U.S. FOOD & DRUG ADMINISTRATION

CDER Case Study: A Microbial Investigation of Contamination by *Burkholderia multivorans*

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Disclaimer

- The comments expressed today are those of the presenter only and do not necessarily represent the official positions or policies of the FDA

Presentation Themes

- *Burkholderia Cepacia Complex* (BCC) and Pharmaceutical Water Systems
- BCC and Biofilm Formation
- BCC and Resistance to Antimicrobial Preservative Systems
- BCC and Aqueous, Non-sterile Drugs

Code of Federal Regulations

- Sec. 211.113 Control of microbiological contamination

a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

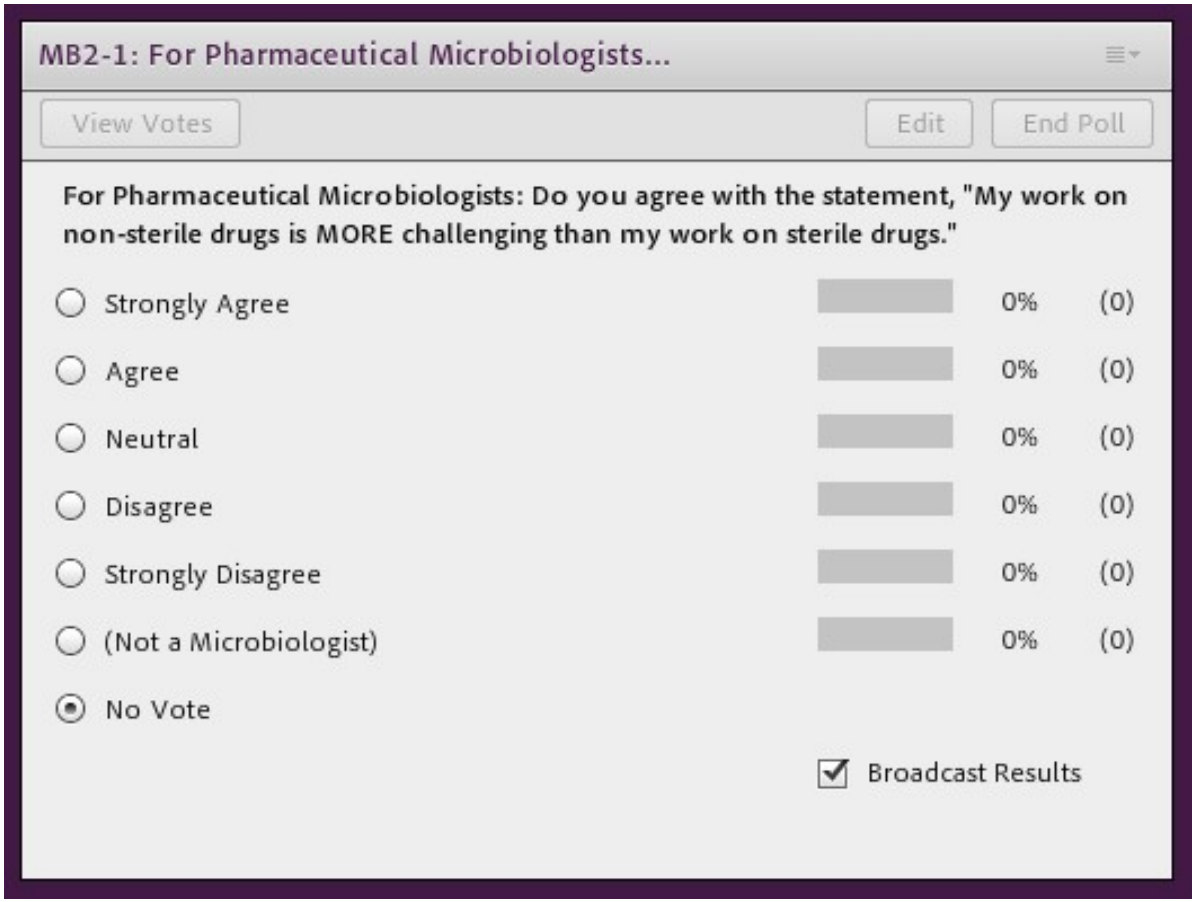
Code of Federal Regulations

- Sec. 211.165 Testing and release for distribution.

b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

FDA U.S. FOOD & DRUG ADMINISTRATION

Poll



CFR: Field Alert Reports

- Sec. 314.81

(1) *NDA-- **field alert report** .* The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written follow up. The report and its mailing cover should be plainly marked: "NDA-- **field alert report**."

CFR: Field Alert Reports

- Sec. 314.81(1)(ii)

Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.

CFR: Field Alert Reports

- FAR Form 3331 is available at:

http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/HumanDrugForms/default.htm

- A blank FAR Form 3331 is on next slide

Form Approved: OMB No. 0910-0001. Expiration Date: December 31, 2017. See PRA Statement on Reverse.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

NDA-FIELD ALERT REPORT

TO: *(NAME AND ADDRESS OF DISTRICT)*

TYPE OF REPORT ☐ Initial ☐ Follow-Up ☐ Final

In accordance with Section 314.81(b)(1)(i) and (ii) of the New Drug Application Regulations (21 CFR 314) promulgated under the Federal Food, Drug and Cosmetic Act, as amended, the following information is herewith submitted:

1. NDA/ANDA

2. NDC No.

3. GENERIC NAME OF DRUG PRODUCT

4. TRADE/BRAND NAME *(if any)* OF DRUG PRODUCT

5. FIRM NAME AND ADDRESS WHERE PROBLEM OCCURRED

6. FEI/CFN

7. DOSAGE FORM, STRENGTH AND PACKAGE SIZE(S)

8. LOT NUMBER(S)

9. EXPIRATION DATE(S) OF DRUG PRODUCTS

10. DATE WHEN NOTIFIED ABOUT PROBLEM(S) OR WHEN PROBLEM(S) FIRST BECAME KNOWN TO APPLICATION HOLDER

11. HOW WAS PROBLEM DISCOVERED

12. STATE PROBLEM(S)

13. ROOT CAUSE(S) OF PROBLEM(S)

14. CORRECTIVE ACTION(S) TAKEN *(if any)* TO PREVENT RECURRENCE OF PROBLEM(S)

15. REMARKS

NOTE: SEPARATE NARRATIVE REPORTS MAY BE ATTACHED IF DESIRED.

REPORTING ESTABLISHMENT

NAME AND MAILING ADDRESS *(Include ZIP Code)*

NAME AND TITLE OF AUTHORIZED REPRESENTATIVE

TELEPHONE *(Include Area Code)*

SIGNATURE OF AUTHORIZED REPRESENTATIVE

DATE SUBMITTED

Add Continuation Page

CDER/OPQ/Office of Surveillance

- FAR is attached
- FDA is meeting with firm to discuss their investigation/plan relative to the FAR
- Request OPQ/DMA SME to provide questions for discussion with firm

CDER/OPQ/Office of Surveillance

- Contacted Clinical Review Division
  - Q: Does the presence of *B. multivorans* in the subject drug product present a risk to patients?

- Clinical Review Division
  - A: Yes, this constitutes a patient risk.

Field Alert Report

- Nasal Spray approved in late 1990s
- Aqueous formulation preserved with BAC
- Two batches positive for *B. multivorans*
- Batches still in firm's control
- Additional "expanded" testing of 10 batches
  - 5 previously negative were now positive

OPQ/DMA Q's for Firm: 1st TCON

- How were the initial batches (XX and YY) of the drug product determined to contain *Burkholderia multivorans*? Was this demonstrated following testing of the drug product according to USP<61>for total aerobic bacteria, or using a *Burkholderia* specific test? What is the concentration of *Burkholderia multivorans* per mL of the drug product in these batches?
- Regarding the additional 10 product batches that underwent expanded testing, how is the "expanded test" different from the test performed at release?

OPQ/DMA Q's for Firm: 1st TCON

- Is the water system that is used to manufacture XX® routinely tested for organisms belonging to the *Burkholderia cepacia complex*?
- We recognize that the investigation of this incident has not yet determined a root cause. Summarize the steps of the drug product manufacturing process that you have tested for evidence of *Burkholderia multivorans*.
- What is your plan for the drug product batches that contain *Burkholderia multivorans*?

TCON: FDA/Firm

- *B. multivorans* was picked up using Bile-Tolerant Gram Neg method in USP<62>
- Batches were TNTC
- Investigation: pipe in purified H_2O system not properly sanitized/engineered = Biofilm
- Firm states system was in control at time US batches were made

FDA Internal MTG Post TCON

- Team
  - CDER/OC
  - CDER/OPQ/OS
  - ORA/DO
  - CDER/OPQ/DMA

- Q: Do we need to recall the 58 batches in US commerce?

FDA Internal MTG Post TCON

- CDER/OPQ/DMA Comments
- Product was approved in late 90s
  - No record of an FDA micro review of the product
  - Unknown:
    - Are all batches subject to microbiological testing at release?
    - If so, what methodology is used?
    - The product is preserved: are the methods suitable for use with the subject drug product?

Additional Qs Forwarded to Firm

- Regarding the 58 lots of XX® that are currently in the US market, provide the test methods, acceptance criteria and data summaries from all microbiological testing performed on the drug product at release. Include data summaries demonstrating that the microbiological test methods are suitable for use with the drug product.
- Provide the stability protocol for XX®. Provide data summaries for any microbiological testing that has been performed to date on the XX® lots that are currently in the US market.

OPQ/DMA Assessment of Firm's Response: Memo for CDER

- The firm routinely performs microbiological release testing on XX® in excess of what is recommended in USP<1111>*Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use.*

OPQ/DMA Assessment of Firm's Response: Memo for CDER

- The microbiological release testing performed on XX® is performed according to methods described in USP<61>*Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* and USP<62>*Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms.*

OPQ/DMA Assessment of Firm's Response: Memo for CDER

- The firm has satisfactorily performed testing to demonstrate that the microbiological test methods are suitable for use with XX®, including in the recovery of *Burkholderia multivorans.*
- The microbiological release test data on the 58 batches of XX® in the US market meet acceptance criteria and are acceptable.

OPQ/DMA Assessment of Firm's Response: Memo for CDER

- Microbiological testing of XX® samples in the stability program is routinely performed. Stability data to date meet acceptance criteria and are acceptable.

OPQ/DMA Assessment of Firm's Response-Summary to CDER

- This reviewer acknowledges that end product release testing presents limitations with regard to predicting quality of a given product batch.
- However, the information provided to the Agency by the firm regarding the microbiological release and stability testing does not suggest that a product recall of the 58 batches of XX® currently in the US market is warranted from the standpoint of microbiological contamination.

Additional Information: Firm's Investigation

- A study was performed to evaluate the growth potential of the contaminant in the drug product
- Of note:
  - The contaminant counts decrease over first few days
  - Day 3: start of log phase growth in the preserved drug
  - Day 7: counts > 10^5 CFU/mL of preserved drug

Growth Kinetic Study: BCC in XX®

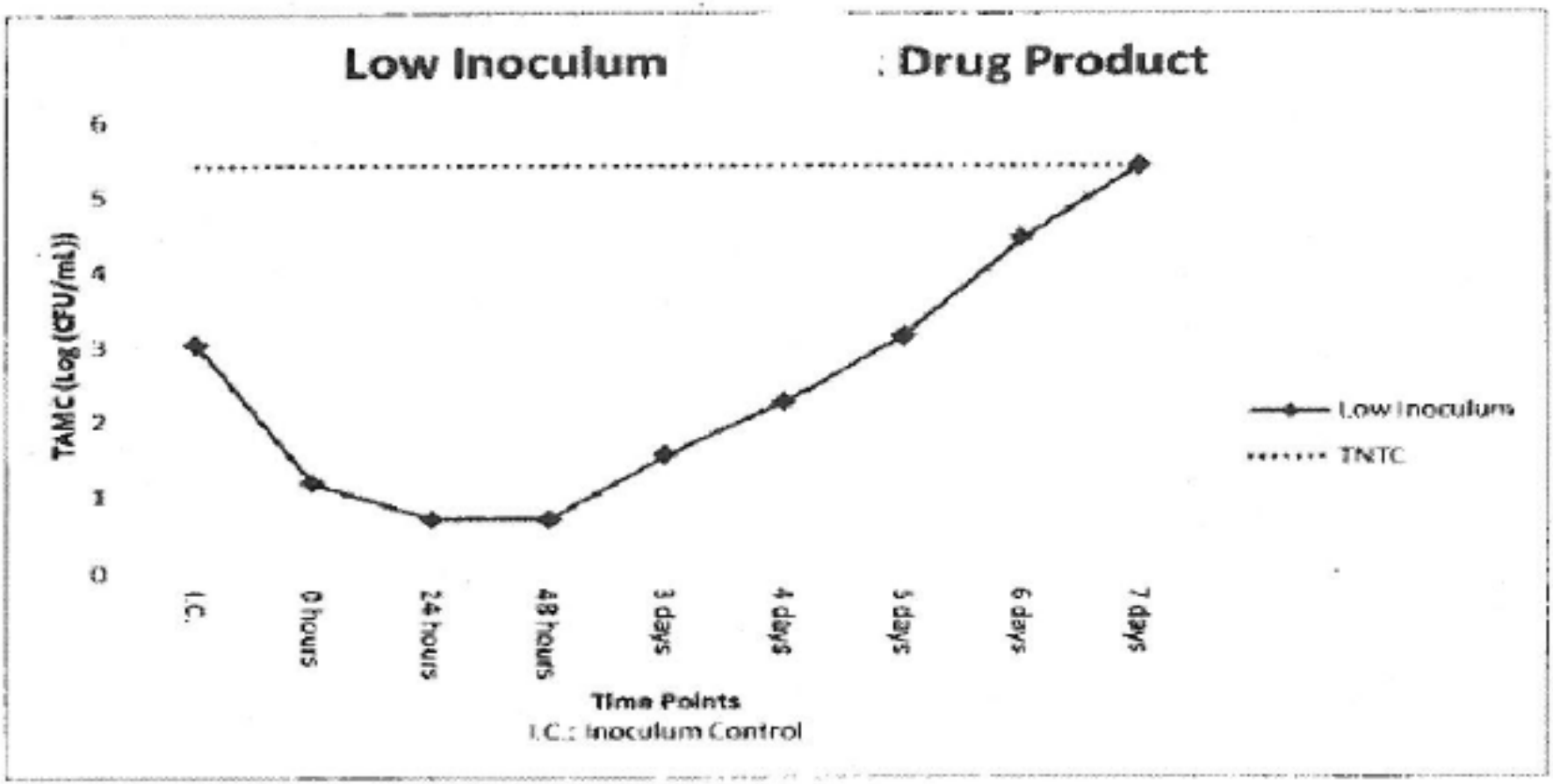


Figure 1 Low inoculum growth kinetics

Growth Kinetic Study: BCC in XX®

- Performing the study provided the firm with an understanding of this organism in this product
- May explain picking up the organism using the "expanded" testing
- Provided the firm with an avenue for corrective actions regarding future micro testing of this product

Additional Information: Firm's Investigation

- Testing was performed on retain samples from batches in US market
- Expanded Testing Sequence:
  - Initial: 10 batches tested with 5 batches positive
  - Next: 25 marketed batches manufactured prior to the original 10
  - None of these batches tested positive

Additional Information: Firm's Investigation

- Information from expanded testing of 35 batches
- Points to timeframe for biofilm formation
- Provided some assurance regarding patient safety and product in the market

Status of Drug Product Batches Following Expanded Testing

DOM	Marketed (Y/N)	Routine Release: Bacteria detected	Investigational Testing : Bacteria detected
2-Oct-14	Y	No	No
13-Oct-14	Y	No	No
18-Oct-14	Y	No	No
21-Oct-14	Y	No	No
3-Nov-14	Y	No	No
5-Nov-14	Y	No	No
9-Nov-14	Y	No	No
28-Oct-14	Y	No	No
12-Nov-14	Y	No	No
12-Nov-14	Y	No	No
16-Nov-14	Y	No	No
29-Nov-14	Y	No	No
14-Dec-14	Y	No	No
04-Jan-15	Y	No	No
13-Jan-15	Y	No	No
18-Jan-15	Y	No	No
01-Feb-15	Y	No	No
04-Feb-15	Y	No	No
14-Mar-15	Y	No	No
13-Apr-15	Y	No	No
20-Apr-15	Y	No	No
26-Apr-15	Y	No	No
29-Apr-15	Y	No	No
03-May-15	Y	No	No
05-May-15	Y	No	No
11-May-15	N	No	No
17-May-15	N	No	No
25-May-15	N	No	No
01-Jun-15	N	No	No
07-Jun-15	N	No	Yes
09-Jun-15	N	No	Yes
14-Jun-15	N	No	Yes
16-Jun-15	N	No	Yes
21-Jun-15	N	No	Yes
24-Jun-15	N	Yes	Yes
29-Jun-15	N	No	No
12-Jul-15	N	Yes	Yes

Summary: Case Study

- No Recall
- Firm implemented corrective actions following investigation
  - Re-engineered the bad plumbing
  - Improved sanitization
  - Eyes are wide open for BCC
  - Expanded micro testing for 12 months
  - Modified start time of microbiological release testing based on growth kinetics study

Summary: General Comments

- Industry wants FDA to base decision making on science and risk
  - for drugs: this means risk to patient

- CDER understands this and we agree
- In cases where scientific data are not available, then patient risk cannot be assessed by CDER, and questions arise

Summary: General Comments

- To avoid negative business outcomes such as:
  - delays in drug approvals
  - FDA enforcement action
  - product recalls

- Industry needs to be ready to provide CDER with scientific data when it is requested

Summary: Final Comments

- CDER Microbiologists understand that

  "*E .coli* Happens"

- The question becomes,

  "How does your firm respond when *E. coli* hits the fan?"

Reference Material

- 21 CFR 211.113(a) Control of microbiological contamination
- 21 CFR 211.165(b) Testing and release for distribution
- 21 CFR 314.81(1)(ii) NDA Field alert reports

THANK YOU

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