MEDASSURE

SECURING YOUR SUPPLY CHAIN

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

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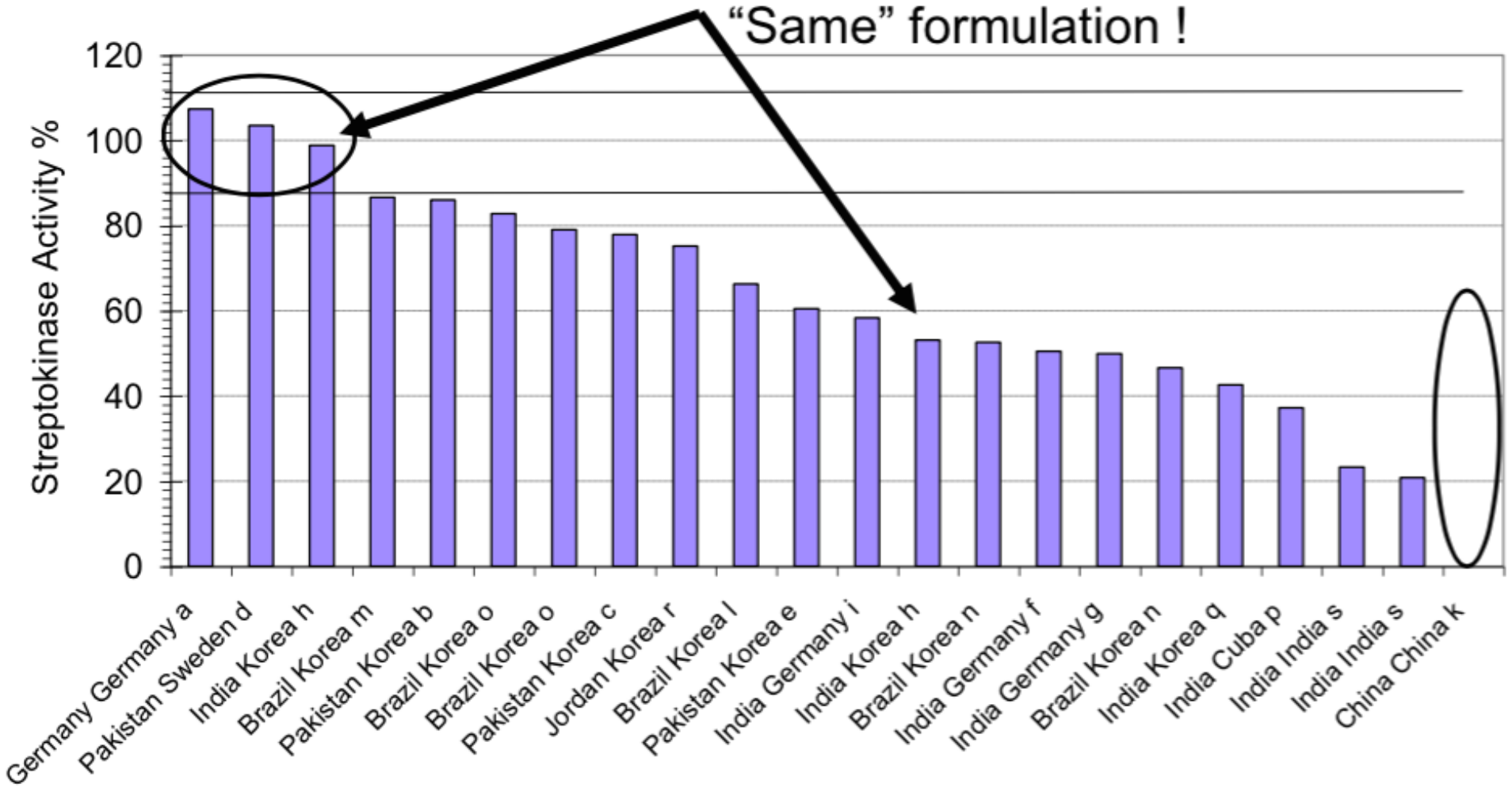
Executive Chairman

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

USAID FROM THE AMERICAN PEOPLE | USP
PROMOTING THE QUALITY OF MEDICINES

POST-MARKET QUALITY SURVEILLANCE PROJECT
MATERNAL HEALTHCARE PRODUCTS
(OXYTOCIN AND ERGOMETRINE)
ON THE GHANAIAN MARKET

FOOD AND DRUGS AUTHORITY FDA GHANA

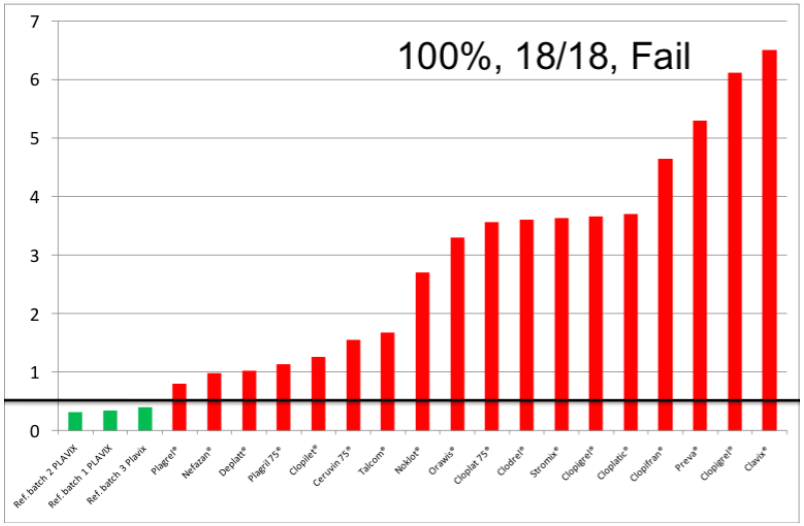
REPORT OF FIRST ROUND

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.

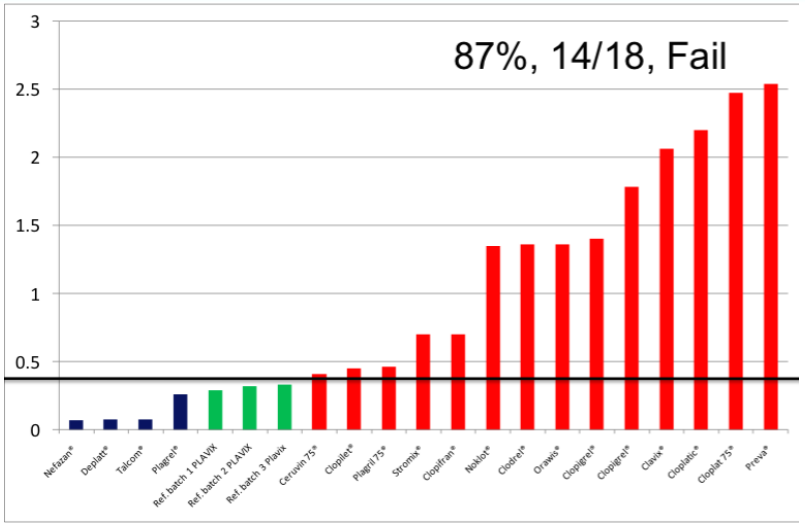
Eighty-six percent (86%) of the Oxytocin samples found on the market were manufactured in China, whereas 90.68% of Ergometrine samples were manufactured in India. Of those collected and tested, 8.11% of Oxytocin samples and 57.63% of Ergometrine samples had been issued marketing authorizations: Two companies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

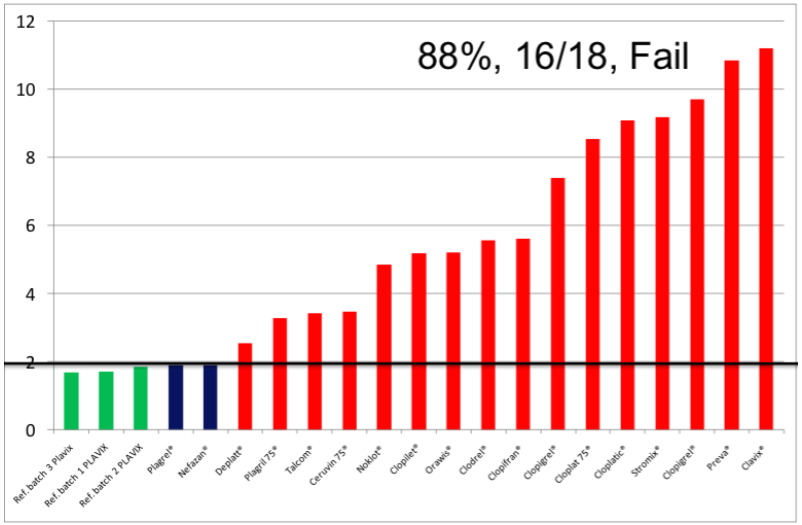
Generic Clopidogrel



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

Impact of excipients

Table 2 Comparison of selected parameters for proprietary versus nonproprietary fingolimod

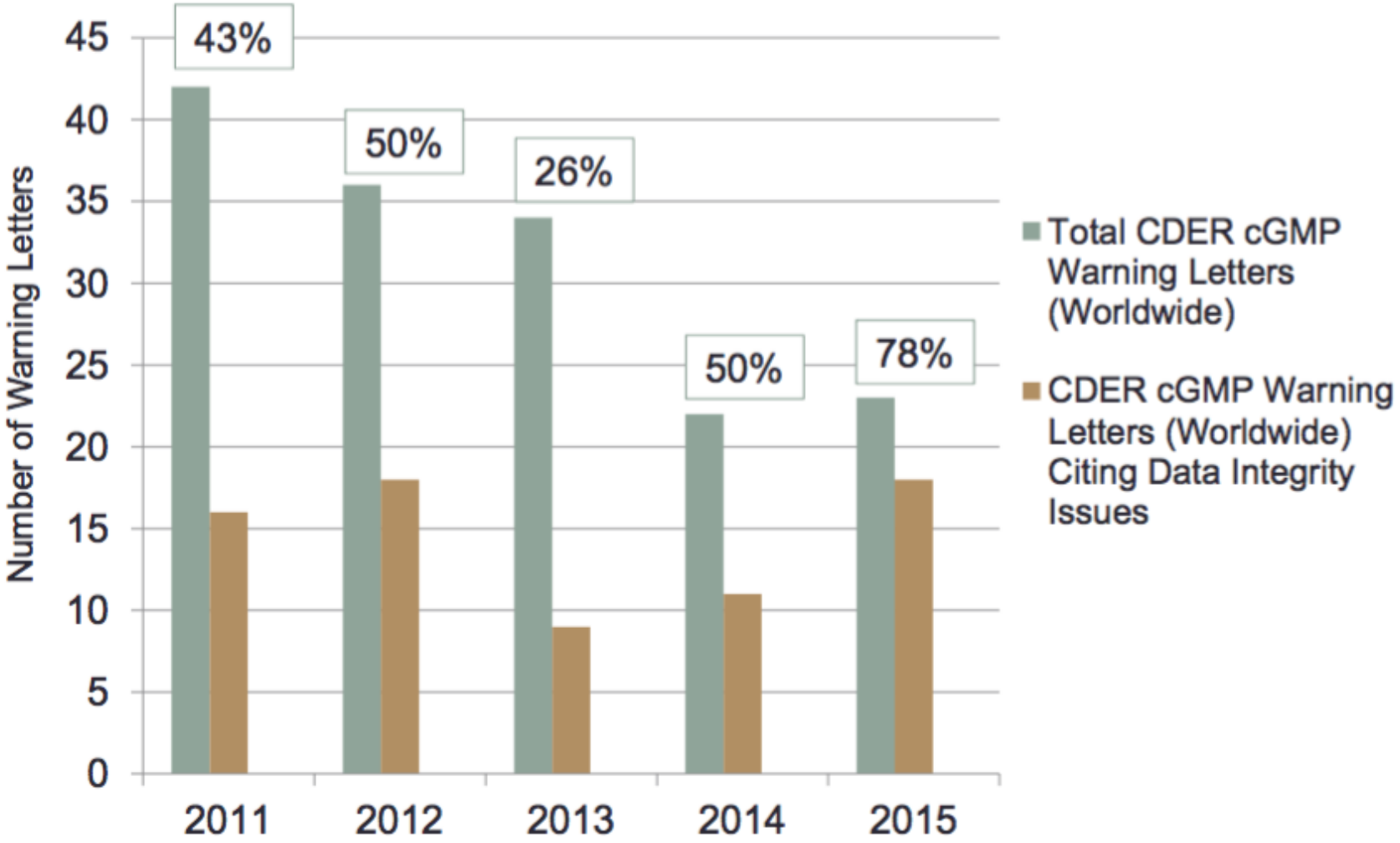
Parameter	Specification (source)	Nonproprietary fingolimod (%)	Proprietary fingolimod (%)
Assay fingolimod (HPLC)	90.0%–105.0% (proprietary specifications; USP generally acceptable: 90.0%–110.0% for oral drug products)	93.11	96.4
Individual unspecified degradation product (HPLC)	Not >0.5% (proprietary 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



Real cost of breach of Data Integrity

Regulatory Details	Lost revenue & hard costs	Opportunity & other costs
Major global manufacturer received WL in early 2012 for a US plant, highlighting GMP and testing issues. This led to reduced output and the eventual closure of the facility for 9 months. The WL was closed out two years later. **Total Cost: $64 million**	**Revenue:** Facility projections reduced by **$20 million** for the remainder of FY 2012. Production shifted elsewhere, mitigating lost revenues post 2012. **Costs: $35 million** in remediation	**Opportunity:** With a historical ROCE of 20%, opportunity cost of reduced profits estimated to be **$9 million.** The impact on delayed ANDAs is unpublished.
Large India-based manufacturer received WL for India facility in late 2015. Previously FDA approved innovator drug rescinded, generic production forced to move. Site re-inspection not likely until Q2 2017. **Total Cost: $113-133 million**	**Revenue:** Projected loss of **$50 million** a year from drug delay for at least the length of the import alert period (estimated at 18 months). Production at facility being shifted elsewhere. **Costs:** Amount of remediation and write- downs expected in 2016 annual report. Estimated to be **$25-$45 million**.	**Opportunity:** With a historical ROCE of 21.6% and net margin of 33%, the opportunity cost of reduced profits and increased expenses estimated to be **$13.5 million.** The impact on delayed NDAs and ANDAs is unpublished.

Real cost of breach of Data Integrity

Regulatory Details	Lost revenue & hard costs	Opportunity & other costs
Global manufacturer received WL and import ban for 2 facilities on Jan 2015 and Mar 2015. Currently in remediation. **Total Cost: $148-178 million**	**Revenue:** Exports dropped $48 million from previous year, after growing 39% over previous 4 years. EBIT dropped $41 million. **Costs:** Amount of remediation and write- downs expected in 2016 annual report. Estimated to be **$40-70 million**.	**Opportunity:** With a historical ROCE of 20% the opportunity cost of reduced profits and increased expense estimated to be **$26 million.** 41 ANDAs and 38 DMFs are in jeopardy of delays.
Large India-based manufacturer received FDA Import alert in early 2013, followed by MHRA recall of multiple products. 2nd facility import alert in late 2013, expanded to all company APIs. All US products recalled early 2015. MHRA closed out late 2015, with FDA close out expected Q2 2016. **Total Cost: $911 million**	**Revenue:** US Revenues dropped from 50% to 24% of totals from 2013-15. Total revenue loss of $760 million expected. **Costs:** Write-off of **$18 million** plus unknown remediation expenses. Further amounts expected in 2016 according to annual report. Estimated to be over **$100 million.**	**Opportunity:** With a historical ROCE of 18.6% the opportunity cost of reduced profits and increased expense estimated to be **$51 million.** **Other:** 7.2 million units recalled, loss of $2.3 billion in market cap

Most common DI violations cited by the US FDA

Citation	CFR	#
Failure to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications & standards	21 CFR 211.194 (a)	21
Failure to exercise appropriate control over computer or related systems to assure that only authorized personnel institute changes to master production & control records	21 CFR 211.68 (b)	15
Failure to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet specifications, whether it has been distributed or not	21 CFR.192	9
Failure to maintain complete information relating to production & control of each batch	21 CFR 211.188	5
Failure to document laboratory activities at the time of performance (pre-dating or backdating records)	21 CFR 211.160 (a)	3
Blending out of specification API with passing batches to meet specification		3
Failure to document production and process control functions at the time of performance	21 CFR 211.100 (b)	2

*Warning letters between April 2013 and April 2015 – One citation per firm, includes more than one example

Failures cited in recent warning letters

- Failed analytic results hidden, time/date settings manipulated, analyses reintegrated to achieve passing results
- Routine retesting of analytic data, deleting original results, systematic disabling of audit trail
- Previously undisclosed laboratory conducting “off-the-book” cGMP analyses
- Substitution of results following failing lab results; failure to record critical values contemporaneously
- Complete batch production records days after operations ended
- Failure to maintain original manufacturing data, contained in rough notes
- Made up impurity profile
- No back ups; cannot reconstruct the original data set
- Altered identity tests
- Lack of controls for unauthorized access
- Trial HLPC injections, retesting samples without reporting original results
- Selective discarding of HPLC data
- Batch release without adequate testing

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.

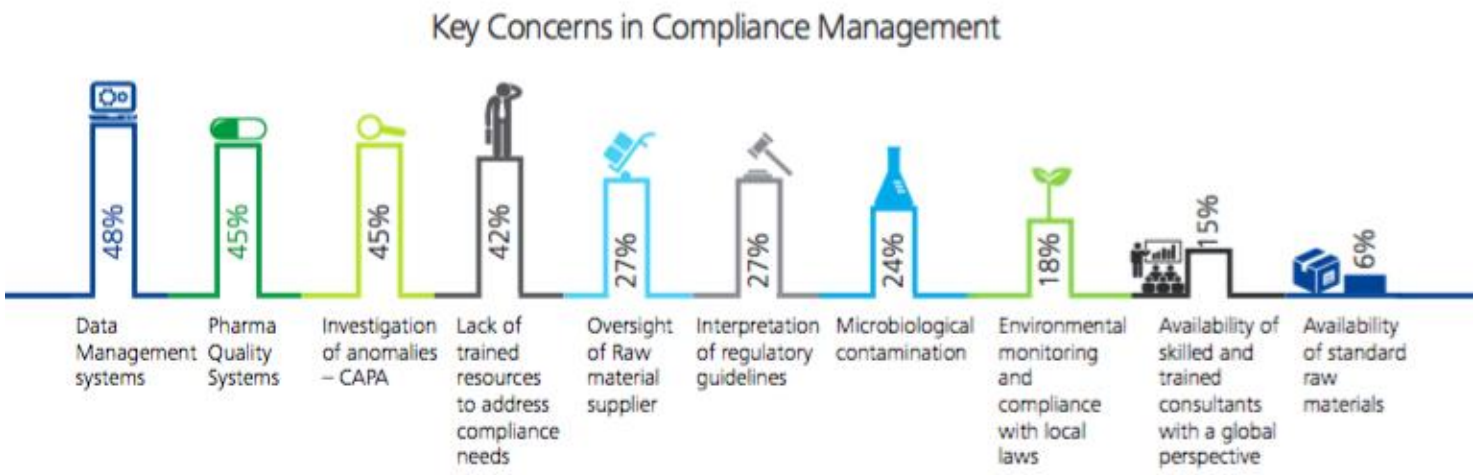
Without a understanding of the TRUE understanding of the root-cause for human misbehavior, companies are taking widespread actions which may not help address the problem in the least.

Unintended Error

Deliberate Falsification

Do we have the right diagnosis?

Here is one perspective



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

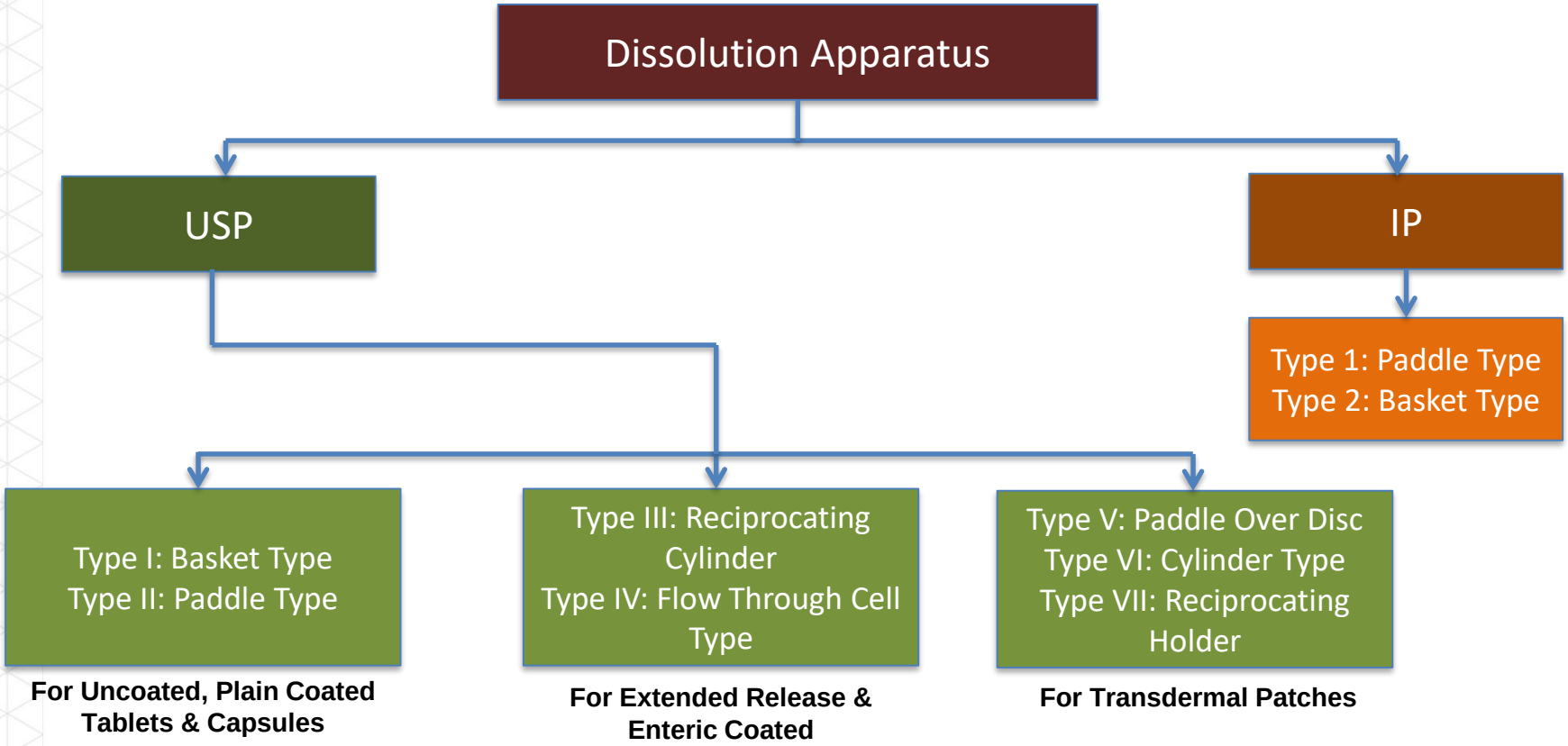
Lets look at it from a different perspective

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

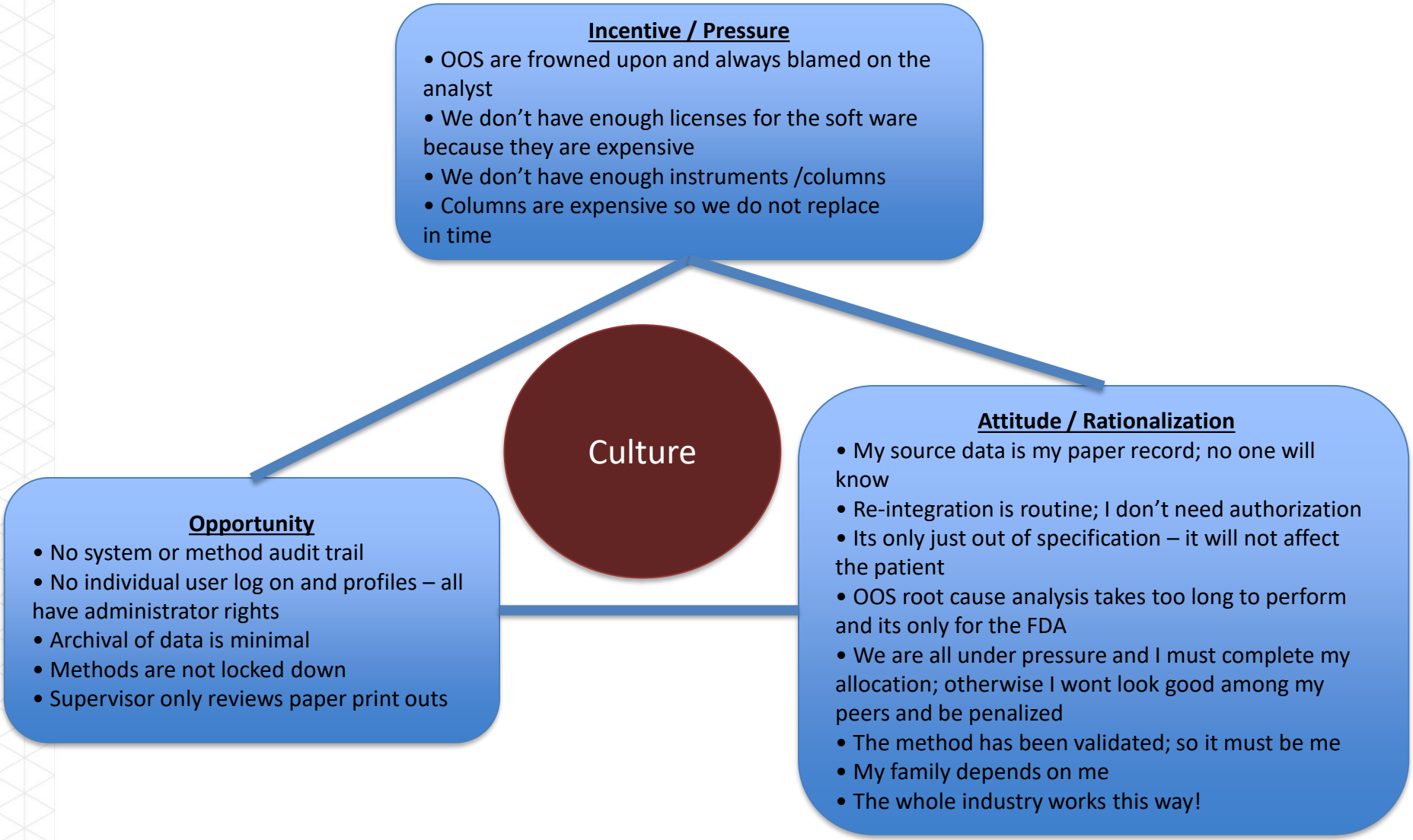
USP VS Country Specific Standards (India)

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

Here is a totally different perspective



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

Leader

nent

Ironically, midway through the Singapore tribunal hearing the Singh broth

Kathuria also referred to how "batches of Cephalexin not meeting colour and clarity criteria and with foreign matter contamination were released..", and an "expert in fabricating false records...I saw the results recorded the bio burden tests and environmental monitoring in the morning using material that he had prepared the previous evening." Cephalexin is a bacterial infection medicine.

decided to revive them and proceed with the acquisition.

Indian Express, August 11, 2016

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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 understadning or insight into why the problem may have occured 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?

“Out of Crisis” by W. Edward Deming*

- As leaders responsible for System Change, top management is most in need of profound knowledge
- Quality is often determined in the Boardroom
- Problems arise when management reacts to common cause or chance variations as if they were a special cause variation
- Prediction based in theory provides a foundation for planning a course of monitored action
- A leader serves people with a clear vision and guidance to empower them. Empowerment means to share ownership in identity
- Giving people a certain degree of control over their work fulfills the need for freedom and provides an opportunity for taking joy in work

The journey of remediation requires leadership with Profound Knowledge as a guide

* MIT Press, 2000

Thank you

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