TUESDAY, APRIL 8:
IMPLICATIONS OF FEDERAL COMPOUNDING LEGISLATION
WELCOME

Kate Gainer, PharmD
Executive Vice President and CEO
Iowa Pharmacy Association
PRESENTERS

Wade Ackerman
Senior FDA Counsel
HELP Committee Chairman Tom Harkin

Lloyd Jessen, RPh, J.D.
Executive Director
Iowa Board of Pharmacy
All speakers report no actual or potential conflicts of interest associated with this presentation.

All speakers report that off-label use of medication will not be discussed during presentation.
LEARNING OBJECTIVES


2. Describe the track and trace provisions of the Drug Quality and Security Act and the impact to the pharmaceutical supply chain.

3. Explain the results of the recent efforts by the Iowa Board of Pharmacy to inspect licensed non-resident pharmacies.

4. Review the responsibilities of the Iowa Board of Pharmacy’s compounding task force.
The Drug Quality and Security Act (DQSA) and the Food and Drug Administration Safety and Innovation Act (FDASIA)

Wade Ackerman, J.D.
Senior FDA Counsel
U.S. Senate Committee on Health, Education, Labor & Pensions
Senator Tom Harkin, Chairman
Drug Quality and Security Act (DQSA)

• Enacted into law on Nov. 27, 2013
• DQSA has two titles:
  – Title 1: Compounding Quality Act
  – Title 2: Drug Supply Chain Security Act

• Title I regarding drug compounding was enacted in response to a 2012 meningitis outbreak associated with contaminated compounded drugs
Title I: Drug Compounding

- Section 102: Voluntary outsourcing facilities (section 503B)
  - Exemptions to certain FDA drug requirements when a drug is compounded by or under the direct supervision of a licensed pharmacist in a facility that elects to register as an outsourcing facility if certain conditions are met:
    - Bulk drug substances
    - Other ingredients
    - Not essentially a copy of an approved drug
    - Prohibition on wholesaling
    - Labeling

- Registration of Outsourcing Facilities and Reporting of Drugs
  - Annual registration
  - Drug reporting by outsourcing facilities
  - Electronic registration and reporting
  - Risk-based FDA inspection frequency
  - Adverse event reporting
  - Fees
Title I: Drug Compounding

• **Section 105: Enhanced Communication**
  – Requires FDA to facilitate meaningful communication between the agency and the State boards of pharmacy about concerns raised, or actions taken, against compounding pharmacies.

• **Section 107: GAO Study**
  – GAO must submit to Congress a report on pharmacy compounding and the adequacy of State and Federal efforts to assure the safety of compounded drugs.
FDA’s Implementation of DQSA Title I

- Guidance on Registration for Outsourcing Facilities
- Guidance on Fees for Outsourcing Facilities
- Interim Guidance on Product Reporting for Outsourcing Facilities
- Request for Nominations of Bulk Drug Substances That May Be Used to Compound by Outsourcing Facilities
- Request for Nominations of Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B

More Information:
- [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm)
Title II: Drug Supply Chain

• Section 202: Pharmaceutical distribution supply chain
  o Definitions
  o Manufacturer requirements
    o Product Identifier
    o Authorized trading partners
    o Verification
  o Wholesale Distributor Requirements
  o Dispenser Requirements
  o Repackager Requirements
  o Waivers, exceptions, and exemptions
Title II: Drug Supply Chain

• Section 203: Enhanced Drug Distribution Society

• Section 204: National Standards for Prescription Drug Wholesale Distributors

• Section 205: National Licensure Standards for Third-Party Logistics Providers
Food and Drug Administration Safety and Innovation Act (FDASIA)

– Signed into law on July 9th, 2012
– Has ten titles covering a range of FDA issues.
Food and Drug Administration Safety and Innovation Act: FDASIA

- Title I – Fees Relating to Drugs
- Title II – Fees Relating to Devices
- Title III – Fees Relating to Generic Drugs
- Title IV – Fees Relating to Biosimilar Biological Products
- Title V – Pediatric Drugs and Devices
- Title VI – Medical Device Regulatory Improvements
- Title VII – Drug Supply Chain
- Title VIII – Generating Antibiotic Incentives Now
- Title XI – Drug Approval and Patient Access
- Title X – Drug Shortages
- Title XI – Other Provisions
  - Subtitle A: Reauthorizations
  - Subtitle B: Medical Gas Product Regulation
  - Subtitle C: Miscellaneous Provisions
  - Subtitle D: Synthetic Drugs
FDASIA: Title X – Drug Shortages

• Section 1001: Discontinuance or interruption in the production of life-saving drugs.
• Section 1002: Annual reporting on drug shortages.
• Section 1003: Coordination: task force on drug shortages.
• Section 1004: Drug shortage list.
• Section 1005: Quotas applicable to drugs in shortage.
• Section 1006: Attorney General report on drug shortages.
• Section 1007: Hospital repackaging of drugs in shortage.
• Section 1008: Study on drug shortages.
Thank You!

If you have any questions, please feel free to email me at Wade_Ackerman@help.senate.gov
THE COMPOUNDING/MANUFACTURING DEBATE
— The NABP/Iowa Nonresident Pharmacy Inspection Project—

HEADLINE NEWS
March-April 2013

“MORE FDA OVERSIGHT OF COMPOUNDING PHARMACIES NEEDED IN LIGHT OF STATE DEFICIENCIES”
4/16/13

“HOW A SHADOW DRUG INDUSTRY TRIES TO AVOID REGULATION”
4/16/13

“COMPOUNDING PHARMACIES GO UNTRACKED”
4/14/13

“CHECKS FIND UNSAFE PRACTICES AT COMPOUNDING PHARMACIES”
4/12/13

“FDA UPS PRESSURE ON COMPOUNDING PHARMACIES AHEAD OF HEARING”
4/12/13

IPA Webinar, April 8, 2014
The Compounding/Manufacturing Debate
— The NABP/Iowa Nonresident Pharmacy Inspection Project—

“FDA ACKNOWLEDGES: WE COULD HAVE DONE MORE TO PURSUE COMPOUNDERS”
4/9/13

“PHARMACIES FEEL MORE HEAT”
3/16/13

“FDA INSPECTS SPECIALTY COMPOUNDING PHARMACIES IN TARGETED ACTION”
3/1/13

“COMPOUNDING PHARMACIES HAVE BEEN LINKED TO DEATHS, ILLNESSES AND SAFETY FAILURES FOR YEARS”
2/7/13

IPA Webinar, April 8, 2014
The Compounding/Manufacturing Debate
— The NABP/Iowa Nonresident Pharmacy Inspection Project—

GOAL:
TO INSPECT APPROXIMATELY 600 PHARMACIES LOCATED ACROSS THE U.S.
THAT ARE LICENSED TO DO BUSINESS IN IOWA

DATES:
FROM DECEMBER 2012 TO DECEMBER 2013

PRIORITIES:
1. STERILE COMPOUNDERS-HIGH VOLUME
2. STERILE COMPOUNDERS-LOW VOLUME
3. NON-STERILE COMPOUNDERS
4. NON-COMPOUNDERS
FDA INSPECTION PROJECT:
(As of April 23, 2013)

FEBRUARY TO APRIL 2013

TARGETED LARGE SPECIALTY COMPOUNDING PHARMACIES

INSPECTIONS OF 45 PHARMACIES LICENSED IN 26 STATES

TEXAS = 7
FLORIDA = 5
NEW JERSEY = 4
MASSACHUSETTS = 3
ALABAMA, MICHIGAN, MISSOURI, NORTH CAROLINA = 2

AR, AZ, CA, CO, CT, GA, IL, IN, KS, MS, NV, OH, OK, PA, SC, TN, UT & VA = 1

-NONE IN IOWA-
GROUND RULES:

OUT OF FAIRNESS TO ALL PARTIES INVOLVED, NO SPECIFIC COMPANIES WILL BE REFERRED TO OR IDENTIFIED DURING MY PRESENTATION. INSTEAD, I WILL SHARE GENERAL OBSERVATIONS AND FINDINGS THAT APPLY TO MANY, IF NOT MOST, OF THE PHARMACIES THAT HAVE BEEN INSPECTED. I WILL ALSO DESCRIBE THE PERPLEXITIES SURROUNDING THE ISSUE OF COMPOUNDING VERSUS MANUFACTURING AND THE RESULTING AND ONGOING CHALLENGES FACING REGULATORS.
CAVEATS

IN ORDER TO ELIMINATE THE POTENTIAL FOR MICROBIAL, CHEMICAL AND PHYSICAL CONTAMINATION, AND TO ENSURE PURITY AND POTENCY OF THE MEDICATION, IT IS IMPERATIVE THAT MANUFACTURERS PERFORM TO A HIGHER LEVEL OF OPERATING STANDARDS.
GENERAL OBSERVATIONS

SAVVY OPERATORS HAVE OPTED TO ENGAGE IN MANUFACTURING PRACTICES WITHOUT IMPLEMENTING CURRENT GOOD MANUFACTURING PRACTICES (cGMPs)—PUTTING PATIENTS AT RISK.

SUCH OPERATORS PRESENT THEMSELVES AS MAINSTREAM, TRADITIONAL COMPOUNDING PHARMACIES RATHER THAN AS MANUFACTURERS, WITH A GOAL OF AVOIDING THE HIGHER LEVELS OF STANDARDS REQUIRED OF MANUFACTURERS.

AS WE HAVE SEEN IN THE NECC CASE, DEATHS FROM CONTAMINATED PRODUCTS CAN OCCUR MONTHS AFTER EXPOSURE.

WIDESPREAD DISTRIBUTION CAN MAKE IT HARDER TO DETECT CONTAMINATED PRODUCTS UNLESS THERE IS A CLUSTER OR UNIQUE ORGANISM.
GENERAL OBSERVATIONS

ALL STATES LICENSE PHARMACISTS TO COMPOUND. BUT THE STATES HAVE VARYING DEGREES OF OVERSIGHT, REGULATION AND ENFORCEMENT.

“OFFICE USE” vs. “SHORT SUPPLY MEDS” IS ADDRESSED BY STATES DIFFERENTLY.

SOME STATES DO NOT ALLOW NON-PATIENT-SPECIFIC COMPOUNDING. IN THOSE STATES, SUCH COMPOUNDING IS CONSIDERED MANUFACTURING.

SOME HOLD THE MISTAKEN BELIEF THAT AS LONG AS A PHARMACY IS REGISTERED WITH THE FDA, ITS COMPOUNDED PRODUCTS ARE APPROVED.

FDA REGISTRATION, HOWEVER, IS NOT THE SAME THING AS FDA DRUG APPROVAL.

JUST BECAUSE A FACILITY IS REGISTERED WITH FDA DOES NOT MEAN THAT IT COMPLIES WITH cGMPs. THIS DICHOTOMY MUST BE ADDRESSED AND RESOLVED FOR THE GREATER GOOD OF THE PUBLIC.
NABP/IOWA PROJECT OBSERVATIONS

USP 797 GUIDELINES ARE NOT UNIFORMLY FOLLOWED BY STERILE COMPOUNDERS, NOR ARE THEY REQUIRED OR ENFORCED UNIFORMLY BY THE STATES. AS A RESULT, THERE IS INCREASED RISK FOR CONTAMINATIONS AND A REDUCED POSSIBILITY OF DETECTING PROBLEMS EARLY.

PREPARING COMPOUNDED STERILE PREPARATIONS (CSPs) IS DIFFERENT THAN MANUFACTURING STERILE PRODUCTS UNDER cGMPs FOR STERILE PRODUCTS. CSPs ARE PREPARED UNDER ASEPTIC CONDITIONS AND HAVE VERY SHORT “BEYOND USE DATES” AS COMPARED TO EXPIRATION DATES OF MANUFACTURED STERILE DRUGS.
BOTH USP 797 AND cGMPs ARE INTENDED TO PREVENT HARM FROM MICROBIAL CONTAMINATION, BACTERIAL ENDOTOXINS, POTENCY VARIABILITY, AND PHYSICAL AND CHEMICAL CONTAMINANTS.

BOTH “BEYOND USE DATES” AND EXPIRATION DATES ARE BASED ON THE RISK OF CONTAMINATION AND VIABILITY OF THE PRODUCT UNDER THE CONDITIONS IN WHICH THE PRODUCT IS PREPARED AND STORED.

cGMPs ARE MORE STRINGENT THAN USP 797 GUIDELINES IN ORDER TO SUPPORT THE LONGER EXPIRATION DATES. FOR EXAMPLE, AIR SAMPLING IN A COMPOUNDING FACILITY IS DONE EVERY SIX MONTHS (DURING CERTIFICATION) BUT UNDER cGMPs, IT IS DONE DAILY.
USP 797 IS THE MINIMUM STANDARD FOR COMPOUNDING PREPARATIONS.

COMPOUNDED PREPARATIONS HAVE LIMITED “BEYOND USE DATES” BASED ON THEIR RISK LEVEL. BEYOND USE DATES FOR LOW RISK LEVEL PREPARATIONS AT CONTROLLED ROOM TEMPERATURE ARE 48 HOURS AND IF REFRIGERATED, 14 DAYS.

WHEN HANDLING HIGH RISK PREPARATIONS THESE BEYOND USE DATES ARE 24 HOURS AT CONTROLLED ROOM TEMPERATURE AND 3 DAYS IF REFRIGERATED.

IF LONGER BEYOND USE DATES ARE ASSIGNED TO PRODUCTS, THERE MUST BE STERILE TESTING DONE IN ACCORDANCE WITH USP STANDARD # 71.
NABP/IOWA PROJECT OBSERVATIONS

FACILITY DESIGN AND EQUIPMENT.

- PRIMARY ENGINEERING CONTROLS (AIR FLOW HOODS)—THIS IS THE PLACE WHERE COMPOUNDING IS ACTUALLY DONE.

- SECONDARY ENGINEERING CONTROLS (CLEAN ROOM OR BUFFER ROOM AND THE ANTE-ROOM)—IT SURROUNDS THE PRIMARY ENGINEERING CONTROL AND REDUCES THE CHANCE OF CONTAMINATION.
ENVIRONMENT QUALITY AND CONTROL.

- THE QUALIFICATIONS OF INDIVIDUALS THAT TEST AND CERTIFY THE PHYSICAL SITE AND EQUIPMENT HAVE NOT BEEN DEFINED. UNTIL RECENTLY THERE WAS NO ACCREDITATION FOR CERTIFIERS. NOW, CETA, THE CONTROLLED ENVIRONMENT TESTING ASSOCIATION HAS DEFINED CRITERIA AND HAS AN ACCREDITATION FOR CERTIFIERS. THESE GUIDELINES ARE REFERENCED IN USP 797:
  - CETA HAS A CERTIFICATION GUIDE FOR STERILE COMPOUNDING FACILITIES
  - CETA HAS A CERTIFICATION MATRIX FOR STERILE COMPOUNDING FACILITIES
- MOST STATES DO NOT DEFINE THE REQUIREMENTS FOR THE CERTIFIER.
- PRESSURE DIFFERENTIALS BETWEEN ROOMS ARE NOT MONITORED.
NABP/IOWA PROJECT OBSERVATIONS

INSUFFICIENT CLEANING IS BEING DONE.

- SUFFICIENT TIME IS NOT BEING ALLOCATED FOR THE APPROPRIATE CLEANING, ESPECIALLY IN 24-HOUR OPERATIONS.

- CLEANING AND DISINFECTING IS IMPORTANT TO REDUCE THE BIO-BURDEN AND THEREFORE THE CHANCE OF CONTAMINATION.
PERSONNEL TRAINING AND MONITORING.

• EVERYONE ENTERING THE CLEAN ROOM MUST BE PROPERLY TRAINED AND GARBED.

• PERSONNEL DO NOT KNOW WHAT TO DO WITH POSITIVE TEST RESULTS.

• PERSONNEL DO NOT KNOW TO EXPECT TEST RESULTS FROM THE FACILITY CERTIFICATION PROGRAMS AFTER THE CERTIFIER HAS LEFT (RESULTS FOR TESTS THAT REQUIRE INCUBATION).

• TESTING NEEDS TO BE BASED ON THE MOST COMPLEX COMPOUNDING THAT IS DONE TO ENSURE THAT EMPLOYEES CAN COMPOUND WITHOUT INTRODUCING CONTAMINATION. THIS INCLUDES FINGERTIP AND MEDIA FILL TESTS.
NABP/IOWA PROJECT OBSERVATIONS

THE CETA GUIDANCE DOCUMENTS WOULD BE A USEFUL TOOL TO REGULATORS AND FACILITIES TO UNDERSTAND THE TESTING THAT IS NEEDED, WHAT WAS ACTUALLY DONE, AND WHAT THE FINDINGS MEAN.

A STICKER ON A HOOD, FOR EXAMPLE, MAY ONLY MEAN THAT THE HOOD WAS TESTED, NOT THAT THE TESTS WERE PASSED.
BEYOND USE DATES ASSIGNED AT ONE FACILITY INSPECTED WERE LONGER THAN DEFINED IN USP 797 WITHOUT HAVING CONDUCTED STERILITY TESTING TO SUPPORT THE EXTENDED TIME.

IN ONE FACILITY, AN INSUFFICIENT NUMBER OF STERILITY TESTS WERE RUN. ONLY ONE UNIT WAS TESTED PER BATCH, WERE A MINIMUM OF FOUR IS REQUIRED TO BE TESTED TO CONFIRM STERILITY.

ONE INSPECTOR NOTED THAT A COMPOUNDED PREPARATION WAS INACCURATELY CATEGORIZED AS A MEDIUM RISK COMPOUND AND THEREFORE THE PRODUCT WAS ASSIGNED INACCURATE BEYOND USE DATES.
ONE PHARMACY REFERRED TO A GENERIC ORDER (INVOICE) AS A PRESCRIPTION, LEADING THE INSPECTOR TO QUESTION WHETHER THE PHARMACY WAS ACTUALLY MANUFACTURING OR COMPOUNDING. IN FACT, THE NON-PATIENT-SPECIFIC PRODUCT WAS PREPARED AND SHIPPED TO DOCTOR’S OFFICES ACROSS THE COUNTRY IN BATCHES OF 25.

IN ONE PHARMACY, RECORDS SHOWED A POSITIVE MICROBIAL TEST RESULT FOR THE ANTE-ROOM, BUT THE PHARMACIST DID NOT KNOW IF IT WAS SIGNIFICANT, AND SHE DID NOT HAVE A PLAN OF ACTION IN THE EVENT OF POSITIVE TEST RESULTS.
NABP/IOWA PROJECT OBSERVATIONS

- Some pharmacies have not fully cooperated with surveyors.
- Some pharmacies were found to be closed and out of business.
- Some pharmacies have relocated without giving proper notice.
- Some pharmacies do not properly monitor temperatures.
- One pharmacy had a letter on file which indicated that the sterile compounding of respiratory medications was suspended while awaiting resolution of an FDA case.
- One pharmacy misrepresented to the Iowa Board that it was only making low and medium risk products when it was actually preparing high risk products including eye drops and amino acids.
- One pharmacy indicated that it did no bulk compounding but the surveyor found bulk compounded items that were improperly labeled.
NABP/IOWA PROJECT OBSERVATIONS

ONE PHARMACY WAS FOUND TO BE COMPOUNDING USING DRUGS THAT DID NOT HAVE THE “USP” DESIGNATION ON THE LABEL. THE SURVEYOR COULD NOT IDENTIFY THE ORIGIN OR MANUFACTURER OF THE DRUGS.

ONE PHARMACY DID NOT COMPLY WITH THE HOMESTATE’S ISO STANDARDS FOR THE CLEAN ROOM AND ANTE-ROOM.
SUMMARY OF IOWA FINDINGS: 1/3/14

- Total nonresident pharmacies inspected: 538
- Pharmacies located in 42 states (69 pharmacies in Florida)
- Pharmacies engaged in compounding: 263 (49%)
  - Both sterile & non-sterile compounding: 113 (21%)
  - Only non-sterile compounding: 85 (16%)
  - Only sterile compounding: 65 (12%)
- High Risk Preparations by Rx: 93 pharmacies
- High Risk Preparations without a Rx: 40 pharmacies
- Medium Risk Preparations by Rx: 121 pharmacies
- Medium Risk Preparations without a Rx: 24 pharmacies
- Low Risk Preparations by Rx: 134 pharmacies
- Low Risk Preparations without a Rx: 23 pharmacies
- Pharmacies doing bulk compounding without a Rx: 158 (29%)
- Pharmacies also licensed as a wholesale distributor: 14
SUMMARY OF IOWA FINDINGS, CONTINUED

- Pharmacy size: From 65 sq. ft. to 163,000 sq. ft.
- Sterile compounding area: From 6 sq. ft. to 2,992 sq. ft.
- Ante-room area: From 2 sq. ft. to 1,000 sq. ft.
- # of Pharmacists per facility: From 1 to 258
- # of Technicians per facility: From 1 to 668
- # of Rxs dispensed per day per facility: Up to 90,000
- # of Rxs dispensed into Iowa per day per facility: From 1 to 1,285
- # of Pharmacies inspected by FDA: 47 (8.7%)
- # of Pharmacies which received a warning letter from FDA: 26 (4.8%)
- # of Pharmacies operating under a waiver granted by the home state: 109 (20%)
- # of Pharmacies routinely inspected by the home state: Unknown

Many Iowa Nonresident Pharmacies have received a Letter of Education or an Administrative Warning. Others will be receiving formal disciplinary action.
GOING FORWARD

- FIRMS WHICH MANUFACTURE DRUGS UNDER THE GUISE OF COMPOUNDING WILL BE SUBJECTED TO ENHANCED FEDERAL OVERSIGHT, AS WELL AS HEIGHTENED STATE SCRUTINY.

- NABP HAS BUILT A NEW SYSTEM AND PROCESS FOR SHARING INFORMATION ABOUT COMPOUNDING FIRMS AND THEIR ACTIVITIES. AS A RESULT, STATE BOARDS OF PHARMACY NOW HAVE A NEW RESOURCE TO DRAW UPON.

- VERIFIED PHARMACY PROGRAM (VPP):
  
  http://www.nabp.net/programs/licensure/verified-pharmacy-program
COMPOUNDING PHARMACY INFORMATION SHARING NETWORK

❖ IDENTIFICATION OF COMPANIES THAT PREPARE COMPOUNDED STERILE PRODUCTS AND NON-STEROILE PRODUCTS.

❖ IDENTIFICATION OF COMPANIES THAT SHIP COMPOUNDED PRODUCTS ACROSS STATE LINES.

❖ IDENTIFICATION OF COMPANIES THAT PREPARE COMPOUNDED PRODUCTS PURSUANT TO PATIENT-SPECIFIC PRESCRIPTIONS.

❖ IDENTIFICATION OF COMPANIES THAT PREPARE NON-PATIENT-SPECIFIC COMPOUNDED PRODUCTS.

❖ INSPECTION RESULTS, IF ALLOWED TO BE SHARED UNDER STATE LAW.

❖ OTHER PERTINENT INFORMATION.
IOWA ACTION PENDING

- New application form for Nonresident Pharmacies is under development which will require much more detailed information.

- New legal requirements for Iowa Nonresident Pharmacies that engage in sterile compounding was proposed by the Board during the 2013 legislative session.

- An Iowa Pharmacy Compounding Task Force has been established and is meeting throughout 2014. The 20-member Task Force is composed of both pharmacists and technicians. The Task Force will review Iowa’s laws and rules pertaining to compounding and will make recommendations to the Iowa Pharmacy Association and the Iowa Board of Pharmacy.
To obtain 1.0 contact hours of continuing pharmacy education credit (0.1 CEU), participants must participate in the webinar activity, and logon to the CEI website to complete the exam.

**Please note registered attendees of this webinar will receive the CPE code tomorrow, Wednesday, April 9th.**

Once successfully completed, click the Submit button that appears in the column of your portfolio titled “CPE Submit”. The CPE Statement of Credit can then be accessed on CPE Monitor, www.MyCPEMonitor.net.
CPE CREDIT

Qd9m7
THANKS FOR ATTENDING!

JOIN US TUESDAY, MAY 13:
OPEN FORUM ON PROPOSED IPA POLICIES

Questions? Contact Laura Miller at lmiller@iarx.org or 515-270-0713