Recent Trends in Compounding Warning Letters and Related Actions

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November 15, 2017
Introduction/Overview

• On Sept. 15, Reuters reported that FDA Commissioner, Scott Gottlieb said that FDA would release draft guidance in the next two months reflecting its intention to adjust its enforcement priorities based on the size of the registered compounders and the riskiness of their products.

• Examine 2017 inspections and warning letters and attempt to identify trends and patterns to discern enforcement priorities

• Identify areas of emphasis for 2017 YTD

• What’s next?
Comparing 2013-16 and 2017 YTD Numbers

2013-16
- More than 350 inspections (almost all received 483s)
- More than 130 Warning letters
- More than 30 state referrals
- About 100 recalls overseen

(Source: Compounding Progress Report, January 2017)

2017 YTD
- 99 483s issued
- 1 Untitled Letter
- 43 Warning Letters
- 36 state referral letters
- 10 recalls overseen
- 12 close-out letters

(Source: FDA.gov)
503B-Specific Numbers for 2017 YTD

- **13** new 503B registrants
- **2** Warning Letters and 1 Untitled Letter
- **9** Warning Letters ever received by a 503B-registrant
Initial Observations

• Relatively small number of 503B warning letters
• Relatively small number of compounding recalls in 2017
• Relatively large number of compounding state referrals in 2017
  • 24 of the 36 (67%) state referrals contained descriptions of deviations from appropriate sterile practice standards.
• FDA criteria for state referral (per Compounding Progress Report)
  • Individual patient prescriptions;
  • Commitment made to take necessary corrective action; and
  • FDA believes that corrective action can be overseen by the state.
2017 Compounding Warning Letters

- 503A
- Insanitary Conditions
- CGMP Violations
- Unapproved New Drugs
- Lack Adequate Directions for Use
Content of 2017 Warning Letters

• **38** (88%) of Warning Letters included observations on insanitary conditions [FFDCA 501(a)(2)(A)]

• **30** (73%) included failing to obtain individual prescriptions, resulting in observations for GMPs and lacking adequate directions (but less frequently, unapproved drugs).

• **9** (22%) compounders [503A] cited for compounding from ineligible bulk drug substance.
  
  • Pharmacies cited for use of: domperidone, peruvian balsam, zinc picolinate, rose geranium oil, chloroacetic acid, m-cresol, saw palmetto, melatonin, short chain fatty acidophilus lactobacillus, coenzyme Q10, GHRP-6, and at least one redacted ingredient.
Absent from Warning Letters

• FDA has not cited any compounders in 2017 letters for:
  • Compounding essentially copies of FDA-approved drugs
    • Including 503B copies without “clinical need”
  • Interstate distribution of excessive quantities of compounded drugs
Serious Examples from Aug. 2016 Draft Guidance on Insanitary Conditions

• Vermin (e.g., insects, rodents) observed in ISO 5 areas or in immediately adjacent areas.
• Visible microbial contamination (e.g., bacteria, mold) in the ISO 5 area or in immediately adjacent areas.
• Non-microbial contamination in the ISO 5 area (e.g., rust, glass shavings, hairs).
• Performing aseptic manipulations outside of the ISO 5 area.
• Exposing unprotected sterile product, including stock solutions, to lower than ISO 5 quality air (e.g., removing it from the ISO 5 area without a robust and intact container closure system).
• Cleanroom areas with unsealed, loose ceiling tiles.
• Production of drugs while construction is underway in an adjacent area without adequate controls to prevent contamination of the production environment and product.
• Consistent and frequent pressure reversals from areas of less clean air to areas of higher cleanliness.
• The “sterilizing filter” is not adequate to accomplish sterilization and is not pharmaceutical grade.
• Temperature and time conditions used for heat sterilization are not lethal to heat- resistant microorganisms.
What’s Next?

• Fewer recalls?
• More 503B registrants?
• Continued emphasis on insanitary conditions and prescriptions
• Continued increasing collaboration with state regulators, including state referrals
• More injunctions?