Third Edition

Extemporaneous Formulations

for

Pediatric, Geriatric, and Special Needs Patients

Rita K. Jew, PharmD, MBA, FASHP
Director of Pharmacy
UCSF Medical Center, Mission Bay Campus
San Francisco, California

Winson Soo-Hoo, RPh, MBA
Senior Director
Department of Pharmacy Services
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Sarah C. Erush, PharmD, BCPS
Clinical Manager
Department of Pharmacy Services
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Elham Amiri, CPhT
Technician Supervisor, Pediatrics
Department of Pharmaceutical Services
UCSF Medical Center, Mission Bay Campus
San Francisco, California

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Preface

Since the inaugural publication of *Extemporaneous Formulations* in 2003, legislation has been introduced to boost pediatric drug research. Following the Food and Drug Administration (FDA) Modernization Act in 1997 and the Best Pharmaceuticals for Children Act in 2002, the Pediatric Research Equity Act in 2003 ensured that new drugs intended for use in children would be studied in children. This Act was extended under the FDA Amendment Act (FDAAA) of 2007 to require sponsors to submit a pediatric assessment with every new drug application to the FDA. The results of the pediatric assessment may require that pediatric studies be submitted before the approval of the adult application or that pediatric studies be deferred until after adult approval as a post-marketing requirement. In addition, the Best Pharmaceuticals for Children Act was also extended for 5 years under the FDAAA. Nonetheless, a gap still exists for pharmaceuticals with appropriate pediatric formulations. There continues to be a need for pharmacists to prepare extemporaneous formulations. This is evident by the fact that 39 new formulations are added to this third edition, and only five existing formulations are reclassified to the "Commercially Available Products" section.

On the other hand, legislation regarding compounding continues to evolve. After the contamination events at the New England Compounding Center as well as other less publicized incidents, the Compounding Quality Act (part of the Drug Quality and Security Act) was passed in 2013 to clearly define the difference between pharmacy compounding and manufacturing through the reinstatement of section 503A and introduction of section 503B of the Federal Food, Drug, and Cosmetic Act. The FDA's Pharmaceutical Compounding Advisory Committee now makes recommendations regarding lists of drugs 503A and 503B compounders may not make. The Committee continues to add to the list of drugs withdrawn/removed from market for safety or efficacy reasons. Therefore, it is important that pharmacists who compound extemporaneous formulations be vigilant in consulting with the list on a regular basis.[1] In addition, various states (such as California) have enacted or are in the process of enacting regulations regarding sterile and nonsterile compounding. It is imperative that pharmacists who compound extemporaneous formulations stay up-to-date with their state regulations.

As with the previous two editions, we performed a comprehensive literature search to identify news drugs with extemporaneous formulations and new formulations of drugs that are in the previous editions. This effort resulted in 39 new formulations. Because two formulations (ganciclovir syrup 100 mg/mL and norfloxacin suspension 20 mg/mL) were deleted due to the active ingredient being discontinued, our grand total is 197 formulations in the third edition. In addition, we have also updated two of the existing formulations—lansoprazole solution 3 mg/mL with new expiration of 7 days and propranolol syrup 1 mg/mL with an alternative diluent. As stated earlier, five existing formulations are reclassified to the "Commercially Available Products" section—enalapril suspension 1 mg/mL, levodopa 5 mg/mL and carbidopa 1.25 mg/mL suspension, mercaptopurine syrup 50 mg/mL, sildenafil suspension 2.5 mg/mL, and sotalol suspension 5 mg/mL. Again, only formulations that have published and documented stability data are included. We continue to provide multiple published formulations of medications with the same concentration as well as formulations

with various concentrations so that readers can choose the most appropriate formulation for their patients or institutions.

New to this edition, we have included the Michigan Pediatric Safety Collaboration's Standardized Concentrations of Compounded Oral Liquids in Appendix D. These standardized concentrations are also denoted by an asterisk (*) on the title of the monograph or (#) for alternative formulations. The Michigan Pediatric Safety Collaboration's standardization project marked the first attempt to standardize concentrations of compounded oral liquids in the United States. This initiative received the Cheers Award from the Institute for Safe Medication Practice (ISMP) in 2014 for the attempt to improve medication safety in pediatric patients in the state of Michigan. Note that not all of the formulations from this initiative are included in this book. Standardized concentrations are excluded mostly because they are supported only by tertiary references that are not substantiated by primary references. Nonetheless, we recognized that this is an extremely important first step to standardization of compounded oral liquids to improve the safety of the pediatric patients we care for, and, hence, we are committed to embrace and promote these standardized concentrations. Finally, we are excited to note that as part of its Safe Use Initiative to reduce preventable harm from medications, the FDA has awarded a 3-year contract to ASHP to develop and implement national standardized concentrations for intravenous and oral liquid medications. We will be sure to include these standardized concentrations in the next edition of this book!

As we embark on the Pharmacy Practice Model Initiative journey and expand the roles and responsibilities of our pharmacy technicians, we have recruited a certified technician as our co-author to help compile new formulations for this book. It is our hope that more pharmacy technicians will take on the advance activities and responsibilities of helping shape best practices in compounding extemporaneous formulations for our patients.

Rita K. Jew
Winson Soo-Hoo
Sarah C. Erush
Elham Amiri

Reference

1. http://www.ecfr.gov/cgi-bin/text-idx?SID=817cc7ee48b2145a155ade1144a24aec&mc=true&node=se21.4.216_124&rgn=div8

Introduction

Legal Considerations

Before a pharmacist engages in extemporaneous compounding activities, it is important to understand the legal implications. Extemporaneous formations compounded by a pharmacist, intended for use in humans, are exempt from three provisions (section 501 [a][2][B] good manufacturing practice, section 502 [f][1] labeling of drugs with adequate directions for use, and section 505 approval of drugs under new drug applications or abbreviated new drug applications) of the Food, Drug and Cosmetic (FD&C) Act provided that the following conditions of section 503A are met[1]:

- The drug product is compounded upon the receipt of a valid prescription order for an individual patient or in limited quantities before the receipt of a valid prescription order based on a history of the licensed pharmacist receiving prescription orders for an individual patient.
- The drug product is compounded by a licensed pharmacist in a state licensed pharmacy or a federal facility.
- The drug product is compounded in compliance with the United States Pharmacopoeia (USP) 795 using USP/NF bulk drug substances, a component of an FDA-approved human drug product or bulk drug substances on a list developed by FDA through regulation.
- The bulk drug substances used is from a manufacturer registered under section 510 of the FD&C Act.
- The bulk drug substances used have valid certificates of analysis.
- The ingredients (other than bulk drug substances) used complies with the standards of an applicable USP or NF monograph and USP chapters on pharmacy compounding.
- The drug product is not on the list of drug products withdrawn or removed from the market because it has been found to be unsafe or not effective.
- The drug products that are essentially copies of commercially available drug products are not compounded regularly or in inordinate amounts by a licensed pharmacist.
- The drug product is not identified by FDA regulation to present demonstrable difficulties for compounding that would result in an adverse effect on the safety or effectiveness of that drug product.
- The compounded drug products are not distributed out of state in more than 5% of the total prescription orders by the licensed pharmacist or licensed pharmacy unless the drug product is compounded in a state that has entered into a memorandum of understanding with FDA.

Compounding

Appendix A outlines the general principles of compounding nonsterile preparations, as described in USP 795 to ensure that preparations compounded are of appropriate strength, quality, and purity. In addition, the recently published USP 800 should be consulted for up-to-date standards for handling and compounding of hazardous drugs.

USP defines stability of an oral liquid formulation as "the extent to which the preparation retains, within specified limits, and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of compounding."[2] When evaluating the stability of a formulation, its chemical, physical, and microbiological stability must be considered. In addition to the properties of the ingredients used to compound the formulation, temperature, radiation, light, air, and humidity are environmental factors that can affect the stability of an extemporaneous formulation. The overall stability of an extemporaneously prepared formulation can also be affected by particle size, pH, the water and solvents used, the container used, and the presence of other chemicals.[3] For this reason, alterations of the formulations listed in this handbook are strongly discouraged. The addition of flavoring agents may affect the pH and other chemical properties of the formulation, hence affecting the shelf life of the formulation. Therefore, if a flavoring agent is needed, it should be added to the dose of the medication immediately before its administration. Flavoring agents should not be added to the entire bottle of the elixir, solution, or suspension unless testing has been performed to confirm the overall stability of the formulation.

The following is a brief description of the preparation methods and techniques, as well as packaging and storage requirements of extemporaneously prepared formulations.

Definitions

*Elixir—A*n elixir is a clear, sweetened, alcohol-containing solution that is used mainly for drugs that are insoluble in water alone. It is usually not as sweet and less viscous than a syrup. The alcohol content of elixirs makes it a less desirable vehicle or base solution for preparing extemporaneous formulations in pediatric patients.

Levigating agent—A levigating agent is used to moisten and soften a tablet to facilitate the preparation of a liquid, especially when a large number of tablets is required or the tablets are extremely difficult to crush. Preferably, the vehicle or base solution used for the product is used as the levigating agent.

Simple syrup—Simple syrup is a sucrose solution that is made with purified water alone.

Solution—A solution is a liquid containing medication that is dissolved in water or other liquids.

Suspending agent—A suspending agent is used to prevent agglomeration of the dispersed particles and to increase the viscosity of the liquid. This allows for slow settling of the drug particles to ensure uniform distribution and accurate measurement of the dose.

Suspension—A suspension is a dispersion containing fine insoluble particles suspended in a liquid medium.

Syrup—A syrup is a concentrated solution of sugar, such as sucrose in water or other aqueous liquid used as a vehicle or base solution to mask the taste of drugs. The high concentration of sugar in syrups provides preservative property as well.

Preparation Methods

The preparation methods of extemporaneous formulations are often determined by the source of the ingredients in the formulation (i.e., injectable, tablet or capsule, and oral liquid). In general, an injectable drug can be measured accurately by a syringe. Oral liquid

should be measured using a graduated cylinder. Graduations on dispensing bottles are not accurate and should not be used as a measuring device unless they are calibrated.

When using tablets or capsules to prepare a formulation, the tablets or capsules must be thoroughly and uniformly pulverized by trituration. Trituration is a process in which substances are reduced to fine particles in a mortar with a pestle. Small particles are more easily dispersed throughout the vehicle or base solution, settle less quickly, and are less likely to cake once they settle. Therefore, particles to be suspended in the vehicle or base solution must be small and uniform to ensure consistency and accuracy of dosing. Once triturated, the powder should be levigated with a levigating agent. The levigating agent is selected on the basis of its ability to form a smooth paste with the powder to be levigated and on its compatibility with the substance. The vehicle or base solution should be added to the paste in increasing amounts and mixed thoroughly. The mixture should be transferred to a graduated cylinder. A small amount of vehicle or base solution should be used to rinse the mortar and the solution then poured into the graduated cylinder. The volume should be adjusted in the graduated cylinder to the quantity required for the formulation. The final product should be placed in the dispensing container.

Ideally, a light-resistant container should be used to protect the contents. It is also important to ensure that the storage condition of the extemporaneous formulations is appropriate. Refrigerator temperature should be maintained between 2 to 8°C (36 to 45°F) for formulations that require refrigeration. Formulations to be stored at room temperature should be maintained between 20 to 25°C (68 to 77°F).

For a comprehensive overview of necessary considerations when preparing extemporaneous formulations, please refer to the ASHP Technical Assistance Bulletin on Compounding Nonsterile Products in Pharmacies (Appendix B) and the ASHP Guidelines on Pharmacy-Prepared Ophthalmic Products (Appendix C).

References

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Part I: Elixir/Solution/Suspension/Syrup