



Patient Safety: Importance of Data Integrity in ensuring quality of medicine

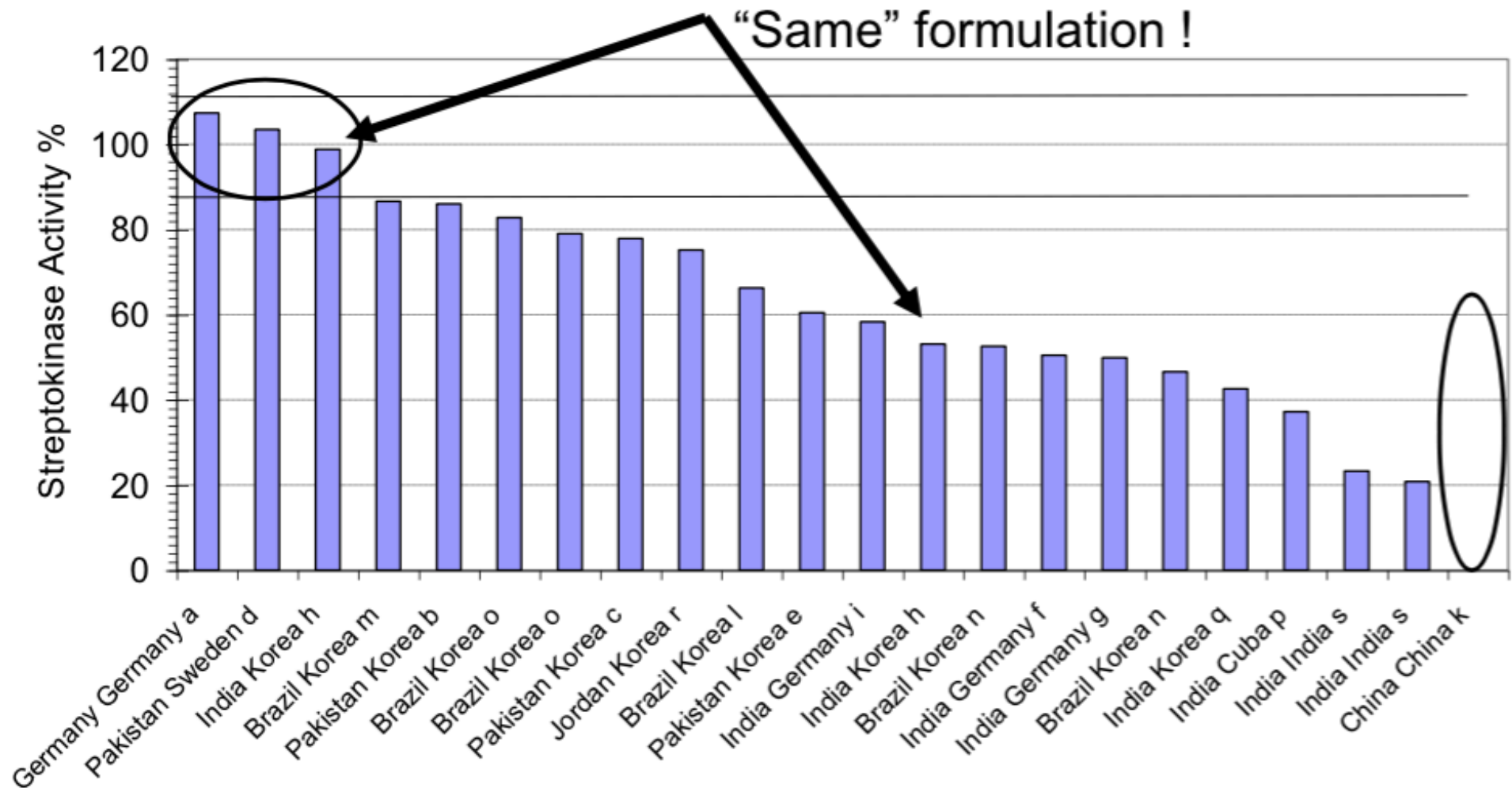
Dinesh S Thakur
Executive Chairman

Context & Agenda



- Data Integrity – why does it matter?
- Real cost of breach of data integrity
- Why does it take so long to fix this problem?
- Closing thoughts

Streptokinase activity



Hermintin et al, European Heart Journal (2005) 26, 933-940

100% of Ergometrine tablets fail assay



POST-MARKET QUALITY SURVEILLANCE PROJECT MATERNAL HEALTHCARE PRODUCTS (OXYTOCIN AND ERGOMETRINE) ON THE GHANAIAAN MARKET REPORT OF FIRST ROUND

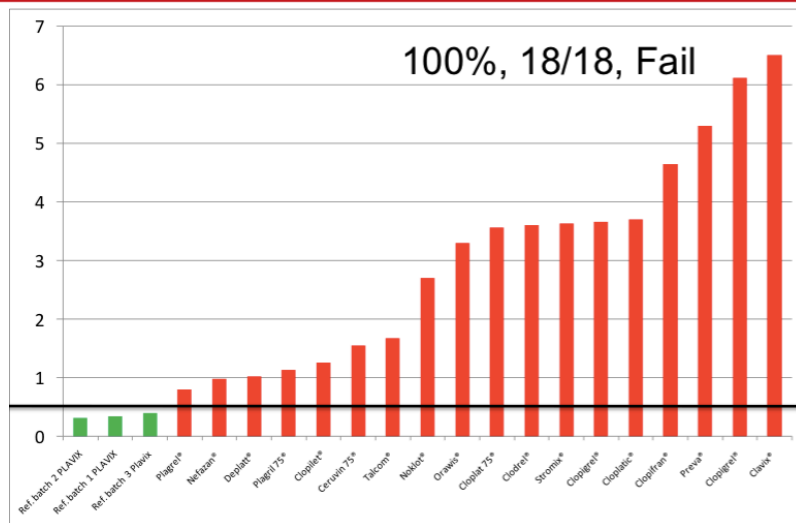


Post-marketing quality surveillance was carried out to assess the quality of uterotonics (Oxytocin and Ergometrine) on the Ghanaian market between August and September 2012. A total of 303 samples— 185 Oxytocin injection, 103 Ergometrine injection, and 15 Ergometrine tablets—were sampled from both public and private hospitals, clinics, medical stores, pharmaceutical outlets, and the informal sector across the ten regions of Ghana.

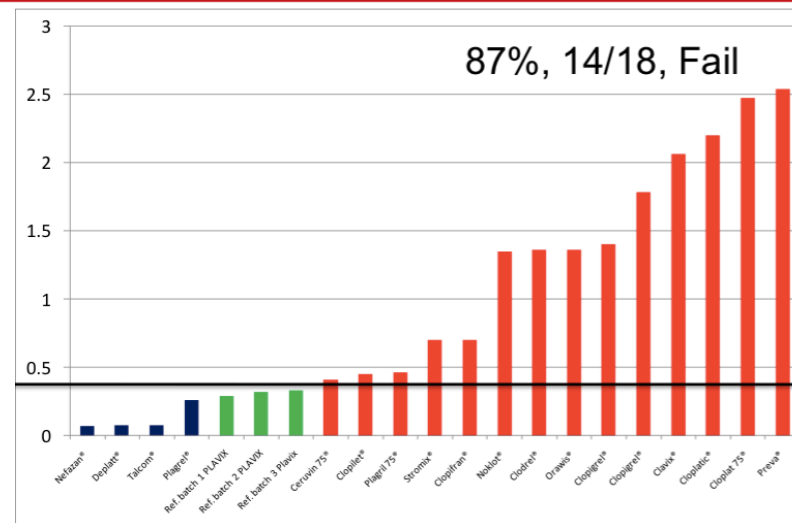
Eighty-six percent (86%) of the Oxytocin samples found on the market were manufactured in China, whereas 90.68% of Ergometrine samples were manufactured in India. Of those collected and tested, 8.11% of Oxytocin samples and 57.63% of Ergometrine samples had been issued marketing authorizations: Two companies supplying Oxytocin and one company supplying

Out of the 169 Oxytocin samples assayed, 55.62% failed. Of the 99 Ergometrine injection samples, 73.74% failed, and all of the 11 (100%) Ergometrine tablets tested failed assay. Two (2) samples of Oxytocin injection and three (3) samples of Ergometrine tablets (two of the three Ergometrine tablets had the same batch number) were determined to be counterfeit products.

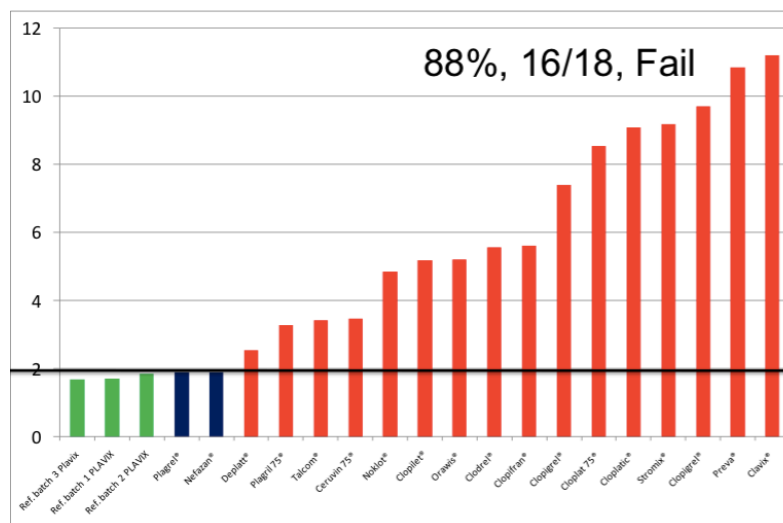
Generic Clopidogrel



R-isomer



Hydrolysis Product



Total Impurities

Analysis of Purity in 19 drug product tablets containing Clopidogrel: 18 copies vs the original brand
Gomez et al., Journal of Pharmaceutical and Biomedical analysis, 34 (2004) 341-348

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Impact of excipients



Table 2 Comparison of selected parameters for proprietary versus nonproprietary fingolimod

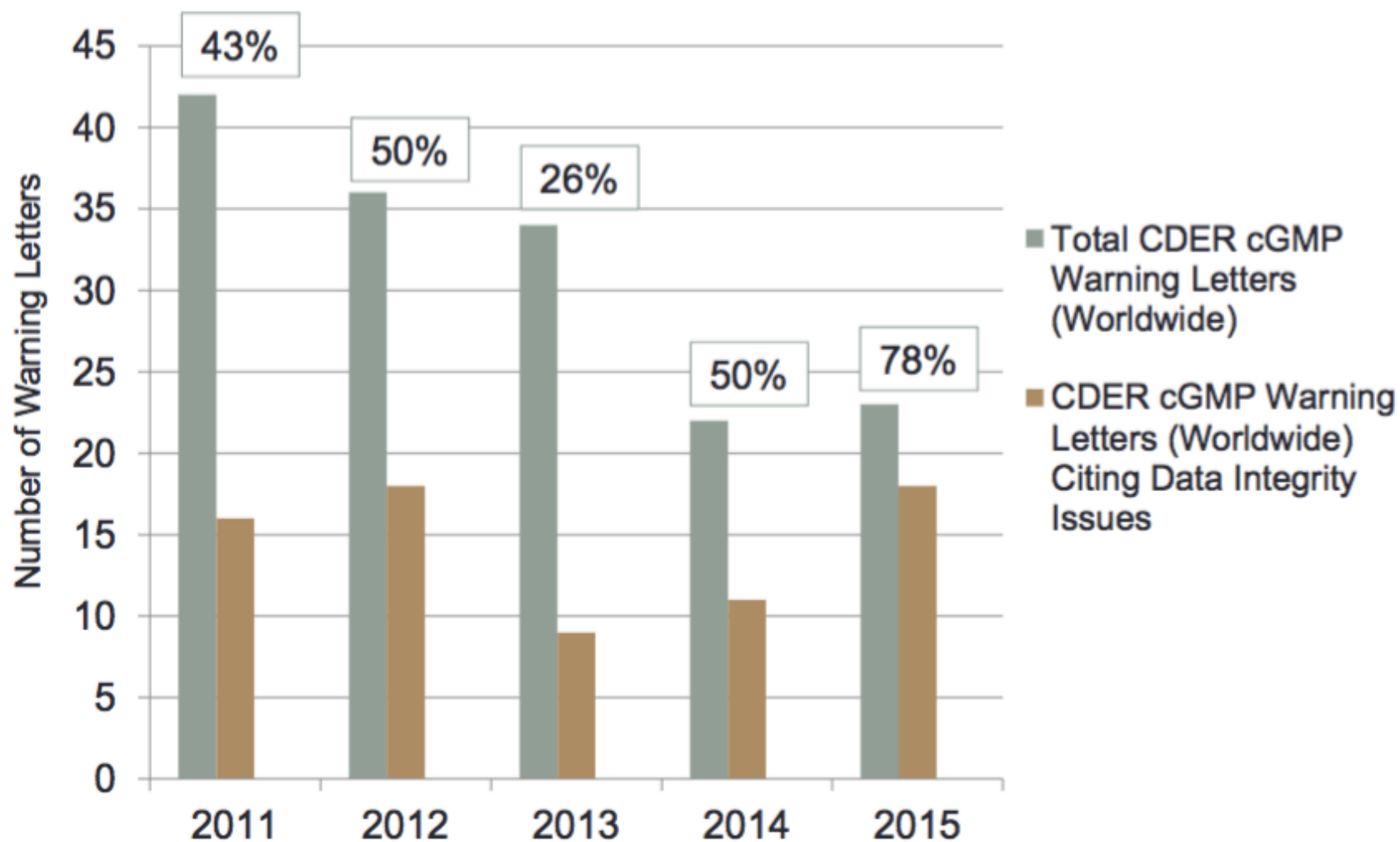
Parameter	Specification (source)	Nonproprietary fingolimod (%)	Proprietary fingolimod (%)
Assay fingolimod (HPLC)	90.0%–105.0% (proprietary specifications; USP generally acceptable: 90.0%–110.0% for oral drug products)	93.11	96.4
Individual unspecified degradation product (HPLC)	Not >0.5% (proprietary and ICH specifications)	7.575	<0.1
Total degradation products (HPLC)	Not >3.5% (proprietary specifications)	9.44	2.55
Content uniformity fingolimod (HPLC)	AV ≤15.0% at level 1 (Ph Eur, USP, JP)	AV 14.4	7.5
Dissolution rate fingolimod after 30 minutes (HPLC)	80% of the declared content (proprietary specifications)	92	96

Note: Data from Novartis Pharma AG, Basel, Switzerland (unpublished data, 2015).

Abbreviations: AV, acceptance value; HPLC, high-performance liquid chromatography; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use specifications; JP, Japanese Pharmacopeia specifications; Ph Eur, European Pharmacopeia specifications; USP, United States Pharmacopeia specifications.

Clinical implications of substandard, non-proprietary medicines in multiple sclerosis : focus on fingolimod, J. Correale et al. Drug Design, Development & Therapy, V10, 2109-2117, 2016

Breach of DI in warning letters



Data Integrity Continuum



Ignorance



Sloppiness



Intentional
Falsification



Outright lies

cGMP regulations do not require determining intent while assessing Data Integrity. Therefore, US FDA observations on Form-483 do not make a distinction between ignorance, sloppiness and malfeasance.

Without a understanding of the TRUE understanding of the root-cause for human misbehavior, companies are taking widespread actions which may not help address the problem in the least.

Unintended Error

Deliberate Falsification

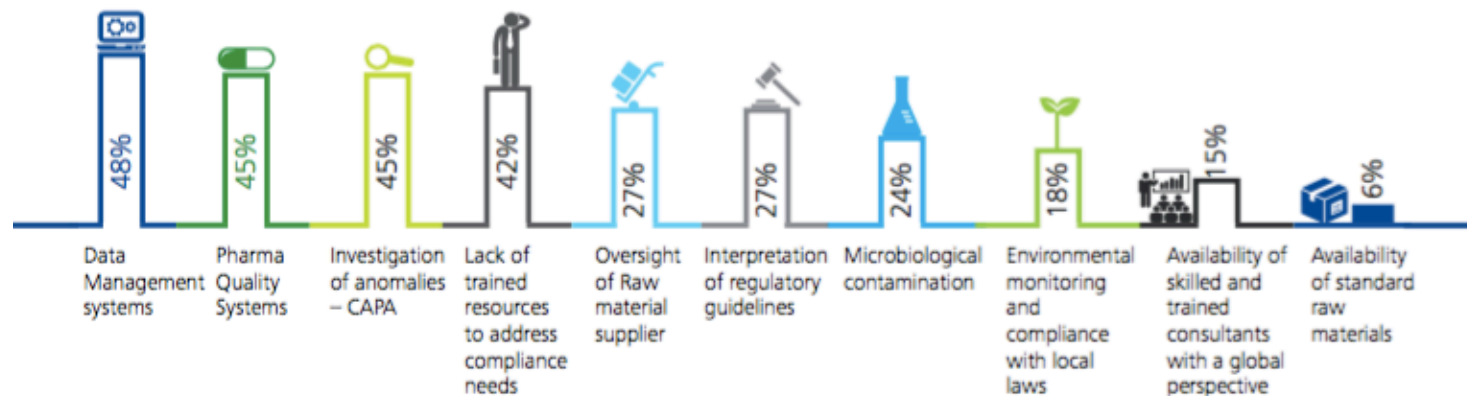
Do we have the right diagnosis?



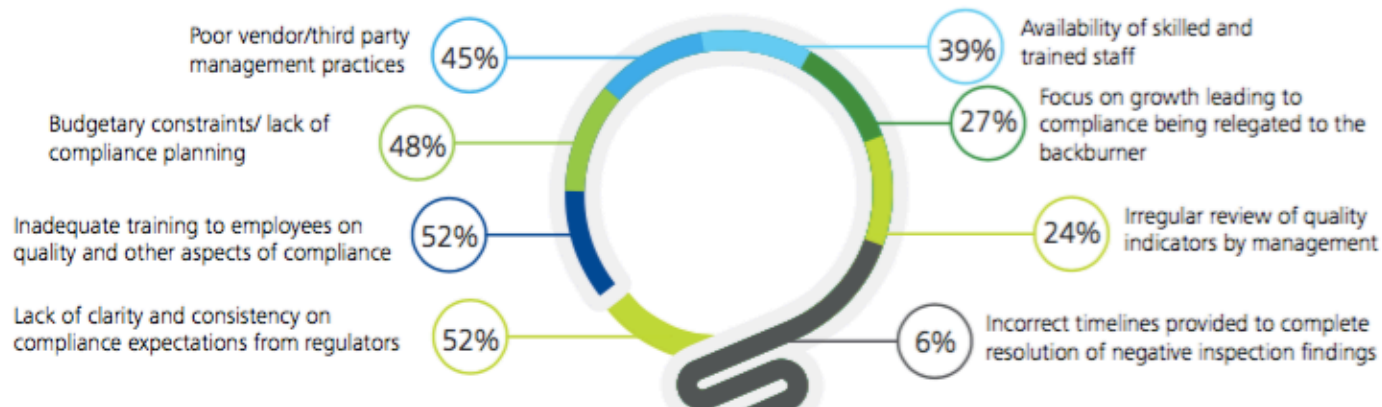
Here is one perspective



Key Concerns in Compliance Management



Difficulties in managing quality related compliance requirements



Source: Deloitte, Managing growth though better compliance management, June 2015

Lets look at it from a different perspective



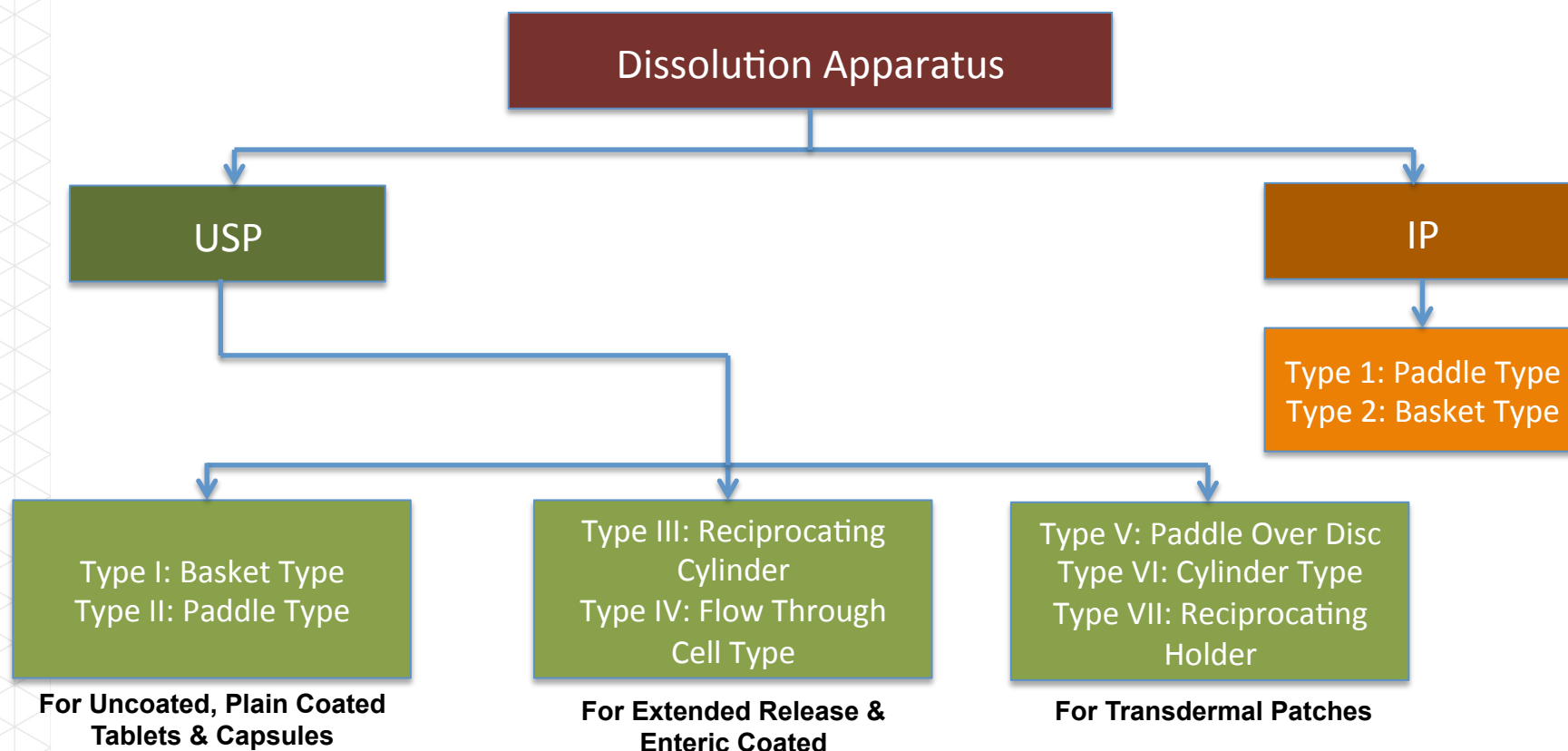
Total Samples Notified by CDSCO as Defective=67	
Quality Issues	% Issues
Disintegration	10
Sterility, Micro, Endotoxins, BET etc.	12
Dissolution	28
Water (Powder Product)	1
Assay	26
Uniformity of weights	6
Related Substance	1
Volume of Injection	1
Particulate Matter	7
Misbranded	3
Defective Absorbent Cotton Wool IP	3

Regulatory Approach to Ensure Quality of Products - An Indian Perspective of Missing Linkage – Kumar N & Jha A, Pharmaceutical Regulatory Affairs

USP VS Country Specific Standards (India)



USP	IP
> 4200 Reference Standards	~700 Reference Standards
99.7% availability	0.5 % availability

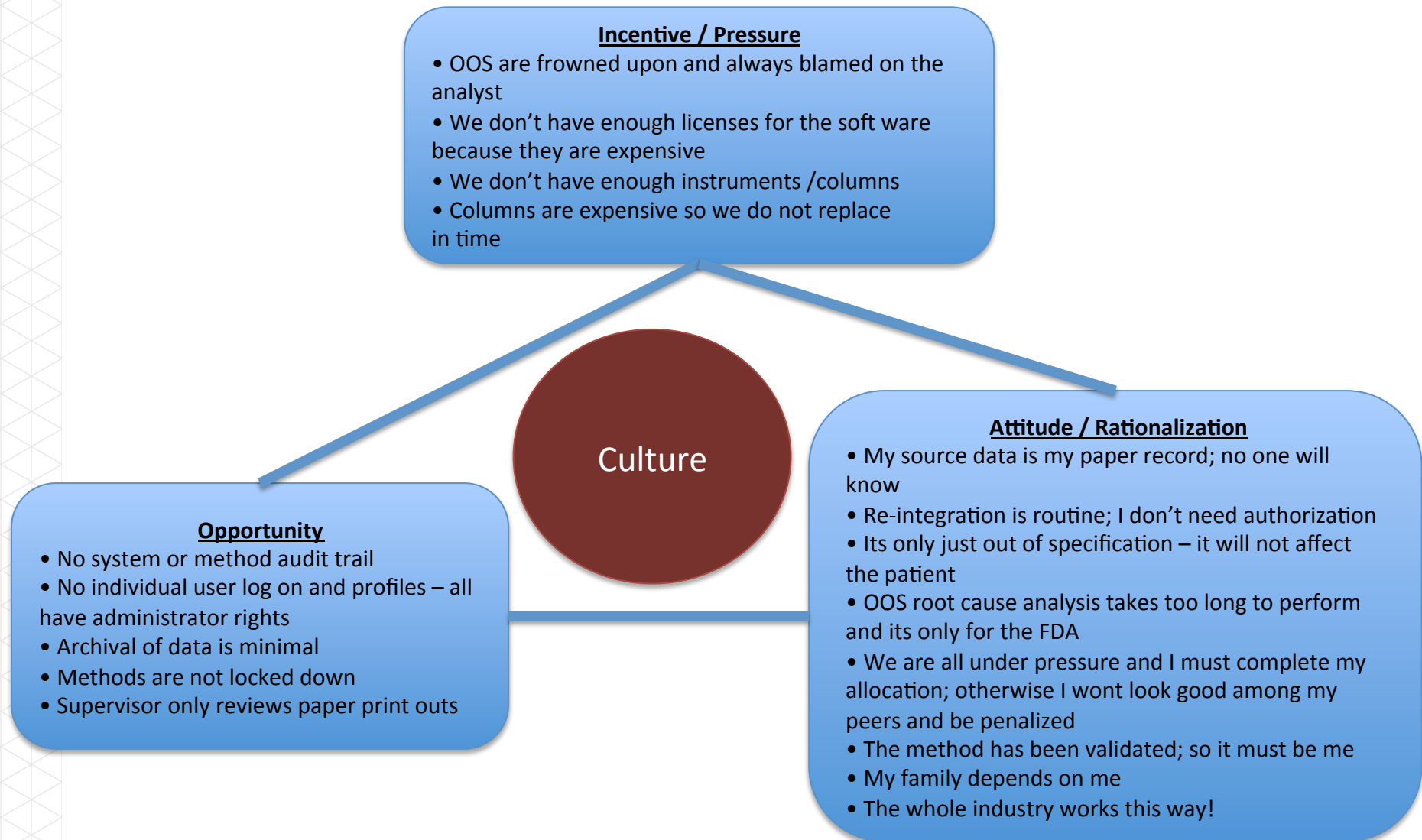


INDIAN PHARMACOPOEIA -2007, P.NO.:179 to182

UNITED STATES PHARMACOPOEIA (USP XXVI), P.NO.:2155 to 2165

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How effective are the corrective actions?



A real life example



- Teva Pharmaceutical Industries Ltd. Vs FERNANDO ESPINOSA ABDALÁ; LEOPOLDO DE JESÚS ESPINOSA ABDALÁ; and PPTM INTERNATIONAL S.à.r.l., filed September 26, 2016 in the Supreme Court of NY: Commercial Division

Cultural determinants of Quality



Leaders

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Ironically, midway through the Singapore tribunal hearing, the Singh brothers said that documents disclosed to Daiichi Sankyo before the signing of share purchase deal — which happened in June, 2008 — had given them enough “cause” to be concerned that Ranbaxy was a “corrupt” organisation. Therefore, the brothers claimed that despite the assurance of Malvinder Singh and his team, Daiichi Sankyo ought to have been aware of such “corrupt” concerns but had decided to ignore them and proceed with the acquisition.

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Reuters, J
Indian Express, A

Indian Express, August 11, 2016

Cultural determinants of Quality



- How do you make the message credible?
- How do you create an environment where employees speak up for what is right?
- How do you empower employees to do the right thing?



Getting to the REAL root cause



- From Rick Friedman's presentation at the FDLI Workshop in Washington, DC – July 14-15, 2014:
 - A large number of recent manufacturing failures can be traced to failures in the firm's Quality System
 - In some cases, the quality system ignored or failed to follow up on customer complaints
 - In other cases, multiple repeated deviations were treated as separate incidents, rather than an obvious trend
 - Another recurring theme has been investigations “to nowhere ...” These end with no additional understanding or insight into why the problem may have occurred and thus no hope for prevention
 - All of these failures suggest a quality management system that is insufficiently empowered or resourced to adequately carry out its essential functions

Where does the buck stop?

Thank you



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