Ten Years of Regulated Outsourcing Facilities: A Decade of Progress, But More to Do.

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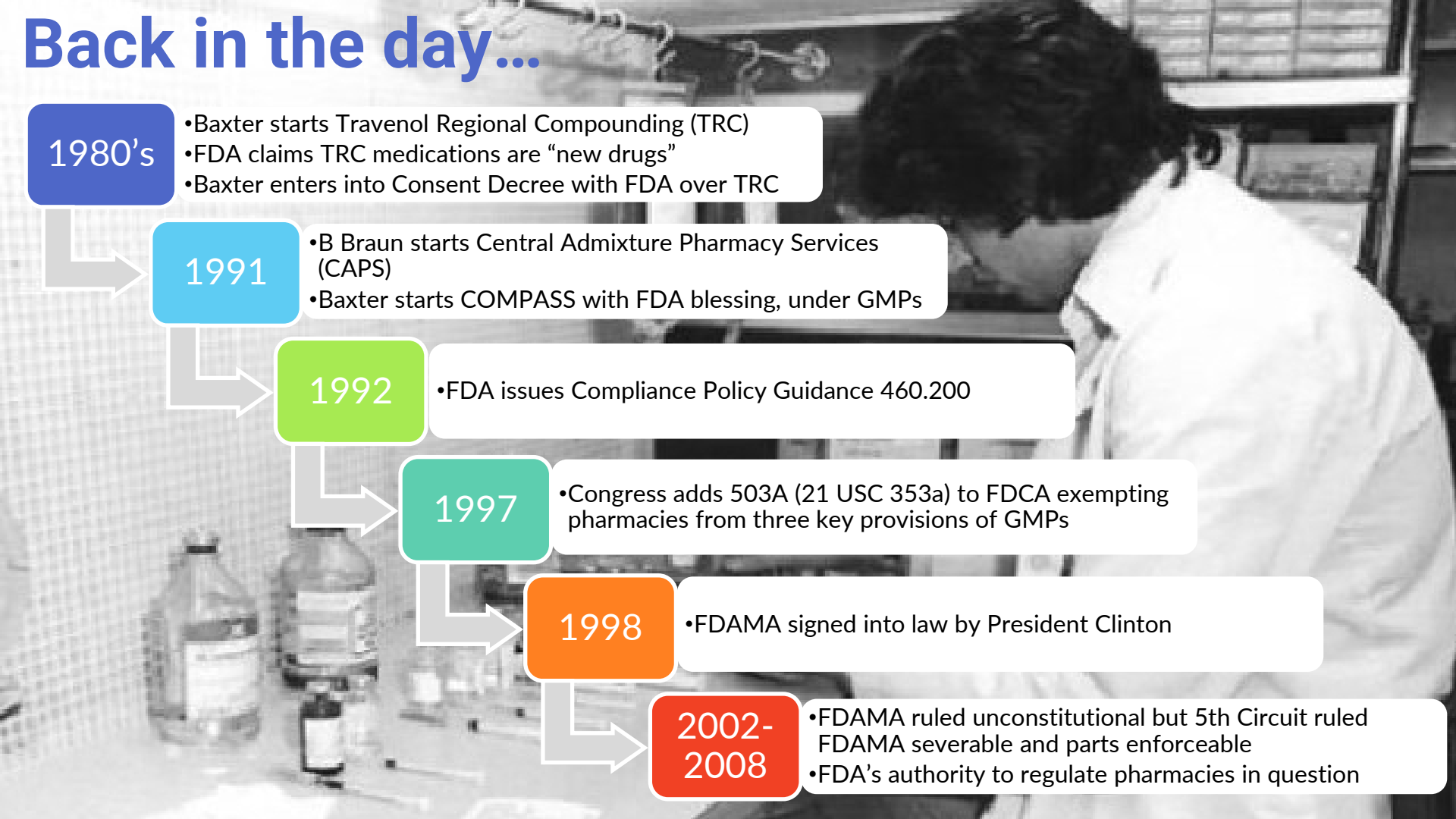
Thought of the Day

“Gradarius Firmus Victoria”

(Taking little steps toward victory)

Back in the day…



1980's
- Baxter starts Travenol Regional Compounding (TRC)
- FDA claims TRC medications are "new drugs"
- Baxter enters into Consent Decree with FDA over TRC

1991
- B Braun starts Central Admixture Pharmacy Services (CAPS)
- Baxter starts COMPASS with FDA blessing, under GMPs

1992
- FDA issues Compliance Policy Guidance 460.200

1997
- Congress adds 503A (21 USC 353a) to FDCA exempting pharmacies from three key provisions of GMPs

1998
- FDAMA signed into law by President Clinton

2002-2008
- FDAMA ruled unconstitutional but 5th Circuit ruled FDAMA severable and parts enforceable
- FDA's authority to regulate pharmacies in question

Yesterday

2000s	•Number of large-scale compounding events results in significant patient harm
2004	•USP Chapter <797> issued, first enforceable sterile compounding standard in the US
2008	•USP Chapter <797> revised, new standard effective June 2008
2012	•NECC tragedy
2013	•The DQSA becomes law, new section, 503B added to FDCA – Outsourcing Facilities- GMP expected •“Bright Line” created by 503A & 503B
2014	•FDA GMP Guidance to 503B Pharmacies
2017	•NECC trial starts •USP <797> to go out for second comment

Today

2018
- Several compounding events since 2000 have resulted in patient harm and death
- Closure of one of the largest 503B OFs

2020
- FDA revises and issues the second revision to the 503B GMPs

2021
- Several Warning Letters/Consent Decree issued

2022
- USP 797 revised

2023
- 10th anniversary of The Drug Quality and Security Act

Ten Years Since the Outbreak

NECC Summary

New England Compounding Center (NECC) Meningitis Outbreak (updated)	
Date	September 21, 2012, to present since patients are still suffering
Location	USA (20 States)
Cause	Fungal meningitis contamination of steroid medication
Injuries	>800 total case count; at least 384 meningitis and spinal infection; 7 stroke; 325 paraspinal/spinal infection; 33 peripheral joint infection; 2 spinal and peripheral joint; some patients recovering from the meningitis are falling ill again. Sufferers of the new infection are now coping with epidural abscesses and infections near the injection site.
Deaths	>100
Judicial	Cadden sentenced to 14.5 years, Chin sentenced to 10.5 years, Svirskiy sentenced to 30 months. Court requires restitution from Cadden and Chin. Both are in Michigan awaiting murder trials. A total of 13 NECC defendants have been convicted of 178 charges.

The Drug Quality and Security Act (DQSA)

- Signed into law by President Obama on November 27, 2013
- Divided into 2 major sections called Titles

Title I – Compounding Quality Act

- Eliminates the unconstitutional provisions of 503A that "…created uncertainty regarding the laws governing compounding."
- Requires FDA to engage in two-way communication with state regulators – identified as a major deficiency in FDA's response to the meningitis outbreak.
- Preserve and protect the practice of traditional pharmacy compounding – safe harbor

* FDA *Guidance for Industry* - Interim Product Reporting for Human Drug Compounding Outsourcing Facilities under 503B of FDCA – DEC 2013

Compounding Quality Act: 503B - Outsourcing Facilities

- 503B OFs must be engaged in the compounding of at least one human sterile drug.
- Can do nonsterile compounding
- Can compound patient-specific medications
- Under Section 503B, pharmacy outsourcers to voluntarily register as “outsourcing facilities,” making them subject to good manufacturing practices, ADE reporting, risk-based inspection, and other standards

* FDA *Guidance for Industry* - Interim Product Reporting for Human Drug Compounding Outsourcing Facilities under 503B of FDCA – DEC 2013

Section 503A (21USC353a) - Traditional Compounding

- State-based regulations – State Boards of Pharmacy
- Traditional, individualized prescriptions
- Requires compliance with USP chapters on compounding
- Subject to USP, SBOP regs, and Insanitary Guidance
- Not to engage in compounding for office use

* FDA *Guidance for Industry* - Interim Product Reporting for Human Drug Compounding Outsourcing Facilities under 503B of FDCA – DEC 2013


Ten years later...
where are we now?

Customers

61- 83% of hospitals surveyed reported purchasing compounded medications from outsourcing entities.[1]

According to Credence Research, the U.S. 503b Compounding Pharmacies Market generated revenue of around USD 1.1 billion in 2022 and is anticipated to grow a CAGR of over 7.80% during the forecast period from 2023 to 2030 to reach around USD 1.9 billion in 2030.[2]

It is common for hospital customers commonly utilize resources to evaluate the robustness of 503B OF operation formally.

1. Pharmacy, Purchasing & Products' 2023 State of Pharmacy Compounding survey. Pharm Purch Prod. 2022;20(4) Supplement: 46.

2. Credence Research Newsletter. April 30, 2023. https://www.linkedin.com/pulse/us-503b-compounding-pharmacies-market-size-worth-usd-19-singh/

Customers

- Optimizing compounding purchasing and in-house preparation
- Lots of opportunities involving drug waste – distribution and inventory systems not optimized
- Navigating Drug Shortages is a daily grind. It is typical for Hospital customers to utilize multiple 503B OFs due to recalls/closures.

503B Registered Entities

- Pre-DQSA OFs did not have GMP guidance from the FDA until 2014.
  - Outsourcing started in 1990s: CAPS and COMPASS
  - Initial focus: PN, Cardioplegia
- Over the past ten years, the number of registered 503B Outsourcing Facilities has been dynamic[1].
  - The number of registered 503B OF entities has averaged between 60-75.
  - The number of deregistered Outsourcing Facilities or out of business is at least 97.

1. FDA website - https://www.fda.gov/drugs/human-drug-compounding/compounding-inspections-recalls-and-other-actions. Accessed on June 6, 2023.

Starting a 503B Outsourcing Facility is expensive, challenging, and requires a focus and commitment to quality, compliance with CGMPs, and substantial product volume to survive.

The most responsible person is accountable to the actions of the organization.

Key Numbers

FDA Inspection Activity[1]	Total 2012-2023
483 issued	1307
483 response	96
Warning Letter Issued	497
FMD-145 issued	243
Warning Letter Response	21
Firm Press Release Recall Letter	127
FDA Press Release	37
FDA Statement	58
Consent Decree	16
Referral Letter	208
DOJ Letter	20
FMD-145	243
Closeout Letter	27
Contract Labs inspected	5
API vendors	6
Total Firms Inspected	864

1. FDA website - https://www.fda.gov/drugs/human-drug-compounding/compounding-inspections-recalls-and-other-actions. Accessed on June 6, 2023.

Typical Pharmacy Compounding Place Setting

Expected CGMP Place Setting

Used with permission. https://rootedinfoods.com/table-etiquette-the-place-setting/

Top 10 Observations in 503B Outsourcing Facilities (2016-Present)[1]

Observation	Occurrences	Percentage	FDA Guidance line # (Jan 2020 Rev 2)
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.	60	52.2%	365-439
The labels of your outsourcing facility's drug products do not include the information required by section 503B(a)(10)(A) and (B).	58	50.4%	1168-1199 In the text of the DQSA (H.R. 3204)

1. Diorio L, Thomas D. Trends in Regulatory Actions for 503B Compounders. Pharm Purch Prod. 2022;20(3):10-18.

Labeling Requirements for Outsourcing Facility Compounded Products

"Compounded drug"	Name, address, phone of outsourcing facility	Lot and batch numbers	Established drug name	Dosage form and strength
Volume	Date compounded	Expiration date	NDC number	"Not for Resale"
	List of ingredients; active and inactive	FDA contact information for adverse events	Directions for use	

Top 10 Observations in 503B Outsourcing Facilities (2016-Present)[1]

Observation	Occurrences	Percentage	FDA Guidance line # (Jan 2020 Rev 2)
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed.	55	47.8%	299-339
Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.	49	42.6%	260-301, 341-363

1. Diorio L, Thomas D. Trends in Regulatory Actions for 503B Compounders. Pharm Purch Prod. 2022;20(3):10-18.

Top 10 Observations in 503B Outsourcing Facilities (2016-Present)[1]

Observation	Occurrences	Percentage	FDA Guidance line # (Jan 2020 Rev 2)
There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.	44	38.3	162-192, 693-718
Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications and identity and strength of each active ingredient prior to release.	32	27.8%	872-991 993-1166

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Top 10 Observations in 503B Outsourcing Facilities (2016-Present)[1]

Observation	Occurrences	Percentage	FDA Guidance line # (Jan 2020 Rev 2)
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.	32	27.8%	693-870
Clothing of personnel engaged in the manufacturing, processing, packing, and holding of drug products is not appropriate for the duties they perform.	28	24.3%	380-388

1. Diorio L, Thomas D. Trends in Regulatory Actions for 503B Compounders. Pharm Purch Prod. 2022;20(3):10-18.

Top 10 Observations in 503B Outsourcing Facilities (2016-Present)[1]

Observation	Occurrences	Percentage	FDA Guidance line # (Jan 2020 Rev 2)
The responsibilities and procedures applicable to the quality control unit are not in writing nor fully followed.	22	19.1%	112-192
Laboratory controls do not include establishing scientifically sound and appropriate sampling plans and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity.	22	19.1%	872-991

1. Diorio L, Thomas D. Trends in Regulatory Actions for 503B Compounders. Pharm Purch Prod. 2022;20(3):10-18.

503B Supervision

- Compounded by or under the supervision of a licensed pharmacist
  - Figurehead or Head of Quality?
  - Few pharmacists have formal CGMP education, training, or experience
    - “Drinking from a firehose”
    - Utilize the FDA Compounding Quality Center of Excellence
    - PDA Technical Reports
  - 503B CGMPs are not “USP 797 on steroids”
  - Formalize the role of the pharmacist to a Qualified Person (QP)
    - Expanded training programs must be established to develop a skilled, trained, and qualified workforce in the 503B market segment.

503B Opportunities

- Adopt advanced aseptic processing technology that minimizes or eliminates the human element in compounding.
    - Employees are the primary source of contamination, and many 483 observations are based on inconsistent and improper employee actions.
- Explore terminal sterilization technology to improve the sterility assurance of compounded medication and minimize or eliminate the risk of “lack of sterility assurance” observations.

US FDA Enforcement

- Timeliness of inspection documents is challenging
  - There is not complete transparency to all the inspection activity and documents generated.
  - On average, it takes 343 days post-inspection to receive inspection documents.[1]

1. Personal conversation with Louis Diorio, LDT Health, Inc. on May 30, 2023.

US FDA

- Employs a methodical approach during inspections of critical activities specified in the CGMPs, but inspections ARE NOT complete evaluations of the operation.
  - Investigator 503B inspection competency vs. big pharma
    - Observations that personal opinion vs. regulatory requirements
  - A “point in time” evaluation of finite aspects of an operation
  - Should the Agency conduct a comprehensive inspection against the current 503B CGMPs during the first or some other interval inspection?

FDA Inspection Documents

- The FDA inspection documents (482s,483s, EIR, Untitled Letters, Warning Letters, FM-145, and Regulatory Meetings) do not provide a clear and unambiguous assessment of the compounding operation.
- Customers, pharmacists, and other healthcare professionals struggle to understand how to use these documents when evaluating potential vendors.

Drug Shortage Determination

Whose list should be used?

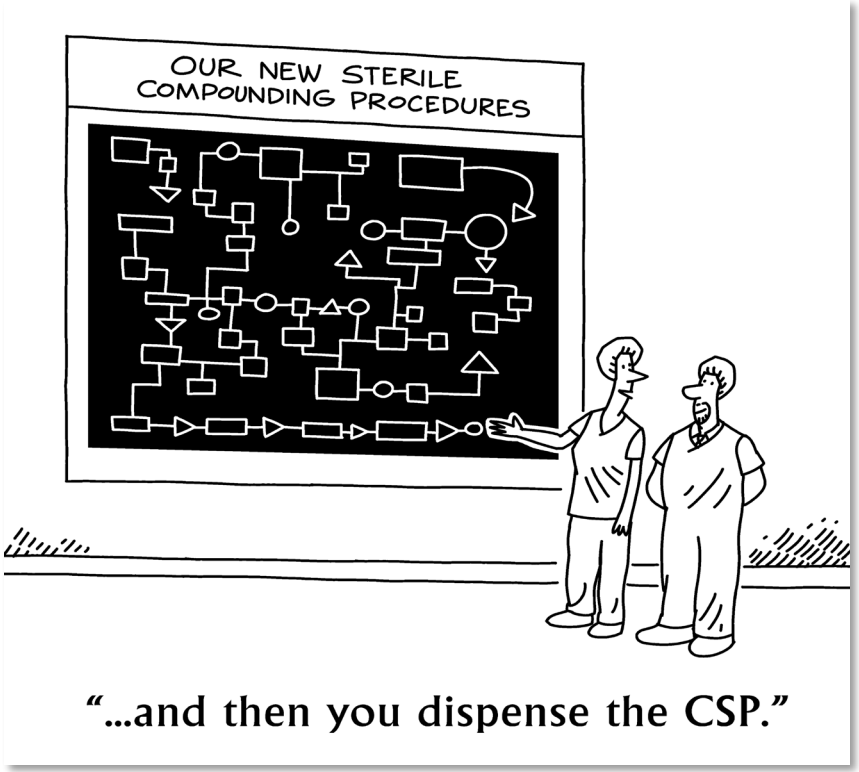
FDA

ASHP/Univ of Utah

Optimize and harmonize

US FDA Guidance

- Uncertainty surrounding the FDA enforcement of guidance documents
- Essentially a Copy – inconsistent observation/enforcement discretion?
- Drug shortage: Lengthen market time from 60 days to 6 months
- 503B Bulks (substance) List
- 503A Bulks (substance) List
  - Category 1-3



Key Takeaways

- The oversight and regulation of the compounding/outsourcing industry have been fraught with challenges and confusion since the 1980s.
- The NECC debacle catalyzed oversight action.
- Clarity did not occur until 2013, with the passage of DQSA.
- Outsourcing Facilities must comply with GMPs.
    - Read the various FDA and industry guidance resources such as the PDA Technical Reports.
- The FDA is actively overseeing the 503B outsourcing industry.
- Having a skilled, trained, and qualified workforce is critical to operating “in a state of control” 503B Outsourcing Facility.
- Implementing advanced aseptic processing and terminal sterilization procedures should be considered to minimize/eliminate the risk of product contamination.

Questions?

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