FDA INSPECTIONAL APPROACH

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OBJECTIVES

- TO LEARN THE BUSINESS OF PHARMACEUTICALS.
- DETERMINE WHY YOUR FIRM MAKES CERTAIN DECISIONS.
- DETERMINE HOW YOUR FIRM MAKES CERTAIN DECISIONS.
- RECOGNIZE WHO IS MAKING DECISIONS.

ULTIMATE QUESTION

• WHY IS IT OK TO RELEASE THE BATCH?

 ANSWER: IT IS OK TO RELEASE BATCH ONLY IF BATCH IS MADE ACCORDING TO cGMPS.

GETTING STARTED

I ASK VERBAL QUESTIONS OF THE PEOPLE INVOLVED IN THE INSPECTION
I NEED TO LEARN WHO THE KEY PLAYERS ARE, THE DECISION MAKERS

OPENING QUESTIONS

- WHAT DOES COMPANY NAME MEAN?
- BUSINESS HISTORY OF FIRM
- GET BACKGROUND OF PEOPLE INVOLVED IN INSPECTION
- INSPECTIONAL HISTORY OF FACILITY
- NUMBER OF PEOPLE AT SITE

- WHAT FDA OPERATIONS DOES YOUR FIRM PERFORM?
- WHO IS IN-CHARGE?
- HOW BIG IS FACILITY? GET CAMPUS MAP OR BUILDING DIAGRAM
- HOURS OF OPERATION
- PERCENT INTERSTATE
- PERCENT WHOLESALE

START OF INSPECTION

- BEST WAY TO START INSPECTION IS TO GIVE A OPENING COMPANY OVERVIEW PRESENTATION. GIVE PRESENTATION ORALLY AND PROVIDE HANDOUT TO INVESTIGATOR
- ALSO PROVIDE INVESTIGATOR WITH BINDER OF ALL PERTAINENT INFORMATION

DOCUMENTATION REVIEW

SOPS: STARTING POINT BLUEPRINT/OUTLINE OF YOUR FIRM'S

DAY TO DAY OPERATIONS

SOPS TELL ME WHAT YOUR FIRM DOES.
 ALSO TELLS ME WHAT YOUR FIRM
 DOCUMENTS OR DOES NOT DOCUMENT

SOPS

 TELL ME WHAT DOCUMENTATION TO ASK FOR. TELL ME WHAT DOCUMENTATION YOUR FIRM GENERATES. ALL FIRMS OPERATE DIFFERENTLY.

SOPS ARE REVIEWED FOR THE FOLLOWING GROUPS

- OPERATIONS
- RECEIVING
- WAREHOUSE
- MANUFACTURING
- PACKAGING
- SHIPPING
- ENGINEERING
- MAINTENANCE

- QUALITY CONTROL
- QUALITY ASSURANCE
- COMPLIANCE
- TECHNICAL SERVICES

SOP CONCERNS

NO SOPS FOR BASIC, NORMAL OR **CRITICAL FIRM OPERATIONS.** There is no assurance that firm operations will be consistent from day to day or from person to person. Also, how can you validate or assure quality if things are always changing i.e. equipment cleaning, batch release, batch record review, equipment operation and calibration.

SOP CONCERNS

 SOPS ARE NOT FOLLOWED. For example when data or documentation referenced in SOP is requested, it is not available. Also, when employees are interviewed or questioned, they are not familiar with SOP requirements or instructions.

SOP CONCERNS

 SOPS ARE NOT SPECIFIC. For example, SOPS read like they were downloaded off the internet or purchased from a consultant. Language used in the SOPS is vague and not enough detail is provided in SOP so that reader could accurately or consistently perform the said task.

DEVIATIONS

• MY MAIN CONCERN

- WEBSTER DEFINITION- "A DEPARTURE FROM NORMALITY".
- MY DEFINITION- "ANYTHING THAT HAPPENS THAT WAS NOT EXPECTED OR PLANNED".

DEVIATIONS

 MY FOCUS IS ON HOW DEVIATIONS ARE HANDLED NOT ON THE FACT THAT THEY OCCURRED. I FULLY EXPECT DEVIATIONS TO OCCUR. IT IS IMPOSSIBLE TO RUN A MANUFACTURING OR TESTING FACILITY WITHOUT DEVIATIONS.

DEVIATIONS

 IF FIRM HAS LOW NUMBER OF DEVIATIONS OR NO DEVIATIONS, IT USUALLY INDICATES DOCUMENTATION PROBLEMS.

 MOST LIKELY, DEVIATIONS OCCUR BUT THE FIRM IS NOT DOCUMENTING OR INVESTIGATING THEM.

AREAS TO LOOK FOR DEVIATIONS

- MANUFACTURING AREAS
- LABORATORIES
- VALIDATION STUDIES (PROCESS AND METHODS)
- EQUIPMENT QUALIFICATIONS

- CALIBRATIONS
- WATER SYSTEMS
- HVAC SYSTEMS
- ENVIRONMENTAL MONITORING

HANDLING OF DEVIATIONS

- DOCUMENT: WHO, WHAT, WHEN, WHERE, HOW, WHY, ETC.
- IF DEVIATION OCCURRED DURING MANUFACTURING IT SHOULD BE FIRST DOCUMENTED IN BATCH RECORD

 IF DEVIATION OCCURRED DURING QC TESTING IT SHOULD BE DOCUMENTED IN NOTEBOOK OR ON WORK SHEET. DOCUMENTATION OF DEVIATION SHOULD BE PART OF RAW DATA AND PART OF THE PERMANENT RECORD.

HANDLING OF DEVIATIONS

 AFTER DOCUMENTATION, DEVIATION SHOULD BE THOROUGHLY INVESTIGATED BY APPROPRIATE DEPARTMENTS

 INVESTIGATION MUST BE DOCUMENTED, TIMELY AND COMPLETE.

HANDLING OF DEVIATIONS

 INVESTIGATIONS INTO DEVIATIONS MUST BE ABLE TO STAND ALONE AS A REPORT, CONTAIN ALL RELEVANT INFORMATION OR HAVE ALL RELEVENT INFORMATION ATTACHED.

 INVESTIGATION DOES NOT CONTAIN ALL PERTAINENT INFORMATION
 THE CONCLUSION OF THE INVESTIGATION IS NOT SUPPORTED BY DATA OR DOCUMENTATION i.e. Was an experiment or test conducted to support the conclusion?

- NO CONCLUSION, INVESTIGATION UNCOVERED NOTHING. USUALLY RELATED TO POOR DOCUMENTATION PRACTICES
- THE INVESTIGATION CONCLUDES TRAINING WAS THE PROBLEM BUT ALL RECORDS SHOW THAT ADEQUATE TRAINING WAS CONDUCTED.

- UNIDENTIFIED LABORATORY ERROR.
 BLAMES SAMPLE PREP BY ANALYST.
- INVESTIGATION ONLY CONSIST OF A PASSING RE-TEST
- ORGINAL HPLC VIAL, STOCK SOLUTION OR SAMPLE NOT RE-ANALYZED OR ALLOWED TO EXPIRE BEFORE IT COULD BE RE-ANALYZED.

- LACK OF ADEQUATE VALIDATION FOR TEST METHODS OR MANUFACTURING PROCESS
- OOS INVALIDATE SOLEY BASED UPON PASSING RE-TEST RESULTS
- INVESTIGATION DOES NOT EXTEND TO VENDOR OR CONTRACTOR

NO PRE-DEFINED RE-TEST PROCEDURES ANALYST THOUGHT MISTAKE OCCURRED

- BUT CONTINUED TESTING ANYWAY
- INVESTIGATION CONCLUDES PRODUCTION PROBLEM BUT NO PROBLEMS DOCUMENTED IN BATCH RECORD

- CORRECTIVE OR PREVENTATIVE ACTIONS NOT PERFORMED. THIS IS THE PROOF THAT THE FIRM BELIEVES THE INVESTIGATION. CAPAS TELL ME HOW MUCH FAITH FIRM HAS IN THE CONCLUSION OF THE INVESTIGATION.
- NO FINAL DISPOSITION FOR LOT, INDEFINITE HOLD STATUS
- INVESTIGATION NOT EXPANDED TO OTHER LOTS MANUFACTURED OR TESTED SAME WAY.

BUSINESS QUESTIONS

- WHY MANUFACTURE ADDITIONAL LOTS IF CAUSE OF FAILURE OR DEVIATION IS UNKNOWN?
- WHY TEST SAMPLES IF METHOD ARE NOT VALIDATED
- WHY MAKE COMMERCIAL LOTS IF THERE IS NO SPECIFIC PROCESS THAT HAS BEEN SHOWN TO BE REPRODUCIBLE

BUSINESS QUESTIONS

WHY LET A PERSON PARTICIPATE IN THE MANUFACTURING OR TESTING OF COMMERCIAL PRODUCTS IF THEY ARE NOT ADEQUATELY TRAINED?
WHY INVALIDATE OOS DATA WITHOUT JUSTIFICATION? IT IS BOUND TO SHOW

UP AGAIN.

REVIEWING INVESTIGATIONS

- REVIEW PROBLEM DATABASES ELECTRONICALLY IF AVAILABLE. GET READ-ONLY ACCESS. DO SORTS BASED UPON: TYPE OF DEVIATION, PRODUCTS, DATES, OPEN, CLOSED OR OVERDUE
- IF NO ELECTRONIC DATABASES, PICK INVESTIGATIONS TO REVIEW FROM LOGBOOK, LIST OR BASED UPON THE SUMMARY-THIS IS NOT IDEAL. WORST CASE-REVIEW THEM ALL.

CHANGE CONTROLS

- WHY IMPORTANT??? NOBODY CHANGES SOMETHING THAT IS WORKING.
- HOW ARE THEY INITIATED, TRACKED, MONITORED, COMPLETED AND IMPLEMENTED.
- VALIDATIOIN IMPACTTRAINING IMPACT

PROBLEMS WITH CHANGE CONTROLS

CHANGE NEVER IMPLEMENTED
CHANGE CONTROL NEVER COMPLETED
CHANGE WAS MADE BUT NO CHANGE CONTROL WAS COMPLETED
CHANGE MADE BUT NO RE-VALIDATION
CHANGE MADE BUT NO RE-TRAINING

OTHER AREAS TO COVER

- WHAT IS DONE WHEN ERRORS OR OMISSIONS ARE FOUND BY BATCH RECORD REVIEWERS
- REVIEW RAW DATA FROM STABILITY BATCHES.
- REVIEW RAW DATA FROM VALIDATION STUDIES, PROCESS, METHOD, OR CLEANING

OTHER AREAS TO COVER

PROJECTS THAT ARE BEING WORKED ON BY TECHNICAL SEVICES. PROBLEMS WITH MARKETED PRODUCTS
ENVIRONMENTAL MONITORING TRENDS
REASONS FOR PRODUCT RETURNS
FIELD ALERTS

OTHER AREAS TO COVER

WHAT IS DONE WHEN OUT OF TOLERANCE EQUIPMENT IS FOUND DURING CALIBRATION?
COMPLAINT FOLLOW-UP
HOW ARE CONTRACTOR DEVIATIONS/INVESTIGATIONS REVIEWED AND HANDLED

FACILITY TOURS

 TOUR ENTIRE FACILITY. TOUR BUILDINGS FROM OUTSIDE TO INSIDE. ASK WHAT IT IS AND WHAT IT DOES. POWER SUPPLY, HVAC, WASTE, WATER, STEAM, AIR, ETC.

 WATCH PRODUCTION HAPPEN, EVENTUALLY SOMETHING WILL FAIL, EITHER EQUIPMENT OR PEOPLE

LABORATORY TOURS

- GO OVER LABORATORY EQUIPMENT, WHAT IS IT AND WHAT DOES IT DO?
- WHERE ARE SAMPLES THAT ARE UNDER INVESTIGATION STORED?
- WATCH ANALYSES BEING RUN, OBSERVE ANALYST TECHNIQUE.
- GO OVER LABORATORY PROCEDURES AND SAMPLE CONTROL.

FDA-483 INSPECTIONAL OBSERVATIONS

 SHOULD INCLUDE LOT NUMBER AND RELATE TO PRODUCT ON THE MARKET. IF NOT, WHAT IS THE SIGNIFICANCE? ROLE OF FDA IS TO PROTECT THE PUBLIC

 MAKE SURE OBSERVATIONS ARE FACTUALLY CORRECT?

FDA-483 INSPECTIONAL OBSERVATIONS

 MAKE SURE YOU UNDERSTAND EACH 483 OBSERVATION, WHY IT IS CRITICAL OR IMPORTANT, WHY IT IS A GMP CONCERN AND WHAT KIND OF RESPONSE OR FOLLOW-UP IS EXPECTED?

ADVICE

 PEOPLE ARE THE CAUSE OF MOST GMP PROBLEMS.

 DO WHATEVER YOU WANT, JUST MAKE SURE IT MAKES SENSE.