Applying Quality by Design Concepts to Pharmacy Compounding

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Abstract

Compounding of medications is an important part of the practice of the pharmacy profession. Because compounded medications do not have U.S. Food and Drug Administration approval, a pharmacist has the responsibility to ensure that compounded medications are of suitable quality, safety, and efficacy. The Federal Government and numerous states have updated their laws and regulations regarding pharmacy compounding as a result of recent quality issues. Compounding pharmacists are expected to follow good preparation prodecures in their compounding practices in much the same way pharmaceutical manufacturers are required to follow Current Good Manufacturing Procedures as detailed in the United States Code of Federal Regulations. Application of Quality by Design concepts to the preparation process for a compounded medication can help in understanding the potential pitfalls and the means to mitigate their impact. The goal is to build quality into the compounding process to ensure that the resultant compounded prescription meets the human or animal patients' requirements.

Pharmacy compounding is the art and science of preparing personalized medications for human and animal patients. Compounded medications can be prepared by combining or altering individual ingredients which are mixed together in the exact strength and in the dosage form required by the patient. Commercially available dosage forms may also be modified to better fit the dosing needs of an individual. These operations may be performed by a licensed pharmacist in response to a prescription written by a properly licensed prescriber based on the medical needs of an individual human or animal patient. Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling.

Compounding of medicines can be traced back thousands of years with compounding pharmacies existing in some form. The Middle East purportedly had the first pharmacy in Baghdad in the first century A.D.[1,2] Compounding pharmacies have been in America since the early 1800s and eventually gave way to the modern pharmaceutical industry. Pharmacy owners of the past like Merck and Dohme from Merck Sharp and Dohme; and Eli Lilly and others went on to

be manufacturers making many of the commercial medications we have today.[3]

With the advent of mass drug manufacturing in the 1950s and 1960s, compounding of medicaments rapidly declined. The pharmacist's role as a preparer of medications evolved to primarily that of a dispenser of manufactured dosage forms.

Current Status

Today, there is an ongoing demand for compounded prescription medications because manufacturers cannot fulfill the needs of all individual patients. A complicating factor that has led to the numerous recent quality issues[4] that plague large-scale compounding pharmacies is the shortage of many necessary drug products, in particular, the generic injectable preparations. Also, with the concept of personalized medicines gaining popularity, many physicians are seeing the benefit of custom-compounded preparations and adding them to their prescription protocols.

The issue of pharmaceutical compounding versus pharmaceutical manufacturing is a complex one that has prompted legislators at the state and federal levels to take action. Over the years, pharmacy compounding, as originally practiced and defined by state pharmacy regulations, has changed significantly. Historically, legally authorized prescribers wrote a prescription for a patient with special medical needs, and the pharmacist prepared a suitable dosage form to meet that individual's requirements. In today's environment, this may no longer be an accurate description of pharmacy compounding. In some cases, it has evolved into a more complex large-scale, manufacturing-type operation. This has prompted individual States and the Federal Government to redefine pharmacy compounding and to update their laws and regulations for the practice of pharmacy.

Patients must rely on the expertise of the individual pharmacist who prepares their compounded medicament for its quality, safety, and effectiveness. It is the pharmacist's responsibility to ensure that all state and federal requirements are met in filling a legal prescription for a compounded medicament individualized for a specific human or animal patient.

Many drugs intended for human use are frequently compounded for a veterinary species (e.g., dog, cat, horse). In these instances, the veterinarian must take into consideration the differences in anatomy and physiology which can impact drug pharmacokinetics and, ultimately, its efficacy and safety.

Additionally, the ingredients added to a drug formulation are intended to provide an optimal chemical and physical environment to ensure the stability of the drug substance and, in some instances,

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aid in its safety and efficacy. A compounded drug preparation may be adversely impacted by the addition of other inactive ingredients which may alter the chemical potency or physical stability of the drug substance.

State's Regulatory Approach

The States are the primary regulator of pharmacies, including community drugstores, large chains, specialty pharmacies, hospitals, etc. The practice of pharmacy, including the licensing of individual pharmacist and pharmacies, is regulated by a State Board of Pharmacy which has primary responsibility for day-to-day oversight. These state rules are updated periodically by the individual State Boards of Pharmacy, which operate in the 50 states. Some of these practice requirements date as far back as 50 years when large drug manufacturers played a much smaller role as the source of medications. These laws and regulations address pharmacy standards and requirements, including items such as required licenses for each facility and for the credentialed pharmacists and other employees who work there. This includes the explicit authority granted to compound or mix pharmaceutical ingredients into a patient-ready preparation.

Some States' Board of Pharmacy Regulations are fairly vague on the topic of compounding, only stating in broad terms that it is a pharmacist's responsibility. Other states have more detailed compounding requirements. Since 2011, at least 16 states enacted laws affecting the practices of compounding pharmacies.[5]

Federal Government

As a result of the legal and regulatory uncertainty and the many negative recent events involving pharmacy compounding[4] and the increasing number of establishments with retail pharmacy licenses engaged in manufacturing and distributing unapproved drugs in a manner that is clearly outside the bounds of traditional pharmacy practice, which violate the United States Food, Drug & Cosmetic Act (FD&C Act),[6] the U.S. Congress in 2013 passed the Drug Quality and Security Act (DQSA).[7,8] This legislation established a clear boundary between traditional pharmacy compounding and compounding manufacturers. It defines a national, uniform set of rules for compounding manufacturers while preserving the states' primary role in traditional pharmacy regulation. It clarifies the U.S. Food and Drug Administration's (FDA's) authority over the compounding of human drugs while requiring the Agency to engage and coordinate with States to ensure the safety of compounded drugs.

The legislation draws a distinction between traditional compounding pharmacies and those making large volumes of compounded drugs without individual prescriptions. Traditional compounding pharmacies will continue to be regulated by State Boards of Pharmacy. Compounding pharmacies that operate outside the scope of traditional pharmacy practice need to register as an Outsourcing Facility, which will be subject to FDA oversight in much the same way as pharmaceutical manufacturers. Patients and providers would have the ability to purchase preparations from Outsourcing Facilities that comply with FDA quality standards. This legislation also bans compounding pharmacies from making a copy of an approved and marketed drug product. The provisions of the DQSA do not apply to veterinary drugs.

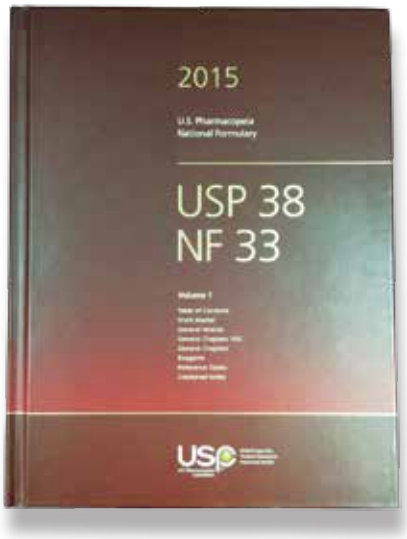
United States Pharmacopeial Convention

The United States Pharmacopeial Convention publishes an official compendium, the

United States Pharmacopeia (USP) in a combined volume with the *National Formulary (NF)* as the *USP–NF*. If a drug ingredient or drug product has an applicable *USP* quality standard, it must conform in order to use the designation "*USP*" or "*NF*." Drugs subject to *USP* standards include both animal and human drugs. *USP–NF* standards also have a role in U.S. federal law; a drug or drug ingredient with a name recognized in *USP–NF* is deemed adulterated if it does not satisfy compendia standards for strength, quality or purity.[9]

There are currently five compounding General Chapters in the *USP–NF*.

- Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations[10] provides guidance on applying good compounding practices in the preparation of nonsterile compounded formulations for dispensing and/or administration to humans or animals. It includes simple, moderate, and complex categories of compounding; definitions of terms (e.g., beyond-use date, hazardous drug, stability); and criteria for compounding of drug preparations (e.g., suitable compounding environment, use of appropriate equipment).
- Chapter <797> Pharmaceutical Compounding—Sterile Preparations[11] provides procedures and requirements for compounding sterile preparations.
- Chapter <1160> Pharmaceutical Calculations in Prescription Compounding[12] provides guidance and assistance to pharmacists in performing the necessary calculations when preparing or compounding any pharmaceutical drug.
- Chapter <1163> Quality Assurance in Pharmaceutical Compounding[13] describes a quality-assurance program as a system of steps and actions that must be taken to ensure the maintenance of proper standards in compounded preparations.
- Chapter <1176> Prescription Balances and Volumetric Apparatus[14] provides information about acceptable balances and volumetric apparatus (e.g., burets, pipets, cylinders, conical graduates, medicine droppers) used to weigh or measure medicinal and other substances required in prescriptions or in pharmaceutical compounding.



An additional General Chapter that should be considered when preparing compounded prescriptions is Chapter <1191> Stability Considerations in Dispensing Practice.[15] General Chapter topics in development that also have implications for Compounding Pharmacists include Hazardous Drugs—Handling in Healthcare Settings and Compounding for Investigational Studies.[16]

General Chapters <795> and <797> are considered mandatory compendia standards, whereas the other General Chapters <1160>, <1163>, <1176>, and <1191> are considered recommendations and do not represent official standards, and thus, limit FDA's enforcement authority in situations which may involve the preparation of potentially adulterated compounded drugs.[9]

U.S. Food and Drug Administration Regulations and Guidance

The Current Good Manufacturing Practices (CGMP) that the FDA uses to regulate the manufacturing practices for the preparation of human and animal drugs are found in the United States Code of Federal Regulations, 21 CFR 210 & 211.[17,18] These regulations cover all aspects of the preparation of drug products from raw materials to end-product testing for release and are inclusive of building and facilities (e.g., design, construction, lighting, maintenance, sanitation), personnel qualifications, receipt and testing of materials, manufacturing procedures, and packaging and distribution of the finished commercial dosage form. Pharmaceutical manufacturers are expected to comply with these rules and regulations and are required to

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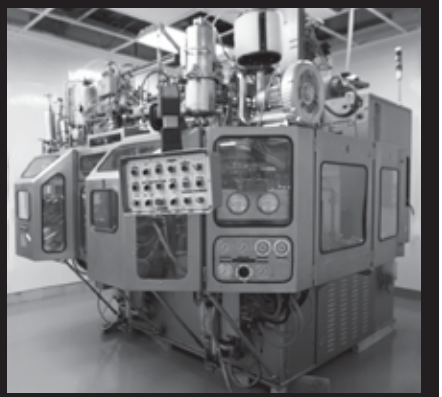

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demonstrate a product's safety, efficacy, and quality throughout the product's shelf life before the FDA will grant them the ability to sell the product in interstate commerce. The regulations that govern the content of a New Drug Application (NDA), including the comprehensive product quality information, and the process for approval are found in 21 CFR 314.[19] For biological products, a Biological License Application (BLA) is regulated under 21 CFR Chapter I, Subchapter F – Biologics - Parts 600-68 – Biologics,[20] while New Animal Drug Applications (NADAs) are controlled under 21 CFR Chapter 1 Subchapter E- Animal Drugs, Feeds, and Related Products, Part 514.[21]

FDA's role in pharmacy compounding has historically been constrained due to the State's having primary responsibility. However, due to a concern that compounding was being used to circumvent the new drug approval process, Compliance Policy Guide 460.200[22] was issued. Unfortunately, due to a number of court challenges,[23-25] this policy guide had limited enforcement impact.

As a consequence of the DQSA legislation which revised Section 503A of the FD&C Act,[7,8] the FDA has issued guidance documents (Table 1) intended to clarify its role and policies with regard to pharmacy compounding for human and animal drugs including small molecules and biological preparations.

Key aspects of these guidance documents are that the quality of the preparation is paramount to ensuring its safety and efficacy. The guidance documents cover:

- Who is regulated by Section 503A of the FD&C Act?
- Who needs to register as an Outsourcing Facility under Section 503B of the FD&C Act?
- Clarification on compounding for office use and patient-specific preparations.
- Provides guidance on CGMP for facilities involved in the manufacture of compounded preparations.
- Product reporting by Outsourcing Facilities and which information must be submitted under Section 503B of the FD&C Act.

TABLE 1. U.S. Food and Drug Administration Guidance Documents on Pharmacy Compounding.

Guidance for Industry: Interim Product Reporting for Human Drug Compounding Outsourcing Facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act. U.S. Department of Health & Human Services. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. December 2013. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377050.pdf.
Draft Guidance for Industry, Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Office of Regulatory Affairs (ORA), June 2014 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400470.pdf
Guidance for Industry: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), July 2014 www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm377052.pdf
Draft Guidance for Industry: Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act, U.S. Department of Health and Human Services , Food and Drug Administration , Center for Drug Evaluation and Research (CDER), July 2014 www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm403496.pdf
Guidance for Industry: Registration of Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), November 2014 www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm377051.pdf
Draft Guidance for Industry: For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act, U.S. Department of Health and Human Services , Food and Drug Administration, Center for Drug Evaluation and Research (CDER), February 2015 www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434171.pdf
Draft Guidance for Industry: Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Office of Compliance/OUDLC, February 2015 www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434174.pdf
Draft Guidance for Industry Compounding Animal Drugs from Bulk Drug Substances, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine (CVM), May 2015 www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM446862.pdf
Animals Drugs, Feeds and Related Products, Part 530 Extralabel Drug Use in Animals, Subchapter E--Title 21—Food and Drugs, Chapter I—Food and Drug Administration, Department of Health and Human Services www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=530
Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products between the State of [insert State] and the U.S. Food and Drug Administration www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounPhar/UCM434233.pdf
Guidance for FDA Staff and Industry Compliance Policy Guides Manual Sec. 608.400 - Compounding of Drugs for Use in Animals (Withdrawn May 2015) www.fda.gov/OHRMS/DOCKETS/98fr/03d-0290-gdl0001.pdf
Guidance for Industry: Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) , February 2015 www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434188.pdf
Draft Guidance for Industry: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) And Center for Biologics Evaluation and Research (CBER) , February 2015 www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434176.pdf

- Adverse event reporting requirements for Outsourcing Facilities.
- The conditions under which repackaging of drug products is permitted.
- What is permitted regarding the mixing, diluting, and repackaging of biological products.

These FDA guidance documents further clarify the conditions under which a compounded prescription must be prepared in order to be exempt from relevant provisions of federal law. Specifically, the drug preparation must:

- Be made for an individual, identified patient based on a valid prescription by a practitioner.
- Be made by a licensed pharmacist in a state or federal licensed facility or by a licensed individual physician.
- Be compounded in compliance with *USP–NF* standards using drug substance and other ingredients in compliance with an established compendia monograph, if available, or other FDA manufacturing requirements.
- Be accompanied by valid certificates of analysis.
- Not be a compounded version of a drug that has been withdrawn from the market due to reasons of safety or efficacy.
- Not be a preparation identified by the FDA as being unsuitable for compounding.
- Not be an exact copy of a commercially available drug product.

Failure to meet these standards will subject the compounder and its preparations to regulatory enforcement by the FDA and federal authorities.

Outsourcing Facilities will be inspected by FDA regulators similarly to conventional pharmaceutical manufacturers and must comply with current CGMP.[17,18] Outsourcing Facilities must register with the FDA.[26] They must indicate if they compound from bulk drug substances and, if so, whether compounding involves sterile-drug preparations. Additionally, they must indicate whether they intend to compound, within the next calendar year, a drug that appears on the FDA's drug-shortage list. In addition, companies need to provide information about the location and address of each facility, as well as a unique facility identifier.

FDA regulates compounding of veterinary drugs through the application of the Extra-Label Drug Use (ELU) rules recited in 21 CFR 530.13[27] and the Animal Medicinal Drug Use Clarification Act (AMDUCA)[28] from FDA-approved animal or human drug products when a veterinarian believes there is no approved animal or human drug product available in the relevant dosage form and concentration to appropriately treat the diagnosed condition. Compounding from human drugs for use in food animals is not allowed if an approved animal drug can be utilized.

Although the FDA considers it a violation of the FD&C Act, it acknowledges the need for compounding from bulk active or raw ingredients within certain areas of veterinary practice. The recently issued Draft Guidance on Animal Drug Compounding from Bulk Drug Substances[29] outlines circumstances when animal drugs compounded from bulk-drug substances may be an appropriate treatment option.

In cases where no approved drug or combination of approved drugs can adequately address a specific patient's need, veterinarians and pharmacists must carefully assess whether the use of an unapproved substance in a compounded veterinary drug is consistent with state and federal law and FDA policy.

Quality by Design (QbD) for product development and manufacture as a concept states that quality can be planned, and that most quality problems relate to the way in which quality is planned.

Quality by Design Paradigm

While pharmacies may engage in large-scale compounding of drugs for commercial distribution if they comply with the new provisions of the DQSA, essentially the same operations performed by a pharmaceutical company are considered manufacturing. The goal, regardless of the descriptive label or who is doing the compounding or manufacturing, should be to provide the patient, human or animal, with consistent assurance of the production of safe, efficacious, and affordable medications.

Quality by Design (QbD) for product development and manufacture as a concept states that quality can be planned, and that most quality problems relate to the way in which quality is planned.[30] The principles of QbD have been used to advance product and process quality in a number of industries. Recently, they have been adopted by the FDA as part of their 21st Century Initiative[31,32] as a vehicle for the transformation of how drugs are developed and manufactured.

The Guidance for Industry, PAT – A Framework for Innovative Pharmaceutical Development, Manufacture, and Quality Assurance,[33] introduced the concept of building quality into the preparation of a drug product through the use of Process Analytical Technology (PAT) in place of end-product testing as a means to ensure it meets its specifications.

As already discussed, compounded drugs historically have not been evaluated by the FDA approval process for consistency of manufacturing. Table 2 details some of the differences between a compounded preparation and a drug product prepared by a traditional pharmaceutical manufacturer required to comply with the Federal Laws and FDA Regulations and Guidance.

With the ongoing changes in the pharmaceutical industry to modernize the drug development and manufacturing paradigm, there clearly should be a concurrent initiative among compounding pharmacists to similarly enhance the practice of pharmacy compounding. The number of recent issues[4,5] within compounding pharmacies highlights the need for enhanced technical and regulatory training of pharmacists involved in compounding activities.

Unfortunately, over the past several decades, the training of pharmacists has

TABLE 2. Historical Comparison of U.S. Food and Drug Administration-approved versus Compounded Drug Products.

CHARACTERISTIC	RESULT	NEW OR GENERIC HUMAN OR ANIMAL DRUG PREPARATION	COMPOUNDED DRUG PRODUCT
Tested in animal species in laboratory and clinical trials	Drug's safety and efficacy is scientifically demonstrated	Yes	No
FDA approval	Manufacturer's ability to prepare product and usage claims are supported with scientific evidence that ensures a safe and effective product	Yes	No
Manufacturing facilities inspected and approved by FDA	Ensures manufacturers compliance with Current Good Manufacturing Practices	Yes	No
Manufactured according to approved regulatory documentation, e.g., NDA, ANDA, BLA, NADA, or ANADA	Ensures each batch is prepared according to a defined formula and process ensuring consistency quality	Yes	No
Analytical testing of drug product prior to release for identity, strength and purity	Ensures each batch meets predefined quality specifications	Yes	No
Ongoing stability testing of drug product	Ensures product meets quality throughout labeled shelf life (Beyond-use Date)	Yes	Unknown
Prescription drug advertising and promotional material submitted to and approved by FDA	Ensures promotional materials to consumers about product use and limitations provides accurate information	Yes	No
Adverse events or lack of efficacy reporting	Unanticipated/negative post approval use experiences can be provided to FDA via various mechanisms	Yes	Yes

ANADA = approved new animal drug application; ANDA = approved new drug application; BLA = biologic license application; FDA = U.S. Food and Drug Administration; NADA = New Animal Drug Application; NDA = New Drug Application

...these actions alone cannot be a substitute for a fundamental understanding of pharmaceutical-quality principles. If this understanding is absent, then mere regulation of compounding will not be successful in achieving the intended outcome.

shifted away from the physical, chemical, and biological sciences needed to understand the formulation and manufacturing of quality products. This is likely due to the growth of the pharmaceutical industry and the growing emphasis on cheaper medicines and more affordable health care. It has required the pharmacist to change his/her role in the health paradigm from a preparer-dispenser to a dispenser-advice giver.

To compensate for this paradigm shift and help enhance the compounding pharmacist's knowledge base, the Federal Government, the FDA, and the States, based on experiences gained from years of dealing with the pharmaceutical manufacturing industry, have attempted to use legislative and regulatory requirements to bring structure and organization to this traditional part of the practice of pharmacy. Additionally, the *USP* has provided quality standards for the preparation of compounded dosage forms. However, these actions alone cannot be a substitute for a fundamental understanding of pharmaceutical-quality principles. If this understanding is absent, then mere regulation of compounding will not be successful in achieving the intended outcome.

There is clearly a need to build quality into compounded drug preparations. In the manufacture of almost all commercial products including foods, quality is built in as part of the manufacturing process. Very few products are release tested prior to distribution to ensure that they meet their design and end-product specifications. If done properly, this same concept can be applied effectively to pharmacy compounding.

The International Committee on Harmonization (ICH) with the cooperation and input of the pharmaceutical industry and global health authorities has issued a series of guidance documents (Table 3) which describe how the concepts of QbD can be applied to the life cycle of a drug product. The concepts outlined in these documents can be readily applied to the development and manufacture of compounded medicaments.

The quality of compounded preparations can be built (designed) into a preparation through a step-wise process which involves follow-

TABLE 3. International Conference on Harmonization-Harmonized Tripartite Quality Guideline Documents.

ICH Q8 (R2) – Pharmaceutical Development
Current Step 4 version dated August 2009
www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

ICH Q9 – Quality Risk Management
Current Step 4 version dated 9 November 2005
www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

ICH Q10 – Pharmaceutical Quality System
Current Step 4 version dated 4 June 2008
www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

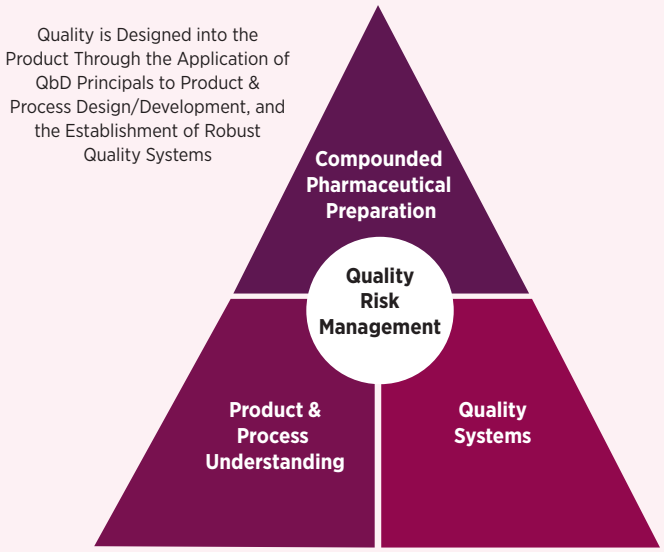
ICH Q11 – Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)
www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.p

Pharmaceutical Quality Training Program for Q8/Q9/Q10
www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10.html

Quality Implementation Working Group on Q8, Q9 and Q10: Questions & Answers (R4)
Current version dated November 11, 2010
www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/Q-IWG_Q_A_R4_Step4_Nov.2010.pdf

ICH Quality Implementation Working Group Points to Consider (R2), ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation
Document date: 6 December 2011
www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtCR2_6dec2011.pdf

FIGURE 1. Pharmacy compounding and Quality by Design.



Adapted from ISPE Washington, DC Conference, June 2007.

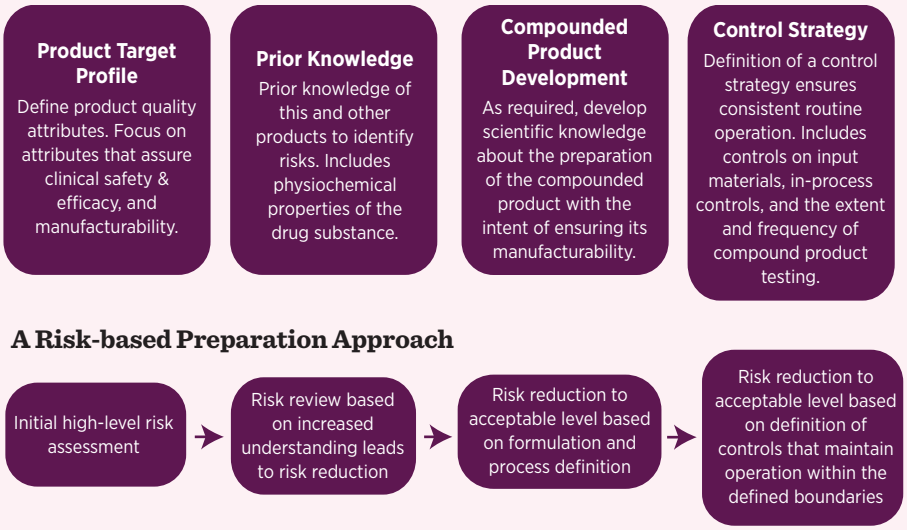
ing good preparation procedures along with product and process understanding, risk identification, evaluation, and minimization, and the implementation of Quality Management Systems (QMS) for documentation, facilities, and personnel (Figure 1).

In applying QbD, a series of steps or stages can be outlined (Figure 2) to achieve the required safety, efficacy, manufacturability, and stability.

- Define the Compounded Product Target Profile. Start with the prescription prepared by the physician or veterinarian which indicates the dose and route of administration, focusing on the delivery of the required quality attributes that assure clinical safety and efficacy.
- Review prior scientific knowledge including the available literature and prior compounding experiences of similar dosage forms.
- Evaluate the physicochemical properties of the drug substance and potential additives which can impact the compounded dosage form.
- Conduct a risk evaluation and assessment to identify, understand, and minimize potential risks associated with the compounded preparation that may impact manufacturability, safety, or efficacy.
- As needed, conduct studies to facilitate and understand the compounded preparation's design and preparation process.
- Develop a Control Strategy to ensure that a compounded preparation with the required quality attributes will be consistently produced. This Control Strategy is derived from the product and process understanding and the risk assessment, and ensures preparation process performance and preparation quality. The control strategy should also include the applicable level of CGMP control and *USP–NF* requirements or recommendations.

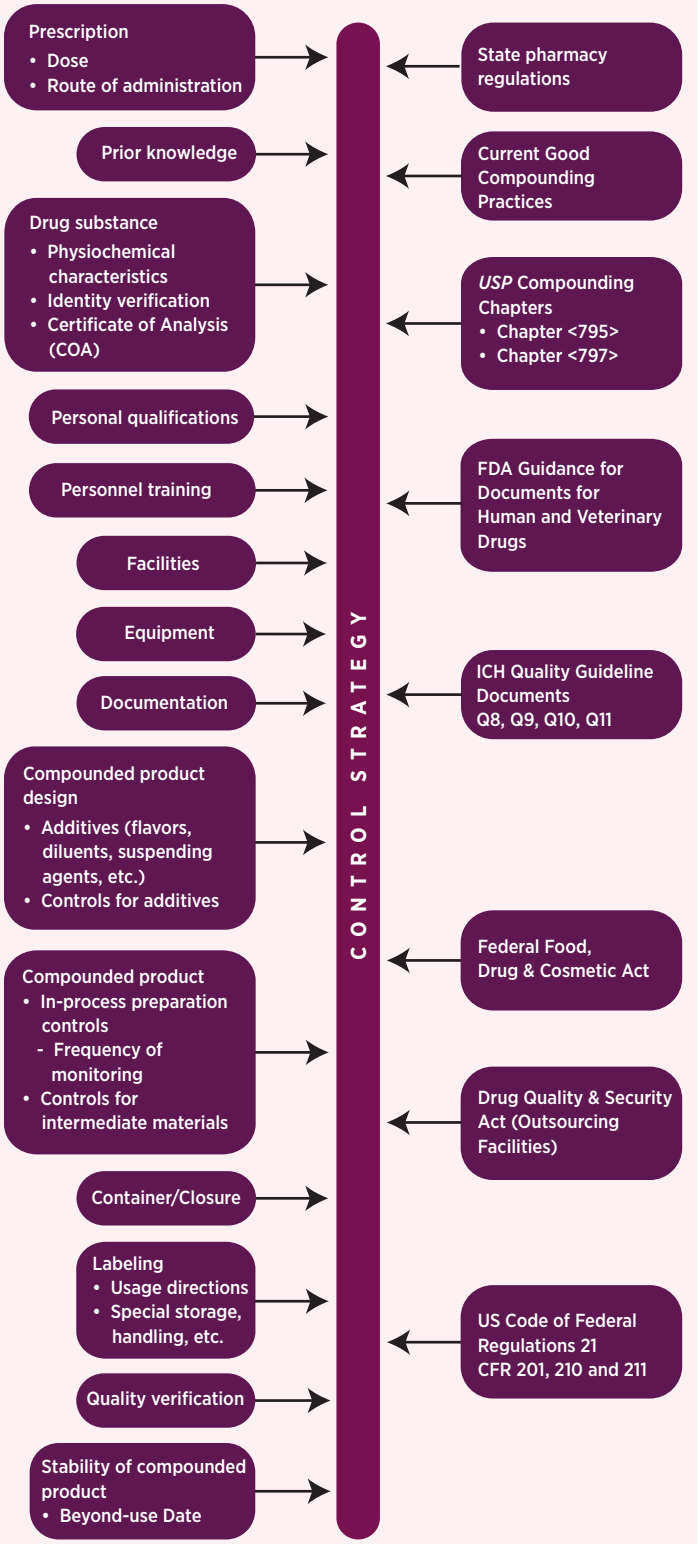
It should be noted that a Control Strategy is not just a concept, nor is it a specification, nor is it optional. There may be more than one approach for a Control Strategy for a product, but, there must be one overall Control Strategy for a given product. A Control Strategy should follow a sequential step-wise process to be effective. A Control Strategy (Figure 4) may involve site-specific aspects

FIGURE 2. A Quality by Design framework for pharmaceutical compounding.



Adapted from ISPE-IQWP QbD Workshop, October 2010.

FIGURE 3. Control strategy considerations for compounded pharmaceutical preparations.



such as facilities or equipment operating conditions, parameters related to the drug substance, drug product or its input or intermediate materials, in-process preparations controls, compounded preparation specification, the frequency of monitoring of the controls, and the container/closure system.

The development of an overall QMS (Figure 3) can aid in organizing and optimizing control systems for monitoring the preparation process performance and product quality, implementing systems for corrective and preventive actions (tracing the root cause of incidents or non-conformities and preventing them from recurring, change management (determining the risk and impact of changes on product quality, safety, and/or efficacy), identifying improvement opportunities, and evaluating audit and product complaints.

Depending on the scope of activities being performed at the compounding pharmacy, the level of QMS can change. Defining the appropriate level of "fit" for QMS control, will be dependent on the complexity of the compounded preparation and its scale of preparation.

Pharmacy Compounding Resources

The compounding pharmacist has numerous state and national associations and accreditation boards that can be drawn on as informational resources on technical and regulatory topics. These include, for example:

- American Pharmacists Association (www.pharmacist.com/)
- International Academy of Compounding Pharmacists (www.iacprx.org/)
- National Alliance of State Pharmacy Associations (http://naspa.us/)
- National Association of the Board of Pharmacy (www.nabp.net/)
- Professional Compounding Centers of America (www.pccarx.com/)

In addition, there are journals and newsletters such as the *International Journal of Pharmacy Compounding* (www.ijpc.com/) and CompoundingToday.com (https://compoundingtoday.com/) dedicated to providing current insights on topics of interest and importance for pharmaceutical compounding.

To further enhance those involved in pharmacy compounding, some of the nation's pharmacy organizations have joined together to create the Pharmacy Compounding Accreditation Board (PCAB; www.pcab.org/). This is a voluntary quality accreditation designation for the pharmaceutical compounding industry. It assesses the nonsterile and sterile pharmacy compounding process as defined by a specific set of standards that concentrate on the quality and consistency of medications produced. It provides a system of standards by which each compounding pharmacy can test its quality processes. It is a mechanism to allow compounding pharmacists to let the public know that they are producing a high-quality compounded medication. PCAB accreditation gives patients, prescribers, and payers a way to select a pharmacy that meets or exceeds quality standards including those published by the *USP*.

There are also organizations, such as R. J. Hedges & Associates (www.rjhedges.com/)[3,4] which can provide ready-made policies and procedures that meet the standards of the *USP*, PCAB, and the

FIGURE 4. An Integrated Approach to Quality Risk Management and Science.

FDA, allowing compounding pharmacies to ensure that they are in compliance with current state and federal requirements.

Summary and Conclusions

Compounding of medications is an important part of the practice of pharmacy. Because compounded medications do not have FDA approval, their quality, safety, and effectiveness cannot be completely verified; therefore, a pharmacist has the responsibility to ensure that compounded medications are of suitable quality, safety, and efficacy. As a consequence of the many recent quality issues with compounded pharmaceutical preparation, the Federal Government and numerous states have updated their laws and regulations regarding the practice of pharmacy and, in particular, pharmacy compounding. Pharmacists are expected to follow good preparation procedures in their compounding practices in much the same way pharmaceutical manufacturers are required to follow CGMP as detailed in the United States Code of Federal Regulations.

Application of the principles of QbD to the preparation of compounded pharmaceutical preparations, including the understanding of the associated risks for every step in the compounding process, and the implementation of a Control Strategy and a QMS can help ensure consistent preparation quality.

There are a number of resources available for the compounding pharmacist to use to ensure that sound practices involving the preparation and its compounding process, facilities, equipment, and personnel are followed. Together, these associations and organizations, along with the available information and guidance from the State Boards of Pharmacy, the *USP*, and the FDA, can assist and should champion the implementation of a QMS for a pharmacy compounding operation.

Whether small or large scale, labeled either compounding or manufacturing, it is about building quality into the preparation process and understanding the pitfalls and taking the necessary actions to ensure that the resultant prescription meets the patient's needs regardless of whether the patients are human or animal.

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References

The references can be found online at www.ijpc.com/webcontent.

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