Assessing the Risk

Metro PDA
June 2, 2009

Agenda

- What is an Objectionable Microbe?
- Pathogens vs. Objectionables
- Just how objectionable is it?
- Consider the risk
- Performing a risk assessment
- Examples
- Questions

What is an objectionable?

A microorganism that is undesirable, offensive, arouses disapproval

What is an objectionable?

FDA casts a wide net

What is an objectionable?

Define it as a microbial contaminant that would adversely affect product safety

http://www.fda.gov/Cder/hdn/cnotes38.htm

What is an objectionable?

An OM poses a threat of patient infection or mortality

What is an objectionable?

An OM is one that adversely affects product stability

What is an objectionable?

An OM is one that reacts with or potentially damages container closure system integrity

What is an objectionable?

For example:

Fermentation creates gaseous pressures that may explode a container

What is an objectionable?

An OM interferes with analytical methods or active ingredient bioavailability

What is an objectionable?

"Objectionable" based upon

- Species
- Numbers
- Dosage form
- Intended use
- Patient population
- Route of administration

OM Summary

- Undesirable and offensive
- Arouses disapproval
- Affects product safety
- Threatens patient infection/mortality
- Affects product stability
- Affects container closure integrity
- Affects methods of analysis
- Diminishes bioavailability

What is an objectionable?

A wide net has been cast

What is a pathogen?

What is a pathogen?

A microorganism that produces disease

http://www.medterms.com/script/main/art.asp?articlekey=6383

What is a pathogen?

Can an objectionable be pathogenic?

What is a pathogen?

Yes!

What is a pathogen?

A pathogen causes disease

An objectionable is undesirable

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Objectionable vs. Pathogenic

So you've found an organism

Now what?

Objectionable vs. Pathogenic

First determine if it's pathogenic

Objectionable vs. Pathogenic

If it is and you can't show it was the result of laboratory or production operator error, then you might have to reject the product

Objectionable vs. Pathogenic

How do you know if it's pathogenic?

Objectionable vs. Pathogenic

FDA *Bad Bug Book*

(Yes this the name of the book)

http://www.foodsafety.gov/~mow/intro.html

Objectionable vs. Pathogenic

The *Bad Bug Book* lists commonly known pathogens

Objectionable vs. Pathogenic

Bad Bug Book **written for food industry but also applicable to pharma, medical device, cosmetic and nutritional supplement industries**

Objectionable vs. Pathogenic

Most related to foods but if found in pharmaceuticals the product should be rejected

Objectionable vs. Pathogenic

Escherichia coli

***Salmonella* spp.**

Clostridium botulinum

Staphylococcus aureus

Campylobacter jejuni

Yersinia enterocolitica* and *Yersinia pseudotuberculosis

Listeria monocytogenes

***Vibrio cholerae* O1**

***Vibrio cholerae* non-O1**

Objectionable vs. Pathogenic

Vibrio parahaemolyticus* and other *vibrios

Vibrio vulnificus

Clostridium perfringens

Bacillus cereus

***Aeromonas hydrophila* and other spp.**

Plesiomonas shigelloides

***Shigella* spp.**

Miscellaneous enterics

Streptococcus

Objectionable vs. Pathogenic

Notable exceptions are *Bacillus cereus* and *Aeromonas hydrophila*

Unacceptable in foods and finished products but in raw materials their presence is debatable

Objectionable vs. Pathogenic

21 CFR 211.113 requires that medicines should be

"free of objectionable microorganisms"

Objectionable vs. Pathogenic

Under section "Control of microbiological contamination," it states:

Objectionable vs. Pathogenic

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

Objectionable vs. Pathogenic Reinforced by 21 CFR 211.165

"Testing and release for distribution:"

Objectionable vs. Pathogenic

"There shall be appropriate laboratory testing of each batch of drug product required to be free of objectionable microorganisms"

Objectionable vs. Pathogenic

Thus, FDA considers OM seriously

What about USP?

Objectionable vs. Pathogenic

USP Microbiological Attributes Chapter <1111> provides little specific guidance

Objectionable vs. Pathogenic

"The significance of microorganisms in nonsterile pharmaceutical products should be evaluated in terms of the use of the product, the nature of the product, and the potential hazard to the user."

Objectionable vs. Pathogenic

USP recognizes
Salmonella, Escherichia coli,
Pseudomonas aeruginosa
and *Staphylococcus aureus*
as potentially hazardous

Objectionable vs. Pathogenic

The big four

Other than these no others are mentioned

Objectionable vs. Pathogenic

USP recommends that certain categories be routinely tested for total counts and specifies indicator microbial contaminants

Objectionable vs. Pathogenic

For example:

- Natural plant, animal and some mineral products for *Salmonella*
- Oral liquids for *E. coli*
- Topicals for *P. aeruginosa* and *S. aureus*
- Articles intended for rectal, urethral, or vaginal administration for yeasts and molds

Objectionable vs. Pathogenic

Neither USP or FDA specifically state what is objectionable

Objectionable vs. Pathogenic

Therapeutic Goods Administration (TGA) recognizes OM but they are also unclear

Objectionable Organisms in a Harmonised World Karen Longstaff Office of Laboratories and Scientific Services (TGA) August 12, 2008

http://www.tga.gov.au/lab/presorganisms.pdf

Objectionable vs. Pathogenic

From the TGA:

Objectionable organisms – the unfortunate misconception

Pharmacopoeial test methods and acceptance criteria:

Objectionable vs. Pathogenic

- Intended for use to detect specified organisms
- Used to demonstrate a medicine or substance meets monograph requirements
- Never intended to detect all potential pathogens

Objectionable vs. Pathogenic

- Acceptance criteria might not be suitable as QC specifications
- Acceptance criteria are minimum requirements to be met
- Simply demonstrating absence of specified organisms is not enough to demonstrate microbial quality

Objectionable vs. Pathogenic

Without any definitive answers, how do I know if it's objectionable?

Objectionable vs. Pathogenic

Can't just count colonies

Individual contaminants need to be considered

Objectionable vs. Pathogenic

There are no definitive answers

All microbes are potentially pathogenic

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Just how objectionable is it?

Burkholderia cepacia

- Commonly found in water
- Considered an environmental microorganism
- Fatal in people with respiratory illnesses (cystic fibrosis)

Just how objectionable is it?

Enterobacter

Just how objectionable is it?

- Ubiquitous
- Found in plants, crops (including lettuce, cabbage, cucumbers, tomatoes, celery, radishes, sprouts, watermelon and fresh fruits) and soil
- Isolated from clinical and environmental samples

Just how objectionable is it?

One species, *sakazakii* is a common isolate from infant formula, cereal, chocolate, potato flour, and pasta

Many vertebrates and invertebrates host the organisms

The Enterobacteria **2nd Edition J. Michael Janda and Sharon L. Abbott**

Just how objectionable is it?

Other *Enterobacteriaceae* can be present in pharmaceutical preparations

- ***Klebsiella* spp. (*Klebsiella oxytoca* and *Klebsiella pneumoniae*)**
- ***Enterobacter* spp. (*Enterobacter cloacae*, *Enterobacter sakazakii*, and *Enterobacter agglomerans*)**
- ***Serratia* spp. (*Serratia marcescens*)**

Just how objectionable is it?

They are widely distributed in nature (soil, water, plants and birds)

"These bacteria are generally considered to be non-pathogenic"

Microbiology in Pharmaceutical Manufacturing **2001 edited by Richard Prince**
"A Basic Primer on Pharmaceutical Microbiology" (Hans Van Doorne)

Just how objectionable is it?

So what's happening?

Environmental organisms may be objectionable?

Pathogenic organisms may be acceptable?

Just how objectionable is it?

YES!

Just how objectionable is it?

What can you do?

Just how objectionable is it?

Risk Assessment

Agenda

- What is an OM?
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Consider the risk

What risk are you actually assessing?

(Don't peek at the next slide)

Consider the risk

Told you not to peek

Consider the risk

The risk of causing harm to a person who uses the product

Consider the risk

Since most microorganisms can make a person ill if found in a product, what do you do?

Consider the risk

Automatically reject it?

Consider the risk

Maybe

Consider the risk

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

ICH Q9 Quality Risk Management http://www.ich.org/LOB/media/MEDIA1957.pdf

Consider the risk

Determining the risk requires a thorough understanding of the situation

Consider the risk

Only an experienced microbiologist can perform a risk assessment

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Performing a risk assessment

Six step process to determine microbial risk

http://www.microbiologyforum.org/PMFNews/PMFNews.12.07.0607.pdf

Performing a risk assessment

1. Absolute number of organisms
2. Microorganism's characteristics
3. Product Characteristics
4. Route of Administration
5. Potential Impact on Patients
6. Propagation Study

Performing a risk assessment

Need to consider all six components before making a final decision

Performing a risk assessment

#1
Absolute number of organisms

Performing a risk assessment

A high number may indicate:

- A problem during manufacturing
- An issue with a raw material
- Microorganisms are thriving in the product or raw material

Performing a risk assessment

If in a preserved product:

- The product's preservative system may not be functioning
- The preservative was missing or incorrectly formulated

Performing a risk assessment

Most materials/products have microbial specs, either from historic or compendial data

For example <20 cfu/gm

Performing a risk assessment

If the specs are exceeded the product is essentially adulterated and should not be used

Performing a risk assessment

Even if the organism is not objectionable/pathogenic the product is adulterated (e.g. finding high levels of *Staphylococcus hominis*)

Performing a risk assessment

What about low levels of potentially objectionable microorganisms?

Bacillus cereus found only in enrichment (eg <10 cfu/gm)?

Performing a risk assessment

1. Absolute number of organisms
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Performing a risk assessment

Characteristics can be determined by textbook, library, internet searches.

Should include synonyms of the organism

Performing a risk assessment

First determine if the organism is a known pathogen

Performing a risk assessment

Second determine if the microorganism may cause spoilage of the product

Performing a risk assessment

Third evaluate its tolerance to unusual conditions

- **Low or high pH**
- **High salt concentration**
- **High sugar concentration (osmotic conditions)**
- **Low water activity**
- **Growth temperature**

Performing a risk assessment

Fourth, determine if it harbors plasmid-mediated antibiotic resistance

Performing a risk assessment

Special concern regarding horizontal transmission of the trait within a vulnerable patient population

Performing a risk assessment

Bacillus cereus found only in enrichment

(e.g. <10 cfu/gm)?

Performing a risk assessment

Bacillus cereus

1. Referenced in *Bad Bug Book*

2. Internet search found description from the University of Florida

http://74.125.45.132/search?q=cache:3ucpXzXYgEUJ:edis.ifas.ufl.edu/FS103+bacillus+cereus+university+of+florida&hl=en&ct=clnk&cd=1&gl=us

Performing a risk assessment

Bacillus cereus

- Spore-forming, Gram positive, facultative anaerobic
- Associated with food poisoning
- Food poisoning results from ingesting heat-stable enterotoxins : a thermostable emetic enterotoxin or a thermosensitive diarrhoegenic enterotoxin.
- Widespread in soil and foods (herbs, spices, milk and vegetables)
- Transmission of disease results from contaminated foods, improper food handling/storage and improper cooling of cooked foodstuffs

Performing a risk assessment

Bacillus cereus

Two types of illnesses:

1. Diarrheal illness caused by heat-labile toxin, accompanied with abdominal pain. An incubation period of 4-16 hours is followed by symptoms lasting 12-24 hours.

2. Emetic illness caused by heat-stable toxin. Associated with ingestion of rice that is not properly refrigerated after cooking. Illness is characterized by vomiting and nausea that usually occur within 1-5 hours upon ingestion of the contaminated food. Sometimes referred to as intoxication.

Performing a risk assessment

Bacillus cereus

Therefore it is a pathogen that even in low numbers would cause a product to be rejected

Performing a risk assessment

Bacillus cereus

But are there exceptions?

Maybe

Performing a risk assessment

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Performing a risk assessment

Bacillus cereus

Where was it found?

In the Finished Product?

In the Raw Material?

Performing a risk assessment

Bacillus cereus

If in the finished product it's much more serious and the product should be rejected if it was not a laboratory or sampling error

Objectionable Microorganisms

Performing a risk assessment

Bacillus cereus

If in raw material what types of finished products will be affected?

Will it be able to propagate?

Will immunocompromised patients or children be using it?

Performing a risk assessment

Bacillus cereus

Not as severe if found in raw material

Therefore there is less risk

Performing a risk assessment

Bacillus cereus

Thus it's difficult to assess the degree of severity without looking at the source of it

Performing a risk assessment

Bacillus cereus

Still risky, though

Need to look at other characteristics

Performing a risk assessment

Let's look at minimum a_w required for growth

Performing a risk assessment

Minimum a_w 0.66-0.65:

Osmophilic yeasts (*Zygosaccharomyces rouxii*),

Molds (*Aspergillus echinulatus, Monascus bisporus*)

Performing a risk assessment

Minimum a_w 0.75 - 0.65:

Xerophilic molds (*Aspergillus chevalieri, A. candidus, Wallemia sebi)*

Saccharomyces bisporus

Performing a risk assessment

Minimum a_w 0.80 - 0.75:

Most halophilic bacteria

Mycotoxigenic aspergilli

Performing a risk assessment

Minimum a_w 0.87 - 0.80:

Most molds (mycotoxigenic penicillia)

Staphylococcus aureus

Saccharomyces

Debaryomyces

Performing a risk assessment

Minimum a_w 0.91 - 0.87:

Many yeasts *(Candida, Torulopsis, Hansenula)*

Micrococcus

Performing a risk assessment Minimum a_w 0.95 - 0.91:

Salmonella

V. parahaemolyticus

C. botulinum

Serratia

Lactobacillus

Pediococcus

Some molds

Yeasts (*Rhodotorula, Pichia*)

Performing a risk assessment

a_w 1.00 - 0.95:

Pseudomonas

Escherichia

Proteus

Shigella

Klebsiella

Bacillus

Clostridium perfringens

Some yeasts

Performing a risk assessment

If the a_w is lower than that required for the isolated organism the risk of it propagating is low

Performing a risk assessment

Bacillus grows between a_w 1.00 - 0.95

If a_w in product is 0.71 there is little risk the organism will propagate

Performing a risk assessment

But it can sporulate

Therefore a_w doesn't tell the whole story

Performing a risk assessment

Look at other product characteristics

Performing a risk assessment

Product container

Performing a risk assessment

Is the container designed to retard access and prevent contamination from the environment?

Performing a risk assessment

Special consideration should be given to an anhydrous medication's exposure to water, providing the potential for proliferation

Performing a risk assessment

What about Related Products?

Performing a risk assessment

What other products are related, either by chemistry and/or packaging?

Performing a risk assessment

Can these products be affected by the organism?

Performing a risk assessment

Batch Records?

Manufacturing History?

Performing a risk assessment

History of product in the marketplace?

Performing a risk assessment

Customer complaints?

Product characteristic summary

- Source (RM, FP)
- Water Activity
- Container
- Related Products
- Batch Record/History
- Customer complaints

Performing a risk assessment

1. Absolute number of organisms
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Performing a risk assessment

Topical

Oral

Inhaled

Injectable

Performing a risk assessment

Normally topicals pose less of a risk than orals

There are exceptions

Performing a risk assessment

Infections from contaminated topicals

- **Antiseptic solutions**

Pseudomonal infections in burn patients

***P. aeruginosa* infection with ear piercings**

Performing a risk assessment

- Creams

Gram negative infections in infants (eczema)

Performing a risk assessment

- **Mouthwashes**

Pseudomonad/*Acinetobacter* infections in ICU patients

Performing a risk assessment

- **Lubricant Gels**

Pseudomonad infection and colonization in neonates (ICU)

Performing a risk assessment

What about Oral dosages?

Performing a risk assessment

Infections from contaminated orals:

- **Mucormycosis – tablets**
- **Listeriosis - tablets**
- ***Acinetobacter* – herbal teas**
- ***Cryptosporidium* - baby gripe water**
- **Immunosuppressed/compromised patients**

Performing a risk assessment

What about Inhalants?

Great care should be taken in classifying any contaminate as not objectionable

Performing a risk assessment

Sampling and culture-based test methods have limitations

Performing a risk assessment

Know what is "normal" for product:

- Numbers and types of organisms usually present
- Deviations should ring alarm bells
- Find root cause not just quick fix
- Thorough and methodical

Performing a risk assessment

What's normal?

- Laboratory error?
- Manufacturing process?
- RM, water or packaging problem?
- Equipment problem?
- Cleaning problem, facility problem?
- Operator error?
- Batch formulated correctly?

Performing a risk assessment

Route of administration requires additional interpretations since there are many exceptions

Performing a risk assessment

1. Absolute number of organisms
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Performing a risk assessment

"Healthy" adults

Infants

Elderly

Immunocompromised

Performing a risk assessment

A healthy adult has a lower risk of being affected by an organism found in ibuprofen than a seasoned person

Performing a risk assessment

What about patient abuse or off-label use?

Can’t be controlled by the manufacturer

Performing a risk assessment

But the reasonable use should be considered as part of the risk analysis

Performing a risk assessment

NSAIDs (Non-steroidal Anti-Inflammatory Drugs) (Ibuprofen, Naproxen, Aspirin) may prevent the death of brain cells (due to THC intoxication) in people who smoke marijuana

Performing a risk assessment

So what does it mean for ibuprofen?

Is the manufacturer at greater risk because someone is taking it while getting high?

Does *B. cereus* pose an even greater risk if found in an excipient?

Performing a risk assessment

Are you liable for off-label use?

Of course you are

Performing a risk assessment

Where does it end?

Do non-sterile products now have to be sterile?

Performing a risk assessment

Can risk be totally eliminated?

Performing a risk assessment

Not an easy task

Performing a risk assessment

One suggestion

Performing a risk assessment

1. Absolute number of organisms
2. Microorganism's characteristics
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Performing a risk assessment

Mimic the *USP* <51> Antimicrobial Effectiveness Test

Performing a risk assessment

Inoculate product with 10^5 CFU/mL or gm of the isolate and take samples every week for four weeks

Performing a risk assessment

If the organism concentration decreases or stays the same, there is a low risk of the organism propagating in the product upon storage

Performing a risk assessment

If the organism increases in numbers, the risk is much higher and the product should be rejected

Risk assessment summary:

1. Absolute number of organisms
2. Microorganism's characteristics
3. Product Characteristics
4. Route of Administration
5. Potential Impact on Patients
6. Propagation Study

Performing a risk assessment

- Not comprehensive
- Serves as a foundation
- Helps determine if risk associated with an organism elevates it to the status of an objectionable microorganism

Performing a risk assessment

Responsibility of determining whether an organism is objectionable, whether it is an environmental isolate or one isolated from a product or raw material, resides with the micro laboratory

Performing a risk assessment

Incumbent upon the lab to perform a risk analysis as diligently as possible, including EM data they collected from the manufacturing facility

Performing a risk assessment

It takes time

It takes fortitude

It takes a brave microbiologist

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Example

1. Absolute number of organisms
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Example

1. TAC: 45 cfu/g; TYM: 80 cfu/g
2. Enterobacter
3. Pre-gelatinized starch (RM)
   a_w = 0.265 (RM), 0.422 (FP)
4. Oral dosage
5. Package Insert: "use cautiously in neonates/young infants; exclude infants"

Example

- **Starch met USP requirements "<1000 cfu/g TAC and <100 cfu/g TYMC"**

AND

- **"Absence of *Salmonella* species and *Escherichia coli*"**

Example - Research

- Enterobacter is ubiquitous
- Found in plants, crops (including lettuce, cabbage, cucumbers, tomatoes, celery, radishes, sprouts, watermelon and fresh fruits) and soil
- Isolated from clinical and environmental samples

Example

One species, *sakazakii* is a common isolate from infant formula, cereal, chocolate, potato flour, and pasta

Many vertebrates and invertebrates host the organisms

The Enterobacteria **2nd Edition J. Michael Janda and Sharon L. Abbott**

Example

Other *Enterobacteriaceae* can be present in pharmaceutical preparations

- ***Klebsiella* spp. (*Klebsiella oxytoca* and *Klebsiella pneumoniae*)**
- ***Enterobacter* spp. (*Enterobacter cloacae*, *Enterobacter sakazakii*, and *Enterobacter agglomerans*)**
- ***Serratia* spp. (*Serratia marcescens*)**

Example

They are widely distributed in nature (soil, water, plants and birds)

"These bacteria are generally considered to be non-pathogenic"

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Example

In the European Pharmacopoeia, 5.1.4 "Microbiological Quality of Pharmaceutical Preparations", products are divided into four categories.

Example

Preparations for oral administration "containing raw materials of natural (animal, vegetable or mineral) origin for which antimicrobial pretreatment is not feasible…" have specified limits for enterobacteria of "not more than 10^2 enterobacteria and certain other gram-negative bacteria per gram or per milliliter".

Example

These specifications take into account the natural origin of certain raw materials of vegetable origin such as pregelatinized starch

Example

USP <2021>

Recommended Microbial Limits for Botanical Ingredients and Products

Example

- **TAC NMT 10^5**
- **TCYM NMT 10^3**
- **Bile-tolerant Gram-negative bacteria NMT 10^3**
- **Absence of *Salmonella* spp. & *E. coli* in 10 g**

Example
Additional information

- Dilution of RM to 10-13.5% of product
- Reduction of the microbial bioburden by compression during tablet formation
- Low water activity levels in FP

Example

Unfortunately no propagation study was conducted

(Too long to wait)

Example Review

1. TAC: 45 cfu/g; TYM: 80 cfu/g
2. Enterobacter
3. Pre-gelatinized starch (RM)
   a_w = 0.265 (RM), 0.422 (FP)
4. Oral dosage
5. Package insert: use cautiously in neonates/young infants; exclude infants

Example

So, is it objectionable?

(Don't peek)

Example

The company said "No"

They based their decision on the risk assessment evidence

Example

Would you be able to say "No?"

Example

It takes a brave microbiologist to say "No"

A tough task

Summary

- What is an OM?
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- Example
- Questions

Example

The bottom line:

Determining what to do is extremely difficult

Example

It takes a brave microbiologist

Example

You can do it!

Thank you

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Questions?

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