DRUG REGULATORY AFFAIRS

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SCOPE

• The scope of regulatory affair (RA) is very broad

• Takes several years for a aspiring professional to comprehend a small segment of this field
SCOPE

• Through the dynamics of RA, firms assure regulatory agencies that the products marketed meet all the regulatory expectations in regards to quality, purity, safety and efficacy.
SCOPE

Submissions:

- IND, NDA, ANDA and DMF

- Their modifications/supplements

- Related correspondence
SCOPE

Reporting/Notifications:

- Annual Reports
- Adverse Drug Events
- Field Alerts
- Recalls
Regulatory Compliance

- Internal Periodic Audits
- External Vendor (supply chain) Audits
- Pre-Regulatory audit
- FDA inspections
SCOPE

Regulatory Compliance

Follow-up to Regulatory Actions:
- 483 Responses
- Untitled letters, Warning letters
- Import Alerts
- Seizures (US only)
- Injunctions (US only)
- Consent Decrees (US only)
The complexity of regulatory affairs is several fold magnified if a drug, device or biological product manufacturer is exporting to several countries.
CHALLENGES TO PROFESSIONALS

RA involves Complex dynamics:

- Multi-dimensional
- Knowledge in science and Technology
- Prolific communication skills
- Deal with people with diverse backgrounds, skills, cultures and personalities
- Deal with conflicting loyalties, motivations, social and ethical responsibilities
CHALLENGES TO PROFESSIONALS

• Deal with conflicting loyalties, motivations, social and ethical responsibilities

  - Most important topic to discuss

  Case in point: Submission of a dossier
CHALLENGES TO PROFESSIONALS

During Submission of a Dossier an RA professional would be:

• Guided by various regulatory guidances
• Receiving input from various departments within the firm about process capabilities and product attribute specifications
• Receiving advise from peers about easy ways to get approvals
• Receiving motivation from the top management through incentives for achieving speedy approvals
FDA Inspections and GMP Challenges

I will discuss several deficiencies which I have observed in my experience as an investigator in India, which I believe, if not addressed, could negatively impact the Indian drug exports.
Challenges – Unrealistic Commitments

• Applications/DMFs with unrealistic commitments
• In the old paradigm firm’s empowered regulator’s by obliging their demands to continually reduce the specifications based on meager data submitted from limited manufacturing experience.
• Unrealistic commitments could also be due to unhealthy competition in the industry.
• Limited knowledge of US regulations and FDA’s expectations
Challenges – Inadequate Development Work

• Process optimization is motivated by regulatory compliance while good science often taking back seat or no seat
• Process development is often not robust
• Too many process changes are made after regulatory submissions
• Process development in early stages often ignored
A Well designed process executed using a poorly written batch record may result in a product with unacceptable and/or variable quality.
Challenges – Inadequate Batch Records

Batch records should:

- Be executable by operators
- Allow for recording of enough critical process information to develop a process signature to facilitate comparison with previous batches
- Allow for identification of beginning and end of unit processes with clarity
- Describe exactly how process is carried out in the plant
Challenges – Inadequate Batch Records

- Wide process parameters are given to the operator without proper guidance
- Important process details are not stated in the BPRs but left in related SOPs
- Results from confirmatory in-process QC tests upon which process decisions are based are not shown in BPRs or not readily accessible
Challenges – Process Validation

• Validation is collection and evaluation of data, from the design stage through product commercialization, which establishes scientific evidence that a process is consistently capable of delivering quality product.

• Continual verification should be performed using a product Lifecycle approach to keep a process in validated state.
Challenges – Process Validation

A firm which has successfully validated a process should be able to:

• Understand the sources and degree of variability in the process inputs and parameters and how they impact the quality attributes of the in-process materials and the drug product

• Control the variability commensurate with the risk
Challenges – Process Validation

Having a robust sampling and testing is an important element of a successful validation plan. The sampling should be scientifically sound and significantly more intense than for routine product release.
Challenges – Data Integrity

Root Causes

• Committing to unrealistic specifications
• Lack of manufacturing capacity
• Unhealthy market competition
• Poor record keeping practices
• Deliberate manipulation of documents and data
Challenges – Data Integrity

Localized
- Constant turnover of staff
- Untrained staff
- Lack of due diligence in hiring
- Lack of robust quality system to detect the problem

Systemic
- Senior Management is involved
- Management unwilling to mitigate a localized problem
Challenges – Data Integrity

Consequences could be Catastrophic to the firm, and significant to the industry and the country

• Loss of credibility worldwide
• Loss of markets
• Staff retention problem
• Deterioration of technical capabilities
Challenges – Data Integrity

Prevention Strategies

• When Localized problem is observed work with your customer and the relevant regulatory agencies
• Be transparent
• Have robust quality systems
Challenges – Supply Chain

• Price pressures may prompt a few firms to substitute inexpensive excipients, raw/starting materials, intermediates and APIs from unapproved or unqualified sources

• FDA has a draft guidance about supply chain management

• The agency is willing to work with any companies or individuals with credible information to mitigate this risk
Challenges – Supply Chain

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Challenges – Supply Chain

• ID testing of incoming materials is a cGMP
• Currently ID testing is performed by many firms on composite sample only even for key raw materials, starting materials and APIs
• A few firms are adopting PAT tools such as NIR for rapid scan of incoming materials
• FDA encourages firms to adopt the PAT tools
Challenges – Supply Chain

Firms need to improve

- Vendor qualification procedures
- Annual vendor performance evaluation and re-qualification
- Vendor disqualification criteria
Challenges – Supply Chain

• FDA recommends that Vendor Qualification be completed for key raw and starting materials and API (for drug product) before releasing the product to the US markets

• Vendor evaluations should not be just based on compliance to specifications or mailed questionnaire

• The evaluations should be based on relative quality comparisons of all critical attributes
Challenges – Facilities

Pharmaceutical cleaning is essential for preventing cross contamination. Cleaning validation is as good as the cleaning procedure it represents. A few concerns about cleaning are:

• Cleaning procedures are not scientifically sound. For example, cleaning of a 2,000-liter reactor with 50-liters of cleaning solution using a bucket and tumbler
• Cleaning procedures as practiced are promoting proliferation of contamination
• Cleaning documentation is often inadequate
Challenges – Facilities

- Pressure differentials are not maintained between the storage and sampling/dispensing areas
- Cleaning between product changeovers in the sampling and dispensing areas is not adequate
Challenges – Quality System

Change Controls
- Change control documents are illegible
- Importance is not ascribed to the description and rationale for change
- Change control management reviews are often not detailed
- Post-change control reviews were not managed and recorded

FDA recommends firms to refer to ICH Q10 guidance
Challenges – Quality System

Deviation Investigations

• Related SOPs are often focused on paperwork
• Managing the Impact of the deviation on the process largely not addressed in the SOPs
• Deviation investigations are often not thorough and feedback is not provided to improve the process.
• CAPA is not managed
Challenges – Quality System

Annual Product Reviews (APR)

• Largely considered as a regulatory requirement
• Not considered as a powerful management tool
• All products manufactured at the site irrespective of target market should be included
• Reviews are done at the end of the year and not on continual basis
Challenges – Quality System

Annual Product Review (APR)
• Only a few firms are charting the quality data
• Reviews are largely focused on regulatory compliance i.e., if any data crossing the specification limits
• Quality data within the specification limits not reviewed for trends
• Special cause deviations within the specification limits are almost never investigated
• Investigation of data outliers are mostly incomplete as it is done after a year
• Statistical tools are not used in interpreting the data
Summary

• FDA encourages firms to adopt a proactive approach to quality management and review quality data on a continual basis.

• Quality is larger in scope than mere compliance to specifications. If firms implement a robust and proactive quality system they would not only produce high quality drug products but also achieve sustained profitability.
Summary

• Diverse educational and work experiences would help to be a successful RA professional

• Takes years of commitment and hard work to understand and appreciate the dynamics of this field

• For entry level professionals working at smaller firms would provide greater understanding of the field

• RA offers boring jobs but passionate carriers

• If you are philanthropic there will be plenty of redeeming value
Good Luck!!

THANKS FOR THE OPPORTUNITY TO SPEAK