FACTS ON DRUG REGULATIONS

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REVIEW ARTICLE

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ABSTRACT

The pharmaceutical products are very much driven by the drug regulation imposed by ministry of health in individual countries. The basic facts on regulations is that they are mandatory and noncompliant are punishable under the law. Further, compliance is not a one time job but it is an exercise to be performed over the life cycle of the drug products. It starts from development of the products and continues till the product is in market. The information, registration, permission and extensions/withdrawals are the primary regulatory requirements for the drug products.

The main focus of drug regulations is to check that safety, quality and efficacy of the drug products over its lifecycle.

Keywords: GLP, GCP, GMP, FDA, regulation, Marketing Authorization.

INTRODUCTION

The regulations for ensuring quality, safety and efficacy of the drug products are increasing by leaps and bounds all over the world. However, still a large number of regulatory professionals are not aware of the current facts and figures on Marketing Authorization Procedures, GMP Compliance, GLP, GCP and Data Integrity.

The most distressing fact is that many of the professionals have incorrect understanding.

This article is specially designed to remind/refresh the basics of drug regulations.

FACTS OF DRUG REGULATIONS

1. The draft guidance is not binding as final rules. However, all final rules are binding on industry and regulators alike. The industry has to operate as per drug regulations and the regulators have to limit their noncompliance notifications within the rules. They cannot impose penalty for acts which are out of the scope the regulations.

2. Final Rules are considered regulating Agencies best statement at the time issued. They are usually modified / amended by the regulators from time to time to make them best fit with changing health requirements.

3. The sole aim of Guidance documents is to provide insight on regulators thinking on the proposed rules. They are not binding legally. FDA cannot be sued based on the guidance provided through Guidance Documents. (1)

4. The worst part of the regulations is that they can be interpreted differently on case to case basis. This sometimes raises the problem during regulatory audits.

5. It is not easy to fight on Regulators decisions. Only big companies with dip pockets and legal staff can challenge FDA. The small companies shall never pickup fights/arguments with the regulating agencies as courts are always inclined to endorse agencies perspective on rules. You cannot win an approval by cross questioning or challenging Regulatory agency officials.

6. Compliance shall not rest on regulations as issued by Regulatory agencies. It shall match with Regulators current opinion on regulations. The different experts at Regulatory agencies may have different opinions on the same subject. It is always your luck who reviews your facility and documents. It is the best practice to get your doubts clarified from Regulatory officials on current regulations from time

to time. Pre-submission discussion with Drug administration official's may be uphill task but it helps a lot.

7. Drug officials have very wide experience on theoretical and practical aspects of regulations. You can learn many facts from them in minutes for which you were struggling over a very long time.

8. Never insult/disrespect/avoid Drug inspectors during their visit. Always cooperate and answer their queries. At the same time never volunteer unwanted information. The Drug officials do help people those who are courteous, open minded, soft spoken and good listeners. FDA has legal provision for face to face discussions to resolve queries on regulatory compliance.

9. Never manipulate/falsify the records. Drug officials are expert in decoding and even proving true facts as false.

10. Currently data integrity is the major concern for marketing authorizations. Further, falsification control /traceability have become major issues for distribution of the drug products.

11. Nearly 50% of noncompliance observed in manufacturing/distribution can be assignable to misunderstanding of the regulations.

12. Interpretation of regulations is not very easy as it can assume different meanings with different interpreters, different situation and different products. You must read the regulations very often and interpret them in broad prospective. The drug regulations cannot be best understood just by reading but by discussion with qualified and experienced personnel.

13. Compliance is not very easy. You must get all your functions/activities checked, approved and authorized before implementing.

14. The Drug Officials are wise. They acquire their skills through continuous audits performed at various sites. You may also enhance your skills through self audits and vendor audits.

15. Drug regulations are not static. They get amended with time to meet new challenges.

16. The drug regulations are primarily focused on:

(a) Export authorization: It is a legal permission granted by Ministry of Commerce of exporting country.
(b) Import Authorization: It is legal permission granted by the "Ministry of Commerce" for drug products.
(c) Marketing Authorization: It is a legal approval of the quality, safety and efficacy of the product and the establishment where it is manufactured by the health authorities of importing country
(d) Post Approval changes
(e) Clinical Trials Authorizations
(f) Post Marketing Surveillance
(g) Data integrity
(h) Labeling, packaging and distribution
(h) Stability Studies, Impurity Profiling, Assay, Validations etc.

17. The corruption/bribes in Clinical Trials/Safety Studies/Bio Studies and at other levels are strictly prohibited. In US Financial certificate is required for marketing Authorization.

18. The drug regulations require protection of patent rights. In US the patent drugs have exclusivity marketing rights for 20 years. Further this right can be further extended for pediatric applications**.**

19. 483 is a powerful instrument with FDA to warn the drug manufacturers for deficiencies in facility design and manufacturing/testing/storage/distribution operations. In severe cases this tool is used to restrict/suspend marketing Authorizations. (2)

20. The regulations allow confidentiality of technical information of the products.

    In US, Canada, Europe, and Japan has system called as DMF which helps maintaining confidentiality of

manufacturing process for API / Excipients / Packaging materials suppliers from end users.

21. The regulations in ICH region is less or more same.

Each country has similar system for registering New Drugs, Generic Drugs, OTC Products, Biological, veterinary products, Medical Devices, Nutritional products.

The regulation in US and Europe are as per follows (3, 4):

Table 1: Comparative table for regulation in US and Europe

Sr. no.	US	European Union
1	NDA	Full MAA
2	ANDA	Abridged MAA
3	DMF for API	ASMF for API
4	Quality certificate for Excipients and API	Certificate of suitability (CEP)
5	Rule 510(k) for PMA for medical Devices	CE Marking for Medical devices
6	Central procedure for Marketing authorization of all products	Central process for MA of Critical Products. However, in addition there are National, MRP and DCP for MA
7	Pharmacopeia Forum for information on changes/amendments in Pharmacopoeia	EDQM has equivalent site for communicating changes in E.P
8	Most of the Regulatory approvals are fees based	All the Regulatory approvals are fees based
9	Compulsory Inspection for NDA/ ANDA	Compulsory Inspection under MAA
10	Application in English	Application in English and/or in Regional language
11	eCTD is mandatory	eCTD is Mandatory. However, some countries do accept Paper copies and NeeS documents.
12	Patent system for the Protection of New Drugs	Patent system for the Protection of New Drugs
13	Environmental Protection	Environmental Protection
14	Priority authorization to Orphan Drugs	Priority authorization to Orphan Drugs
15	Structured product Labeling	Mock labels, Actual labels, Braille, Labeling.
16	At least one Pivotal Batch (Production) for authorization of ANDA	Three production batches for MA
17	Partial Clinical Trials for Biogenerics	Partial Clinical Trials for Biogenerics
18	SUPAC Guidelines for variation Filing	Variation Filing Guidelines

22. FDA provides Training and advice on eCTD and other regulatory submissions. It checks and advises on corrections till the application is updated to required standard.

23. Many regulatory authorities including FDA maintain the negative list of traders/manufacturers/exporters/importers. Their activities are specifically monitored for noncompliance.

24. Drug Inspectors are very smart. They have capability to decode all your codes and discover the deficiencies. Generally, it is not possible to hide non compliances from them

25. Regulatory compliance requires information/record in wells structure format which is easy to read, understand and assess**.** The regulatory agencies often issues specific forms and data sheets for recording the information.

26. The drug regulations require compliance to standards described in respective Pharmacopoeia for all drug products including API, Excipients, Finished dosage Forms, Medical Devices, Veterinary drugs, Biological, Phytochemical, Nutritional products, medicinal herbs.

27. The regulations demand compulsory approval of protocols for all clinical studies/nonclinical studies/bio studies. The regulations also require audit of clinical trial /bio-studies data.

28. The regulation requires compulsory compliance to GMP without which the drug is deemed as adulterated.

29. The regulation requires investigation and elimination of Root cause for all nonconformities.

30. The regulation requires that every person in drug manufacturing must perform Annual Review of Quality of the products and must take suitable action to correct out of trend situations.

31. The Regulating agencies requires that the label must display true information on the following heads:

    - Generic Name
    - Brand name if any
    - Composition per tablet/capsule or per 5 ml
    - Total quantity (e.g. 100 tablets, 30 ml)
    - Reference to quality standards of each ingredient and preparation as a whole
    - Maximum Retail price (in some countries)
    - Storage Conditions
    - Warnings/Cautions/Dosing Instruction as applicable
    - Name of the Manufacturer/Importer/Distributor as applicable
    - Mfg. License No.
    - Date of Mfg. and date of expiry
    - Proper graphic signs to highlight the particular information
    - Bar Code

32. The regulation requires that drug manufacturer must inform minor changes at least once at the anniversary date of marketing authorization.

33. It is compulsory to withdraw the complete lot of drug from the market as and when any adverse report or critical deficiency is observed /reported in the relevant drug products.

34. The regulations require that development, manufacturing, storage and distribution functions shall be executed under the supervision of an expert person only and relevant records shall be maintained beyond the expiry date of the products.

35. The regulation insists proper training of all the personnel involved in manufacturing and distribution chain.

36. The regulators are also concerned with safety at work place, health of the personnel involved in manufacturing, prevention of environmental /water pollution.

37. The drug regulating agencies respect Patent/Trade mark laws. They prohibit infringement of patents. Further they preserve confidentiality of all technical

information. The applications are generally evaluated on the first come first served basis.

38. The drug regulations respect and permit the following trading styles:

a) Own Manufacturing and direct marketing in other countries
b) Own Manufacturing and marketing through agency
c) Contract manufacturing in partial or full
d) Imports for exports to third countries
e) Import of API/Excipients for Manufacturing Finished Dosage Forms

CONCLUSION

The drug regulations are becoming more and more stringent. Every now and then new amendments or new regulations are introduced to combat falsifications/short cuts/ noncompliance by the industry. The regulations for Manufacturing, data integrity, validations, Impurity profiling, Import, export, storage and distribution are becoming complex.

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CONFLICT OF INTEREST

Author declares that there are no conflict of interest.

REFERENCES

1. FDA Guidance Documents. Regulatory Information [Internet]. 2012 March 12 [cited, 2014 March 2]; Available from: http://www.fda.gov/regulatoryinformation/guidances/
2. FDA Warning letter. Inspections, Compliance, Enforcement, and Criminal Investigations [Internet]. 2014 [cited, 2014 March 12]; Available from: http://www.fda.gov/iceci/enforcementactions/WarningLetters/default.htm
3. FDA. Guidance, Compliance, & Regulatory Information. [Internet]. 2014 [cited, 2014 March 18]; Available from: http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/default.htm
4. European Medicines agency. Human Regulatory. [Internet]. 2013 [cited, 2014 March 23]; Available from: http://www.ema.europa.eu/ema/

