SNEEF

Medical Device Update

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Presentation Outline

- 510(k) Process – making a subjective decision with objective evidence
- The Pendulum Swings a Second Time
- 510(k) Process Changes – Examples/Effects
- Impact, Future and Company Response

Company Background/Perspective

- Seven years at FDA
  - **Boston District**
  - **Scientific Reviewer at CDRH/ODE**
- Seventeen (17) years in Mid – Senior Management at Start-ups and Mid Size Medical Device Companies
  - **Regulatory Strategy**
  - **Clinical Study Design/Management**
  - **Quality Systems/Compliance**

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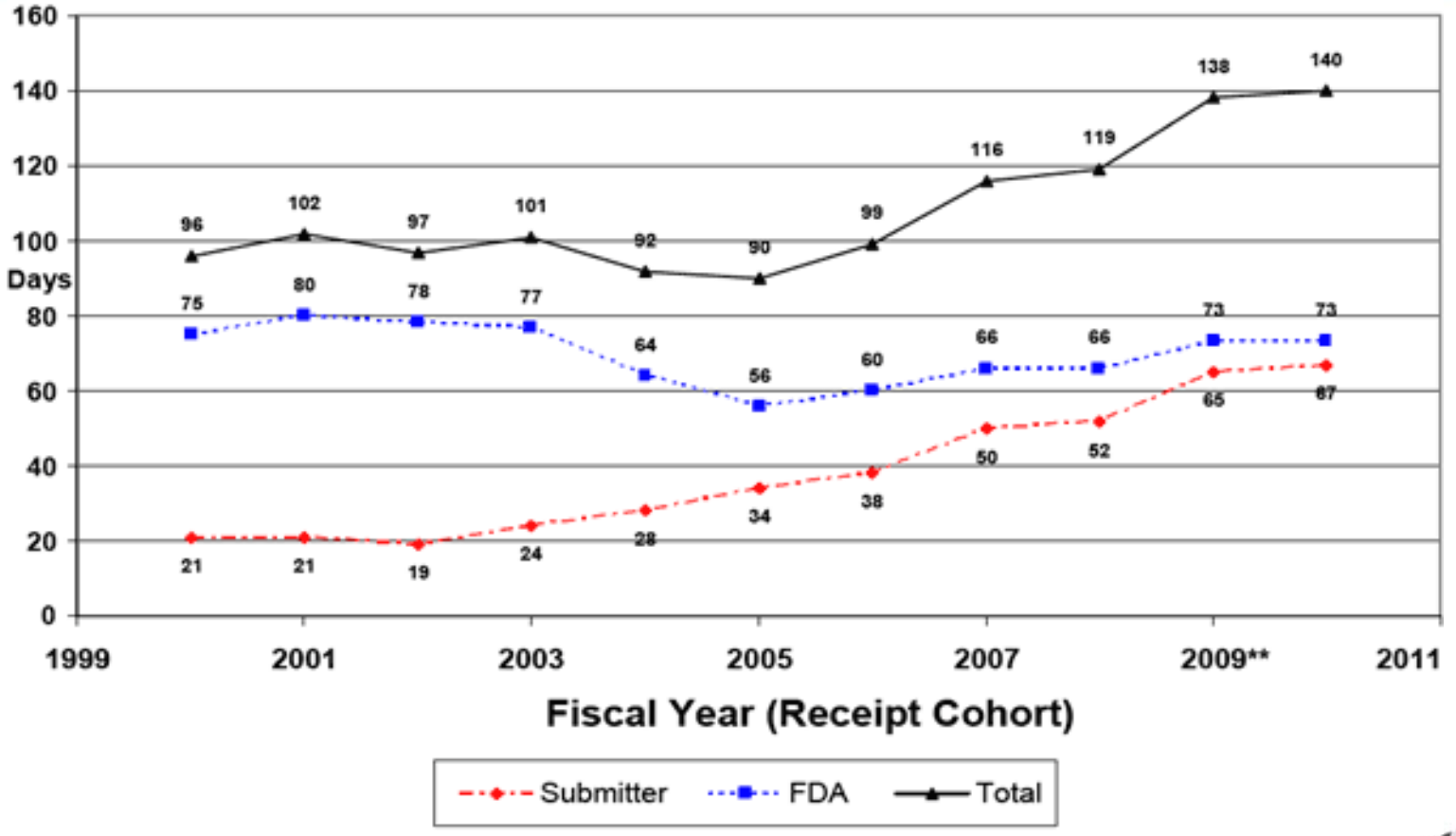
Regulatory Pathway to US Market

510(k) Process

Regulatory Pathway to US Market

- 510(k) Pathway (Premarket *Notification)*
  - **Demonstrating Equivalence to a Legally Marketed PreAmendment or 510(k) cleared Medical Device**
  - **90 Day Review Cycle**
- PMA Pathway (Premarket Approval)
  - **Demonstrating Reasonable Assurance of Safety and Effectiveness**
  - **180 Day Review Cycle**

Regulatory Pathway to US Market



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Regulatory Pathway to US Market

- The 510(k) pathway has been the preferred pathway as the result of
  - **Shorter product development cycle to market**
  - **Lower development cycle cost**
  - **Regulatory clearance (substantial clearance) based primarily on**
    - Use of design specification comparison to predicate devices
    - limited preclinical testing and rare clinical study requirements

Regulatory Pathway to US Market

- The investment community also enjoyed these benefits with shorter time horizons on investments (when compared to biotech/pharma)
- These expectations have been turned upside down by the recent change in policy and increased unpredictability of the 510k review process

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Regulatory Pathway to US Market

- Predictability of 510(k) process
  - **The "substantial equivalence" decision by CDRH/ODE are "judgment" calls**
  - **They are based on a comparison (subject/predicate devices) of**
    - Intended use
    - Design specifications
    - Risk Assessment
    - Performance Testing (if required)

Regulatory Pathway to US Market

- Evidence used by CDRH to render a subject device as ***equivalent*** has fluctuated significantly over the past 34 years
- Evidence contained in a 510(k) can be categorized into
  - **Design specifications (including intended use)**
  - **Performance testing**
- This evidence is developed during the design control process (Product Development)

Regulatory Pathway to US Market

- The “level of evidence” is influenced by
  - **Reviewer experience**
  - **Technical expertise**
  - **Regulatory interpretation by staff**
  - **Administrative influence**
  - **Medical device performance in the field**
- Much of this has been confirmed in the Center’s recent internal review of the 510k process

Regulatory Pathway to US Market

Question 2: In reviewing a laser 510(k) application, the predicate device was cleared for skin resurfacing and the new device would like to add wrinkle removal in conjunction with skin resurfacing. The reviewer has determined that there are no differences in therapeutic effect; therefore this represents

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. A new indication.	18.2% (37)	15.0% (3)
B. A new intended use.	15.3% (31)	5.0% (1)
C. The same intended use.	10.8% (22)	15.0% (3)
D. Both (A) and (C).	**55.7% (113)**	**65.0% (13)**

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CDRH/ODE Review Policy Changes

Pendulum Swings

The Pendulum Swings - Decisions from the Past Haunt Current Decision and Policy

- Pendulum Swing 1 – The Kessler Era – 92 - 97
  - **TMJ implants – Proplast (1992)**
  - **Reprocessing (Cleaning/Disinfection/Sterilization) of Medical Devices**
  - **Medical Lasers – 1992**
  - **Bard Cardiac Catheters**
  - **Off Label Promotion of Medical Devices by Doctors/Dentists**

The Pendulum Swings - Decisions from the Past Haunt Current Decision and Policy

- Pendulum Swing 2 – Ongoing
  - **2010 Withdrawal of 510(k) clearance of Menaflex**
  - **BMPs and ectopic bone formation**
  - **CMS noncoverage decisions on dynamic spinal implants**
  - **Change of Device to Drug Designations (DBM, Drug/Device Combos)**
  - **Off Label Use/Promotion of Medical Devices – Unapproved human experimentation**
    - Synthes
    - Anulex

510k Process – Pendulum Swings

- ODE before Pendulum Swing 2
  - **Design Specification Creep**
    - Implant Materials were defined by stating compliance to raw material specifications/standards not finished device specifications
    - Rigid fixation systems for fusion procedures (spine) were equivalent to rods with polymers/dynamic segments cleared for “dynamic fusion”. No clinical data was required.
    - Human tissue to metal to synthetics to resorbable synthetics without clinical data

510k Process – Pendulum Swings

- ODE before Pendulum Swing 2
  - **“Intended use creep”**
    - Clearances included general intended uses and differences in intended use statements were allowed
    - An example, urological ablation devices evolved from ablating urological tissue to treating benign prostatic hyperplasia without clinical data

510k Process – Pendulum Swings

- ODE after Pendulum Swing 2
  - **Intended use**
    - Expect intended use that are identical to predicate devices
    - Where ODE believes they made a mistake in the past, expect delays in your clearances and great difficulty in obtaining predicate intended use
    - If differences are significant or mistakes have occurred from ODE's perspective expect clinical study requests

510k Process – Pendulum Swings

- ODE after Pendulum Swing 2
  - **Design Specifications**
    - Expect much greater detail in your design specifications
    - Where ODE once accepted statements about design/materials, they are now expecting objective evidence (including confirmation of finished device specifications)

510k Process – Pendulum Swings

- ODE after Pendulum Swing 2
  - **Performance Testing**
    - Expect the use of risk assessment tools to determine if design changes or design differences (to predicate) require performance testing
    - Expect very few assumptions to be made in the comparison process
    - Expect simple statement of standards conformance to be confirmed by actual performance testing
    - The trigger to request performance testing is very sensitive

510k Process – Pendulum Swings

- ODE after Pendulum Swing 2
  - **Bottom line**
    - Expect risk assessment techniques (e.g., design FMECA) to drive the review
    - Expect field experience to influence your 510(k) review
    - Expect more performance testing

CDRH/ODE Review Policy Changes

Examples and effects

510k Process – Examples/Effects

- Review Issues
  - **Mechanical testing assumptions consistently used over the past 10 years ignored on most recent submissions**
  - **New requirements to analyze MAUDE reports in 510ks**
  - **MRI compatibility testing requirements after a submission has gone through two reviews**
  - **Specifications for ablation instruments commonly accepted as adequate evidence for equivalence now require bench testing**
  - **Clinical study requirements for changes in intended use and design modifications**

510k Process – Examples/Effects

- Creating an Unlevel Playing Field
  - **Requiring a company to take the IDE/PMA route when a direct competitor is marketing their device for the same indication (off label)**
  - **Requiring specific labeling for one company but not required for any other device in the same market and same indication. No technology differences existed.**

510k Process – Examples/Effects

- Open Communication Issues
  - **Refusing to meet face to face when FDA has significantly changed their concerns regarding a submission that has already gone through previous reviews. Changes would have huge timeline and financial consequences on a start up.**

FDA Defends 510k review process

- CDRH performed an internal analysis of 510(k) review times
  - **Cause of initial request for Additional Information (AI letter) from ODE**
  - **Cause of 2nd AI request**

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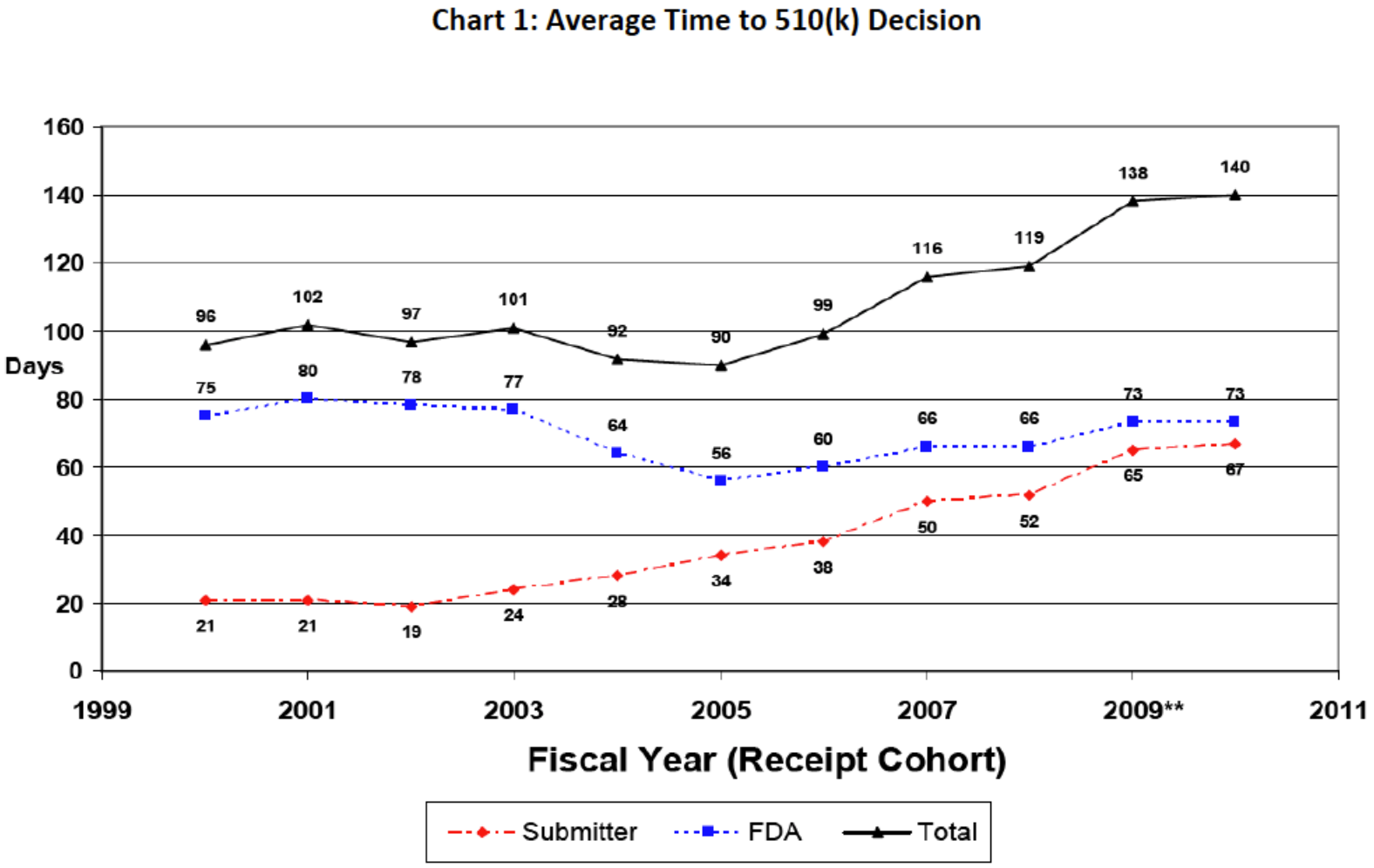
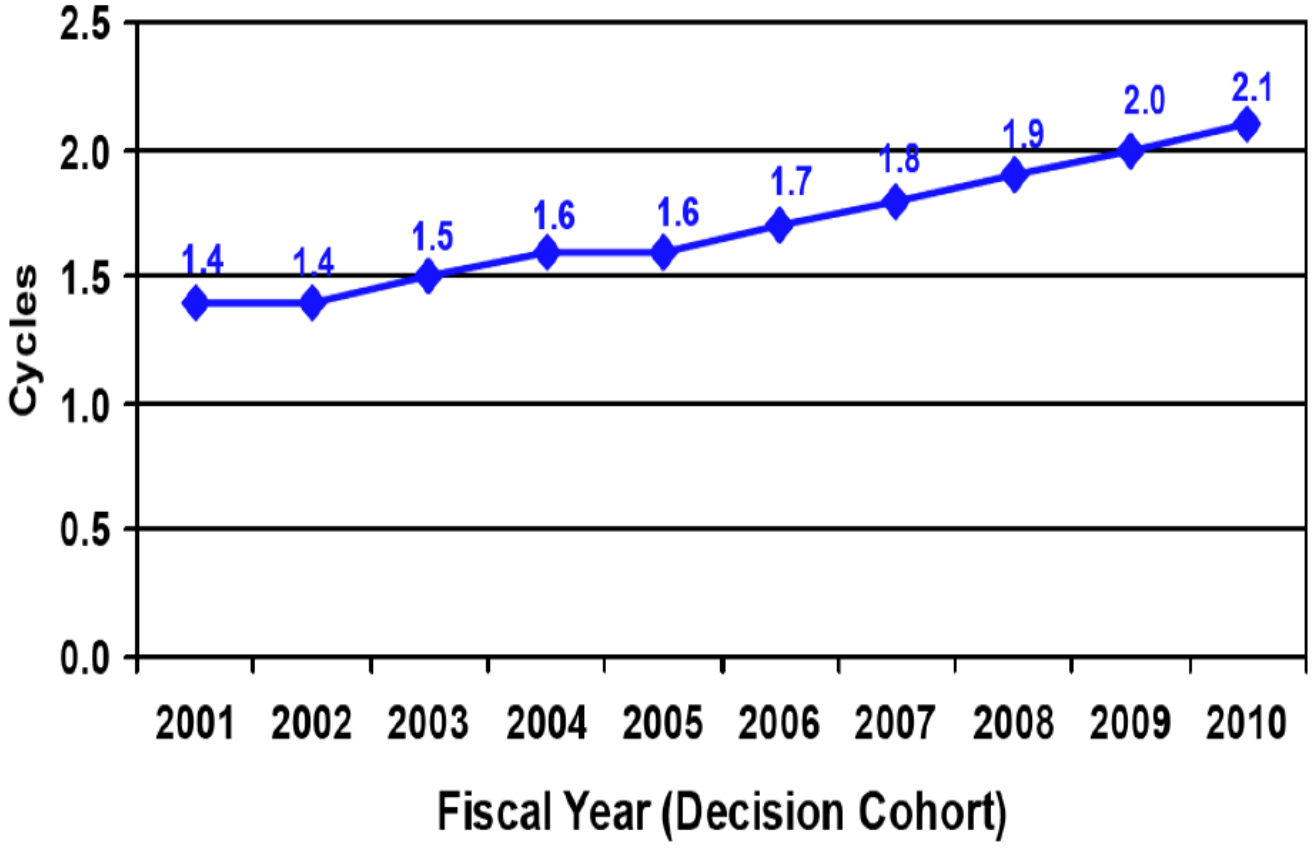
FDA Defends 510k review process



*SE and NSE decisions only: Averages may not sum to total due to rounding
** 2009, 2010 some cohort still open as of July 5, 2011 data may change

FDA Defends 510k review process

Chart 2: Number of Review Cycles per 510(k) Submission



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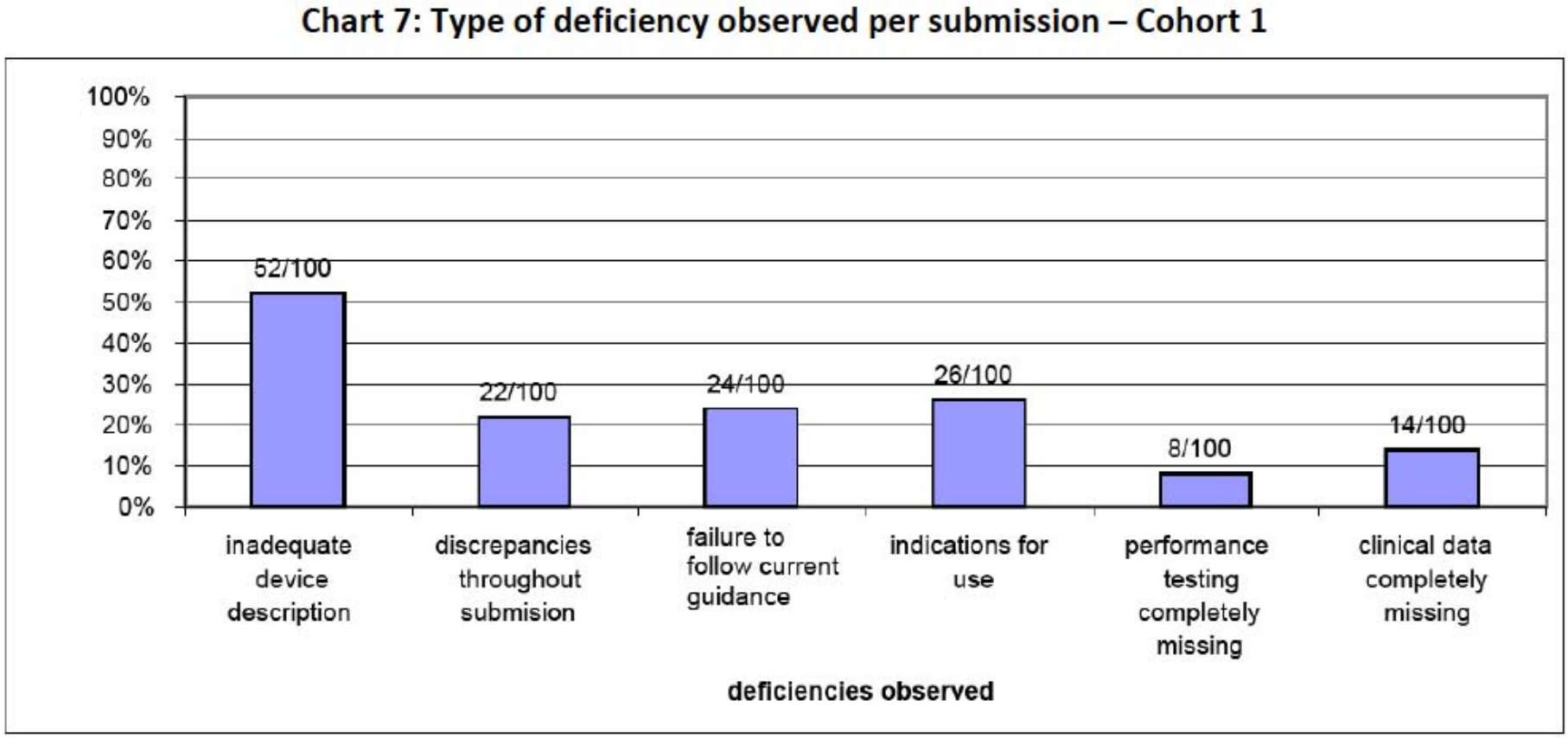
FDA Defends 510k review process

- Conclusions reached based on internal analysis of 510(k) review times
  - **Poor submission quality primary cause of initial AI letter**
    - Inadequate device description
    - Inconsistent indication for use statement throughout submission
    - No performance testing
    - No clinical data
  - **Applicant not providing a complete answer to reviewers question(s)**

FDA Defends 510k review process



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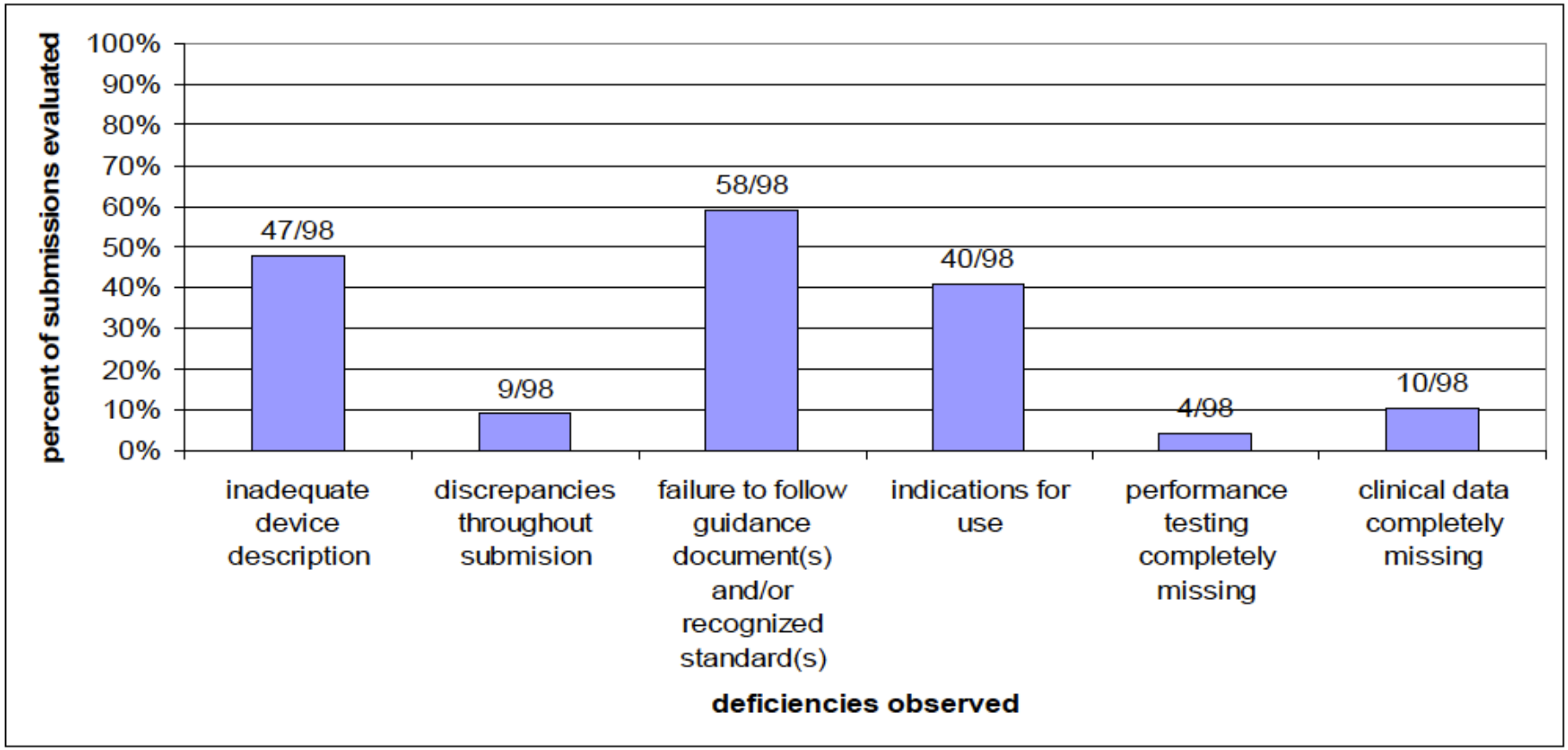
FDA Defends 510k review process



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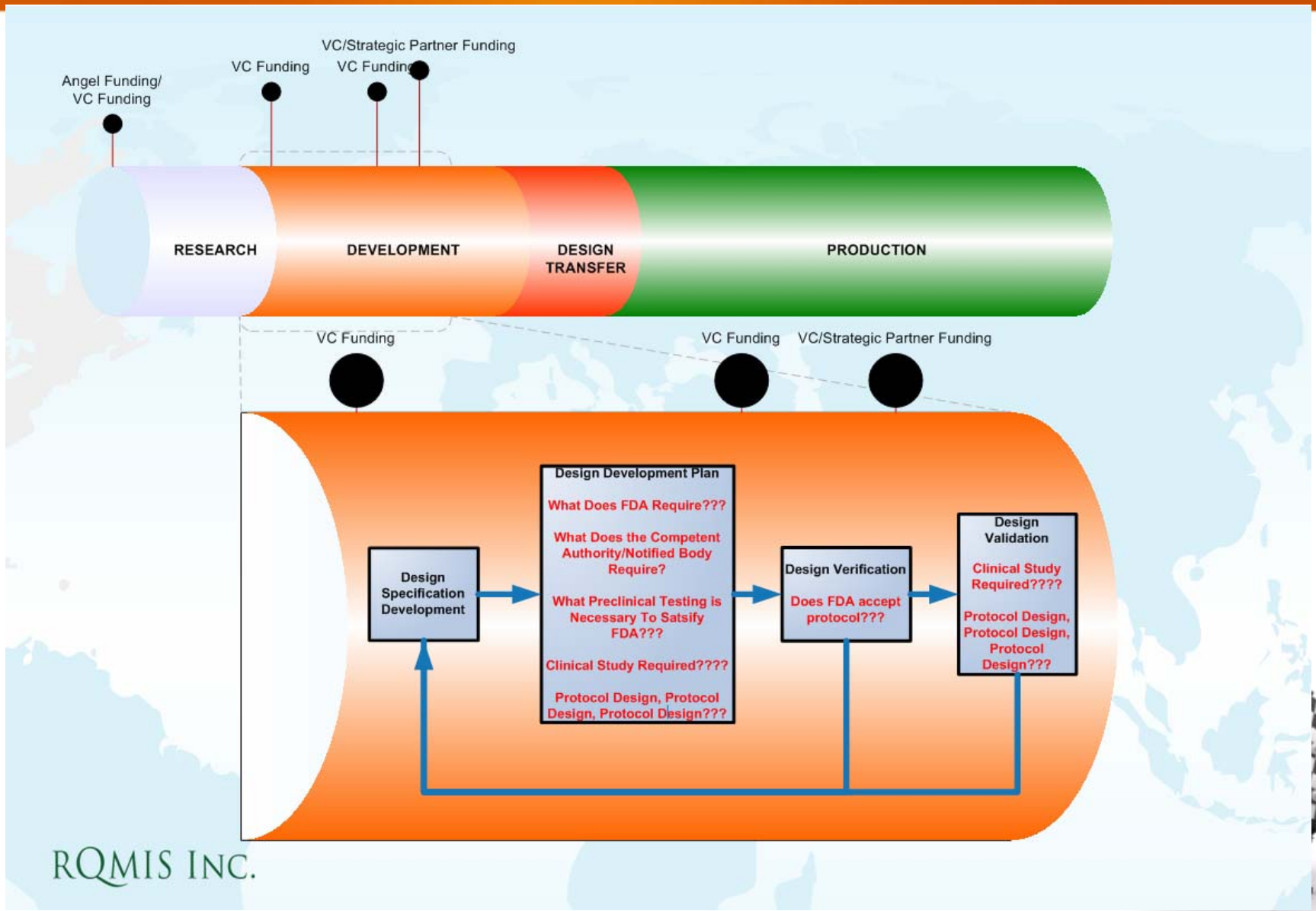
CDRH/ODE Review Policy Changes

IMPACT, future and company response

FDA IMPACT - PRODUCT DEVELOPMENT/FUNDING



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510k Process – Future?

- CDRH 2011 Strategic Goals
  - **Fully Implement a Total Product Life Cycle Approach**
  - **Enhance Communication and Transparency**
  - **Strengthen Our Workforce and Workplace**
  - **Proactively Facilitate Innovation and Address Unmet Public Health Needs**
    - **CDRH Medical Device Innovation Initiative**
- CDRH continues to believe that a more scientific rigorous process needs to be put in place

510k Process – Future?

- Is CDRH changing their approach?
  - **NO**
- The Center will continue to ratchet up what they believe is better science/engineering reviews
- They will attempt to incorporate risk assessment techniques to drive their questions
- They will chose to ignore past “mistakes”
- These reviews will increasingly require clinical data

510k Process – Company Response

- Understand the clinical environment your device will be used in
- Seriously apply risk management techniques during product development/design control
- Include within this risk assessment a comparison of your product to the likely predicate device(s) you will be using in premarket submissions
- Design a sound scientific/engineering/verification/validation plan as part of design controls
  - **Don't design your plan based on "what your competitors had to do" or "what FDA required of your competitors"**

510k Process – Company Response

- Confirm your regulatory strategy with Agency input
- Maintain this regulatory strategy during deployment
- A well written regulatory submission

- *The above techniques have been applied to recent 510(k) submissions with success*

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Questions

Thank you