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The Unfortunate Aftermath of the US-FDA Slamming API Factories

An in-depth look at the calamitous effects of recent FDA warning letters and import bans and how this affects the pharmaceutical industry; API manufacturers and formulation companies.

Prime examples of how API factories should have acted to avoid getting themselves into hot water. How does all of this affect end patients and what the Trump administration can do in order to mitigate the outcome.

FDA U.S. FOOD & DRUG ADMINISTRATION

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The FDA has Issued 235 Warning Letters Globally from 2013 – 2016 (end of fiscal year)

Table 1: FDA Drug GMP Warning Letters, FY2013-FY2016

	FY2013	FY2014	FY 2015	FY 2016
Total	41*	49**	43	102
Compounding pharmacies (U.S. only)	3 (7%)	27 (55%)	24 (57%)	56 (55%)
U.S. (non-compounders)	13 (32%)	4 (8%)	3 (7%)	11 (11%)
OUS	25 (61%)	18 (37%)	16 (38%)	35 (34%)
Breakdown By Facility Type (U.S. & OUS), Excluding Compounding Pharmacies				
API sites	5	8	9	19
Drug product (non-compounders)	29	12	9	23
API and drug product	3	2	1	4

*Includes one repackager not counted as either API or drug product

**Includes one warning letter regarding combination products, considered drug product

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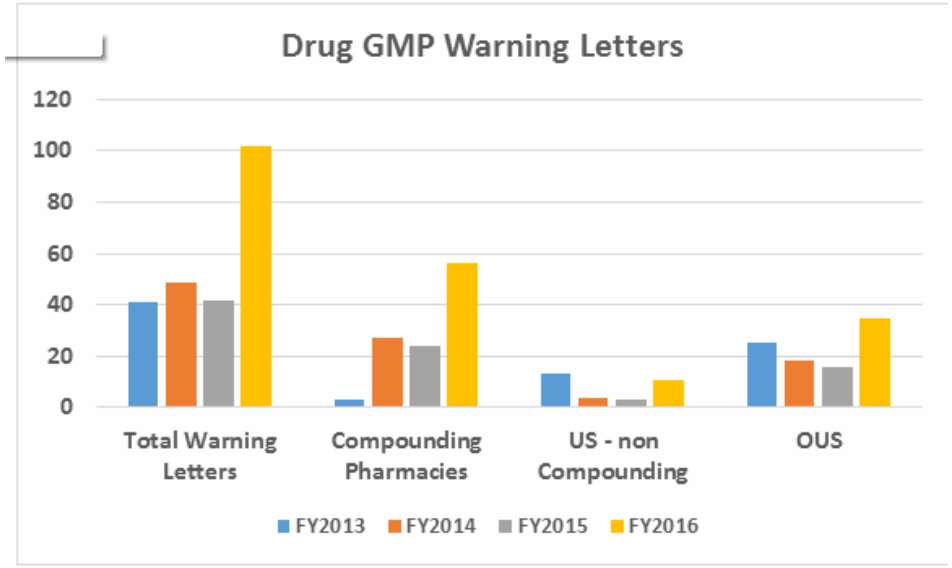
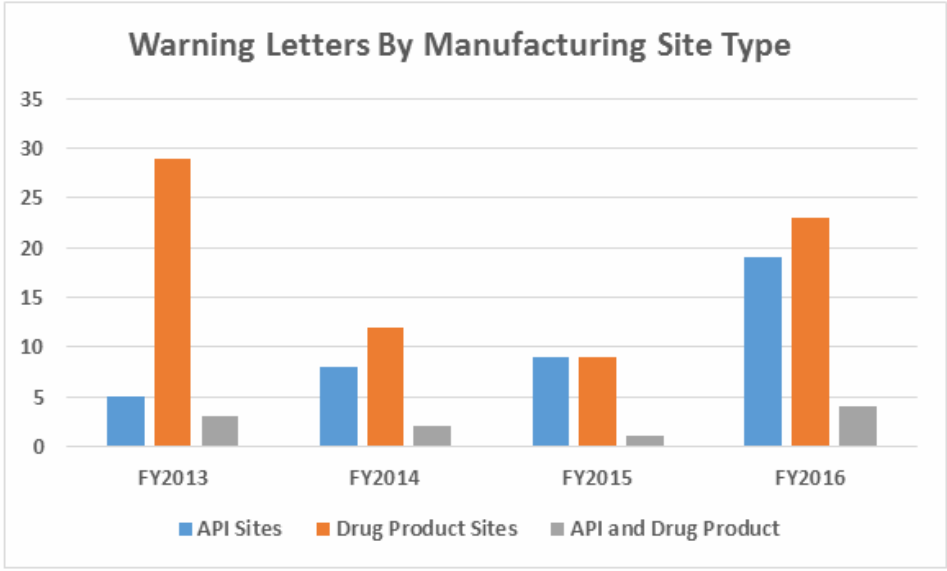
From 2013 through 2016, a total of 51 API and API / drug product sites received warning letters



23 API and API / drug product sites received warning letters in FY 2016 alone



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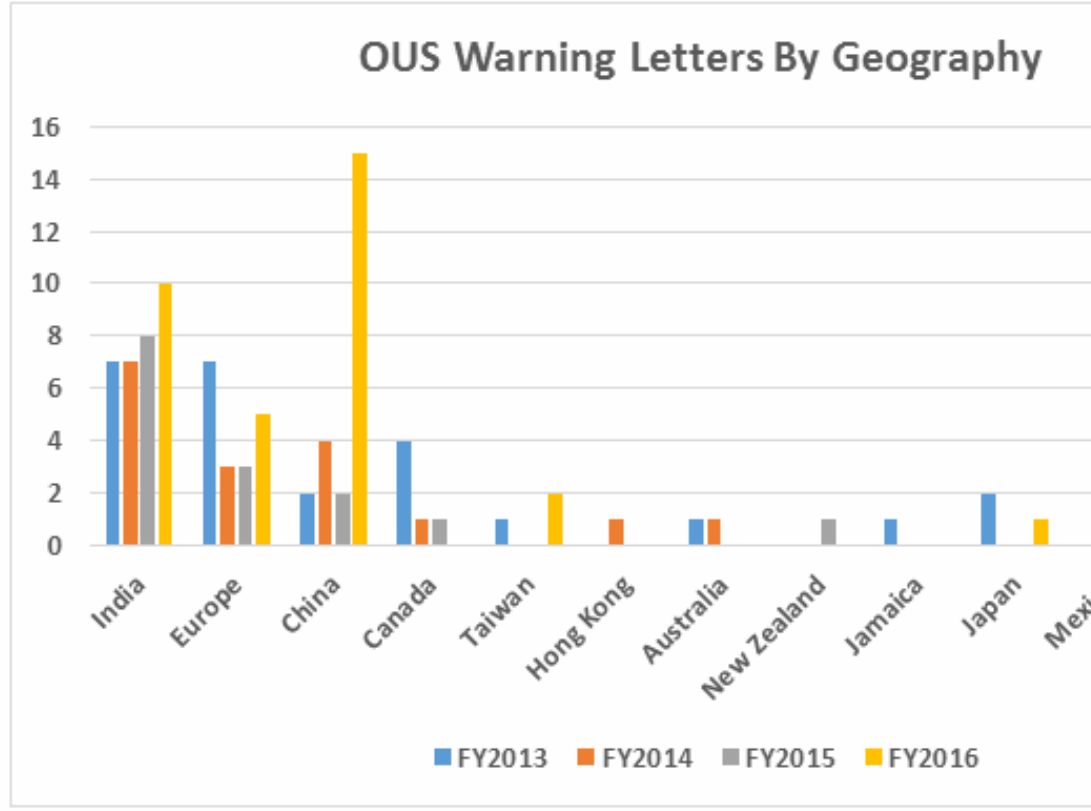
Geographic distribution of warning letters issued outside the U.S.

Table 2: Drug GMP Warning Letters Regarding Sites Outside the U.S.

Country / Geography	FY2013	FY2014	FY2015	FY2016	Total
India	7	7	8	10	32
China	2	4	2	15	23
Europe	7	3	3	5	18
Canada	4	1	1		6
Taiwan	1			2	3
Japan	2			1	3
Hong Kong		1			1
Australia	1	1			2
Brazil				2	2
New Zealand			1		1
Jamaica	1				1
Mexico		1			1
Thailand			1		1



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35 Warning Letters were issued regarding OUS, and 17 of these were associated with import alerts for failure to comply with drug GMPs.

Table 3: Import Alerts Associated With FY2016 Warning Letters

Country	FY2016 Warning Letters	Number of Warning Letter Sites Subject to Import Alerts
China	15	9
India	10	6
Japan	1	1
Brazil	2	1

FDA Import Alert # 66-40

- Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs

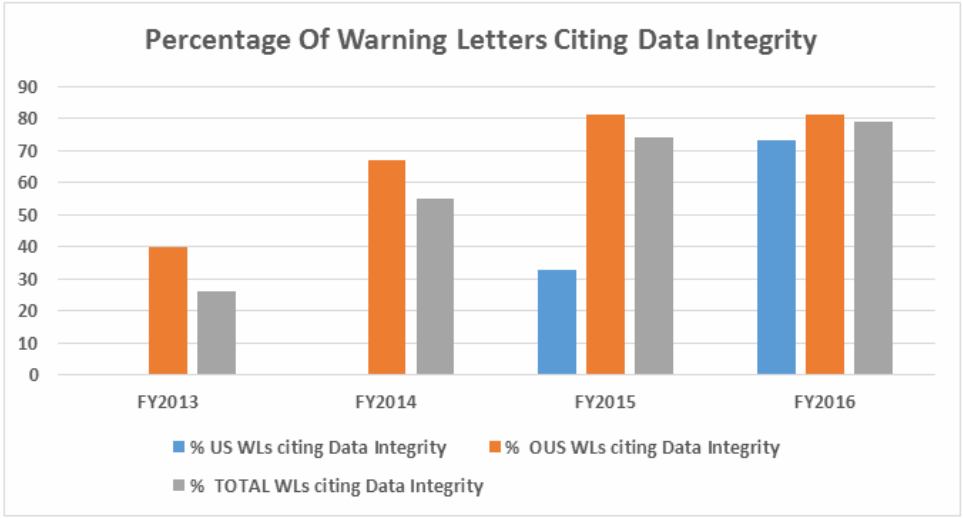
FDA Import Alert # 99-32

- Detention Without Physical Examination Of Products From Firms Refusing FDA Foreign Establishment Inspection

Data Integrity Deficiencies In Warning Letters

Table 4: Warning Letters Citing Data Integrity Deficiencies (Excluding Compounding Pharmacies)

	FY2013	FY2014	FY2015	FY2016
Total warning letters	38	22	19	46
U.S. warning letter sites with data integrity citations	0 of 13 (0%)	0 of 4 (0%)	1 of 3 (33%)	8 of 11 (73%)
OUS sites with data integrity citations	10 of 25 (40%)	12 of 18 (67%)	13 of 16 (81%)	29 of 35 (81%)
Total number of warning letters citing data integrity	10 of 48 (26%)	12 of 22 (55%)	14 of 19 (74%)	37 of 46 (79%)



Peter Werth, President and Chief Executive Officer of ChemWerth, July 2016: Data integrity has no relationship with product quality

- Because the analyst (often) knows the result is not correct for reasons not related to API quality (gross errors/laboratory gross errors).

  They do not want to conduct an expensive, time-consuming, and cumbersome OOS (out-of-specification) investigation.

  Therefore, they delete the data, weigh out new samples, fix the problem, analyze, and either receive acceptable results or rejection results

- OOS API batches will be rejected and returned to the API manufacturer. The same does not apply to pharmaceutical companies that produce both API and finished dosage. They can hide information.

- Data integrity is more of an issue with companies that manufacture both API and dosage form

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SOCMA affiliate, Bulk Pharmaceuticals Task Force (BPTF), 2016 meeting with Dr. Janet Woodcock (Director of the FDA's Center for Drug Evaluation and Research)

- Over 300 Asian sites that produce APIs for OTC formulations
- Most of these sites have never been visited by the FDA
- The FDA is fully prepared to complete this task within three years

SOCMA
Society of Chemical Manufacturers & Affiliates

BPTF
Bulk Pharmaceuticals Task Force

New FDA commissioner Scott Gottlieb

- “a physician, a cancer survivor, a venture capitalist and a government insider who has long said **he wants to tear down the wall of FDA regulations he believes is holding back innovation**” (CNN, April 4th 2017)

- Gottlieb's viewpoint on the FDA mirrors that of his potential boss: The agency needs an overhaul to reduce bureaucratic red tape and speed the drug pipeline.
- In a January meeting with pharma executives, Trump laid out a plan to deeply cut the FDA's regulatory playbook. "Instead of it being 9,000 pages, it'll be 100 pages," Trump told the group. "We're also going to be streamlining the process so that from your standpoint, so that when you have a drug, you can actually get it approved - if it works - instead of waiting for many, many years.“
(CNN, April 4th 2017)

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Scott Gottlieb And The Future Of The FDA

- Gottlieb noted that he thought there was an opportunity to implement reforms within the current regulatory framework under the Hatch-Waxman Act.

  For example, Gottlieb suggested that it may be possible to compress Phase II and III clinical trials to create a more efficient drug approval system.

- Gottlieb also indicated that he would be open to re-thinking and modernizing the current over-the-counter (OTC) monograph system

  (April 25, 2017, Law360, the Senate Committee hearing on the nomination of Scott Gottlieb

- He has penned several op-eds criticizing the slowness of FDA drug approvals and its rules governing generic drugs, among other pharma issues.
- In a three-hour committee hearing earlier this month to consider his nomination, **Gottlieb spoke about streamlining FDA regulations. But he also emphasized that the FDA must uphold standards of safety and efficacy for the products it regulates.**

  (April 27, 2017, Xconomy National)

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Drug Shortages – No End in Sight

- Government Accountability Office (GAO): FDA's Ability to Monitor Drug Shortages Remains a Concern

- Despite commitment from FDA leadership to improve drug availability, GAO says it no longer considers FDA's action plan to be effective

(RAPS, 16 Feb 2017)

RAPS REGULATORY AFFAIRS PROFESSIONALS SOCIETY
Driving Regulatory Excellence™

- We Are Endangered By Drug Shortages - And The FDA Shares The Blame

- As of March 31, **195 drugs**–many of them essential for treating patients in emergency rooms, outpatient clinics and ICUs were in short supply in the US, most are generic injectable medications, including analgesics, cancer drugs, anesthetics, products needed for cardiovascular and psychiatric emergencies

(Forbes, July 6, 2016)

Forbes

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503B – Outsourcing Facilities – FDA regulated pharmacies

503A versus 503B practice[9,10]

503A	503B
All pharmacies that compound.	Voluntary.
Regulated by State board of pharmacy.	Regulated by FDA.
Compliance to USP 797, 795, etc.	Compliance to USP 797, etc.
Require patient-specific prescriptions.	Prescriptions are optional.
Patient-specific needs. Triad (doctor-patient-pharmacist)	Standardized dosing.
Limit on bulk compounding. Restriction on compounding copies.	If shortage, can compound extra. Manufacturers of sterile compounding.
No “office use”	Can compound for office use.
Not yet to be resolved.	No limit on distribution to interstates.
No difficult compounding.	Can compound some difficult compounds if able to resolve “difficulties”.

FDA
503B REGISTERED

Imprimis offers $1 alternative to Turing's $750 pill

- Imprimis, a California compounding pharmaceutical company, said in October it would make the alternative—a compounded formulation of the active ingredient in Daraprim, pyrimethamine, and another drug, leucovorin—available for less than $1 per pill.

- That compares with a price of $750 per pill for the drug provided by Turing Pharmaceuticals, the company that acquired Daraprim earlier this year and dramatically raised its price from $13.50 a tablet to $750.

  (CNBC, Dec 1, 2015)

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LGM Pharma is an innovation-driven API company, involved in distribution of quality cGMP pharma ingredients to leading pharmaceutical companies.

In case your primary API source has been placed on import alert –

How can LGM help ?
What can we do for you ?

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Consultative Approach

LGM Pharma provides APIs for initial research and more complex development work towards product commercialization by providing raw materials from top quality GMP certified manufacturers. Our manufacturing partners have the necessary regulatory credentials and are able to provide technical packages, letters of access (LoAs) to registered DMFs as well as complete documentation towards any regulatory filings.

Close collaboration with many world-class cGMP compliant and EU & US-FDA inspected and approved manufacturers gives us several key advantages in the scope of knowledge, technical expertise, market trends, quality and regulatory documentation.

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Based on the scale and scope of development projects with which we are involved, LGM Pharma is able to provide our customers with a seasoned perspective and valuable insight.

Our industry experience enables us to support our clients throughout the entire pathway of drug development, from discovery through commercial production.

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We specialize in supplying our customers with a wide range of APIs supported by integrated technical capabilities and access to complete regulatory DMF documentation.

Our products originate from our API manufacturing partner sites who are approved by the leading regulatory authorities, such as the US-FDA, EDQM, TGA, UK-MHRA, PMDA etc.

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Our Added Value Proposition

- Our product portfolio includes a wide range of GMP APIs, with access to complete documentation available upon request (CTD/CEP/DMF/ASMF).
- We ensure full regulatory documentation & complete technical capabilities from the outset, backed by our approved manufacturing partners.
- Our manufacturing partner sites are fully accredited and certified by all major regulatory authorities (US-FDA, EDQM, TGA, MHRA, PMDA, ANVISA, COFEPRIS etc…).

Continued >

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Our Added Value Proposition

- Solid knowledge and experience working with various formulation development and drug delivery companies (DDS).
- We are ready to facilitate the most stringent API specifications towards your specific finished dosage forms.
- Extensive experience towards product submissions to the regulatory authorities (IND, NDA, ANDA, 505(b)(2) etc..).

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Possessing unparalleled competitive intelligence on API resources and pharma market positioning, we leverage our information resources in order to assist our clients in making the most informed choices regarding primary and secondary API sources.

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Quality Commitment

When it comes to purchasing your APIs, we believe that quality is key.

That's why our number one priority is providing our customers with the highest quality pharmaceutical ingredients.

Our APIs originate from manufacturing partners with full compliance to strict cGMP guidelines and who are inspected and approved by the leading regulatory authorities, such as EDQM, TGA, UK-MHRA, PMDA and US-FDA.

Our continuous evaluation towards improved quality and GMP processes assures you of the highest degree of confidence in the quality of our products.

We work directly with QA, process engineers, scientists, and IP specialists, in order to resolve any analytical, quality or regulatory issues.

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Expert Pharmaceutical Capabilities. Assured cGMP Excellence.

Diverse API Portfolio

- Supplying a wide range of APIs, covering all major therapeutic classifications
- US-DMF/CEP/ASMF regulatory documentation available upon request
- GMP certified & US-FDA approved API manufacturing facilities

Continued >

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Diverse API Portfolio

The following is a list of our supported therapeutic classifications:

- Anti-Asthma / COPD
- Anti-Cancer / Antineoplastic
- Anticonvulsants (Anti-Epileptics)
- Antidepressants
- Anti-Diabetic
- Anti-Emetics
- Anti-Fungals
- Anti-Hyperlipidemics
- Anti-Hypertensives
- Anti-Migraines
- Anti-Parkinsons
- Anti-Thrombotics
- Antibiotics
- Antihistamine
- Antiretroviral / Anti-HIV
- Contrast Agents
- Erectile Dysfunction (ED)
- Immunosuppressants
- Monoclonal Antibodies (mAbs)
- Prostaglandins
- Synthetic Peptides

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APIs for Drug Delivery Systems

The area that excites LGM more than anything is working with other innovation driven companies that are focused around various drug delivery technologies.

Nasal devices, fast dissolving film strips, sublingual spray, microscopic ophthalmic stents, topical patches and orally disintegrating tablets are all amazing drug delivery technologies that our business development team is involved with regularly.

Continued >

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APIs for Drug Delivery Systems

We supply APIs that are tailor-made to suit your application.

We work to solve your challenge - API solubility, nano particle size, taste masking etc –
Our dedicated team has years of experience dealing with these same technical issues.

Inhalation

Ophthalmic

Transdermal

Sublingual

Injectables

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Thank you for your attention!

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