Data Integrity Issues in Dissolution Testing

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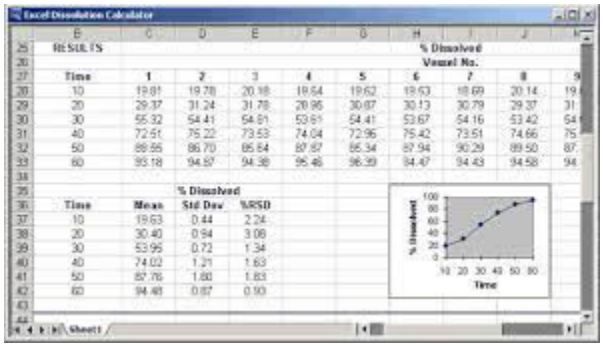
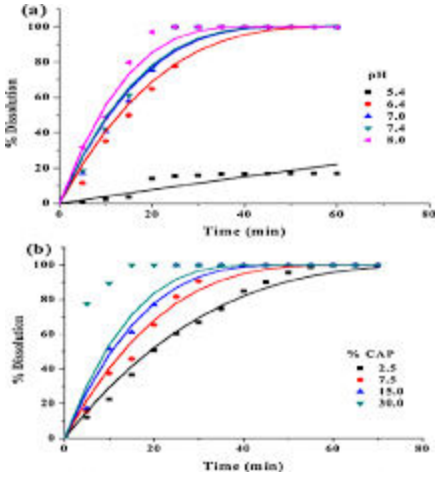
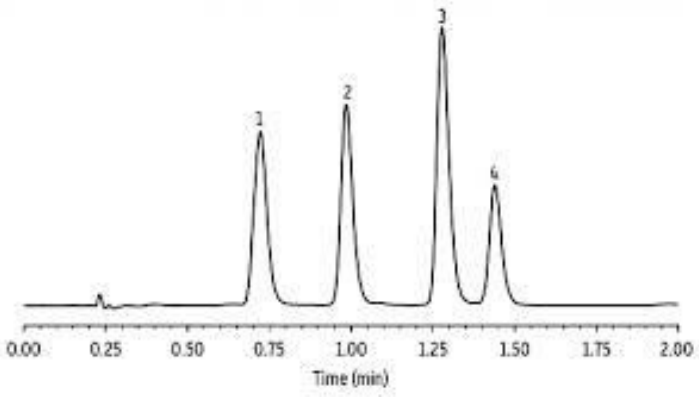
DRUG DEVELOPMENT PROCESS
OVERVIEW

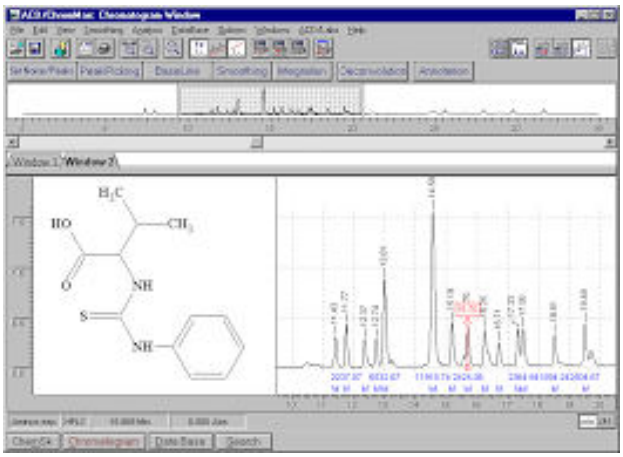
- Drug Discovery
- Screening
- Pre-Clinical Testing
- IND Application
- Phase I Clinical Trials
- Phase II Clinical Trials
- Phase III Clinical Trials
- New Drug Application (NDA) / Biologics License Application (BLA)
- Phase IV and Beyond



Time (min)	Cumulative Percentage Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	38.04	41.46	57.38	20.85	26.67	34.49
10	77.21	79.51	89.84	41.43	61.95	93.55
15	91.79	93.65	99.68	58.32	94.28	100.7




1
2
3
4
0.00
0.25
0.50
0.75
1.00
1.25
1.50
1.75
2.00
Time (min)



Results

Output

…. Data is data ….

Data is data …….

Data is data …….

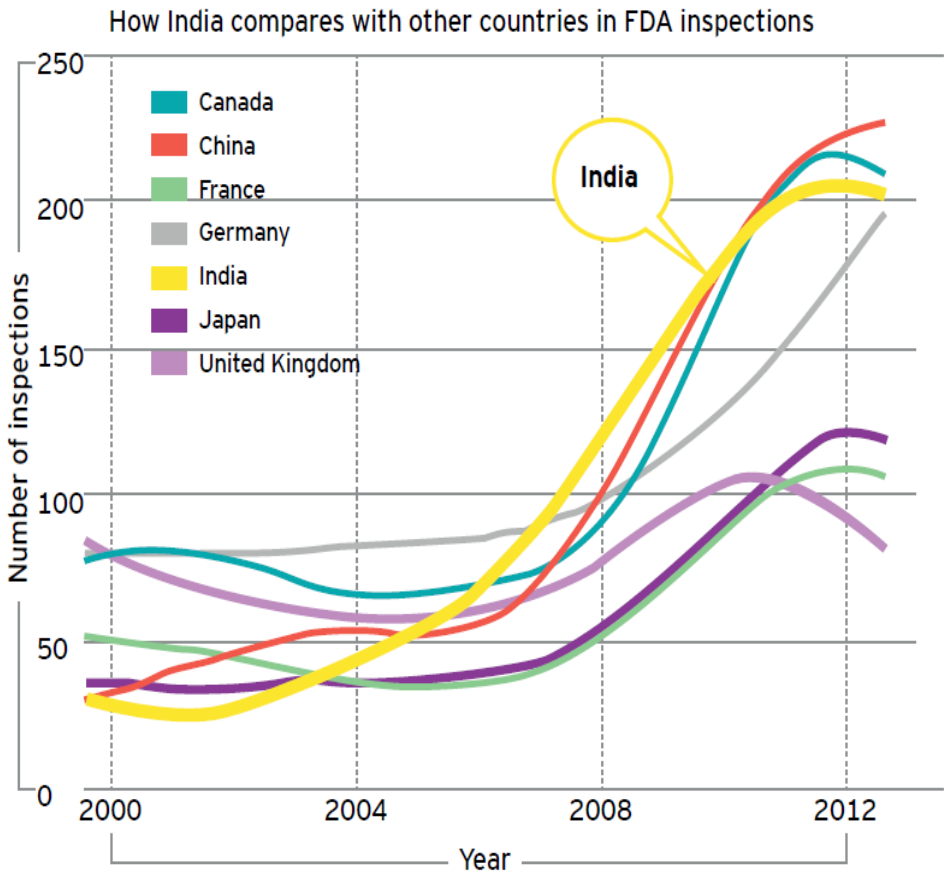
Data is data …….

THEN WHAT ….

Of course,

- INSPECTION
- AUDIT
- REVIEW
- DATA SOURCE VERIFICATION
- ***Integrity !!!!!!***

The most watched nations in FDA inspections[5]



Top 10 Most cited deficiency groups 2016

Ranking	Groups	Critical	Major	Others
1	Quality System	38	449	772
2	Sterility Assurance	34	190	162
3	Production	20	191	543
4	Complaints and Recall	11	80	110
5	Qualification/Validation	10	123	232
6	Premises & Equipment	9	113	464
7	Computerised Systems	9	44	120
8	Personnel	8	42	150
9	Documentation	2	166	646
10	Quality Control	2	42	192

U.S. FDA

Current expectations and guidance, including data integrity and compliance with cGMP

CDER

March 30, 2017

Time to Revisit Fundamentals ….

- **Data**
- **Integrity**
- **Data Source Verification**
- **Data Integrity**

…. DATA ….

Information, especially facts or numbers, collected to be examined and considered and used to help decision-making, or information in an electronic form that can be stored and used by a computer

Distinct information that is formatted in a special way. **Data** exists in a variety of forms, like text on paper or bytes stored in electronic memory

Dictionar(ies) ….

Integrity ….

APPROVING the quality of being honest and having strong moral principles that you refuse to change

Cambridge Oxford Dictionary, 2016

Verification

The act or process of confirming or checking the accuracy of**:**

- the state of being confirmed, or
- having the accuracy of checked.

Webster Dictionary, 2015

Data Source Verification

The process by which ***data*** within the case report form (CRF) or other ***data*** collection systems are compared to the original ***source*** of information (and vice versa)

Medical Dictionary, 2014

Data Integrity

Data integrity is the maintenance of, and the assurance of the accuracy and consistency of, **data** over its entire life-cycle, and is a critical aspect to the design, implementation and usage of any system which stores, processes, or retrieves **data**.

Business Dictionary, 2016; Wikipedia 2016

What is ***DATA INTEGRITY***

Data integrity refers to the completeness,

consistency, and accuracy of data.

Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

US FDA Guidance, April 2016; EMA; WHO 2015

DI – *Not a New Concept ….*

Principles from the paper-and-ink era still apply:

- § 211.68 requires that backup data are exact and complete, and secure from alteration, inadvertent erasures, or loss
- § 212.110(b) requires that data be stored to prevent deterioration or loss
- §§ 211.100 and 211.160 require that certain activities be documented at the time of performance and that laboratory controls be scientifically sound
- § 211.180 requires true copies or other accurate reproductions of the original records; and
- §§ 211.188, 211.194, and 212.60(g) require complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed.

US FDA 2016 (post Publn. Draft Guidance)

Noncompliances not confined to *Falsification and Fraud*

The main data integrity issues concern poor data management [95%] and falsification and fraud [5%] !!

Data Integrity

GLOBAL ISSUE !!

Noncompliances from the EMA, Warning Letters from the US-FDA, Canada, the UK and Italy as well as China and India.

It is not just a problem for Asia – it is a Global Issue !!

Data Integrity
Non-compliance issues

Potential causes/reasons (**not limited to**) . . . .

- Poor communication (written/oral)
- Unaware of expectations
- Levels of Training/Expertise
- Lack of clarity in documentation needs
- Personnel habits/idiosyncracies
- Poor data management
- QA leading to corrective action – too late to be meaningful
- Financial/Economic impact
- Willful (falsification/fraud/etc.)
- Time constraints/deadlines
- Others

DATA INTEGRITY (hype !!!!)

- Media loves ‘juicy’ info to report
- D Integrity – viewed in negative context/negative backdrop
- Two Agency independent inspections – diagonally opposite findings
- Delineating ‘***unintentional error***’ and ‘***willful/intentional misconduct***’
- Benefit of the doubt
- Innocent until proven guilty
- Element of ***Subjective*** versus ***Objective*** Assessment

DI … DI … DI …DI ….DI ….

We can –

- ***Discuss***
- ***Debate***
- ***Lecture on***
- ***Speak about***
- ***Present***
- ***Webinars***
- ***Etc.***

till cows come home !!!…..

Foundation pillars of Integrity

- Trust
- Communication
- Responsibility (***Individual and Collective***)

Guiding Principle ….

TRUST but VERIFY !!!!

If You Find a Data Integrity Problem

- Disclose it to regulators
- Determine the scope
- Commit to voluntary remediation

FDA is much more willing to work with firms that voluntarily disclose and commit to fixing problems

The 3P Mantra ….!!!!

- **P**roactive
- **P**rospective
- **P**ride of Possession/Ownership

THANK YOU

DHANYAWAAD !!

धन्यवाद

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Please ….

- ***Only easy/simple questions that I can answer !!!!***

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