Medication Safety Committee Meeting - Addendum

Wednesday, April 4, 2018

California Hospital Association - Boardroom

1215 K Street, Ste 800

Sacramento, CA, 95814

Conference Call Option:

Meeting Book - Medication Safety Committee Meeting

AGENDA

MEDICATION SAFETY COMMITTEE
MEETING MINUTES
January 10, 2018 / 10:00 a.m. – 2:00 p.m.

CHA
1215 K Street, Suite 800
Sacramento, CA

Members Present: Eddie Avedikian, Loriann DeMartini, Candace Fong, Jeannette Hanni, Kathy Ghomeshi, Susan Herman, Virginia Herold, Rory Jaffe, Christine Low, Dan Ross, Diana Schultz, Rita Shane, Terri Vidals

Members on Call: John Christensen, Kevin Dorsey-Tyler, Lisa Hall, Nasim Karmali, Doug O'Brien, Sarah Stephens

Members Absent: Carolyn Brown, Katie Choy, Edna DeLeon, Dan Dong, Mary Foley, Amy Gutierrez, Randy Kajioka, Cari Lee, Lori Nolan, Christopher Patty, Richard Rabens, Art Woo

Guest: Randi Agata, Vicky Ferrarsi

CHA Staff: BJ Bartleson, Staci Grabill, Lori Richardson, Debby Rogers

I. CALL TO ORDER/INTRODUCTIONS – Hanni/Fong

The committee meeting was called to order by co-chairs at 10:00 a.m. Ms. Hanni briefly reviewed operational items.

II. REVIEW OF PREVIOUS MEETING MINUTES – Hanni/Fong

The minutes of the October 11, 2017, Medication Safety Committee meeting were reviewed.

IT WAS MOVED, SECONDED AND CARRIED:

- *ACTION: Minutes approved as presented*

III. OLD BUSINESS

A. Sterile Compounding Changes - Herold

Referring to the documents provided in the meeting book, Ms. Hanni discussed proposed changes to the regulations. Ms. Bartleson referred members to the December Board of Pharmacy (BoP) meeting report provided in the meeting book. Ms. Herold discussed compliance with USP 800 and stated those that received sterile compounding construction waivers received a questionnaire to complete. The BoP is pushing for hospitals to become compliant.

Ms. Hanni then moved on to the draft comments created by CHA asking Ms. Herold if this is the best way to provide the BoP feedback, or should the comments be voiced directly to the Board in the February Board Meeting. Ms. Herold stated the written comments are good. This allows CHA and this group to provide detailed comments during the comment period. Members discussed missing pieces and concerns with the changes of the board regulations, as

well as their process in labeling and handling hazardous drug such as Pitocin and other reproductive and chemotherapy drugs.

Per Ms. Hanni, the comment letter should include the crosswalk to labeling, and suggested wording.

- *ACTION: Sterile Compounding subgroup to make changes to the hazardous medication proposed definition and circulate to the committee for additional input prior to finalizing and forwarding to the BoP. Per Ms. Shane, USP 800 FAQs would be a good information resource.*

B. Board of Pharmacy Construction Waivers/Process/CAU – Hanni/Fong

Waivers – Ms. Herold addressed backlog. In many cases BoP is waiting for a response from hospitals on BoP's request for additional items. Ms. Herold advised members to give BoP 30-days to complete their process.

CAU – Mr. Christensen stated he does not have the power to speed up the process, but is taking note of member concerns and will discuss with his team. Ms. Bartleson referred members to the roundtable process memo and the CDPH checklist for review and discussion.

Ms. Rogers discussed CAU as related to sterile compounding. She advised members that are ready for inspection and seem to be on hold, to work through Ms. Rogers to ensure the delay gets addressed.

- *ACTION: Mr. Rogers and Ms. Hanni to work with Mr. Christensen to raise CAU issues to Ms. Lee from CDPH.*

C. Medication Safety Toolkit Update - Bartleson

Ms. Bartleson reminded members the tools have been posted to the CHA website. She requested members to forward outstanding items to her and she will ensure they get posted.

- *ACTION: Toolkit webpage comes back with an error message. CHA staff to work on fixing the link.*

D. Education Next Steps – Bartleson

Referencing the memo included in the meeting book, Ms. Bartleson discussed the topic of education with regard to sterile compounding. General consensus is that formal education should wait until the hazardous language has been finalized.

- *ACTION: Information only.*

E. Medication Reconciliation Next Steps - Shane

Ms. Bartleson introduced this discussion then turned the conversation over to Ms. Shane who provided detailed information on the *Cost of Harm Due to Incorrect Medication Lists* document provided in the meeting as well as her work on providing bill language to Senator Stone.

- *ACTION: Ms. Shane to confirm with Senator Stone she can share the bill language with committee members, and if so, forward the language directly to committee members.*

F. IV Minibag Shortage – Hanni/Fong

Ms. Bartleson advised the group that she will be participating in a call with AHA and Baxter to discuss further. Mr. Avedikian provided an example of a hospital issue that Ms. Herold weighed in on.

- *ACTION: The Board of Pharmacy is unable to extend BU dates for shortages*

G. Hospice Facility and Use of ADD – Bartleson

Ms. Bartleson discussed the information and provided a brief update referencing the information provided in the meeting book.

- *ACTION: CHA will continue to monitor the legislation proposed.*

H. 340B Update – Bartleson

Ms. Bartleson briefly discussed the Medicare document and memo provided in the meeting book.

- *ACTION: Information only.*

IV. LEGISLATION AND REGULATORY

A. Antibiotic Stewardship Program – Rogers

Ms. Rogers discussed the information included in the meeting book, as well as, answered questions presented by members.

- *ACTION: Information only.*

V. NEW BUSINESS

A. Advanced Pharm Tech Role - Herold

Ms. Herold reached out to Ms. Bartleson to see if the committee could provide feedback. Ms. Bartleson outlined the information provided by members. The goal is to create more of a career path for pharmacy technicians. Ms. Herold fielded questions presented by committee members.

Ms. DeMartini provided an update on California Society of Health System Pharmacists activities regarding pharmacy technician programs

- *ACTION: Ms. Ghomeshi to forward Ms. Bartleson additional information she has come across regarding this issue.*

B. **AHA Leadership Summit - Bartleson**

Ms. Bartleson took a moment to thank Ms. Stephens, Ms. Ghomeshi, and Ms. Shane for their work in providing abstracts to the American Hospital Association for possible inclusion in a future program.

- *ACTION: Information only.*

C. **Emergency Regulations - Bartleson**

- *ACTION: Discussed in Old Business section.*

V. STANDING REPORTS

A. Board of Pharmacy (BoP) – Herold

Ms. Herold outlined current BoP activities which includes:

- Will be sponsoring several legislative bills
- Proposing changes to the CURES system
- Billboards for opioid abuse
- CE video for the requirement of 2 unites of BoP CE for license renewal
- CE event on drug abuse scheduled for January 27, 2018

B. CDPH – Lee, Woo, Christensen

Mr. Christensen briefly reviewed his tasks from this meeting as discussed earlier.

C. CSHP – DeMartini/Dong

Ms. DeMartini provided a brief update on recent CSHP activities

D. CALNOC – Foley

No update provided

E. ACNL – Foley

No update provided

F. CHPSO – Jaffe

Dr. Jaffe discussed the

- small-bore connector issue
- engaged in a 3-year program to work on an outpatient simulator. They will be using CHPSO data to feed into it.

G. CAHF – Hall

No update provided

VI. OTHER BUSINESS

VII. NEXT MEETING

Wednesday, April 4, 2018

VIII. ADJOURNMENT

Having no further business, the committee adjourned at 1:40 PM

2018 AHA Leadership Summit Presentation Proposals

Session Title *	Model for Success: How California Hospital Association's Integrative Collaboration Supports Safe Sterile Compounding Practices

Session Summary

Please provide a detailed summary of the session including a description of its focus and participant learning objectives.

While there is no official word limit for this summary, we suggest keeping it under 500 words. *

In recent years, sterile compounding has been an area of focus for many healthcare stakeholders, particularly after the tragic outbreak of meningitis that resulted in multiple patient infections and deaths throughout the country. The California Hospital Association (CHA) Medication Safety Committee has chosen to provide leadership and guidance to the healthcare community to promote the highest standards related to the safe and effective preparation and use of medications, in alignment with the mission of the committee. This session aims to describe CHA's collaborative approach to addressing sterile compounding regulations and provide senior executive audience members with an opportunity to:

1) Describe the structure and membership of a multi-faceted state medication safety committee;

2) Explain the importance of an interdisciplinary collaboration amongst several clinical, safety, and regulatory bodies to improve safety of compounded sterile products;

3) Compare and contrast strategies to disseminate resources and recommendations for a variety of healthcare setting.

The California Hospital Association (CHA) Medication Safety Committee is an interagency and interdisciplinary committee comprised of members from various organizations involved in providing or overseeing patient care services in the state. The purpose of the Medication Safety Committee is to promote safe medication practices in the state of California by acting as a resource of safe medication expertise, providing a venue for the coordination of medication safety activities and making

recommendations related to medication safety legislation and regulations. The committee is composed of state regulators and licensing boards, professional societies and associations, quality organizations for healthcare, and practitioners from many different settings.

Through collaboration between the California Board of Pharmacy (BoP), the California Department of Public Health (CDPH), the California Society of Health-System Pharmacists (CSHP), the Office of Statewide Health Planning and Development (OSHPD), and pharmacist representatives, the committee was able to create tools and solutions to support improving the quality and safety of sterile compounded products.

Please explain how this session is targeted toward to a senior executive level audience.

While there is no official word limit for this section, we suggest keeping it under 500 words. *

Sterile compounding regulatory changes represent a unique and difficult challenge for hospitals across the nation. This presentation will provide executive leadership a unique and important review of how a California Hospital Association Medication Safety Committee was able to bring multiple regulatory bodies and clinicians to the table to tackle a complex problem. This information can be utilized to help executives define and promote performance improvement and patient safety activities applicable to their institutions in an effort to meet new and more restrictive standards for compounded sterile products. Members of the CHA Medication Safety Committee will present high level strategies to leverage regulatory agencies to align and promote patient safety. These concepts and strategies are necessary and applicable to meet regulatory requirements from multiple agencies that were not aligned prior to implementation.

Select a content area: *	Quality and Safety Improvements for Optimal Performance
Main Contact Name *	Dr Katayoon Kathy Ghomeshi
Main Contact Title *	Medication Safety Officer
Main Contact Organization *	UCSF Medical Center

Speaker One Name *	BJ Bartleson RN, MS, NEA-BC
Speaker One Title *	Vice President, Nursing & Clinical Services
Speaker One Organization *	California Hospital Association

Brief Bio for Speaker One *

BJ Bartleson provides leadership in developing, communicating and implementing CHA policy related to nursing, emergency services, trauma and medication safety. She is recognized statewide and nationally as a nurse leader with more than 40 years of experience as a Chief Nurse Executive, educator, researcher, clinician, manager and expert in multiple areas of acute patient care management and nursing practice.

BJ received her Bachelor of Science degree with distinction at the University Of Virginia School Of Nursing in 1978, and her master's degree in nursing administration at the University of California, San Francisco, in 1990. She served as the 2010 Association of California Nurse Leaders president and was on the board of the American Organization of Nurse Executives for more than 10 years. She has also served on the CHA Board of Trustees and the American Hospital Association Regional Policy Board.

Speaker One Speaking References: Please include information on any conferences/meetings/events where the speaker has spoken in the past, as well as contact information for people who can vouch for the speaker's content knowledge and presentation abilities at those events. *	N/A

Provide a brief description of Speaker One's organization (bed size, services, etc) *

The California Hospital Association (CHA) is the statewide leader representing the interests of California's hospitals and health systems with the Legislature, administration and regulatory agencies. Established as a not-for-profit corporation, CHA's three corporate members are the Hospital Council of Northern and Central California (Hospital Council), Hospital Association of Southern California (HASC) and Hospital Association of San Diego and Imperial Counties (HASD&IC). Under a consolidated membership and dues structure, hospitals and health systems are members of both their Regional Association and CHA.

Based in Sacramento, CHA provides leadership in health policy and advocacy, representing nearly 400 hospitals and health systems.

Do you have additional speakers? *	Yes
Speaker Two Name *	Dr Katayoon Kathy Ghomeshi PharmD, MBA, BCPS, CPPS
Speaker Two Title *	Medication Safety Officer
Speaker Two Organization *	UCSF Medical Center`

Brief Bio for Speaker Two *

Katayoon Kathy Ghomeshi, PharmD, MBA, BCPS is a Medication Safety Officer at UCSF Medical Center and Health Sciences Assistant Clinical Professor at UCSF School of Pharmacy. She is also the Residency Program Director and primary preceptor for the PGY2 in Medication-Use Safety and led in developing the program at UCSF Medical Center.

Dr. Ghomeshi completed a PGY2 Medication-Use Safety Residency at the Johns Hopkins Hospital. During her residency, she trained at the Institute for Safe Medication Practices and the American Society of Health-System Pharmacists. Prior to that, she completed a PGY1 Managed Care Pharmacy Residency

at Kaiser Permanente. Dr. Ghomeshi earned her Doctor of Pharmacy degree from the University of Maryland School of Pharmacy in Baltimore, Maryland. Dr. Ghomeshi completed a Master of Business Administration from the University of Baltimore/Towson University. She holds a Bachelor of Science in Neurobiology, Physiology, and Behavior from the University of California, Davis.

Dr. Ghomeshi is an appointed member of the ASHP Section of Inpatient Care Practitioners Advisory Group on Medication Safety, as well as the California Hospital Association Medication Safety Committee. Dr Ghomeshi's professional interests include designing safe medication-use systems with high leverage risk reduction strategies, evaluating human factors and medication errors, and fostering a culture of safety. She enjoys collaborative, interdisciplinary safety initiatives and empowering others to be leaders in Medication and Patient Safety.

Speaker Two Speaking References: Please include information on any conferences/meetings/events where the speaker has spoken in the past, as well as contact information for people who can vouch for the speaker's content knowledge and presentation abilities at those events. *	Speaker for UCSF Medical Center Patient Safety Week 2016 Speaker at CSHP Seminar 2016, Speaker at ASHP Summer Meeting 2017, Speaker at CSHP Seminar 2017 Keynote Speaker for UCSF Interprofessional Education Course (with Dr. Bob Wachter) 2016, 2017 Speaker for HQI National Healthcare Quality Week 2017 Speaker at ASHP Midyear Clinical Meeting 2017 contact information available by request
Provide a brief description of Speaker Two's organization (bed size, services, etc) *	UCSF Medical Center in San Francisco, Calif. is ranked No. 5 on the Best Hospitals Honor Roll by US News and World Report. It is nationally ranked in 15 adult and 9 pediatric specialties and rated high performing in 9 adult procedures and conditions. It is a general medical and surgical facility. It scored high in patient safety, demonstrating commitment to reducing accidents and medical mistakes. It is a teaching hospital with ~ 750 licensed beds

Speaker Three Name *	Dr Sarah Stephens PharmD, BCPS, CPPS
Speaker Three Title *	Medication Safety Coordinator
Speaker Three Organization *	Kaweah Delta Health Care District

Brief Bio for Speaker Three *

Sarah Stephens, PharmD, BCPS, CPPS is the Medication Safety Coordinator for Kaweah Delta Health Care District. She serves as a preceptor for PGY1 Pharmacy Practice Residents and pharmacy students from the University of California, San Francisco. Dr. Stephens' pharmacy career has spanned over a decade with a primary clinical focus in acute care adult internal medicine and 6.5 years in academia at the University of Utah College of Pharmacy. Current initiatives and research interests include reducing medication errors in the areas of anticoagulation and pain management, improving transitions of care with an emphasis on discharge medication reconciliation, and evaluating safety culture. Dr. Stephens is a member of the California Hospital Association Medication Safety Committee and served on the Section of Inpatient Care Practitioners Educational Steering Committee and the Medication Safety Section Advisory Group for the American Society of Health-System Pharmacists.

Provide BOTH speaking references and a brief description of Speaker Three's organization in the box below. *	ASHP Summer Meeting 2017 The Kaweah Delta Medical Center is a 581-bed hospital located in Visalia, California, United States. It is operated by the Kaweah Delta Health Care District, a political subdivision of the State of California which is governed by an elected board of directors. Kaweah Delta Medical Center in Visalia, Calif. is rated high performing in 9 adult procedures and conditions by US News and World Report. It is a general medical and surgical facility. It scored high in patient safety, demonstrating commitment to reducing accidents and medical mistakes

PROPOSED AMENDMENTS TO SENATE BILL NO. 1254

SENATE BILL **No. 1254**

Introduced by Senator Stone

February 15, 2018

An act to add Section 4118.5 to the Business and Professions Code, relating to healing arts.

LEGISLATIVE COUNSEL'S DIGEST

SB 1254, as introduced, Stone. Hospital pharmacies: medication profiles *or lists* for high-risk patients.

Existing law, the Pharmacy Law, a willful violation of which is a misdemeanor, provides for the licensure and regulation of pharmacists, intern pharmacists, pharmacy technicians, and pharmacies by the California State Board of Pharmacy. Existing regulatory law requires a pharmacy to maintain medication profiles on all patients who have prescriptions filled at that pharmacy, except under specified circumstances.

This bill would require a pharmacist at a hospital pharmacy to obtain an accurate medication profile *or list* for each high-risk patient upon admission and discharge of the patient. The bill would authorize an intern pharmacist or a pharmacy technician to perform ~~that function if the intern pharmacist or pharmacy technician has successfully completed training and proctoring by a pharmacist and where a quality assurance program is used to monitor competency. The bill would require the board to adopt regulations specifying the training and proctoring required to be completed.~~ *the task of obtaining an accurate medication profile or list for a high-risk patient if certain conditions are satisfied. The bill would require the hospital to determine what constitutes a*

high-risk patient for purposes of the bill's provisions based on the populations served by the hospital.

By ~~expanding~~ *placing new requirements on a pharmacist, this bill would expand* the scope of ~~a crime, the bill would~~ *an existing crime and would, therefore,* impose a state-mandated local program.

The California Constitution requires the state to reimburse local agencies and school districts for certain costs mandated by the state. Statutory provisions establish procedures for making that reimbursement.

This bill would provide that no reimbursement is required by this act for a specified reason.

Vote: majority. Appropriation: no. Fiscal committee: yes. State-mandated local program: yes.

The people of the State of California do enact as follows:

Page 2

SECTION 1. Section 4118.5 is added to the Business and Professions Code, to read:

4118.5. (a) At a hospital pharmacy, a pharmacist shall obtain an accurate medication profile *or list* for each high-risk patient upon admission and discharge of the *high-risk* patient. ~~A~~

Amendment 1

(b) Notwithstanding any other law, a pharmacy technician or a pharmacy intern may perform ~~this function if the pharmacy technician or pharmacy intern has successfully completed training and proctoring by a pharmacist and where a quality assurance program is used to monitor competency.~~ *the task of obtaining an accurate medication profile or list for a high-risk patient if both of the following conditions are satisfied:*

Amendments 2 & 3

(1) The hospital pharmacy has a quality assurance program, which is under the direction of the pharmacist-in-charge, to monitor competency.

(2) The hospital has established policies and procedures for training and proctoring pharmacy technicians or pharmacy interns and the pharmacy technician or pharmacy intern has completed that training and proctoring.

Amendment 4

~~(b) The board shall adopt regulations specifying the training and proctoring required to be completed pursuant to this section.~~

Amendment 5

(c) The hospital shall establish criteria regarding who is a high-risk patient for purposes of this section based on the patient populations served by the hospital.

Page 2

SEC. 2. No reimbursement is required by this act pursuant to Section 6 of Article XIII B of the California Constitution because the only costs that may be incurred by a local agency or school district will be incurred because this act creates a new crime or infraction, eliminates a crime or infraction, or changes the penalty for a crime or infraction, within the meaning of Section 17556 of the Government Code, or changes the definition of a crime within the meaning of Section 6 of Article XIII B of the California Constitution.

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Senate Bill 1254 Fact Sheet

Intent: High risk patients are at significant risk for medication-related harm when they are admitted to the hospital and this risk persists at discharge as shown by the significant number of medication errors at each of these steps.

This bill is intended to protect these patients when they are most vulnerable by having pharmacy staff ensure accuracy of medication lists upon admission and discharge. The bill is based on the growing body of evidence that pharmacy staff perform these functions more accurately than usual care and free up time for physicians and nurses to take care of patients' acute care needs.

Why is this bill important?

Evidence demonstrates that there are 8 errors/high risk patient's medication list or history which result in an average of 3 errors/patient when they are admitted. Errors are reduced by 80% when the lists or histories were obtained by pharmacists or trained technicians in the emergency department in comparison to usual care. https://www.beckershospitalreview.com/quality/cedars-sinai-sees-80-drop-in-medication-errors-when-drug-histories-are-taken-down-by-pharmacy-staff.html In the ambulatory setting, medication lists are generally entered into electronic health records by medical assistants who lack indepth training in medications. In electronic health records, these lists become the basis of hospital medication orders and discharge prescriptions. Errors on medications lists at admission create errors when patients go home

Which hospital pharmacies are intended to be included?

Hospitals that have an onsite hospital pharmacy would be included.

What is the definition of a high risk patient?

Since populations vary amongst hospitals, the intent is to allow each hospital to develop criteria for high risk patients analogous to the requirement for determining which drugs are high-alert. It is anticipated that pharmacists would collaborate with physicians, nurses and executive management in developing the criteria. They could start with a limited population, e.g. advanced heart failure (NYHA Class IV) or stroke, and determine whether to add other high risk populations in the future based on their experience.

When would this bill if approved go into effect?

We have been told that it would likely be in the next year which allows time for planning and implementation

What is the timeframe for obtaining a list relative to the admission?

The hospital would responsible for determining the timeframe. Ideally, this should be done within 24 hour of admission but there may be exceptions determined by the hospital.

What is meant by obtaining an accurate medication list?

Obtaining an accurate medication list is determining what medications (prescription and non-prescription) the patient is currently taking including dose, frequency and route if the patient/caregiver is able to provide this information. Additional sources of information that can be used, if available, include a medication list brought in by the patient/family/caregiver, the medication list from the last patient encounter in the electronic medical record, the patient's physician's office, electronic prescription data such as Surescripts® or the patient's pharmacy. A best possible medication list obtained using this approach would be considered to be an accurate medication list since it is based on the information available at the time.

What happens if there is a medication error based on the medication list?

If an error occurs, it would be no different than the current situation since each professional, physician or allied health professional and pharmacist is responsible for determining if medications listed are appropriate for ordering during the inpatient admission based on patient-specific conditions, diseases, concomitant drugs, etc.

How are accurate medication lists determined at discharge?

Pharmacy staff would review the prior to admission, hospital and discharge medication lists to identify errors such as duplicates, omissions, contraindications, etc. Pharmacy staff would notify the physician or allied health professional of any discrepancies or errors and work with them to correct these, update the discharge list and correct any erroneous prescriptions. This would include but not be limited to initiating medications that were omitted and discontinuing medications not indicated. For example, an opioid ordered on a post-operative patient who already was on an opioid that they had received just before being hospitalized would be discontinued.

What is the benefit to community pharmacies?

Prescriptions received when patients are discharged from the hospital would not require as many clarifications and the risk of medication errors would be reduced. This would free up time for community pharmacists and also reduce their liability.

Appendix

Quick Summary

Up to 70% of patients have errors on their medication lists and up to 59% of these have the potential to cause moderate to severe harm. A recent study in high risk patients demonstrated 8 errors per patient which resulted in an average of 3 errors per patient when they were admitted to the hospital. There was an 80% reduction in medication errors when pharmacists and trained technicians obtained medication lists in comparison to standard care and the risk of patient harm was also significantly reduced. This is likely because busy clinicians focus on the acute needs of the patient whereas pharmacy staff have the training and advanced skills to focus on the ensuring accuracy and appropriateness of medications. Additionally, electronic health records enable continuation of medication orders even if they are wrong. Medication errors lead to adverse drug events, emergency department visits and hospitalizations of which 20% percent are medication-related. Medicare patients in California on drugs known as high risk for harmful events have a readmission rate of 21.7%. At discharge, up to 80% of patients have at least one medication error at discharge and patients with errors had a 30-day hospital readmission rate 57% higher when pharmacists did not correct these errors at discharge. Currently, the lack of defined responsibility to ensure medication lists are accurate at hospital admission and discharge places patient at significant risk for harm. Pharmacy staff in acute care hospitals have the expertise to perform this essential function.

Subject: SB1447

Feedback from Santa Clara Valley Medical Center, Narinder Singh, Director, Pharmacy Services. Strongly oppose.

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The Department of Pharmacy at Santa Clara Valley Medical Center Hospital & Clinics strongly oppose SB1447.

The bill is limiting access to care for the most vulnerable population. By requiring licensing of each automated drug delivery system (ADDS), the California State Board of Pharmacy is making it difficult for the pharmacies to manage drug distribution in out-patient clinics. Licensing each unit will require additional paperwork that has to be maintained and renewed every year. This is burdensome activity that adds no value to patient care.

In addition, by limiting the number of licenses per pharmacy, (Page 99, line 28) “A pharmacy may only obtain five simultaneous ADDS licenses”, the Board is further restricting access to medications utilized/administered to our patient care in the clinics.

Therefore Santa Clara County strongly opposes this bill. Thank you for considering our feedback.

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Carolyn H. Brown
Director, Quality and Safety
Santa Clara Valley Medical Center

Controlled Substance Reconciliation

Candace Fong, PharmD
System Director of Pharmacy &
Medication Safety
April 2018

Dignity Health™

Effective April 1, 2018

Pharmacies and Clinics Must Count Schedule II Drugs Every 3 Months

The Board of Pharmacy has adopted a new regulation requiring pharmacies and clinics to perform a periodic inventory reconciliation for all controlled substances, including a physical count of Schedule II controlled substances every three months.

The regulation – Title 16, California Code of Regulations (CCR) section

CII Drugs

Continued from Page 1

1715.65 – is intended to help pharmacists detect and stop drug loss and diversion in pharmacies and to reduce the supply of controlled substances available for misuse and abuse in California communities. The new rule will take effect April 1, 2018.

Section 1715.65 requires pharmacies and clinics to compile an inventory reconciliation report of all federal Schedule II controlled substances at least every three months. The inventory must be a physical count – not an estimate – of all Schedule II drugs. The inventory must be compared with a review of drugs that entered and left the pharmacy since the previous inventory reconciliation. All records used to complete the reconciliation must be kept in the pharmacy or clinic for three years.

Possible causes of overages must be identified and incorporated into the reconciliation report. Losses must be reported to the Board of Pharmacy within 30 days of discovery – unless the cause is theft, diversion or self-use, which must be reported within 14 days.

Inventory reconciliation reports must be dated and signed by the persons performing the inventory and countersigned by the pharmacist-in-charge (PIC) or clinic professional director.

The biennial count of controlled substances required by the U.S. Drug Enforcement Administration (DEA) may serve as one of the inventories required by section 1715.65, as long as the biennial inventory was performed within three months of the previous inventory required by the new rule.

Section 1715.65 also requires a new pharmacist-in-charge (PIC) to complete an inventory reconciliation report for Schedule II drugs within 30 days of becoming PIC. In addition, the regulation encourages an outgoing PIC to perform an ending inventory before leaving.

For inpatient hospital pharmacies, separate quarterly inventory reconciliation reports must be done for federal Schedule II drugs within the pharmacy and for each satellite location.

Section 1715.65 also requires PICs for hospital pharmacies and for pharmacies servicing automated drug delivery systems (ADDS) to ensure all controlled substances used in ADDS devices are accounted for and that access to the devices is restricted to authorized personnel.

Dignity Health.

1715.65. Inventory Reconciliation Report of Controlled Substances – Effective April 1, 2018

1715.65. Inventory Reconciliation Report of Controlled Substances

(a) Every pharmacy, and every clinic licensed under sections 4180 or 4190 of the Business and Professions Code, shall perform periodic inventory and inventory reconciliation functions to detect and prevent the loss of controlled substances.

(b) The pharmacist-in-charge of a pharmacy or consultant pharmacist for a clinic shall review all inventory and inventory reconciliation reports taken, and establish and maintain secure methods to prevent losses of controlled drugs. Written policies and procedures shall be developed for performing the inventory reconciliation reports required by this section.

(c) A pharmacy or clinic shall compile an inventory reconciliation report of all federal Schedule II controlled substances at least every three months. This compilation shall require:

(1) A physical count, not an estimate, of all quantities of federal Schedule II controlled substances. The biennial inventory of controlled substances required by federal law may serve as one of the mandated inventories under this section in the year where the federal biennial inventory is performed, provided the biennial inventory was taken no more than three months from the last inventory required by this section;

(2) A review of all acquisitions and dispositions of federal Schedule II controlled substances since the last inventory reconciliation report;

(3) A comparison of (1) and (2) to determine if there are any variances;

(4) All records used to compile each inventory reconciliation report shall be maintained in the pharmacy or clinic for at least three years in a readily retrievable form; and

(5) Possible causes of overages shall be identified in writing and incorporated into the inventory reconciliation report.

- New Process

1715.65

(d) A pharmacy or clinic shall report in writing identified losses and known causes to the board within 30 days of discovery unless the cause of the loss is theft, diversion, or self-use in which case the report shall be made within 14 days of discovery. If the pharmacy or clinic is unable to identify the cause of the loss, further investigation shall be undertaken to identify the cause and actions necessary to prevent additional losses of controlled substances.

(e) The inventory reconciliation report shall be dated and signed by the individual(s) performing the inventory, and countersigned by the pharmacist-in-charge or professional director (if a clinic) and be readily retrievable in the pharmacy or clinic for three years. A countersignature is not required if the pharmacist-in-charge or professional director personally completed the inventory reconciliation report.

(f) A new pharmacist-in-charge of a pharmacy shall complete an inventory reconciliation report as identified in subdivision (c) within 30 days of becoming pharmacist-in-charge. Whenever possible an outgoing pharmacist-in-charge should also complete an inventory reconciliation report as required in subdivision (c).

Current policy

2 signatures

1715.65 – Hospital Pharmacy Specific

(g) For inpatient hospital pharmacies, a separate quarterly inventory reconciliation report shall be required for federal Schedule II controlled substances stored within the pharmacy and for each pharmacy satellite location.

(h) The pharmacist-in-charge of an inpatient hospital pharmacy or of a pharmacy servicing onsite or offsite automated drug delivery systems shall ensure that:

(1) All controlled substances added to an automated drug delivery system are accounted for;

(2) Access to automated drug delivery systems is limited to authorized facility personnel;

(3) An ongoing evaluation of discrepancies or unusual access associated with controlled substances is performed; and

(4) Confirmed losses of controlled substances are reported to the board.

Excludes ADC

Report losses

Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4008, 4037, 4080, 4081, 4101, 4104, 4105, 4105.5, 4110, 4113, 4119.1, 4180, 4181, 4182, 4186, 4190, 4191, 4192, and 4332, Business and Professions Code and 1261.6, Health and Safety Code.

Title 16. Board of Pharmacy
Order of Adoption

Adopt section 1715.65 in Article 2 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1715.65. Inventory Reconciliation Report of Controlled Substances

(a) Every pharmacy, and every clinic licensed under sections 4180 or 4190 of the Business and Professions Code, shall perform periodic inventory and inventory reconciliation functions to detect and prevent the loss of controlled substances.

(b) The pharmacist-in-charge of a pharmacy or consultant pharmacist for a clinic shall review all inventory and inventory reconciliation reports taken, and establish and maintain secure methods to prevent losses of controlled drugs. Written policies and procedures shall be developed for performing the inventory reconciliation reports required by this section.

(c) A pharmacy or clinic shall compile an inventory reconciliation report of all federal Schedule II controlled substances at least every three months. This compilation shall require:
   (1) A physical count, not an estimate, of all quantities of federal Schedule II controlled substances. The biennial inventory of controlled substances required by federal law may serve as one of the mandated inventories under this section in the year where the federal biennial inventory is performed, provided the biennial inventory was taken no more than three months from the last inventory required by this section;
   (2) A review of all acquisitions and dispositions of federal Schedule II controlled substances since the last inventory reconciliation report;
   (3) A comparison of (1) and (2) to determine if there are any variances;
   (4) All records used to compile each inventory reconciliation report shall be maintained in the pharmacy or clinic for at least three years in a readily retrievable form; and
   (5) Possible causes of overages shall be identified in writing and incorporated into the inventory reconciliation report.

(d) A pharmacy or clinic shall report in writing identified losses and known causes to the board within 30 days of discovery unless the cause of the loss is theft, diversion, or self-use in which case the report shall be made within 14 days of discovery. If the pharmacy or clinic is unable to identify the cause of the loss, further investigation shall be undertaken to identify the cause and actions necessary to prevent additional losses of controlled substances.

(e) The inventory reconciliation report shall be dated and signed by the individual(s) performing the inventory, and countersigned by the pharmacist-in-charge or professional director (if a clinic) and be readily retrievable in the pharmacy or clinic for three years. A countersignature is not required if the pharmacist-in-charge or professional director personally completed the inventory reconciliation report.

(f) A new pharmacist-in-charge of a pharmacy shall complete an inventory reconciliation report as identified in subdivision (c) within 30 days of becoming pharmacist-in-charge. Whenever possible an outgoing pharmacist-in-charge should also complete an inventory reconciliation report as required in subdivision (c).

(g) For inpatient hospital pharmacies, a separate quarterly inventory reconciliation report shall be required for federal Schedule II controlled substances stored within the pharmacy and for each pharmacy satellite location.

(h) The pharmacist-in-charge of an inpatient hospital pharmacy or of a pharmacy servicing onsite or offsite automated drug delivery systems shall ensure that:

(1) All controlled substances added to an automated drug delivery system are accounted for;

(2) Access to automated drug delivery systems is limited to authorized facility personnel;

(3) An ongoing evaluation of discrepancies or unusual access associated with controlled substances is performed; and

(4) Confirmed losses of controlled substances are reported to the board.

Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4008, 4037, 4080, 4081, 4101, 4104, 4105, 4105.5, 4110, 4113, 4119.1, 4180, 4181, 4182, 4186, 4190, 4191, 4192, and 4332, Business and Professions Code and 1261.6, Health and Safety Code.

FAQs: Inventory Reconciliation Regulation

On April 1, 2018, a new board regulation took effect – California Code of Regulations, title 16, section 1715.65, "Inventory Reconciliation Report of Controlled Substances."

The board believes this regulation will aid pharmacies and clinics in preventing and identifying losses of controlled drugs earlier than without such measures.

The following information is intended to respond to questions asked of the board regarding this new regulation. As with any regulation, the board seeks compliance at the earliest possible time. For the first few months, the board will focus on education to promote understanding about the regulation. During the transition, any inspection will focus on the pharmacy or clinic's good faith efforts to comply with the regulation.

The regulation text can be found at http://www.pharmacy.ca.gov/laws_regs/1715_65_ooa.pdf.

Here is a summary of CCR section 1715.65 by subsection:

(a) – Requires all pharmacies, and all clinics licensed under Business and Professions Code section 4180 or 4190 ("clinics"), to perform periodic inventory and reconciliation functions for all controlled drugs. (Note: No frequency of these duties is specified in the regulation except for Schedule II drugs.)

(b) – Requires the pharmacist-in-charge (PIC) or the clinic's consultant pharmacist to:
(1) establish and maintain secure methods to prevent losses of controlled drugs;
(2) establish written policies and procedures for performing reconciliation reports; and
(3) review all inventory and reconciliation reports.

(c) – Requires each pharmacy or clinic to prepare a **quarterly** inventory reconciliation report of all federal Schedule II medications, which is based on:
(1) A physical count of all federal Schedule II medications at the time of each inventory;
(2) A review of all acquisition and disposition records since the last inventory;
(3) A comparison of 1 and 2 to identify any differences (losses or overages).
(4) Collection and retention of records to compile each inventory report
(5) Written identification of sources of losses or overages in the report. The report must identify the possible causes of losses or overages.

(d) – Requires a pharmacy or clinic to file a report of losses to the board within 30 days of discovery or within 14 days if theft, self-use or diversion by a board licensee is the cause. If the cause is unknown, requires the pharmacy or clinic to further investigate to identify the causes and to take corrective action to prevent additional losses.

(e) – Requires the inventory reconciliation report to be signed and dated by the individuals performing the inventory, and countersigned by the PIC or professional director (for a clinic).

(f) – Requires a new PIC to complete an inventory reconciliation report within 30 days of becoming PIC. Encourages the outgoing PIC to do an inventory reconciliation report before leaving.

(g) – For INPATIENT HOSPITAL PHARMACIES: Requires a separate quarterly inventory reconciliation report for federal Schedule II drugs stored within the pharmacy and for each of the pharmacy's satellite locations.

(h) – For any pharmacy servicing an AUOMATED DRUG DELIVERY SYSTEM (regardless of location), requires the PIC to:

(1) Ensure that all controlled substances added to any automated drug delivery system are accounted for;

(2) Ensure that access to any automated drug delivery system is limited to authorized facility personnel only;

(3) Ensure that any discrepancy or unusual access to the controlled substances in the automated drug delivery system is evaluated; and

(4) Ensure that confirmed losses are reported to the board timely.

1. **The regulation took effect April 1, 2018. Must I conduct my initial inventory beginning on April 1, 2018?**

   No, the board expects pharmacies and clinics to transition to satisfy the inventory reconciliation requirements over a short period of time, but not necessarily by April 1.

2. **Are there any drugs in addition to federal Schedule II controlled substances affected by the requirement to do a physical count and reconciliation each quarter?**

   No, the regulation requires a quarterly count and reconciliation of only federal Schedule II drugs. California and the federal government have separate controlled substances schedules, although there is much similarity between the two. Nevertheless, the board determined that the federal Schedule II drug list is a more current and complete schedule, as well as the federal list is the reference for reporting dispensing into the Controlled Substances Utilization Review and Evaluation System (CURES) in California.

3. **Can a pharmacy or clinic estimate (instead of physically counting) federal Schedule II medications for the quarterly inventory?**

   No, a physical count of every Schedule II medication is required for the quarterly inventory reconciliation report.

4. **Subsection (a) of the regulation requires a pharmacy or clinic to "periodically" perform inventory and reconciliation functions for controlled substances. Does this mean every quarter I must count and reconcile all controlled substances?**

   No. However, periodically (and under federal law at least every two years) all controlled substances must be inventoried. The board encourages more frequent counting of

controlled medications to prevent losses of Schedule III, IV and V drugs. The regulation only specifies the frequency of reconciliation duties for federal Schedule II drugs; the appropriate frequency for all other controlled drugs should be determined by the standard of practice in the community under the circumstances of the pharmacy.

5. **Does a perpetual inventory system satisfy the requirements of this regulation?**

   No, the use of a perpetual inventory system does not satisfy the regulation. The regulation requires both a physical count and reconciliation with all acquisitions and dispositions must be performed every 90 days.

6. **If I use a perpetual inventory, can I use the physical counts made for the perpetual inventory instead of physically counting the drugs specifically for the inventory reconciliation report?**

   It depends. The regulation requires a physical count of each Schedule II medication every quarter, which is then used as part of the inventory reconciliation analysis and report. If, for example, the pharmacy or clinic physically counts the specific drug stock each time a Schedule II drug is dispensed or acquired, that count might be used to fulfill the physical count required by the inventory reconciliation regulation, but the PIC or consultant will need additional data. For any drug where there were no dispositions or acquisitions during the quarterly reconciliation period (and therefore no physical count through the perpetual inventory system), a physical count of the Schedule II drug must be made because each drug must be physically counted at least quarterly.

7. **I have a recent physical count for each Schedule II drug. What do I compare that to? What do I do with that information?**

   For each medication, the PIC or consultant would start with the physical count of the medication from the last inventory reconciliation report and:
   1. Add all acquisitions, and subtract all dispositions, that occurred during the reconciliation period (no greater than 90 days) to identify the amount of drug stock that should be on hand (expected drug stock).
   2. Compare the expected drug stock to the actual physical inventory count.
   3. If there is a difference, attempt to identify the source of overage or shortage. **NOTE:** If there is a discrepancy and the recent physical count is from a perpetual inventory system, the board urges the facility to initiate a supplementary physical count of the medication. Determine if the facility needs to take corrective action, including modify its policies and procedures, conduct an investigation, institute additional security or modify its practices.
   4. Whether or not there is a discrepancy, the results must be recorded in your inventory reconciliation report.

8. **Does an inpatient hospital pharmacy or a pharmacy servicing onsite or offsite emergency kits (e-kits) have to complete an inventory reconciliation report for the Schedule II controlled substances contained within the e-kits?**

   There is no specific reconciliation report for the kits themselves, although a pharmacy's replenishment of Schedule II drugs removed from the emergency kits would be part of a pharmacy's disposition of medication.

9. **An inventory reconciliation report of all Schedule II controlled substances shall be compiled at least every 3 months, and in order to complete such a report the inventory must be compared with a review of drugs that entered and left the pharmacy since the previous inventory reconciliation. Since no reconciliation report exists before April 1, 2018, does that mean that the first inventory reconciliation report will not be due before July 1, 2018?**

   To initiate the reconciliation process and establish a baseline for future inventory reconciliation reports, a physical count of all Schedule II medications must be undertaken. The board would generally expect a pharmacy to perform this count on or after April 1, 2018. To allow time to develop meaningful written policies and procedures for the inventory reconciliation process, the board recommends a pharmacy or clinic perform the inventory counts within the first 90 days after April 1 (i.e., August 1, 2018).

   Additionally, any new PIC on or after April 1, 2018, is required to prepare a report. Within the first three months after April 1, 2018, the board would expect the new PIC, within 30 days, to have performed an inventory count of all Schedule II medications consistent with to the requirements to prepare an inventory reconciliation report.

10. **An initial inventory does not appear to be required as part of this rule change. Since a reconciliation report cannot be compiled without an initial reference count, would it be appropriate for pharmacies or clinics to perform a physical count of all Schedule II drugs during the initial 3-month period (after April 1st), and then begin reconciliation processes after July 1st?**

    Yes. See the response above.

11. **A new PIC must complete an inventory reconciliation report within 30 days of becoming pharmacist-in-charge. If there is a PIC change on April 1st, 2018, how can the PIC create a reconciliation report, given there may not be a recent inventory or reconciliation report to refer to?**

    In this specific case, if prior data was unavailable because of the implementation date of the regulation, the board would expect the PIC to at least perform an inventory of all Schedule II medications consistent with the requirements to prepare the reconciliation report within 30 days (May 1, 2018).

12. Should the inventory reconciliation report encompass only significant losses, as defined by the DEA, or should the report encompass any discrepancy? If the former, doesn't a pharmacy's or clinic's filing of DEA Form 106 with the DEA already provide the requested information to the Board of Pharmacy, if the Board of Pharmacy receives a copy of that report?

California law requires that any loss of controlled substances be reported to the board within 30 days, and reported within 14 days where drug theft, self-use or diversion have been committed by a board licensee. These are existing requirements, predating the inventory reconciliation requirements. The regulation restates the reporting of drug loss requirements for clarity. A DEA Form 106 may be used to make this report to the board.

13. If my pharmacy or clinic is unable to identify the cause of the loss, should we wait to report the loss to the board until the cause is determined?

No, reporting is required for any loss of controlled substances within, at most, 30 days regardless if a cause of the loss was identified. Should a cause of the loss be identified later, an additional report can be made to the board. If the cause of the loss is theft, diversion or self-use by a board licensee, the report must be made within 14 days.

However, the regulation also directs that "further investigation shall be undertaken to identify the cause and actions necessary to prevent additional losses of controlled substance" where the source of a loss cannot be readily identified.

14. Will the board create a new process for reporting Schedule II controlled substances drug losses? Is there a standard form or email address to submit this information?

The board will not create a new or additional process for reporting the loss of controlled substances. A DEA Form 106 or a written statement containing specified details of the loss is sufficient. The current processes are detailed at http://www.pharmacy.ca.gov/licensees/facility/dea106.shtml

15. Does a pharmacy have to maintain actual paper documents of the records used to compile each inventory reconciliation report? Are electronic records acceptable?

All records used to compile each inventory reconciliation report shall be maintained in the pharmacy or clinic for at least three years in a readily retrievable form. Provided the records are readily retrievable, electronic records are acceptable.

16. Can the inventory reconciliation report be completed by multiple persons?

Yes, all persons involved in performing the inventory must sign and date the report, which also must be countersigned by the PIC or professional director (if a clinic).

FDA guidance 503B compounders
Monday, March 26, 2018 10:25:17 AM
FDA503b.pdf

Dear CHA Medication Safety Committee:

We have placed an additional item on next week's new business agenda. Please review this FDA guidance that addresses what bulk substances 503B compounders can use. These outsourcing facilities can either compound drugs by starting from an FDA-approved product and altering that drug — such as by making a pill into a liquid solution — or they can compound drugs by starting from a bulk drug substance, if an attribute of the FDA-approved drug would make the final product inappropriate or unsafe for certain patients.

In general, the guidance says FDA favors compounding from FDA-approved medicines, because compounding from bulk drug substances represents a greater risk to patients, and because this type of compounding involves more steps of greater complexity. Compounding from bulk substances when it is not necessary can also undermine FDA's drug approval process by reducing the incentive for drug companies to seek both brand and generic drug approval.

The agency said there should be a sound clinical reason to compound from a bulk drug substance and outlined how it would determine whether such a need exists.

Please review and be prepared to bring feedback to the committee, next Wednesday at the meeting. BJ

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Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sara Rothman at 301-796-3110.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2018
Compounding and Related Documents

Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION AND SCOPE

This guidance sets forth FDA's policy for evaluating bulk drug substances nominated for use in compounding by outsourcing facilities registered under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b).[2] Section 503B of the FD&C Act directs FDA to develop a list of bulk drug substances for which there is a clinical need (the 503B Bulks List). Drug products compounded using bulk drug substances on the 503B Bulks List qualify for certain exemptions from the FD&C Act provided the other conditions in section 503B are met. This guidance addresses FDA policies for developing the 503B Bulks List, including the Agency's interpretation of the phrase *bulk drug substances for which there is a clinical need*, as it is used in section 503B. This guidance also addresses the factors and processes by which the Agency intends to evaluate and list bulk drug substances.[3]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER) and in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] This guidance addresses FDA's evaluation of bulk drug substances nominated by members of the public for use in compounding under section 503B. FDA may also evaluate bulk drug substances for other reasons, including on its own initiative, and in that case expects that its analysis would be take into account the factors described in this guidance.

[3] FDA previously solicited nominations of bulk drug substances to be considered for the 503B Bulks List and issued the guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* regarding certain interim regulatory policies for outsourcing facilities that compound drug products using bulk drug substances while the 503B Bulks List is being developed. That interim policy remains in effect while FDA evaluates substances for the 503B Bulks List. We update guidances periodically. To make sure you have the most recent version of a guidance, be sure to check the Agency's guidance website at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Section 503B of the FD&C Act

Section 503B of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by an outsourcing facility to be exempt from the following three sections of the FD&C Act: section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications); section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and section 582 (21 U.S.C. 360eee-1) (concerning drug supply chain security requirements).[4]

Drug products compounded under the conditions in section 503B are not exempt from current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act.[5] Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound.[6] Outsourcing facilities may or may not obtain prescriptions for identified individual patients and can, therefore, distribute compounded drugs to healthcare practitioners for "office stock," to hold in their offices in advance of patient need.[7]

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for exemptions under section 503B is that the outsourcing facility may not compound a drug using a bulk drug substance unless (a) the bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need, or (b) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FD&C Act at the time of compounding, distribution, and dispensing.[8]

For purposes of section 503B, *bulk drug substance* is defined to mean "the same as an active pharmaceutical ingredient as defined in 21 CFR 207.1(b)."[9] *Active pharmaceutical ingredient* is

[4] Section 503B(a) of the FD&C Act.

[5] Compare Section 503A(a) of the FD&C Act (exempting drugs compounded in accordance with that section) to Section 503B(a) of the Act (not providing the exemption from CGMP requirements).

[6] Section 503B(b)(4), 503B(b)(5), *passim*.

[7] Section 503B(d)(4)(C).

[8] Section 503B(a)(2)(A) of the FD&C Act.

[9] 21 CFR 207.3.

defined as "any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body," but the term "does not include intermediates used in the synthesis of the substance."[10,11]

Bulk drug substances used in compounding under section 503B must also meet certain other statutory requirements, including the following: (1) if an applicable monograph exists under the United States Pharmacopeia, National Formulary, or another compendium or pharmacopeia recognized by the Secretary under section 503B, the bulk drug substance must comply with the monograph; (2) the bulk drug substance must be manufactured by an establishment that is registered under section 510 of the FD&C Act; and (3) the bulk drug substance must be accompanied by a valid certificate of analysis.[12]

B. Compounding, Generally

Compounded drugs can serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product, such as patients who have an allergy and need a medication to be made without a certain dye or hospital inpatients who need infusions of a drug combined with a particular diluent. However, they also pose a higher risk to patients than FDA-approved drugs. In 2012, contaminated injectable drug products that a state-licensed compounding pharmacy shipped to patients and health care practitioners across the country caused a fungal meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection.[13] This was the most serious of a long history of outbreaks and other serious adverse events, including overdoses, associated with contaminated, superpotent, or otherwise poor quality compounded drugs.

In response to this outbreak, Congress enacted the Drug Quality and Security Act (DQSA), which, among other things, added new section 503B to the FD&C Act and created the new category of compounders known as outsourcing facilities.[14] Drug products compounded by

[10] Section 503B(a)(2) and 21 CFR 207.1.

[11] Inactive ingredients are not subject to section 503B(a)(2) of the FD&C Act and will not be included in the 503B Bulks List because they are not included within the definition of a bulk drug substance. Pursuant to section 503B(a)(3), inactive ingredients used in compounding must comply with the standards of an applicable United States Pharmacopeia or National Formulary monograph, if a monograph exists.

[12] Section 503B(a)(2) of the FD&C Act. A compounded drug product only qualifies for the exemptions in section 503B if it is compounded by an outsourcing facility that compounds all its drugs, both sterile and nonsterile, in accordance with all of the conditions of section 503B. Sections 503B(a)(11), (d)(4)(A)(iii). A complete list of the statutory conditions that must be met for a drug product to qualify for the exemptions in section 503B appears in the guidance *For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

[13] See http://www.cdc.gov/HAI/outbreaks/meningitis.html.

[14] See Pub.L. No.113-54, §102(a), 127 Stat. 587, 587-588 (2013). Other compounders, which are not the subject of this guidance, are regulated under section 503A of the FD&C Act. These include licensed pharmacists in State-licensed pharmacies or Federal facilities, and licensed physicians, who have not registered an outsourcing facility

outsourcing facilities in accordance with the conditions of section 503B are exempt from FDA drug approval requirements and the requirement that they be labeled with adequate directions for use.[15] Because compounded drug products are not FDA-approved, they have not undergone FDA premarket review for safety, effectiveness, and quality. Although outsourcing facilities must comply with CGMP requirements and are inspected by FDA according to a risk-based schedule, their drug products lack a premarket inspection and finding of manufacturing quality that is part of the drug approval process. Because compounded drug products are subject to a lower regulatory standard than FDA-approved drugs, they should only be used by patients whose medical needs cannot be met by an FDA-approved drug.

C. Compounding Drugs From Bulk Drug Substances

Outsourcing facilities sometimes compound drug products using bulk drug substances to meet the medical needs of patients that cannot be met by an approved drug product or by a drug product compounded from an FDA-approved drug product. A patient may need a drug product compounded using the bulk drug substance because the FDA-approved drug that includes the bulk drug substance as a component also includes inactive ingredients or additional active ingredients that are inappropriate for the patient population. For example, certain inactive ingredients that may be appropriate for the route of administration of the FDA-approved drug product may not be appropriate for another route of administration. Similarly, an outsourcing facility might compound a drug product from a bulk drug substance when patients have an allergy to an inactive ingredient in the approved drug product containing that bulk drug substance. In situations such as these, compounding from bulk drug substances could meet an important patient medical need.

In other situations, however, compounding using the FDA-approved drug product instead of a bulk drug substance would meet patients' medical needs and present less risk. For example, outsourcing facilities often dilute FDA-approved drug products to produce intravenous bags for hospitals. Similarly, when pediatric or elderly patients are unable to swallow an FDA-approved tablet, outsourcing facilities can sometimes manipulate (e.g., crush) the tablet to produce a liquid. In general, compounding using bulk drug substances presents a greater risk than compounding using FDA-approved drug products.

The source, safety, and quality of the starting material are better known and established when an FDA-approved drug product is used instead of bulk drug substance for compounding. FDA-approved drug products are subject to premarket review for safety, effectiveness, and quality, and are manufactured by a facility that is subject to premarket assessment, including site inspection. After the premarket assessment, FDA conducts routine, risk-based inspections to verify that the manufacturer has systems in place to assure proper design, monitoring, and control of manufacturing processes and facilities. In addition, during pre-market review of FDA-

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with FDA. Drug products compounded by section 503A compounders are exempt from sections 505 (new drug approval requirements), 502(f)(1) (labeling with adequate directions for use), and 501(a)(2)(B) (CGMP requirements) if the conditions of section 503A are met, including that compounding is based on the receipt of valid prescriptions for identified individual patients (section 503A(a)). In general, section 503A compounders do not register with and are not routinely inspected by FDA, and they are primarily overseen by the states.

[15] Section 503B(a).

approved drug products, the quality standards and controls with respect to ingredients, and the specific processes and facilities used to produce the bulk drug substance and drug products, are similarly assessed. This includes a review of evidence to evaluate the safety of the bulk drug substance and any inactive ingredients used in the product. For example, FDA evaluates whether the sponsor's proposed specifications for purity, potency, and other attributes of the bulk drug substance are appropriate for its use in the drug product, and whether studies demonstrate that the levels of impurities are not unsafe and the bulk drug substance will be stable through the product's expiration date. In contrast, the quality standards, specifications, and controls for bulk drug substances used in compounding have not been assessed by FDA, and such bulk drug substances may be manufactured by a facility that is not subject to FDA premarket assessment, including premarket site inspection to verify manufacturing operations are in control.

Compounding from bulk drug substances also involves more complex and numerous inter-related manipulations by the compounder than compounding drugs from FDA-approved drug products, and involves the compounder addressing risks related to ingredient quality. For example, to compound a sterile drug product from a non-sterile bulk drug substance, the outsourcing facility first acquires ingredients that were made under conditions that result in low and known bioburden levels, including limits on endotoxins. It handles the materials to avoid contamination by harmful microorganisms or compounds and then performs a sterilization process, such as sterile filtration followed by aseptic filling. The outsourcing facility then either maintains the sterility of the material through subsequent manipulations or performs terminal sterilization. If an outsourcing facility performs any of the sterilization steps improperly, such as by failing to control air quality or maintain aseptic conditions, the drug may fail to achieve sterility or be further contaminated. If a terminal sterilization step is performed improperly, the drug could fail to achieve sterility, or the conditions of the sterilization process could cause the drug to degrade, resulting in a lower strength (sub-potent) and an increase in impurities. In contrast, compounding a sterile drug product using an FDA-approved sterile drug product does not entail sterilizing a non-sterile substance. Rather, the outsourcing facility would ensure that the sterile drug product being compounded retains its sterility.

Compounding from bulk drug substances also increases the potential for errors that could result in a sub-potent or super-potent product. Such compounding involves certain operations, such as weighing, handling, or mixing, that depend, in part, on the unique characteristics of different types of bulk drug substances (e.g., powders, liquids) such as powder flow properties, hygroscopicity, and liquid viscosity. Failure to take into account these characteristics can adversely impact weighing, handling, mixing, or other compounding operations. In addition, these operations are generally conducted under circumstances in which cross-contamination is more likely to occur. For example, these operations may involve the use of powders, which are often similar in appearance and challenging to control. This can result in mix-ups (e.g., accidental use of wrong materials or contaminated equipment), carryover of residues, and airborne transfers of potential contaminants. In contrast, compounding drug products using FDA-approved drug products generally does not present the same degree of risk. For example, when an FDA-approved product is not a powder, compounding with the approved drug will not involve several of the considerations and steps described above and is therefore less likely to lead to errors.

Finally, compounding a drug product from a bulk drug substance that is a component of an FDA-approved drug when there is no clinical need to do so, perhaps because of economic incentives, undermines the drug approval process. For example, use of bulk drug substances to compound a formulation of a needed concentration, route of administration or dosage form rather than simply diluting or otherwise manipulating the approved drug reduces the incentive for sponsors to invest in and seek FDA-approval of such drugs. The drug approval process is critical to ensure patient access to pharmaceuticals whose quality, safety and effectiveness have been established.

In light of the foregoing concerns about drug quality and the integrity of the drug approval process, section 503B's limitation on the 503B Bulks List to substances for which there is a clinical need serves important public health functions. First, it helps to limit patient exposure to drugs that have not been demonstrated to be safe and effective, and that may be of substandard quality, to those situations in which the drug is necessary for patient treatment. Second, it preserves the incentives for sponsors to invest in the research and testing required to obtain FDA approval, thereby helping to maintain a supply of high-quality, safe, and effective drugs.

D. Process for Developing the 503B Bulks List

In the *Federal Register* of December 4, 2013 (78 FR 72838), FDA requested nominations for specific bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List. In response to that request, interested groups and individuals nominated a wide variety of substances. However, many of those nominations were not for substances used in compounding as active pharmaceutical ingredients or did not include sufficient information to allow FDA to evaluate the nominated substance. To improve the efficiency of the process for the development of the list of bulk drug substances, FDA reopened the nomination process in the *Federal Register* of July 2, 2014 (79 FR 37750), and provided more detailed information on what it needs to evaluate nominations for the list. On October 27, 2015 (80 FR 65770), the Agency opened a new docket, FDA- 2015-N-3469, to provide an opportunity for interested persons to submit new nominations of bulk drug substances or to re-nominate substances with sufficient information. This docket is currently open.

If the information provided by the nominator did not include sufficient supporting information for FDA to evaluate,[16] the nominator should re-nominate the substance with sufficient supporting information if it wishes to ensure that the bulk drug substance will be reviewed for potential inclusion on the 503B Bulks List.

In June 2016, FDA published the guidance for industry *Interim Policy on Compounding Using Bulk Drug Substance Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. This guidance, which was revised in January 2017, sets forth interim regulatory policies for outsourcing facilities compounding using bulk drug substances and provides information about the Agency's procedures for establishing the 503B Bulks List.

[16] If the substance was not nominated with adequate supporting information, it will appear in Category 3, as described in FDA's guidance, *Interim Policy on Compounding Using Bulk Drug Substance Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

As explained in the interim guidance, as FDA evaluates bulk drug substances, it intends to publish a notice for public comment in the *Federal Register* that describes its proposed position on each substance along with the rationale for that position.[17] After considering any comments on FDA's proposals regarding whether to include nominated substances on the 503B Bulks List, FDA will consider whether input from the Pharmacy Compounding Advisory Committee (PCAC) on the nominations would be helpful to the Agency in making its determination, and if so, it will seek PCAC input.[18] Depending on its review of the docket comments and other relevant information before the Agency, the Agency may finalize its proposed determination without change, or it may finalize a modification to its proposal to reflect new evidence or analysis regarding clinical need. FDA will then publish in the *Federal Register* a list identifying the bulk drug substances for which it has determined there is a clinical need and FDA's rationale in making that final determination. FDA will also publish in the *Federal Register* a list of those substances it considered but found that there is no clinical need to use in compounding and FDA's rationale in making this decision.

FDA intends to maintain a current list of all bulk drug substances it has evaluated on its website, with separate lists for bulk drug substances it has placed on the 503B Bulks List and those it has decided not to place on the list. FDA will only place a bulk drug substance on the 503B Bulks List where it has determined there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance. If a clinical need to compound drug products using the bulk drug substance has not been demonstrated, based on the information submitted by the nominator and the information considered by the Agency, the Agency will not place a substance on the 503B Bulks List.

FDA intends to evaluate the substances nominated for the 503B Bulks List on a rolling basis. FDA will evaluate and publish in the *Federal Register* its proposed and final determinations in groups of bulk drug substances until all nominated substances that were sufficiently supported have been evaluated and either placed on the 503B Bulks List or identified as bulk drug substances that were considered but determined not to be appropriate for inclusion on the 503B Bulks List.

FDA will not consider a substance for inclusion on the 503B Bulks List if the substance is not eligible for the exemptions available under section 503B, such as biological products subject to licensure in a biologics license application under section 351 of the Public Health Service Act or substances that appear on the list of drugs that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or ineffective.

Below, we discuss the Agency's interpretation of *clinical need* as used in section 503B(a)(2), factors the Agency intends to use to evaluate bulk drug substances that have been nominated, and certain additional procedures the Agency intends to follow during its review.

[17] This procedure is set forth in section 503B(a)(2)(A)(i).

[18] Section 503B does not require FDA to consult the PCAC before developing a 503B Bulks List.

III. POLICY

In the next section, we discuss how we interpret *bulk drug substances for which there is a clinical need*, and in the following section we provide a more detailed discussion of the analysis we intend to conduct in evaluating bulk drug substances that have been nominated for inclusion on the 503B Bulks List.

A. Bulk Drug Substance for Which There Is a Clinical Need

1. Clinical Need Standard

Section 503B authorizes FDA to publish a list identifying "bulk drug substances for which there is a clinical need." FDA interprets this to mean that the 503B Bulks List may include a bulk drug substance if:

(1) there is a clinical need for an outsourcing facility to compound the drug product, and

(2) the drug product must be compounded using the bulk drug substance.

This interpretation is consistent with the text of section 503B(a)(2)(A), and the purpose of the 503B Bulks List, which is to identify the bulk drug substances that can be used in compounding under the exemptions in section 503B, provided the other conditions in that section are met. The Agency's interpretation also furthers the broader purposes of the Act by (1) helping to protect patients from risks of compounding from bulk drug substances where there is no clinical need to do so and (2) protecting the integrity of the drug approval process. FDA intends to use the analysis discussed below in determining whether there is a clinical need for a nominated bulk drug substance.

The Agency does not interpret supply issues, such as backorders, to be within in the meaning "clinical need" for compounding with a bulk drug substance. We note that section 503B of the FD&C Act already allows compounding from bulk drug substances if the drug product compounded from such bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing. Similarly, FDA does not interpret considerations of cost to be within the meaning of "clinical need."

2. Inclusion of a Bulk Drug Substance on the 503B Bulks List

There may be situations in which FDA's finding of clinical need is limited to the use of the bulk drug substance to make drug products with certain attributes, such as specific strengths, routes of administration, or dosage forms. In such a case, the Agency may tailor the proposed entry on the 503B Bulks List to the use of the bulk drug substance to compound a drug product with those attributes. For example, if the Agency were to find a clinical need for a bulk drug substance to be used to compound a drug product for topical use, it may limit the entry of that bulk drug substance on the 503B Bulks List to use of the substance to compound drug products for topical use.

Additionally, when a bulk drug substance that is a salt or ester of an active moiety is listed, FDA intends to include only that particular salt or ester on the 503B Bulks List. The base compound and other salts or esters of the same active moiety are different bulk drug substances and would therefore not be included.

FDA's evaluation of the nominated substances will be, necessarily, far less rigorous and less comprehensive than the Agency's review of drug products as part of the new drug approval process. The new drug approval process is conducted based on extensive data submitted in new drug and abbreviated new drug applications, which are not available for the nominated substances. Additionally, the Agency's review during the drug approval process includes premarket evaluation of the specific drug product (i.e., the finished dosage form containing the active ingredient and any inactive ingredients); its proposed labeling; the applicant's chemistry, manufacturing, and controls information; and a premarket assessment of the establishments where approved drug products will be manufactured. The Agency will not have the same type, quality, or amount of information about the compounded drug product when it evaluates whether there is a clinical need to compound using the nominated bulk drug substance.

Therefore, the inclusion of a drug substance on the 503B Bulks List should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug product compounded using the substance. Nor should it be assumed that drug products compounded using substances on the 503B Bulks List have been proven to be safe and effective under the standards required for Agency approval. Any person who represents that a compounded drug product made with a bulk drug substance that appears on the 503B Bulks List is FDA-approved, or otherwise endorsed by FDA generally, or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act.

B. Analysis for Evaluating Nominated Bulk Drug Substances

1. Overview of Proposed Analysis

FDA intends to use a two-part analysis, described more fully in section III.B.ii, below, in evaluating substances nominated for placement on the 503B Bulks List to determine whether there is a clinical need.

For Part 1 of this two-part evaluation, FDA intends to determine whether the bulk drug substance is a component of an FDA-approved product. For purposes of this inquiry, FDA will generally consider a bulk drug substance to be a component of an FDA-approved drug product if the bulk drug substance is the same as the active pharmaceutical ingredient in an FDA-approved drug product.[19]

If the bulk drug substance is not a component of an FDA-approved product, FDA will proceed to Part 2 of its evaluation to determine whether the substance is clinically necessary.

[19] The active pharmaceutical ingredient is as defined in the approved product labeling.

If the bulk drug substance is a component of an FDA-approved drug, FDA intends to conduct a threshold review based on the following questions:

(a) Is there a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that (i) an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and (ii) the drug product proposed to be compounded is intended to address that attribute?
(b) Is there a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product?

If FDA answers "no" to either threshold question, the Agency does not intend to include the nominated bulk drug substance from the 503B Bulks List. If the Agency answers "yes" to both questions, it intends to proceed to Part 2 of the analysis.

The Agency intends to use Part 2 to evaluate bulk drug substances that are components of FDA-approved drugs if the questions in Part 1 are answered in the affirmative, and to evaluate bulk drug substances that are not components of FDA-approved drug products. The Agency proposes to conduct a balancing test, described more fully below, under which FDA would consider each factor in the context of the others and to balance them, on a substance-by-substance basis, to determine whether the substance is appropriate for inclusion on the 503B Bulks List. The balancing test includes the following factors:

(a) The physical and chemical characterization of the substance;
(b) Any safety issues raised by the use of the substance in compounding;
(c) The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
(d) Current and historical use of the substance in compounded drug products, including information about the medical condition(s) that the substance has been used to treat and any references in peer-reviewed medical literature.

Under Parts 1 and 2 of its analysis, FDA intends to evaluate the nominated bulk drug substances in the context of information provided by the nominators about the drug products proposed to be compounded and the proposed uses of those drug products. The Agency may also consider additional uses of the bulk drug substances that were not described in the nomination, such as those that are described in public comments submitted to the Agency or that are otherwise identified during the Agency's review, if the Agency concludes they may be relevant to its decision whether to place a bulk drug substance on the 503B Bulks List. The Agency may request additional information from nominators or persons who have submitted relevant docket comments to help inform its review.

2. Explanation of Analysis

a. Part 1

i. Subpart 1(a): Need for a Compounded Drug?

Under Subpart 1(a), FDA intends to consider whether there is a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that (i) an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and (ii) the drug product proposed to be compounded is intended to address that attribute.

Unless an attribute of the FDA-approved drug is medically unsuitable for certain patients, and a drug product compounded using a bulk drug substance that is a component of the approved drug is intended to address that attribute, there is no clinical need to compound using that bulk drug substance. Rather, it would unnecessarily expose patients to the risks associated with drug products that do not meet the standards applicable to FDA-approved drug products for safety, effectiveness, quality, and labeling and would undermine the drug approval process. Accordingly, unless FDA can answer "yes" to the two questions in Part 1(a) of its analysis, the Agency intends to find there is no clinical need for compounding using the bulk drug substance.

In the Part 1(a) threshold test, FDA will focus on the rationale for compounding from a bulk drug substance that appears in the nomination or that FDA otherwise identifies. For example, several nominations state that patients need a drug product compounded using the bulk drug substance because the FDA-approved drug that includes the bulk drug substance as a component also includes inactive ingredients or additional active ingredients that are inappropriate for the patient population. Other nominations state that the FDA-approved drug is for use by routes of administration or in dosage forms that are inappropriate for the patient population. For these examples, FDA will evaluate whether the inactive ingredients, additional active ingredients, the route of administration, or the dosage forms are attributes of the FDA-approved products that make them unsuitable and impart unacceptable risk for certain patients for the conditions that FDA is evaluating. If so, FDA will consider whether the compounded drug products are intended to address those attributes by, for example, excluding the inactive ingredients or additional active ingredients or using a different route of administration or dosage form.

Whether there is an attribute of the FDA-approved drug product that makes it medically unsuitable for some patients for the conditions that FDA has identified for evaluation and, if so, whether the compounded drug product addresses that attribute, will be determined on a case-by-case basis. For example, if an approved drug product contains peanut oil, patients with a peanut allergy treated with the FDA-approved drug product may develop a serious allergic reaction.[20] Accordingly, FDA would likely determine that a proposal to produce a compounded drug product without the peanut oil to address the condition described in the nomination would proceed through Part 1(a). Or, if a drug product is approved with two active ingredients in a fixed combination, but FDA has received or identified information indicating that it is known, within that specialty, on the basis of competent evidence, that some patients need just one active ingredient and are likely to have an adverse clinical reaction to the second active ingredient, and there is no FDA-approved drug product containing the one active ingredient they need, then FDA would likely determine that a proposal to compound the single-ingredient product from a bulk drug substance would proceed through Part 1(a).

[20] See Footnote 21.

In general, broad statements that a compounded drug product with an attribute that differs from the FDA-approved drug is necessary for certain patients, without sufficient evidence that the attribute makes the FDA-approved drug medically unsuitable for specific patients for the condition that has been identified for evaluation, will not be adequate. For example, general statements that a preservative-free drug needs to be compounded because some patients may have an allergy to the preservative in the approved drug likely would not be an acceptable reason for compounding from bulk drug substances, unless the preservative is well known to be a clinically significant allergen for some patients who are administered the drug. Similarly, minor changes in dosage form, such as from tablet to capsule, are unlikely to fulfill a clinical need that cannot be met by the approved drug. Nor is the combination of multiple active ingredients to allow for administration of fewer products likely to represent a clinical need for purposes of this factor.

ii. Subpart 1(b): Need for a Drug Compounded from a Bulk Drug Substance?

Under Subpart 1(b), if there is an FDA-approved drug product that incorporates the nominated bulk drug substance, FDA intends to consider whether there is a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than an FDA-approved drug product. This is because in order to place a bulk drug substance on the 503B Bulks List, FDA must determine that there is a clinical need for outsourcing facilities to compound a drug product *using the bulk drug substance*. Accordingly, the Agency intends to find that there is no clinical need to compound using a bulk drug substance unless the nomination identifies a drug product that must be produced from the bulk drug substance rather than from an FDA-approved drug product.

To make this assessment, FDA intends to consider the difference or differences between the proposed compounded drug product and the FDA-approved product. Whether the compounded drug product must be prepared by starting from a bulk drug substance will be assessed case by case, considering the proposed differences between the products, the basis provided by the nominator for why it intends to use the bulk drug substance rather than the FDA-approved drug to compound the proposed drug product, and other relevant information, including the type and number of manipulations necessary to produce the proposed drug from the FDA-approved product versus the bulk drug substance and their potential impact on the overall quality of the resultant drug product. For example, FDA is likely to determine that a drug product that is being proposed to be compounded without an active or inactive ingredient (e.g., an allergen) in the approved product must be compounded from a bulk drug substance rather than the FDA-approved drug because of the difficulties and complexities likely to be associated with removing an ingredient from a finished drug product. In contrast, FDA is likely to determine that a drug product that is being proposed to be compounded in a lower concentration than an FDA-approved product (e.g., for a pediatric patient) should be compounded from the FDA-approved product because a more dilute drug product can often be formulated from an approved drug product with minimal, simple manipulations (e.g., adding a diluent to an approved drug).

b. Part 2

For bulk drug substances that are components of an FDA-approved drug, FDA only intends to proceed to Part 2 if the Agency answers "yes" to the questions in both subpart 1(a) and subpart 1(b). FDA's analysis of bulk drug substances that are not components of FDA-approved drugs will start with Part 2.

In Part 2 of its evaluation, FDA intends to balance the four factors described below. Whether the factors in Part 2 taken together weigh in favor of or against a finding of clinical need will inform FDA's proposal to include or exclude nominated bulk drug substances from the 503B Bulks List.

i. Subpart 2(a): Physical and Chemical Characterization

Under the first factor, the physical and chemical characterization of the bulk drug substance, FDA intends to consider each substance's purity, identity, and quality. Based on attributes such as the substance's molecular structure, stability, melting point, appearance, likely impurities, and solubilities, FDA would determine whether the substance can be identified or compounded consistently based on its physical and chemical characteristics. If a substance cannot be well-characterized, or is not chemically and physically stable after compounding, or requires conditions to prevent degradation that cannot be accomplished reliably, this factor would weigh against its inclusion on the 503B Bulks List because there would be no assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities considered by the Agency.

With respect to bulk drug substances that are components of FDA-approved drug products, FDA will have already determined the bulk drug substance in a particular drug product possesses chemical and physical characteristics suitable for inclusion as an active ingredient in an FDA-approved product. However, bulk drug substances that are components of FDA-approved drug products may present different challenges. In addition to concerns related to purity of substances from sources that have not been evaluated during the premarket approval process, there may be physical and chemical characterization concerns, such as stability or bioavailability concerns, when they are used to compound drug products, that differ from the approved product in their formulation, route of administration, strength, or other features. FDA therefore intends to consider whether such concerns are associated with use of the bulk drug substance to compound a particular drug product.

ii. Subpart 2(b): Safety Issues Raised by Use of the Substance in Compounding

Under the second factor, FDA intends to consider the safety issues raised by the use of a nominated bulk drug substance in compounding. With respect to nominated bulk drug substances that are not components of FDA-approved drug products, based on FDA's review of the substances nominated to date, it is unlikely that the substances will have been thoroughly investigated in *in vitro* or in animal toxicology studies, or that there will be well-controlled clinical trials to substantiate their safe use in humans. Thus, in evaluating these substances, the Agency is likely to have at its disposal very limited information, or in some cases no information, of the type and quality that is ordinarily required and evaluated as part of the drug approval process.

Therefore, to evaluate substances that are not components of FDA-approved drug products, the Agency intends to rely on information, such as reports in peer-reviewed medical literature, about each substance's pharmacology, acute toxicity, repeat dose toxicity, mutagenicity, developmental and reproductive toxicity, and carcinogenicity, or other data that relates to safety. The Agency may also rely on reports and abstracts in the literature or reported to FDA about adverse reactions associated with human use of the substances, or other appropriate information. FDA also intends to consider the availability of approved drug products or drug products that follow an over-the-counter monograph (OTC monograph products) as treatment options for the conditions being considered. The existence of such approved drug products or OTC monograph products would likely weigh against inclusion on the proposed list when the toxicity of the bulk drug substance appears to be significant or where there are other safety concerns associated with the use of the substance in compounded drug products.

With respect to bulk drug substances that are components of FDA-approved drug products, FDA will have already determined that a drug product that includes the bulk drug substance as a component is shown to be safe for its intended use under the conditions described in its approved product labeling. However, when a bulk drug substance that is a component of an FDA-approved drug product is used in compounding, differences between the resulting compounded drug product and the approved drug product may raise safety concerns (e.g., issues arising from different formulations, routes of administration, or strengths). Additionally, there may be relevant differences between the proposed uses or intended patient population of the FDA-approved drug and a compounded drug product (e.g., if the compounded drug product is specifically proposed for a pediatric population and the FDA-approved drug is indicated for adults). In evaluating the potential impact of such differences on the safety of the compounded drug product, FDA intends to rely on available safety information, such as peer-reviewed scientific literature, reports to FDA about adverse reactions relevant to the difference or differences, and FDA's expertise to evaluate safety risks associated with drug products proposed to be compounded from the nominated bulk drug substance.

iii. Subpart 2(c): Available Evidence of Effectiveness or Lack of Effectiveness

Under the third factor, FDA proposes to consider evidence of the substance's effectiveness or lack of effectiveness for an identified use, including but not limited to reports in peer-reviewed medical literature, if any such evidence exists. In the new drug approval process, applicants are required to demonstrate effectiveness under the substantial evidence standard described in section 505(d) of the FD&C Act. FDA recognizes that few, if any, of the substances nominated for the 503B Bulks List that are not components of approved drug products will have been studied in adequate and well-controlled investigations sufficient to satisfy the standard in the drug approval process. In evaluating these bulk drug substances, the Agency would consider relevant evidence concerning effectiveness that is available.

For example, for substances that are not components of approved drug products, but have been widely used for a long period of time, the literature may include anecdotal reports of effectiveness for a particular use or reports of clinical trials suggesting possible effectiveness.

Conversely, the literature may contain anecdotal or clinical evidence that a substance did not show effectiveness for a particular use in a reasonably designed trial. Further, information about other available treatments may affect FDA's evaluation. For a bulk drug substance that is proposed to be used to compound drug products to treat a serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy, particularly when there are approved drug products that may be appropriate for treatment. In those cases, the existence of drug products approved to treat the condition would likely weigh against inclusion on the 503B Bulks List, and the availability of no or minimal effectiveness data, trials that do not demonstrate effectiveness, would weigh more heavily against placement on the list in FDA's balancing of the relevant factors.

With respect to bulk drug substances that are components of FDA-approved drug products, FDA will have already determined that a drug product that includes the bulk drug substance as a component is effective for its indicated use under the conditions described in its approved labeling. Additionally, in Part 1(a) of the analysis, the Agency will already have considered whether there is a basis to conclude that an attribute of the FDA-approved drug product makes it unsuitable to treat certain patients for the medical condition described in the nomination. However, when the bulk drug substance that is a component of an FDA-approved drug product is used in compounding, differences between the compounded drug product and the FDA-approved drug product may raise effectiveness concerns arising, e.g., from a different formulation, route of administration, or strength. Additionally, effectiveness concerns may be raised by differences between the FDA-approved drug product and the compounded drug product in terms of their proposed uses or intended patient population. FDA intends to consider whether such effectiveness concerns are associated with use of the bulk drug substance to compound a particular drug product.

iv. Subpart 2(d): Historical and Current Use in Compounding

Under the fourth factor, FDA intends to consider the historical and current use of the substance in compounding drug products, which may include the length of time the substance has been used in compounding; the medical conditions it has been used to treat; the patient population it has been used to treat; how widespread its use is and has been, including use in other countries; whether it is typically used to compound drugs that healthcare providers maintain in their offices in advance of identifying individual patients; and relevant references in peer-reviewed medical literature. Documentation of this information may include reference to past medical textbooks or medical specialty professional organization guidelines that describe the use of the drug.

The longer a substance has been used in compounding drug products and the broader its use,[21] particularly to compound drug products for office stock,[22] the more this factor will generally weigh in favor of inclusion of the substance on the list. In contrast, if FDA's analysis suggests that the historical and current use of the substance in compounding has been minimal or non-existent, or the nominator has not provided information supporting its historic use in compounding, the more this factor would generally weigh against inclusion of the substance on the 503B Bulks List.

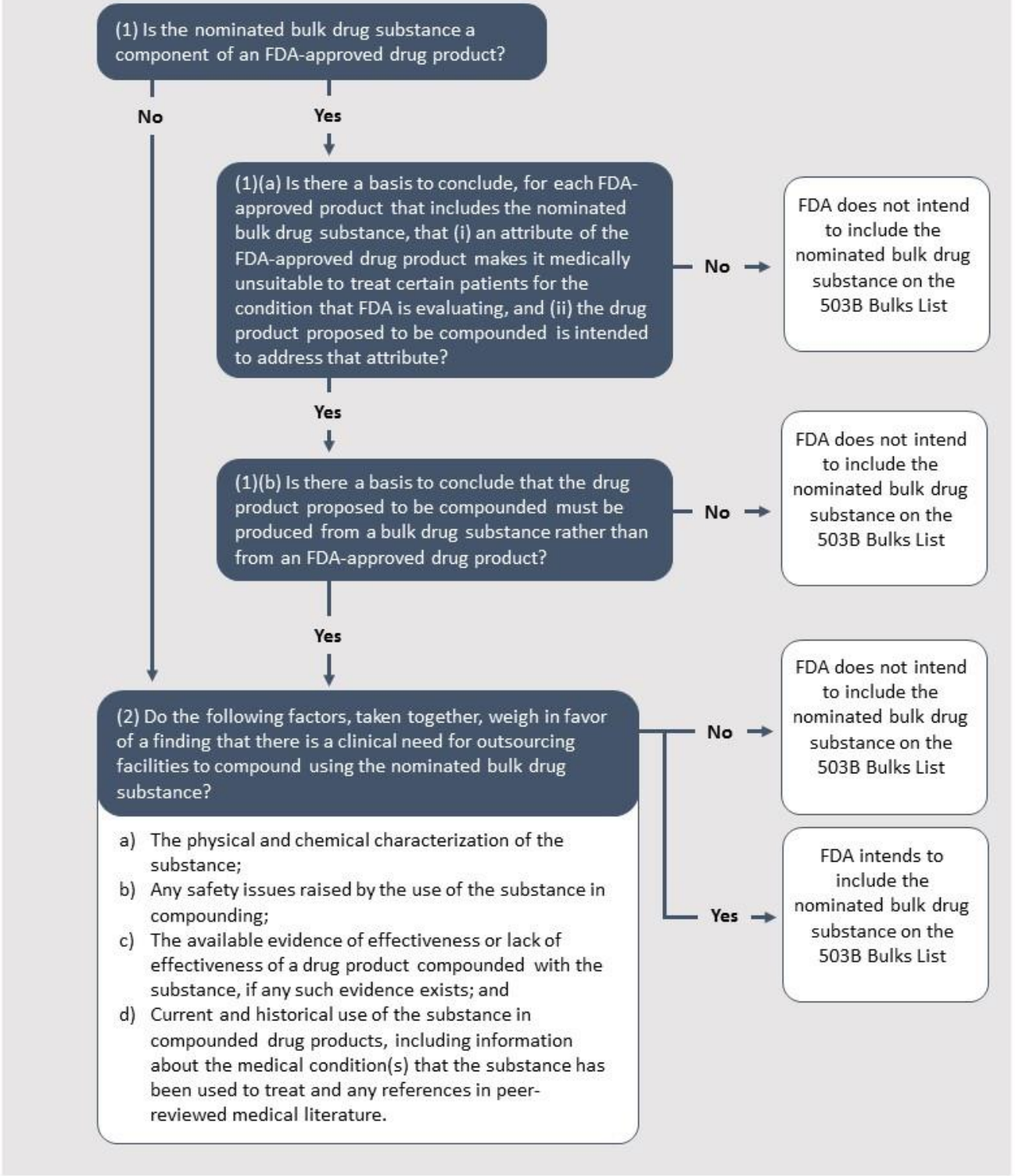
In weighing this factor for bulk drug substances that are components of FDA-approved drug products, FDA intends to consider evidence, if available, of whether the substance has been used to compound drug products that are intended to address an attribute of the FDA-approved drug product that makes it unsuitable to treat certain patients for the condition that FDA has identified for evaluation.

[21] For example, in the description of Part 1(a) of this analysis, we noted that an example of a situation in which an attribute of the approved drug product may make it medically unsuitable to treat certain patients for the condition identified for evaluation is when a patient who has a peanut allergy needs to be treated with an approved drug that contains peanut oil. In general, this factor would weigh more heavily in favor of including of the bulk drug substance on the 503B Bulks List if there is information that a significant portion of the population of the United States has a peanut allergy and therefore uses a compounded drug rather than the approved drug, compared to information that a bulk drug substance is to be compounded to treat few patients with an uncommon, non-urgent condition.

[22] In conducting this analysis, the Agency proposes to note the extent of compounding drug products using a nominated bulk drug substance for office stock, because outsourcing facilities are the only entities that can distribute compounded drug products without first receiving prescriptions for identified individual patients. In contrast, compounding under section 503A must be based on the receipt of a valid prescription for an identified individual patient. Section 503A(a). See FDA's guidance for industry *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

For example, if there is information that the drug compounded from the nominated bulk drug substance is maintained in physicians' offices to treat patients who present with infections in emergency situations, this factor may weigh more heavily in favor of including the bulk drug substance on the list, compared to information that a bulk drug substance is used to compound a drug product that does not need to be administered in the office in non-emergency situations.

APPENDIX A: HOW FDA GENERALLY INTENDS TO EVALUATE BULK DRUG SUBSTANCES THAT HAVE BEEN NOMINATED FOR INCLUSION ON THE 503B BULKS LIST



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THE NATIONAL URGENCY FOR OPIOID STEWARDSHIP

The opioid epidemic in America is an urgent public health crisis with devastating consequences. According to the U.S. Centers for Disease Control and Prevention, nearly two million Americans have a prescription-related opioid use disorder (OUD), and 46 people die from a prescription opioid-related overdose every day—more than a four-fold increase since 1999. These staggering statistics demand coordinated commitment from healthcare organizations and communities to improve opioid stewardship so that patients can be assured safe and effective pain management that reduces their risk of OUD and overdose.

Our nation faces an urgent an escalating public health crisis in the opioid epidemic. *The National Quality Partners Playbook™: Opioid Stewardship* is a critically important tool for frontline providers to more safely and effectively manage patients' pain.

SHANTANU AGRAWAL, MD, MPHIL, PRESIDENT AND CEO, NATIONAL QUALITY FORUM

Prescription opioids are powerful medications to help manage pain. These drugs, which include oxycodone, hydrocodone, morphine and methadone, benefit many individuals, including those undergoing active cancer treatment, those receiving palliative or end-of-life care, and some with acute pain. However, prescribing opioids for long-term, chronic non-cancer pain without fully understanding the addictive properties of opioids has contributed to widespread misuse. Clear connections also have emerged between the use of prescription opioids and the use of illicit opioids such as heroin, which is growing across the nation.

NQF'S FUNDAMENTAL ACTIONS TO SUPPORT OPIOID STEWARDSHIP

The National Quality Forum's *National Quality Partners (NQP) Playbook™: Opioid Stewardship* provides essential opioid stewardship guidance for healthcare organizations and clinicians across care settings. Developed with input from more than 40 experts and national stakeholders from the public and private sectors, the *NQP Playbook™* identifies seven fundamental actions to support high-quality, sustainable opioid stewardship programs:

1. **Promoting leadership commitment and culture,** including allocating resources and support from organizational leaders.
2. **Implementing organizational policies** to support evidence-based approaches to multimodal pain management.
3. **Advancing clinical knowledge, expertise, and practice** to ensure clinicians are trained in and understand the science of pain, evidence-based pain management strategies, and patient communication techniques.
4. **Enhancing patient and family caregiver education and engagement** so they are fully informed about risks and benefits of appropriate pain management options and are active participants in decisions about pain management plans.
5. **Tracking, monitoring, and reporting performance data** on opioid prescribing, patient-reported outcomes, adverse events, and the use of prescription drug monitoring programs (PDMPs) to identify opportunities for improvement and assess the impact of opioid stewardship efforts.
6. **Establishing accountability** to articulate clear expectations for creating, promoting, and maintaining a culture of opioid stewardship.
7. **Supporting collaboration with community leaders and stakeholders** to achieve maximum impact.

The *NQP Playbook™* is an important step that will help us establish urgency around developing a comprehensive program for better pain treatment—one that will lead to sustainable approaches to preventing and mitigating against our current national substance abuse emergency.

PAUL CONLON, PHARMD, JD, SENIOR VICE PRESIDENT, CHIEF QUALITY & PATIENT SAFETY, TRINITY HEALTH, AND CO-CHAIR OF THE NQP OPIOID STEWARDSHIP ACTION TEAM

The *National Quality Partners (NQP) Playbook™* includes examples for implementation, potential barriers and suggested solutions, and sample tools and resources for each fundamental action area. Implementation examples—organized by basic, intermediate, and advanced—offer approaches based on anticipated level of resources and effort. The goal is for organizations to determine which approaches are best for them based on their own organizational context. Healthcare organizations and leaders may find the *NQP Playbook* content relevant across care settings, including acute, ambulatory, and home and community-based care.

LOOKING TO THE FUTURE

The *NQP Playbook* encourages healthcare organizations to develop realistic measurement strategies to assess key areas such as clinician prescribing patterns and the use of non-pharmacologic pain management options. In addition, the *NQP Playbook* identifies important drivers of change that can impact and advance opioid stewardship—including licensure, education, accreditation, payment, reimbursement, workforce management, and the use and integration of PDMPs into electronic health records—and urges federal entities, accreditation agencies, and partners in quality improvement to support action in these areas.

Download the *NQP Playbook* in the **NQF Store.** Questions? Contact National Quality Partners at nationalqualitypartners@qualityforum.org

NATIONAL QUALITY PARTNERS™ OPIOID STEWARDSHIP ACTION TEAM

NQF gratefully acknowledges the **National Quality Partners Opioid Stewardship Action Team** members for providing technical consultation as NQF developed and produced the *NQP Playbook: Opioid Stewardship.*

- Centers for Disease Control and Prevention
- Trinity Health
- Aetna
- Agency for Healthcare Research and Quality
- American Academy of Orthopaedic Surgeons
- American Academy of Physical Medicine and Rehabilitation
- American Nurses Association
- American Physical Therapy Association
- American Society of Health-System Pharmacists
- Appriss Health
- BlueCross BlueShield Association
- Centers for Medicare & Medicaid Services
- Council of Medical Specialty Societies
- Dental Quality Alliance
- Elevating Home
- Geisinger Health System
- Harborview Medical Center
- Health Resources and Services Administration
- HealthPartners
- Henry Ford Health System
- Heron Therapeutics
- Hospice and Palliative Nurses Association
- Hospital Corporation of America
- IBM Watson Health
- Institute for Behavioral Healthcare Improvement
- Institute for Healthcare Improvement
- Kaiser Permanente
- Kentuckiana Health Collaborative
- Magellan Health, Inc.
- Mayo Clinic
- Memorial Sloan-Kettering Cancer Center
- Partners Behavioral Health Management
- Patient & Family Centered Care Partners, Inc.
- Pharmacy Quality Alliance
- Premier Healthcare Alliance
- Press Ganey Associates
- Substance Abuse and Mental Health Services Administration
- U.S. Pharmacopeial Convention
- Veterans Health Administration
- Vizient, Inc.