:Session 6: The Pivotal Case Study (How the "simple mistake" can lead to a warning letter)

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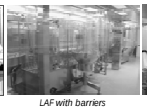
Aseptic Manufacturing……*Past to Present…*

Aseptic processing has improved remarkably since mid 1900's, including…..


Sterilization of articles, 1917


Conventional clean room


LAF with barriers


Complete Isolator , RABs

- Improved cleanroom garments and a better understand of modes of contamination
- Improved cleanroom designs and operational performance
- More comprehensive employee training and qualification programs.
- Improved aseptic processing equipment requiring fewer line interventions
- Well-established validation programs incorporating sound change-control practices to ensure continuing reliability of the processes
- Implementation of advanced contamination control technologies such as isolators, restricted access barrier systems (RABS),.

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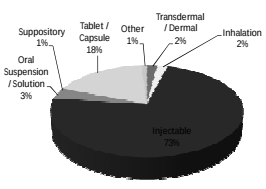
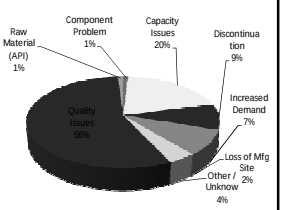
Drug Shortages ……

Drug Shortages; Dosage Form wise



Injection Shortages; Reasons



Source: US Drug Shortages by Russel Wesdyk, 2011

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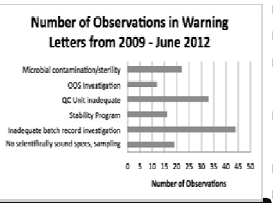
FDA WL…Most common violations…..



- Lax Out-of-Spec (OOS) investigations…
- Inadequate stability testing…
- Lack of scientifically sound specs, sampling plans, standards or test procedures…
- Lax microbial contamination/sterility procedures…
- Inadequate QC unit…
- Inadequate batch record investigation…

Drug GMP Warning Letters by Category…..

Dosage Forms	FY 05	FY 06	FY 07	FY 08	FY 09	FY 10	FY 11	FY 12	FY 13
Oral solid	-	6	2	4	7	16	9	7	3
API	2		1	3	7	8	17	8	6
Oral liquid	1	1	1		3	6	4		2
Topical	2	1	2	3	4	6	6	6	12
Miscellaneous	3	4	1		6	5	4	9	3
Injectable	2	3	6	2	3	4	13	9	9
Inhalable	2	-	1	-	-	-	-	-	-
Repacker	3	1	1	1	2	2	-	-	4
Compounder	-	-	-	-	-	-	-	-	4
Testing lab	-	-	-	-	-	1	-	-	-
Veterinary	2	4	2	1	1	1	-	1	-
Biologics	1		2	1	1		-	-	-
Total	**18**	**20**	**19**	**15**	**34**	**49**	**53**	**40**	**43**

Source: The Gold Sheet, Feb 2014

FY 2013 Drug GMP Warning Letter Cites…..

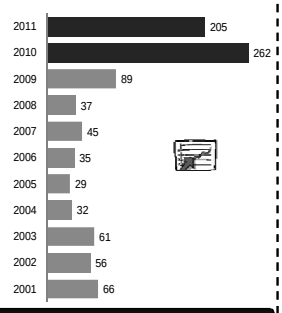
Subject	Number of letters
Production record review	18
Testing and approval or rejection of components	14
Stability testing	14
General requirements, laboratory controls	12
Design and construction features	12
Control of microbiological contamination	11
Written procedures, deviations	10
Testing and release for distribution	10
Equipment cleaning and maintenance	7
Personnel qualifications	5
QC unit responsibilities	4
Special testing requirements	4
Personnel responsibilities	4
Laboratory records	4
Automatic, mechanical and electronic equipment	3
Master production and control records	3
Sampling and testing of in-process materials	3

Subject	Number of letters
General requirements, records and reports	3
Batch production and control	1
Control of components	1
Equipment design, size, and location	1
Drug product containers and closures	1
Expiration dating	1
Washing and toilet facilities	1
Building maintenance	1
Penicillin contamination	1
Sanitation	1
Ventilation and air filtration	1
Time limitations on production	1
Returned drug products	1
Reserve samples	1
Total	**154**

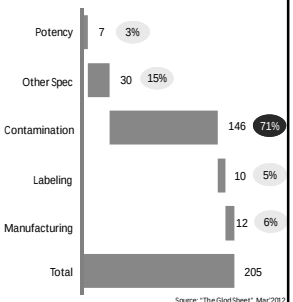
Source: The Gold Sheet, Feb 2014

Recalls……

Drug Recalls : Injectables (2001 – 2011)



Drug Recalls by Problem Area : 2011



Source: "The Glod Sheet", Mar'2012

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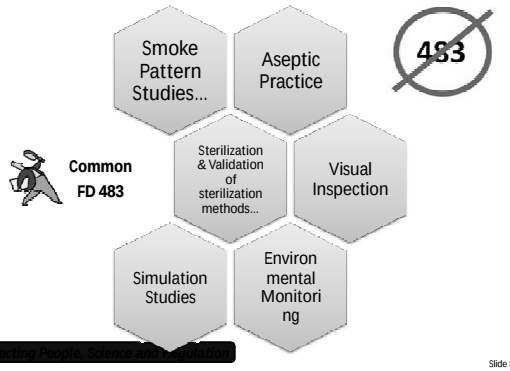
FD 483's: Most common violations….



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Quality…..Common Deficiencies

Training:

- Lack of cGMP Knowledge
- Employee not trained on their specific job function prior to performing,
  - Temporary employee, Contract employee, Employee performing "non-critical" functions
- cGMP training not tailored to the firm's training needs
- No formal system to identify and track training needs for each employee
- Refresher cGMP training not conducted with sufficient frequency.
- Personnel not trained when procedures are revised.
- No effectiveness or competency / skills checks, especially for technical duties.
- Trainers not qualified to train.
- **Employee not proficient in language of SOPs**
- Employee are trained but do not follow SOPs
- **Frequent operator error as the root cause of investigations**

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Is this Important to you?

Yes!

Since January 2010, FDA has issued 66 compliance actions with failure to adequately train employees as one of the issues – at finished dosage sites alone!

This includes 28 Warning Letters, 3 injunctions and 1 seizure.

Quality.....Common Deficiencies

Training.....WL Examples

- *Your firm failed to ensure that each person engaged in the manufacture, processing, packing or holding of a drug product has the education, training and experience, or any combination thereof to enable that person to perform his or her assigned function.*
- *For example: an employee examining microbial plates was unable to read and accurately record microbial counts.*
- *Employee functioning in roles supporting your sterile operations that were not following the procedures that govern their activities, such as glove change frequency, handling of dropped objects, personnel monitoring and sample acquisition.*
- *Other WL related training deficiencies;*
  - *Training for specific job functions*
  - *Training for general cGMP*
  - *Repeated failure of personnel to follow procedures*

Quality.....Common Deficiencies / WL

Data Integrity.....

- Incomplete or altered data
- **Backdating**
- Fabricating data
- **Discarding data**
- **Testing into compliance**
- Failure to retain raw data
- Turning off audit trail capabilities
- **Password sharing / Common Password**
- Inadequate controls for access privileges
- Manipulating integration parameters

Quality.....Common Deficiencies / WL

Quality Control Data

- Test results for one batch were used to release other batches (This occurred at least for 3 batches – at three unrelated firms)
- Destruction of raw data not meeting specification
- **Missing raw data**
- **Re-writing laboratory note books**
- **Refusing to allow FDA to talk to employees**
- **Growth on microbiological plates was observed and recorded as no growth** (Happened at three unrelated firms manufacturing sterile finished dosage forms)

Making up records during an FDA inspection

- **Batch Records**
- **Training Records**

Quality.....Common Deficiencies / WL

Media Fills

- Reconciliations
- Not taking all the units filled.
- All operators / interventions are not included.
- + Ve / - Ve controls / GPT.
- Trained microbiologist / Operators for visual inspection of media fill vials.
- Not simulating actual process.

Quality.....Common Deficiencies / WL

Personnel Practices

- **Use of non-sterile gloves in aseptic area.**
- **Visible holes and flaking in the gloves. Broken primary packing of gloves.**
- Rapid movement of the operators in the aseptic area.
- **Not properly gowned. Loose head gear & goggle.**
- Hand movements over the half stoppered vials.
- Use of non autoclavable papers and pens in the aseptic area.
- **Keeping hands on waist when at rest.**
- Frequent manipulations. Keeping entire body in the path of unidirectional airflow.

Facility & Equipment…..Common Deficiencies / WL




- Surfaces & Finishes…., Ducting & Piping…., Sinks & drains…
- **Toilet flush not working properly.**
- Cold Rooms: Water leakages and presence of microbial growth.
- Tools maintained in the aseptic area are rusted & not sterilized prior to use.
- **Use of adhesive taps.**
- **Rusting on light fixture. Dented doors. Chipping Paints.**
- Change Rooms….Gradient, Entry & Exit, Interlocking, Access Control
- Entry / Exit door into the vial filling area has no mechanism to slow the door when closing creating significant air flow disruption within the filling area.


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Production System…..Common Deficiencies / WL


- **Differences in automatic logging & then equipment manual entries for process controls.**
- Reporting of deviation / incidence.
- **Sequential log not maintained.**
- Calibration / revalidation frequencies not maintained for equipment / instrument.
- **Not recording of all the steps involved in the process – carry out unauthorized steps.**

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Material System…..Common Deficiencies / WL

- **Old & rejected lots were found.**
- Failed to determine why FIFO & CAPA was not followed.
- Manipulation in the RM reconciliation.
- No proper storage condition. Warehouse was not air conditioned.
- Vendor qualification - Supplier capability to control supply chain.
- **Wooden pallet – Not properly sanitized / treated – Fungus growth.**

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Packing & Labeling…..Common Deficiencies / WL

- Lack of written procedures describing identification, handling and examination.
- Validation of Pkg line is deficient.
- **Missing / error labels.**
- **Improper Line clearance.**
- No proper tracking system to back trace in case of any market complaint / recalls.
- No specimen or copy of approved label and all other labeling in the master production and control record.

Laboratory Control…..Common Deficiencies / WL

- **All calculations are not included, performed during testing.**
- Failure to have a stability program to monitor stability characteristics.
- Reporting results without testing.
- **Use of trial injection.**
- **Unexplainable sequence of injection in HPLC – audit trails**
- **Unlabeled materials / Samples / Containers.**
- Established laboratory control mechanisms are not followed and documented at the time of performance.
- Failure to conduct thorough complaint investigations.
- No scientifically sound and appropriate specifications designed to assure identity, strength, quality and purity.
- No written records and appropriate validation data of computer or other automated processes.
- Disinfection Efficacy on different surfaces

References…..

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- "The Gold Sheet", March'2012.
- "The Gold Sheet", Feb'2014.
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- Validation times, June' 2014.