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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

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Tips and Hints for Quality Compounding

GOALS AND OBJECTIVES

Goal: To provide time-saving and cost-saving tips and hints in the practice of pharmaceutical compounding.

Objectives: After reading and studying the article, the reader will be able to:

1. Discuss various factors that should be considered in the design and development of a compounding pharmacy.
2. Describe some time-saving ideas that can be easily implemented in a compounding pharmacy to become more efficient.
3. Discuss some methods of possibly extending the beyond-use dates of compounded preparations.
4. List at least 5 different pieces of equipment that can be purchased to make compounding more efficient and productive.

Tips for Quality Compounding

Note: This is the second Secundum Artem on the topic of tips and hints to enhance the efficiency and quality of pharmacy compounding; the first appeared in Secundum Artem, Volume 5, Number 1, available online at www.paddocklabs.com. This issue covers tips on the Facility, Compounding Equipment, Quality Testing Equipment, Ingredients, Procedures, Calculations, Preservation, Sterilization, and Depyrogenation, and Beyond-Use Dating. A subsequent issue will cover tips and hints on Tablets, Lollipops, Sticks, Gel-Creams, Pastes, Otic, Nasal, Packaging and Labeling, Shipping and Distribution, Patient Counseling and Administration, and Sweeteners.

Introduction

As pharmaceutical compounding continues to increase and becomes more formalized with increased emphasis on quality control and associated practices, it is important that pharmacists implement efficient and effective procedures at their practice sites.

Over the years, many pharmacists make observations and implement changes in procedures that enhance their practice; many of these can be passed along to others for their use. These "tips" or "hints" can be quite valuable, time-saving, and cost effective. The purpose of this article is to introduce a collection of tips that apply to many aspects of pharmacy compounding. Additions are welcome so these lists can become more complete.

Quality Compounding

An essential feature of any compounding pharmacy is a good quality control program; its purpose is to ensure that a preparation is compounded properly and is stable for its duration of use. Although most compounding pharmacies do not have fully equipped quality control laboratories, they can implement a basic program and expand with time. All employees involved in testing must be adequately trained and provided with appropriate equipment and SOPs. Proper testing can result in cost savings and better compounded preparations. Many tips and hints can result in time and cost-savings for quality testing.

Loyd V. Allen, Jr., Ph.D., R.Ph.

- *Professor Emeritus, University of Oklahoma College of Pharmacy*
- *Editor in Chief, International Journal of Pharmaceutical Compounding*
- *Dr. Allen is not affiliated with Paddock Laboratories Inc.*

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Tips and SOPs

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.

Tips on the Facility (General and Aseptic)

General Facility

* Use a facility-design consultant with experience in the type of compounding planned for the facility.
* 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 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 total 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 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.
* Install lab-grade dishwasher with attached purified water input.
* Use 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.
* In select critical compounding situations, humidity control of the compounding room may be indicated.
* Prepare a separate, segregated "weighing" area in the compounding room if possible.
* When cleaning countertops, first wash with water to remove water-soluble materials. This can be followed by alcohol to remove alcohol-soluble materials. If alcohol is used first, it may precipitate some substances resulting in more difficult removal.

Aseptic 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 aseptic compounding area.
* 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 anteroom. 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 clean room 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 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 the 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.
* Use dust covers as appropriate for compounding equipment in the non-sterile 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 (human blood products, etc.), 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 also 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". Sand 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. The sand can be used in the sandbath for a long time and clean up is minimal.
* Pyrex glass baking dishes are convenient and work well in the compounding laboratory.
* 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, 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 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 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 warranteed 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 a UPS (Uninterruptible Power Supply).
* 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 and validated methods.
* 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.

Tips on Ingredients

* Ingredients should only be purchased from reliable vendors.
* Certificates of Analysis should be obtained with each order of ingredients and retained according to the SOP on document retention.
* Material Safety Data Sheets should be readily available, either in print or electronic form, as required by the individual state boards of pharmacy.
* The Certificates of Analysis of "Active Pharmaceutical Ingredients" (APIs) with a wide potency acceptance level, outside the 98%-102%, should be checked and adjustments made in the calculations to accommodate wide variations. (If the acceptance level is 90-110% and the C of A shows potency of 91%, then an adjustment must be made to accommodate this level of activity or the final compounded preparation may be out of specifications.
* Use high-quality suppliers of chemicals for compounding. It is the pharmacists' responsibility to "check them out" and confirm everything is appropriate.
* Use of the same supplier usually results in more consistent raw materials of the same physical characteristics, including particle size, pH, etc.
* Color-coded press-on "dots" can be applied to raw material containers designating the month of expiration. This speeds the process of monthly checking for expired substances.
* Purchase liquid concentrates whenever available and appropriate for use.
* Sufficient ingredients for preparing the prescription should be available without the necessity of mixing lot numbers of individual ingredients.

Tips on Procedures

* Evaluate the rationale of the prescription; if okay, proceed.
* On new formulations, take time to review the physical and chemical properties of the ingredients and determine whether or not any incompatibilities may occur.
* During the review, confirm the final preparation will be as desired (solution, suspension, cream, gel, etc.).
* Will each active ingredient be stable in the intended formulation?
* The actual yield should be checked and should be consistent with the theoretical yield.
* Procedures for specific formulations should be identically performed by different individuals so the final preparation will be the same.

Tips on Calculations

* All components of the formula must be clear and precise.
* One individual should work out the calculations. Separately and without looking at the other's calculations, a second individual should work out the calculations. Finally, compare the answers.
* All calculations should become a part of the compounding record.
* Use exact equivalents throughout calculations and round off the final answer. The use of approximate equivalents may introduce uacceptable errors in calculations.

Tips on Preservation, Sterilization and Depyrogenation

* Preservative Concentrates can speed up the addition of a preservative to a preparation. An example would be methylparaben and propylparaben in glycerin.
* A routine program of sterility testing should be in place by every pharmacy involved in sterile compounding. This involves selection of a number of samples on a regular basis for sterility testing from those compounded.
* Check the pH of all aqueous liquid preparations containing preservatives for confirmation of the proper pH range suitable for the preservative.
* Preservatives must be in solution to be effective. Confirm their solubility in the compounded preparation.
* In emulsions, the preservative must be soluble in the aqueous phase and have a greater tendency for

partitioning into the aqueous phase to be effective.

* Preservatives in the aqueous phase must be in their non-ionized state for optimum effectiveness.
* Terminal sterilization is best, but in-process sterilization is acceptable.
* Autoclaving is a form of terminal sterilization.
* Sterile filtration is in-process sterilization because a packaging step follows.
* Validate sterilization processes on a regular basis.
* Contract laboratories may be beneficial in some cases for sterilization activities, especially gamma and ethylene oxide sterilization.
* Follow the temperature and pressure in an autoclave run to confirm there are no "air pockets" in the autoclave; this would be indicated by below-normal levels of temperature and pressure.
* At the completion of a filtration process, immediately remove the filter (the filter retains particulates/microorganisms and they may continue to grow and may either grow through the filter or release endotoxin materials).
* When filtering low concentration solutions, confirm the drug is not being sorbed to the filter or tubing material. Lipophilic drugs tend to be the most problematic.
* Clean equipment used in aseptic compounding, rinse with sterile water for injection, depyrogenate and seal with foil for later use.

Tips on Beyond-Use Dating

CONDITION		DRUG SOURCE	BUD
NonSterile	Nonaqueous liquids/solids	Commercial product	6 months or 25% of time remaining for commercial drug product
		USP/NF Ingredient	6 months
Nonsterile or Sterile with sterility testing program in place	Aqueous		14 days stored in a refrigerator
Nonsterile	All other preparations		30 days
Sterile-No sterility testing program			
Risk Level	**Room Temp**	**Refrigeration**	**Freezer (<-20° C)**
Low	48 hours	14 days	45 days
Medium	30 hours	9 days	45 days
High	24 hours	3 days	45 days

* Use the chart above to determine if any options are available for enhancing the BUD of a compounded preparation.
* Solids can be assigned a 6 month BUD. If this type of a BUD is needed, it may be possible to alter the formulation to a solid for later reconstitution. The solids may be packaged in multiple containers for later reconstitution individually as required.
* Nonaqueous liquids can be assigned a 6 month BUD. If this type of a BUD is needed, it may be reasonable to change the vehicle from an aqueous vehicle to a nonaqueous vehicle that can also be sweetened, flavored, etc.
* If an aqueous liquid is required, it may be feasible to divide the preparation into multiple containers and freeze a portion of them. They can be individually removed from the freezer, thawed and used as required.
* In sterile compounding, the use of sterile ingredients may enable a longer BUD as it would involve compounding at a lower risk level.

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Please circle the most appropriate answer for each of the following questions. There is only ONE correct answer per question.

1. Purified water USP can be obtained by:
   I. distillation
   II. reverse osmosis
   III. deionization
   A. I only
   B. III only
   C. I and II only
   D. II and III only
   E. I, II and III

2. Sterile water for injection can be obtained by:
   I. distillation
   II. reverse osmosis
   III. deionization
   A. I only
   B. III only
   C. I and II only
   D. II and III only
   E. I, II and III

3. Limiting access to the ante and buffer areas for aseptic compounding serves to:
   A. Save cleanup time
   B. Minimizes chances for contamination
   C. Minimizes chances for errors
   D. Enhances efficiency
   E. All the above

4. Which of the following solvents should be first used when cleaning spilled items?
   A. Acetone
   B. Alcohol
   C. Bleach
   D. Glycerin
   E. Water, Purified

5. Which of the following is permitted inside an aseptic compounding facility (buffer room)?
   I. cardboard/fiberboard cartons
   II. dry erase marker
   III. clean, sanitized cart
   A. I only
   B. III only
   C. I and II only
   D. II and III only
   E. I, II and III

6. Which of the following is considered a method of "destructive" testing?
   A. pH
   B. Physical observations
   C. Weights
   D. Volume
   E. Sterility testing

7. Split samples can be used for:
   I. confirmatory testing
   II. testing laboratories for accuracy and consistency
   III. testing only part of a batch
   A. I only
   B. III only
   C. I and II only
   D. II and III only
   E. I, II and III

8. For the most part, out-of-specification results are due to:
   I. substandard ingredients
   II. personnel failures
   III. equipment problems
   A. I only
   B. III only
   C. I and II only
   D. II and III only
   E. I, II and III

9. Calculations involving compounding preparations:
   A. should be worked out by at least 2 people individually.
   B. should be done using approximate equivalents.
   C. should be delegated to technicians.
   D. need not become a part of the compounding record.
   E. all the above.

10. A formulation for a aqueous suspension (14 days BUD in a refrigerator) of an orally administered drug may possibly be altered to achieve a longer BUD by:
    I. dispensing the powders in multiple containers with instructions to reconstitute as needed.
    II. changing the vehicle from a aqueous to a nonaqueous vehicle.
    III. preparing the formulation, packaging in multiple containers and freezing with instructions to remove one container, thaw and use, as appropriate.
    A. I only
    B. III only
    C. I and II only
    D. II and III only
    E. I, II and III

11. My practice setting is:
    A. Community-based
    B. Managed care-based
    C. Hospital-based
    D. Consultant and other

12. The quality of the information presented in this article was:
    A. Excellent B. Good C. Fair D. Poor

13. The test questions correspond well with the information presented.
    A. Yes B. No

14. Approximately how long did it take you to read the Secundum Artem article AND respond to the test questions?

    _____

15. What topics would you like to see in future issues of Secundum Artem?

    _____

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