

Data Integrity Issues in Dissolution Testing

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Presented at

SPDS

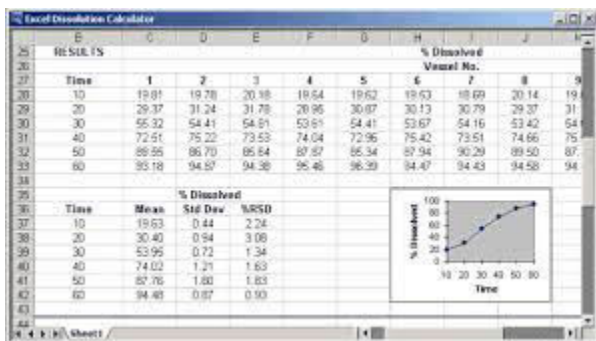
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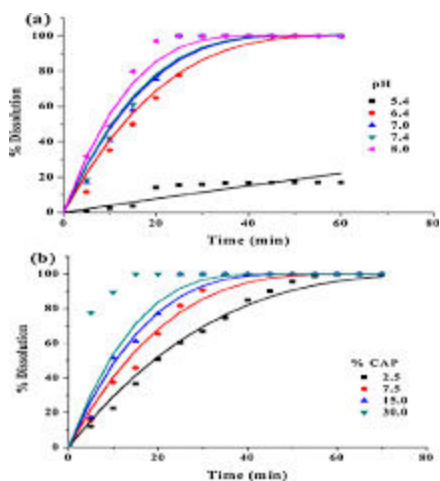
DRUG DEVELOPMENT PROCESS *OVERVIEW*

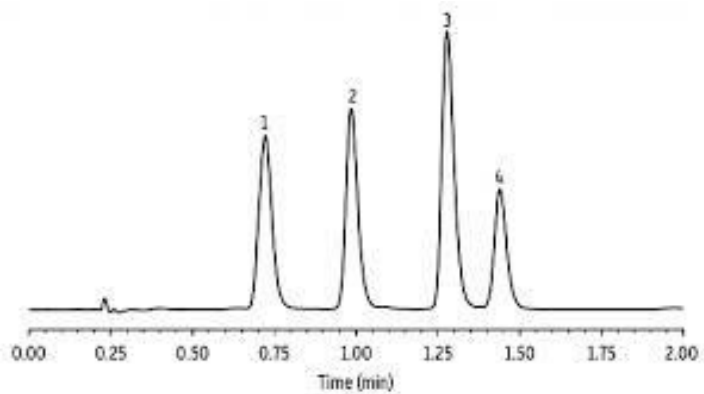
- **Drug Discovery**
- **Screening**
- **Pre-Clinical Testing**
- **IND Application**
- **Phase I Clinical Trials**
- **Phase II Clinical Trials**
- **Phase III Clinical Trials**
- **New Drug Application (NDA) /
Biologics License Application
(BLA)**
- **Phase IV and Beyond**

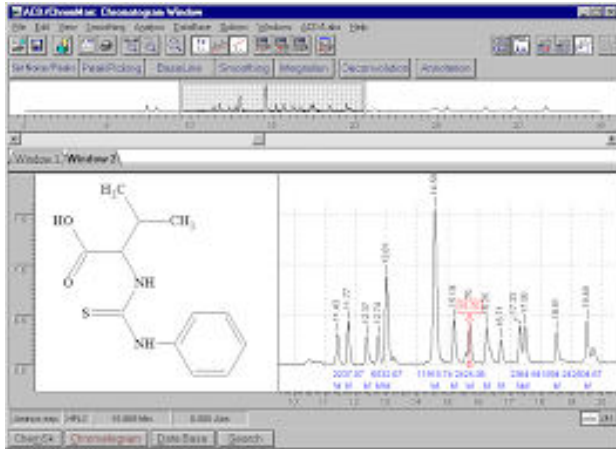




Time (min)	Cumulative Percentage Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	38.04	41.46	57.38	20.85	26.67	34.49
10	77.21	79.51	89.84	41.43	61.95	93.55
15	91.79	93.65	99.68	58.32	94.28	100.7







Results

Output

	35294	35148	35279	35398	35529	35648	35772	35890	36022	36147
18.90133	4104	4160	4279	4330	4389	4518	4595	4686	4821	4938
18.9512	4131	4189	4277	4358	4396	4561	4593	4651	4835	4906
18.92167	4129	4168	4268	4337	4389	4569	4574	4656	4851	4934
18.93343	4103	4190	4275	4278	4401	4399	4543	4653	4815	4906
18.944	4129	4199	4262	4290	4370	4568	4578	4645	4820	4915
18.95467	4126	4164	4245	4275	4370	4565	4635	4660	4827	4926
18.96533	4101	4175	4286	4375	4392	4577	4667	4675	4820	4927
18.976	4104	4200	4286	4347	4408	4587	4648	4651	4824	4952
18.98667	4119	4209	4280	4337	4422	4605	4642	4697	4827	4955
18.99733	4146	4212	4303	4330	4450	4575	4710	4693	4854	4992
19.008	4185	4212	4301	4351	4485	4620	4725	4738	4872	5016
19.01867	4216	4355	4317	4368	4506	4668	4763	4784	4940	5091
19.02933	4259	4323	4407	4423	4575	4729	4849	4902	5040	5175
19.04	4323	4378	4467	4501	4618	4816	4831	4942	5136	5259
19.05067	4411	4482	4569	4620	4741	4931	5048	5082	5271	5356
19.06133	4529	4566	4675	4750	4865	5038	5108	5196	5399	5530
19.072	4653	4735	4856	4885	4999	5156	5405	5370	5613	5757
19.08267	4855	4912	5041	5101	5286	5454	5607	5613	5881	6030
19.09333	5069	5155	5252	5313	5466	5687	5852	5896	6167	6331
19.104	5262	5383	5499	5579	5881	5959	6142	6281	6572	6696
19.11467	5575	5652	5766	5831	6053	6276	6482	6573	6898	7137
19.12533	5856	5984	6252	6335	6385	6473	6529	6477	6621	6697
19.136	6189	6162	6261	6240	6325	6504	6512	6481	6621	6679
19.14667	6160	6180	6287	6268	6299	6487	6499	6483	6621	6678
19.15733	6157	6200	6227	6240	6273	6478	6495	6486	6596	6674

.... Data is data

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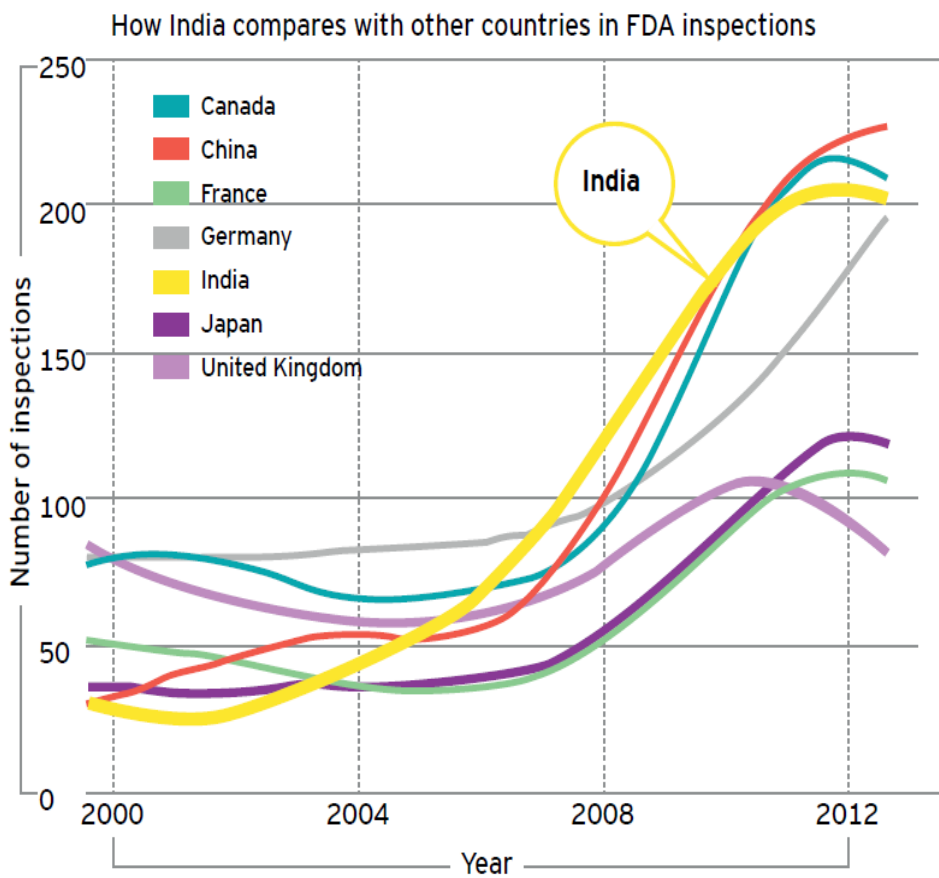
Data is data

THEN WHAT

Of course,

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

The most watched nations in FDA inspections⁵



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 Publ. 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!!!!

- **Proactive**
- **Prospective**
- **Pride of Possession/Ownership**

THANK YOU

DHANYAWAAD !!

धन्यवाद

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Please ...

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

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