Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Introduction to Data Integrity

IPA Advanced GMP Workshops, India, November 2017


FDA Warns Two Chinese Drugmakers for Data Integrity Violations
Frogs, fungus and falsified data - Indian firm falls foul of US FDA
EU Bans Non-Compliant Active Ingredients from a Pfizer Site
The guidance is out there.
FDA Cites Another Company for Data Integrity Violations
So why are companies struggling?
The strife of Pii: UK MHRA finds GMP deviations at two facilities
India Ratings revises Marksans Pharma's Outlook to Negative; affirms 'IND A'
EMA Recommends Suspending Alkem Drug Over Flawed Studies
Detail
FDA Warning Letter Slams Another Asian API Firm On Data Integrity

Data integrity:

The extent to which all data are complete, consistent and accurate throughout the data lifecycle.

International history

- Publicised data integrity failures date back to early 2000’s
- 2013: increased focus on data integrity
  - Increasing failures identified
  - Change in regulatory approach.

Has increased focus solved the problem?

- No……

- In 2015:
  - 35% EU ‘statements of non-compliance’ for Data Integrity
  - Significant number of USFDA Warning Letters
  - MHRA inspection findings*:
    - 121 Major, 218 Other deficiencies had references relevant to DI
    - 20 Major DI deficiencies in regulatory action cases
    - 10 Major DI deficiencies under compliance management.

(* Dosage form inspections Jan-Oct 2015)

Why is data integrity still an issue?

- Nothing new
  - Requirements in place for many years
  - No change in basic data expectations
    - **A**ttributable
    - **L**egible
    - **C**ontemporaneous
    - **O**riginal
    - **A**ccurate.

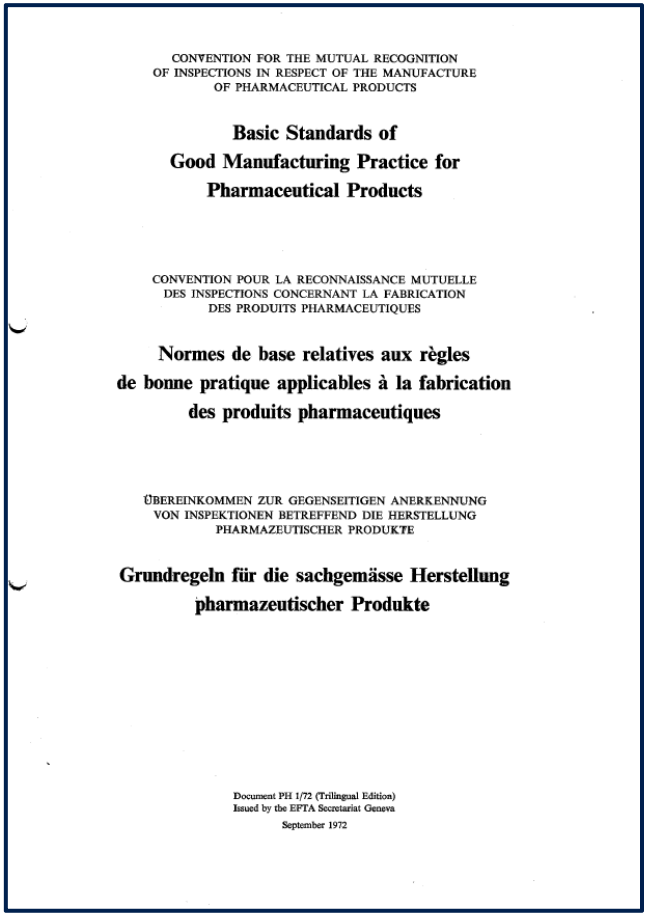
Existing PIC/S GMP requirements

	Basic Requirements for Medicinal Products (Part I): Chapter 4 (June 2011) Chapter 6 (October 2014)	Basic Requirements for Active Substances used as Starting Materials (Part II): Chapter 6 / Chapter 5 (Sept 2014)	Annex 11 (Computerized Systems) (June 2011)
Attributable	[4.20], [4.21, c & i], [4.29, e]	[6.14], [6.18], [6.52]	[2], [12.4], [15]
Legible	[4.1], [4.2], [4.7], [4.8], [4.9], [4.10]	[5.43] [6.11], [6.14], [6.15], [6.50]	[7.1], [9], [10], [17]
Contemporaneous	[4.8]	[6.14]	[12.4], [14]
Original	[4.9], [4.27], [Paragraph "Record"]	[6.14], [6.15], [6.16]	[8.2], [9]
Accurate	[4.1], [6.17]	[5.40], [5.45], [6.6]	[Paragraph "Principles"], [5], [6], [10], [11]

Historical expectations

PIC/S GMP Guide 1972:

- '[copies of master documents]….which avoids transcription error….'
- records enabling recreation of batch history
- 'all records shall be legibly written….and traceable'
- 'dated signature of the persons who performed each activity'



CONVENTION FOR THE MUTUAL RECOGNITION
OF INSPECTIONS IN RESPECT OF THE MANUFACTURE
OF PHARMACEUTICAL PRODUCTS

Basic Standards of
Good Manufacturing Practice for
Pharmaceutical Products

CONVENTION POUR LA RECONNAISSANCE MUTUELLE
DES INSPECTIONS CONCERNANT LA FABRICATION
DES PRODUITS PHARMACEUTIQUES

Normes de base relatives aux règles
de bonne pratique applicables à la fabrication
des produits pharmaceutiques

ÜBEREINKOMMEN ZUR GEGENSEITIGEN ANERKENNUNG
VON INSPEKTIONEN BETREFFEND DIE HERSTELLUNG
PHARMAZEUTISCHER PRODUKTE

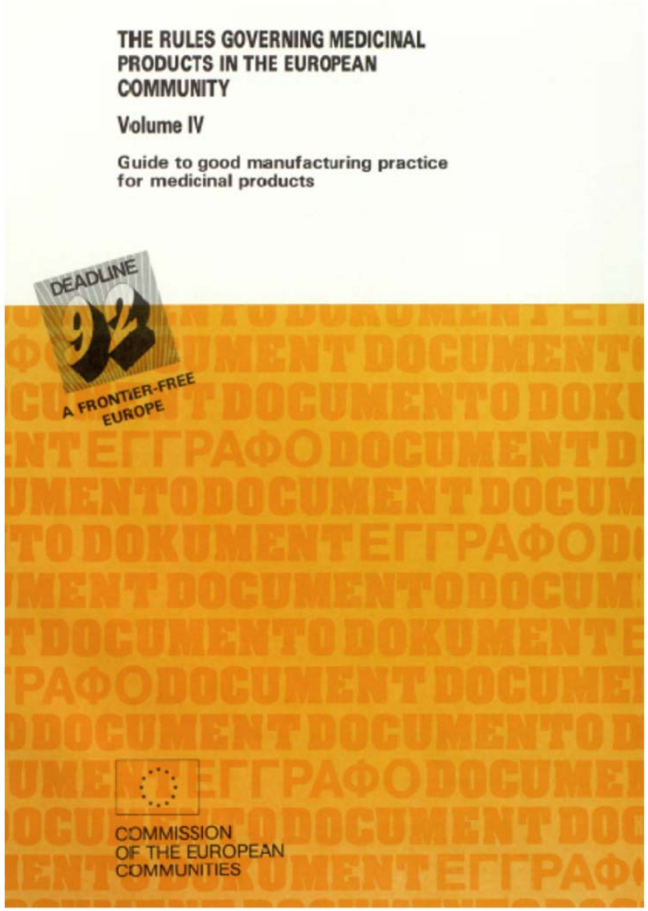
Grundregeln für die sachgemässe Herstellung
pharmazeutischer Produkte

Document PH 1/72 (Trilingual Edition)
Issued by the EFTA Secretariat Geneva
September 1972

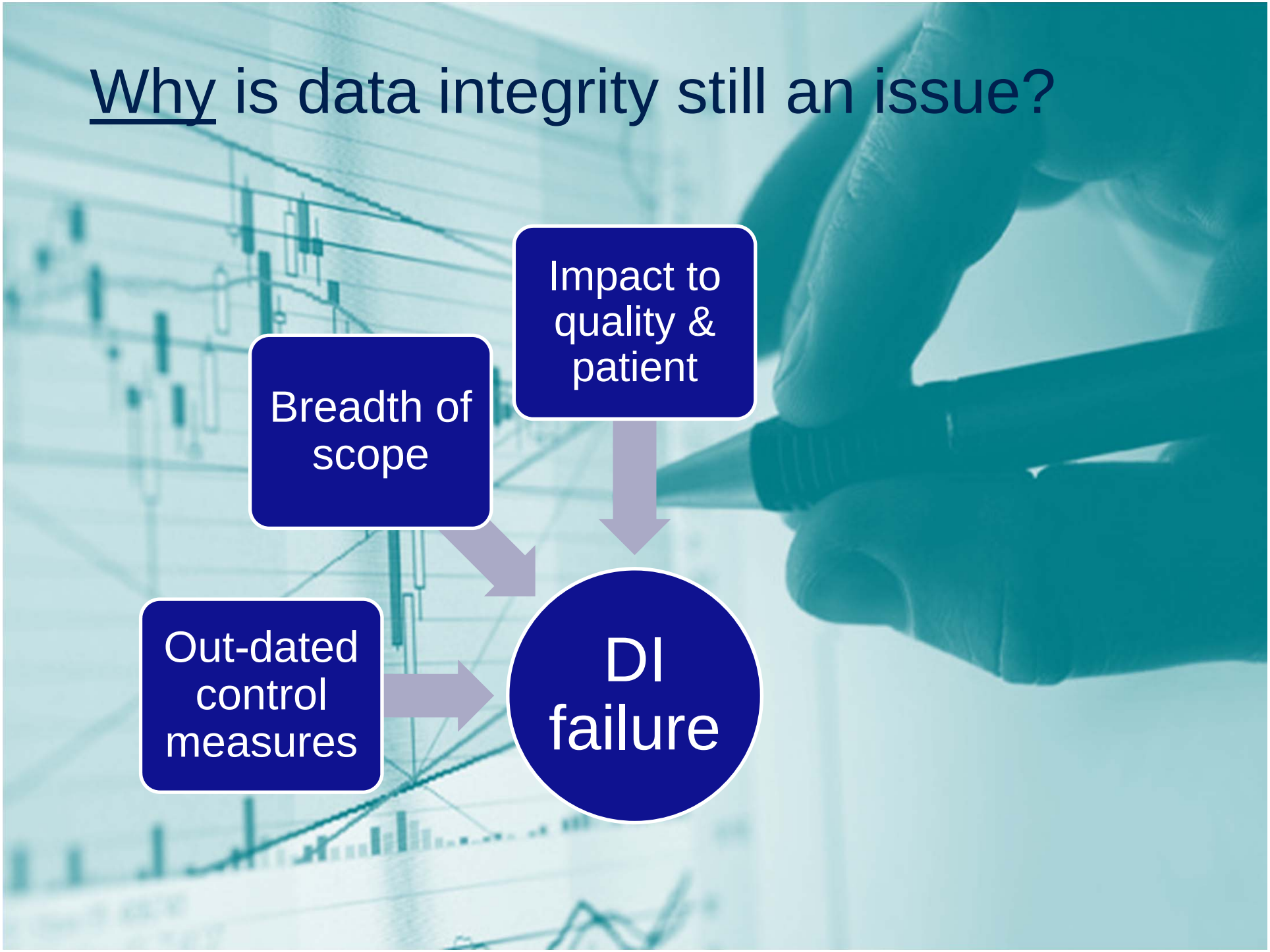
Historical expectations

EU GMP January 1989:

- "…entries made in clear indelible handwriting…."
- "[alterations]…signed and dated….permit reading of original….reason recorded"
- " …records completed at the time each action taken..."
- "…accuracy of records should be checked…"
- "…name of persons carrying out activities…".



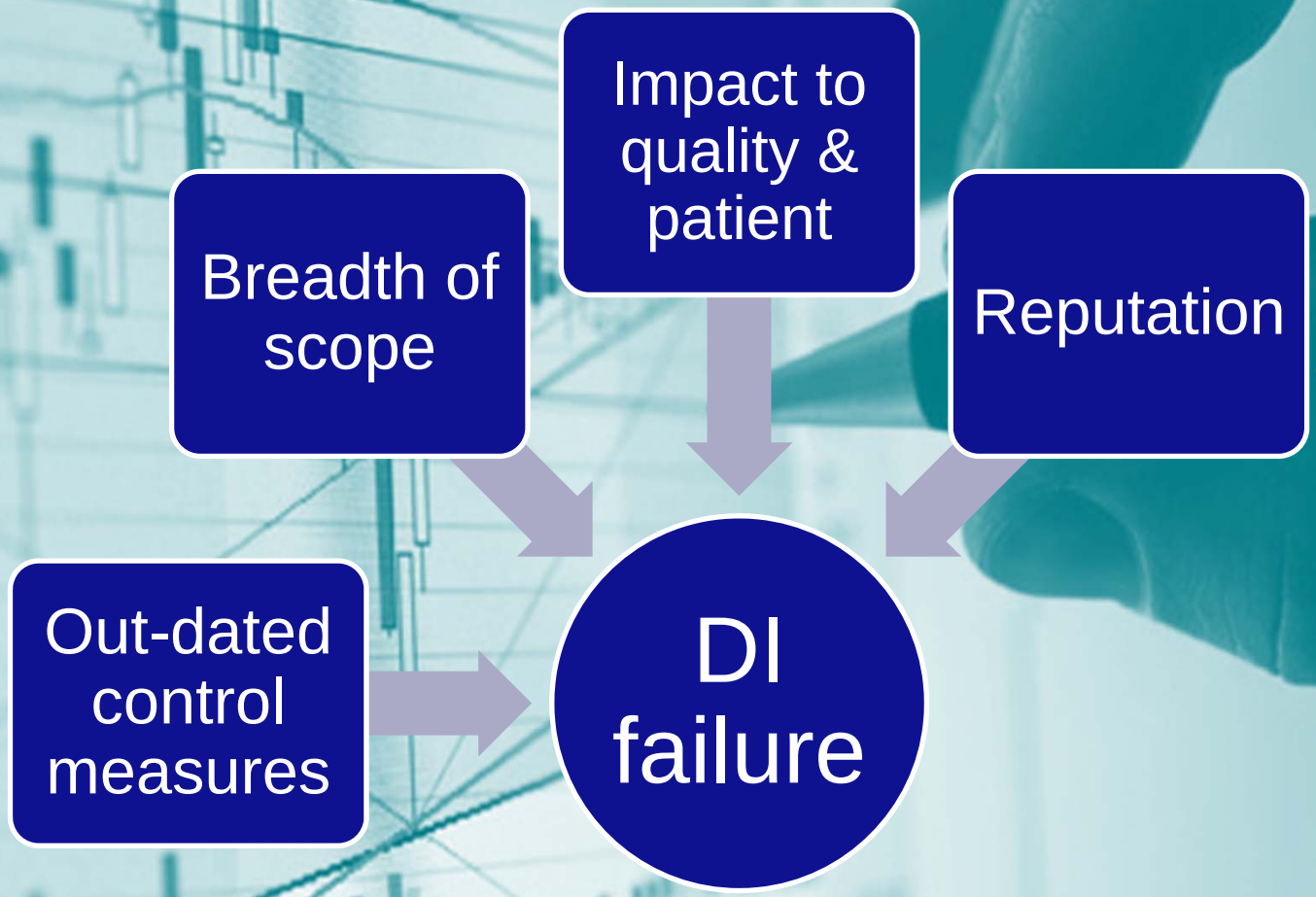
Why is data integrity still an issue?



Impact to quality and patient

- Important daily decisions regarding safety, efficacy and quality of medicines are based on data
- Unreliable data is a significant barrier to providing safe and effective medicines
  - “Precision guesswork”
- Safety / efficacy risks from substandard or falsified medicines.

Why is data integrity still an issue?



DI failure vs defect: reputational impact

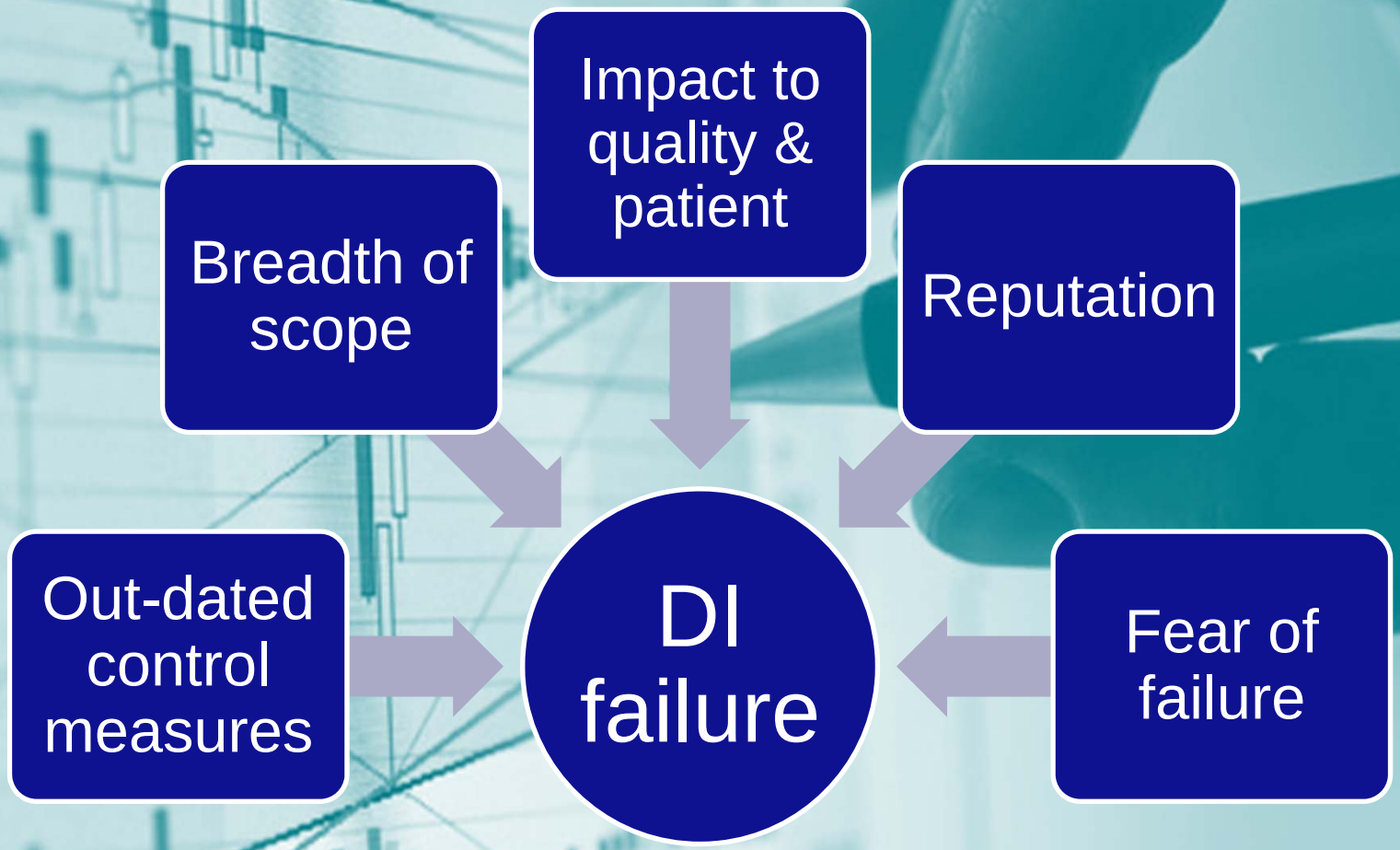
Alleged falsification of emissions data

- €26bn (~20%) loss in share value
- 4.8% global reduction in 2015 sales; first drop in 11 years
- (General Motors increased 8%)
- €1bn cut in investment

Software fault: engine stops and all electrics fail while vehicle in motion

- 59,000 cars recalled in 40 markets
- Transient impact to share price (-3%)
- Share price continues upward trend.

Why is data integrity still an issue?

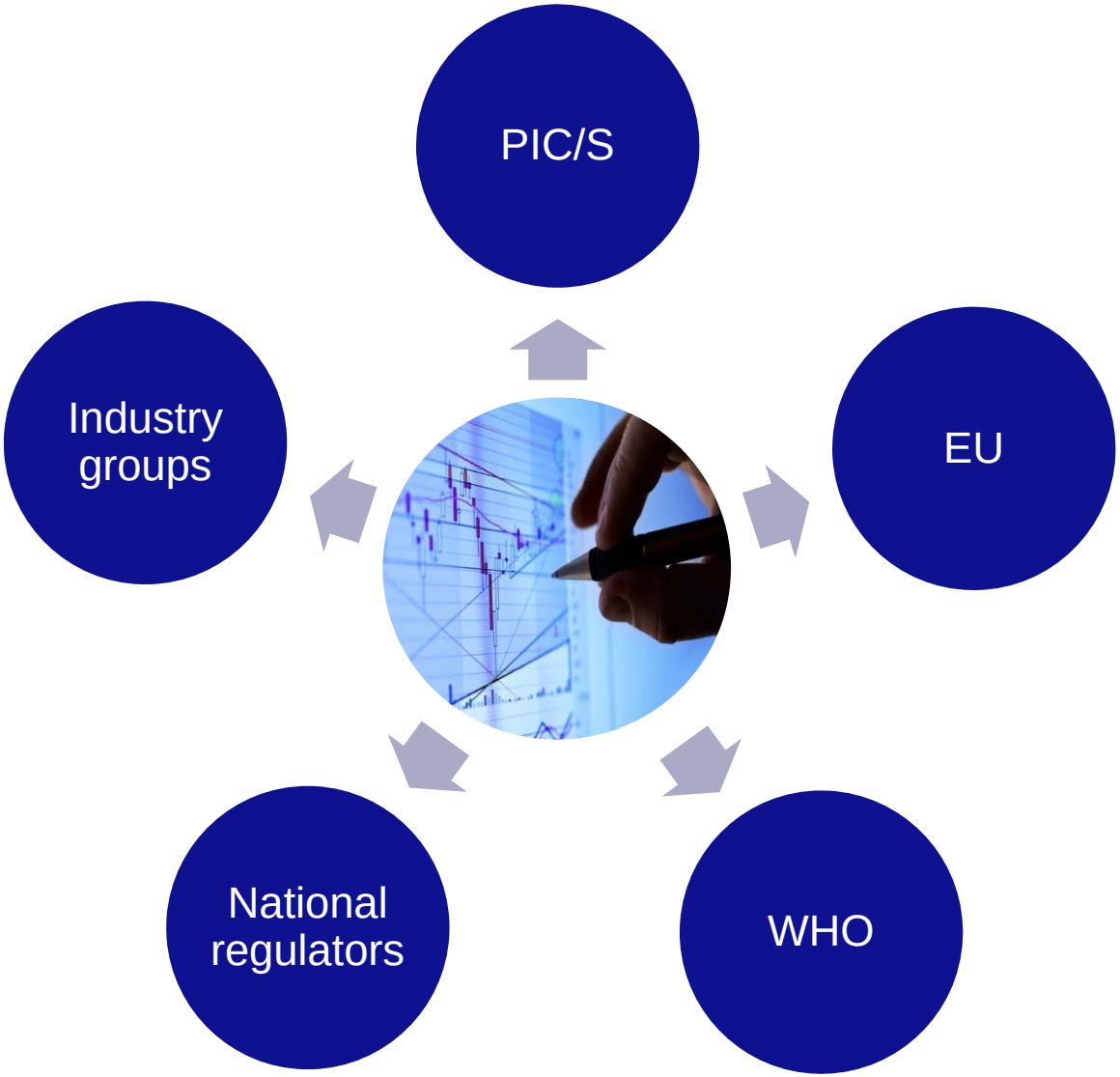


DI failure: Fear of failure

- Causes the wrong behaviour
  - Panic
  - Disproportionate management action: ‘zero tolerance’
- Complexity of proposed remediation
  - Aspirations vs action
- Quality Risk Management approach
  - Risk identification, mitigation and communication
  - Balanced with other GMP priorities
  - Perfection is a barrier to progress.

International regulatory collaboration

International data integrity collaboration



International data integrity collaboration

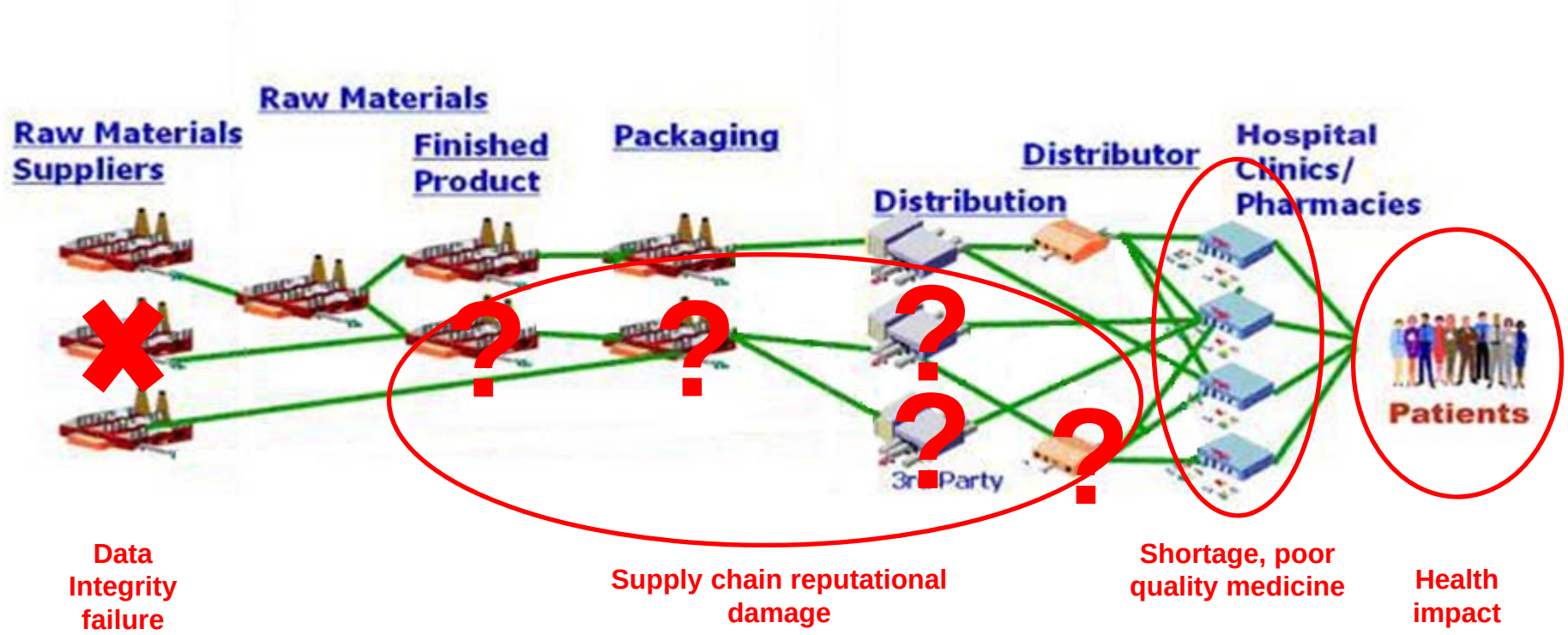
- International convergence in data integrity standards
- Inspectorates better equipped to:
  - Identify data integrity failures
  - Manage post-inspection actions and remediation plans
- Cooperation between international regulators
  - Shared / common training
  - Exchange of information
  - Joint inspections
  - Coordinated market actions.

MHRA actions

- Continuing work
  - Inspections
  - Training (Inspectorate)
  - Regulatory capacity-building with PIC/S, WHO
  - Education and guidance documents (Industry)
    - Blog
    - GMP guidance published Q1 2015
    - GxP guidance in draft
  - Encouraging a reporting culture between Industry and Regulators.

Data Integrity in the Global Supply Chain

Supply chain:
Influence of others around me



Supply chain: data integrity considerations

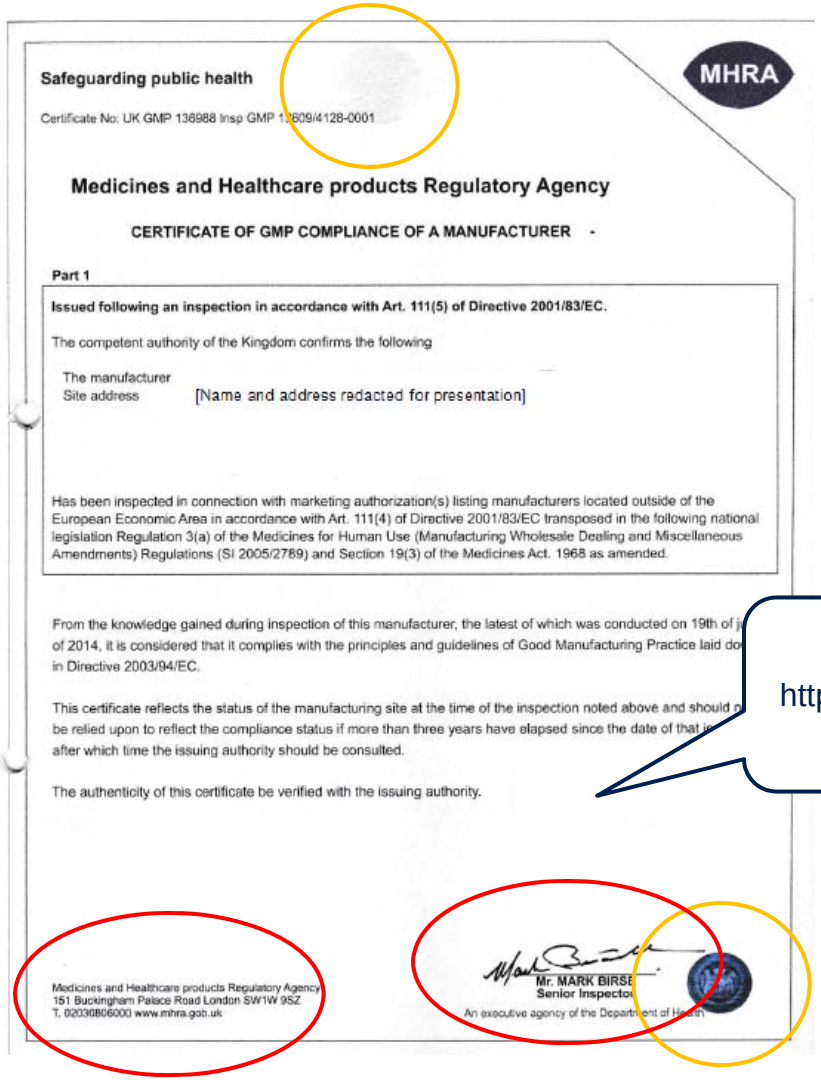
- Global supply chain requires a global approach to data governance
  - Interaction between contract giver and acceptor
  - Verifying equivalence of data management systems
  - Challenges of remote data verification.

Supply chain: can we trust summary reports?

- Audit / self inspection scope - focus on data integrity
  - Summary documents can be reviewed off line
  - Capacity vs output
  - Where contracts permit, perform horizontal checks
    - Across batches, across products

- What is the company's approach:
  - Data lifecycle and risk management
  - Data governance.

Regulators are also affected…….



Safeguarding public health

MHRA

Certificate No: UK GMP 136988 Insp GMP 13609/4128-0001

Medicines and Healthcare products Regulatory Agency

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER -

Part 1

Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC.

The competent authority of the Kingdom confirms the following

The manufacturer
Site address [Name and address redacted for presentation]

Has been inspected in connection with marketing authorization(s) listing manufacturers located outside of the European Economic Area in accordance with Art. 111(4) of Directive 2001/83/EC transposed in the following national legislation Regulation 3(a) of the Medicines for Human Use (Manufacturing Wholesale Dealing and Miscellaneous Amendments) Regulations (SI 2005/2789) and Section 19(3) of the Medicines Act. 1968 as amended.

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 19th of j
of 2014, it is considered that it complies with the principles and guidelines of Good Manufacturing Practice laid do
in Directive 2003/94/EC.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should n
be relied upon to reflect the compliance status if more than three years have elapsed since the date of that in
after which time the issuing authority should be consulted.

The authenticity of this certificate be verified with the issuing authority.

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Mr. MARK BIRSE
Senior Inspecto

An executive agency of the Departm

Verify authenticity at:
http://www.eudragmdp.ema.europa.eu/

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