Washington State Department of Health

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Regulation of Drug Compounding – An Overview

INFORMATION FOR THE PHARMACY QUALITY ASSURANCE COMMISSION

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This document aims to provide an overview of the Pharmacy Quality Assurance Commission's (PQAC) compounding regulatory framework since the passage of House Bill 1800 (HB 1800). This document is broken into three sections:

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Executive Summary

- USP has a number of official chapters that establish standards for compounding. Two of these chapters are considered by USP to be compendially required (USP 795 and USP 797).
- USP has a chapter establishing standards for the handling of hazardous drugs that became official on December 1, 2019 (USP 800). Although official, USP 800 is considered informational only by USP.
- USP also has a chapter establishing standards for radiopharmaceuticals that is published but will not be official until December 1, 2020 (USP 825). When official, USP 825 will be considered informational only by USP.
- In 2013, the legislature passed HB 1800 that required PQAC licensees to comply with the minimum standards of the official USP as it applies to sterile and nonsterile products (RCW 18.64.270(2)). The legislature did not identify which chapters of USP apply to sterile and nonsterile products, nor did the legislature say only official compendially required USP chapters could be enforceable in Washington.
- PQAC has required compliance with USP 795 and USP 797. As part of its rules rewrite project PQAC adopted a rule identifying USP 795, USP 797, USP 800, and USP 825 as comprising the minimum standards for drug compounding (WAC 246-945-100). PQAC aims to provide licensees clarity around its expectations with the new compounding rule.

United States Pharmacopeia (USP)

Background

The USP is a nonprofit organization focused on advancing public health. USP's mission is to "improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods." USP is not a governmental entity but "works closely with government agencies, ministries, and regulatory authorities around the world to help provide standards of identity, strength, quality, and purity that can help safeguard the global supply of medicines, dietary supplements, and food ingredients."

USP publishes the official text of the USP and National Formulary (NF). According to USP "all text in the [USP] or [NF] that has reached its official date is 'official text'" of the USP. "Although all text of the USP–NF that has reached its official date is 'official text,' not all official text states requirements with which compendial users must comply." Consequently, some of the official USP-NF text is considered compendially required and some of the official text is considered informational only. A General Chapter numbered below 1000 (or above 2000 for dietary supplements) becomes compendially required when it is: (i) referenced in a monograph, (ii) referenced in another applicable General Chapter numbered below 1000 (or above 2000, for dietary supplements), or (iii) referenced in General Notices.

While the USP does distinguish between official text that is compendially required and official text that is informational only, the USP also reiterates that it "has no role in enforcement" and the United States Food and Drug Administration (FDA) or other governmental authority e.g. PQAC, could require regulated persons or organizations to comply with any chapter of the USP-NF as long as the requirement is expressly addressed in law or rule.

USP and Chapter Development

USP is governed by three bodies: the USP Convention membership, the Board of Trustees, and the Council of Experts and its Expert Committees. Two of the Expert Committees recommended by the Council of Experts are the "Compounding" and "Chemical Medicines Monographs 4" Expert Committees.

The "Compounding" Expert Committee's work plan includes the development and revision of standards applicable to compounding and handling of sterile and nonsterile drugs, including hazardous drugs. This includes development and revisions to USP 795, USP 797, and USP 800.

The "Chemical Medicines Monographs 4" Expert Committee's work plan targets "[p]sychiatric, psychoactive, neuromuscular, aerosol, and imaging drug substance and drug product monographs intended for human use. The Expert Committee is also comprised of the <825> Radiopharmaceutical Compounding Expert Panel who developed USP 825.

PQAC Specific USP General Chapter Summaries and Current Status

USP General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations (USP 795) is the USP General Chapter that provides "standards for compounding quality nonsterile preparations." The current USP 795 was made official on January 1, 2014 and was made compendially required by a General Notice. On July 1, 2019, USP published a revised version of USP 795. The revised version of USP 795 is currently under appeal and is not official. The latest update from USP was issued on May 26, 2020, which stated USP intended to do additional

stakeholder work to address concerns raised in the appeals related to beyond-use-date (BUD) provisions i.e. expiration dates of compounded medications.

USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations (USP 797) is the USP General Chapter that provides standards for the preparation of "compounded sterile medications to help ensure patient benefit and reduce risks such as contamination, infection or incorrect dosing." The current USP 797 was made official on May 1, 2008, and was made compendially required by a General Notice. On July 1, 2019, USP published a revised version of USP 797. The revised version of USP 797 is currently under appeal and is not official. The latest update from USP was issued on May 26, 2020, which stated USP intended to do additional stakeholder work to address concerns raised in the appeals related to beyond-use-date (BUD) provisions i.e. expiration dates of compounded medications.

USP General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings (USP 800) describes standards applicable to "healthcare personnel who receive, prepare, administer, transport or otherwise come in contact with hazardous drugs and all the environments in which they are handled." USP 800 was originally published by USP on February 1, 2016, but did not become an official General Chapter of the USP until December 1, 2019. USP 800 is considered by USP to be informational only and not compendially applicable until the resolution of the pending appeals related to USP 795 and USP 797. However, USP does "encourage[] utilization of [USP 800] in the interest of advancing public health."

USP General Chapter <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging (USP 825) provides "uniform minimum standards for the preparation, compounding, dispensing, and repackaging of sterile and non-sterile radiopharmaceuticals for humans and animals that occur as part of state-licensed activities." USP 825 was originally published on June 1, 2019, but will not become an official General Chapter of the USP until December 1, 2020. USP 825 will be considered informational only and not compendially applicable, but USP does "encourage early adoption and implementation of [USP 825] to help ensure a safe environment and protection of healthcare practitioners and others when handling radiopharmaceuticals."

To summarize:

- The following USP General Chapters are official **and** compendially required:
  - USP 795 (version made official on January 1, 2014), and
  - USP 797 (version made official on May 1, 2008).
- The following USP General Chapter is official **and** informational only (not compendially required):
  - USP 800 (version made official on December 1, 2019).
- The following USP General Chapter *will become* official **and** informational only (not compendially required):
  - USP 825 (version will be become official on December 1,2020).
- The following USP General Chapters are published but are **not** official:
  - Revised USP 795 (published on July 1, 2019), and
  - Revised USP 797 (published on July 1, 2019).

PQAC - Compounding Regulation and USP Chapters

While PQAC has regulated compounding since its existence, this section will focus on compounding regulation since the passage of HB 1800 that was passed by the legislature in 2013.

HB 1800

As originally drafted, the purpose of HB 1800 was to require PQAC (Board of Pharmacy at the time) to "adopt rules to authorize the compounding of ophthalmic medications for use by a physician for nonspecific patients." The proponent of the bill (Washington Academy of Eye Physicians and Surgeons) stated the bill was required due to PQAC citing pharmacies who were providing nonpatient specific compounded medications to providers without a prescription or a manufacturer license (*see* oral committee testimony at 1:26:45). The Department of Health and Washington State Pharmacy Association had concerns about the bill, but agreed to either defer to PQAC on rulemaking or work with the proponent of the bill (*see* oral committee testimony at 1:30:25).

As HB 1800 made its way through the legislative process an amendment was offered by Senator Parlette on the Senate floor which was adopted. The amended bill ultimately passed through the legislative process. Significantly, the amendment that was adopted included the requirement that compounded products meet the minimum standards of the "official USP as it applies to nonsterile products and sterile administered products." None of the legislative history of the bill, including the Senate floor debate recordings, give much indication of the legislative intent behind the inclusion of USP standards.

PQAC did not adopt any new compounding rules in response to HB 1800 until the most current rules rewrite project. Although PQAC did engage in substantial rulemaking activity in response to HB 1800, no final rules were adopted because of the anticipated publication of USP 800 and revised versions of USP 795 and USP 797. Eventually, through the creation of inspection worksheets, stakeholders were informed that PQAC intended to enforce the standards of USP 795 (version made official on January 1, 2014) for nonsterile products, and USP 797 (version made official on May 1, 2018) for sterile products.

PQAC did have two chapters of rules that existed prior to HB 1800 relating to compounding (chapters 246-878 and 246-871 WAC) and these continued to be enforced. In early 2018, PQAC confronted the issue of whether it should repeal WAC 246-878 (Good Compounding Practices) and WAC 246-871 (Pharmaceutical-Parental Products for Non-Hospitalized Patients). After an evaluation of these rules it was determined that two of the rules (WAC 246-871-030(c) and WAC 246-871-080(1)) imposed requirements that were not addressed in the USP chapters. On June 8, 2018, PQAC adopted a directive that PQAC will no longer enforce these two specific rules. Finally, as of July 1, 2020, these two chapters of WAC will no longer be enforced in their entirety due to the promulgation of WAC 246-945 and completion of PQAC's rules rewrite project.

USP 795

The current version of USP 795 became official on January 1, 2014. This was approximately six and a half months after HB 1800 was effective (it became effective on May 7, 2013). Since its official date, PQAC has considered this version of USP 795 to be an enforceable standard in Washington.

USP 797

The current version of USP 797 became on May 1, 2008. Since the passing of HB 1800, PQAC has considered this version of USP 797 to be an enforceable standard in Washington.

USP 800

USP 800 was originally published on February 1, 2016, but did not become an official General Chapter of the USP until December 1, 2019. During 2017, PQAC began to evaluate its approach to USP 800 and originally worked under the impression that USP 800 would become an enforceable standard in Washington when made official by USP, in a similar manner to USP 795 when it became official on January 1, 2014.

In anticipation of this official date, PQAC had to determine: (i) how and when USP 800 would be enforceable in Washington; (ii) how PQAC will reconcile perceived conflicts between USP 795, USP 797, L&I's hazardous drugs rules, and USP 800; and (iii) will PQAC allow early adoption of USP 800 standards by its licensees.

PQAC's first substantive discussion of these issues took place at a compounding subcommittee on October 10, 2017. The culmination of this meeting was a recommendation to PQAC that USP 800 would become the standard in Washington once USP makes it official, there were two conflicts between USP 800 and USP 797, and licensees could engage in early adoption of USP 800 and would not be found deficient or subject to enforcement action.

This subcommittee meeting recommendation was taken to PQAC and culminated in PQAC adopting Policy Statement #60 – Regulation of Handling of Hazardous Drugs. This policy statement clarified that PQAC will allow early adoption of USP 800, and would not find licensees deficient when adhering to the standards of USP 800 that are in direct conflict with USP 797.

In February 2018, PQAC amended Policy Statement #60 – Regulation of Handling of Hazardous Drugs to clarify that after consultation with L&I it had been determined that licensees who are compliant with USP 797 and USP 800 "will be considered compliant with LNI's General Occupational Health Standards rules on Hazardous Drugs (WAC 246-62-500 *et al*)."

PQAC then addressed the potential enforceability of USP 800 at its September and October 2019 business meetings. In the October 2019 business meeting, PQAC reaffirmed its Policy Statement #60 – Regulation of Handling of Hazardous Drugs in a 12-0 vote. Consequently, PQAC continued to allow early adoption of USP 800 and chose not to specifically enforce USP 800, even when USP 800 became official on December 1, 2019.

At the December 2019 business meeting, PQAC voted to adopt rule language as part of the rules rewrite project that would identify the specific chapters of USP that licensees would have to comply with when engaged in compounding. This draft language did become rule on July 1, 2020 and is codified at WAC 246-945-100 and included USP 795, USP 797, USP 800, and USP 825.