QUALITY AND ITS ROLE IN PRECLINICAL RESEARCH

MN ASQ MEETING - 4/11/17

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Further, Together

DEFINITION OF QUALITY

- The FDA has not published a definition of “quality”.

- Per Merriam-Wester: quality is the standard of something as measured against other things of a similar kind; the degree of excellence of something.

DEFINITION OF QUALITY

- The FDA has been pushing for a "complete quality system approach".
- The FDA defines a complete quality system approach as "the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management in the conduct of nonclinical laboratory studies".
- This is intended "to build quality into planning, conducting, and reporting a nonclinical laboratory study and to help ensure data quality and integrity".

*Source: Good Laboratory Practice for Nonclinical Laboratory Studies proposed rule change Docket No. FDA-2010-N-0548

KEY COMPONENTS OF A COMPLETE QUALITY SYSTEM

- Key components of a complete quality system:
  - Organization and personnel
  - Facilities
  - Equipment
  - Standard operating procedures
  - Test and control articles
  - Protocols & study conduct
  - Records and reports

*Source: Good Laboratory Practice regulations 21 CFR part 58

RISKS OF AN INADEQUATE QUALITY SYSTEM

1. FDA Action
2. Inefficient / Ineffective R&D System
3. Impact to the Customer

FDA Action

FDA ACTION

Enforcement Type	FY16 Summary Numbers
Seizures	4
Injunctions	17
Warning Letters	14590
Recall Events	2847
Recalled Products	8305
Drug Product Debarments	1
Food Importation Debarments	0

Source: FDA FY 2016 - Enforcements Statistics

FDA ACTION

Financial impact of FDA action:

- 483 Observation = $0.1 million
- Warning Letter = $1 million
- Recall = $2 million
- Consent Decree = $400 million

Source: McKinsey Center for Government - The Business Case for Medical Device Quality

FDA ACTION

Preclinical research warning letter analysis:

Table 3.--Deficiencies Found During GLP Inspections

Citation associated with	2006	2007	2008	2009	2010	2011	2012
Organizational or personnel inadequacies	48	36	30	46	38	50	54
Study reports or study records	29	20	19	35	19	14	15
Test article, equipment, mixtures, or reagents	25	29	9	15	11	12	11
SOPs	12	13	7	8	11	11	12
Study conduct	9	16	10	16	11	7	5
Protocol	16	2	5	6	4	1	3
Animal care	7	5	5	5	2	2	1

Source: TURBO Inspectional Observation Datasets of Bioresearch Monitoring (BIMO) GLP Inspections, Fiscal Years 2006-2012, http://www.fda.gov/ICECI/EnforcementActions/ucm250720.htm.

Source: RIA Good Laboratory Practice for Nonclinical Laboratory Studies proposed rule change Docket No. FDA-2010-N-0548

FDA ACTION

5 Immeasurable Costs of a Warning Letter

1. **Reputation Damage** – Publicly posted warning letters are the leading cause of reputation damage among Pharmaceutical, Biotech, and Medical Device companies.
2. **Competitor Leverage** – Competitors will utilize a company's mistake to enhance their own market position.
3. **Loss of Business** – Warning letters can affect contracts, both new and current.
4. **Stockholder Confidence** – Shareholders will lose confidence in a company that receives a warning letter or 483.
5. **Diversion away from jobs** – Warning letters divert management and other personnel's attention, away from their daily activities, to work to correct the errors and avoid possible litigation.

Source: Blue Mountain Quality Resources

Inefficient / Ineffective R&D System

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INEFFICIENT / INEFFECTIVE R&D SYSTEM

Cost of product development

- The average cost to bring a low-to-moderate 510(k) product from concept to market is $31 million.
- High-risk PMA costs averaged $94 million.

Source: FDA Impact on U.S. Medical Technology Innovation

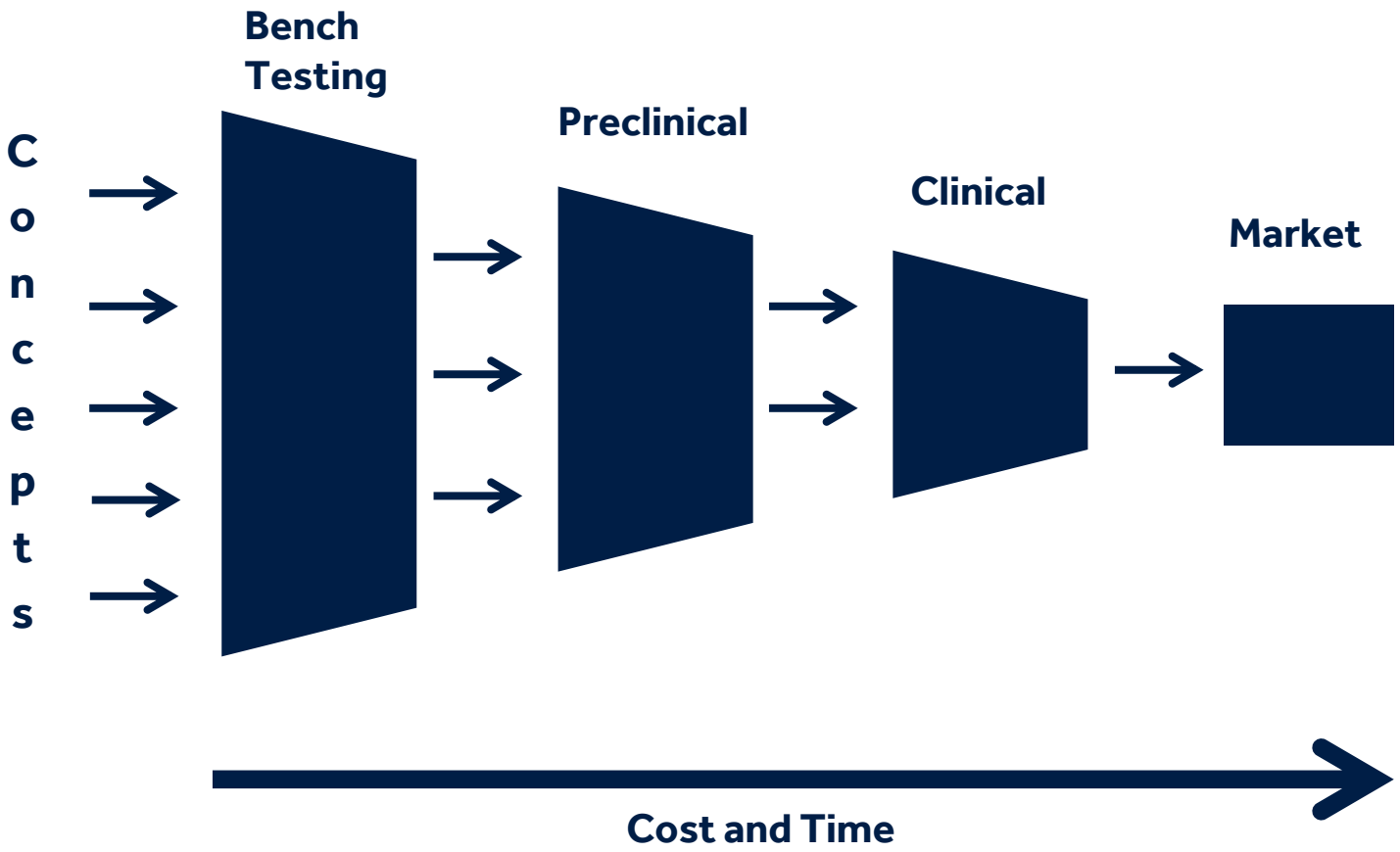
INEFFICIENT / INEFFECTIVE R&D SYSTEM

Quality is key to "Failing Fast"

- A fail-fast system is one which immediately reports any condition that is likely to indicate a failure.
- A complete quality system is intended to "**ensure data quality and integrity**".
- Information that is lacking quality or integrity can lead to incorrect conclusions.
- Incorrect conclusions can mean shelving viable projects or sending non-viable projects further down the R & D process.

INEFFICIENT / INEFFECTIVE R&D SYSTEM

R & D cycle



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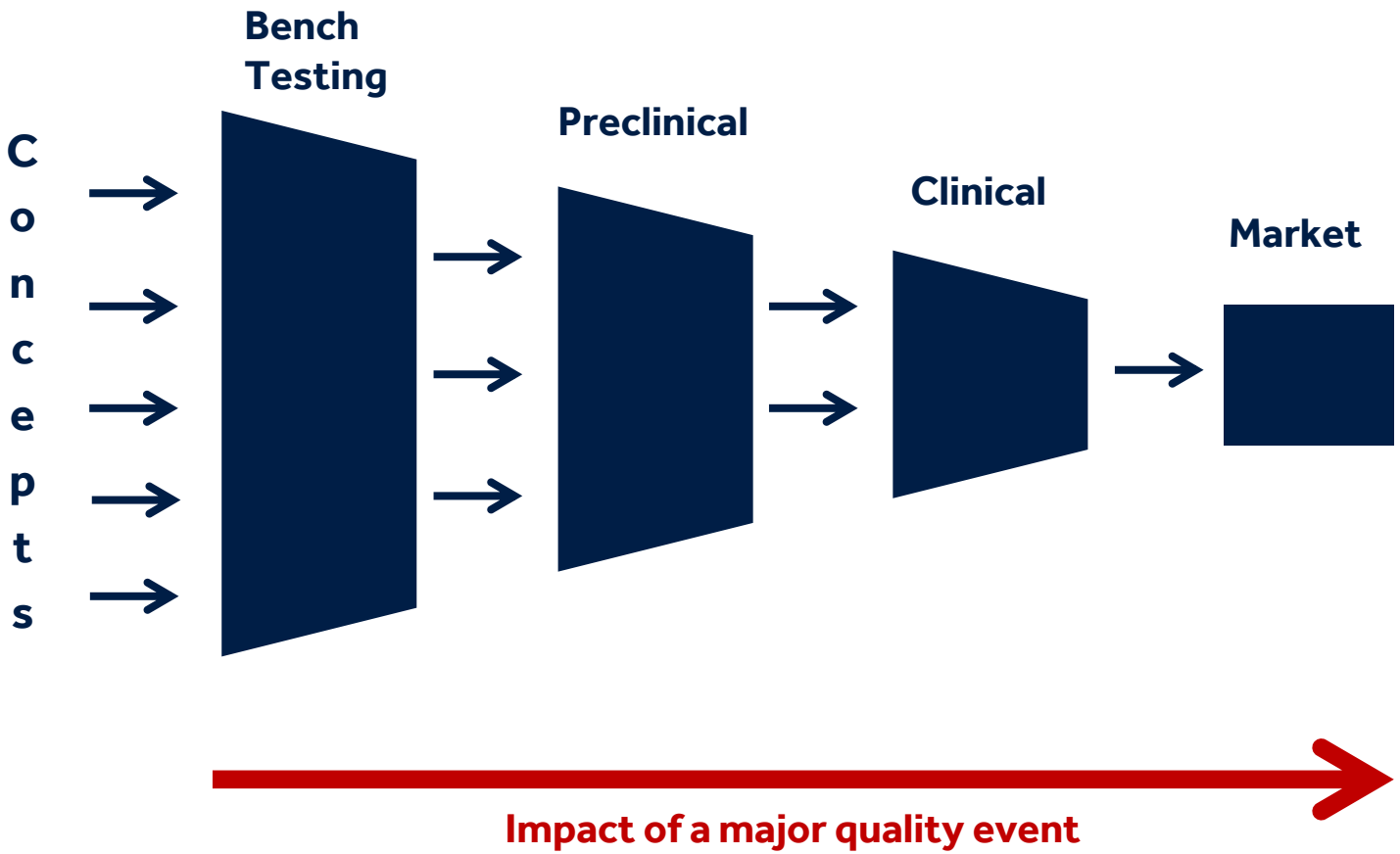
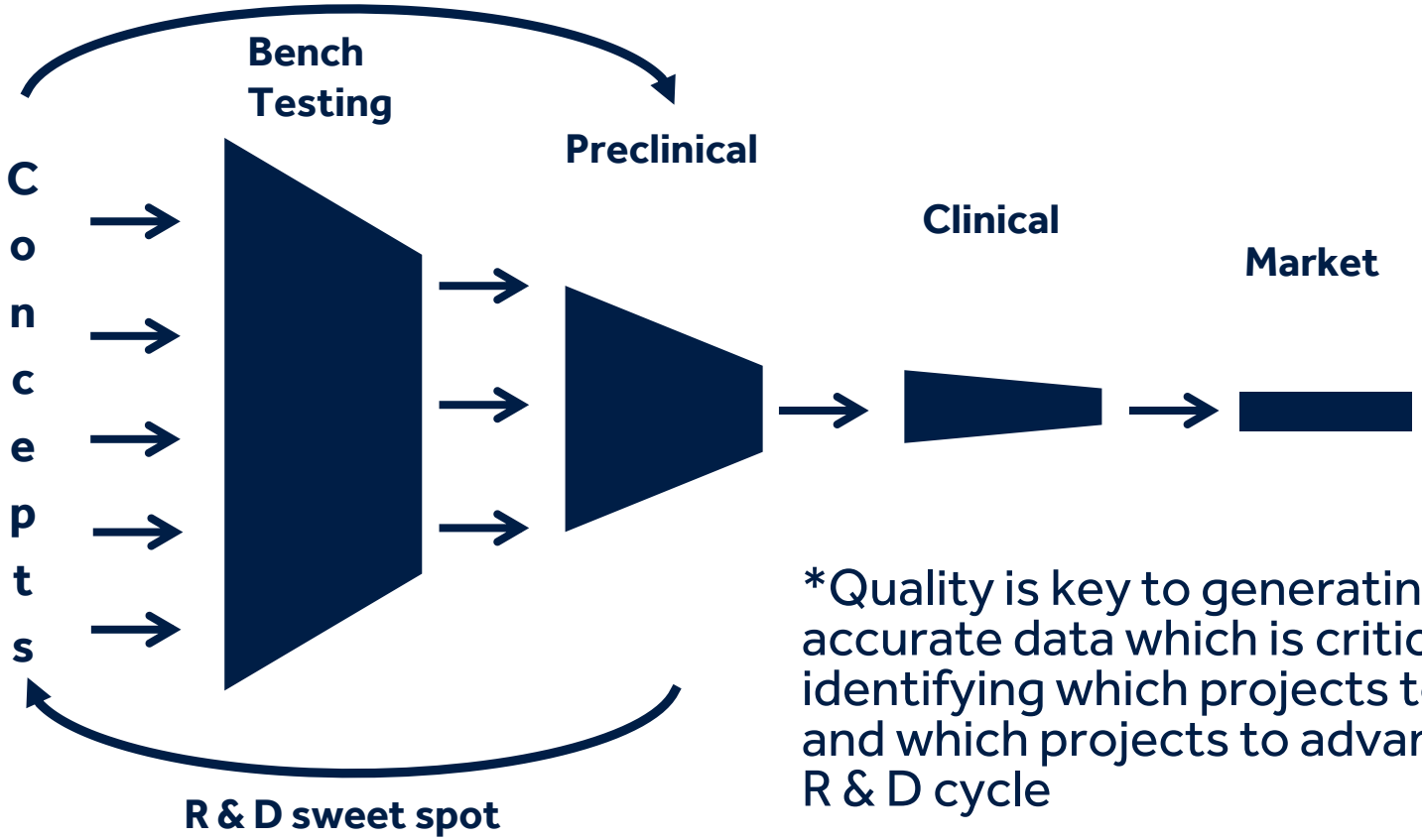
INEFFICIENT / INEFFECTIVE R&D SYSTEM

R & D cycle



INEFFICIENT / INEFFECTIVE R&D SYSTEM

Quality driven R & D cycle



*Quality is key to generating reliable, accurate data which is critical in identifying which projects to shelve and which projects to advance in the R & D cycle

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INEFFICIENT / INEFFECTIVE R&D SYSTEM

Examples of quality events*: Unqualified personnel performing work

- Human surgeon performing device implants in animals.
- Implant was not performed correctly due to animal model anatomical differences.
- Data from the study did not represent the actual performance of the device.
- Issues were not discovered until the clinical trial.
- Impact would be greater if clinical trials were skipped and animal model data was used for submission. Looking at a recall event.

*All examples of quality events in this presentation are hypothetical.

INEFFICIENT / INEFFECTIVE R&D SYSTEM

Examples of quality events: Lack of equipment calibration

- Critical data was collected on an non-calibrated or non-validated system.
- The data collected was not accurate.
- Incorrect conclusions were drawn from the data on the safety and performance of the device.
- Actual performance was not discovered until further into the R & D cycle (GLP study or clinical study).

INEFFICIENT / INEFFECTIVE R&D SYSTEM

Examples of quality events: Lack of test and control article characterization

- Test article evaluated was version 1.0.
- There was a lack of test article characterization documentation.
- Substantial changes to the test article design were made after the study was initiated.
- Data was acquired and submitted for test article version 3.0 even though the data did not accurately represent that version.
- Oversight discovered in submission process, submission stalled.

INEFFICIENT / INEFFECTIVE R&D SYSTEM

Examples of quality events: Data integrity issues

- Critical safety data was collected but was not verified as accurate or complete.
- Data was submitted to a qualified statistician and analyzed.
- Safety conclusions were drawn from the data and submitted to the FDA.
- Upon review of the data during FDA audit, several data sets were found to have data integrity issues: data misattributed to the wrong test system, incomplete data sets, data revisions without traceability.
- Possible 483.

Impact to the Customer

IMPACT TO THE CUSTOMER

Recalls impact patient lives.

Most Commonly Recalled Products:

Recalls	Pro code	Product description	Specialty
176	IYE	ACCELERATOR, LINEAR, MEDICAL	Radiology
153	LLZ	SYSTEM, IMAGE PROCESSING, RADIOLOGICAL	Radiology
130	FRN	PUMP, INFUSION	Gen Hospital
115	JAK	SYSTEM, X-RAY, TOMOGRAPHY, COMPUTED	Radiology
109	MKJ	AUTOMATED EXTERNAL DEFIBRILLATORS	Cardiovascular
106	GEI	ELECTROSURGICAL, CUTTING & COAGULATION & ACCESSORIES	Surgery
101	JJE	ANALYZER, CHEMISTRY, FOR CLINICAL USE	Chemistry
98	JQP	CALCULATOR/DATA PROCESSING MODULE, FOR CLINICAL USE	Chemistry
97	GKZ	COUNTER, DIFFERENTIAL CELL	Hematology
96	JWH	PROSTHESIS, KNEE, PATELLOFEMOROTIBIAL, SEMI-CONSTRAINED	Orthopedic

Source: FDA Medical Device Recall Report FY2003 to FY2012

IMPACT TO THE CUSTOMER

Recall summary:

Number	Regulation Subpart Title	Class I	Class II	Class III
820.30	Design controls and related subparts	703	1,759	36
820.80	Receiving, in-process, and finished device acceptance	204	1,068	61
820.70	Production and process controls and subparts	119	830	58
820.90	Nonconforming product	17	415	28
820.75	Process Validation	16	390	30
820.50	Purchasing controls	19	366	29
820.130	Device packaging	0	377	5
820.120	Device labeling and related subparts	2	271	29
820.25	Personnel	0	159	2
820.100	Corrective and preventive action	0	122	7

- **R&D activities are in this category**

Source: FDA Medical Device Recall Report FY2003 to FY2012

IMPACT TO THE CUSTOMER

Concept of do no harm.

Our customer base includes our parents, spouses, children, friends and even ourselves.

Earl Bakken, founder of Medtronic:

"Earl also benefits from medical technology. He openly acknowledges that his pacemaker, insulin pump and heart stents have given him 10+ years of "extra life," time he has put to good use, with heavy community involvement in both Minnesota and Hawaii."

Source: The Inspiration - Earl Bakken's legacy and the inspiration behind the Bakken Invitation Award.

SUMMARY & DISCUSSION

Quality is critical to an effective preclinical research program

- Reduces the likelihood of FDA actions.
- Improves the efficiency and effectiveness of the R & D program.
- Protects our customers.

- **The cost of a quality event greatly outweighs the cost of building quality in from the start.**

SUMMARY & DISCUSSION

Thank you for your time

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