Review of Warning Letters Issued by US FDA from 2015-17

PRESENTATION BY LAKSHMI ANANTH

Under Guidance of

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RATIONALE

- Responsibility of Regulatory Affairs staff is to look after Labelling follows regulatory authorities.
- More time complexity as products are increasing.
- Present technology can automate things.

INTRODUCTION

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With 1100$ Billion Revenue, United States Stands ahead in Pharmaceutical Industry. Exporting to US is a great opportunity leveraged by many countries.

So, US FDA was formed to check quality standards of medicines. Since inception FDA is issuing warning letters efficacy claims and inappropriate safety.

Source: https://www.fda.gov/AboutFDA/WhatWeDo/History/

Warning letter is considered as an official message from US-FDA indicating that manufacturer has violated some sort of rule in regulatory activity.

FDA defines Warning letter as..,

"A Correspondence that notifies regulated industry about violations that FDA has documented during inspections or investigations"

Source: https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

ANATOMY OF LETTER

Title and addressee

Title, mode of delivery and addressee to highest member of organization

Inspection details & Promised corrections

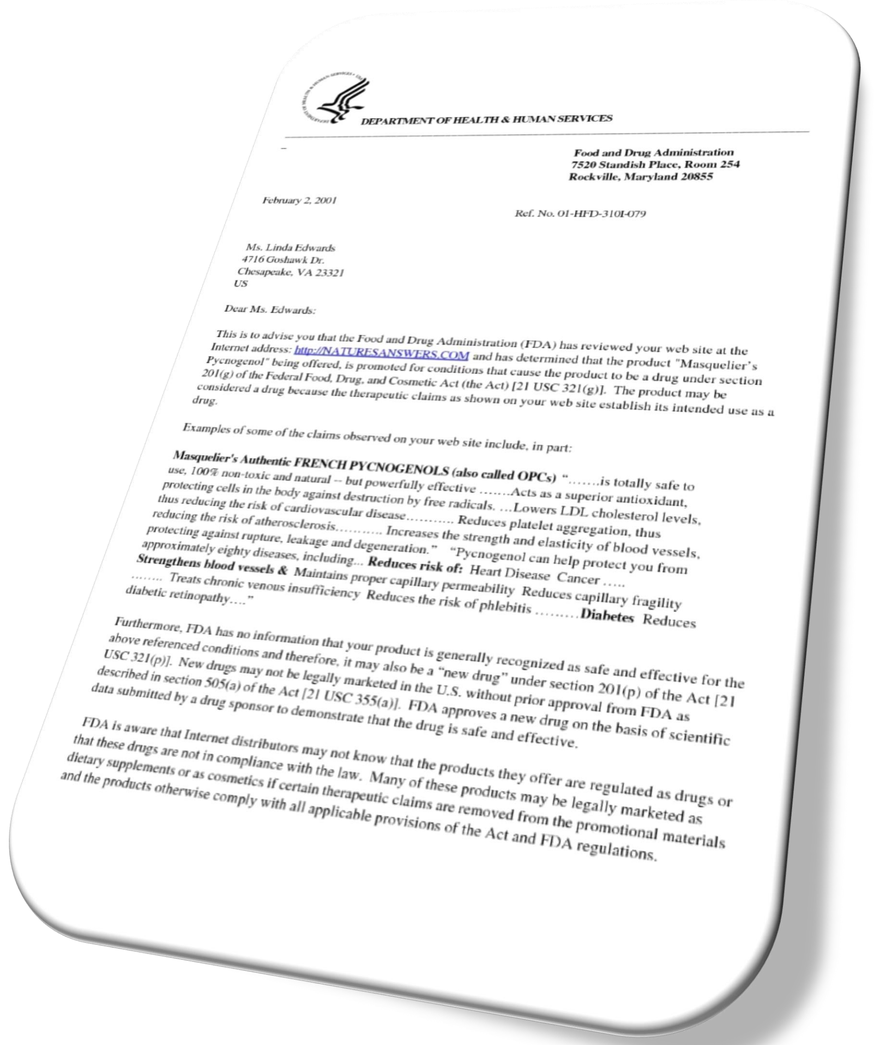
Inspection details with date and any promised correction by facility head

Response request and Warning Statement

Generally 15 days for response time is given. Also contains statement warns that FDA can enforce if issue is not corrected.

Issuer and Standardized closing text

Address of Issuing head office and standard closing text recommending to make corrections and taking responsibility.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
7520 Standish Place, Room 254
Rockville, Maryland 20855

February 2, 2001

Ref. No. 01-HFD-310I-079

Ms. Linda Edwards
4716 Goshawk Dr.
Chesapeake, VA 23321
US

Dear Ms. Edwards:

This is to advise you that the Food and Drug Administration (FDA) has reviewed your web site at the Internet address: http://NATURESANSWERS.COM and has determined that the product "Masquelier's Pycnogenol" being offered, is promoted for conditions that cause the product to be a drug under section 201(g) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 USC 321(g)]. The product may be considered a drug because the therapeutic claims as shown on your web site establish its intended use as a drug.

Examples of some of the claims observed on your web site include, in part:

Masquelier's Authentic FRENCH PYCNOGENOLS (also called OPCs) "……is totally safe to use, 100% non-toxic and natural -- but powerfully effective …….Acts as a superior antioxidant, protecting cells in the body against destruction by free radicals. …Lowers LDL cholesterol levels, thus reducing the risk of cardiovascular disease……. Reduces platelet aggregation, thus reducing the risk of atherosclerosis……. Increases the strength and elasticity of blood vessels, protecting against rupture, leakage and degeneration." "Pycnogenol can help protect you from approximately eighty diseases, including... **Reduces risk of:** Heart Disease Cancer ….. **Strengthens blood vessels &** Maintains proper capillary permeability Reduces capillary fragility …… Treats chronic venous insufficiency Reduces the risk of phlebitis ……**Diabetes** Reduces diabetic retinopathy…."

Furthermore, FDA has no information that your product is generally recognized as safe and effective for the above referenced conditions and therefore, it may also be a "new drug" under section 201(p) of the Act [21 USC 321(p)]. New drugs may not be legally marketed in the U.S. without prior approval from FDA as described in section 505(a) of the Act [21 USC 355(a)]. FDA approves a new drug on the basis of scientific data submitted by a drug sponsor to demonstrate that the drug is safe and effective.

FDA is aware that Internet distributors may not know that the products they offer are regulated as drugs or that these drugs are not in compliance with the law. Many of these products may be legally marketed as dietary supplements or as cosmetics if certain therapeutic claims are removed from the promotional materials and the products otherwise comply with all applicable provisions of the Act and FDA regulations.

Source: https://www.fda.gov/ICECI/default.htm

CLASSIFICATION

- Drugs and Pharmaceuticals
  - Drugs for Human use
  - Drugs for Veterinary use
  - Biologicals
  - Medical Devices
- Food products
  - Food and Nutrient Supplements
  - Seafood and poultries
  - Packed foods
- Tobacco products
- Cosmetics

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RESEARCH OBJECTIVE

To understand what the major violations in case of drugs, biologicals, and medical devices from Warning Letters.

RESEARCH METHODOLOGY

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- **STUDY TYPE**

  Descriptive and retrospective study.

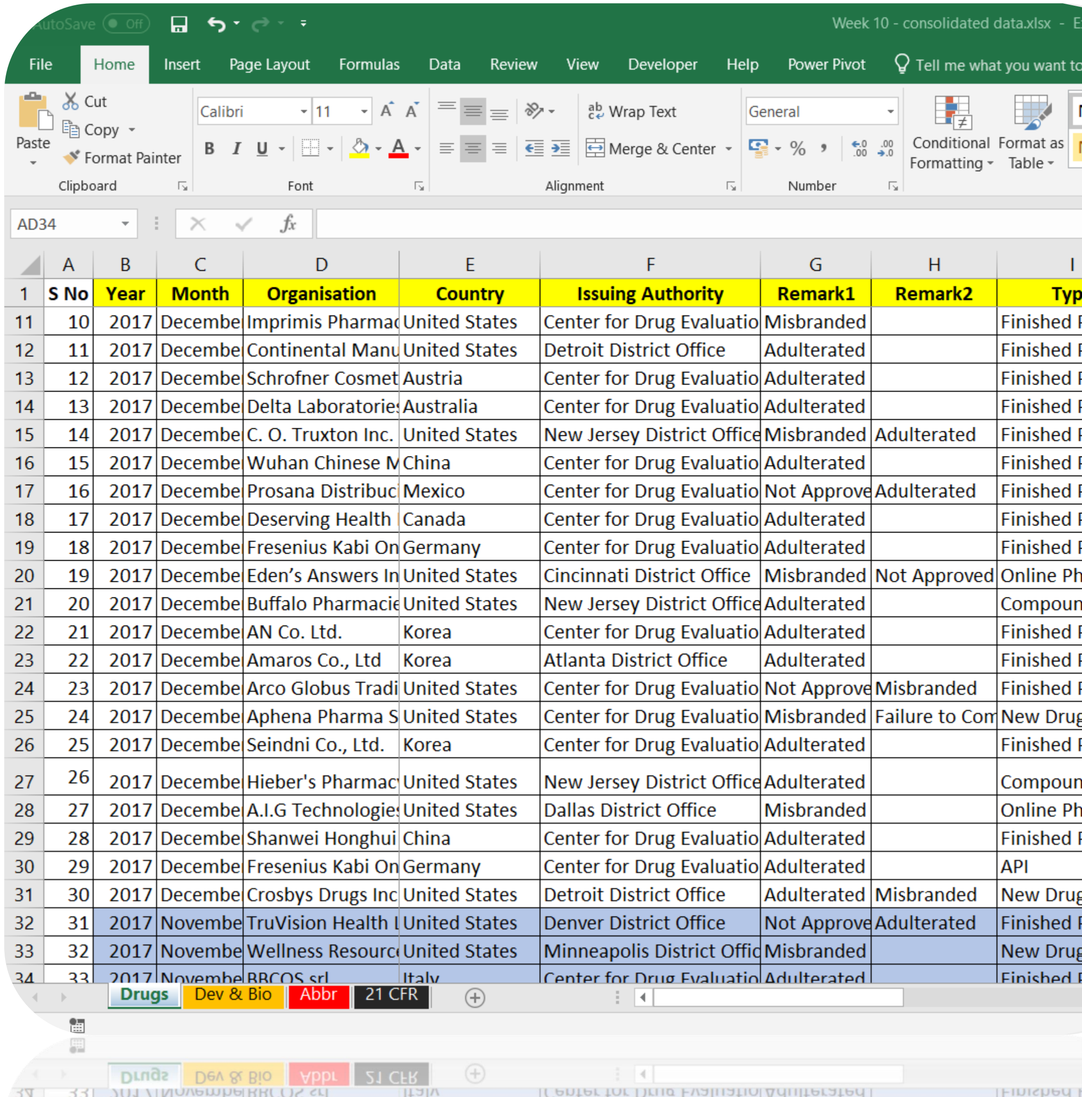
  Secondary Desk Review.

- **DATA SOURCE**

Publicly available FDA letters sent to pharmaceutical companies from 2015 to 2017 were reviewed. A standard data collection tool was developed, including all categories violations and data is collected manually.

- **STUDY DURATION**

  February to April 2018, (12 weeks)



	A	B	C	D	E	F	G	H	I
1	S No	Year	Month	Organisation	Country	Issuing Authority	Remark1	Remark2	Typ
11	10	2017	Decembe	Imprimis Pharmac	United States	Center for Drug Evaluatio	Misbranded		Finished F
12	11	2017	Decembe	Continental Manu	United States	Detroit District Office	Adulterated		Finished F
13	12	2017	Decembe	Schrofner Cosmet	Austria	Center for Drug Evaluatio	Adulterated		Finished F
14	13	2017	Decembe	Delta Laboratorie	Australia	Center for Drug Evaluatio	Adulterated		Finished F
15	14	2017	Decembe	C. O. Truxton Inc.	United States	New Jersey District Office	Misbranded	Adulterated	Finished F
16	15	2017	Decembe	Wuhan Chinese M	China	Center for Drug Evaluatio	Adulterated		Finished F
17	16	2017	Decembe	Prosana Distribuc	Mexico	Center for Drug Evaluatio	Not Approve	Adulterated	Finished F
18	17	2017	Decembe	Deserving Health	Canada	Center for Drug Evaluatio	Adulterated		Finished F
19	18	2017	Decembe	Fresenius Kabi On	Germany	Center for Drug Evaluatio	Adulterated		Finished F
20	19	2017	Decembe	Eden's Answers In	United States	Cincinnati District Office	Misbranded	Not Approved	Online Ph
21	20	2017	Decembe	Buffalo Pharmacie	United States	New Jersey District Office	Adulterated		Compoun
22	21	2017	Decembe	AN Co. Ltd.	Korea	Center for Drug Evaluatio	Adulterated		Finished F
23	22	2017	Decembe	Amaros Co., Ltd	Korea	Atlanta District Office	Adulterated		Finished F
24	23	2017	Decembe	Arco Globus Tradi	United States	Center for Drug Evaluatio	Not Approve	Misbranded	Finished F
25	24	2017	Decembe	Aphena Pharma S	United States	Center for Drug Evaluatio	Misbranded	Failure to Com	New Drug
26	25	2017	Decembe	Seindni Co., Ltd.	Korea	Center for Drug Evaluatio	Adulterated		Finished F
27	26	2017	Decembe	Hieber's Pharmac	United States	New Jersey District Office	Adulterated		Compoun
28	27	2017	Decembe	A.I.G Technologie	United States	Dallas District Office	Misbranded		Online Ph
29	28	2017	Decembe	Shanwei Honghui	China	Center for Drug Evaluatio	Adulterated		Finished F
30	29	2017	Decembe	Fresenius Kabi On	Germany	Center for Drug Evaluatio	Adulterated		API
31	30	2017	Decembe	Crosbys Drugs Inc	United States	Detroit District Office	Adulterated	Misbranded	New Drug
32	31	2017	Novembe	TruVision Health I	United States	Denver District Office	Not Approve	Adulterated	Finished F
33	32	2017	Novembe	Wellness Resourc	United States	Minneapolis District Offic	Misbranded		New Drug
34	33	2017	Novembe	BBCOS srl	Italy	Center for Drug Evaluatio	Adulterated		Finished F

RESEARCH METHODOLOGY

- **SAMPLE SIZE**

A total of 1875 warning letters reviewed from 2015 January to 2017 December and out of which 694 were related to drugs and pharmaceuticals and 1181 letters were related to food and food products.

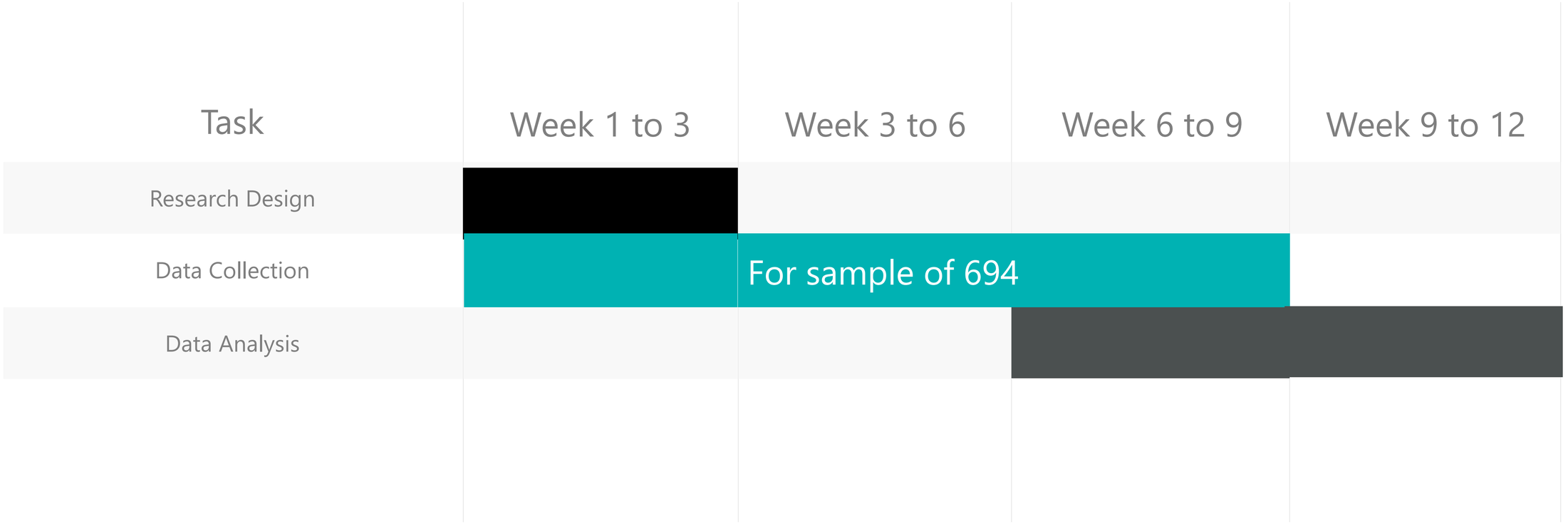
- **SAMPLE INCLUSION & EXCLUSION CRITERIA**

- Only Warning letters related to Drugs, Medical devices, Biologicals were included in Sample.
- Warning Letters related to Veterinary Drugs, Food, tobacco and cosmetics were excluded.

Year	Drugs	Medical Devices & Biologicals	Food	Total
2015	64	146	492	702
2016	166	60	425	651
2017	213	45	264	522

Sample size = Drugs+ Medical devices & Biologicals; n = 694

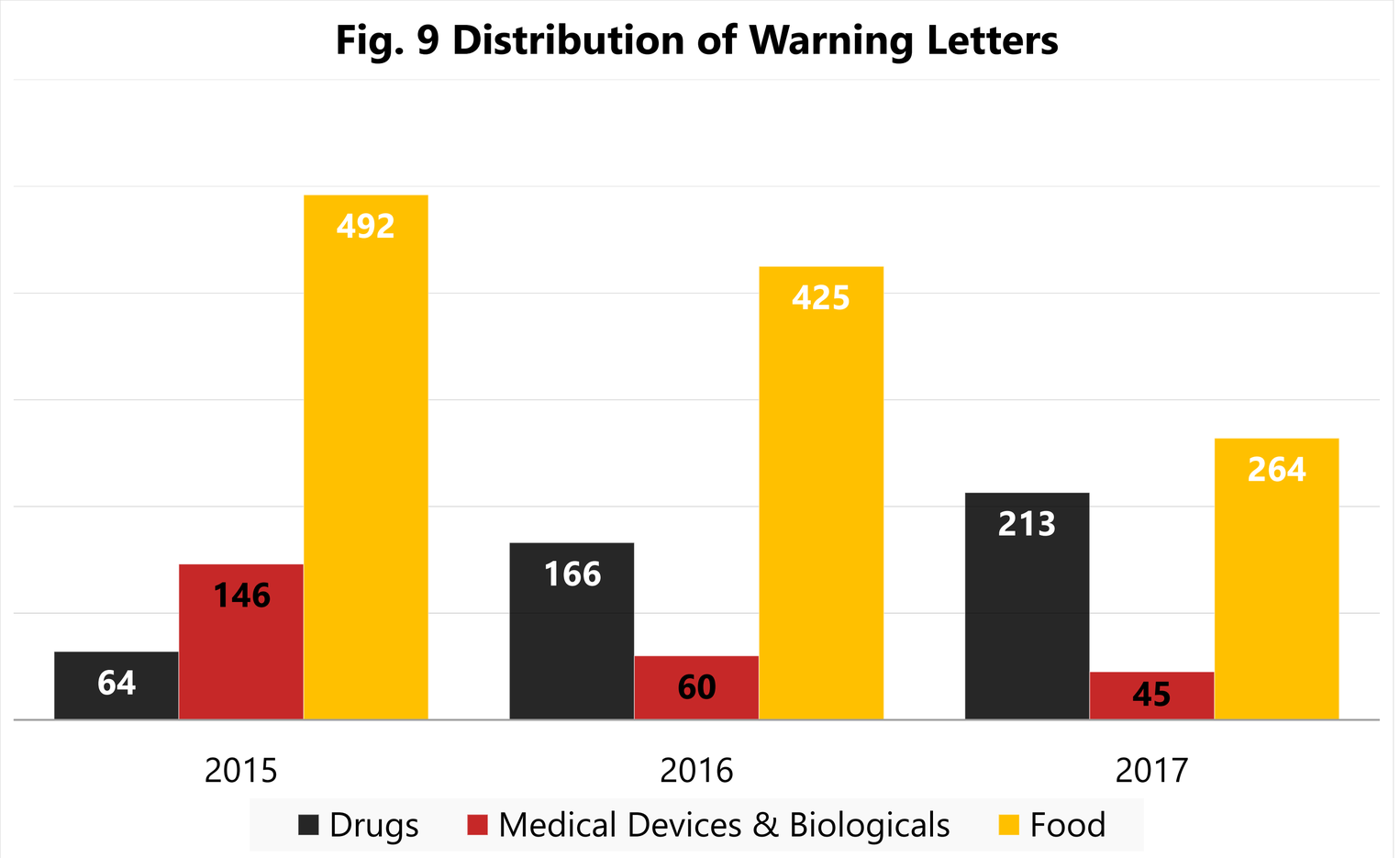
RESEARCH METHODOLOGY



Research plan for Review of Warning Letters Issued by US FDA from 2015-17

RESULTS AND FINDINGS

Distribution of Letters



Drugs: Increase in warning letter

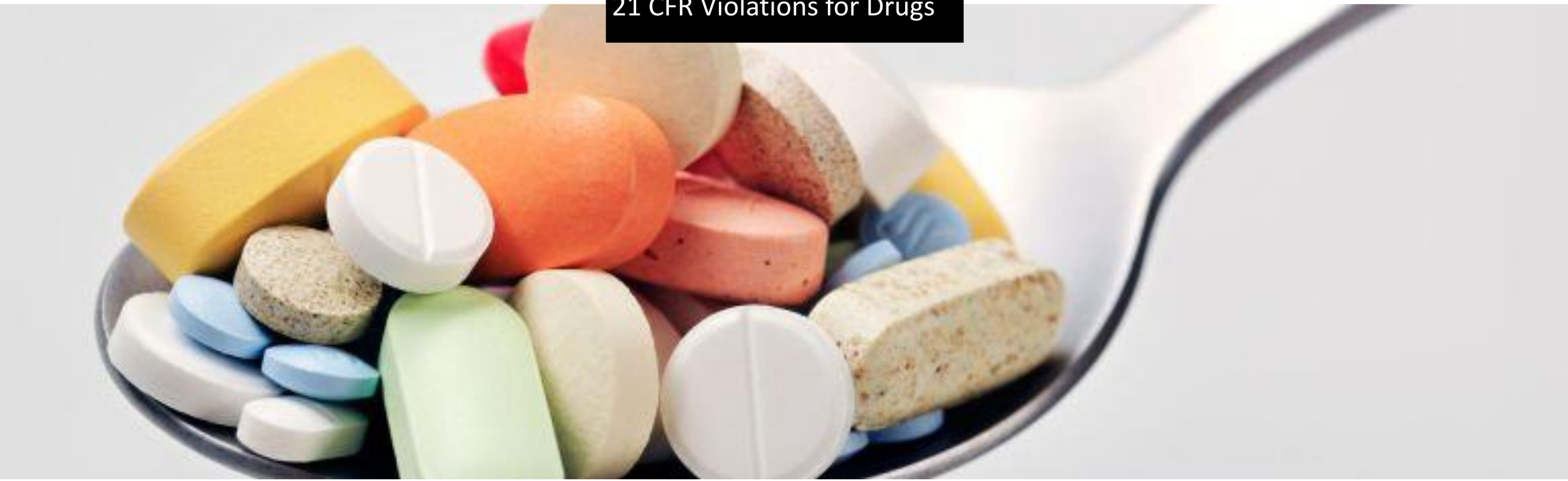
Medical Devices & Biologicals: Decrease in warning letter

Food: Decrease in warning letter

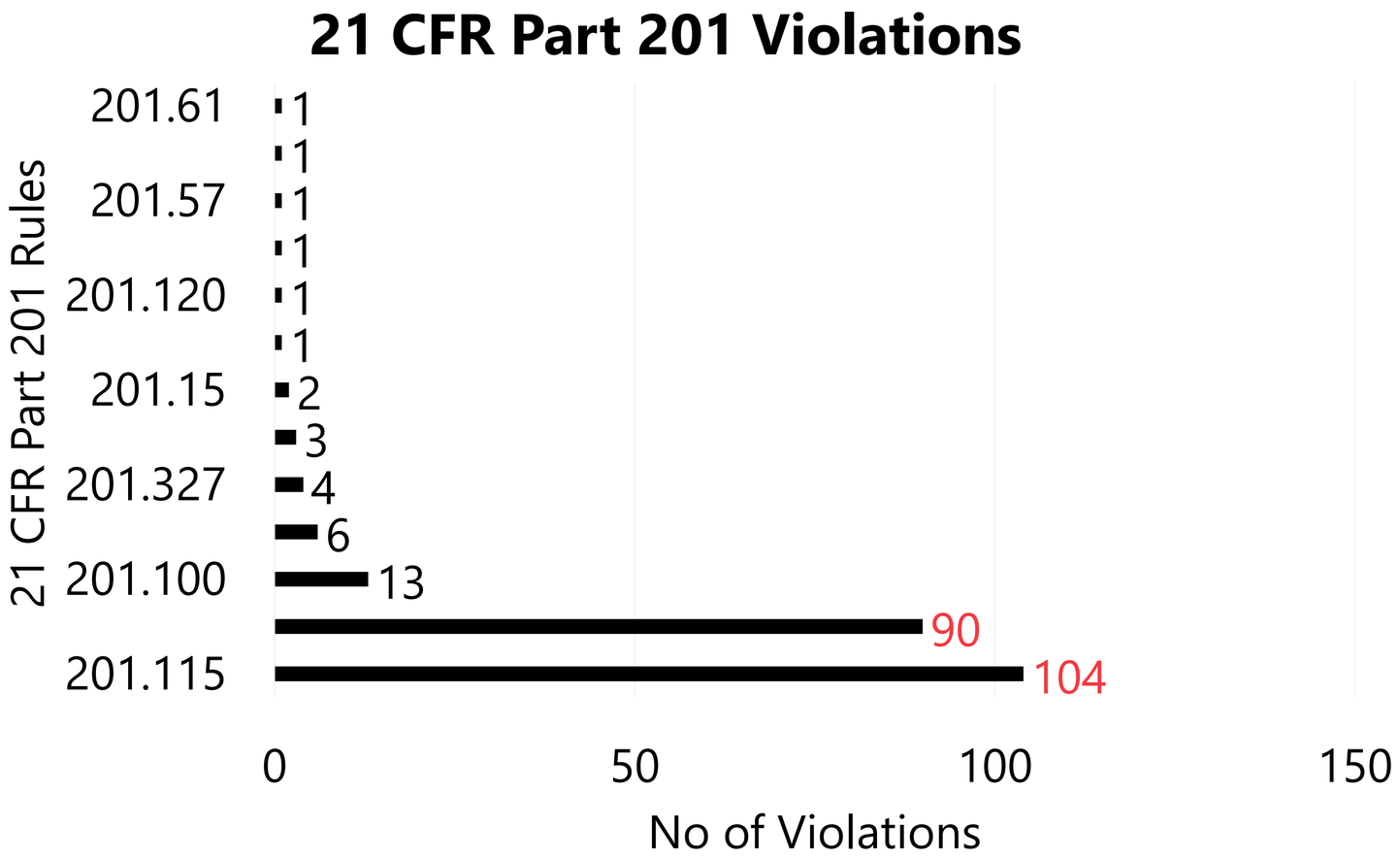
Source: https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

DRUGS

21 CFR Violations for Drugs



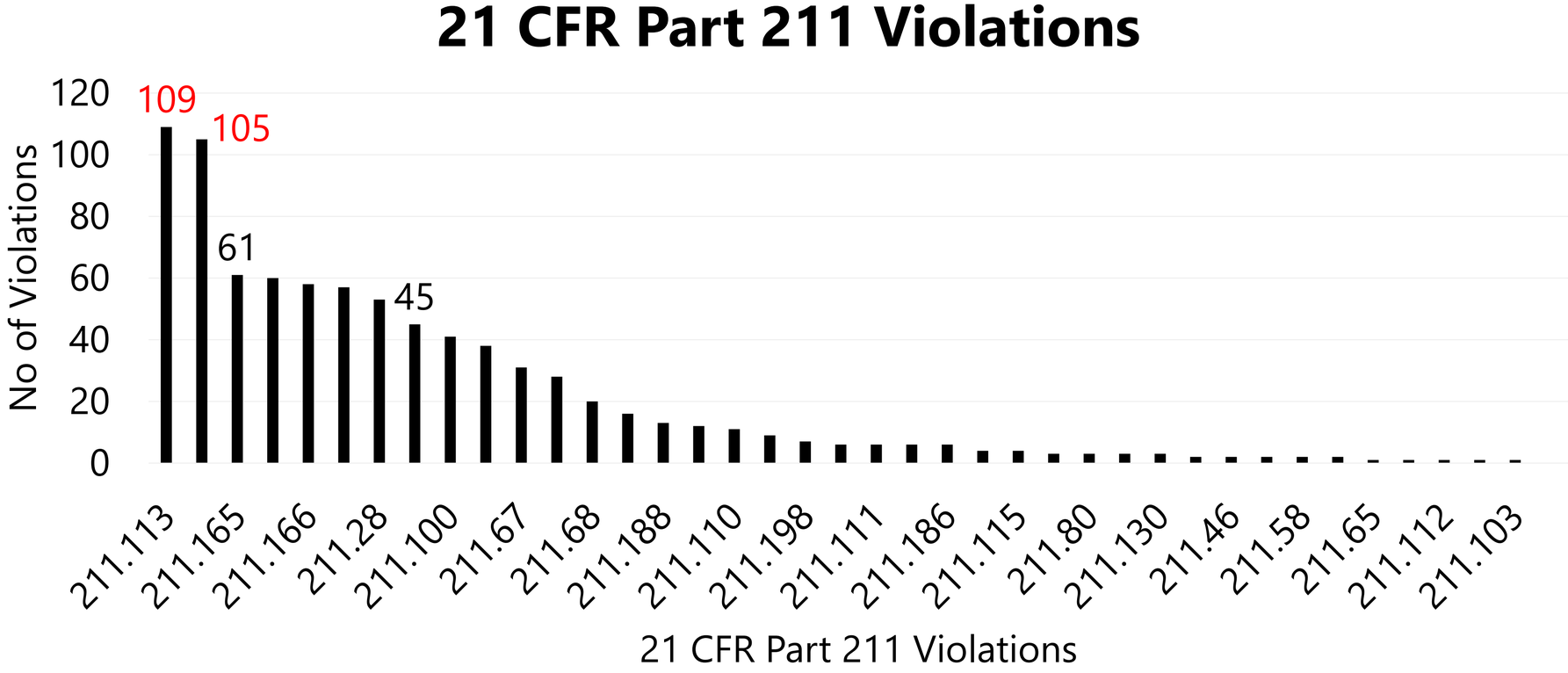
Part 201 Violations



201.115	Exemptions to New Drugs.
201.5	Drugs; adequate directions for use.

Source: https://www.ecfr.gov

Part 211 Violations



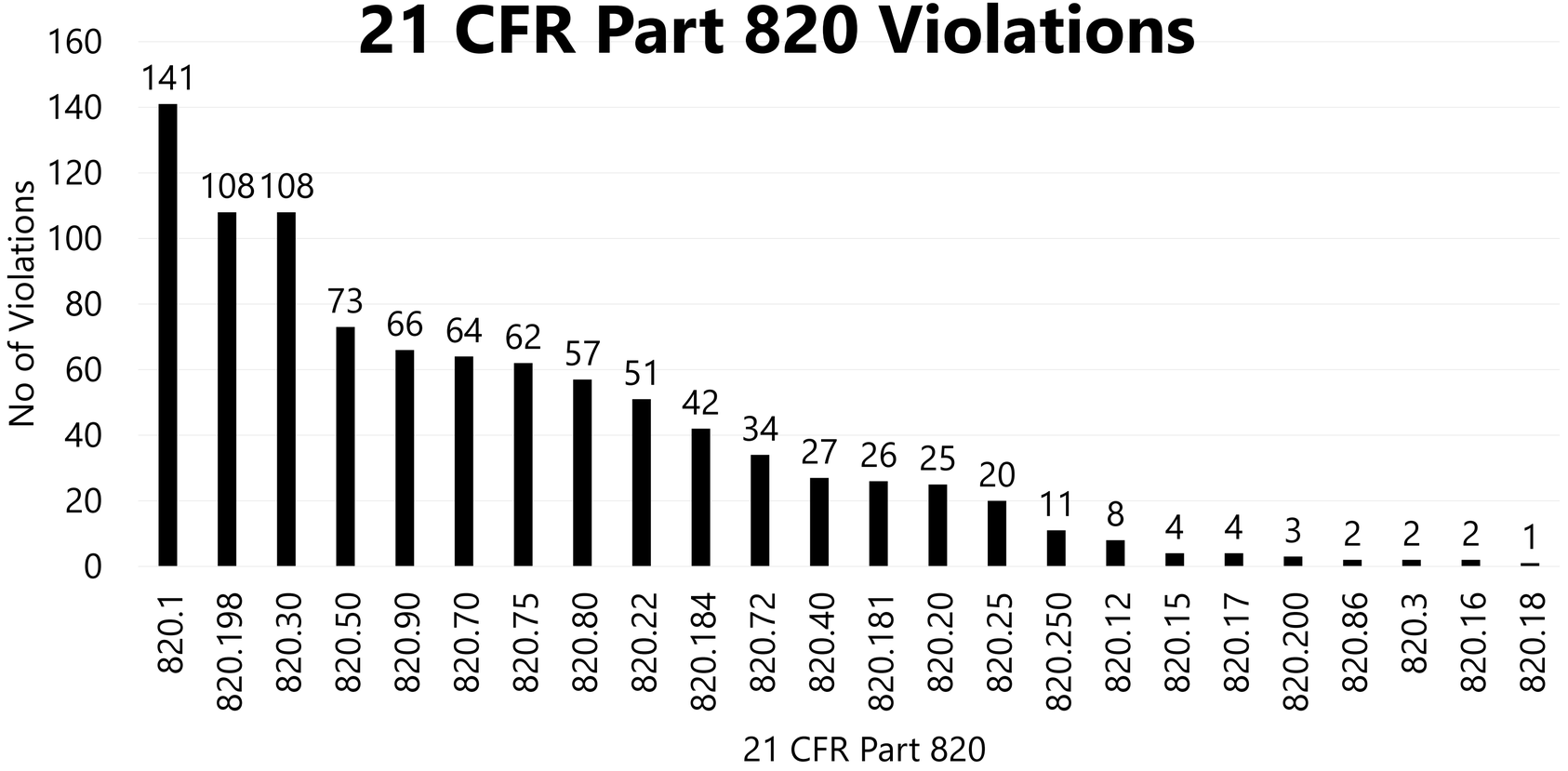
211.113	Production and process control; Control of microbiological contamination.
211.165	Laboratory Controls; Testing and release for distribution.

Source: https://www.ecfr.gov

MEDICAL DEVICES & BIOLOGICALS

21 CFR Violations

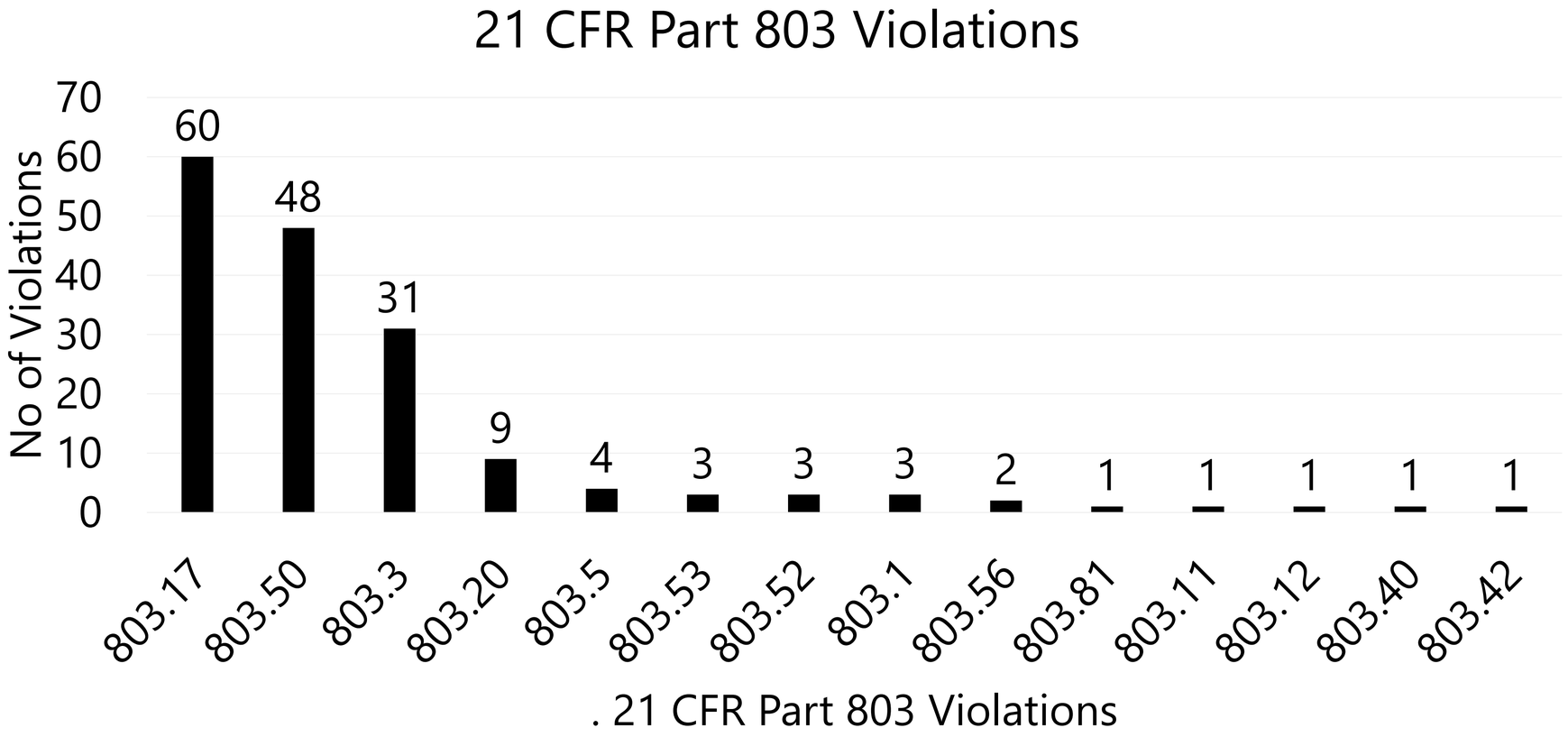
Part 820 Violations



820.1	Scope.
820.198	Records; Complaint Files
820.30	Design Controls

Source: https://www.ecfr.gov

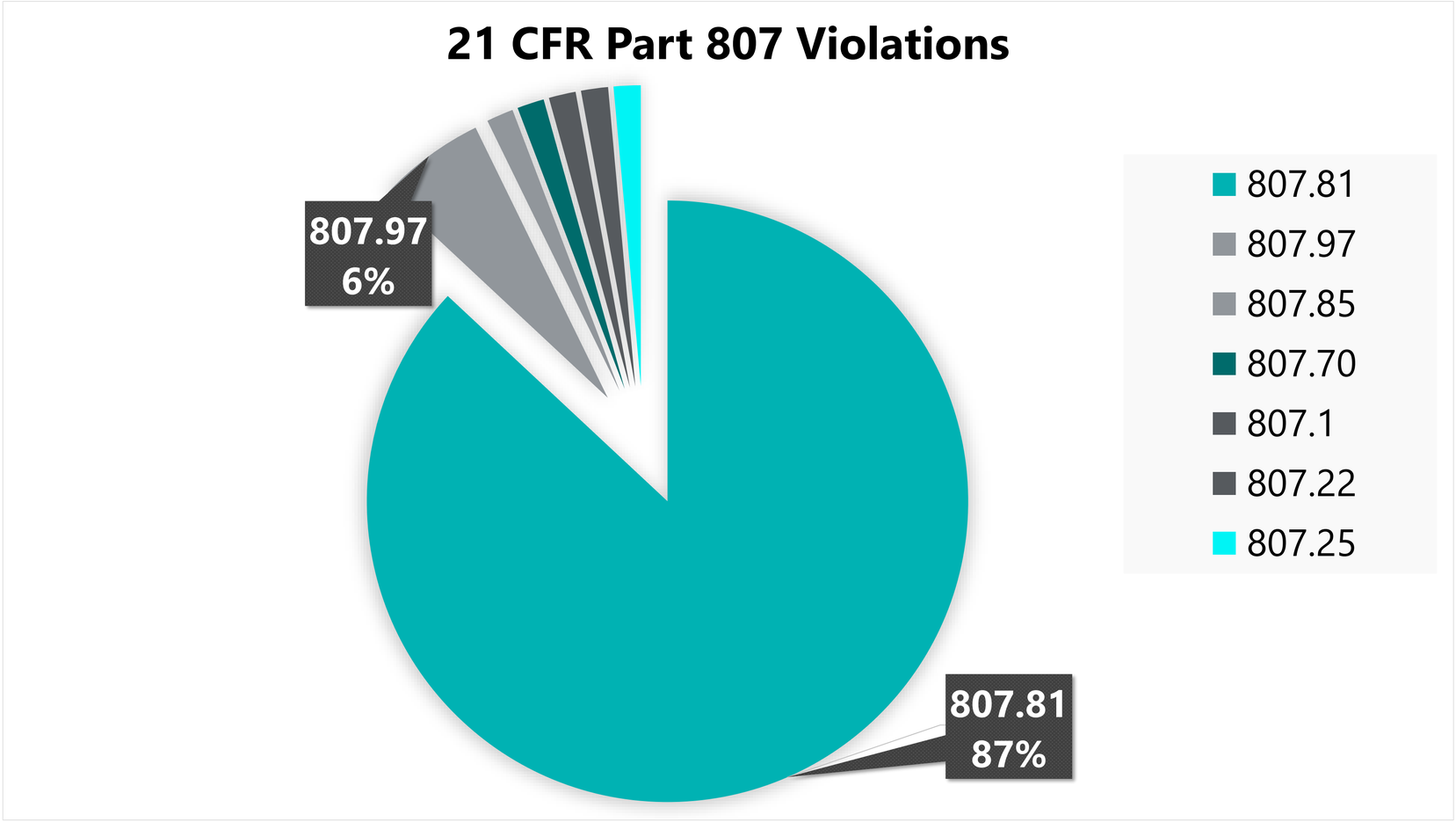
Part 803 Violations



803.17	Requirements for developing, maintaining, and implementing written MDR procedures.
803.50	Reporting requirements to Manufacturer.

Source: https://www.ecfr.gov

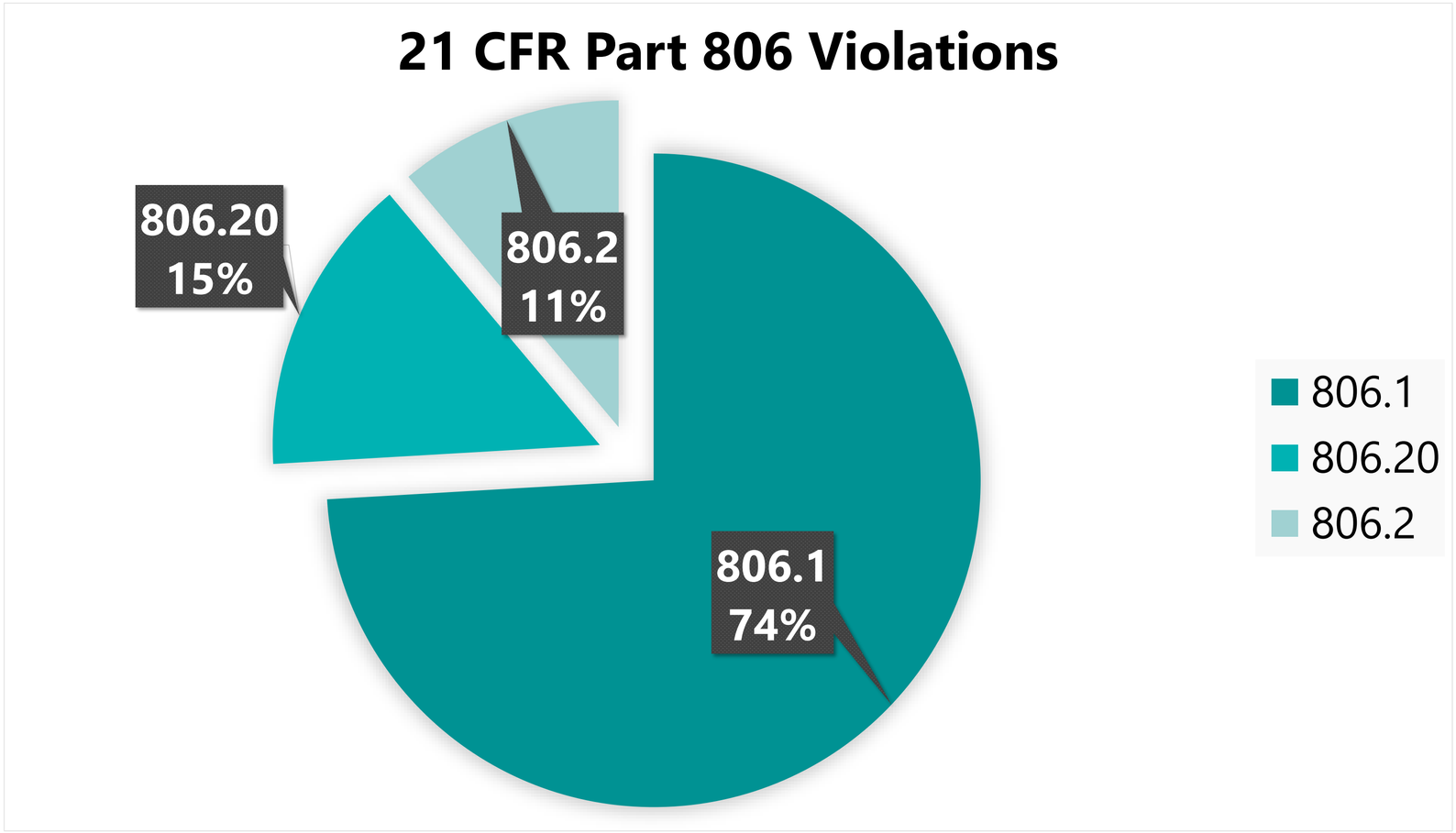
Part 807 Violations



807.81	Requirements of Premarket notification submission.
807.97	Misbranding by reference to Premarket notification

Source: https://www.ecfr.gov

Part 806 Violations



806.1	Scope.
806.20	Records of corrections and removals not required to be reported.
806.2	Definations

Source: https://www.ecfr.gov

CONCLUSION

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- Violations for online pharmacies(US) include misbranding(56), *labelling issues(18)*, sale of not approved medicines(36) and internet marketing with false or misleading claims(3).
- Violations for API, drugs and formulations(ROW) include *labelling(201)* adulteration(209), misbranding(92). It also includes few false or misleading claims.
- Violations for medical devices(ROW) include adulteration(223), QSR(187), pre-market approval(26) , investigational device exemptions(26) and misbranding(49)

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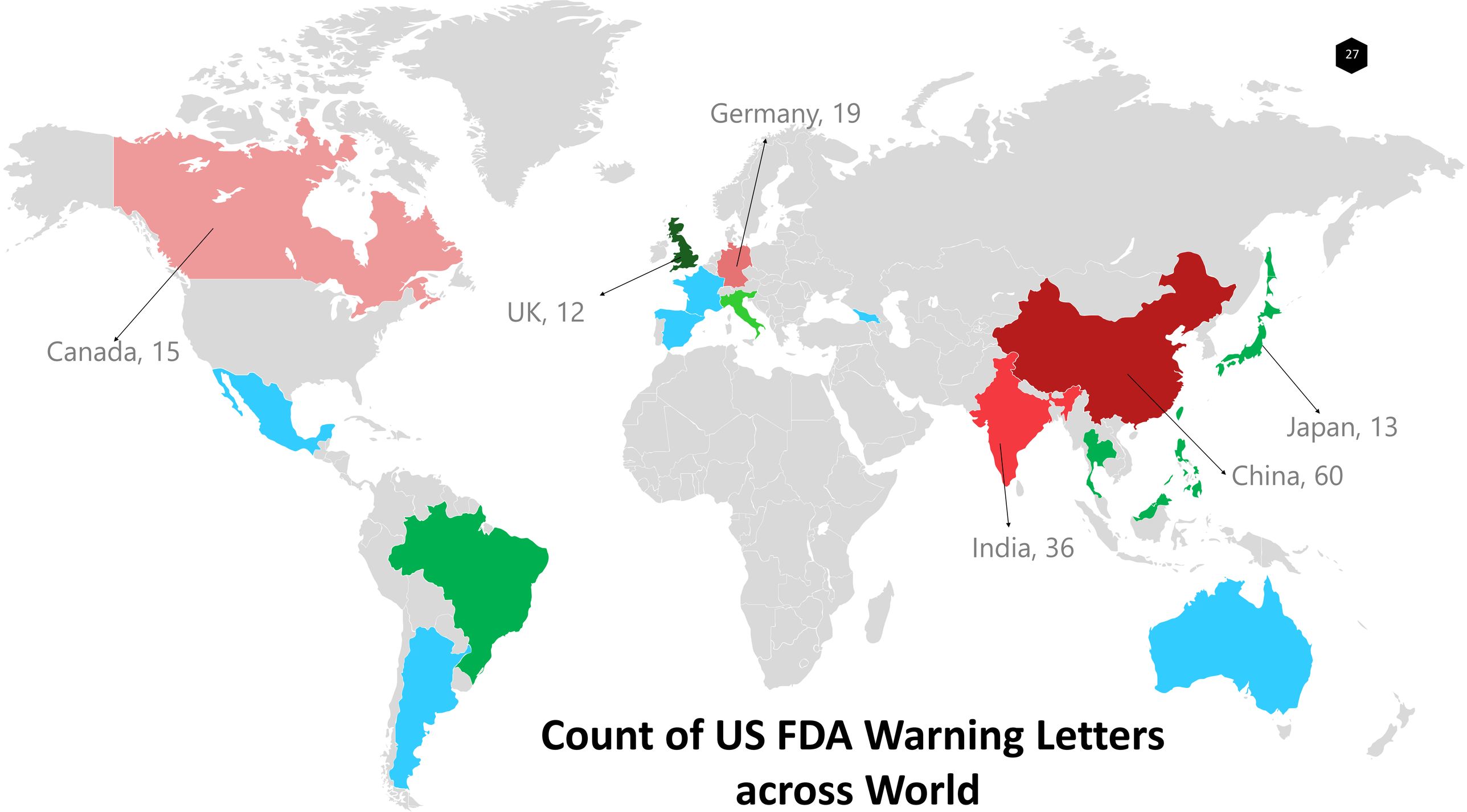

Count of US FDA Warning Letters across World

THANK YOU