RESEARCH PAPER

Evaluating Data Integrity Issues in the Pharmaceutical Industry and Proposing Solutions Through the Pharmaceutical Education Curriculum.

Buddaraju Vivekananda Raju[1], B.Babu[2]*, Smita Jain[3], JanoriousWinka Jayaprakash[4], Jayaprakash Narayanan Jaganathan[5], Nagarajan Janaki Sankarachari Krishnan[6]

[1,6]Department of Pharmaceutical Analysis, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu. vivek.buddharaju@gmail.com

***Corressponding Author:** Dr.B.Babu
***Associate professor**Department of pharmaceutical analysis, JSS College of pharmacy, Rock lands, Ooty, The Nilgiris, Tamil Nadu **Email ID-** babu@jssuni.edu.in

ABSTRACT
The pharmaceutical manufacturing industry generates large data from multiple activities, like preparation, processing steps in drug product manufacturing. During the processes of drug product manufacturing, testing, and release of product, multiple activities are being recorded to explain the end-to-end processes of getting the drug to reach patients, and all the generated data must be Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, and Available (ALCOA-plus)[1]. Recently, EMA guidelines on computerized systems have introduced a tenth criterion, further refining the ALCOA framework to ALCOA++, which includes Traceability, ensuring that data is traceable throughout the entire process and its lifecycle, including all changes made[2]. Each drug manufacturing will be recorded with unique batch number or batch code to track its life cycle of manufacturing, testing, release and this will generate large data manually or electronically in the pharmaceutical manufacturing industry[3]. As the industry is highly regulated to ensure product quality, by consider the safety of the patient. Pharmaceutical Regulators assess life cycle of data to ensure its authenticity and transparency to confirm that it is truly executed on real time and free from Data integrity noncompliance[4]. Survey includes Data integrity existence and its consequences in the pharmaceutical industry by evaluating i) experienced experts/leaders across the pharmaceutical manufacturing industry and ii) understanding views of professional pharmacy students about Data integrity knowledge[5] in their curriculum per cGMP requirements
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1. Introduction

The pharmaceutical industry is consistently improving its manufacturing processes in compliance with current Good Manufacturing Practices (cGMP)[6]. However, inappropriate recording, reporting and management of data are still a substantial problem for pharmaceutical industry[7]. Regulatory agencies are citing data integrity (DI) issues across the globe, which are causing problems for Drug manufacturers in supplying medicines to market [8].

Documenting or recording of any value during the process of manufacturing, testing, release and distribution of pharmaceutical product is must and as per GMP / GDP requirements[9] "If it is not documented, it did not happen" means that unless an event is documented or recorded in appropriate way, it is not considered to have occurred.

Pharmaceutical Regulatory agencies review and assess the product development process, manufacturing process, testing process and their results through the data recordings, hence (here you can put flow of the process) integrity of data is utmost priority to regulators to understand and consider that the products manufactured are meeting requirements[10] of Safety, Identity, Strength, Purity, and Quality.

As per all the guidelines in pharmaceuticals industry it is considered that Quality is not accidental, and it is a continuous practice adopts from Drug product development to release of the Drug product to market and performing the development, manufacturing, testing and release of products accurately by meeting Data integrity ALCOA+ ("attributable, legible, contemporaneous, original and accurate" + stands for "complete, consistent, enduring and available" principles per cGMP requirements[11]. Recently EMA guidelines on computerized systems have introduced Traceability, further refining the ALCOA framework to ALCOA++, to ensure data is traceable throughout the entire process and its lifecycle, including all changes made[2]. if the Drug manufactures failed to demonstrate the integrity of data generated, then regulators consider as generated data is falsified and untrustworthy, with that regulators and agencies will not have confidence on rest of the generated data too and approval to manufacture and distribute drug product will not be granted[12].

Table: 1, ALCOA ++ details

A → Attributable

*Author for Correspondence: Email: babu@jssuni.edu.in

L → Legible
C → Contemporaneous
O → Original
A → Accurate
P → Complete
L → Consistent
U → Enduring
S → Available
++ → Traceable

2. Background and plan of Work

As per the 2019 FDA Drug shortages task force report, it evident that quality issues are contributing for 62% of Drug shortages, out which unwanted Data integrity issues are the major noncompliance factor reasoning for quality issues. Currently Indian pharmaceutical and biopharmaceutical industry growing at rapid pace and a greater number of companies are facing Data integrity noncompliance's out of inspections. As a result of that, wanted to understand the contributions of pharmaceutical education system towards mitigations of Data Integrity issues in industry.

Research focused on below aspects

• Review and understand the consequences of data integrity issues, reviewed USFDA warning letters and categories of non-compliances associated with them[13].

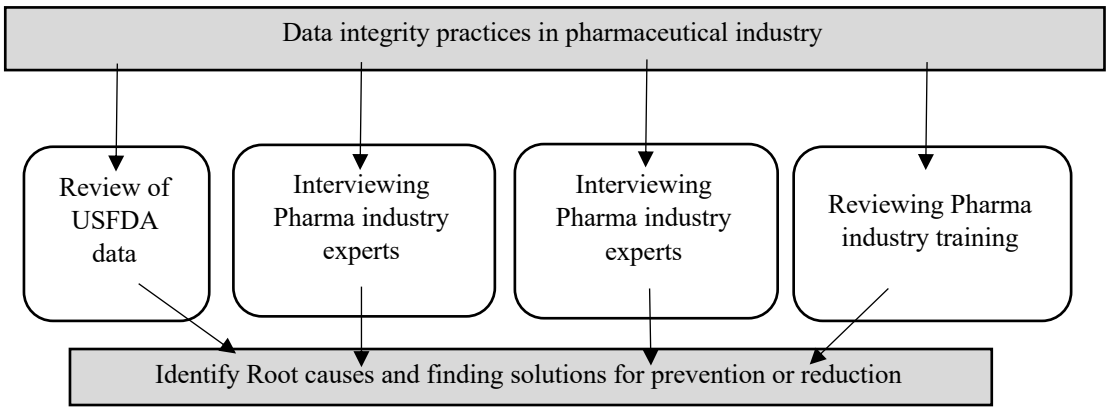
• To evaluate knowledge coming from education regarding data integrity requirements and practices in the pharmaceutical industry[14].

• To identify the significance of Academics to inculcate working practices without integrity in data reporting[14].

• To identify the effective training in pharmaceutical industry with respect to data integrity[15].

• To find out what are the actions needed to remove or mitigate data integrity practices in industry[15].

Figure: 1, Research workflow chart



Data integrity issues in pharmaceutical industry is not limited any specific function or work and it can be seen / done at receipt of material to dispatching of final product, hence ensuring data integrity is out most important in each step of drug manufacturing. Data integrity is nothing but scientifically unsound or technically unjustified omission, manipulation or alteration of procedures and system or data that bypasses the required parameters to make results appear as appropriate which is basically a Data integrity practice.Some of the Data integrity practice's examples listed below[16]:

- Erasing / deleting of non-compliant data.
- Using a previous calibration without executing current calibration.
- Deliberate Improper peak integration
- Modification of records
- Alteration of instrument / equipment to get desired results.
- Spiking more than required to improve recoveries.
- Forging another person's name or signature.
- Disabling audit trails
- Performing multiple calibration runs to attain desired one.
- Over dilution of samples or misrepresentation of reporting limits.
- Deliberately deviating from the defined procedure / instruction / policy.
- Fabrication of any company GxP records.
- Acknowledging the results which is not performed by them.
- Erasing or hiding quality data or records.
- Manipulation of test results to release the product.
- Violation of company code of business conduct.
- Mishandling or unauthorized removal or destruction of confidential or sensitive information.

Inspectors / auditors will always look for trustworthiness of presented data during verification and always they

verify the life cycle of data generation, maintenance. as an example, when data mentioned about any material specified as part of manufacturing or testing, it is essential to have reconciliation of material from its purchase to its usage.

USFDA considers every Data integrity observation as critical 483, (the FDA Form 483 is officially called a "Notice of Inspectional Observations") and with that US FDA doesn't allow manufactures to release Drugs into US market, unless they reinspect and found that proper systems are in place to avoid Data integrity issues.

All the employees who are working in Biopharmaceutical or pharmaceutical manufacturing companies are bound to follow Data integrity principles all the time, even if one 483 was identified during review or inspection that may have a serious compliance impact on whole company quality and that may stop company from manufacturing and supplying drugs to USA.

Always agencies emphasize organizations on following current Good Manufacturing Practices (cGMP), and it is the responsibility of organizations to train all the employees on cGMP practices. It is pharmaceutical or biopharmaceutical companies' responsibility to make sure no data integrity practices are following by their employees in any manufacturing, testing or other activity during their operations and documentation by regular training and conducting internal audits in defined frequencies.

More than 40% of generic medicines dispensed in the U.S. were made in India. Over past decade FDA and other regulatory agencies have increased focus on Data Integrity compliance. Regulators have trained and evolved to get ahead of quality issues especially such as Data Integrity issues[17].

USFDA agency is more stringent, which gives more importance to Data Integrity principles and practices. considering the dependency of Indian pharmaceutical industry on US market revenue and dependency of US people on Indian generics for accessible cost-effective medicines, with that it is considered to use US FDA agency data and principles for research work[18].

Getting data integrity right is not an easy task. It requires a concentrated, continuous effort to develop and maintain the policies, culture, and discipline required to avoid Data integrity regulatory issues[19].

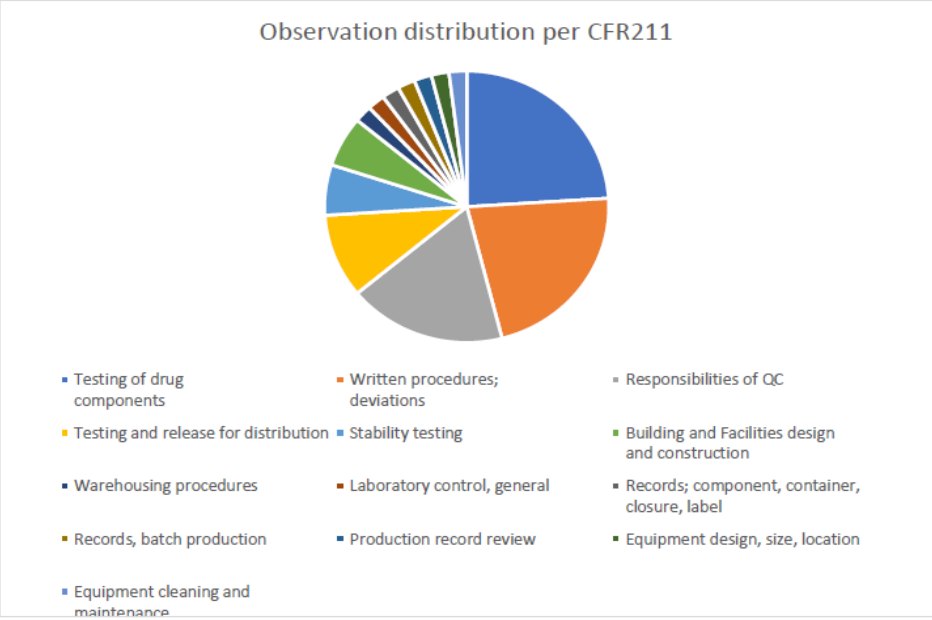
As part of research to understand the consequences of data integrity issues, reviewed USFDA warning letters and categories of non-compliances associated with them[20].

Reviewed FDA dashboard to identify trends in GxP compliance/environment to focus on Data integrity issues in the pharmaceutical industry (Biologics and Drugs industries are only considered and Food/cosmetics, Tobacco, veterinary are not considered being they do not come under pharmaceutical drug products). Time frame considered for the collection of warning letters data is for the period of 1st January to 31st March 2023 (as per our initiated research time frame) considered as sample to understand whole GxP compliance/environment in the pharmaceutical industry.

Per USFDA dashboard (1st January to 31st March 2023) 17 warning letters were issued for the period considered for review. Geographical distribution is verified, and warning letters were issued to companies in United states, China, India, Japan, Italy, Puerto Rico and Turkey.

Total of 50 Observations (originally given in the 483s), were issued to 17 drug making companies (as mentioned above w.r.t geographical segregation) while 7 for companies manufacturing combination products/medical devices.

Figure: 2, US FDA observations distribution chart



Note: Above compliance trends are from 17 Warning Letters issued by USFDA agency in between 1st January to 31st March 2023.

From above Figure 1, the 483 citations were given to drug making companies on "Testing of drug components", "Written procedures; deviations", and "Responsibilities of quality control unit" are on the top three noncompliance's out of all observed.

Categorized the above listed observations categories to understand, if Data integrity is included in that and details are as follows:

Table: 2, top 3 noncompliance's per US FDA observations or 483 forms

Category	Observations
(Observations given by USFDA to companies, which led to WLs) it can be concluded that there are three main areas that are in focus of GxP assessments (and found noticeable deficiencies for): Good Documentation Practices/ Data Integrity	- Inadequate data / record management - Missing data - Missing second verification (contemporaneous)
Preventive Maintenance	- Inadequate room / equipment labelling. - Peeling painting - Cracks on the floor/ceiling
QC Activities	- Samples are not taken. - Test methods are not updated.

Note: above compliance trends are mainly from Warning Letters.

Per table: 2, after categorization of observations from USFDA, improper handling of data and documentation (Data integrity and good documentation practices) are contributing to 483's and warning letters in pharmaceuticals industry, with the above details it is evident that DI noncompliance's are reporting in pharmaceutical industry across the globe[21], and they are the primary reasons for the warning letters issued in pharmaceutical industry. Pharmaceutical industry in India is also majorly affected with DI noncompliance's from past few years, which resulted in employee layoffs, closure of manufacturing plants and business, with that worked to identify possible solutions to mitigate or remove DI noncompliance risk to growing pharmaceutical industry[22].

2.1. Interviewing Pharma industry experts

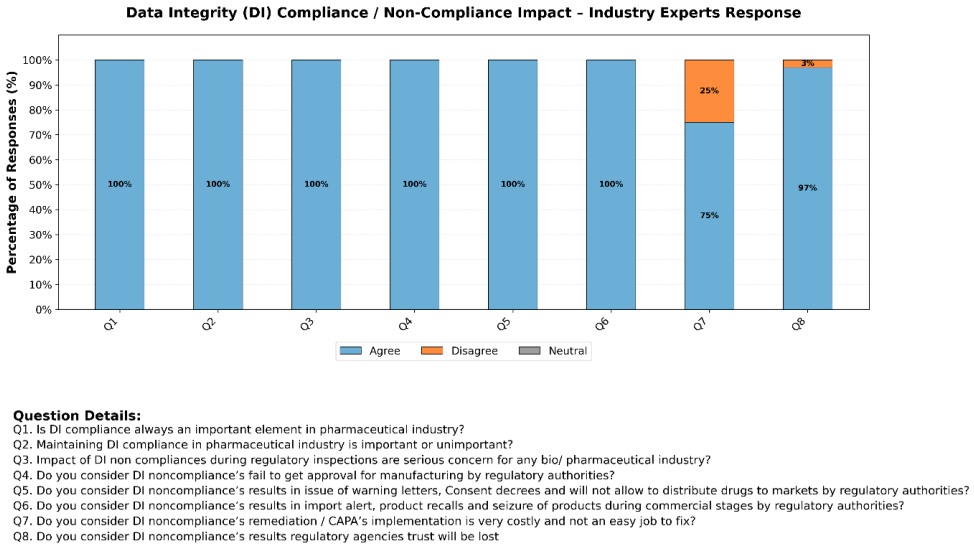
Selection criteria for assessment is considered with below criteria:

a. Pharma Industry experts who are having minimum of 10 years of pharmaceutical industry experience is considered to seek the reliable feedback.

b. Different companies were chosen to understand the feedback based on their situations point of view.

c. All the core departments such were chosen to understand their feedback on Data Integrity requirements and expectations.Survey outcome about Data Integrity requirements and expectations are as follows:

Figure: 3, industry experts survey response



d. 100% experts agree / believe that:

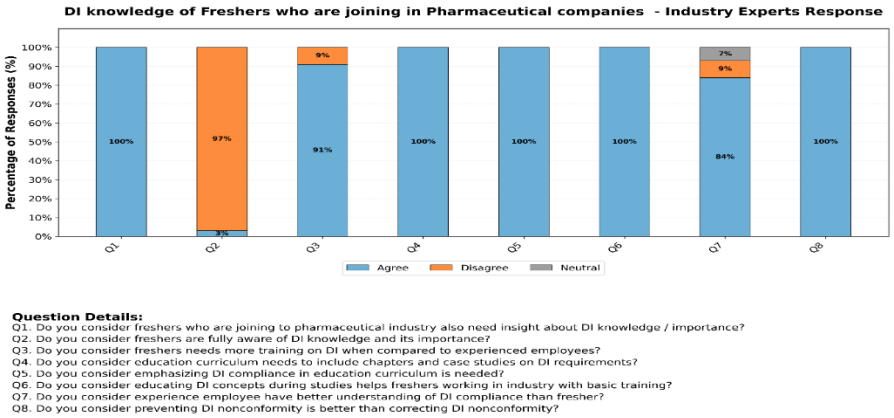
- DI compliance always an important element in pharmaceutical industry[23].
- Maintaining DI compliance in pharmaceutical industry is "Important."
- Impact of DI non compliances during regulatory inspections are serious concern for pharmaceutical industry.
- DI noncompliance's fail to get approval for manufacturing by regulatory authorities.
- DI noncompliance's results in issue of warning letters, Consent decrees and will not allow to distribute drugs to markets by regulatory authorities.
- DI noncompliance's results in import alert, product recalls and seizure of products during commercial stages by regulatory authorities.

e. 75% experts believe that DI noncompliance's remediation is very costly and not an easy job to fix.

f. 97% experts believe that DI noncompliance's results regulatory agencies trust will be lost.

Survey outcome about Data Integrity knowledge of freshers who are joining in pharmaceutical industry are as follows:

Figure: 4, industry experts survey response



g. 100% pharma industry experts believe that Freshers joining to pharmaceutical industry needs appropriate knowledge on Data integrity.

h. 97% pharma industry experts still believe that freshers need more DI knowledge and its importance.

i. 91% pharma industry experts believe that freshers need more training on DI when compared to experienced employees.

j. 100% pharma industry experts believe that education curriculum needs to include DI chapters, case studies, and emphasizing its importance on DI compliance will improve working in industry with minimal training.

k. 84% pharma industry experts believe that experience employee have better understanding of DI compliance than freshers.

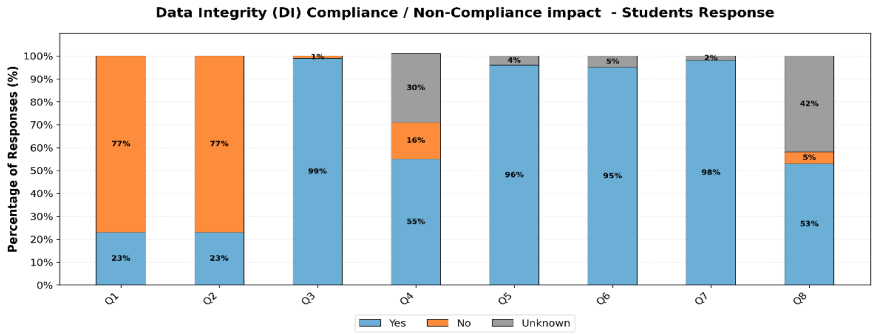
l. 100% pharma industry experts believe that preventing DI nonconformity is better than correcting DI nonconformances.

Conclusion from "100% experts believe education curriculum needs to include DI chapters, case studies, and emphasizing its importance on DI compliance will improve working in industry with regular industry training".

2.2. Interviewing Pharmacy students

Selection and participation Criteria for assessment is as follows:

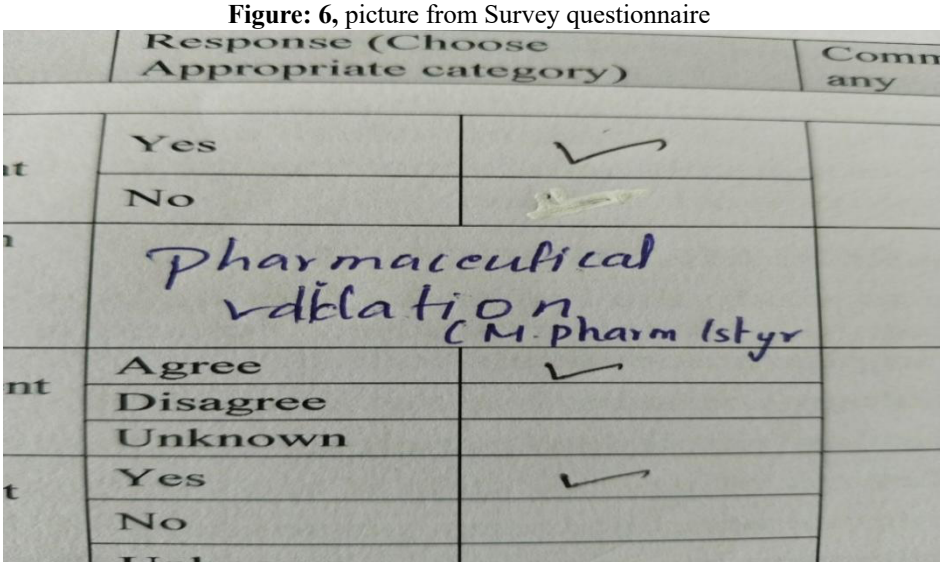
Figure: 5, Pharmacy students survey response



Question Details:
Q1. Any of your course (B. pharm or M. Pharm subject / curriculum has information on what is Data Integrity (DI)?
Q2. In which class / semester / subject has lesson on Data integrity and its compliance requirements (if no lesson is part of your curriculum, then this not applicable for you)
Q3. Is DI compliance always an important element in pharmaceutical industry?
Q4. Do you aware DI noncompliance's fail to get approval for manufacturing by regulatory authorities?
Q5. Do you consider education curriculum needs to include chapters and case studies on DI requirements?
Q6. Do you consider emphasizing DI compliance in education curriculum is needed?
Q7. Do you consider educating DI concepts during studies helps working in industry with additional basic training?
Q8. Do you consider preventing DI nonconformity is better than correcting DI nonconformity?

a. Targeted to collect response from 100 students across the M. Pharmacy departments to understand their feedback and calculate the % of the survey response about data integrity understanding, requirements and its significance.
b. Master's in pharmacy students were considered, because they can give response about bachelors in pharmacy and masters in Pharmacy curriculum as well.
c. Total 111 students from M. Pharmacy (1st and 2nd year students) were participated in the survey.
d. Survey includes students of 2 different colleges from departments such as Pharmaceutics, Pharmaceutical Analysis, Pharmacology, Industrial Pharmacy, Quality Assurance and Regulatory Affairs.
Survey outcome response as follows:
e. 77% pharma students responded that Data integrity concepts were not thought in pharmacy academics.
f. Rest of the students (23%) were responded that they were thought about Data integrity orally or in Seminars. Out of which 3 (3%) students used whitener (refer figure 6) to answer, which is not recommended as per Data integrity compliance requirement.

Figure: 6, picture from Survey questionnaire



g. 96% pharma students responded that Data integrity concepts should be included pharmacy academics and rest of the students were unknown about its inclusion requirements.
Conclusion from pharma students is that pharmacy curriculum offers only limited (through seminars or orally) or no information on Data Integrity requirements [24] and 96% students expressed that Pharmacy curriculum needs to include chapters and case studies on DI requirements and 4% students unknown about DI inclusion in academics.

2.3. Reviewing Pharma industry training on Data Integrity

Reviewed training systems in industry and details are as follows:
a. All the employees are training on Good Documentation Practices and Data Integrity program

despite experience and qualification of employees are different from each other.

b. Industry in general follow below mentioned review system in compliance to ALCOA+ principles [23].

- Self-inspection program [26]
- Continuous Monitoring [27]
- Periodic Verification
- Audit Program / CAPA / Retraining [27]
- Escalation mechanism

Despite, continuous audits [28], providing training [28] and with having above controls in place pharma industry is facing serious concerns with respect to Data integrity noncompliance's. Conclusion from review of training systems is that all the employees are trained and treating in same manner [29], where newly joined employees (freshers) were not getting extra trainings or case studies to understand the importance and severity of the Data Integrity noncompliance [30]. Experienced employees already exposed to industry regulations[25] and non-conformances, however newly joined employees are not getting enough insights on Data Integrity concepts or case studies which is conformed in the survey provided by industrial experts, students in previous reports.

3. Assessment and Conclusion

Upon review of USFDA dashboard for warning letters and 483 observations, which gives a clear insight on Data integrity issues existence at pharmaceutical industry and DI is the most concerning noncompliance issue to receive warning letters from agency where drug manufactures face challenges to manufacture and distribute lifesaving drugs. Even as per the recent Quality Management Maturity (QMM)[31], Data integrity is key Quality element to provide confidence on Quality culture and transparency of organization data. All the Pharmaceutical Industry experts (100%) participated from the various departments and organizations are responded that DI compliance is important, and it is must to get an agency approval for manufacturing of pharmaceutical drugs. All the Pharmaceutical Industry experts (100%) participated from the various departments and organizations are responded that, new joiners to pharmaceutical industry needs appropriate knowledge on Data integrity and all of them responded that education curriculum needs to include DI chapters, case studies, and emphasizing its importance on DI compliance will improve working in industry with minimal training.

Pharmacy students responded that Data integrity education in pharmacy curriculum offers only limited or no information on Data Integrity requirements and 96% students expressed that Pharmacy curriculum needs to include chapters and case studies on DI requirements and 4% students unknown about DI inclusion in academics. All the employees are training on Good Documentation Practices and Data Integrity program with ALCOA+ principles in the pharmaceutical industry, however pharmaceutical industry treating all the employees in same manner, where newly joined employees (freshers) were not getting extra trainings or case studies to understand the importance and severity of the Data Integrity.

Our research doesn't intend to say that Data integrity in pharmaceutical industry is only due to less or no knowledge coming from academics, however pharmacy academics are not giving enough knowledge to students on industry main concern of Data Integrity. Research or survey absolutely confirms that pharmacy academics need inclusion of Data Integrity chapters and case studies to provide needed knowledge to students.

Both Industry experts and pharma students voiced out about the need of DI education in pharmacy curriculum to meet the industry current facing challenges and requirements.

4. Proposed solution and recommendation

Pharmacy academics are expected to meet the requirements of pharmaceutical industry requirements, which is the reason there are different departments in pharmacy Masters education are established. Pharmaceutical industry facing growing challenges with Data integrity Both Industry experts and pharma students collectively voiced out about the need of DI education in pharmacy curriculum to meet the industry current facing challenges and requirements.

After reviewing good documentation practices and Data integrity training program in pharmaceutical industry it is identified that no different or extra training is providing to new joiners from academics.

Our research doesn't intend to say that Data integrity in pharmaceutical industry is only due to less or no knowledge coming from academics, however pharmacy academics are not giving enough knowledge to students on industry one of the main facing compliance challenges that is Data Integrity. From our studies we are concluding that from pharma industry experts and pharma students absolutely confirms that pharmacy academics need inclusion of Data Integrity chapters and case studies to provide needed knowledge to students.

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