A Process Verification Model for Quality Assurance in a Compounding Pharmacy

ABSTRACT
There are virtually thousands of examples of uses of the “process” model of quality assurance in modern industrial applications, so the precedent for this type of quality-assurance and quality-control program is well established and thoroughly accepted. The initiation of a process verification model for quality assurance and control, and the documentation involved in the process, constitute appropriate proof that a compounding pharmacy is developing quality preparations, which in turn can be used to improve a pharmacy’s operation.

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A process verification model for quality assurance and control in a compounding pharmacy is explained and illustrated in this article. The underlying concepts are discussed with respect to current quality-control practices. Perspective is drawn from the United States Food and Drug Administration’s (FDA) parametric release program and recently initiated Process Analysis Technology initiative. Adoption of this process by compounding pharmacies is recommended and an eight-step plan for getting started is presented.

Undoubtedly, one of the most frequent comments heard from compounding pharmacists goes something like this:

I know that I should have a quality program, but I don’t know what to test, and it’s so expensive. Do you have a plan that I can use that will give me a good indication that I am doing a quality job in my pharmacy, and won’t break my budget in testing costs?

I often follow this question with one of my own: “Did you ever wonder how someone can know that all the things that they make are of the highest quality when they cannot test everything that they make?” And then I provide a classic example. Just before World War II, an army general, while inspecting an ammunition plant, asked the plant manager how he knew that a specific bullet was good. “Easy,” said the plant manager, “you shoot it!” “But,” replied the general, “then you don’t have the bullet any longer, and besides, you cannot shoot every bullet to make sure that it is good.” I am sure that there are numerous other examples that illustrate this same point, including the compounding pharmacy, where, for a whole host of reasons, you cannot test every preparation you make. So what is a responsible pharmacist to do? Fortunately, there is an answer to this perplexing problem: You verify that the process used to make the item is correct, and then you periodically check the preparation to make sure that the verified process is still operating as designed.

THE “PROCESS VERIFICATION” MODEL
As a first step in understanding process verification, “process” and “verification” are defined.

Process: In general, a process is a set of interrelated steps that leads to a conclusion. In pharmacy compounding, a process usually is defined by a standard operating procedure (SOP) that specifies the steps, in sufficient detail, that define how a pharmaceutical preparation can be made exactly the same way, producing the same preparation each and every time, by anyone skilled in the art and science of compounding. Several key points are important in this definition:

- The steps must insure that the preparation is the same each time it is made, which implies that all critical steps be spelled out clearly.
- The process assumes that someone skilled in the art and science of compounding will be following the steps. This allows the process SOP to be written in a concise and straightforward manner. A good general rule to follow is that the SOP should be written so that a trained compounder (pharmacist or technician) could make the compound without asking for any further directions. It assumes, however, that the compounder has a basic understanding of compounding. For example, you could
specify “mix using geometric trituration” and not need to define exactly what this means, because someone skilled in compounding knows what it means.

Verification: In general, the objective of verification is to assure that a selected product meets its specified requirements. This includes verifying the design and the ability to consistently produce the design with the resources usually available for the task. Verification demonstrates, through assessment of the product, that the system fulfills its specified requirements. Verification usually involves two steps, initial testing of the product to verify that the process has been designed and executed properly, and then random testing of the product to assure that the process does not fall out of control. It also includes in-process testing to assure that the critical steps are completed properly.

In pharmaceutical compounding, a process is verified by testing the finished compounded preparation to make sure that it meets its intended purpose. For nonsterile compounds, this usually includes testing for potency; for sterile compounds, it includes testing for particulates, sterility, and bacterial endotoxins, in addition to potency. Verification testing also may include qualities such as color, texture, presentation, and elegance. Once the process is verified, a random testing schedule is established to insure that the process stays in control.

With this in mind, it is now possible to look at your pharmacy from a “process” point of view, rather than a “preparation” point of view. You probably have significantly fewer processes in your operation than preparations. For example, you most likely have a process for making creams, which may include preparations such as progesterone creams, testosterone creams, and estrogen creams. The process is undoubtedly the same, even though the active ingredients vary. Using the process verification model, you need to verify only the process in your quality-assurance program.

Another example is capsule making. Here you may have two distinct processes, one that takes the active directly and mixes with the excipient, and another that takes the active from an initial trituration mixture. Most likely, all of the capsules you make fall into one of these two general processes; therefore, verification of these two processes using a representative capsule made from each process is what you need for a valid quality-assurance program.

One additional activity that greatly improves the reliability of the process validation model is in-process testing. This activity involves quality control of your process all along the way to the final product or preparation. Actually, compounders have been employing in-process testing for years; they just do not recognize it as a quality-control activity. The following are three examples:

1. When you weigh out an ingredient for a preparation and record the weight, you are performing an in-process quality check. If the weight is not correct, you stop and re-weigh until it is correct. Sounds a little bit simplistic, but this is a true in-process quality-assurance check.

2. Another common procedure is the addition of a colorant to a powder mixture being blended in a mortar. You visually check to assure a proper mix before proceeding to the next step. If you record this observational check on the worksheet, it is a valid in-process quality-assurance check.

3. When making low-concentration preparations such as triiodothyronine (T3) capsules, an intermediate concentration of the active is usually made (T3 aliquot @ 1:1000). Testing the potency of this aliquot is a recommended in-process test to assure that the final concentration of the T3 in the capsule is correct.

If you are questioning whether this method has any supporting or historical evidence that it is a valid approach to quality assurance, the information in the following paragraphs should ease those concerns. A more detailed explanation of how to get started using this quality-assurance model is provided later in this article.
of most pharmaceutical manufacturers, virtually all manufacturing throughout the world has accepted these principles of quality assurance, quality control, and process improvement.

To illustrate this point, I often ask the question, “Do you think any major oil company makes four million gallons of gasoline, and then asks, is it good?” No, they have verified their process, they keep it in control by in-process monitoring, and then they are confident that what comes out of the process and into those large tanks of gasoline you see along the road is a high-quality product. In fact, when I was working in process control in 1981, we instrumented a new petrochemical plant with more than 150 in-process chemical analyzers that continuously measured the composition of the product throughout the process, the data of which was used to optimize the process for maximum quality at minimum operational expense. This was more than 25 years ago, evidence that this approach has stood the test of time.

I do not suggest that the FDA has not accepted the process verification approach. In fact, in 1985, the FDA approved supplemental new drug applications, for certain large-volume parenteral drug products, that substituted parametric release for routine lot-by-lot end-product sterility testing. As defined by the FDA, parametric release is a sterility release procedure based upon effective control, monitoring, and documentation of a validated sterilization process cycle [emphasis added] in lieu of release based upon end-product sterility testing.

In this process method of release, all the parameters of in-process testing must be met before the lot is released. In summary, these include (see the cited article for a complete description):

- Parenteral drugs are to be terminally heat sterilized.
- The sterilization process cycle has to be validated to achieve a safety factor of $10^6$ log reduction in microbial bioburden.
- All cycle parameters must be defined as critical (time, temperature, pressure) or noncritical (cooling, heating time).
- The closure system must be validated over the product's intended shelf life.
- Bioburden testing must be done on each batch of presterilized drug product, and any identified microorganisms must be shown to be nonresistant to the sterilization cycle.
- Biological indicators are to be used in each sterilizer load to evaluate cycle lethality.
- Documentation is required for everything.

Recently, the FDA undertook a new program to encourage the pharmaceutical industry to upgrade its manufacturing process capability in regard to modern quality-control and in-process testing. This initiative is known within the FDA as Process Analysis Technology (PAT), and a quick search of Google for “FDA PAT” returns more than 600,000 hits.

**CURRENT FDA—PROCESS ANALYSIS TECHNOLOGY INITIATIVE**

The following is excerpted from the FDA's 2004 Guidance to Industry—PAT.

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, today, significant opportunities exist for improving pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control.

Unfortunately, the pharmaceutical industry generally has been hesitant to introduce innovative systems into the manufacturing sector for a number of reasons. One reason often cited is regulatory uncertainty, which may result from the perception that our existing regulatory system is rigid and unfavorable to the introduction of innovative systems. For example, many manufacturing procedures are treated as being frozen and many process changes are managed through regulatory submissions. In addition, other scientific and technical issues have been raised as possible reasons for this hesitancy. Nonetheless, industry’s hesitancy to broadly embrace innovation in pharmaceutical manufacturing is undesirable from a public health
perspective. Efficient pharmaceutical manufacturing is a critical part of an effective U.S. healthcare system. The health of our citizens (and animals in their care) depends on the availability of safe, effective and affordable medicines.

Pharmaceuticals continue to have an increasingly prominent role in healthcare. Therefore, pharmaceutical manufacturing will need to employ innovation, cutting-edge scientific and engineering knowledge, along with the best principles of quality management to respond to the challenges of new discoveries (e.g., novel drugs and nanotechnology) and ways of doing business (e.g., individualized therapy, genetically tailored treatment)....

In order to accomplish these changes within the pharmaceutical industry, the FDA is encouraging the industry to adopt PAT principles into their manufacturing processes. Broadly defined, again by the PAT Guidance document, PAT is considered:

...to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. It is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design. Consequently, the tools and principles described in this guidance should be used for gaining process understanding and can also be used to meet the regulatory requirements for validating and controlling the manufacturing process.

PROCESS VERIFICATION IN THE COMPOUNDING PHARMACY

Given this statement, it would seem only logical that compounding pharmacies adopt the process verification model for their quality-assurance and control-testing programs. In fact, the compounding pharmacy application is ideally suited for this type of program for several reasons, as follows:

- Most pharmacies have a limited number of processes that cover the majority of their compounded preparations. This makes documentation of the process and training of personnel in performing these processes a manageable effort.
- Pharmacy processes are typically more straightforward and simpler than most processes in the pharmaceutical manufacturing industry.
  >> The processes start, in most cases, from United States Pharmacopeia (USP) or National Formulary (NF) materials with accompanying Certificates of Analysis.
  >> Most processes are simple operations such as mixing, blending, filling, and filtering. No chemical transformations are involved (i.e., we are not making the actives).
  >> The scale of operation is small in comparison to industrial operations.
  >> The processes are ideal for multiple in-process checks.
- The skill of the personnel involved is often superior to that in a general manufacturing operation. Pharmacists and pharmacy technicians are trained, tested, and often certified to perform the manipulations required for the processes involved.
- In-process inspections that verify that the process is in control can be easily built into the SOPs of the pharmacy. Many of these tests can be done within the pharmacy without additional expensive equipment. For example:
  >> Printing the weight of the active used in the preparation, and reviewing and signing the tape verifying that it is correct, is a good in-process procedure for all weighed items.
  >> Documenting the weight of final solid dosage forms to confirm that they are within acceptable limits is an excellent in-process quality-control check.
  >> A simple and inexpensive sterility test can be performed on every sterile preparation by streaking an agar plate and incubating for 14 days. Periodic USP Chapter <71> sterility...
testing, performed on a regular schedule, is then a verification that your overall sterility process is in control.

- Final preparation testing is available from a variety of third-party laboratories, which can test the potency and/or sterility and bacterial endotoxin content of the compounded preparation; this is the ultimate verification of the process.

IMPLEMENTATION

Of course, all the theory and planning are for naught if a quality-assurance plan is not implemented in the pharmacy. If you already have an active quality-assurance and quality-control program, review its goals in light of the points just listed. You may be able to make it more effective if you adopt several of the concepts of the process verification model. If you do not have a quality-control plan in place, or you just randomly test your preparations, then the following might work in your operation:

1. Decide that you are going to have a written quality-assurance and quality-control plan using the process verification model as its underlying mode of operation.

2. Determine which of your processes would be a good candidate to start the program:
   a. The preparations that are made most frequently
   b. The highest risk process, i.e., preparations that could do the most harm if they were not made to the highest quality standards
   c. The process that gives you the most trouble

3. Write an SOP for that process.
   a. Make the SOP as general as possible.
   b. Make sure all critical steps are explained clearly.
   c. Consider variables in the process and explain what to do if encountered.
   d. Consider in-process tests that can be documented during the process and define what is acceptable and not acceptable as a result of the test. (For example, if the weight is not within 1% of the target weight of the active, re-weigh the active.)
   e. Document what will be done if an end-preparation test fails (e.g., a laboratory potency test result falls outside the limit of acceptability).

4. By way of an SOP, train your personnel to insure that they understand and follow the SOP exactly when they are making a preparation using the process. (This may be the most difficult step in implementation.)

5. Compound a preparation using the process and SOP.

6. Perform end-product testing to verify that the preparation meets its expected quality.
   a. Where possible, perform final testing in the pharmacy and document the results.
   b. Where not possible to do onsite, send the preparation to a third-party laboratory for tests.

7. Set up a schedule for retesting preparations that are made with the process. This can either be on a time basis (e.g., once every 3 months) or on a batch-made basis (e.g., test every twenty-fifth batch). This testing procedure is called skip-lot testing and has been the subject of several published articles.


Once the initial process is underway, you can go back and tackle the next implementation. You may then consider a testing routine that checks processes on a rotating monthly basis, weighted in favor of your most frequently used process. For example, if you have processes for creams, troches, capsules, and suppositories, but the majority of the time you are making capsules, a rotating testing program on a monthly basis may look like this:

Month 1: Capsules
Month 2: Creams
Month 3: Capsules
Month 4: Troches
Month 5: Capsules
Month 6: Suppositories

CONCLUSION

There are virtually thousands of examples of uses of this “process” model of quality assurance in modern industrial applications, so the precedent for this type of a quality-assurance and quality-control program is well established and thoroughly accepted. The important thing is to implement the quality-control plan and document the results. The process verification data can be used not only as appropriate proof that you are making a preparation with excellent quality, but also to improve your pharmacy’s operation.

REFERENCES


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