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Class I/II IVD Devices Exemptions Final Project

FDA-Industry IVD Roundtable Meeting

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IVD Exemptions Project- Presentation Overview

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Background

Risk Based Approach for Diagnostics

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Modernizing Regulatory System

through Risk Based Approach

– FDA oversight of safety and effectiveness of all diagnostic tests

– Align regulatory oversight with patient risk/benefit

Risk Based Approach Core Concepts

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Exempt lower risk diagnostic tests from premarket review

Established analytes using established methods and/or well-characterized platforms

Low risk to patients from incorrect test results – based on clinical applications & mitigation via laboratory/ regulatory controls (risk management principles)

Apply a risk-based approach to determine intensity of review for non-exempt tests

Focus FDA review resources on higher risk tests (e.g. novel biomarkers and/or novel technologies, methods, platforms)

Risk Based Model: Exemption and Tier Triage

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- Builds on strengths of current classification system and review structure
- Recognizes FDA authority of safety and effectiveness of all diagnostic tests based on risk benefit profile, regardless of where produced
- Recognizes all regulatory controls that FDA has at its disposal
- Exempts IVD devices based on ISO 14971, Annex H Risk Management approach
- Otherwise reserved devices are subject to tier triage risk-based review

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Objectives

Objectives

- Support the MDUFMA goal for exemption of Class I/II devices from premarket review
- Develop a systematic, risk assessment process that can be used to identify IVD test systems suitable for exemption from premarket review
- Provide a list of proposed low-risk IVD exemption candidates to FDA (based on risk management principles)
- Strong industry commitment; nearly 2 year project

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Description of Approach

Approach

- Assess risks from incorrect test results, based on input from physicians and other clinical experts
- Classify IVDs according to the degree of risk to patients from incorrect/delayed test results
- Identify exemption candidates based on FDA criteria, including the degree of risk to patients
- Compare results to any adverse event histories (no candidates have adverse event reports)
- Engaged independent consultants to develop the risk assessment process and facilitate its application to Class I/II IVD devices

Project Overview

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- OIVD feedback on general approach
- Conducted pilot study (risk assessments of 7 analytes/test systems) in September 2008
- Completed identification of IVD candidates in September 2009
  - Focus on inherent clinical risk
  - Comprehensive review of MDR data

IVD Exemption Criteria

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Overall approach: Tests representing low risk to patients based on risk management principles (inherent clinical risk and mitigation)

The following seven exemption criteria and four limitations are based on criteria published by FDA.* All criteria must be met to qualify for an exemption from premarket notification

1. The clinical application of the test results is well established.
2. The performance characteristics are well established.
3. The laboratory use and quality control of the test system are regulated under CLIA.
4. Device malfunctions or anticipated use errors would not present a high public health risk or lead to a high degree of morbidity or mortality.

* In 63 FR 3142 dated Jan 21, 1998, and in *"Procedures for Class II Device Exemptions from Premarket Notification, Guidance for Industry and CDRH Staff,"* issued Feb 19, 1998

IVD Exemption Criteria

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5. Changes in performance characteristics that could affect safety and effectiveness either:

   a) will be detected by users, using control mechanisms integral to the device and/or conventional laboratory control procedures, before exposing patients to harm; or

   b) will not cause serious injury or lead to a life-threatening situation for a patient (e.g., due to an incorrect diagnosis or inappropriate treatment).

6. The device does not have a history of adverse events associated with failures to meet its performance specifications or otherwise perform as intended.

IVD Exemption Criteria

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7. The device conforms to Special Controls specified by the FDA in Guidance Documents. For example, where appropriate to provide additional assurance of safety and effectiveness, FDA could specify:

   a) minimum analytical performance specifications and/or product standards;

   b) traceability of calibrator values to a recognized reference material/reference measurement procedure;

   c) evaluation protocols for validating analytical performance claims;

   d) device-specific design or manufacturing requirements; and/or

   e) specific risk mitigation information in the instructions for use.

IVD Exemption Criteria

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An exemption would not apply if any one of the following were true:

1. The IVD medical device is intended for a substantially different medical purpose than the intended use described in the classification regulation;
2. The IVD medical device is intended for a medical purpose specifically excluded from exemption;
3. The IVD medical device is based on a novel technology that has not been previously cleared or approved by FDA; or
4. The IVD medical device is based on a method principle that is specifically excluded from exemption.

Risk Assessment Methodology

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- Qualitative risk assessment
  - ISO 14971:2007
- Physicians and other clinical experts assessed risk of incorrect/delayed test results
- Evaluated 94 analytes/test systems as possible exemption candidates
  - Class I Reserve List
  - Class II (considered 70% of current OIVD 510(k) workload plus any additional nominations from industry)

Risk Concepts

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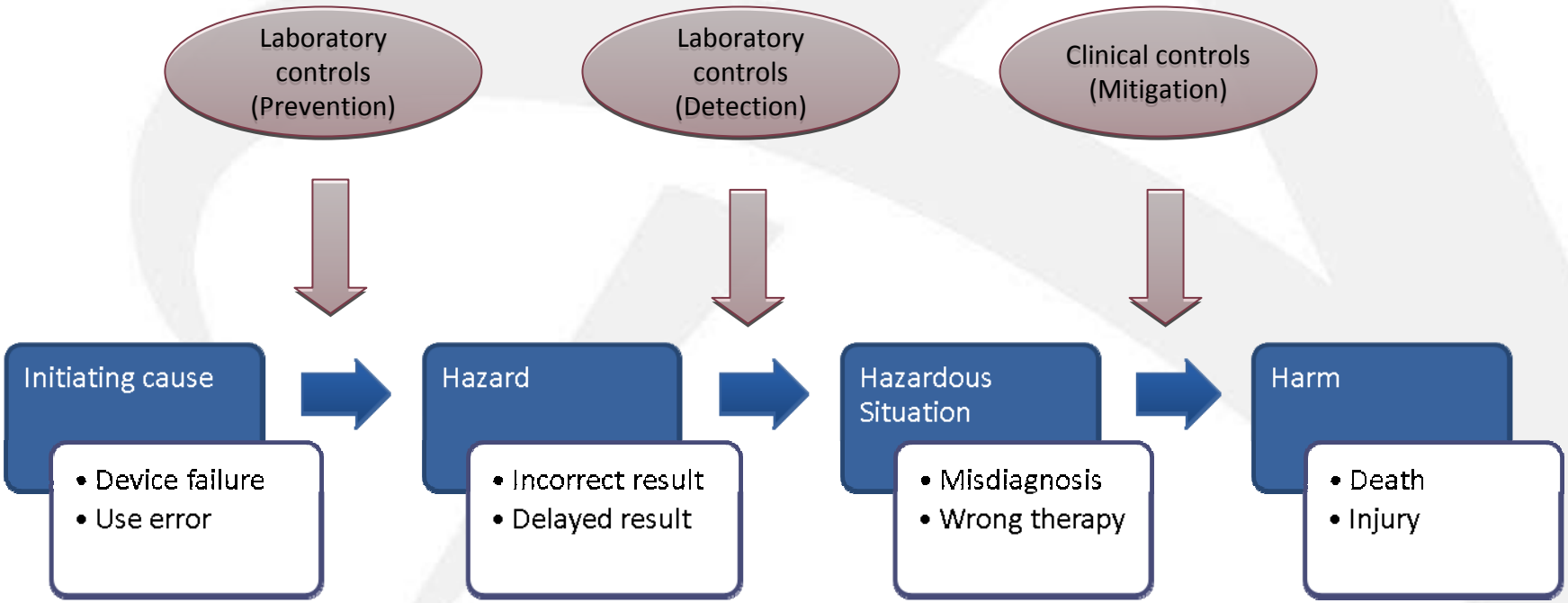
Sequence of Events Indirectly Leading to Risk



Risk Concepts

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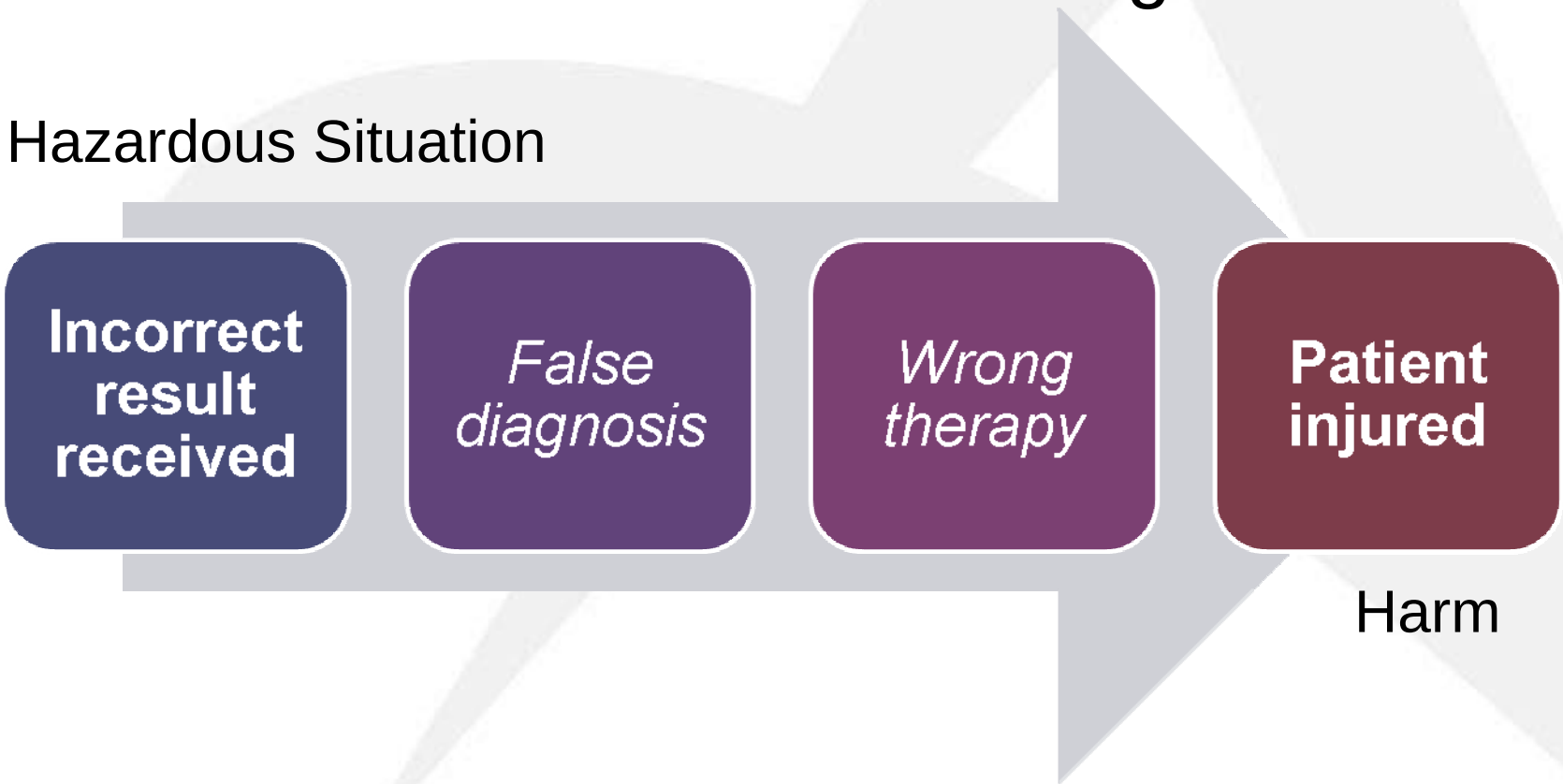
Hazardous Situation Leading to Harm



Methodology

- Risk factors that were considered:
  - Likelihood incorrect result will affect diagnosis, treatment or patient management
  - Likelihood inappropriate decision will lead to harm
  - Severity of the resulting harm
- Independent consultant analyzed IVD MDRs for actual injuries/deaths and hazardous situations
- Probability of harm and severity of harm—risk matrix

Probability of Harm

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Probability	Definition
Likely to occur	Reasonable expectation that injury could occur to a patient if a clinician received incorrect test results.
Possible to occur	In certain conditions and circumstances injury could occur, but would not be expected in ordinary use of the test results in clinical medicine.
Unlikely to occur	Injury to patients is not expected to occur in foreseeable circumstances.

Severity of Harm

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Severity	Definition
Death/Serious Injury	Injury/illness resulting in death; life-threatening; permanent impairment/ damage to a body function/structure; or necessitates medical or surgical intervention to preclude permanent impairment/damage.
Injury but not serious injury	Patient is not exposed to a life-threatening situation, no permanent bodily impairment or damage occurred, and medical intervention was not required to preclude permanent bodily impairment or damage.
Negligible injury	No impairment or damage that significantly affected bodily structure or function.

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Risk Assessment Results

Identification of IVD Candidates

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IVDs were grouped based on degree of risk to patients from an incorrect test result reported to a physician.

- **Proposed Candidates: Candidate for immediate exemption. No adverse events from these test systems (30)**
- Additional potential candidates (with adequate laboratory mitigation, or regulatory guidance). No adverse events from these test systems (25)
- All candidate tests represent low risk to patients based on risk management principles
- Remaining IVDs evaluated were not submitted as candidates (39)

Risk Classification and Candidates

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Analytes/Test Systems Proposed for Immediate Exemption

	Proposed Candidates
Chemistry	10
Toxicology	7
Hematology	0
Microbiology	3
Immunology	10

Proposed Candidates

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Clinical Chemistry Test Systems

- Acid phosphatase
- Albumin
- Alkaline phosphatase
- Amylase
- Aspartate aminotransferase (AST)
- Iron-binding capacity
- Nitrite (nonquantitative)
- Testosterone
- Total thyroxine
- Uric acid

Proposed Candidates

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Toxicology Test Systems

- Amphetamine
- Phencyclidine
- Nicotine, Cotinine, metabolites
- Cocaine and cocaine metabolite
- Methamphetamine
- Quinine
- Cannabinoids

Proposed Candidates

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Microbiology Test Systems

- Campylobacter fetus serological reagents
- Epstein-Barr virus serological reagents
- Parainfluenza virus serological reagents

Proposed Candidates

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Immunology Test Systems - I

- Antinuclear antibody
- Alpha-1-antitrypsin
- Antineutrophil Cytoplasmic Antibodies (ANCA)
- Acetylcholine receptor autoantibodies
- Autoantibodies to Glutamic Acid Decarboxylase
- Liver/kidney microsome, type 1 autoantibodies

Proposed Candidates

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Immunology Test Systems - II

- Immunological specific skin autoantibodies
- Indirect Immunofluorescence for Autoantibodies
- Insulin Autoantibody Kit
- Radioallergosorbent (RAST)

Conclusions

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1. Proposed IVD test system candidates present low inherent risks.
   - These Product Codes represent well-established test systems
   - The analytes are well-established in clinical medicine
   - Can be exempted from 510(k)

Conclusions

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2. Additional IVD test systems represent potential candidates where risks can be mitigated by an effective laboratory quality management system as required by CLIA ’88, or regulatory guidance.
    - Examples: proficiency testing, method verification, QC monitoring, preventive maintenance, corrective actions.
    - These laboratory controls reduce the overall residual risk to patients by minimizing the likelihood that incorrect test results would be reported by the laboratory.
    - It may be possible to exempt these test systems.

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Recommendations

Recommendations

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1. Exempt test systems that meet the criteria (all of the product codes submitted as proposed candidates)
2. Investigate whether laboratory controls or guidance documents for test systems (for additional potential candidates) are adequate to mitigate the risks.
3. Where appropriate, develop Guidance Documents and other Special Controls to mitigate the risks of other test systems.
4. Using the forum provided by CLSI, work with manufacturers and laboratories to develop consensus guidelines to reduce the risks from test systems.

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