U.S. FOOD & DRUG ADMINISTRATION

Endotoxin Update

OSMA Spring Educational Meeting
The Key Bridge Marriott · Arlington Virginia
Thursday, April 19th, 2018

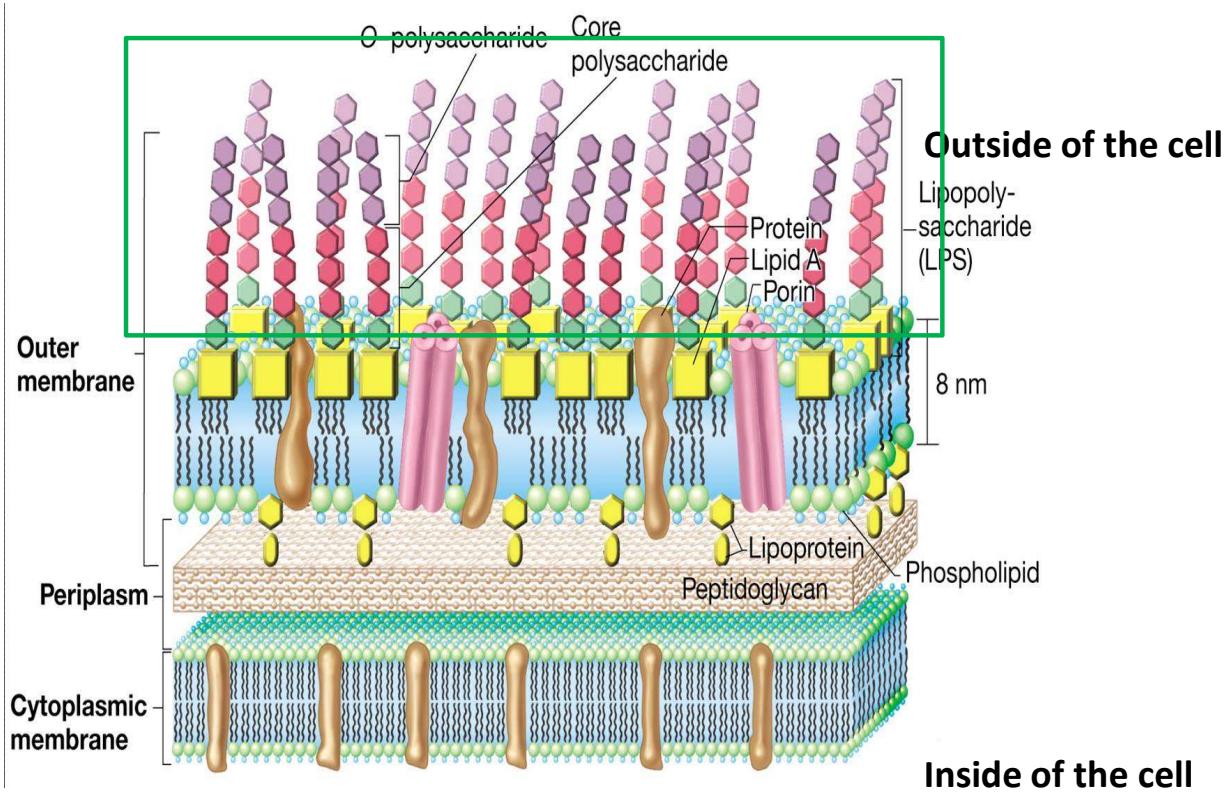
Elizabeth Gonzalez, PhD
Microbiologist
Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Outline

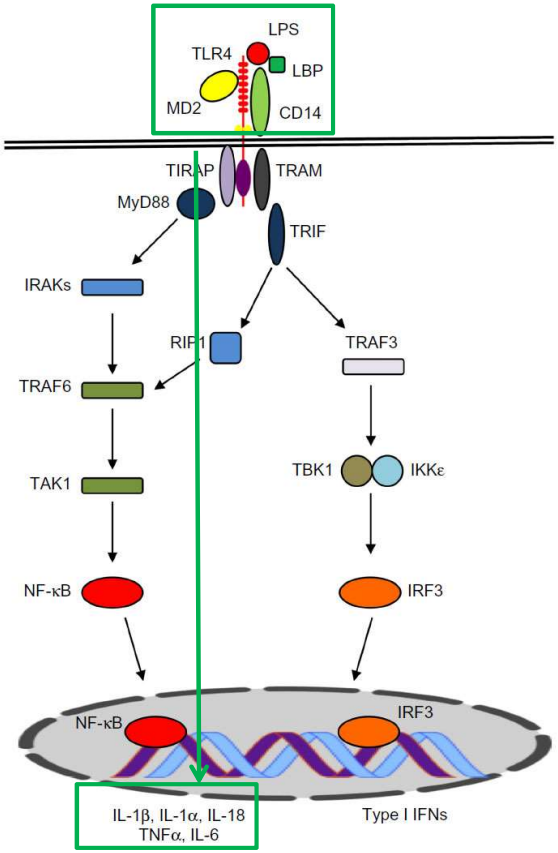
- What are pyrogens?
- Endotoxin testing
- Specific Questions

What are pyrogens?

- Substance that cause a fever response
- Bacteria-sourced pyrogens
  - Encompass a variety of bacteria components
  - Strongest elicitor is bacterial endotoxin
- The *Limulus* amoebocyte lysate assay (LAL) is the most sensitive and specific test for LPS


O- polysaccharide
Core polysaccharide
Outside of the cell
Lipopoly-saccharide (LPS)
Protein
Lipid A
Porin
Outer membrane
8 nm
Lipoprotein
Phospholipid
Peptidoglycan
Periplasm
Cytoplasmic membrane
Inside of the cell

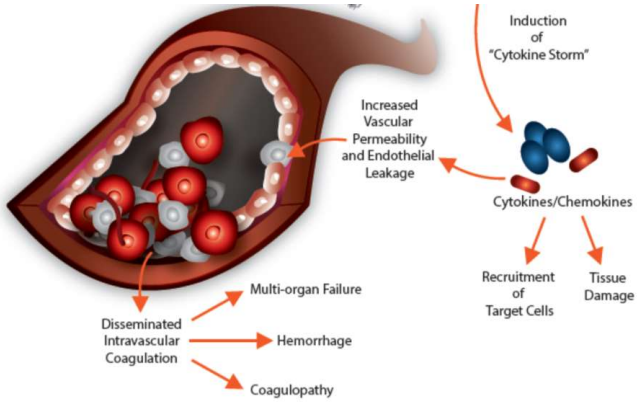
Molecular Mechanisms

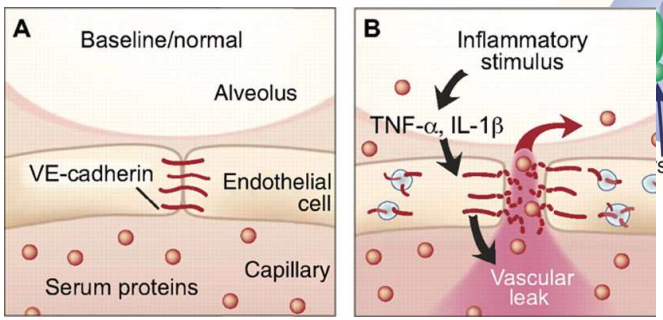


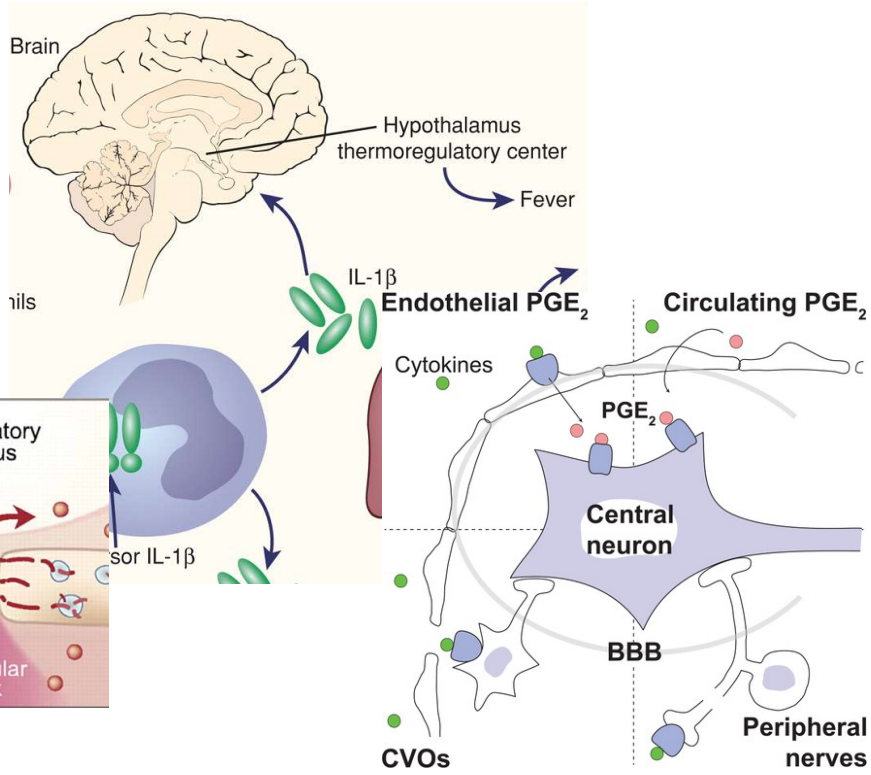
Binding of LPS to receptors on the membrane of human cells leads to cytokine production.

Molecular Mechanisms

- Inflammatory Cytokines
  - Fever
  - Attracts white blood cells (chemokines)
  - Vascular Leakage







Why are they relevant to implanted orthopedic devices?

- Local response
  - Aseptic loosening leads to >40,000 joint revisions/year in US
  - Endotoxin leads to cytokine release, inflammation, and bone resorption
  - Animal studies have demonstrated that endotoxin contamination on implants inhibit osseointegration and decrease the force required to pull the implant out
- Systemic response
  - Less likely due to indirect contact through lymphatic system
  - More serious consequences – shock, organ failure

Greenfield M, Bi Y, Ragab A, Goldberg V, Nalepka J, Seabold J. 2004 Does endotoxin contribute to aseptic loosening of orthopedic implants? J Biomed Mat Res. 72B: 179–185.

Bonsignore L, Anderson J, Lee Z, Goldberg V, Greenfield E. 2013 Adherent lipopolysaccharide inhibits the osseointegration of orthopedic implants by impairing osteoblast differentiation. Bone. 52(1): 93–101.

Why is batch testing recommended?

- Contamination can be sourced to:
  - Raw materials
  - Manufacturing equipment and processes
  - Personnel and handling
- No recommendations in recognized standards on how to perform pyrogen removal validation
- Therefore, the default recommendation is that every batch is tested

Alternatives to Batch Testing

As long as it is confirmed that the specified endotoxin limits are met at the time of 510(k) clearance, we will not be individually assessing alternatives to batch testing for adequacy during the premarket review, since this largely falls under QSR and manufacturing process controls.

2016 FDA 510(k) Sterility Guidance

The sponsor should provide the information outlined below:

a. a description of the method used to make the determination that the device meets pyrogen limit specifications (e.g., bacterial endotoxins test (BET), also known as the *Limulus* amebocyte lysate (LAL) test);

b. a statement confirming that endotoxin testing will be conducted on every batch or if not, information regarding the sampling plan used for in-process testing and/or finished product release, as recommended in the FDA guidance, Pyrogen and Endotoxins Testing: Questions and Answers" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM310098.pdf);

c. identification of the chosen testing limit; and

d. an explanation supporting the selected endotoxin limit.

Current Advisory

- You have provided an alternative to batch testing plan to monitor endotoxin levels on your device in further production. Please note the following advisory comments. We recommend that you consider, and maintain on file, the following about your alternative plan:
  - Explicit description as to how adequate safeguards are incorporated to ensure that non-conforming product does not reach patients (e.g., a timeline that enables recovery of product from inventory or distribution if monitoring systems detect failures).
  - How your plan is based on adequate historical data from earlier batch testing (as relevant). (The Agency recommends beginning with maximum coverage and adjusting sampling plans as confidence increases in the prevention of endotoxins in manufacturing processes.)
  - Identification of endotoxin limiting or reduction steps, and subsequent potential endotoxin contributing steps.
  - Sufficient documentation showing qualification and control over manufacturing processes, including component materials, manufacturing materials (e.g., water quality) and processes (e.g., passivation method specifications), environment and manufacturing lines to assure that endotoxin levels are within specifications. These may include (per AAMI ST72, section B.10):
    - Heat: 250-300°C for 30-120min (note: injection molding is often not sufficient)
    - Acid or base hydrolysis (e.g., passivation with nitric acid (see ASTM A967))
    - Oxidation (may lyse cells) – (e.g., anodization; may not sufficiently reduce pyrogens)
    - Water quality and specifications (e.g., distillation, reverse osmosis, for adequate time)
- Regardless of the method used to ensure endotoxin levels are within specifications, the effectiveness of the process should be supported by literature, and/or adequate validation.
  - Inclusion of an alternative sampling plan, for use if a failure occurs.

OSMA Endotoxin Q1: Out of Specification

Question: As an alternative for batch testing, a method has been proposed to use process control procedures. This includes the assessment of out of specification measurements.

One of the previous questions from FDA was how to contain and address product manufactured in a process with an out of specification point. A total recall of released product could negatively impact patients due to lack of device availability.

We would contend that an out of specification measurement can and will happen in any process. If this happens and the firm has procedures to address this situation, will this be sufficient for continued processing if documented and justified?

Response: FDA agrees that the sponsor should have a plan for dealing with out of specification results and that the response should be risk-based and not limited to recall.

OSMA Endotoxin Q2: Testing Per Package

Question: Can it be confirmed that, as is now stated in the new ST72 standard, that the testing required is on product contained in a single package and not the full systems for large implant products?

Response: The endotoxin limit is being applied to a sterile barrier system

OSMA Endotoxin Q3: Inclusion Criteria

Question: Are accessories to the surgical procedure included in those recommended for endotoxin testing according to ST72? For example jigs, blades, pointers, trials, etc. Materials usually found in a loaner tool set.

Response:

- Surgical accessory devices do not remain in the body following the procedure
- Endotoxin testing is therefore not needed for these devices

OSMA Endotoxin Q4: Testing Endpoint

Question: Since any surgical implantation results in local inflammation, the risk of inflammation is known for this effect and is well studied. Is it acceptable that for orthopedic implants, localized inflammation should be listed as a known risk but not one associated with endotoxin if below a tested limit?

Response: FDA agrees that if the device meets FDA-recognized endotoxin limits (typically 20 EU/device*) this is sufficient to address the concern regarding endotoxin-mediated inflammation

* Could be lower if the device is in contact with cerebrospinal fluid or is an ophthalmic device

OSMA Endotoxin Q5: Inclusion Criteria

Question: Are temporary implants (e.g., mandible extractors, external fixation pins) able to be removed from endotoxin testing if resulting risk assessments conclude endotoxin is not a risk?

Response:

- FDA does not believe that the time an implant is in contact with the patient should be the deciding factor for whether or not the device should be non-pyrogenic.
- A pyrogenic response could be caused either by a contaminated device in contact with the patient for 24 hours or by one that is in contact for 30 days.
- A risk based assessment could be used to determine that an alternative to batch testing may be appropriate.

OSMA Endotoxin Q6: Testing Final Finished Device

Question: For products such as bone cement where there is a powder and liquid component but each cannot be tested individually, these are currently mixed with sterile non-pyrogenic water made into testable coupons and tested as per the standard for releasing lots. Is this an acceptable practice?

Response:

- FDA recommends that the LAL testing be performed on the final finished device, which should include the same components, mixing, and handling that would be used in the final product.
- In the case of the bone cement, creating testable coupons allows the final form of the device to be tested for endotoxin.

Questions?