ABSTRACT
Undeniably, one of the most important considerations in a compounding pharmacy’s procedures is quality. Developing a comprehensive quality-control potency program must begin with the most basic activities performed at a compounding pharmacy to the most crucial activities. If the basics are not met, the crucial activities of compounding sterile and non-sterile preparations and the quality of the end product are in jeopardy. Basic definitions are provided in this article as well as a discussion on a three-step method on setting up a quality-control potency testing program, to include (1) process design and how to reduce the potential of variations and mistakes in compounded preparations, (2) process verification, and (3) how to set up a sampling plan to monitor ongoing quality. Also included are suggestions on how to get started on the development of a quality-control potency testing program.
A common question raised by many pharmacists is: “I know I should be testing my preparations, but I don’t know where to start. Do you have something that I can use to guide me in developing a quality-control testing program?” With the current attention compounding is receiving on popular radio and television programs, as well as the national press, there is no doubt that pharmacists are concerned about the quality of their preparations. However, developing a comprehensive quality-control (QC) program is not a simple matter, especially when one considers the wide range of activities performed at various compounding pharmacies.

While the design and implementation of a full quality-assurance (QA) program is beyond the scope of this article, a good place to begin is with the implementation of a QC potency testing program for the pharmacy. Since the testing requirements for the sterility and endotoxins of sterile preparations are expertly covered in *United States Pharmacopeia (USP)* Chapter <797>, this article will discuss potency testing of sterile and nonsterile compounds only.

Before we begin, it may be helpful to set out some testing program objectives:
1. It should be cost effective, as testing is expensive, especially with third-party laboratories.
2. There should be a statistical underpinning for the program.
3. It should be simple to implement.
4. It should provide information to improve the operation of the pharmacy.

**BASIC TERMS**

**Quality Assurance**

Wikipedia defines quality assurance as:

> …refers to planned and systematic production processes that provide confidence in a product's suitability for its intended purpose…. It is a set of activities intended to ensure that products (goods and/or services) satisfy customer requirements in a systematic, reliable fashion.1

Two key principles characterize QA: (1) “fit for purpose” (the product should be suitable for the intended purpose) and (2) “right first time” (mistakes should be eliminated). QA includes raw materials, assemblies, products, and components; services; and management, production, and inspection processes.

It is important to realize also that quality is determined by the intended users, clients, or customers, not by society in general. It is not the same as “expensive” or “high-quality.” Even goods with low prices can be considered quality items if they meet a market need.

**Quality Control**

QC activities, as opposed to QA, deal with assurance and failure testing in design and production of products or services, to meet or exceed customer requirements. So we see that QC is really the measurement side of QA. QC testing allows us to quantitatively assess the acceptability of our product or preparation as measured against a set of objective requirements, with the understanding that if these requirements are met, our customers will be satisfied with our product or service. In compounding preparations, the objective measure of the potency of a preparation is usually ±10% of the labeled claim for the active(s) in the preparation. This is true for the majority of compounded preparations, as well as manufactured pharmaceuticals, with only a few exceptions, which are specified in their specific monographs defined in the *USP*, published by the United States Pharmacopeial Convention, Inc.

**Process**

It is also important to remember that when we test a product (or preparation) we are also testing the process that was used to make it. This understanding will be critical in our development of a testing program for the pharmacy. In pharmacy compounding, a process is a set of interrelated steps that specifies and defines how a preparation can be made exactly the same each and every time by anyone skilled in the art and science of compounding. In the pharmacy, we may have a process for capsule making, one for topical creams, and another for sterile suspensions in oil. Fortunately, all together we probably have less than a dozen different processes in the pharmacy. Looking at the pharmacy from a “process” perspective when implementing a quality-control testing program immensely simplifies our task.

**Preparation Testing**

Preparation testing is considered by many pharmacists to mean measurement by a third-party contract laboratory. While this is certainly true, there are a host of other activities that take place within the pharmacy that also can be defined as “testing.” In fact, I am a proponent of doing as much of this type of testing as possible in-house...
because (1) it is cost effective, (2) it has immediate feedback, and (3) it develops an awareness within the entire staff that quality is important. What I usually find is that if this type of testing is done, it is usually not documented; therefore, the results are never used to help the pharmacist improve the processes within the pharmacy. We will cover this aspect of testing in more detail later in this article.

### STEP 1: PROCESS DESIGN

You may wonder how process design comes into a discussion on quality testing? Very simply, as one of my experienced mentors explained to me on my first job working in a quality-control laboratory. He said, “Sonny, you can never test quality into anything. If it isn’t designed right in the first place, all the testing in the world won’t make it better!” So before you start doing any testing, whether it is in-pharmacy or being sent out to a contract laboratory, make sure that you have a well thought-out and documented process. In fact, this philosophy is the latest thing in pharmaceutical manufacturing, called “Quality by Design” (QbD). The importance of this principal is illustrated by a Google search of “pharmaceutical QbD,” which returns more than 100,000 citations. So before we get into the discussion about testing programs, it may be worthwhile to spend a little time discussing how we design a compounding preparation process. And, before we jump into the design of a process, it may be instructive to explore where poor quality originates, or the outcomes we are trying to prevent. In general, there are two overall causes of poor quality:

1. **Process Variation**
   - When the process does not give the intended result, then you have a process variation. Such variations range from the process having a “fundamental error,” where even if it were performed exactly as documented the results would not be acceptable, to “small” variations which are not sufficiently documented to indicate their criticalness. After reviewing countless preparation formulations, I have found very few fundamental errors. Usually these are the result of transcription errors or, more rarely, chemical compatibility errors. I recently tested a simple sterile preparation for potency three times before requesting the formula worksheet, only to find out that the pharmacist was making the preparation correctly, but the weight of the active was only 15% of the label weight specified. Once this fundamental error to the process was corrected, the preparation tested within specification. In my experience, most process variation problems are due to technique or, more clearly, variation in technique among those doing the compounding. “How” to design a process to reduce these variations is discussed elsewhere in this article.

2. **Mistakes**
   - Regrettably, compounding mistakes are a reality. Random mistakes are almost impossible to detect by less than 100% testing, and, unfortunately, they often lead to the most detrimental effects in quality. However, if we realize that these problems exist, and we put our mind to it, there are ways we can design a process to make it somewhat “mistake proof.”

### Reducing Mistakes by Process Design

I want to cover this first because, when confronted about random human mistakes, most people throw up their hands and claim it is a problem that cannot be controlled. Nothing could be further from the truth, as illustrated in two recent books, *Why We Make Mistakes* by Joseph T. Hallinan and *Make No Mistakes* by C. Martin Hinckley. These books address the topic of mistakes from two different perspectives, but on reading both you begin to understand that we can do something about the “random human mistakes” that may be made in our pharmacy.

**Why We Make Mistakes**

Hallinan, whose book was recently summarized in *Readers Digest*, explores 13 ways in which we make mistakes and offers suggestions as to what we can do in our everyday life to reduce these errors. I believe that three of his reasons are particularly appropriate to compounding:

1. **When we multitask, we get stupid—the brain slows down when it has to juggle tasks.** He cites several experiments that have been performed showing that multitasking can take longer to accomplish tasks even if it does not result in mistakes being made. How many times have you been in the middle of a compounding preparation only to be called away to deal with something unrelated? What about listening to an iPod during compounding, almost a universal activity? What are the consequences of not fully concentrating on the job at-hand? Maybe the first step in our compounding process should be to get rid of all distractions so you can concentrate on the important job at-hand!
2. We see, but we don’t see—sometimes we can look at something and still not see it.
Or we see what we think we should see. What happens when we check the weight of an active on the print-out tape from the balance? Can we mistake a 3.000 gram reading for one that should really be 0.300 grams because we know that it should be 0.300 grams? In our compounding training class, each student makes a batch of 100 capsules at 3 mg caffeine/capsule. To do this, the students weigh out 0.300 grams of caffeine. Recently, we tested one batch where the results were 30 mg/capsule. When I called the student to see if they remembered compounding the capsules, they insisted that they had only weighed out the 0.300 grams of caffeine. Knowing this, maybe our process should call for us to write down the weight when checking a preparation, to confirm that it is what we verified as correct from the tape.

3. We think we are better than we are—or we all think we are above average.
It is striking how overconfident we all are; however, this overconfidence causes us to commit errors that when examined critically are recognized immediately. Amazingly, it has been shown that as the tasks get more complicated, our overconfidence goes up, not down.
All of us think that we can perform better than we actually do. In fact, it has been shown that so strong is our belief in our own abilities that we often believe we can control even chance events like flipping a coin. This brings to mind the scenario of the pharmacist who told me that she didn’t need a testing program because her preparations were perfect. I chuckled, but was taken aback with her stern scowl, realizing that she really meant what she said!

Not to leave us hanging, Hallinan proposes a number of things we can do to keep mistakes at bay in our everyday lives. Among the more interesting with regard to our pharmacy experience are:

1. Think negatively—when designing a task, ask what could go wrong. In this case, the power of negative thinking may open up areas that can prevent mistakes from happening.

2. Slow down—and do one thing at a time.

3. Use constraint—simple mental aids can often keep us on the right track. Just like the A B C song helps us remember the alphabet, mental aids can help us prevent errors.

Make No Mistakes
This leads very nicely into the work by Hinckley. Hinckley has written extensively in the pharmaceutical literature about the role of mistakes in the production of drugs. His approach is somewhat different than Hallinan in that Hinckley assumes that mistakes will be made and it is up to us to design systems and processes that make it impossible, or at least difficult to make them.

At first you may think that this is an almost impossible task, but there are countless examples all around you doing just that. Have you ever tried to put diesel fuel into your gasoline tank by mistake? You cannot do it because the diesel nozzle will not fit into your gas tank receptacle. How about trying to plug a 110-V AC plug into a 220-V AC outlet? The plug doesn’t fit. How about putting a notch in a part so that it will only fit into position the correct way—like the battery or memory card in your digital camera. Maybe these mechanical systems are easy compared to the processes we have in a compounding pharmacy, but these everyday examples of “mistake proofing” may be illustrative of what we can learn to do when designing a compounding process.

Let me give you several examples to get you thinking along these lines:

1. If implemented, PK Compounding Software makes it impossible for you to use the wrong chemical in a formula log. The software requires that you scan a code from the chemical container which must match the code on the formula for you to proceed. If it doesn’t match, the software will not let you continue with the compounding until you correct the mistake and obtain the right chemical.

2. Similarly, this software can be tied to your balance and automatically record the weight of a chemical being weighed. If the weight is not within specified limits of error, again the software alerts you and prevents you from proceeding with the compounding.

3. Another convenient feature of the software is that it automatically corrects the weights and volumes of a formula for a different total amount of preparation to be made. While the calculations should always be checked for accuracy, this feature may “mistake proof” calculation errors when preparing different amounts of a preparation.

The Compounders’ Network List server is a free e-mail-based resource for sharing compounding information with your peers. E-mail messages sent to the list are reviewed and then forwarded to all participants, allowing everyone to share information on the compounding issues of today. The CNL is available at CompoundingToday.com.
4. Color is a very effective way to help “mistake proof” a process. Preparations that could be confused, as with multiple concentrations of the same active, are often prepared with different colored caps. Triturations of critical powders, such as the 1:1000 mix of T3, are often colored to help in the mixing process, but, if consistent (i.e., T3 is always red), can also provide a visual indication that the compounder is using the right mix.

5. Checklists are sometimes an effective way to eliminate mistakes. Have you ever noticed that even a veteran airline pilot uses a checklist to make sure that he has not forgotten something before taking off or landing. Maybe because his life also is at risk if he makes a mistake that has something to do with his diligence, but I suspect it is really because it has been learned over many years that this behavior prevents mistakes. How many times have you seen a compounding pharmacist using a checklist when compounding? Or is it, “I’ve made this 100 times before, I know what I am doing” that prevails?

6. It has also been shown that making a process simpler helps reduce mistakes. Taking a complex process and breaking it up into smaller and more manageable sub-processes often can help in reducing the fatigue that can lead to mistakes.

One thing I must say is that compounders are both novel and inventive. So I am sure once they begin to think about ways in which their processes can be made “mistake proof” we will see a number of examples of how this can work in a pharmacy. In fact, when recently talking to a compounding pharmacist at a quality-control seminar, he was explaining ways in which he builds into his processes “forced compliance”—if a critical step was not performed, the compounder could not proceed. Maybe this is a good scenario of “mistake proofing.”

Hinckley goes on in his discussion of “mistake proofing” to offer suggestions as to how to develop an atmosphere that encourages the adoption of these mistake elimination processes.

1. Don’t punish or reward unintentional mistakes—an open environment is necessary to learn from mistakes.

2. Provide rewards for “mistake proofing” suggestions.

3. Implement “mistake proofing.”

4. Reward successful “mistake proofing.”

5. Put pressure on management to teach and apply these techniques.

I believe that the most important of these is number three, for without implementation nothing else will happen to improve the quality of the process.

Process Design to Reduce Variation

As stated, it has been my experience that most out-of-specification compounded preparations are the result of what I call “technique.” It is rare that I see a formulation error where the active or excipients are not as intended or of the wrong amount. Conversely, I review many formula worksheets which are very detailed in specifying all the ingredients in the preparation but have nonexistent instructions on how to actually perform the compounding process. A good compounding process should include a complete list of ingredients and clearly-stated instructions to allow the preparation to be made in exactly the same manner each and every time. The next time you are in your kitchen look at a good cookbook and notice how much space in each recipe is given to explaining what to do with the ingredients. On a quick review of my Betty Crocker Cookbook, I estimate that about two-thirds of the recipe involves directions on how to combine the ingredients. If this detail is warranted in a cookbook, why do so many compounded preparations have only minimal processing instructions?

While general compounding formulas that are downloaded from a Website database, or even a formula provided by a trusted colleague, are good starting points, they are not always directly applicable to your pharmacy. You need to modify the processing instructions to fit your specific pharmacy, your equipment, and your personnel. You may be able to trade off a comprehensive training program in the pharmacy for detailed instructions in the process. It may be better to train (and test) your compounders in the art of geometric trituratio rather than put detailed instructions into each formula.

There is a fine balance between having the compounding instructions so long and detailed that they are ignored and having them so short that they leave out critical steps. A good example is mixing in an electronic mixer and measuring the mixing time can depend not only on the size of the container but also on how the mixture is loaded into the mixing container. It would seem to me that this step should warrant more than the one-line statement I see on most worksheets—“mix ingredients.”

It also is important to recognize and make note of things that may change. For example, packing statistics for powders can vary significantly between excipients, between different lots of the same excipient, or for micronized or nonmicronized powders. The amount of water in an active ingredient or the assay of the active also may significantly change the amount you need in a formula. Would this not be important enough to warrant a note in the instructions to check the Certificate of Analysis for the particular lot of chemical that you are using in the preparation?

When writing a formula worksheet process, it may be a good idea to take note of one of the mistake-proofing ideas from the section Reducing Mistakes by Process Design in the discussion of thinking negatively. Ask yourself, or better your technician or those doing the compounding in the pharmacy, “What could go wrong in making this preparation?” When you have answered this question, you can then review the process to make sure that you have covered that eventuality with clear instructions.

Finally, you may want to specify in-house quality tests that can be performed on the finished preparation. Many pharmacists do this routinely, but few document the results and, as we are all coming to realize, if you don’t document something, you didn’t do it! Simple inspections like color uniformity, absence of particulates in an injection, and fill accuracy can be specified on the worksheet for a simple confirming initial by an inspector. Your pharmacy balance also can be a powerful in-pharmacy quality tool. If you make 100 capsules, you can use it not only to determine the weight variation of the capsules but also to weigh all 100 capsules to make sure, on a gross basis, that you have done things correctly. Making suppositories? Weigh the empty mold and then weigh the filled mold. Does your average suppository weight confirm that you made the preparation correctly? If these simple in-pharmacy quality test are called for in the compounding process, they will be completed and become part of the documented compound preparation database.
STEP 2: PROCESS VERIFICATION

When you have your process completed, you need to make sure that it works properly. The best way to do this is to make a compounded preparation using the process and then have it tested. If you have specified in-pharmacy testing into the process, complete and document these tests first. Then, send your preparation to a third-party contract laboratory for potency testing. There are three possible outcomes:

1. The preparation will be within the +/- 10% specification required.
2. The preparation will be outside the specification range.
3. The preparation will meet specification, but you will not be satisfied with the results.

If outcomes 2 or 3 are realized, you need to go back to the process and examine the steps to determine how to correct or narrow the results. Your contract lab may be able to help with this, as many problems can be detected when testing a preparation.

You also may want to test your process several times with other personnel performing the compounding or with different chemicals. This type of testing measures the robustness of your process or how well it performs to various external effects. A process that does not give acceptable results when small unforeseen changes are made may not perform over time as you would expect. Nevertheless, the key to maintaining a good, in-control process is to do as much as possible to keep lot-to-lot differences at a minimum. Knowing pharmacists and pharmacy technicians, this may be the most difficult part of your process-control task.

The impulse to change something “on the fly” because it looks easier or takes less time is a constant challenge. You will need to impress on all those doing the compounding that they must follow the process exactly each and every time. Small deviations that creep into processes have unknown consequences on the final preparation, so once you have a “verified process” be demanding that it be followed exactly.

This is not to say that if you find a better way to do something that you shouldn’t incorporate it into the process; not doing so would be foolish. However, the change should be evaluated from all points of view, the process modified, documented, and then re-verified to assure that it produces a compound preparation that meets all requirements.

STEP 3: SET UP A SAMPLING PLAN TO MONITOR ONGOING QUALITY

Once you have the process verified you need to make sure that it stays in-control. This is best done by setting up a sampling plan to test a
compounded preparation that was made using the process on a regular basis. This type of sampling can be thought of as an adaption of the skip-lot testing plans that are explained in many quality-control texts. In short, skip-lot testing means that only a fraction of the compounded preparation lots are tested. This mode of preparation testing is efficient in terms of cost, time, and effort. However, skip-lot testing should only be used when it has been demonstrated that the quality of the overall product or preparation is very good. This admonition is very important in that not all of the lots made will be tested. Again, this testing approach places a high requirement on the process verification step discussed above. If you do not have a well-documented and tested process, using a skip-lot testing plan may not represent your overall quality.

Most statistical texts will recommend a random process for selecting how this testing should be performed. However, it is consensus of opinion that a fixed interval test schedule may in fact be a better option, and it is much easier to implement within the pharmacy. The utility of this modified skip-lot approach is that you can specify the frequency of the quality testing depending upon the process. For example, if you are making a T3 triturate, you may want to specify that it is tested every time it is made (100% tested). However, if you are making a preparation that is somewhat less exacting, such as a topical pain gel, you may want to set the interval at every 30 lots (3% tested).

The challenge in a hectic pharmacy atmosphere is how best to keep track of these testing requirements. If you use compounding software, it may be possible to build in an automatic reminder system to notify you that a specific preparation should be tested for potency. It may be a simple matter to identify the pharmacy processes—for instance, let’s say you come up with ten individual processes. You could then assign each compounding log worksheet to a process and whenever it was opened and completed the computer would add a counter to the appropriate process. When the counter reached the specified testing number, the computer would flag the compounder that the current preparation should be sent for testing.

Taking an idea from the Kanban inventory system, a manual system may work just as well as a sophisticated computer system. You would again identify the compounding processes in your pharmacy and assign each formula worksheet to a particular process. For each process, you could have a 1- to 10-numbered pill jar set up on the “testing shelf.” Whenever a preparation is made, the compounder would note the corresponding process and put a bean (or placebo capsule) in the corresponding pill jar. When the jar is filled to the line representing the testing frequency, the next lot is sent for testing, and the jar is emptied and the process resets itself. While this may not be as exact as computer scheduling, it is an easy solution and overall accomplishes the same thing—reminds the pharmacist to send the preparation for testing.

**GETTING STARTED**

An important aspect of the approach outlined in this article is that you can implement these testing procedures one at a time in the pharmacy. It is not an “all-or-nothing” system. Start by picking what activities you do most within the pharmacy or choose the process that has the most risk of having quality problems. You may want to have several processes for common tasks such as capsule making—one for capsules where the active is a major part of the capsule, such as progesterone, and another where the actives are at very low levels, such as Bi-est capsules.

Pick one process to start, review the existing process, and make changes in light of the discussion previously covered. Note the worksheets that are appropriate to that process, and adapt the worksheets to make sure the process is specified on the worksheet along with instructions for completing the Kanban procedure.

Verify the process by sending several samples, maybe compounds made by different technicians, out for testing by a contract laboratory. This may happen over several weeks or months, depending upon your schedule. Once you are satisfied that you have a verified process, begin the Kanban process of skip-lot testing.

If you have a test that falls out of specification, you will need to determine what caused the error. This is critically important since the statistical basis of skip-lot testing assumes that you have a verified process and that the quality is of the highest caliber. An error represents an error in your process that must be investigated, documented, and corrective action taken. Sometimes we learn more from our mistakes than from what we do perfectly, so don’t ignore the out-of-specification results.

Over time, you will begin to accumulate data that can be analyzed to help you improve the operation and overall quality of your pharmacy. Long-term trends and control charts are some of the quality-control tools that you may be able to use to track your “quality.” You may even be able to post some of these in the pharmacy to show your patients that you value supplying a preparation that is exactly what the doctor ordered.

**CONCLUSION**

Undeniably, one of the most important considerations in a compounding pharmacy’s procedures is quality. Developing a comprehensive quality-control potency program must begin with the most basic activities performed at a compounding pharmacy to the most crucial activities. If the basics are not met, the crucial activities of compounding sterile and nonsterile preparations and the quality of the end product are in jeopardy. Basic definitions are provided in this article as well as a discussion on a three-step method on setting up a quality-control potency testing program, to include (1) process design and how to reduce the potential of variations and mistakes in compounded preparations, (2) process verification, and (3) how to set up a sampling plan to monitor ongoing quality. Also included are suggestions on how to get started on the development of a quality-control potency testing program.

**REFERENCES**