BIOCOMPATIBILITY EVALUATION- A MOVING TARGET?

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OBJECTIVE OF THIS PRESENTATION

- Recognize the gap between what industry understands and FDA expects

- Describe the costs
  - Additional testing
  - Not understanding the expectations

- Identify the information needed to understand the underlying problems with biocompatibility and previous assessments so industry can contribute to the solution

WHAT IS BIOCOMPATIBILITY?

- Webster Medical Dictionary defines biocompatibility as:
  - the condition of being compatible with living tissue or a living system by not being toxic or injurious and not causing immunological rejection

- Breaking this down, biocompatibility comprises
  - Not being toxic,
  - Not being injurious, and
  - Not causing immunological rejection

WHY DOES BIOCOMPATIBILITY MATTER?

- In other words, what device failure modes are we looking to avoid?

- From the definition,
  1. Toxic – i.e., introducing a material that is poisonous to the patient
  2. Injurious – i.e., introducing a material that injures the tissue (usually by contact)
  3. Immunological rejection – i.e., introducing a material that activates the patient's immune system in a negative way

HOW CAN BIOCOMPATIBILITY OF A DEVICE BE EVALUATED?

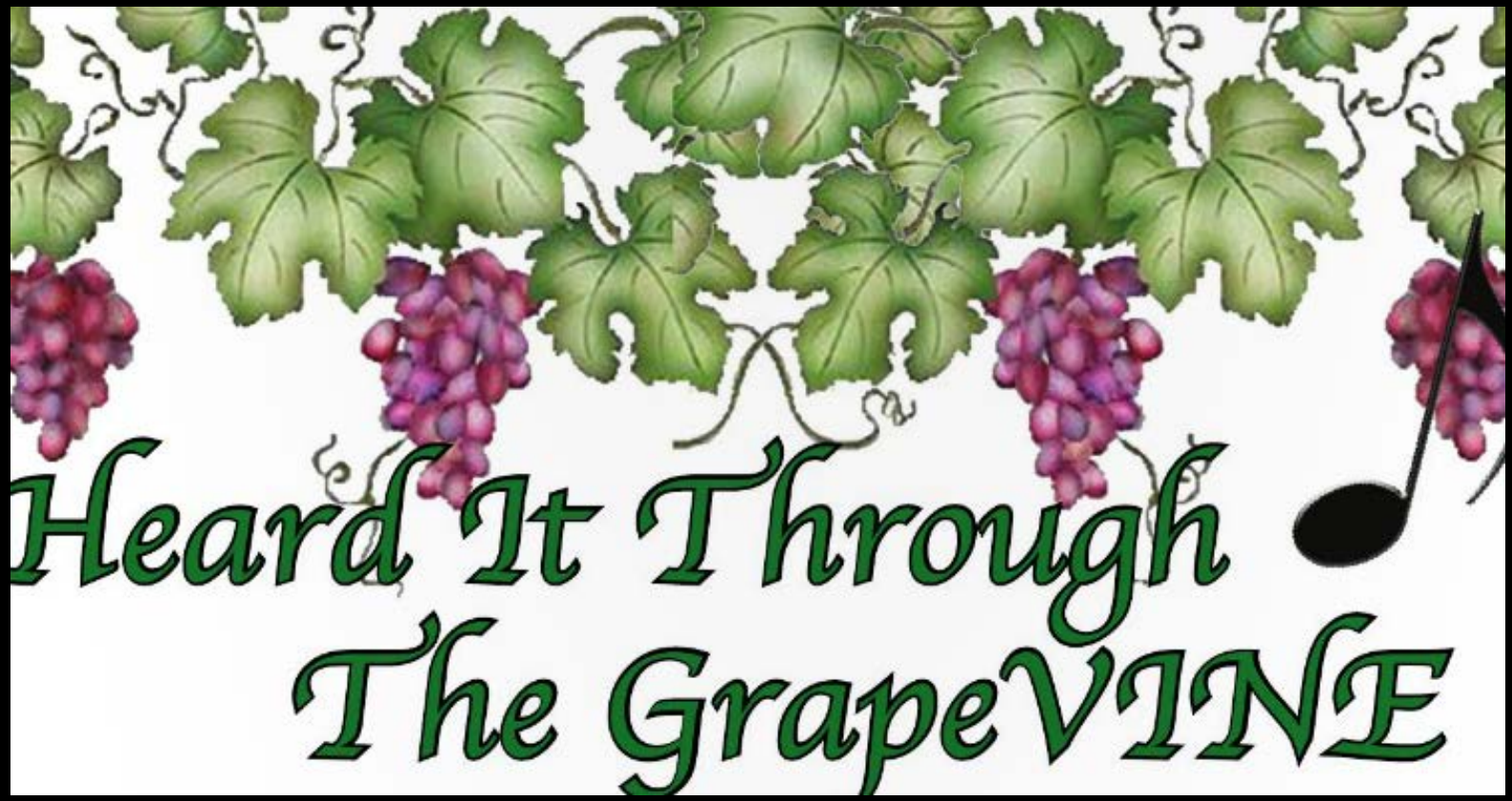
- Several types of evaluations are available
  - *In vitro* and *ex vivo* studies – ISO 10993
  - Animal studies
  - Clinical studies
- Each type of evaluation has strengths and limitations
- We can best understand the biocompatibility of a device by synthesizing multiple types of information
- Goal is to minimize – *not eliminate* – risk.
- It seems appropriate to apply risk assessment methodology to biocompatibility risks

CLINICAL AND REGULATORY EXPECTATIONS

- Clinical
  - Device should not cause adverse reaction in the patient
- Regulatory
  - IDE
  - 510(k) or PMA
  - These requirements appear to have changed at FDA
    - Information that was previously sufficient seems to no longer be sufficient
    - Rationale for these changes is not well understood by industry

The scope of information required today by FDA to provide sufficient confidence in device biocompatibility may not be well understood by industry

ILLUSTRATIVE STORIES



It's a semi-true story, believe it or not
I made up a few things, and there's some I forgot...

-Jimmy Buffett

STORY 1: INDUSTRY MISUNDERSTANDINGS OF FDA EXPECTATIONS

- Company developed a stainless steel implant
  - a material FDA acknowledges has a long history of safe use in legally US-marketed medical devices
- Company submitted application with a full suite of biocompatibility testing per ISO 10993 and in accordance with FDA guidance, demonstrating low safety risk
- Application *disapproved,* with FDA requirement for multiple additional biocompatibility tests (including tests not defined in released standards or guidance)
- Company incurred ~$30K of additional test costs and multiple month delay
- Unclear to them what risk is being mitigated by this additional testing

STORY 2: INDUSTRY MISUNDERSTANDINGS OF FDA EXPECTATIONS

- Company had a request for atypically extensive biocompatibility testing on MP35N for an implant with no unusual manufacturing processes
  - Expensive tests
  - Lengthy tests

- This was surprising
  - The material has been used as a permanent implant for decades in many other products
  - The material meets ASTM F562

- Unclear to them what risk is being mitigated by this additional testing

STORIES 3+: INDUSTRY MISUNDERSTANDINGS OF FDA EXPECTATIONS

- An established chemical characterization protocol from [a well-known contract testing vendor] is now *not acceptable* to FDA…
- A product line extension with some manufacturing changes but no changes to materials and no issues with clinical performance required extensive biocompatibility testing
- . . . You get the idea . . .

THE TRUE COSTS OF HAVING TO REPEAT BIOCOMPATIBILITY TESTING

- There are two costs of having to repeat biocompatibility testing for a device
  - Money
  - Time
- Money
  - Direct costs (to the test lab)
    - Typically $35,000 - $75,000 for a delivery system with known materials
    - Can range $75,000 - $250,000 for an implant
    - More if repeat animal studies are required
  - Indirect costs (*often dwarf direct costs*) – ***Often overlooked!***
    - Company team must be paid during the delay
    - Months of salary+benefits x many people on the team: $100,000's
- Time
  - Typically 3-5 months for a delivery system
  - Can be 6-12 months for an implant

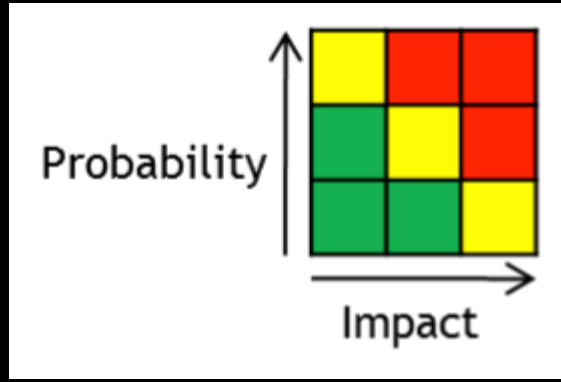
This is great industry motivation to meet FDA expectations *on the first biocompatibility submission*

A COMPANY HAS MUCH TO LOSE…

Manufacturers and regulators have aligned interests on biocompatibility

- A device must work to be successful for a company (help patients, generate growing revenue stream, provide returns for investors)
- No company wants to put a non-biocompatible device into clinical use
- A company has much to lose if a device is not biocompatible
  - Revenue
  - Reputation
  - Perhaps even their livelihood – *a small company (or a division of a larger company) may not survive a device failure in the clinic*

GAP ANALYSIS: FDA EXPECTATIONS VS. INDUSTRY UNDERSTANDING



- The FDA perspective on biocompatibility appears different from how other aspects of devices are evaluated – is it risk-based?
- Can we highlight some general takeaways from the industry examples?
- Can we generate some discussion between FDA and industry to clarify the expectations (at a practical level)?

BACK TO OUR GOALS

- Recognize the gap between what industry understands and FDA expects
- Describe the costs
  - Not understanding the expectations
  - Additional/repeat testing
  - Money and time
- Identify the information needed to understand the problems with biocompatibility and previous assessments so industry can contribute to the solution

THANK YOU!