Recent Trends in Compounding Warning Letters and Related Actions

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November 15, 2017

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- On Sept. 15, Reuters reported that FDA Commissioner, Scott Gottlieb said that FDA would release draft guidance in the next two months reflecting its intention to adjust its **enforcement priorities** based on the size of the registered compounders and the riskiness of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

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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

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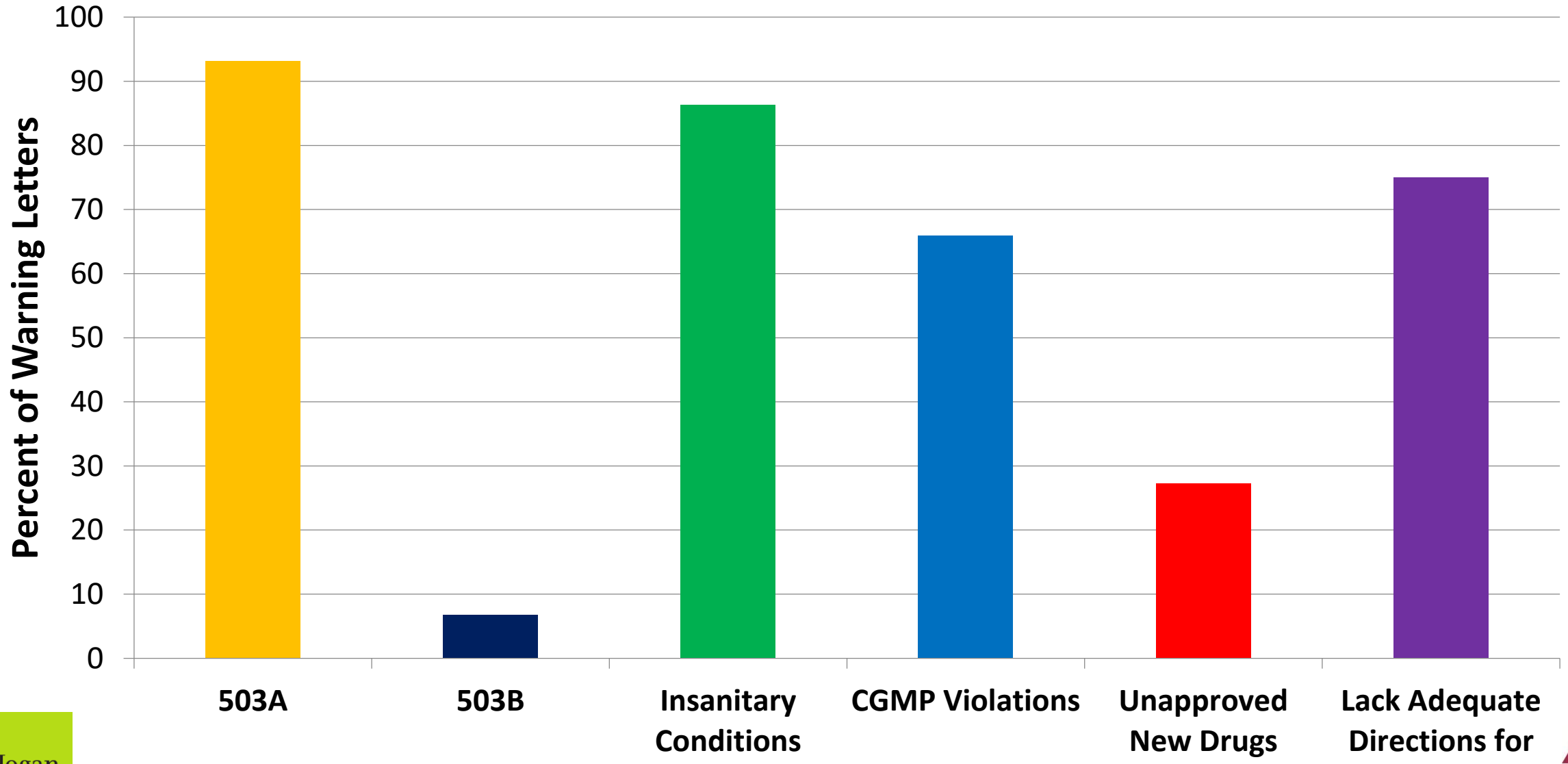
Initial Observations

- 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



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

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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?