Agenda

- FDA Warning Letter Statistics.
- Industry Offenders?
- Drug vs. Biologics Trends.
- FDA Inspectional Observational Summaries.
- Top 5 violations from 2015.
- Warning Letters by European Country.
- Warning Letters for Ireland.
- Change in Regulatory Focus.
How many Warning Letters have FDA issued in the last 10 years?

53,992

22 Warning Letters per day.....
Which industry is the worst offender?

#1 – Food ~ 50%  
#2 – Medical Devices ~ 20%  
#3 – Drugs ~ 12 to 14%  

#4 – Bioresearch ~ 5 to 6%  
#5 – Veterinary ~ 4 to 6%  
#6 – Biologics ~ 3 to 4%  

Drugs, Bioresearch and Biologics account for ~ 20% of all FDA warning letters.....
FDA Warning Letters – Drugs vs. Biologics Trend

- Drug related warning letters represent 12 – 14%.....
- Biologics related warning letters represent 3 – 4%.....
- Ratio of Drug warning letters increasing to 85% (from 70%).....
- Ratio of Biologics warning letters decreasing to 15% (from 30%).....
FDA Inspectional Observations

http://www.fda.gov/iceci/inspections/ucm250720.htm

- Categorised by Industry.
- Last 10 years available to view and download in Excel....
FDA Warning Letters – FY15 Summary

http://www.fda.gov/ICECI/Inspections/ucm481432.htm

3% relate to Biologics
6% related to Bioresearch
14% related to Drug products

Food (47%) and Medical Devices (21%) still dominate.....

<table>
<thead>
<tr>
<th>Center Name</th>
<th>483s Issued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologics</td>
<td>123</td>
</tr>
<tr>
<td>Bioresearch Monitoring</td>
<td>253</td>
</tr>
<tr>
<td>Devices</td>
<td>1008</td>
</tr>
<tr>
<td>Drugs</td>
<td>678</td>
</tr>
<tr>
<td>Foods</td>
<td>2300</td>
</tr>
<tr>
<td>Human Tissue for Transplantation</td>
<td>81</td>
</tr>
<tr>
<td>Parts 1240 and 1250</td>
<td>66</td>
</tr>
<tr>
<td>Radiological Health</td>
<td>17</td>
</tr>
<tr>
<td>Veterinary Medicine</td>
<td>294</td>
</tr>
<tr>
<td>Sum Product Area 483s from System*</td>
<td>4850</td>
</tr>
</tbody>
</table>
## FDA Drug Related Warning Letter Summary – Top 5 Violations from 2015

<table>
<thead>
<tr>
<th>Cite Id</th>
<th>Reference Number</th>
<th>Short Description</th>
<th>Long Description</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1105</td>
<td>21 CFR 211.22(d)</td>
<td>Procedures not in writing, fully followed</td>
<td>The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically, ***</td>
<td>160</td>
</tr>
<tr>
<td>3603</td>
<td>21 CFR 211.160(b)</td>
<td>Scientifically sound laboratory controls</td>
<td>Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [</td>
<td>130</td>
</tr>
<tr>
<td>2027</td>
<td>21 CFR 211.192</td>
<td>Investigations of discrepancies, failures</td>
<td>There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed. Specifically, ***</td>
<td>124</td>
</tr>
<tr>
<td>1451</td>
<td>21 CFR 211.113(b)</td>
<td>Procedures for sterile drug products</td>
<td>Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed]. Specifically, ***</td>
<td>104</td>
</tr>
<tr>
<td>1361</td>
<td>21 CFR 211.100(a)</td>
<td>Absence of Written Procedures</td>
<td>There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Specifically, ***</td>
<td>95</td>
</tr>
</tbody>
</table>

**#1 - Procedures not followed…..**

**#2 - Laboratory controls not scientifically designed / implemented…..**

**#3 - Failure to investigate thoroughly…..**

**#4 - Sterile product contamination…..**

**#5 - Lack of scientifically designed procedures…..**
### FDA Biologics Related Warning Letter Summary – Top 5 Violations from 2015

<table>
<thead>
<tr>
<th>Cite Id</th>
<th>Reference Number</th>
<th>Short Description</th>
<th>Long Description</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>76</td>
<td>21 CFR 606.100(b)</td>
<td>Maintained and followed</td>
<td>Written standard operating procedures including all steps to be followed in the [collection] [processing] [compatibility testing] [storage] [distribution] of blood and blood components for [homologous transfusion] [autologous transfusion] [further manufactur]</td>
<td>59</td>
</tr>
<tr>
<td>98</td>
<td>21 CFR 606.100(c)</td>
<td>Thorough investigations</td>
<td>Failure to [perform a thorough investigation] [make a record of the conclusions and follow-up] of [an unexplained discrepancy] [a failure of a lot or unit to meet any of its specifications]. Specifically,***</td>
<td>24</td>
</tr>
<tr>
<td>155</td>
<td>21 CFR 606.160(b)</td>
<td>Required records</td>
<td>Failure to maintain [donor] [processing] [storage and distribution] [compatibility testing] [quality control] [general records]. Specifically,***</td>
<td>16</td>
</tr>
<tr>
<td>160</td>
<td>21 CFR 606.160(a)(1)</td>
<td>Person performing, test results, interpretation</td>
<td>Records fail to [identify the person performing the work] [include dates of the various entries] [show test results] [include interpretation of the results] [show the expiration date assigned to specific products] [be as detailed as necessary] so as to pr</td>
<td>16</td>
</tr>
<tr>
<td>154</td>
<td>21 CFR 606.160(a)(1)</td>
<td>Concurrent documentation</td>
<td>Records are not concurrently maintained with the performance of each significant step in the [collection] [processing] [compatibility testing] [storage] [distribution] of each unit of blood and blood components so that all steps can be clearly traced. Sp</td>
<td>13</td>
</tr>
</tbody>
</table>

#1 - Procedures not followed…..

#2 - Failure to investigate thoroughly…..

#3 – Failure to maintain records…..

#4 – Records do not provide full traceability…..

#5 – Records not concurrently maintained…..
Warning Letter issued 14\textsuperscript{th} April 2016…..

To Managing Director of Indian Pharmaceutical company…..

Audit performed 16\textsuperscript{th} – 23\textsuperscript{rd} March 2015…..

…..5 to 7 days?

Significant deviations from cGMP cause your drugs to be adulterated (FD&C Act)…..

Company responded to FDA on 9\textsuperscript{th} April 2015…..

…..13 days after audit.

Final warning letter took over a year to issue due to severity of violations…..
“Un-investigated complaints related to product being sub-potent or contaminated with filth”.

“Only 2 of the 17 complaints on the torn sheet were recorded in the company’s official complaint system”.

“Our investigator found a torn sheet of paper on the floor of the warehouse titled “Product Quality Complaints”.

“A torn page from a production record was found in the trash”.

“Discrepancies were found between the torn page and the official batch record”.

“Your firm did not investigate the deviation or unacceptable practice of discarding a batch record”.

“Your firm did not identify a root cause to assess the quality impact before releasing the lot”.

“Your firm did not identify a root cause to assess the quality impact before releasing the lot”.
“Electronic signatures on C of A’s were uncontrolled images rather than software generated electronic signatures”.

“Results on C of A’s could be modified after they had been approved by the Quality Unit”.

“Failure of computerised systems to have sufficient controls to prevent unauthorised access or changes to data”.

“Our investigator found numerous “OOS” moisture results generated between July 2012 and March 2015”.

“This indicates a quality problem or an inadequate moisture test method”.

“The OOS results were not documented or investigated as your staff were not aware of these requirements”.

“Failure of computerised systems to have sufficient controls to prevent unauthorised access or changes to data”.

“Our investigator found numerous “OOS” moisture results generated between July 2012 and March 2015”.

“This indicates a quality problem or an inadequate moisture test method”.

“The OOS results were not documented or investigated as your staff were not aware of these requirements”.
Warning Letter issued 30th December 2015…..

To owner of US based stem cell company…..

Audit covered 3 facilities…..

Audits performed:
• 27th July to 8th Sept 2015…..
• 27th July to 11th Sept 2015…..
• 27th July to 19th Sept 2015…..

Single investigator….?…..Multiple investigators at each site…..32 to 40 days?

Warning letter took 4 months to issue…..
FDA Biologics Related Warning Letters - 2016

“Failure to validate the aseptic manufacturing process”.

“Manufacturing personnel were observed using poor aseptic techniques”.

“No written procedures to prevent microbial contamination of the product”.

“You failed to perform sterility testing of products that were administered between Feb 2013 and Aug 2015 at the 3 facilities”.

“No procedure to confirm the quality of products used in the manufacturing process”.

“Failure to establish and follow written procedures for manufacturing”.

“Failure to maintain laboratory controls to ensure the safety and effectiveness of the product”.

“Failure to provide batch records which document each step of the production process”.

“You failed to perform sterility testing of products that were administered between Feb 2013 and Aug 2015 at the 3 facilities”.

“Failure to establish and follow written procedures for manufacturing”.

“Failure to maintain laboratory controls to ensure the safety and effectiveness of the product”.

“No procedure to confirm the quality of products used in the manufacturing process”.

“You failed to perform sterility testing of products that were administered between Feb 2013 and Aug 2015 at the 3 facilities”.

“Failure to establish and follow written procedures for manufacturing”.

“Failure to maintain laboratory controls to ensure the safety and effectiveness of the product”.

“No procedure to confirm the quality of products used in the manufacturing process”. 
“Failure to ensure that equipment was maintained and calibrated. No IQ, OQ or PQ evidence available. You routinely move equipment between facilities without any requalification”.

“Failure to monitor environmental conditions during manufacture to prevent contamination”.

“Failure to control products used in the manufacturing process before being released by QA”.

“No procedure for documenting complaints”.

“Your firm does not have an established Quality Unit responsible for the release of materials”.

“No procedure for cleaning production equipment”.

“Lack of traceability of components used in manufacturing process”.
“Country” – Warning Letters over 10 Years

**FDA Warning Letters - How Well Is Ireland “Performing”… ?**

10 Year Total: FDA Warning Letter by: European Country

- **4% of Warning letters issued to Ireland.**
- #4 best country in Europe.
- x4 less than UK.

<table>
<thead>
<tr>
<th>Country</th>
<th>FDA Warning Letters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>5</td>
</tr>
<tr>
<td>Belgium</td>
<td>14</td>
</tr>
<tr>
<td>Denmark</td>
<td>13</td>
</tr>
<tr>
<td>France</td>
<td>34</td>
</tr>
<tr>
<td>Germany</td>
<td>81</td>
</tr>
<tr>
<td>Hungary</td>
<td>2</td>
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<tr>
<td>Ireland</td>
<td>12</td>
</tr>
<tr>
<td>Italy</td>
<td>44</td>
</tr>
<tr>
<td>Netherlands</td>
<td>9</td>
</tr>
<tr>
<td>Spain</td>
<td>27</td>
</tr>
<tr>
<td>Switzerland</td>
<td>23</td>
</tr>
<tr>
<td>UK</td>
<td>53</td>
</tr>
</tbody>
</table>
“Ireland” – Warning Letters over 10 Years

FDA Warning Letters by Year for Search Shown

- 2005: 1
- 2006: 0
- 2007: 1
- 2008: 3
- 2009: 0
- 2010: 0
- 2011: 1
- 2012: 2
- 2013: 1
- 2014: 3
- 2015: 0

Low number of WL’s
No trends observed.
No WL’s in 2015.....
Change in Focus: FDA HPLC Warning Letters

**2005 to 2010**

**2011 to 2015**

**Country**

% of FDA HPLC Warning Letters (Country)

**USA Largest**: 75% of HPLC Warning Letters

**India Largest**: 41% of HPLC Warning Letters
Change in Regulatory Focus: FDA HPLC

% "Cause" of HPLC Warning Letters

Range of Reasons
Calibration / Qualification Largest

Fewer “Technical” Reasons
Data Integrity Largest
Thank you for your attention.