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Industry View of Outsourcing

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Disclaimer

I am the Chief Pharmacy Officer of Baxa Corporation. That role provides me the perspective to address the outsourcing issue with no conflict of interest regarding the outcome of that discussion.



Learning Objectives

- Identify at least one liability that you retain after outsourcing work to a pharmacy.
- Enumerate three items you should verify as part of qualifying an outsourced vendor.
- Discuss the application of USP <797> requirements to an outsourcing vendor as it relates to beyond-use dating.



Reasons to Outsource

- Cost of outsourcing is less than cost of in-house production
- Outsourcing company has competencies or facilities that we do not have
 - Technical expertise or equipment
 - Already makes a product we want to sell
- Outsourcing company produces products that we would like to add to our product line



Two Types of Outsourcing

- Contract manufacturer/service –
 - Primary company retains identity of the “manufacturer of record”
 - Primary company is required to ensure compliance with regulatory requirements
- Private Label/Distribution Relationship
 - Outsourcer becomes the manufacturer of record
 - Outsourcer must independently meet regulatory requirements



What They Have in Common...

- Marketplace perceives the primary company as the maker of the product – it is branded with their name.
- Primary company has an ongoing responsibility to ensure that this outsourcing company continues to be an appropriate partner.
- In either case, the primary company can outsource some quality/regulatory processes, but remains responsible to the market.



Examples from Baxa

- Contract Services
 - Manufacture of syringe strips for IntelliFill[®] i.v.
 - Manufacture of IntelliFill i.v.
 - Sterilization of sterile tube sets
- Private Label
 - MicroFuse[®] syringe infuser
 - Infuse[™] T10



Qualification – The Things We Look For

- Facilities and expertise consisted with the contracted work
- Presence of an ongoing and functional quality system
 - Policies and procedures
 - Internal audit system
- Documentation to support claims
- Appropriate licensures/registrations



For a medical device company, this means we must perform site visits and vendor qualification on a regular basis, usually at least annually



Even when there are no regulatory requirements to consider, we must always recognize that our customers will not distinguish between products or services we have outsourced, and products and services we have not. Our customers hold US responsible.



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Outsourcing of Sterile Compounding Services

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Disclaimer

"Although I am a member of the 2010-2015 USP Compounding Expert Committee, I am speaking today in my individual capacity and not as a member of the Committee or as a USP representative.

The views and opinions presented are entirely my own. They do not necessarily reflect the views of USP, nor should they be construed as an official explanation or interpretation of <797>."



History of Compounding

- All states license pharmacists to compound
 - States laws vs. Federalism
 - The federal government through the FDA is arguing that patient safety is in jeopardy
- Schools of pharmacy do not teach sterile compounding skills
 - AJHP article: 1 in 6 graduates prepared for sterile work
- Compounding is an essential component of pharmacy practice

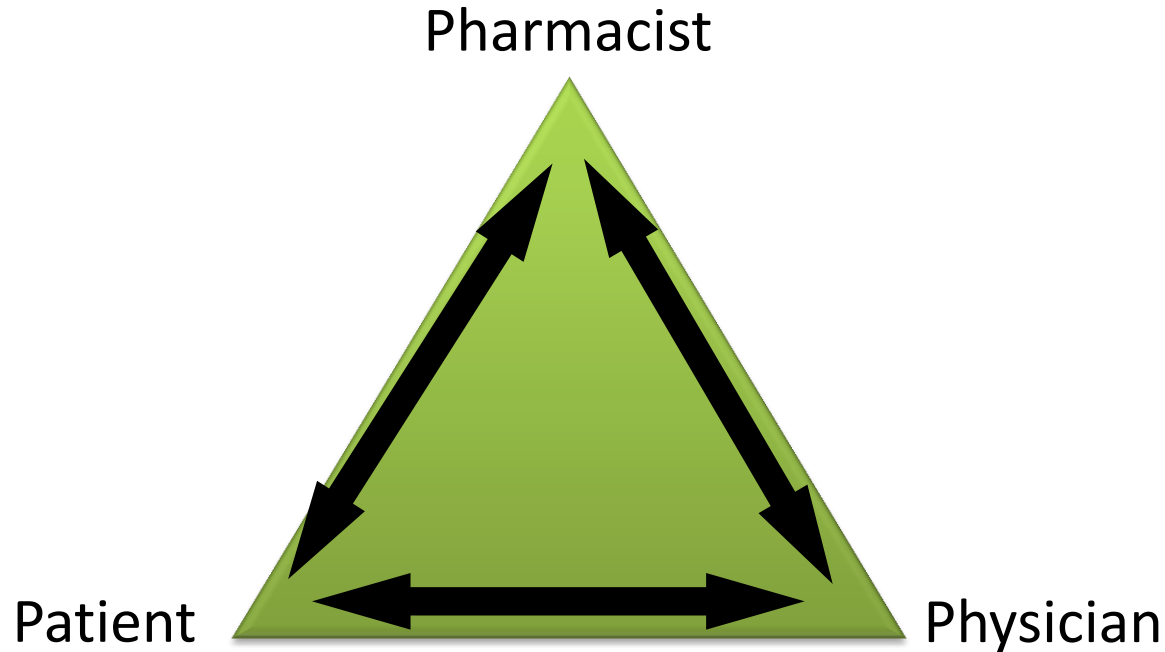


History of Compounding

- Pharmacy compounding is simply the art and science of preparing customized medications for patients
- Compounding is legal under state law
- Non-patient specific compounding is permitted by state boards of pharmacy
 - Shared Services
 - Central Fill Operation
 - Outsourcing



Pharmacy vs. Manufacturing



The Patient-Physician-Pharmacist triad (IRON TRIAD) is one of the critical elements of pharmacy that is not present in manufacturing.

History of Compounding

The government (essentially FDA) argues that the compounding of drugs is in violation of the 1938 Food Drug and Cosmetic Act and that compounding was essentially legalized in 1997 with FDAMA.



Value of Responsible Compounding

"...the government recognizes that traditional pharmacy compounding historically has and continues to serve an important public purpose - allowing physicians and pharmacists, working together, to develop customized therapies for patients for whom commercially manufactured drugs are not suitable for various medical reasons."

- U.S. Government response:
Medical Center Pharmacy, et al. v. John Ashcroft, et al.



Reasons for the Increase in Pharmacy Compounding

- Limited dosage forms
- Limited strengths
- Home health care
- Hospice
- Non-available drug products/combinations
 - National Drug Shortages
- Orphan drugs
- Veterinary compounding
- New therapeutic approaches



Comparison of Practitioner Compounding vs. Industrial Manufacturing

| Attribute | Compounding | Manufacturing |
|--|--|---|
| Quantity, duration, and distribution of medication | small, short, and local (patient-MD-RPh triad) | large, long, and nationally to wholesalers and pharmacies |
| Approximate history | -from unrecorded BC era -A USP founding purpose | Since late 1800s |
| Main legal regulation | State Pharmacy Boards | FDA |
| Quality and performance testing | little or none | pre-, in-, and post-process |
| Therapeutic paradigm | matches drug to patient | matches patient to drug |
| <p>United States Pharmacopeia (USP) Compounding Pharmacy Stakeholders Forum August 21, 2001, USP Headquarters, Rockville, MD David W Newton, PhD, Chair of USP Parenteral Compounding Expert Committee</p> | | |



Outsourcing

- Outsourcing pharmacies may be required by state boards of pharmacy to register with the FDA as a manufacturer
 - Several states do not permit licensed pharmacies to prepare and sell/dispense non-patient specific doses to another pharmacy for future dispensing
- States that permit NPS compounding typically require:
 - Registration/Notification to the State Board of Pharmacy
 - Clear delineation of responsibilities
 - Written contract
 - Shared computer system



Outsourcing

- Registration with the FDA is voluntary
 - Pharmacy Manufacturing¹
 - Regional Admixture Pharmacy¹
- Currently there is NO clear guidance from the FDA re: pharmacy compounding operations
 - New guidance document expected by end of 2011
- FDA expects these operations to comply with 21 CFR 210 and 211.

¹ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm079755.htm>



What are the cGMPs?

- A set of current, scientifically sound methods, practices or principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure and potent products.
- In place to prevent
 - Sub-potency or super-potency
 - Contamination
 - Unpredictable safety or efficacy
 - Misbranding



What are the cGMPs?

- “cGMP” is used interchangeably with GMP and stands for “**current** good manufacturing practices”
- The cGMPs are **not** best practice standards
- cGMPs are **minimum** guidelines for practice in the manufacture, processing, packing or holding of drug products to be administered to humans or animals.
- cGMPs establish “what to do” **not** “how to do”
- cGMPs can be applied to small or large organizations
- cGMPs are **not** technology specific
- The cGMPs are constantly changing, evolving, improving and are the cornerstone of manufacturing practice.
- The cGMPs are contained in the Code of Federal Regulations (CFR)

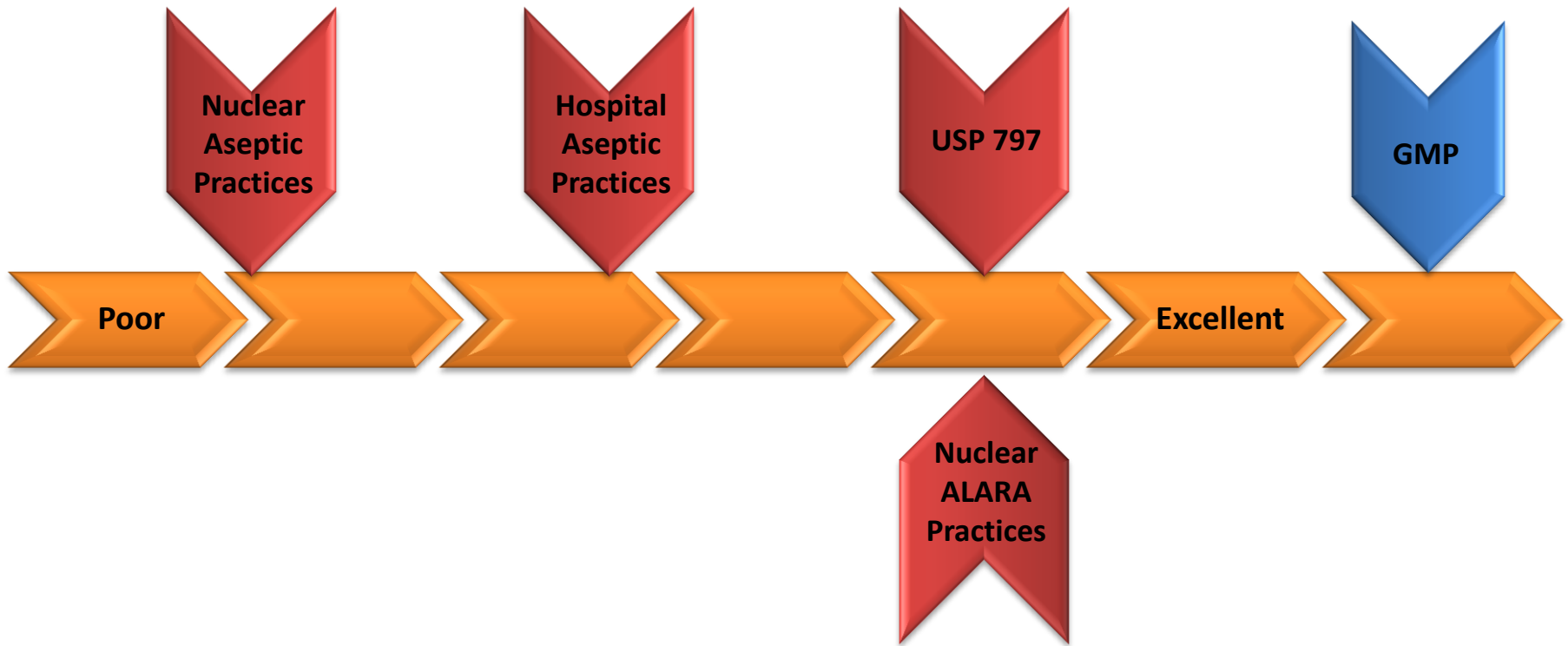


cGMPs apply to:

- Finished pharmaceuticals
- Drug Substances or Active Pharmaceutical Ingredients
- Prescription and OTC drugs
- New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA)
- Approved and unapproved drug products
- Investigative New Drug Application (INDA)



Spectrum of Aseptic Processing Practices



Approved or Unapproved Drugs

- FDA approves drugs, packaging, labeling and their marketing material (claims)
- FDA inspects facilities of manufacturers who manufacture approved drugs to ensure compliance with 21 CFR 210 and 211.
 - The FDA does not approve or certify manufacturing operations
- Outsourcing pharmacies are technically creating a “new drug entity”



Compounded CSPs from Outsourcing Pharmacies

- These compounded doses have NOT been approved by the FDA and have not been evaluated for safety or efficacy
- CSPs from FDA registered outsourcing pharmacies are NOT the same as drugs from “big pharma”
- A compounded medication with a NDC number does not mean that the drug is approved



US Food and Drug Administration

- In lieu of a detailed ANDA or NDA submission to the FDA, outsource vendors are expected to have the ability to link its CSPs to specific patient to whom the CSPs are ultimately dispensed*
- Outsource vendor is responsible for assuring that the hospital have in place the necessary controls to link vendor prescription products, by lot, control numbers, or otherwise, to specific patients (to ensure that CSPs can be traced to patients in the event of a recall)

*<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm075828.htm>



National Drug Code (NDC)*

- The Drug Listing Act of 1972 requires registered drug establishments to provide the Food and Drug Administration (FDA) with a current list of all drugs manufactured, prepared, propagated, compounded, or processed by it for commercial distribution. (See Section 510 of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. § 360)).
- Drug products are identified and reported using a unique, three-segment number, called the National Drug Code (NDC), which is a universal product identifier for human drugs.
- FDA inputs the full NDC number and the information submitted as part of the listing process into a database known as the Drug Registration and Listing System (DRLS).
 - Compounded drugs from outsourcing pharmacies may not be listed in the FDA DRLS.

* <http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm>



Reflection Point



“Doveryai, no proveryai”

“Trust but verify”

Former President Ronald Reagan



Outsourcing

- What are your and your hospital's responsibilities?
 - Do know what is in your contract?
 - One contract detailed the following requirements:
 - Customer shall be responsible for determining whether any compounded solution provided under this Vendor Agreement is clinically correct, appropriate or accurate for prescribing to any particular patient and for any particular disease or condition, and for determining and recording the individual patients that receive the medications”



BUD and Sterility Testing

- In addition to “relevant” sections of 21 CFR 210 and 211, the FDA has required registered outsourcing pharmacies to comply with USP Chapter <797>.
- Most if not all outsourcing pharmacies claim to meet or exceed USP Chapter <797> requirements
- Areas of interest is sterility testing and beyond-use dating



BUD and Sterility Testing

- Since compounded drugs from outsource pharmacies have not been approved, how do you know if their assigned BUD is valid
 - You have the right to demand documentation and substantiation of stability and dating of drugs
 - Sign a non-disclosure agreement if necessary
 - How does the vendor ensure that the drugs are sterile?
 - Per batch testing, process validation or some other means?



BUD and Sterility Testing

- Insuring the quality of APIs (active pharmaceutical ingredients)
 - National drug shortages are challenging the ability to source APIs
 - Where is your outsourcing vendor getting the drugs they are using?
 - Commercially available?
 - Primary vendors or brokers?
 - Prepared from non-sterile ingredients?
 - Demand notification if APIs are compounded from non-sterile ingredients



Vendor Qualification

- Conduct an onsite visit of operation at least annually
- Review the following information during audit:
 - Summary of any regulatory inspection reports from SBOP or FDA
 - CAPA (corrective and preventive action) program, employee training records, sterility and stability data
 - How does management ensure operational control and fitness?
 - Observe personnel work practices and compare against vendor policy and procedure



Summary

- State BOP laws form the foundation of compliance for pharmacies
- **BUT** pharmacies that voluntarily register with the FDA are required to comply with *additional* regulation which plainly stated means that
 - There are comprehensive, detailed written SOPs;
 - There is ZERO gap between what SOP says and what staff actually do;
 - The written documentation demonstrates ZERO gap 100% of the time; and
 - The manufacturer demonstrates that their processes are “in control” through consistent and routine monitoring to identify and close gaps as well as identify potential changes to improving patient safety.
- Accrediting organizations such as TJC have no relevance to FDA operations

