IVD Hazards, Patient Harm and Risk Controls

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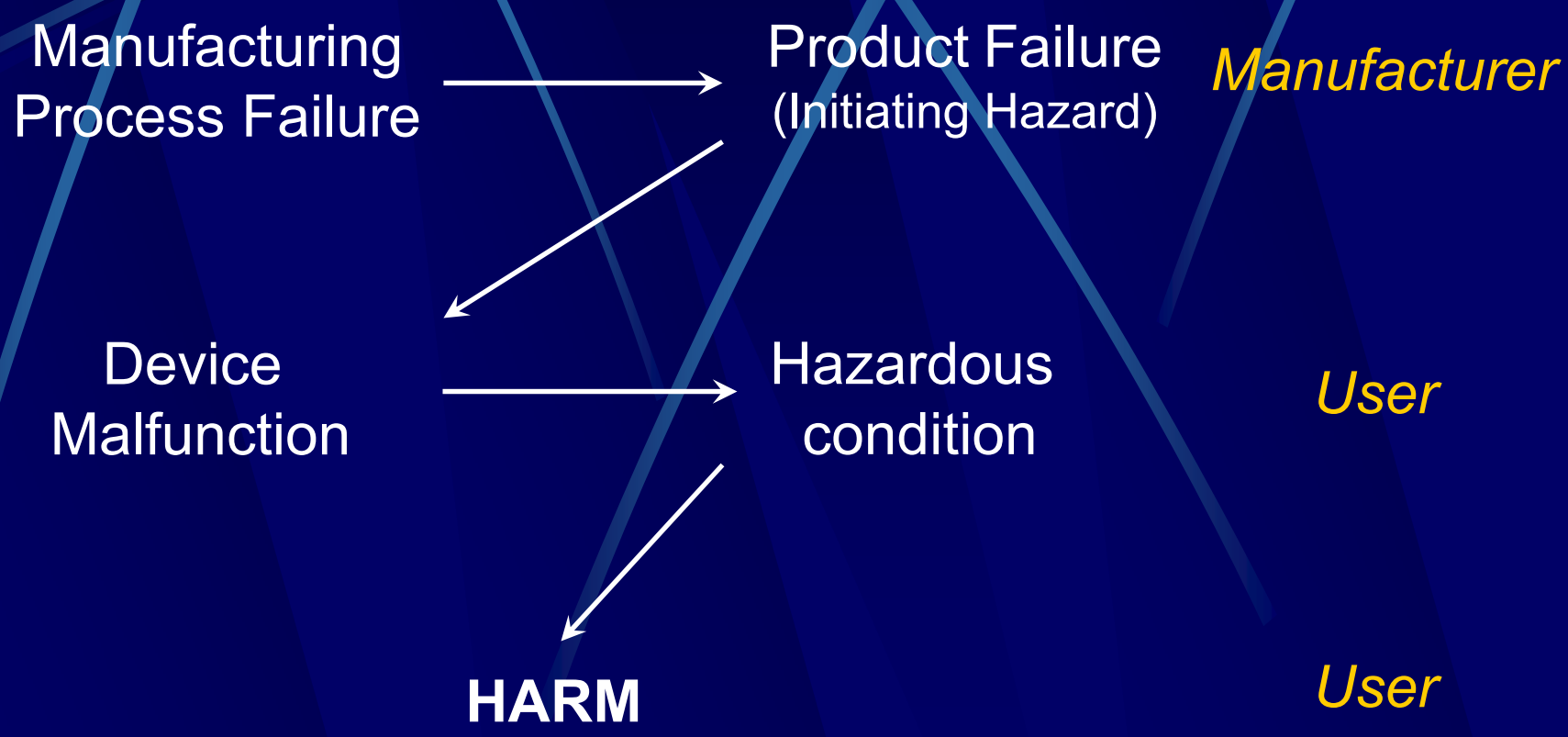
Direct Hazard



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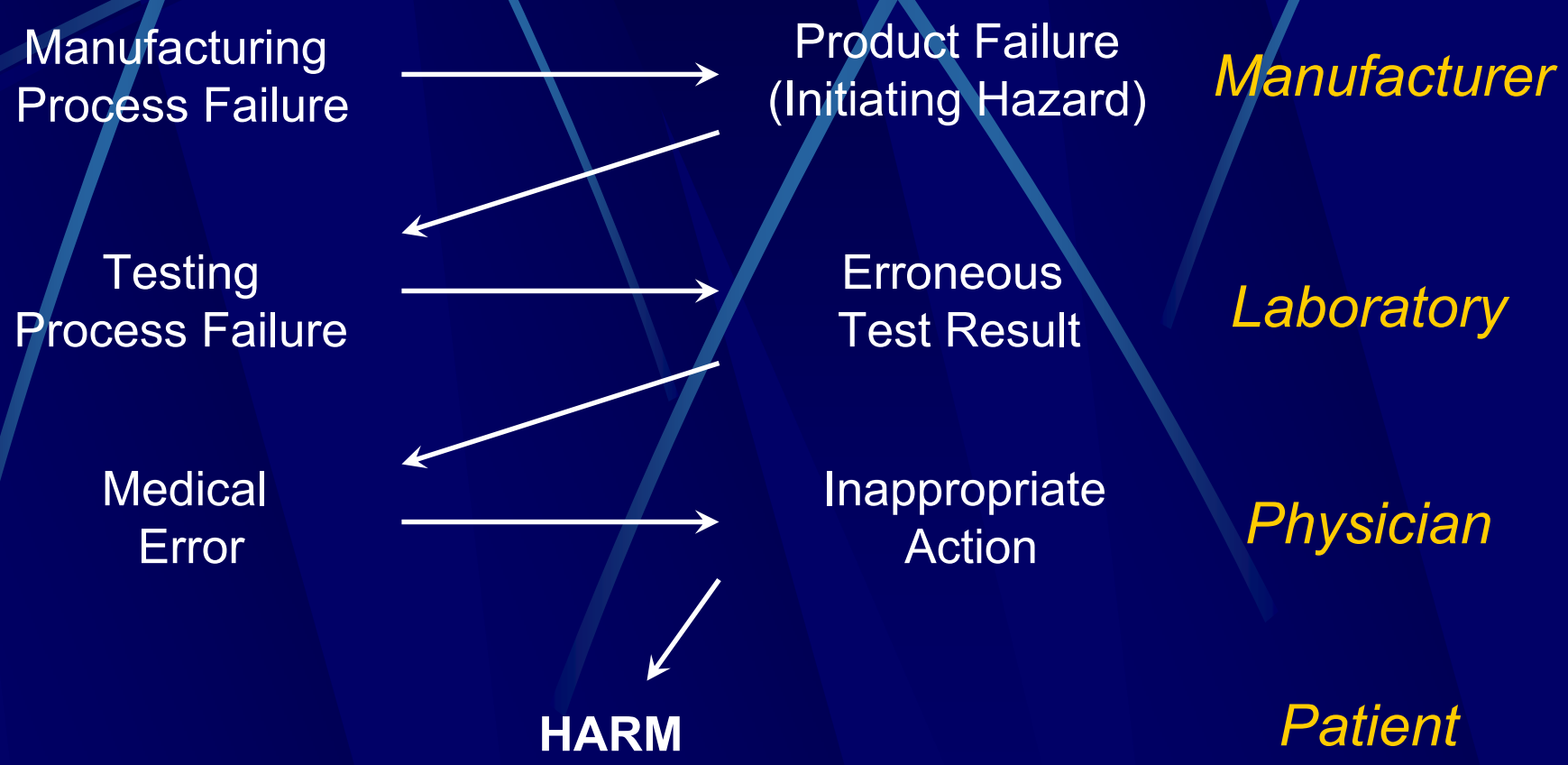
Indirect Hazard



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IVD Characteristics Related to Safety

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

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IVD Patient Hazards

- Inaccurate Result
  - Lower/higher than true value
  - False positive
  - False negative
- No Result / Delayed Result

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IVD Patient Hazards

- Fault condition
  - Reagent lot variability
  - Calibrator traceability error
  - Instrument failure
  - Control ineffective
- Normal use
  - Inherent analytical error rate

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Potential Harm

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

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Estimating Severity

- Requires understanding:
  - analytical performance requirements
  - medical uses of test results
  - potential harm from medical decisions
- Qualified medical input is essential !

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Severity of Harm

Severity	ISO 14971 Definition
Catastrophic	Results in death
Critical	Results in permanent impairment or life-threatening injury
Serious	Medical intervention required to prevent permanent impairment/damage to a body structure
Minor	Minor injury or temporary impairment not requiring medical intervention
Negligible	Inconvenience or temporary discomfort

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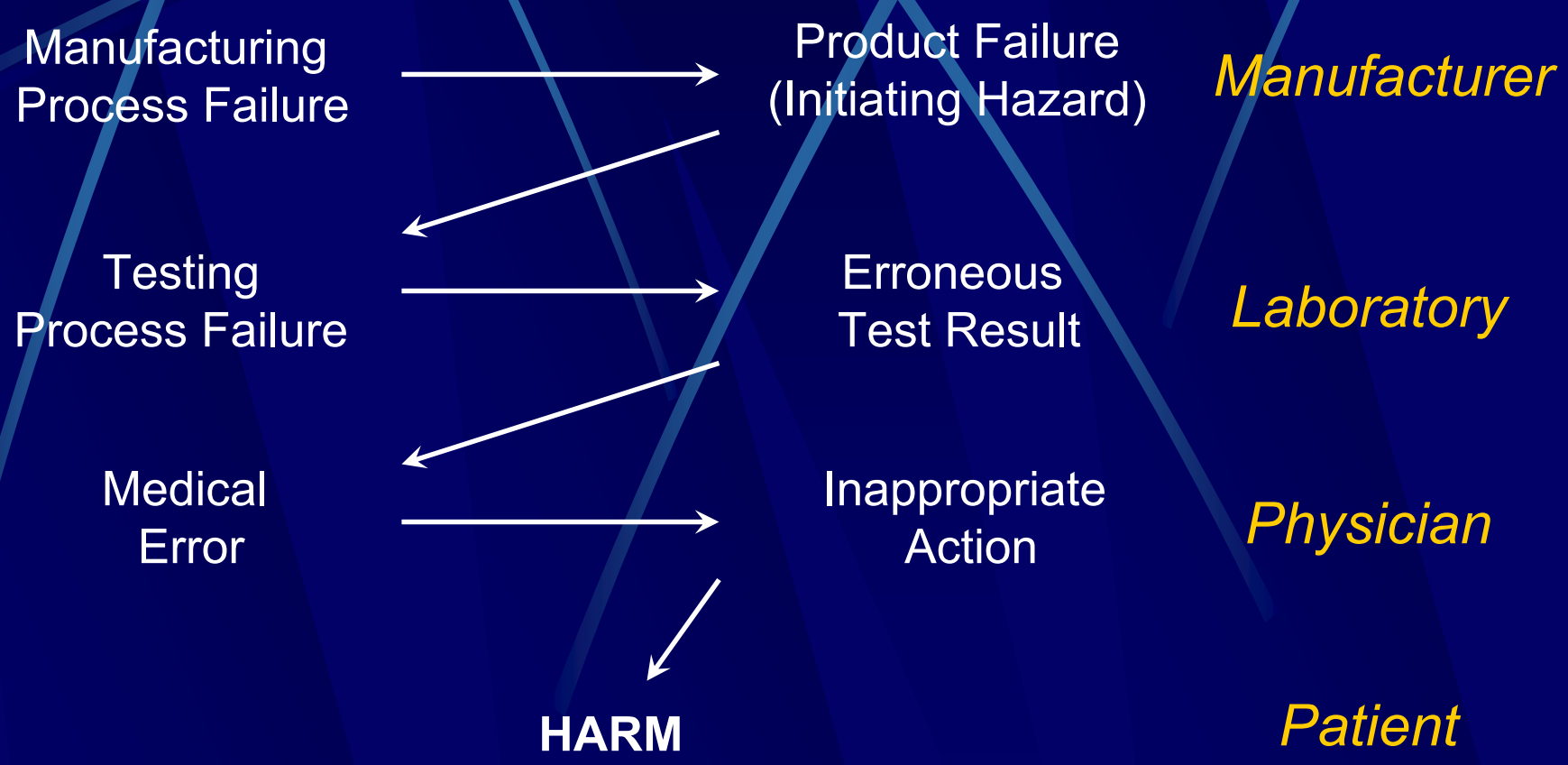
Risk Estimation

- Potential harm =
  - Severity of harm x
  - Probability of occurrence

Indirect Hazard



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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

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Probability of Occurrence

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

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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)

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Probability of Occurrence

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

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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)

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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

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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

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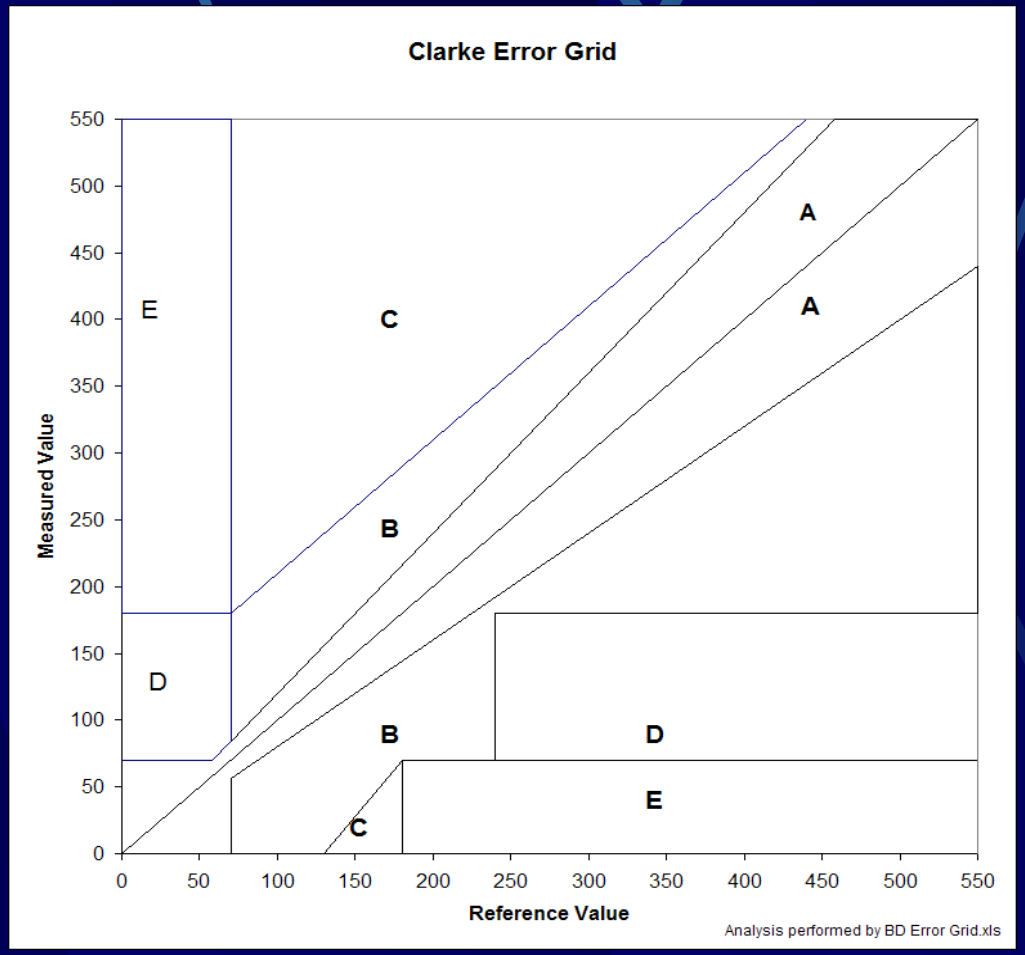
Clarke Error Grid



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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

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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

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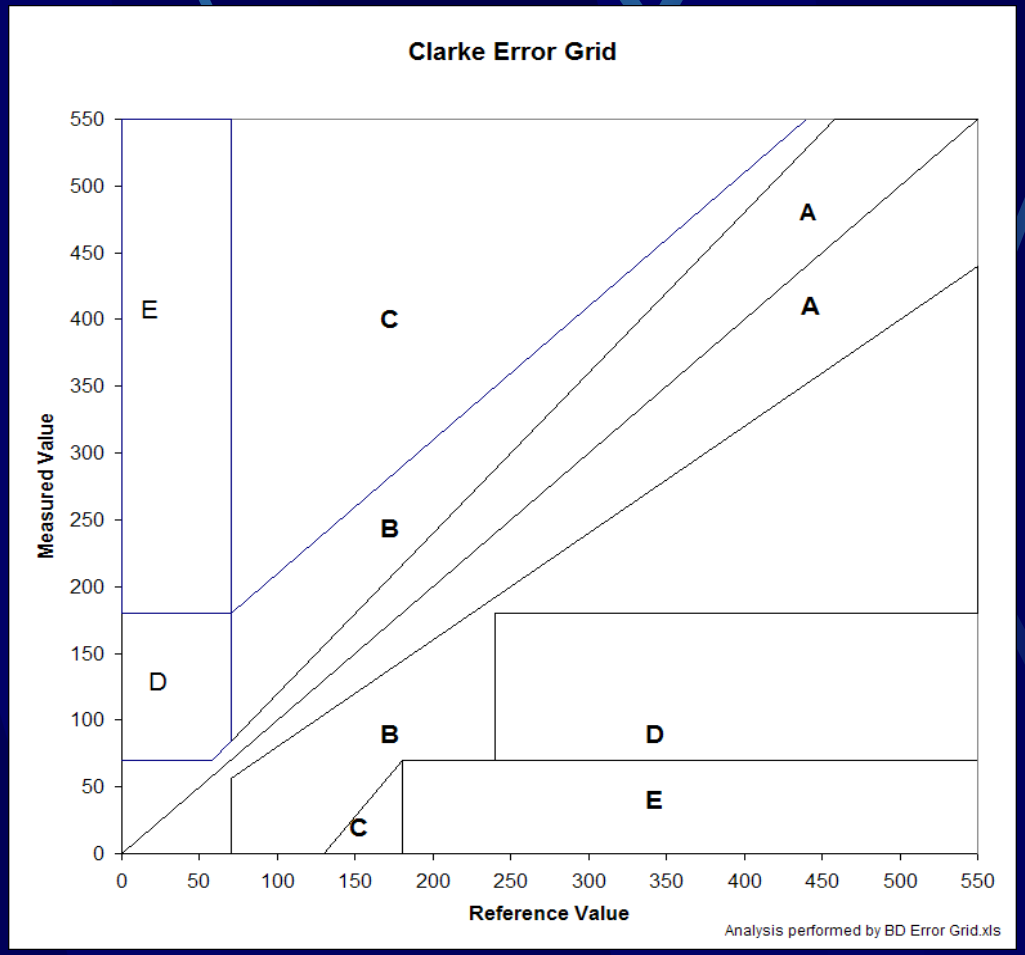
Clarke Error Grid



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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

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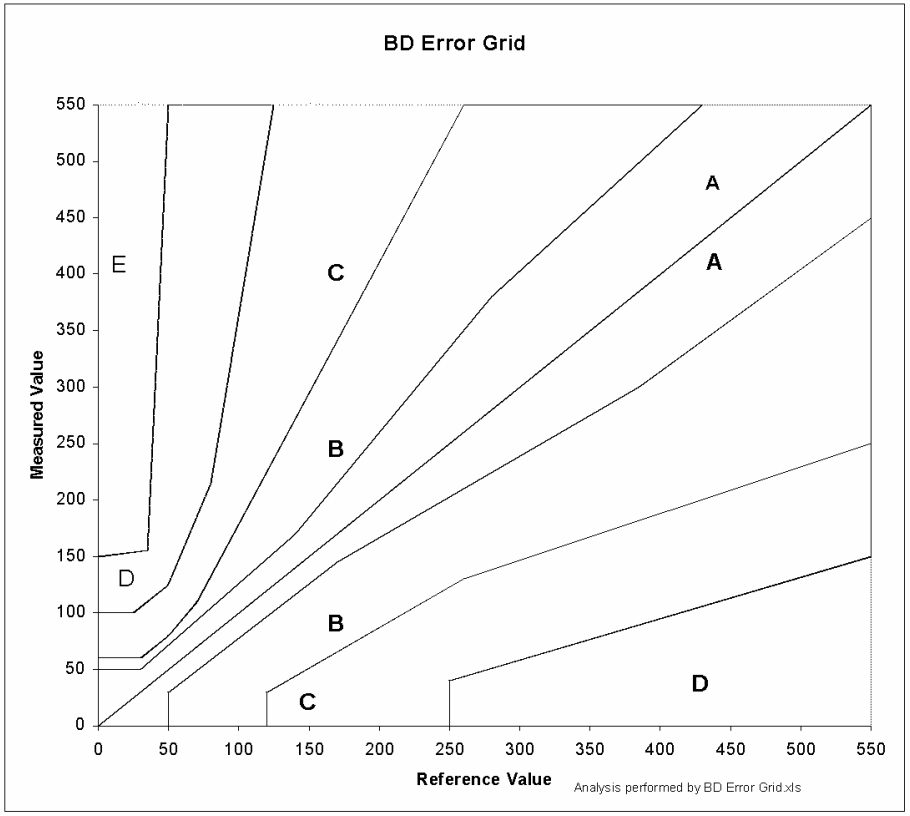
Parkes Error Grid



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Parkes Error Grid

Physician survey:

1. Review clinical scenario
2. Identify glucose decision levels
3. Assign medical risk to errors at each decision level

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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.

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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

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Parkes Survey

Action	Code	Range
Emergency treatment low glucose	1	___ - ___
Take glucose (tablets/food)	2	___ - ___
No action needed	3	___ - ___
Take insulin	4	___ - ___
Emergency treatment high glucose	5	___ - ___

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Parkes Survey

Action	Code	Range
Emergency treatment low glucose	1	< 50
Take glucose (tablets/food)	2	50 - 70
No action needed	3	70 - 120
Take insulin	4	120 - 360
Emergency treatment high glucose	5	> 360

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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

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Parkes Survey

Meter range	Patient's actions	Actual value is in range	Degree of Risk
1	Emergency treatment for low BG	1, 2, 3, 4, 5	A, __ __ __ __
2	Take glucose	1, 2, 3, 4, 5	__ A, __ __ __
3	No action needed	1, 2, 3, 4, 5	__ __ A, __ __
4	Take insulin	1, 2, 3, 4, 5	__ __ __ A ,__
5	Emergency treatment for high BG	1, 2, 3, 4, 5	__ __ __ __ A

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Parkes Survey

Meter range	Patient's actions	Actual value is in range	Degree of Risk
1	Emergency treatment for low BG	1, 2, 3, 4, 5	A, B, B, C, D
2	Take glucose	1, 2, 3, 4, 5	B, A, B, C, D
3	No action needed	1, 2, 3, 4, 5	C, C, A, C, D
4	Take insulin	1, 2, 3, 4, 5	E, D, C, A, B
5	Emergency treatment for high BG	1, 2, 3, 4, 5	E, D, D, C, A

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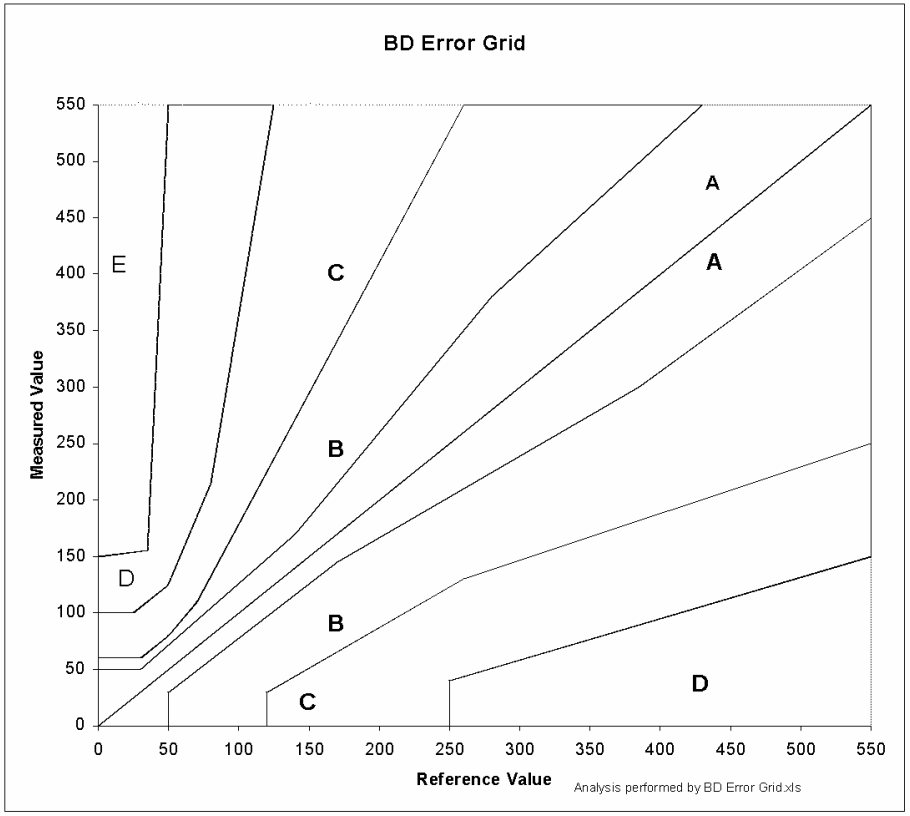
Parkes Error Grid



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Risk Controls

Design, Manufacturing and Testing Processes

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Risk Management Process

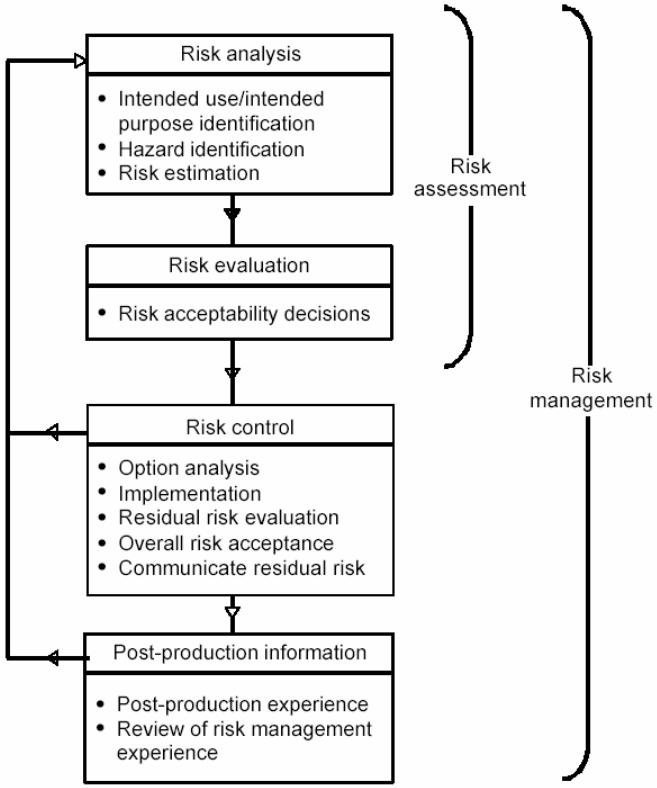

Figure 1 — A schematic representation of the risk management process for illustration

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Risk Reduction

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

ISO 14971

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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

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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

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Risk Control

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

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Risk Control

- First step: option analysis
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Risk Controls

Product	*Self-testing device*
Safe Design	*Accuracy insensitive to sample volume*
Protective Measure	*No result if insufficient sample volume*
Risk Communication	*Error message if sample volume insufficient*

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Risk Controls

Product	*Hepatitis assay*
Safe Design	*Reduce % of false negatives*
Protective Measure	*Calibrate cutoff point with each run*
Risk Communication	*Warning for false negative consequences*

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Risk Controls

Product	*Single Use Reagent Unit*
Safe Design	*Self destruction after use*
Protective Measure	*Obvious indication after first use*
Risk Communication	*Warning for consequences of reuse*

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Risk Control Options

Safety by Design (Product)

- Measurement precision
- Calibrator traceability
- Antibody specificity
- Detector sensitivity
- Analyzer reliability

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Risk Control Options

Safety by Design (Manufacturing)

- Automation
- Validated processes
- Validated test methods
- Six-sigma process capability

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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

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Risk Control Options

Protective Measures (Manufacturing)

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

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Risk Control Options

Protective Measures (Laboratory)

- QC system
- Delta checks
- Positive specimen identification
- Backup testing capabilities

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Risk Control Options

Risk Communication

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

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Risk Controls

Manufacturing / Testing Processes

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

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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

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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

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Thank you!

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