

# **GMP Updates and Trends**

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# Office of Pharmaceutical Quality

## Division I



ME	{	NWE
NH		
VT		
MA		
RI		
CT	{	NYK
NY		
NJ	{	NWJ
PA		
DE	{	PHI
WV		
MD	{	BLT
DC		
VA		

# Agenda

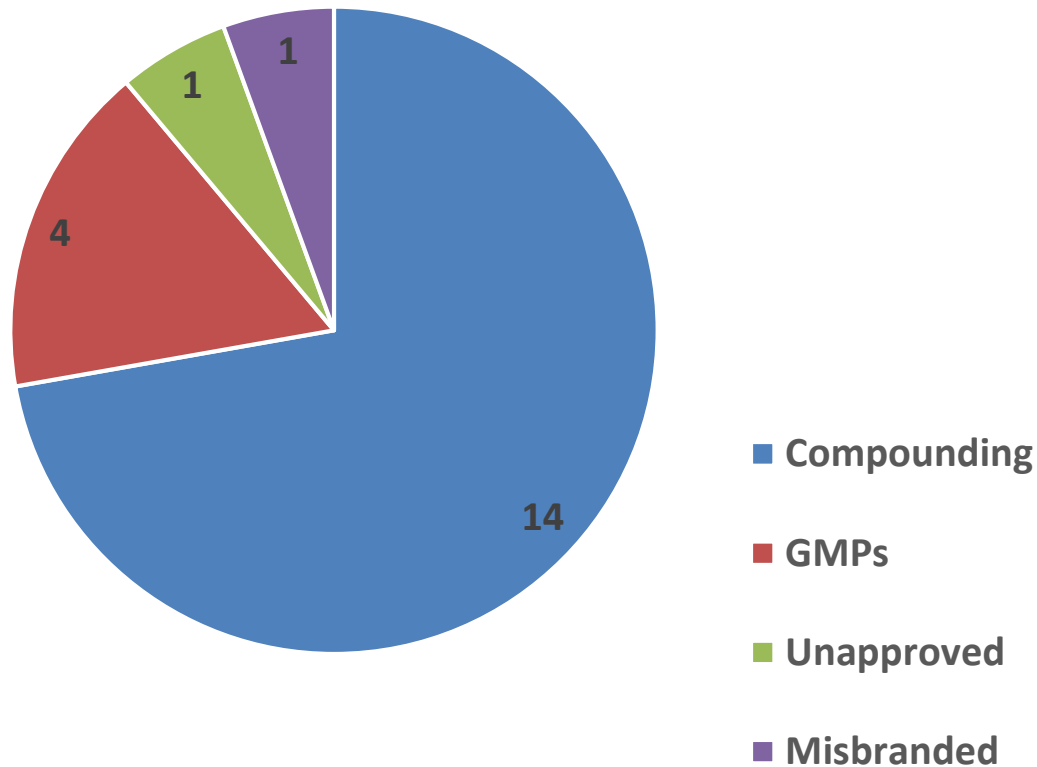
- Enforcement trends for Division I
  - Overall Metrics
  - Compounding Trends
  - GMP Trends
  - Questions

# FDA Pharma Division I Compliance Metrics

	WLs	Injunctions	Regulatory Meetings
Division I	20	2	13
Worldwide	151	6	47

Timeframe: 05/15/17-05/03/18

# Pharma Division I Warning Letters



Timeframe: 05/15/17-05/03/18

# **COMPOUNDING TRENDS**

# Requirements under FD&C Act for Compounding Firms



FD&C Section	<a href="#">501(a)(2)(A)</a>	<a href="#">501(a)(2)(B)</a>	<a href="#">502(f)(1)</a>	<a href="#">505</a>	<a href="#">582</a>
FDCA Requirement	Insanitary conditions	CGMPs	Adequate directions for use	New drug	Supply chain security
503A conditions not met	Yes	No	No	No	N/A
503A conditions met	Yes	Yes	Yes	Yes	N/A
503B conditions met	Yes	Yes	No	No	No
503B conditions not met	Yes	Yes	Yes	Yes	Yes

# Insanitary conditions

- FD&C Act Sec. 501(a)(2)(A):  
A drug or device shall be deemed to be adulterated “if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health”
- Applies to all drug facilities
- [Guidance for Industry: Insanitary Conditions at Compounding Facilities](#)

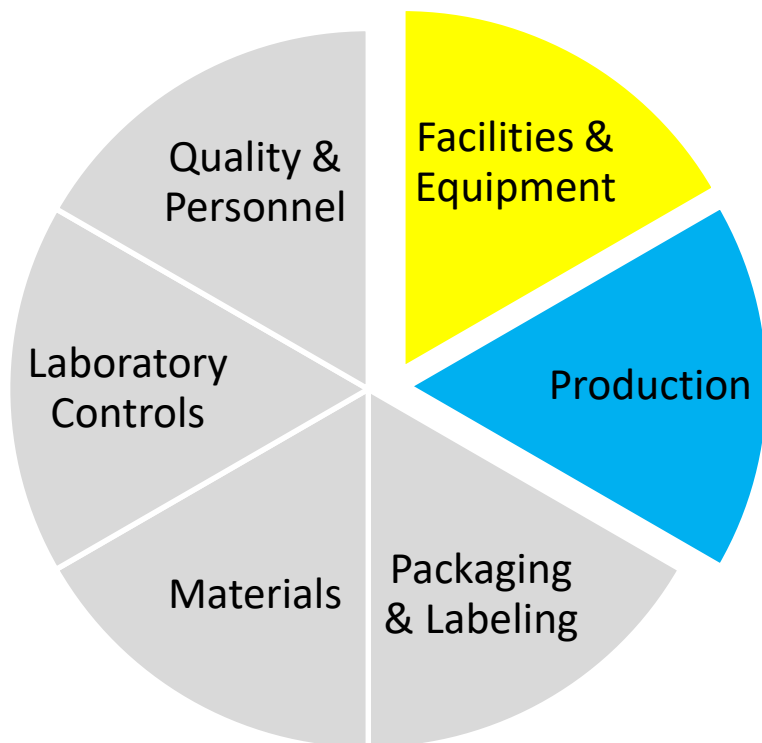


# Insanitary conditions

## *Examples:*

- Difficult to clean surfaces in cleanrooms (e.g. rust, wood, carpeting)
- Failure to perform environmental monitoring of aseptic processing areas
- Failure to adequately clean/disinfect aseptic processing areas
- Inadequate controls to prevent cross-contamination with beta-lactam antibiotics, cytotoxic agents, or hormones
- Poor aseptic practices
- Media fills do not represent most challenging conditions

# Insanitary Conditions have correlate GMP citations

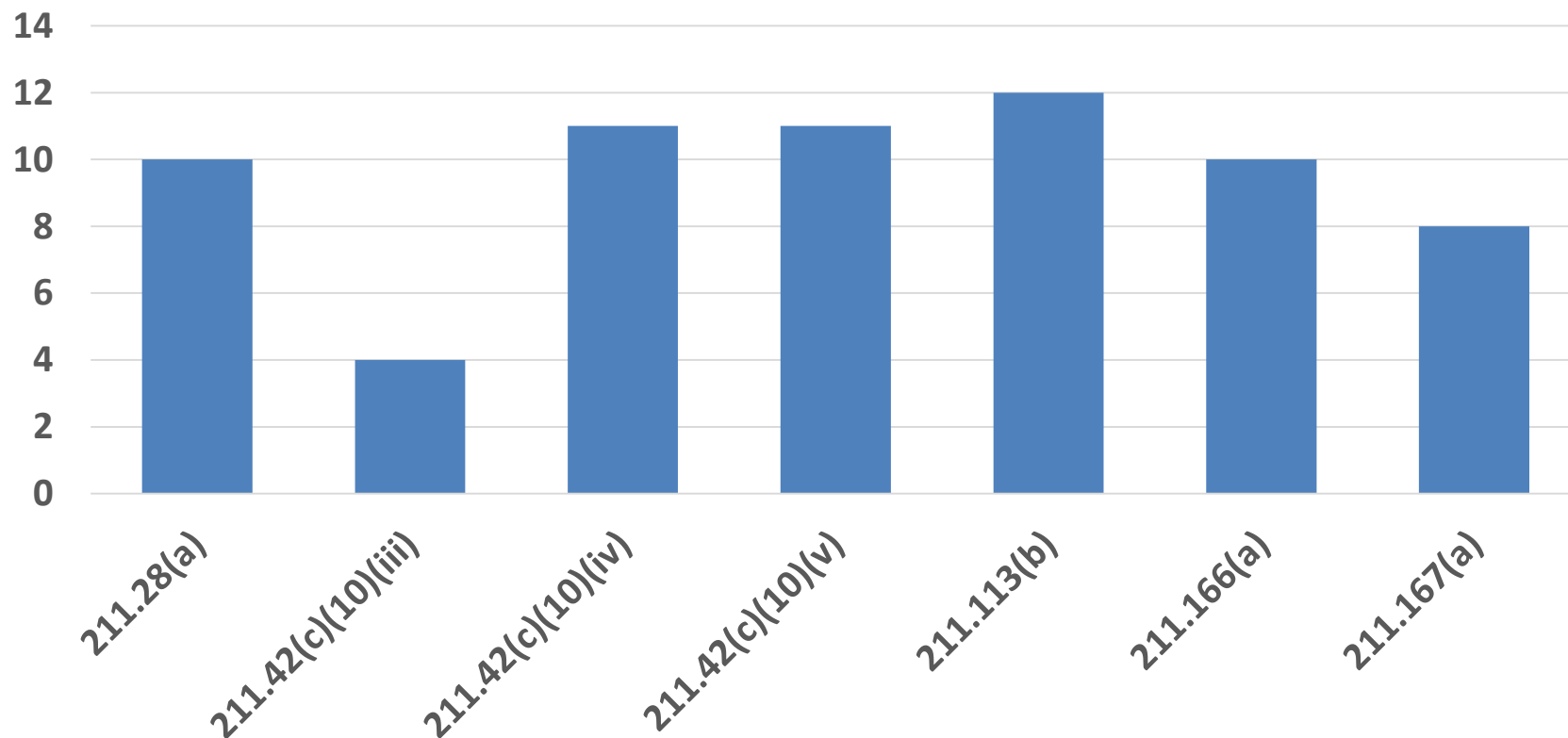


CGMP	Insanitary condition (Sec. 501(a)(2)(a))
211.42(c)(10)(i)	Cleanroom surfaces not easily cleanable
211.42(c)(10)(iv)	Failure to conduct environmental monitoring in ISO 5
211.42(c)(10)(v)	Failure to adequately clean/disinfect ISO 5
211.67(a)	Failure to clean/maintain equipment/utensils to prevent contamination
211.113(b)	Poor aseptic practices
211.113(b)	Media fills do not represent most challenging conditions

# Conditions of Section 503A

- Firms commonly fail to comply with 503A through violation of the following conditions:
  - Failing to receive valid prescriptions for individually-identified patients [503A(a)]
    - Noted in 19/38 (50%) of Division I WLs
    - *Draft Guidance: Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act, [December 2016](#)*
  - Bulk drug violations[503A(b)(1)(A)(i)]
    - Noted in 10/38 (26%) of Division I WLs
    - *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act, [January 2017](#)*
- Failure to follow these requirements means the firm cannot claim exemption from FDCA Sections such as 501(a)(2)(B).
  - WLs reflect this by citing these firms for CGMPs.

# Top 503A WL citations



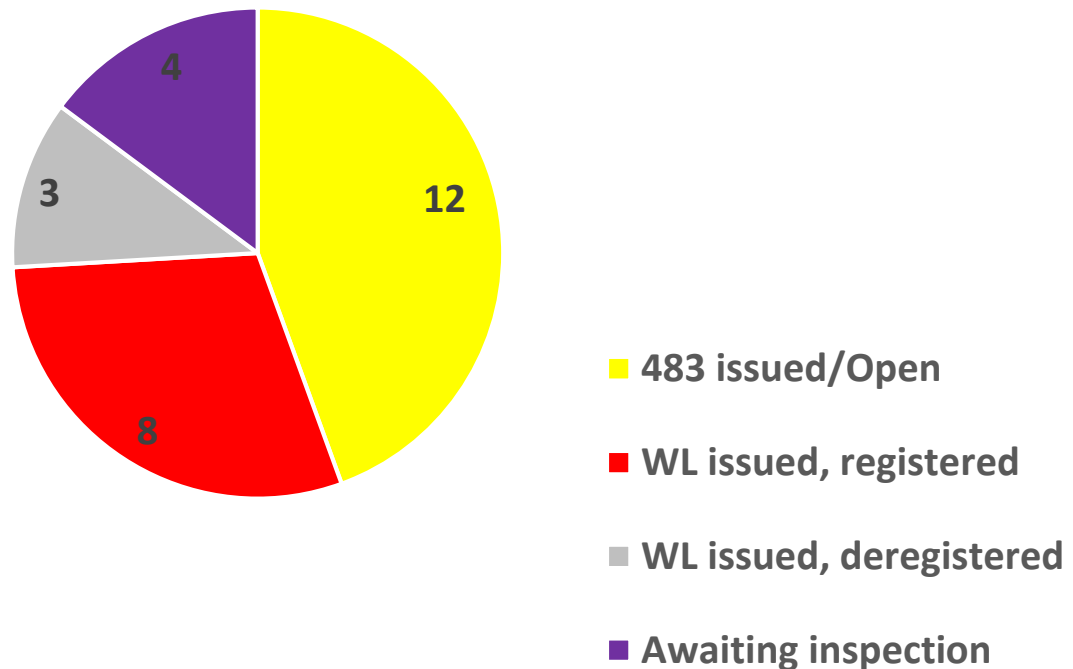
Based on Division I WL data 2008-Present

# Conditions of Section 503B

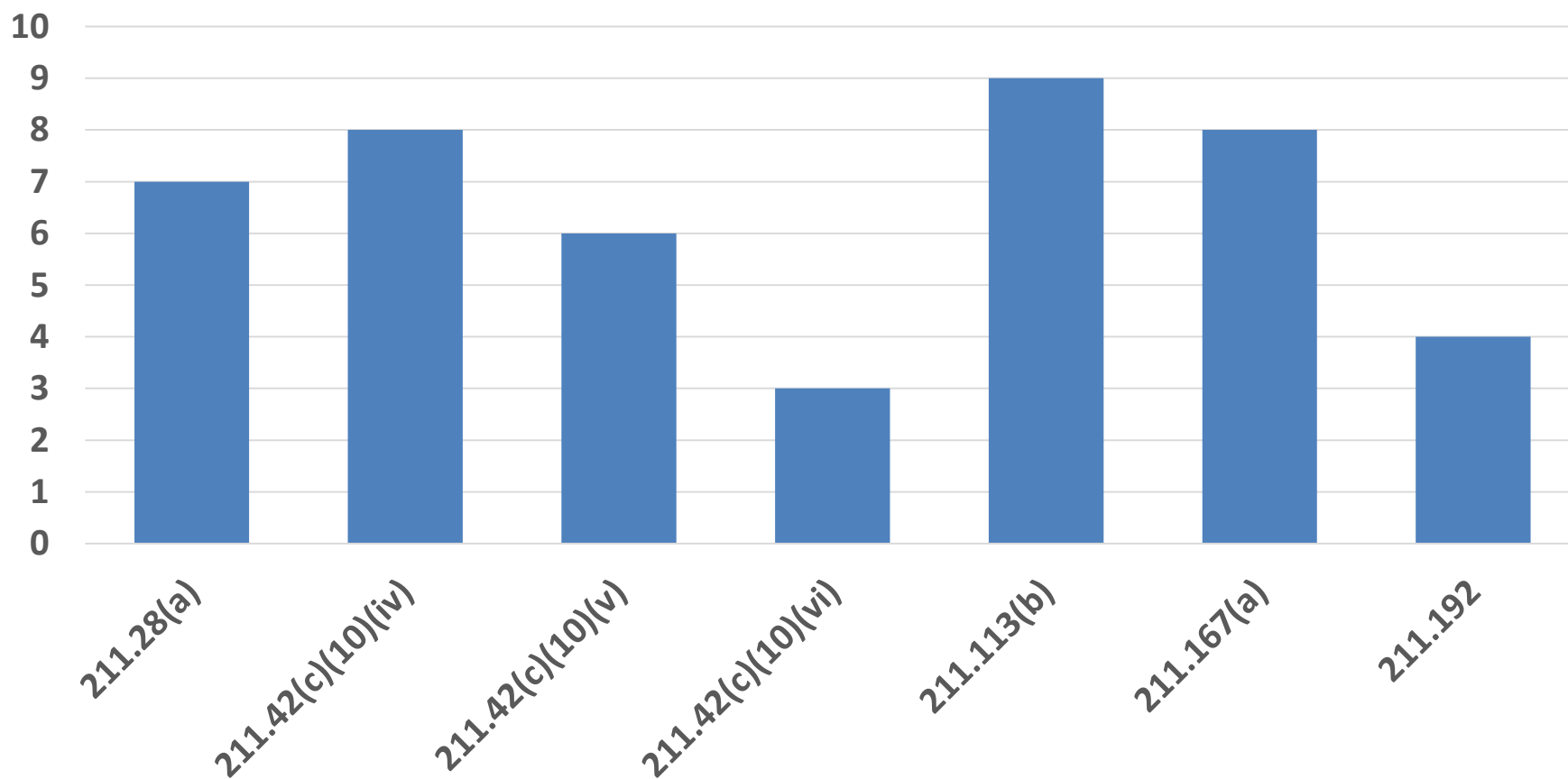
- Firms commonly fail to comply with 503A through violation of the following conditions:
  - Failure to report drug listing (503B(a)(1)).
    - Noted in 6/12 Division I WLs
    - Reporting is [semiannual](#).
  - Bulk drug violations (503B(a)(2))
    - *Guidance for Industry Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act, [January 2017](#)*
- Failure to follow these requirements means the firm cannot claim FDCA exemptions for labeling, new drugs, and supply chain.

# 503B facilities

- 73 503B facilities are registered nationwide
- 16 (22%) are located in Division I



# Top 503B WL citations



Based on Division I WL data 2014-Present

# Common citations

## 503A and 503B

**211.28(a)**  
**Personnel gowning**

**211.42(c)(10)(iv)**  
**Environmental monitoring**

**211.42(c)(10)(v)**  
**Cleaning/disinfecting ISO5**

**211.113(b)**  
**Validation of  
aseptic/sterilization  
process**



# **GMP TRENDS**

# Homeopathic Drugs

- December 18, 2017 [initiative](#) from Commissioner Gottlieb.
- Risk-based enforcement approach to homeopathic drug products targeting products:
  - With reported safety concerns
  - That contain or claim to contain ingredients associated with potentially significant safety concerns (noted in most recent WLs)
  - For routes of administration other than oral and topical;
  - Intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions;
  - For vulnerable populations
  - That do not meet standards of quality, strength or purity as required under the law.

# Homeopathic WLs common citations

**211.100(a)**  
**Process validation**

**211.110(a)**  
**In-process controls**

**211.84(d)**  
**Raw Material Testing**

# Homeopathic Drugs

## **Process validation WL example:**

“You manufacture various homeopathic drugs from ingredients that pose potentially toxic effects. For example, some of your drugs include the ingredient *Nux vomica*, which contains strychnine. Strychnine is a highly toxic, well-studied poison that is used as a rodenticide.

“You released numerous lots of homeopathic drugs without validating your manufacturing process. ... Especially for drugs that contain ingredients with potentially toxic effects, failure to validate manufacturing processes could expose patients to unnecessary risks due to the lack of knowledge about and control over sources of variation.”

# Homeopathic Drugs

## In process controls WL example :

“You failed to establish adequate in-process controls for drug products manufactured from active ingredients (e.g., *Nux vomica*, *Atropa belladonna*, *Aconitum napellus*, and *Gelsemium sempervirens*) that pose potentially toxic effects.

“Your *Testing and Control of In-Process Products* SOP states, ‘In process testing is performed only if necessary since testing is done for finished products.’ Your finished product testing ... does not include testing for content uniformity. Although you perform some in-process testing, your control criteria are insufficient to comply with CGMP because they are highly subjective, requiring human manipulation and visual assessment.”

# Homeopathic Drugs

## Component testing WL example:

“You do not test each component of your homeopathic drug products for identity prior to using components in your drug manufacturing process. You also failed to establish the reliability of your suppliers’ analyses, and to test each component for conformity with all appropriate written specifications for purity, strength, and quality.

“For example, *Nux vomica* contains strychnine, a highly toxic poison. Our inspection findings indicate that you did not conduct strychnine assay testing of the *Nux vomica* mother tincture lot #CH91 as required by the Homeopathic Pharmacopeia of the United States.”

# Any questions?



