IVD Hazards, Patient Harm and Risk Controls

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Direct Hazard

Manufacturing Process Failure → Product Failure (Initiating Hazard) → Hazardous condition → HARM

Device Malfunction → HARM
Indirect Hazard

Manufacturing Process Failure → Product Failure (Initiating Hazard)

Testing Process Failure

Medical Error

Erroneous Test Result → Inappropriate Action

HARM

Manufacturer

Laboratory

Physician

Patient
IVD Characteristics Related to Safety

- Chemical
- Mechanical
- Electrical
- Biological
- Analytical performance
  - Accuracy (Precision & Trueness)
  - Specificity
  - Sensitivity
IVD Patient Hazards

- Inaccurate Result
  - Lower/higher than true value
  - False positive
  - False negative

- No Result / Delayed Result
IVD Patient Hazards

- Fault condition
  - Reagent lot variability
  - Calibrator traceability error
  - Instrument failure
  - Control ineffective

- Normal use
  - Inherent analytical error rate
Potential Harm

- Physician might:
  - take potentially harmful action (unnecessary surgery, medication, treatment)
  - fail to take actions necessary to prevent injury, illness or death
Estimating Severity

Requires understanding:

- analytical performance requirements
- medical uses of test results
- potential harm from medical decisions

Qualified medical input is essential!
## Severity of Harm

<table>
<thead>
<tr>
<th>Severity</th>
<th>ISO 14971 Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catastrophic</td>
<td>Results in death</td>
</tr>
<tr>
<td>Critical</td>
<td>Results in permanent impairment or life-threatening injury</td>
</tr>
<tr>
<td>Serious</td>
<td>Medical intervention required to prevent permanent impairment/damage to a body structure</td>
</tr>
<tr>
<td>Minor</td>
<td>Minor injury or temporary impairment not requiring medical intervention</td>
</tr>
<tr>
<td>Negligible</td>
<td>Inconvenience or temporary discomfort</td>
</tr>
</tbody>
</table>
Risk Estimation

Potential harm = Severity of harm \times Probability of occurrence
Indirect Hazard

Manufacturing Process Failure → Product Failure (Initiating Hazard)

Testing Process Failure → Erroneous Test Result

Medical Error → Inappropriate Action

HARM → Patient

Manufacturer → Laboratory → Physician
Probability of Occurrence

Combined probabilities that:

1. device will produce inaccurate result
2. laboratory will fail to detect error and report the result
3. physician will fail to recognize error and will act (or not act) on the result
4. physician’s action (or inaction) will harm the patient
Probability of Occurrence

1. Likelihood the device would generate an inaccurate test result
   - fault mode
   - normal use
   - unintentional use error
   - reasonably foreseeable misuse
Probability of Occurrence

2. Likelihood erroneous result would be detected by laboratory / user
   - incoming materials QA
   - instrument error codes
   - trueness/precision controls
   - effectiveness of QC procedures
   - plausibility checks (delta checks, critical values, likelihood)
Probability of Occurrence

3. Likelihood erroneous result would be detected by physician / patient
   - context (signs, symptoms, medical history)
   - confirmatory test
   - corroboration by other data
Probability of Occurrence

4. Likelihood physician would act on the erroneous test result

- sole basis of diagnosis
- directly leads to medical intervention
- major determinant of therapy
- monitors critical body function
- screens blood or organs (transplantation)
Probability of Occurrence

5. Likelihood physician’s action/inaction would harm the patient
   - potential for injury, illness or death
   - irreversible, such as resection or abortion
   - extent intervention is reversible
   - intervention needed to prevent harm
   - transfusion/transplantation
Error grid analysis

- Introduced by Clarke et al. for glucose self-monitoring (1987)
- Non-statistical classification of risk
- Grid divided into risk levels
- Assigns clinical significance to each error
Clarke Error Grid
Error grid analysis

Underlying assumptions (Clarke)

- Target glucose = 70 - 180 mg/dL
- Patients will only correct glucose outside that range
- Corrective treatment not appropriate if causes glucose levels outside target range
- Failure to treat glucose outside target range is not appropriate
Clarke Error Grid

Risk levels
A  SMBG accuracy requirement
B  Error >20% but treatment benign or none
C  Overcorrection of acceptable BG levels
D  Failure to detect & treat dangerous BG
E  Contradictory treatment
Clarke Error Grid
Parkes Error Grid

- Consensus risk criteria
- Parkes et al., *Diabetes Care* (2000)
- Survey of 100 endocrinologists
  - (questionnaire at www.bdchc.com)
- No assumptions about risk levels
- Eliminates discontinuities
Parkes Error Grid

BD Error Grid

© 2003 Powers Consulting
Parkes Error Grid

Physician survey:
1. Review clinical scenario
2. Identify glucose decision levels
3. Assign medical risk to errors at each decision level
Parkes Survey

Scenario: Type 1 Diabetes

- Well educated 19 year old male, type 1 diabetes; trying to achieve normal blood glucose control; intensive therapy, has hypoglycemic unawareness.
Parkes Survey

For this scenario:
- Five possible actions patient could take depending on blood glucose reading
- Fill in glucose ranges that would lead to these actions
- Make ranges continuous - no overlaps
## Parkes Survey

<table>
<thead>
<tr>
<th>Action</th>
<th>Code</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency treatment low glucose</td>
<td>1</td>
<td>____ - ____</td>
</tr>
<tr>
<td>Take glucose (tablets/food)</td>
<td>2</td>
<td>____ - ____</td>
</tr>
<tr>
<td>No action needed</td>
<td>3</td>
<td>____ - ____</td>
</tr>
<tr>
<td>Take insulin</td>
<td>4</td>
<td>____ - ____</td>
</tr>
<tr>
<td>Emergency treatment high glucose</td>
<td>5</td>
<td>____ - ____</td>
</tr>
<tr>
<td>Action</td>
<td>Code</td>
<td>Range</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>Emergency treatment low glucose</td>
<td>1</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Take glucose (tablets/food)</td>
<td>2</td>
<td>50 - 70</td>
</tr>
<tr>
<td>No action needed</td>
<td>3</td>
<td>70 - 120</td>
</tr>
<tr>
<td>Take insulin</td>
<td>4</td>
<td>120 - 360</td>
</tr>
<tr>
<td>Emergency treatment high glucose</td>
<td>5</td>
<td>&gt; 360</td>
</tr>
</tbody>
</table>
Parkes Survey

Risk levels

A  No effect on clinical action
B  Altered clinical action — little or no effect on clinical outcome
C  Likely to affect clinical outcome
D  Significant risk to patient
E  Dangerous consequences possible
## Parkes Survey

<table>
<thead>
<tr>
<th>Meter range</th>
<th>Patient’s actions</th>
<th>Actual value is in range</th>
<th>Degree of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Emergency treatment for low BG</td>
<td>1, 2, 3, 4, 5</td>
<td>A, ___ ___ ___</td>
</tr>
<tr>
<td>2</td>
<td>Take glucose</td>
<td>1, 2, 3, 4, 5</td>
<td>___ A, ___ ___</td>
</tr>
<tr>
<td>3</td>
<td>No action needed</td>
<td>1, 2, 3, 4, 5</td>
<td>___ ___ A, ___</td>
</tr>
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<td>4</td>
<td>Take insulin</td>
<td>1, 2, 3, 4, 5</td>
<td>___ ___ ___ A ,___</td>
</tr>
<tr>
<td>5</td>
<td>Emergency treatment for high BG</td>
<td>1, 2, 3, 4, 5</td>
<td>___ ___ ___ ___ A</td>
</tr>
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<td>1</td>
<td>Emergency treatment for low BG</td>
<td>1, 2, 3, 4, 5</td>
<td>A, B, B, C, D</td>
</tr>
<tr>
<td>2</td>
<td>Take glucose</td>
<td>1, 2, 3, 4, 5</td>
<td>B, A, B, C, D</td>
</tr>
<tr>
<td>3</td>
<td>No action needed</td>
<td>1, 2, 3, 4, 5</td>
<td>C, C, A, C, D</td>
</tr>
<tr>
<td>4</td>
<td>Take insulin</td>
<td>1, 2, 3, 4, 5</td>
<td>E, D, C, A, B</td>
</tr>
<tr>
<td>5</td>
<td>Emergency treatment for high BG</td>
<td>1, 2, 3, 4, 5</td>
<td>E, D, D, C, A</td>
</tr>
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Parkes Error Grid

BD Error Grid

Reference Value

Measured Value

E

C

B

A

D
Risk Controls

Design, Manufacturing and Testing Processes
Figure 1 — A schematic representation of the risk management process for illustration
Risk Reduction

When risk reduction is required, control risks so that residual risks associated with each hazard are judged acceptable

*ISO 14971*
Risk Control

- Risk controls may reduce:
  - Severity of potential harm
  - Probability of occurrence of harm
  - Both

- IVD assays - severity of harm is determined by medical decisions
Risk Control

Integrated approach is required in the following priority order:

- inherent safety by design
- protective measures in the medical device or the manufacturing process
- information for safety

ISO 14971
Risk Control

- First step: option analysis
- If risk reduction is not practicable, manufacturer must conduct risk/benefit analysis of residual risk
Risk Control

- First step: option analysis
- If risk reduction is not practicable, manufacturer must conduct risk / benefit analysis of residual risk
## Risk Controls

<table>
<thead>
<tr>
<th>Product</th>
<th>Safe Design</th>
<th>Protective Measure</th>
<th>Risk Communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-testing device</td>
<td>Accuracy insensitive to sample volume</td>
<td>No result if insufficient sample volume</td>
<td>Error message if sample volume insufficient</td>
</tr>
</tbody>
</table>
## Risk Controls

<table>
<thead>
<tr>
<th>Product</th>
<th>Hepatitis assay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safe Design</strong></td>
<td><em>Reduce % of false negatives</em></td>
</tr>
<tr>
<td><strong>Protective Measure</strong></td>
<td><em>Calibrate cutoff point with each run</em></td>
</tr>
<tr>
<td><strong>Risk Communication</strong></td>
<td><em>Warning for false negative consequences</em></td>
</tr>
</tbody>
</table>
## Risk Controls

<table>
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<tr>
<th>Product</th>
<th>Single Use Reagent Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe Design</td>
<td>Self destruction after use</td>
</tr>
<tr>
<td>Protective Measure</td>
<td>Obvious indication after first use</td>
</tr>
<tr>
<td>Risk Communication</td>
<td>Warning for consequences of reuse</td>
</tr>
</tbody>
</table>
Risk Control Options

Safety by Design (Product)
- Measurement precision
- Calibrator traceability
- Antibody specificity
- Detector sensitivity
- Analyzer reliability
Risk Control Options

Safety by Design (Manufacturing)
- Automation
- Validated processes
- Validated test methods
- Six-sigma process capability
Risk Control Options

Protective Measures (Product)
- QC materials included in kit
- Specimen suitability detector
- Positive specimen ID
- Bar coded reagents (exp. dates)
- Refrigerated on-board reagents
Risk Control Options

Protective Measures (Manufacturing)

- QA incoming materials
- In-process tests
- Defect detection system
- Product release testing
- Reagent stability monitoring
Risk Control Options

Protective Measures (Laboratory)

- QC system
- Delta checks
- Positive specimen identification
- Backup testing capabilities
Risk Control Options

Risk Communication
- Warning statements / Labels
- Limitations / Interferences
- Performance characteristics
- QC recommendations
- Error messages
Risk Controls

Manufacturing / Testing Processes

- Determine critical control points (HAACCP)
- Enhance controls at critical steps (identified by FTA / FMEA)
Risk Management

- Regulatory requirement in all major markets for manufacturers
- Even if not required, minimizing risk is expected by the norms of society
- ISO process provides a systematic approach that fits into a quality system
Risk Management

- Controls required for IVD medical devices that pose risk to patients
- Most erroneous results are caused by pre- and post-analytical failures
- Clinical laboratories would benefit from a systematic risk management process
Thank you!
References


21 CFR. 820, "Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation."

References


- EN 1441, “Risk Analysis for Medical Devices,” (Brussels: European Committee for Standardization, 1997)


References


References


References

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