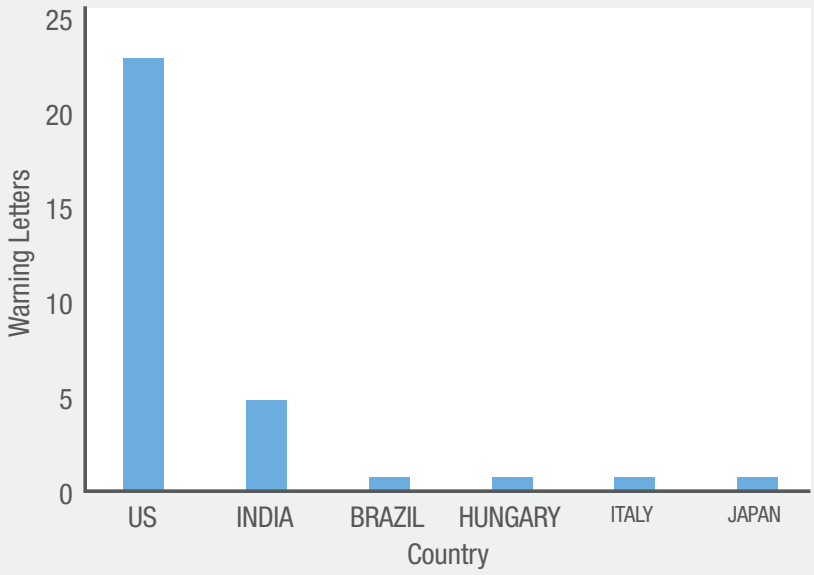
HEIGHTENED FDA ENFORCEMENT FOR STERILITY ISSUES

by Maxine Fritz and Andy Barnett

We will never forget the tragedy that unfolded in 2012. An outbreak of fungal meningitis was traced to the New England Compounding Center and sickened over 800 people with 64 fatalities. This led to the passage in 2013 of the Drug Quality and Security Act, which gave greater authority to the U.S. FDA to regulate compounding pharmacies. As a consequence, since January 2015, 15 compounding pharmacies have received warning letters for significant violations of CFR 211 regulations relating to sterility control.

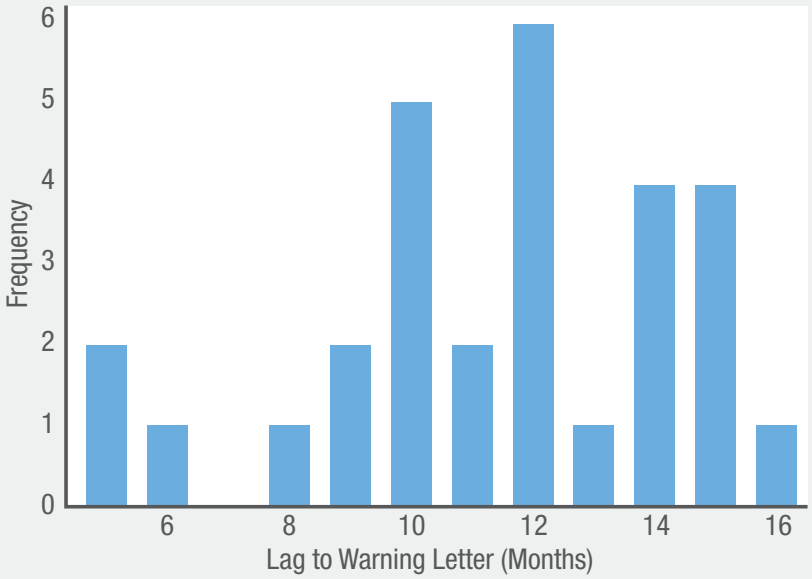
No doubt some of the compounders were caught off guard when they realized they are now subject to the regulations in 21 CFR Parts 210 and 211 and were hit with warning letters. The last thing we want at NSF is for our pharma customers to be subject to regulatory action or risk patient health, so we analyzed all of the warning letters issued to pharma and biologic manufacturers for sterility issues since 2015. Our analysis covers hundreds of pages of detail from 32 warning letters. Based on these findings, we would encourage you to review your quality systems and process controls and consider whether you need to shift or increase your efforts to close your compliance gaps. And remember, we are here to help.

Sterility: Warning Letters



This chart shows the number of warning letters issued over the past two years by country. The United States tops the list with 23 warning letters, but 15 of those are for compounding pharmacies. Overseas manufacturers can expect the enforcement "wave" to hit soon. Since October 2016, four of the last six warning letters were issued to foreign manufacturers, and two of those sites were also given import alerts.

Histogram of Lag: 483 to Warning Letter



This chart shows how long it usually takes for a FDA 483 to turn into a warning letter. (Full disclosure: Three warning letters had very long delays of two years due to special circumstances, so they were excluded from the chart.) Most facilities can expect at least eight to ten months allowance to resolve issues. But be careful! If the FDA is not satisfied that you are making progress, the warning letter may come much sooner.

Compounders are hit with slightly more sterility-related citations than traditional pharma plants (4.1 versus 3.7, respectively), but the difference is not statistically significant. This is a good indication that we can lump all the findings together to see what the FDA looks for during inspections.

Citation	Description	Count	% of WLs	Cum %
211.113	Control of Microbial Contamination	31	97%	25%
211.42c	Controls to Prevent Contamination	25	78%	45%
211.192	Investigations	15	47%	57%
211.28a	Gowning	12	38%	66%
211.160	Stability Testing	7	22%	72%
211.160	Laboratory Controls	7	22%	78%
211.68b	Data Access/Control/Integrity	6	19%	82%
211.167	Test each Batch for Sterility/Particulates	6	19%	87%
211.194	Laboratory Records	5	16%	91%
211.67	Equipment Cleaning	5	16%	95%
211.63	Equipment Design	2	6%	97%
211.58	Equipment Maintenance	1	3%	98%
211.110	In-Process Testing	1	3%	98%
211.165b	Release Testing	1	3%	99%
211.84(d)(6)	Component Testing	1	3%	100%

The table above shows a summary of the regulations cited by the FDA. From the top row, we see that 31 out of 32 (97 percent) warning letters cited regulation 211.113, Control of Microbial Contamination. There were 125 citations in total, so 211.113 accounts for 25 percent of all the citations. If users focus on the top half of the table (seven citations) they will cover over 80 percent of the observations cited in the warning letters.

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We recommend that you focus your initial efforts on the "vital few." Pay particular attention to these items in management reviews. Conduct special internal audits and monitor non-conformances to create metrics around these regulations and trend performance over time. See Journal Issue 35 for more advice on KPIs and tracking quality metrics. Once these systems are in control, you can move on to other items in the table.

Here are a few items that have tripped up other manufacturers:

- Not incubating rejected (integral) vials during media fills
- Inadequate smoke studies that do not show the effects of interventions
- Inadequate rationale or inappropriate location of settle plates and NVP probes
- Ineffective cleaning agents or methods (repeated contamination incidents)
- Not identifying contaminants (even if triggered by alert limits rather than action limits)
- Partial release of a batch with incomplete investigation and inadequate justification

There are so many more incidents and practices that jeopardize sterility assurance. The FDA now routinely advises manufacturers to engage a third-party cGMP consultant to conduct an assessment of the sterility assurance program. NSF has industry-leading experts in environmental monitoring, sampling, aseptic processes, investigations and much more. We can help with identification and remediation.

For any questions and should you need assistance, please contact us at **mfritz@nsf.org** or **+1-202-828-1585**.

ABOUT THE AUTHORS

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