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Steps to Improve Quality in the Compounding Lab

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Abstract

Quality-control guidelines and processes have progressed considerably in the past eight years since the first publication of the United States Pharmacopeia regulations. Many state boards of pharmacy have put additional emphasis on quality control in their regulations. Fortunately, there are many resources available to the compounding pharmacist today, from third-party quality-control testing laboratories to extensive training programs to assist in the goal of operating at the highest quality levels. This article provides some common-sense steps to improve the quality of a compounding pharmacy's preparations.

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There have been significant changes in the approach to quality in the compounding pharmacy. The topic of quality in the compounding pharmacy was addressed by the *United States Pharmacopeia (USP)* in *USP Chapter <795> Pharmaceutical Compounding—Non-sterile Preparations* and *USP Chapter <797> Pharmaceutical Compounding—Sterile Preparations*, along with several other chapters. Many compounding pharmacists, given the new guidelines and the increased attention by their state board of pharmacy, embarked on programs to make “quality” a cornerstone of their practice.

Shortly after these chapters were issued, the Pharmacy Compounding Accreditation Board (PCAB) was formed, which put further emphasis on the establishment and documentation of

practices that result in a high level of quality in the pharmacy. Journal articles and presentations at pharmaceutical compounding conferences have further heightened awareness of quality issues and offered guidance in implementing quality procedures in the pharmacy.

Looking back over the past eight years reminds me of the old saying “We have come a long way Baby”! However, if I have learned anything about quality, it is that when we look back rather than forward, we often get into trouble. With this in mind, I thought it would be useful to offer several observations on quality in the compounding lab to guide pharmacist as they look forward. I have a list of five steps to improve quality, as follows:



STEP 1:

Take Personal Responsibility for Quality

Quality starts at the top of any organization, so the first step in implementation of a quality culture is for the person in charge to take personal responsibility for leading the charge. Some may think that this means coming up with a quality statement and putting it in a frame on your office wall. While that may help remind you, it is actually your actions that speak the loudest to all the employees in your organization.

Do you have a training program that includes aspects of quality assurance and quality control for new employees? And more importantly, what do you do for continued training of established workers? When was the last time one of your employees went to an offsite training session for compounding techniques? When they returned to the pharmacy did they recommend changing any of your long-term practices, and, if so, what was your response? Have you implemented a quality-testing program where you have validated your compounding processes? Have you set up a random testing program for potency testing of your preparations? Do you have a sterility and bacterial endotoxin test program for compounded sterile preparations (CSP)? If you are testing your preparations, what do you do with the results of the tests? Do you review the test results with your staff at your regular employee meetings, or do you just file them away in case someone from the state board happens to ask for your testing results?

How do your employees feel about questionable preparations, those that may not look exactly right or may seem different from when they last made the preparation? Are they more apt to toss it out and make it again or are they more concerned with what you may say if they admit that there may be something amiss with the preparation? How would you respond to their question as to what to do in this case? All these situations add up to the quality culture of the pharmacy, and the inescapable point that it is set in place and starts at the top. When I

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was working in the chemical industry, I was impressed by the quality culture at DuPont. This culture started at the top of the organization, but the interesting thing was that as a result, it permeated down to each and every employee, so they all felt part of the quality team. At that time, DuPont had one of the best quality records in the whole chemical industry.

thought of a low-quality preparation as one that does nothing for the patient because they are using it improperly. A pharmacist at that same pain seminar recounted his procedure for regular follow up with his pain cream patients to make sure that the preparation was effective. How often do we think and follow a prescription all the way through to its final outcome, and is this not the true meaning of a quality preparation?

I could continue with many examples similar to those above, but, suffice to say, we must continually be in both learning and teaching modes to assure the quality of what we do as compounding pharmacists. Thank goodness our world is changing, as a static environment would be pretty boring. But, we must always remind ourselves and those in our pharmacy team that we must never cease to learn what is new and pass that information on to those that can benefit from our knowledge.



STEP 2:

Educate Your Staff and Users

One of the things that I truly enjoy about compounding is that it is continually changing and evolving as we find new and interesting dosage forms, exciting new clinical treatments, and improved ways to deliver our unique solutions to patients. From new topical excipient base formulations that have been experimentally shown to carry the active pharmaceutical ingredient (API) as they effectively penetrate the skin, to innovative cream applicators that make dosing more accurate and convenient, compounders are continually changing and improving how we serve our patients and our communities. How does one keep up with all the changes that are happening while still having time to run and grow a business?

If you are compounding sterile preparations, when was the last time you or one of your staff attended a sterile compounding course? *USP* Chapter <797> was issued only eight years ago and has already undergone a significant revision. Similarly, *USP* Chapter <795> has undergone a substantial revision since it was first published in the early 2000s. We have also seen substantial changes to how compounding is actually done in a pharmacy. Automatic electric mortars and pestles (EMP), mills, capsule machines, and blenders are continually evolving and being used regularly in pharmacies. As an aside, one of the most common mistakes we see in testing the potency of creams can be attributed to inadequate mixing. When I find that the preparation was made using an EMP, my first questions are “What size container did you use and at what speed and for how long did you mix the preparation?” Most respondents are amazed to learn that if they are mixing a low concentration active, in a 200-mL container at a speed of 5, to get a good mix takes over eight minutes! How many compounders are still using baggies for mixing low-level hormone capsule powders? This used to be the standard of practice until we discovered that the electrostatic hormones stick to the bag and you are left with subpotent capsules? If you are compounding sterile preparations, do you know that you must qualify competency via a media-fill-test procedure and a finger touch test at least twice a year?

At a recent pain seminar, the comment was made that one of the main reasons patients do not get the benefit from the amazing new topical pain creams, is that they do not know how to use them. They do not know *where* to apply, *how often* to apply, and *how* to apply the medication. This example reminded me of the fact that the quality of a preparation is really a measure of its fit for use, or said in a different way, does it solve the patients’ problem? How many of us have ever



STEP 3:

Keep It Simple Smarty

When it comes to assuring quality in any business, the old adage to Keep It Simple Smarty (K.I.S.S.) is sage advice. The opposite of simple is often complex, and with this comes the ever-present errors and mistakes that cause poor quality.

Keeping activities, processes, and procedures simple is no easy matter, so what are some of the things that a compounding pharmacist can do to make things simpler?

1. Break down complex tasks into simple sub-tasks that can be completed easily. Then combine these sub-tasks into the final solution.
2. Make sure that your instructions for any task are clear and understood by those completing the task.
3. Ask your team to help in developing the processes and procedures, with the objective of keeping things simple.
4. Use technology only when appropriate. For example, a simple check-off sheet to record that you cleaned the floor in the cleanroom may be better than a computer database application. On the other hand, the use of compounding software can make things not only easier, but much more efficient, and improve quality in the process.
5. Write things down—keep a simple note pad in your pocket to keep notes to yourself.
6. Do not try to do two things at once, do one well, finish, and then go on to the other task.
7. Slow down when things become difficult.
8. Approach each task with a smile—a happy person makes accomplishing even the most difficult task easier.





STEP 4:

Understand Why People Make Mistakes

Traditionally, quality assurance in most-manufacturing applications focuses primarily on the reduction of variance in the process. It is assumed that the cause of non-compliance or poor quality can be attributed to variations in the process of assembling the product, out of tolerance parts, or a host of other variables associated with the manufacturing process. This has resulted in programs such as Six-Sigma, which focus on reducing variance from all sources so that the end product meets a very tight specification.

In pharmaceutical compounding, we have followed similar methodologies to improve the quality of the final preparations that are made. A formula worksheet is developed that expresses the quantity of all the ingredients in the preparation, and instructions are provided as to the best way to compound the ingredients into the final preparation. In an effort to reduce out of specification preparations, more formula worksheets are now giving explicit directions for things like order and time of mixing in various mechanical devices being used more often in the pharmacy. Formulations are compounded and then checked for accuracy or validated by third-party laboratories for things like sterility, endotoxins, and active ingredient potency. In many cases, as further testing shows deviation from the desired concentration of the active, analysis of the "validated process" is undertaken and changes are made to reduce these variations. Depending on the sophistication of the quality effort, aides such as quality-control charts and defect-analysis programs are initiated with the purpose of reducing the variation in the preparation, all with the objective of higher quality.

While this focus on the reduction of variance in processes as a tool for improved quality is absolutely necessary and returns substantial benefits, it is not the only thing that needs to be addressed when considering the overall quality of compounded preparations. Random *human mistakes* can and in many cases do make a contribution to poor quality in the pharmacy. Unfortunately, it is mistakes that are usually responsible for the

more catastrophic quality episodes in pharmaceutical compounding.

While many may conclude that there is little that can be done about human mistakes, there is a surprising amount of research to the contrary. However, it may be best to first explore the question "Why do people make mistakes?"

Posing such a question as a Google search returns a staggering 131 million citations, so maybe turning to Google is the first mistake. However, the cited references do bring up a number of interesting sources as to why people in general make mistakes and why even smart people make dumb mistakes. Three of my favorite books cited are those by Joseph Hallinan; Madeleine Van Heckle; and Ore and Rom Brahman. While there is a wealth of information in these books, some of the more illustrative reasons for mistakes include¹⁻³:

1. We often ignore details and skim as we read and follow directions.

Our minds are amazingly able to gather information that seems reasonable and rational but on closer inspection we find that important details are missed. Some believe that our use of the Internet and our reliance on summaries presented in search engines are further contributing to this skimming tendency. When we are following a procedure that we may not have done for some time, do we follow in detail or do we skim and miss a step? The following example clearly demonstrates how adaptable our mind is when reading and our ability to make apparent sense out of gibberish:



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2. We are often wrong but surprisingly never in doubt. What we do not know can sometimes hurt us.

Here is a simple mathematical problem that illustrates this point:

John has three apples.

Mary has two apples.

If John gives Sam one apple and Mary gives Sam one apple, how many apples does Sam have?

Most people would say “two” but consider if Sam already has two, three, or more apples to start. Do we have enough information to answer the question? Apparently not!

This example illustrates two common mistakes: (1) we often do not ask ourselves if we have enough information to solve a problem, and (2) we jump to the first correct answer and then stop solving the problem. We never consider if there are other correct answers to the problem. However, the bigger question is how do we know what we do not know? Maybe we need to carefully consider a problem and ask ourselves what we may not know before we jump to a seemingly correct answer.

3. We are so concerned with getting things accomplished that we believe multitasking is the answer to improved productivity.

Numerous studies have shown that switching from task to task is actually less efficient than working on one project at a time. This is because as we switch tasks we forget about one task to concentrate on the other. Studies have shown that this “forgetting rate” can be as high as 40 percent, and it takes up to fifteen minutes to regain a level of concentration after a distraction.

I also think we sometimes go overboard with these conclusions. Is listening to an iPod while working on a simple task really deep multitasking? On the other hand, taking a phone call in the middle of a demanding task is certainly an interrupting influence. The problem is, what could be called, “multitasking creep.” Using the iPod today is okay but tomorrow having a hands-free telephone and talking while deep in a task is now also acceptable.

4. Our brain and our eyes are not always in sync. Or, sometimes, we don't see what we think we are seeing.

Sometimes we see something that is not really there, and other times we fail to see things that are clearly present. How and what we see has as much to do with our state of mind as with our eyes. A common example of this is the cartoon in most newspapers where we are asked to determine the difference between two similar scenes. Do the differences jump out immediately or do you have to really study the two pictures to determine the differences.

Other examples are the numerous visual optical illusions that seem so perplexing. (For some examples see the website: <http://www.illusion-optical.com>).

5. We have difficulty accepting feedback from others, especially when we all believe that we are above average.

When I am speaking to training classes in compounding techniques, I often state that one of the issues affecting quality involves

the fact that we all see ourselves as above average, which makes it difficult to receive feedback on how we are doing something. I also mention that men in general see themselves higher on the scale than women. After some polite snickering, I remind them that this can be a real problem in the pharmacy and maybe we could learn from what others are doing to combat this phenomenon.

An airplane cockpit and a hospital operating room are two places where the old paradigm of one person in charge and all others follow is changing rapidly. What is happening is that all the people in these differing work environments are being trained to act as a team.

When anyone, regardless of their position, sees something that may be wrong they are encouraged to speak up. While it is changing slowly in hospitals, it has rapidly taken hold in aviation cockpits and has been credited with one of the things that has led to a reduction in airline accidents.



STEP 5:

Apply What We Have Learned to Improve Compounding in the Pharmacy

Pointing out where we can expect to find quality problems in the pharmacy is only the first phase of the improvement process, what one now needs to do is implement activities and adopt processes that result in solving these problems. Even knowing what to do may not solve the problem. You have to get those actually responsible for doing things to be open to learning new ways and often changing time-ingrained practices.

Re-evaluate your Attitude About Mistakes in the Pharmacy

Of critical importance is to have an open and nonjudgmental attitude concerning unintentional mistakes in the pharmacy. When someone makes a mistake, encourage the recognition and acknowledgement of the error and seek ways to prevent it from happening again. Avoid punishing those who admit their problems, but rather treat it as a chance for the whole pharmacy to learn. An interesting book by Ken Blanchard⁴ on training killer whales at Sea World develops this philosophy in more depth. His central point is that you get optimum results if you reward good behavior and redirect poor performance, but avoid to all possible extent criticizing the unwanted activity. Additionally, here are some specific action items you may want to adopt:

1. Integrate checklists into your compounding processes.

The use of a checklist, even for simple tasks, has been shown to substantially reduce errors. In his book on implementing checklists in a hospital environment, Atul Gawande⁵ relates how a simple five-step checklist substantially reduced infections associated with the



insertion of a central line catheter. When implemented at hospitals in Michigan's intensive care units, the infection rate dropped by 66 percent, with many hospital rates going to zero. Checklists are also used extensively in aviation, so much so that Boeing has a complete department devoted to developing checklists to cover almost any conceivable situation a pilot may encounter.

The question is, if the checklist has been shown to reduce errors and eliminate mistakes so effectively, why are they

not used in compounding formulation worksheets? Is compounding so much simpler than flying a plane or inserting a catheter that a checklist would be useless? Maybe our compounding worksheet instructions should take the form of a simple step-by-step checklist of activities that could be verified with a check mark when completed.

2. Use automation to help mistake proof your activities.

Modern compounding software offers several tools to assist the pharmacist in "mistake proofing" their processes. Mistake proofing refers to making it impossible, or at least very difficult, to make a specific mistake. We all benefit from these practices in our daily lives with such things as making it impossible to plug a 115-volt appliance into a 220-volt outlet, or the inability to put diesel fuel into our automobile gas tank (the nozzle is larger than the opening). Automation in the compounding pharmacy with compounding software can be set to:

- Adjust, automatically, the quantity of all ingredients in a formula based on the total amount needed to compound
- Adjust for the purity of the active ingredient in the formula
- Verify that the chemicals specified in the formula are the ones that are being used in the compounding process



- Assure that the weights of the chemicals used in any formula are within specified weight tolerance limits

When set to mistake-proof condition, if any of the above conditions are not met, the computer flashes a warning and asks the compounding pharmacist if they want to proceed. Until the error is acknowledged and corrections made, further progress is halted.

Automation can also help in tracking and controlling inventory within the pharmacy, keeping accurate records of compounded formulas, and tracking compound lots, in addition to the more traditional dispensing software used in most pharmacies. While I am on the subject of mistake proofing, I should also mention that there are a number of other nonautomation things that can be adopted to help reduce mistakes. Simple ideas like color coding to distinguish similar items or, if you are not using a computer system, having your balance tied to a printer to verify the weights of chemicals used in formulas.

3. Make sure you do not overlook the active ingredient specified in the Certificate of Analysis

In my experience, one of the biggest reasons for out-of-specification (OOS) CSPs comes as the result of not recognizing the need to check the Certificate of Analysis (CofA) for the active pharmaceutical. Each lot of the active may also have a slightly different assay, water content, or loss on drying so it is important that you also check for each new lot number.

The CofA offers information on four important items for the active:

- 1. The form of the active**—is it a salt or the base form of the chemical? If the formula calls for the active to be dosed on the base and you are using the salt, you will need to make sure that you have properly adjusted the weight of the active in the preparation. Common mistakes like lidocaine versus lidocaine hydrochloride (HCl) and fentanyl versus fentanyl citrate are examples.
- 2. The description of the active** is an excellent way to make sure that the chemical has maintained its quality. If the active is described as a fine white powder, and your chemical is a fine white powder with black specs in it, I would suggest using another lot of the active.
- 3. The assay of the active** is a measure of its potency. While the majority of the actives used in the pharmacy are near 100%, there are a number of actives, notably antibiotics, which can be substantially below 100%. Also, most assays are determined after the water content of the active has been removed. For example, if the active contains 8% water and the assay is 100%, the powder only contains 92% of the active.
- 4. The water content of the active** is stated as either "water" or "LOD" (Loss On Drying). Water usually refers to bound water, such as water of hydration in an active like bupivacaine HCl monohydrate, where LOD usually refers to absorbed water. LOD is the water content determined just after manufacturing of the active. A high LOD may signify that the active is hygroscopic and should be a warning to the pharmacist that over time it may absorb additional water from the environment.

While the above are items of particular importance, the CofA also contains a wealth of information that may be important to a specific formulation, so checking it for each new lot number is a good idea.

4. Know the Solubility of the Active Ingredient

Solubility of the active ingredient is another area where we frequently see OOS problems. Recently, several compounders have tried to make a sterile solution of alpha lipoic acid at 200 mg/mL. The references for the active indicate that the sodium salt is “soluble” in water. However, most do not understand that soluble means that a maximum concentration of 100 mg/mL may be possible. In practice, we have found that these estimates are sometimes optimistically high, and, as in this case, a concentration much over 50 mg/mL is difficult if not impossible. The bright color of this compound easily hides the fact that there may be undissolved crystals in the solution, which are filtered out on sterilization of the compound, leaving the active on the filter and the preparation much lower in potency than thought.

This type of OOS problem could have been easily discovered by initially verifying the compounding process of this preparation.



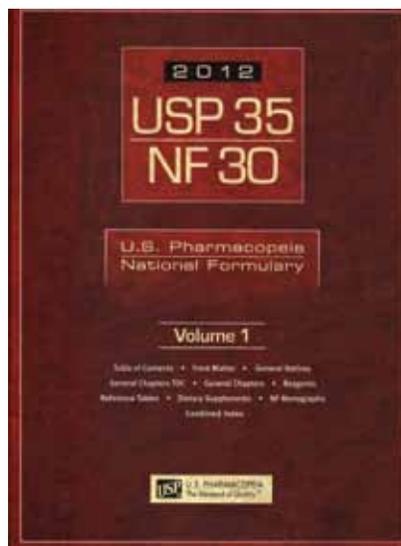
For a further discussion on this process see the International Journal of Pharmaceutical article titled *A process verification model for quality assurance in a compounding pharmacy.*

5. Mixing

Both in sterile and nonsterile compounding, we see “mixing” as one of the primary reasons for OOS preparations. In sterile formulations, many think that powders mix instantaneously or at least quickly. We often have to remind them that it takes time for the mixing and solubility of the active to go into solution. Heat does not always help as some have discovered when trying to make 25-mg/mL methylcobalamin, which goes into solution best when mixed cold. This is also true for 10-mg/mL sodium hyaluronate where cooling the solvent buffer works wonders for solubility. One of the exercises done in a sterile compounding training class is to make 2000-mcg/mL baclofen. A syringe-to-syringe mixing method is used, and the instructors caution the students that putting the baclofen into solution is not easy, so they would like to see the syringe

before the preparation is filtered. In many cases, there are still baclofen particles in the solution when the students think it has been mixed sufficiently. Filtering the preparation before it is mixed and solubilized leaves some active on the filter and results in a subpotent drug.

In nonsterile preparations, we see problems when low-level hormones are compounded into either capsule or cream dosage forms. It is not easy to get a homogeneous mix at 1 mg/mL or less, and trying to make a 1:1000 dilution trituration takes skill and patience. Those compounders that consistently test these preparations and get commendable quality can testify that it takes time and a process that does not vary from batch to batch.



6. Follow USP Chapter <797> and USP Chapter <795> Guidelines

If you do not have a copy of the two primary USP guidelines to compounding, I suggest that you get them and familiarize yourself with the best current thinking regarding what it takes to compound a quality preparation. You may also want to download the current requirements for PCAB certification. Even if this is not in your immediate plans, knowing what are considered acceptable quality procedures may shed some light on the operation of the pharmacy.

As an aside, if your state regulations are more permissive in the key quality points, especially with regard to USP Chapter <797>, you may be well advised to follow

the more strict USP guidelines for your own peace of mind.

Conclusion

Quality-control guidelines and processes have progressed considerably in the past eight years since the first publication of the USP regulations. Many state boards of pharmacy have put additional emphasis on quality control in their regulations. Fortunately, there are many resources available to the compounding pharmacist today, from third-party quality-control testing laboratories to extensive training programs to assist in the goal of operating at the highest quality levels.

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