperature and under refrigerated conditions is shown in Table 3. Table 4 summarizes the calculations of the peak purity and the relative degradation percentage of the drug.

**DISCUSSION**

The HPLC method was properly validated. In brief:

1. Linearity, the slope and intercept are close to 1 and 0, respectively, thus confirming the absence of a proportional and constant systematic error in each model; the correlation coefficient (R²) was equal to 0.9961.
2. Repeatability (i.e., the intra-series variance) expressed in percent relative standard deviation (RSD %) was systematically below 0.52.
3. Intermediate precision, which is the sum of intra- and inter-series variances (RSD %) was systematically below 1.84.
4. The trueness expressed in terms of recovery (%) were ranging from 99.96% to 100.10%.
Further, the HPLC method was shown to be stability indicating, by forcing the degradation of hydrocortisone and separating the DP peaks from that of the main analyte. A slight degradation of the drug was shown under acid, oxidizing, and also heated conditions; conversely, base caused a quick destruction of the drug.

As shown in Figure 1, the initial potency of hydrocortisone in suspension was 1.88 mg/mL; this value remained stable despite the daily opening of the bottles, from the first day to the 28th day of this part of the study. The value was 94.0% of the theoretical compounding target set at 2 mg/mL; the T=0 result, was set as the baseline value for all other time points tested. The assay results varied between 1.74 mg/mL (T=21) and 1.88 mg/mL (T=0) at room temperature storage conditions, and between 1.73 mg/mL (T=21) and 1.89 mg/mL (T=28) under refrigerated conditions. In both storage conditions, all samples at each time point were within specifications, and all RSD %s were below 10%. Moreover, each chromatogram was clear of DP peaks and had the same chromatographic profile. Regarding the pH summarized in Table 1, their values were steady; they were found between 4.67 and 4.89.

As shown in Figure 2, the initial potency of hydrocortisone in suspension was 1.88 mg/mL; this value remained stable despite the daily opening of the bottles, from the first day to the 28th day of the study. The value was 94.0% of the theoretical compounding target set at 2 mg/mL; the T=0 result, was set as the baseline value for all other time points tested. The assay results varied between 1.74 mg/mL (T=21) and 1.88 mg/mL (T=0) at room temperature storage conditions, and between 1.73 mg/mL (T=21) and 1.89 mg/mL (T=28) under refrigerated conditions. In both storage conditions, all samples at each time point were within specifications, and all RSD %s were below 10%. Moreover, each chromatogram was clear of DP peaks and had the same chromatographic profile. Regarding the pH summarized in Table 1, their values were steady; they were found between 4.67 and 4.89.

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Note: Bottles filled with the mixture at the targeted concentration of 2 mg of hydrocortisone hydrochloride per mL were maintained either at room temperature or in refrigerated conditions according to United States Pharmacopeia specifications.

| TABLE 1. Physicochemical Stability of Hydrocortisone in InOrpha throughout a 28-Day Period, with a Daily Opening of the Bottles from Day 0 of the Galenic Shaping. |
|---|---|---|---|---|---|---|
| ELAPSED TIME (T= DAYS) | % RECOVERY AT ROOM TEMPERATURE (n=6) | PH VALUE AT ROOM TEMPERATURE (n=6) | % RECOVERY AT 2°C TO 8°C (n=6) | PH VALUE AT 2°C TO 8°C (n=6) |
| T=0 | 100.00 | 4.67 | 100.00 | 4.68 |
| T=7 | 93.25 | 4.74 | 95.02 | 4.74 |
| T=14 | 96.52 | 4.81 | 94.84 | 4.89 |
| T=21 | 92.63 | 4.82 | 91.96 | 4.80 |
| T=28 | 98.25 | 4.78 | 100.24 | 4.79 |

Note: Bottles filled with the mixture at the targeted concentration of 2 mg of hydrocortisone hydrochloride per mL were maintained either at room temperature or in refrigerated conditions according to United States Pharmacopeia specifications.

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<td>PH VALUE AT ROOM TEMPERATURE (n=6)</td>
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Note: Bottles filled with the mixture at the targeted concentration of 2 mg of hydrocortisone hydrochloride per mL were maintained either at room temperature or in refrigerated conditions according to United States Pharmacopeia specifications.

| TABLE 3. Microbiological Stability of Hydrocortisone in InOrpha throughout a 28-Day Period with a Daily Opening of 12/24 Bottles from Day 0 of the Galenic Shaping, and throughout a 56-Day Period with a Daily Opening of 12/24 Bottles from the 28th Day of the Galenic Shaping. |
|---|---|---|---|---|---|---|
| TOTAL AEROBIC MICROBIAL COUNT (CFU/mL) [PRESENCE OF E. COLI] |
| Elapsed Time (T=days) | T=0 | T=7 | T=14 | T=21 | T=28 | T=35 | T=42 | T=49 | T=56 |
| Bottles stored at room temperature |
| <10 | <10 | <10 | <10 | <10 | <10 | <10 | <10 | <10 |<10 |
| [No] | [No] | [No] | [No] | [No] | [No] | [No] | [No] | [No] | [No] |
| Bottles stored at 2°C to 8°C |
| <10 | <10 | <10 | <10 | <10 | <10 | <10 | <10 | <10 |<10 |
| [No] | [No] | [No] | [No] | [No] | [No] | [No] | [No] | [No] | [No] |

Daily opening from day 0; 2Daily opening from day 28

Finally, and whatever the conditions, suspensions were considered microbiologically stable; the Total Aerobic Count was less than 10 CFU/mL without any growth E. coli.
CONCLUSION

It has been demonstrated that hydrocortisone is stable in InOrpha suspending agent for 28 consecutive days upon daily bottle opening and for a maximum of 42 consecutive days with a first opening from the 28th day of the compounding time, when stored either at room temperature or under refrigerated condition. It is important to emphasize that, throughout the study period, the microbiological quality of the mixture was never altered by repeated opening of bottles; this argument is in favor of a multidose use of the vials, subject to application with appropriate rules of hygiene. The new formulation offers a flexible and effective alternative when compared to the tablets of hydrocortisone, and especially for the benefit of pediatric practice. To obtain official and specific status of Hospital Preparation, the new formulation of hydrocortisone was submitted to an authorization application to the French National Agency for Medicines and Health Products Safety (i.e., Agence Nationale de Sécurité du Médicament et des produits de santé [ANSM]).

TABLE 4. Peak Purity of Hydrocortisone in InOrpha.

<table>
<thead>
<tr>
<th>STRESS CONDITION</th>
<th>PURITY SCORE (0/00)</th>
<th>% DEGRADATION</th>
</tr>
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<tbody>
<tr>
<td>Water (reference)</td>
<td>1000.0</td>
<td>0</td>
</tr>
<tr>
<td>HCl (0.1 M)</td>
<td>1000.0</td>
<td>32.0</td>
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<tr>
<td>NaOH (0.1 N)</td>
<td>999.3</td>
<td>73.1</td>
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<tr>
<td>H2O2 3 %</td>
<td>1000.0</td>
<td>23.6</td>
</tr>
<tr>
<td>Temperature (100°C)</td>
<td>1000.0</td>
<td>22.6</td>
</tr>
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</table>

Note: The peak purity was determined under the following physicochemical stressing conditions: a) acido-basic exposure (i.e., hydrochloride [0.1M] and NaOH [0.1N]); b) temperature, starting at 50°C and increased by 10°C steps until 100°C; and c) oxidative exposure (i.e., H2O2 at 3%).

FIGURE 1. Concentration profiles (mean values) vs. time of hydrocortisone in InOrpha throughout a 28-day period with a daily opening of 12/24 bottles from day 0 of the galenic shaping.

FIGURE 2. Concentration profiles (mean values) vs. time of hydrocortisone in InOrpha throughout a 56-day period with a daily opening of 12/24 bottles from the 28th day of the galenic shaping.

REFERENCES


Address correspondence to Dr. Alexandre Amin, Clinical Pharmacy Department, HU Necker-Enfants Malades, 149, rue de Sèvres, 75743 Paris, France. E-mail: alexandre.amin@nck.aphp.fr
Stability of Tranexamic Acid in 0.9% Sodium Chloride, Stored in Type 1 Glass Vials and Ethylene/Propylene Copolymer Plastic Containers

Susan V. McCluskey, RPh, BS Pharm Matthew D. Sztajnkrycer, MD, PhD Donald A. Jenkins, MD Scott P. Zietlow, MD Kathleen S. Berns, MS, RN Myung S. Park, MD

ACKNOWLEDGMENT
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INTRODUCTION
Hemorrhage remains a significant cause of potentially survivable traumatic injury. Worldwide, traumatic injury accounts for 9% of total deaths.1 Exsanguinating hemorrhage is reported to be responsible for 35% of prehospital deaths and 33% to 40% of deaths within the first 24 hours from the time of injury.2,3 While tourniquets may be life saving when employed prior to the onset of shock, they are ineffective in the management of junctional hemorrhage or non-compressible truncal trauma.1,4,5 Recent experience has suggested a role for tranexamic acid in these patients.6–8 Tranexamic acid, a synthetic derivative of lysine, inhibits fibrinolysis by blockade of lysine binding sites on the endogenous thrombolytic agent plasminogen.9 Previous clinical trials have demonstrated improved survival outcomes in patients administered tranexamic acid as a 1-gram load over 10 minutes followed by a 1-gram infusion over 8 hours.5,8 Ideally, tranexamic acid is to be started within 1 hour from the time of injury and not later than 3 hours from the time of the injury.10 Such time constraints suggest a role for tranexamic acid in the prehospital care of traumatically injured patients. To aid with timely administration of tranexamic acid, diluted and ready to administer tranexamic acid solutions were proposed to be added to medications stocked in both the aeromedical transport helicopters and Emergency Department at Mayo Clinic Hospital—Rochester Saint Marys Campus. Small volume dilutions were deemed

ABSTRACT
Tranexamic acid has recently been demonstrated to decrease all-cause mortality and deaths due to hemorrhage in trauma patients. The optimal administration of tranexamic acid is within one hour of injury, but not more than three hours from the time of injury. To aid with timely administration, a premixed solution of 1 gram tranexamic acid and 0.9% sodium chloride was proposed to be stocked as a medication in both the aeromedical transport helicopters and Emergency Department at Mayo Clinic Hospital—Rochester Saint Marys Campus. Since no published stability data exists for tranexamic acid diluted with 0.9% sodium chloride, this study was undertaken to determine the stability of tranexamic acid diluted with 0.9% sodium chloride while being stored in two types of containers. Stability was determined through the use of a stability-indicating high-performance liquid reverse phase chromatography assay, pH, and visual tests. Tranexamic acid solutions of 1 gram in 0.9% sodium chloride 65 mL were studied at predetermined intervals for 90 days in ethylene/propylene copolymer plastic containers, protected from light, and at both controlled room and refrigerated temperatures. Tranexamic acid solutions of 1 gram in 0.9% sodium chloride 50 mL were studied at predetermined intervals for 180 days in clear Type 1 borosilicate glass vials sealed with intact elastomeric, Flourotec-coated stoppers, stored protected from light at controlled room temperature. Solutions stored in the ethylene/propylene copolymer plastic containers at both storage temperatures maintained at least 98% of initial potency throughout the 90-day study period. Solutions stored in glass vials at controlled room temperature maintained at least 92% of initial potency throughout the 180-day study period. Visual and pH tests revealed stable, clear, colorless, and particulate-free solutions throughout the respective study periods.

The authors’ are affiliated with the Mayo Clinic, located in Rochester, Minnesota, in the following capacities: Susan V. McCluskey, Pharmacy Production Laboratory Pharmacist; Matthew D. Sztajnkrycer, Associate Professor and Consultant, Department of Emergency Medicine; Donald A. Jenkins, Consultant, Division of Trauma, Critical Care and General Surgery, Associate Professor of Surgery, College of Medicine, Medical Director, Trauma Center; Scott P. Zietlow, Consultant, Division of Trauma, Critical Care and General Surgery, Department of Surgery; Kathleen S. Berns, Medical Transport Clinical Nurse Specialist; Myung S. Park, Consultant, Associate Medical Director of Trauma, Basic Science Research, Assistant Professor of Surgery, College of Medicine.
optimal to allow for rapid administration while maintaining an acceptable space footprint.

No published stability data exists for tranexamic acid mixed with 0.9% sodium chloride, other than a notation in the package insert that it should be used on the day of preparation. This study was undertaken to determine the stability of tranexamic acid 1 gram mixed with 0.9% sodium chloride in two types of containers stored for a minimum of 90 days.

METHODS

Preparation of Tranexamic Acid Samples

Two containers were used to study tranexamic acid samples; one an ethylene/propylene copolymer plastic container, the other a glass vial. Each container was filled with tranexamic acid 1 gram and 0.9% sodium chloride. Total volume of solution in the containers was 65 mL and 50 mL, respectively, due to container design and compounding considerations.

Solutions prepared for stability studies in ethylene/propylene copolymer plastic containers were compounded by the addition of 1,000 mg tranexamic acid injection (Lots 111014 and 111015, Tranexamic Acid Injection 1000 mg/10 mL single-dose vial; Mylan Institutional LLC, Rockford, Illinois) through the elastomeric port of the ethylene/propylene copolymer plastic container preloaded with 55 mL of 0.9% sodium chloride (Lot J1J927, 50 mL partial fill in a 100-mL PAB container; B/Braun Medical Inc., Irvine, California), for a total volume in the container of 65 mL. The 65-mL fill was calculated from the addition of 10 mL of tranexamic acid, 50 mL of 0.9% sodium chloride stated container volume, and 5 mL of 0.9% sodium chloride estimated manufacturer overfill in the container. Twelve ethylene/propylene copolymer plastic containers containing this solution were compounded. Six were stored at controlled room temperature (20°C to 25°C, light protected) and six were stored at refrigerated temperature (2ºC to 8ºC, light protected). Samples were tested at predetermined intervals over a 180-day period.

The other type of container was composed of a glass vial, an elastomeric stopper, and a metal seal. Test solutions to be stored in this container were compounded by the addition of 1,000 mg (10 mL) tranexamic acid injection to 40 mL of 0.9% Sodium Chloride for Injection USP (Lot C871903; Baxter Healthcare Corporation, Deerfield, Illinois). The resulting 50-mL solution was transferred aseptically to an in-house washed and sterilized clear Type 1 borosilicate glass 50-mL vial (No. 223745; Wheaton, Millville, New Jersey). An elastomeric stopper coated with Flourotec on the plug (Item 19700022; West Pharmaceutical Services, Lititz, Pennsylvania), which was previously sterilized in-house, was inserted to close the vial opening. The stopper was subsequently held in place by an aluminum seal (Item 51201125, West Pharmaceutical Services). This resulted in an intact container, with no puncture holes in any surface. Six solutions in glass vials were compounded and submitted for study evaluation at controlled room temperature (20°C to 25°C, protected from light). Samples were tested at predetermined intervals over a 180-day period.

Equipment and Chromatographic Conditions

Analysis of tranexamic acid using high-performance liquid chromatography (HPLC) reverse phase with an ultraviolet detector was performed by Analytical Research Laboratories (Oklahoma City, Oklahoma) using the Agilent Series 1100 HPLC System and Agilent Model 1100 Diode-Array Detector (Agilent Technologies, Waldbronn, Germany). The chromatographic conditions consisted of 95% mobile phase A and 5% mobile phase B. Mobile Phase A was a mixture of 24 grams of sodium phosphate monobasic, analytical grade (Lot 8901K; MP Biomedicals, New Brunswick, New Jersey), 1.200 mL of Nanopure Water, HPLC Grade (Analytical Research Laboratories), 10 mL of triethylamine, HPLC grade (Lot ZT0072; Spectrum, New Brunswick, New Jersey), 2.8 gram of sodium dodecyl sulfate (Lot 2AB0769; Spectrum), 800 mL of methanol, HPLC grade (Lot KKL15G; Pharmco-Aaper, Brookfield, Connecticut), and adjusted to a pH of 2.0 with phosphoric acid, analytical grade (Lot ZI0222; Spectrum). Mobile Phase B consisted of acetonitrile, HPLC grade (Lot 121151; Fisher Scientific, New Brunswick, New Jersey). Flow rate was set at 1.0 mL/min, injection sample volume at 20 mL, and detection wavelength at 220 nm. Chromatographic separation was performed using Waters, Symmetry C18, 250 × 4.6 mm, 5 mcm column (WAT054275; Waters, Wexford, Ireland). Software used was HPLC ChemStation Version A.10.02 (Windows XP).

A benchtop pH meter (Hanna Checker 1-Digital pH tester with HI 1270 Combination pH Electrode; Hanna instruments, Woonsocket, Rhode Island) was used for pH determination. The meter was calibrated using reference standards of pH 4.00 and 7.00 (Items B1166 and B1165; Spectrum Chemical, Gardena, California).

An inspection box (IV Inspection Light Box; Health Care Logistics Inc., Circleville, Ohio) was used with visual examinations. It consisted of a 4X magnification glass in the foreground and a background containing a split black and white panel illuminated with white fluorescent lights located at the bottom and top of the box.

Stability-indicating Capability of Assay

The HPLC analytical method used for this study was demonstrated to be stability indicating by forced degradation. Tranexamic acid (Lot Y07397, Cyclokapron Injection 100 mg/mL; Pharmacia & Upjohn, New York, New York) and 0.9% sodium chloride solution (Lot P275255; Baxter Healthcare) were subjected to a variety of chemical and physical stresses. Stress conditions included exposure to heat/humidity (80°C with water bath for four hours), ultraviolet light (short wavelength UV light for 24 hours), acidic conditions (Lot 1AC1034, hydrochloric acid 1N; Spectrum, New Brunswick) mixed with sample to a concentration of 0.1N hydrochloric acid, then incubated at 37°C for three days, basic conditions (Lot 1080320, sodium hydroxide 1N; AQUA Solutions, Deer Park, Texas) mixed with sample to a concentration of 0.1N sodium hydroxide, then incubated at 37°C for three days, and oxidation (Lot MKBD1010, hydrogen peroxide 30%; Sigma-Aldrich, St. Louis, Missouri) mixed with sample to a concentration of 3% hydro-
Stability Analysis

Assessment of chemical stability was based on recovery of tranexamic acid using the above described stability-indicating HPLC method. A standard curve for tranexamic acid (Lot FOH312, Tranexamic Acid USP reference standard, purity 0.998 mg/mg; United States Pharmacopeia, Rockville, Maryland) was developed using five concentrations (5.01, 10.02, 15.03, 20.04, and 25.05 mg/mL), which were 25% to 125% of the 20-mg/mL assay level. The slope of the resulting standard curve was statistically different from zero with r² >0.99. Single point standards of approximately 15 mg/mL (glass vials) and approximately 20 mg/mL (ethylene/propylene copolymer plastic containers) were used to quantitate the samples. The standard solution was prepared by quantitatively transferring a weight of Tranexamic Acid USP reference standard and brought to volume with water. Test solutions were removed from their containers and analyzed as is (i.e., no dilutions or sample preparation).

Three ethylene/propylene copolymer plastic container sample solutions from both storage conditions (refrigerated and controlled room temperatures) were tested for potency initially (day 0), and on days 3, 7, 14, 21, 30, 60, and 90 with a single assay per sample. Three glass-container sample solutions at controlled room temperature were tested for potency initially (day 0) and on days 30, 60, 90, 120, and 180 with duplicate assays per sample. Results from each set of containers and storage condition were used to calculate the mean ± standard deviation (SD). Percent of tranexamic acid remaining for each time point was determined from the average of the day 0 measurement. Chemical stability was defined as the retention of 90% to 110% of the initial tranexamic acid drug concentration.12

Visual and pH testing was undertaken using three sample solutions from each of the container/storage conditions. All solutions were assessed by a single observer for appearance, clarity of solution, and color with the aid of the inspection box at each time point. Visual stability was defined as the retention of the original clear, colorless, and visually particulate-free solution. After visual inspection, a 3-mL quantity was removed from each sample. Duplicate pH testing was performed with this removed quantity on days 0, 1, 3, 7, 14, 21, 30, 60, and 90 for solutions in ethylene/propylene copolymer plastic containers and on days 0, 30, 60, 90, 120, and 180 for the solutions in glass vials. Results from the three duplicate determinations at each time point were used to calculate the mean ± SD. pH stability was defined as the maintenance of original pH value within the range of ± 0.5 pH units.

RESULTS

Validation of the High-performance Liquid Chromatographic-ultraviolet Assay Method

The most significant degradation occurred in samples exposed to hydrogen peroxide resulting in a retention of 95% of the original tranexamic acid concentration (5% degradation). A small amount of degradation (0.2%) occurred with exposure to sodium hydroxide. Retention time of the tranexamic acid peak was at 8.7 minutes. Peaks representing decomposition products of tranexamic acid were identified at retention times of 2.9, 4.2, 6.2, and 6.6 minutes and were resolved from the tranexamic acid peak. Chromatographic profiles of a tranexamic sample prior to stress (control), a hydrogen peroxide control, and a tranexamic acid sample after stress with hydrogen peroxide are presented in Figures 1A, 1B, 1C, and 1D.
Tranexamic Acid Stability Evaluation

Potency results, using the stability-indicating HPLC method, for the solutions in ethylene/propylene copolymer plastic containers stored at controlled room temperature, resulted in initial (day 0) amounts of 0.976 gram, 0.985 gram, and 0.971 gram per 65 mL. The mean percentage of day 0 concentration recovered (presented as mean ± SD) was 99.600% ± 0.200 (day 3), 101.467% ± 0.231 (day 7), 102.500% ± 0.265 (day 14), 103.300% ± 0.557 (day 21), 104.400% ± 0.265 (day 30), 99.500% ± 0.173 (day 60), and 100.300% ± 0.173 (day 90). Potency results for the refrigerated solutions in copolymer plastic containers showed initial (day 0) amounts of 0.992 gram, 0.975 gram, and 1.005 gram per 65 mL. The mean percentage of initial concentration recovered (presented as mean ± SD) was 94.433% ± 0.153 (day 3), 101.333% ± 0.115 (day 7), 102.700% ± 0.693 (day 14), 104.067% ± 0.651 (day 21), 103.967% ± 0.153 (day 30), 98.833% ± 0.058 (day 60), and 99.433% ± 0.252 (day 90) (Figure 2).

Potency results for the solutions in glass vials stored at controlled room temperature, resulted in initial (day 0) amounts of 1.086 ± 0.001 gram, 1.087 ± 0 gram, and 1.087 ± 0.01 gram per 50 mL. The mean percentage of initial concentration recovered (presented as mean ± SD) was 95.767% ± 0.231 (day 30), 92.633% ± 0.115 (day 60), 96.967% ± 0.058 (day 90), 94.567% ± 0.058 (day 120), and 99.267% ± 0.115 (day 180) (Figure 3).

pH values (presented as the mean ± SD) for samples in ethylene/propylene plastic copolymer containers stored at controlled room temperature were 6.9 ± 0.2 (day 0), 6.8 ± 0.2 (day 1), 6.8 ± 0.6 (day 3), 7.0 ± 0.1 (day 7), 7.0 ± 0.1 (day 14), 7.0 ± 0.1 (day 21), 7.0 ± 0.1 (day 30), 6.9 ± 0.1 (day 60), and 7.0 ± 0.1 (day 90). Values for the samples stored at refrigerated temperature were 7.2 ± 0.4 (day 0), 6.9 ± 0.1 (day 1), 7.4 ± 0.0 (day 3), 7.0 ± 0.3 (day 7), 7.0 ± 0.1 (day 14), 7.1 ± 0.0 (day 21), 7.1 ± 0.1 (day 30), 6.8 ± 0.1 (day 60), and 7.0 ± 0.1 (day 90). Values for samples in glass vials stored at room temperature were 7.0 ± 0.1 (day 0), 7.1 ± 0.1 (day 30), 7.2 ± 0.1 (day 60), 7.3 ± 0.1 (day 90), 7.2 ± 0.0 (day 120), and 7.3 ± 0.1 (day 180) (Figures 4 and 5).

Visual inspections of all samples (ethylene/propylene copolymer containers and glass vials) revealed clear, colorless, and particulate-free solutions throughout the study periods.

Results from the visual, pH, and HPLC potency tests described that tranexamic acid 1 gram in 0.9% sodium chloride 65 mL maintained 98% of the original potency for 90 days when stored in ethylene/propylene copolymer plastic containers, protected from light, under both controlled room and refrigerated temperatures. Original potency of 92% was maintained for 180 days when tranexamic acid 1 gram in 0.9% sodium chloride 50 mL was stored in type 1 glass vials, protected from light, at controlled room temperature.

DISCUSSION

According to data from the National Center for Injury Prevention and Control, unintentional injury is the leading cause of death for individuals 1 to 44 years of age. In a large multi-national, randomized, placebo-controlled trial, tranexamic acid significantly reduced all-cause mortality and deaths due to bleeding. Tranexamic acid administration is optimal when used within 1 hour from time of injury, but is associated with adverse events and potential harm when started beyond 3 hours.

Note: The stressed profile demonstrated complete baseline resolution of degradants and impurities from the tranexamic acid peak, which was detected at a retention time of 8.7 minutes. Peaks corresponding to degradation products were observed at 4.2, 6.3, and 6.6 minutes. The peak at 9.8 minutes is observed in the control and is not a degradation product. The large deflection in the peroxide-stressed sample at 2 minutes is due to the hydrogen peroxide.
from the time of injury.\textsuperscript{10} Due to the time constraints on tranexamic acid administration, the development of a tranexamic acid autoinjector has been suggested for field deployment in the prehospital and combat setting.\textsuperscript{13} We hypothesized that in the absence of a commercially available autoinjector, containers filled with 1 gram of tranexamic acid in 0.9% sodium chloride might be prepared ahead of time and be made available for immediate administration in the prehospital environment.

A recent study demonstrated the stability of undiluted tranexamic acid ampules at various temperatures for 1, 2, 4, and 12 weeks and found that tranexamic acid remained effective when stored under conditions likely encountered in the prehospital environment.\textsuperscript{15} However, no published stability data exists for tranexamic acid mixed with 0.9% sodium chloride for more than 24 hours.

This study has several limitations inherent in the translation of basic science to the bedside. This was a carefully controlled stability study performed at controlled room and refrigerated temperatures. The United States Pharmacopeia (USP) defines controlled room temperature as between 20°C to 25°C (68°F to 77°F), with a mean kinetic temperature less than 25°C (77°F).\textsuperscript{35} According to the manufacturer, tranexamic acid should be stored at USP-defined controlled room temperature conditions.\textsuperscript{12} In the prehospital environment, controlled room temperatures may not always be feasible, resulting in the potential for increased degradation and decreased physical and chemical stability over time.\textsuperscript{17-19}

This study evaluated the chemical and physical stability of tranexamic acid over time. It did not address issues of sterility maintenance over time that must be taken into account when assigning 90- or 180-day beyond-use dating. Compounding the solutions under strict aseptic conditions, performing appropriate validated batch specific sterility testing, and maintaining solution sterility along with package integrity throughout the storage period is vital to the assignment of the appropriate beyond-use date. Failure to follow these procedures can have catastrophic consequences, as highlighted by the recent fungal meningitis outbreak caused by suboptimal compounding conditions at a pharmacy where the contaminated injections were made.\textsuperscript{20}

**CONCLUSION**

Solutions of tranexamic acid 1 gram in 0.9% sodium chloride 65 mL stored in ethylene/propylene copolymer plastic containers (protected from light, at controlled room and refrigerated temperatures) and solutions of tranexamic acid 1 gram in 0.9% sodium chloride 50 mL stored in type 1 glass vials (protected from light at controlled room temperature) remained stable chemically for 90 and 180 days, respectively.

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**REFERENCES**


**FIGURE 2.** Potency over time of tranexamic acid 1 gram in 0.9% sodium chloride 65 mL stored in ethylene/propylene copolymer plastic containers.

Initial average concentration of tranexamic acid samples at controlled room temperature was 0.977 ± 0.007 gram per 65 mL.

Initial average concentration of tranexamic acid samples at refrigerated temperature was 0.991 ± 0.015 gram per 65 mL.

Three samples were assayed at each time point with a single analysis. Error bars represent the high and low results.

**FIGURE 3.** Potency over time of tranexamic acid 1 gram in 0.9% sodium chloride 50 mL stored in glass vials at controlled room temperature.

Initial average concentration of tranexamic acid samples was 1.086 ± 0.001 gram per 50 mL.

Three samples were assayed at each time point with duplicate analysis. Error bars represent the high and low results.
FIGURE 4. pH results over time of tranexamic acid 1 gram in 0.9% sodium chloride 65 mL stored in ethylene/propylene copolymer plastic containers at controlled room and refrigerated temperatures.

Three samples were assayed at each time point with duplicate analysis. Error bars represent the high and low results.

FIGURE 5. pH results over time of tranexamic acid 1 gram in 0.9% sodium chloride 50 mL stored in glass vials at controlled room temperature.

Three samples were assayed at each time point with duplicate analysis. Error bars represent the high and low results.


Address correspondence to: Susan V. McCluskey, RPh, BS Pharm, Mayo Clinic, Pharmacy Production Laboratory Pharmacist, 201 West Center Street, E1 1-420 Pharmacy Services, Rochester, MN 55902. E-mail: mccluskey.susan@mayo.edu
As the dust settles after passage of the Compounding Quality Act (Title I, Drug Quality and Security Act of 2013), pharmacists and veterinarians are left to ponder the future of veterinary compounding, since the Act applies to compounding human drugs only. Of particular concern is the issue of compounding from bulk substances or active pharmaceutical ingredients (APIs). The legality of compounding from APIs has been a longstanding debate among pharmacists, veterinarians, veterinary drug manufacturers, and the Center for Veterinary Medicine, Food and Drug Administration (FDA). The Animal Medicinal Drug Use Clarification Act (AMDUCA), passed in 1994 and implemented in 1996, specifically legalized veterinary compounding from approved veterinary and human products with few restrictions for non-food animals. The Act, however, did not include language that specifically included compounding from bulk substances (APIs). The FDA interprets this omission as making all compounding from bulk substances illegal, even though they recognize its necessity for some drugs. Although this issue has been debated in federal court, final resolution to the issue remains elusive.

Recently, the American Veterinary Medical Association (AVMA) formed a Compounding Task Force to examine veterinary compounding issues and to propose federal legislation pertaining to veterinary compounding. According to their April 16, 2014 news release, the task force will likely address the “legality of compounding from bulk substances, anticipatory compounding, maintaining office stocks of compounded products, and dispensing compounded products from office stocks.”

It is vital that compounding pharmacists organizations address these issues in a proactive manner as well. There are clearly medications for non-human species that must be compounded from bulk substances, including, but not limited to potassium bromide, cisapride, metronidazole benzoate suspension, transdermal formulations, and drugs that are currently unavailable due to manufacturer backorders. It is essential that any proposed legislation allow pharmacists access to reliable bulk chemicals in a timely manner without undue regulatory obstacles or red tape.

Clearly, there also are compounds that need to be compounded using approved products (e.g.,itraconazole, trilostane) due to documented bioavailability issues when APIs are used instead of the approved products. Currently, pharmacists have limited access to approved veterinary products when needed for compounding, since most veterinary drug manufacturers limit sales of their products to veterinary clinics. Therefore, any proposed legislation that might limit certain compounds to reformulation of approved veterinary products must also include provisions guaranteeing compounding pharmacists access to those products. Another issue that remains the subject of considerable conversation and debate among veterinarians is their need to stock non-patient-specific compounded medications obtained from compounding pharmacies (anticipatory compounding) not only for administration to patients while in the hospital, but also for administration after the patient goes home. Most veterinarians lack training and do not have facilities or equipment for appropriate compounding.
except for simple reformulations of non-sterile medications. Some states currently allow practitioners to stock compounded medications obtained from a compounding pharmacy for “in-clinic” administration, while others do not. The issue of dispensing these compounds, which involves relabeling and often repackaging, creates additional clinical and liability issues for veterinarians and pharmacists. One example of clinical concern to veterinarians is the sporadic availability of some commercial sterile ophthalmic medications. Patients can easily lose an eye without immediate access (i.e., the availability of “office-stock” compounds) and/or uninterrupted therapy (i.e., the ability to dispense compounded medications from office stocks), yet it is often difficult for pharmacists to assign an appropriate and documented beyond-use date for “office-stock” compounded medications. Added to that concern is the increased potential for liability if dispensing errors occur.

Veterinary drug manufacturers are also concerned about this practice, since they believe that allowing veterinarians to dispense compounded medications from “office stock” could be used to circumvent the drug-approval process.

Compounded medications are an essential component of veterinary medicine, yet compounding mishaps in veterinary medicine resulting in animal deaths have tainted the trust some veterinarians have in compounding pharmacists. The most recent example is the death of four horses and the illness of six others in two states attributed to treatment with a compounded medication of toltrazuril and pyrimethamine. The compounds contained toxic amounts of pyrimethamine. The first question that comes to mind is “Why was this compound prescribed when there are multiple approved products available for treating horses with equine protozoal myeloencephalitis?” Obviously, this question is directed to the prescriber—the veterinarian. The second question, directed at the compounding pharmacist, is “How could a compounding error of this magnitude occur if appropriate quality control measures were followed?” Both of these questions beg to be answered. It is clear that pharmacists and veterinarians must work together to make sure that the compounded medications prescribed and dispensed are appropriate (i.e., designed to meet an individual patient’s therapeutic need that cannot be met by an approved product) and that the finished compounds are formulated under United States Pharmacopeia guidelines with appropriate quality-control measures.

What can individual compounding pharmacists do to assure a strong future for veterinary compounding? Note: The following important suggestions are the same for compounding preparations for human patients as they are for veterinary patients.

1. Make sure the prescribed compound is appropriately formulated. When there is an approved product available, use sound professional judgment in deciding whether or not it is appropriate to use that product as the starting point, considering the formulation, excipients, and whether or not there are bioavailability issues with the API that require special formulation.
2. Make sure the APIs used are obtained from a reputable FDA-registered facility that can assure the content and purity of the chemical.
3. Make sure there are plenty of checks and balances with appropriate supervision over compounding personnel and procedures.
4. Make sure all compounding decisions are patient-centered and lack influences of profit over patient needs.

Pharmacy organizations must collaborate with the AVMA so that any legislation proposed and ultimately enacted will result in enhanced care for veterinary patients through appropriately prescribed and compounded medications.

Address correspondence to Dinah G. Jordan, BSPh, RPh, PharmD, FSVHP, DICVP, Chief of Pharmacy Services & Clinical Professor, College of Veterinary Medicine, Mississippi State University, Mississippi State, MS 39762. E-mail: MintJulep@cvm.msstate.edu
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