The Importance of Quality Control and Regulatory Compliance of Active Pharmaceutical Ingredients: Recent Study

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Abstract: This brief review presents the international approaches to assessment of the content of geotaxis impurities (residual solvents and various inorganic and organic impurities) in pharmaceuticals. Nowadays, it has become necessary to provide not only purity profile but also impurity profile of a particular pharmaceutical product because of national and international regulations. These aspects along with significance of the quality, efficacy and safety of pharmaceuticals, including the source of impurities, kinds of impurities, control of impurities and regulatory aspects are discussed. The supply of essential medicines of good quality has been identified as one of the prerequisites for the delivery of health care system of any country as poor-quality medicines can harm or even kill consumers. The presence of unwanted chemicals in a particular medicine, even in extremely small quantities, may influence its efficacy and safety. Unlike in other industries, a medicine is a dynamic product whose color, consistency, weight, and even chemical identity can change between manufacture and ultimate consumption. Hence, quality of pharmaceuticals has been a concern of the people of the whole world, and is now receiving critical attention from regulatory authorities. Impurities in pharmaceutical products are of great concern not only due to the inherent toxicity of certain contaminants, but also due to the adverse effect that contaminants may have on drug stability and shelf-life. In pharmaceutical and drug products, impurities are the unwanted chemicals (organic, inorganic and residual solvents) that remain with the active pharmaceutical ingredients (APIs), or develop/added during formulation, or upon aging. Organic impurities are the most common impurities found in every API which get incorporated normally during the multi-step synthesis process despite proper care. For achieving great deals with efficacy and safety parameters of pharmaceutical product control the in process quality consideration with ingredients and maintain good regulatory documents are matter most.

Key Words: - Ingredients, pharmaceutical product, quality control, ethical standards, safety and efficacy.

I. INTRODUCTION

An important goal of IPCC good practice guidance is to support the development of national green house gas inventories that can be readily assessed in terms of quality and completeness. It is good practice to implement quality assurance and quality control (QA/QC) procedures in the development of national greenhouse gas inventories to accomplish this goal.[1] This guidance establishes good practice consistent with the Revised 1996 IPCC Guidelines for National Greenhouse Gas Inventories (IPCC Guidelines). The QA/QC good practice guidance outlined here reflects practicality, acceptability, cost effectiveness, existing experience, and the potential for application on a worldwide basis. A QA/QC programme contributes to the objectives of good practice guidance, namely to improve transparency, consistency, comparability, completeness, and confidence in national inventories of emissions estimates. The outcomes of the QA/QC process may result in a reassessment of inventory or source category uncertainty estimates. For example, if data quality is found to be lower than previously thought and this situation cannot be rectified in the timeframe of the current inventory, the uncertainty estimates ought to be re-evaluated. The terms ‘quality control’ and ‘quality assurance’ are often use are described as[2]:

DEFINITION OF QA/QC Quality Control (QC) is a system of routine technical activities, to measure and control the quality of the inventory as it is being developed. The QC system is designed to: (i) Provide

routine and consistent checks to ensure data integrity, correctness, and completeness; (ii) Identify and address errors and omissions; (iii) Document and archive inventory material and record all QC activities. QC activities include general methods such as accuracy checks on data acquisition and calculations and the use of approved standardised procedures for emission calculations, measurements, estimating uncertainties, archiving information and reporting. Higher tier QC activities include technical reviews of source categories, activity and emission factor data, and methods.[3]

II. QUALITY MANAGEMENT SYSTEM FOR API MANUFACTURERS

The laboratory or organization management should establish, implement and maintain a quality management system appropriate to the scope of its activities, including the type, range and volume of testing and/or calibration, validation and verification activities it undertakes. The laboratory management should ensure that its policies, systems, programs, procedures and instructions are described to the extent necessary to enable the laboratory to assure the quality of the test results that it generates.[4]

Control of documentation-

Documentation is an essential part of the quality management system. The laboratory should establish and maintain procedures to control and review all documents (both internally generated and from external sources) that form part of the quality documentation. A master list identifying the current version status and distribution of documents should be established and readily available.

Control of records-

Records provide evidence of conformity to requirements. They should be legible, readily identifiable and retrievable. A documented procedure should define the control needed for identification, storage, protection, retrieval, retention time and disposition. The control of records includes hard copies as well as electronically stored data. Records should be established, at least for raw materials, intermediates, labelling, packaging materials, batch production, laboratory data, including Certificates of Analysis and stability data, calibration, distribution, complaints and returns. A procedure for the review of batch production and laboratory records is required.[5]

Management Responsibility-

Top management should provide evidence of its commitment to the development and implementation of the Quality Management System (QMS) and continual improvement of its effectiveness by:

•communicating to the organization the importance of meeting customer as well as regulatory (GMP) and legal requirements, including environmental, health and safety aspects,

• applying risk management,

• establishing the quality policy,

• ensuring that quality objectives are established,

• conducting management reviews,

• maintaining appropriate conditions throughout the organization for processes and systems,

• ensuring the availability of resources, particularly enough manpower, suitably trained.[6]

Resource Management-

Resource management compromises provision of resources, infrastructure, human resources and the work environment. The top management has to provide an adequate number of personnel qualified by appropriate education, training, and/or experience to perform work and meet the requirements. Top management has to ensure that the organization determines, provides and maintains the infrastructure needed to conduct operations (e.g. manufacturing, testing and support) according to contemporary standards. Infrastructure comprises buildings (including utilities and workspaces), equipment and computerized systems. Top management should ensure that the work environment has a positive influence on motivation, satisfaction and performance of people in order to enhance the performance of the organization.

Product Realization –

The product realization includes all the different value adding activities for the realization of product, starting from customer requirements up to shipment of product to the customer in the mutually agreed quality. The realization process consists of different activities such as planning of the product realization, customer-related issues, design and development, purchasing, production, service provision and control of

monitoring and measuring devices. The design and development process comprises planning, determination, review and verification of inputs and outputs and the control of changes. Purchased items which could impact final product quality should be purchased to defined requirements according to written procedures from an approved supplier. There should be written procedures describing receipt, initial visual check of labels and containers, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials. The suitability of devices used to monitor product characteristics for the intended purpose should be confirmed, and they should be checked, calibrated and regularly maintained. This includes computerized systems, laboratory instruments, reference materials, standard analytical solutions and buffer solutions used for process controls.

III. QUALITY AND COMPLIANCE IN QUALITY CONTROL LABORATORIES :

Quality systems are always inspected. The scope of this primer covers inspections of quality systems and laboratory control systems. During inspections, the FDA verifies that a firm's procedures and processes are in compliance with FDA GxP regulations such as Good Laboratory Practices, Good Clinical Practices, and Good Manufacturing Practices. If the FDA inspections identify deviations from the regulations, they will issue inspectional observations using 483 forms, also referred to as "483s" or inspectional observations. Depending on the severity of the deviations, instances of repeat observations, and a firm's response to the 483, the FDA may issue a formal letter listing some or all deviations of the 483, called an FDA Warning Letter.

While regulations and guidelines may typically endure unchanged for many years, interpretations, inspection, and enforcement practices undergo frequent changes and should be monitored regularly. Warning Letters, establishment inspection reports, and 483s (if publicly available) are ideal sources to find out what inspectors are looking for at specific times, and FDA press releases provide information on current FDA inspection policies.

In the last two years, an increasing number of firms have received FDA 483 inspection observations and Warning Letters. The FDA publishes most of the warning letters and some 483s and establishment reports on the Internet.[7]

Primary objectives of regulatory inspections are to (1) verify that the data measured in quality control laboratories are reliable and accurate, and (2) ensure that only safe and effective drugs are authorized for marketing and released for product shipment. QC laboratories are considered high-risk areas because they are often the final step verifying the quality of the drug prior to shipment. Therefore, they should follow GMP regulations to demonstrate the quality and integrity of data. Being in compliance is a prerequisite for successful FDA inspection. This chapter will give a brief overview of GMP requirements for pharmaceutical QC laboratories.

Compliance requirements for QC laboratories can be divided into two categories:

1. General quality system requirements that apply to all regulated activities within a firm, e.g., control of documents, internal audits, and qualification of personnel. These are called quality system requirements and typically are subject to the quality system inspection. Most of them are not specific to laboratories. 2. Laboratory-specific technical requirements that apply to specific situations in a laboratory, e.g., validation of analytical methods, verification of compendial methods, qualification of equipment, validation of computer systems, sampling, review, and approval of test reports.

Compliance Overview –

The overall impact of regulations on a pharmaceutical laboratory can be best illustrated by looking at the whole sample/data workflow (Figure 1). The upper part of the figure shows a typical laboratory workflow of samples and test data, together with key requirements underneath. The middle part shows GMP compliance requirements that are applicable to the entire sample or data workflow. The lower part shows general quality assurance requirements that are applicable not only to regulated laboratories but also to other departments within a firm.

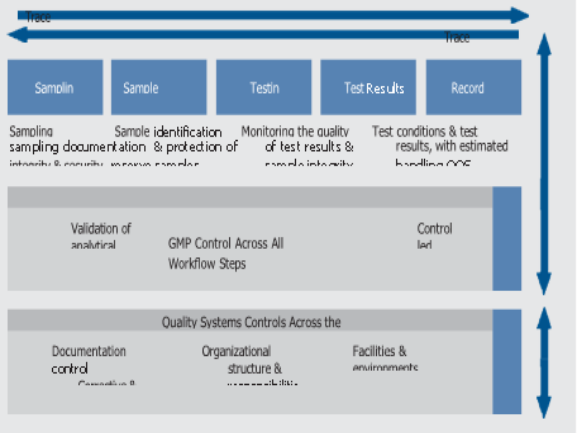

Figure 1: Quality Systems and Compliance along the Sample and Data Workflow

Compliance for Individual Workflow Steps –
All the individual workflow steps as shown in Figure 1 have specific requirements. These include:
•Sampling-
Sampling of substances, materials, or products for subsequent testing should follow a well-documented procedure. A sampling plan with a description of the sampling system, how sampling is performed, and by whom, should be in place. Sampling data should be recorded, such as sampling procedure used, location, the identification of the person who took the sample, and equipment used for sampling and environmental conditions, if relevant.
• Sample Handling-
Laboratories should ensure proper identification and protection of samples from the time the sample is taken until the time of its disposal. Receipt, protection, storage, processing, retention, and disposal should be described in a procedure. The procedure should include provisions for protection against deterioration, loss, or damage during transportation, handling, and storage.
•Testing-
Procedures for testing should ensure that only validated methods are used, that the equipment is qualified, and that sufficient system suitability test runs are conducted. Specifications and acceptance criteria should be defined for the sample to be tested. Procedures and parameters for testing should be documented. This includes laboratory testing during the manufacture of APIs, raw material, and testing of finished products to the extent that cGMP regulations apply.
• Test Results-
Test results should be signed by the analyst and reviewed and approved by a second person, e.g., the analyst's supervisor or a member of the QA staff.
• Record Management-
All records associated with testing should be archived. Such records include certificates of analysis (COA), instrument and method parameters, supporting information such as chromatograms and spectra, and equipment qualification records. The archiving period is defined by individual regulations and can range from 6 to 15 years, and even beyond.

Compliance across All Workflow Steps-
Some compliance requirements are applicable for all workflow steps. These are listed in the middle section of Figure 1, and include:
• Validation of analytical methods and procedures-
GMPs require analytical methods and procedures to be validated to demonstrate suitability for their intended use. The ultimate objective of the method validation process is to provide evidence that the method does what it is intended to do – accurately, reliably, and reproducibly. Typical method characteristics to be validated are: precision of amounts, reproducibility, specificity, linearity, accuracy, robustness, limit of quantitation, and limit of detection.
• Equipment calibration and qualification-
All equipment that impacts regulated activities should be qualified and computer systems should be validated. The objective is to provide evidence that the equipment and computer systems are suitable for intended use.
• Equipment maintenance-
Equipment should be well maintained to ensure proper ongoing performance. Procedures should be in place for regular preventive maintenance of hardware to detect and fix problems before they can have a negative impact on analytical data.
• Controlled environmental conditions-
Environmental conditions such as temperature and humidity should be controlled and monitored to ensure that they do not adversely affect the performance of equipment and material. Environmental requirements are typically provided by suppliers of equipment and material.

IV. PHARMACEUTICAL MANUFACTURING: ACTIVE PHARMACEUTICAL INGREDIENTS AND FINAL FORMULATIONS

Pharmaceutical manufacturing occurs in two general steps. First, firms convert raw materials into Active Pharmaceutical Ingredients (APIs). API production is a highly sophisticated, technically demanding chemical and biochemical fermentation and/or synthesis process. APIs constitute a significant portion of the total cost for a drug. For example, on average, 40-50% of the cost of goods sold for generic oral solids comes from APIs.[[8]] Commodity API manufacturing tends to be a high-volume, low-margin business where economies of scale play an important role. The average commodity API profit margin is less than 10%. In fact, many large bulk API exporters from India work with a 3% margin on exported products.[[9]] The second step in pharmaceutical manufacturing is the final formulation of the drugs. Unlike the chemical business of API production, final formulations belong to the manufacturing sector. During this process, firms first mix APIs and excipients (other non-active ingredients), then either press the mixture into pills and tablets or prepare powders for solutions or filling of capsules, and finally, package the product for the public or private market. Final formulations require different skills and equipment than does API manufacturing.[[10]]

With so many API producers, API manufacturers have specialized and target their manufacturing based on a combination of the market opportunities and firm skills. Some examples of targeting strategies follow (list is non-exhaustive):

• Timing patent expirations:

APIs for drugs that have recently come off patent in developed countries. Firms can often achieve high profit margin with these drugs. As more and more firms pick up the newly off-patent drug, the cost will slowly fall back to marginal production cost.

• Mastering complex manufacturing: Complex APIs for drugs in developed countries are often difficult for firms to manufacture and provide a barrier to entry.

• Exploiting gaps in the patent coverage: As an innovator firm must register its drug in a country to receive patent protection, some firms can exploit gaps in a drug's patent coverage.

• Targeting major program drugs: APIs for major program drugs (e.g. HIV/AIDS, TB, and Malaria) for developing countries often have significant international funding. As firms needs to have WHO PQ or Stringent Regulatory Authority (SRA) approval to qualify, this limits competition while allowing firms to get large-volume orders.

• Competing in generic bulk drugs:

APIs for older drugs sold in developing countries usually have few barriers to entry and firms can operate on thin margins while still achieving significant revenues through scale.

V. THE CHALLENGES OF APIS OF CURRENT REVIEW

In general, the global API market is an efficient market based on commodities. However, two potential challenges may impede equality of access to quality APIs for small final formulators in developing countries.

1. Transparency: Small local final formulating firms procuring APIs on the global merchant market, usually from API-manufacturing firms located in either India or China, can find that navigating the market is challenging, especially when procuring non-WHO GMP or SRA approved APIs. Furthermore, as historically, Chinese API manufacturers could not directly export but had to go through a state-owned trading company, many Chinese API manufacturers still use such trading companies. [[11]]

2. Market price moves too low: API manufacturers are finding their margins squeezed and are under tremendous pressure to produce more for less or leave the market. Final formulators continuously push for lower API prices as they face incredible price competition themselves, to the point of sometime focusing more on market share than on profitability.[[12]] At the same time, raw material prices and environmental costs are rising. For example, Piramel Healthcare in India recently left the ibuprofen API market as they could not compete;[[13]] three producers in China now manufacture it. [[14]]

3. Small markets: API manufacturers may be hesitant to dedicate capacity to a small or declining market. In general, an API manufacturer would not be interested in a small / declining market if either all of its capacity was fully utilized for other products (and the manufacturer determined it was not wise to build more capacity at that moment) or if the manufacturing of the

required API could not easily fit it into its production schedule (e.g. the API requires larger than normal changeover of production lines or a different technology). As such, some neglected disease APIs and small market APIs still get overlooked.

4. Economies of scale: These economies of scale function relative to the market size – one market may be only large enough to sustain one manufacturer while another market could sustain hundreds. Once an API manufacturer has achieved a significant economy of scale on a small market, it often does not make sense for any other manufacturer to enter. As a result, the scaled manufacturers can become monopolists and charge higher prices. However, these higher prices could draw new competitors into the market, unless the API firm can prevent it by taking advantage of its size to control the raw materials or some other aspect of the market[.[15]]

5. Visibility: A lack of visibility into the supply chain may be the root of many challenges faced by the pharmaceutical industry. Today, the global pharmaceutical industry is knee-deep in a journey to solve the visibility problem by attaching product identifiers to every product and creating a system for all to access.

6. Logistics coordination: Differences in process permeate the industry, making any change in standards or control difficult to implement.

7. Compliance: Roughly 80% of active pharmaceutical ingredients and 40% of finished drug product are imported into the U.S. from overseas. Manufacturers in India and China, in particular, are a key source of the generic drugs prescribed to Americans in ever-increasing volumes.

It's not just manufacturing, though. Shippers and distributors will soon have to comply with regulations under the Drug Supply Chain Security Act, which requires any company wishing to sell pharmaceuticals in the U.S. to facilitate product "traceability" by 2023. Enforcement of the first stage of the law has been delayed by one year, but meeting the new standards for traceability and serialization will require significant changes and investment through the supply chain.

8. Cold-chain shipping: While all API are sensitive to the rigors of cross-border shipping, biologics in particular are heat sensitive and susceptible to contamination. Keeping these drugs cold, then, is a crucial part of the supply chains that connect drug makers to patients. [[16]]

The main objectives of the review of the study Active pharmaceutical ingredients supply chain in India, Europe, United States, China and Canada.

The Indian pharmaceutical industry accounts for at least 35% of bulk drug filings in the US. Post-TRIPS, the Indian pharmaceutical landscape is set to change permanently. Local pharmaceutical majors are moving up the international value chain, focusing on generics marketing in Europe and the US to complement their already-strong presence in bulk active pharmaceutical ingredient (API) supply and to capitalize on the record number of drugs set to go off-patent over the next five years. [[17]]

Supply chain reliability (SCR) :

Pharmaceutical supply chains are comprised of several stakeholders – ranging from suppliers of the Active Pharmaceutical Ingredients (APIs) to health systems. Among these entities, the API suppliers, manufacturing plants, and manufacturing lines are most likely to have disruptions that lead to shortages.[[18]],[[19]] To focus the scope of our analysis, we will concentrate on these three components. Our goal is to produce closed-form equations that can calculate the expected shortages of a given pharmaceutical supply chain. Expected shortages are given as a percent of demand, and reliability in this context is the ability of the supply chain to meet demand.

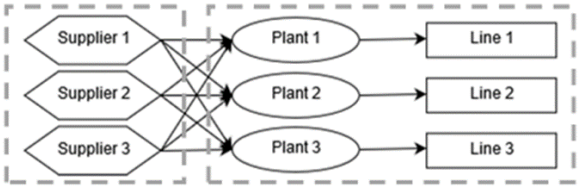

Figure 2. Example supply chain with a (3,3,1) configuration: 3 suppliers, 3 plants, and 1 line in each plant. The two subsystems are designated in dashed boxes.

An example of the configuration is presented in Figure 2. It includes three API suppliers, three plants, and one line in each plant. Each may be disrupted. For example, the plant as a whole may be shut down because of regulatory action due to contamination [[20]] or by a natural disaster such as Hurricane Maria.[[21]]Manufacturing plants and lines are considered separate entities in the model to reflect the different levels of disruption that can affect a plant. Components have different distributions of disruptions and recovery as well as different preventative

measures. That is, a second plant guards against large-scale disruptions but does not affect within-plant issues; a second line has the opposite benefit.

The two subsystems (API suppliers and plant-lines) operate in series. The reliability of the system as whole is the product of these two subsystems. Within each subsystem, the components (or groups of components) operate in parallel; only one is needed for the stage to be considered available. Within the plant-line subsystem, the groups (combination of plant and line(s)) operate in series; both a plant and at least one line are needed to be available for the component to be considered available. The lines are associated with specific plants, but the API suppliers can send materials to any plant, as in existing literature. [22] We assume that each component has adequate capacity to supply all demand. In summary, for the drug to be produced, at least one supplier and one plant-line combination must be available; this is called "system availability." If the company is not able to meet demand, this is designated "system disruption."

We assume that each component fails or recovers independently of the other components. We consider the overall risk of disruption to a component rather than specific types of disruptions. The rates of component failure and recovery vary by the type of component. For example, lines can have different recovery rates than suppliers.

The global pharmaceutical API supply chain :

Supply chain management is the integration, planning, and management of all of the processes across the system of resources from the earliest raw material supplier through the sourcing, logistics, manufacturing, and distribution networks to the customer. The base of supply chain management is the efficient integration and planning of demand and supply across companies. Planning is not only at the tactical level, but also at the strategic level.[23]

India and China-

India also fears that the new law could be an attempt to check its exports of cheap generics (copied versions of off-patent medicines) to markets in Latin America and Africa as large Pharma companies, many of them based in the EU, feel threatened by the country's cheap but high-quality medicines. In addition to that, the US has made it compulsory for Active pharmaceutical ingredients (APIs) to be manufactured locally though nearly 80% of the raw material requirement is supplied by China and India. The decision has already sent Indian pharmaceutical exporters into a tizzy, as it will significantly impact Indian drug exports. Before the new norms came into effect, US - based companies were allowed to procure APIs from countries like India and China, make the fixed formulations (final product) in the US and sell the drugs to the US government. Pharmexcil-Indias pharmaceutical export promotion council and has approached the Commerce Ministry, requesting authorities to intervene and resolve the issue. [24]

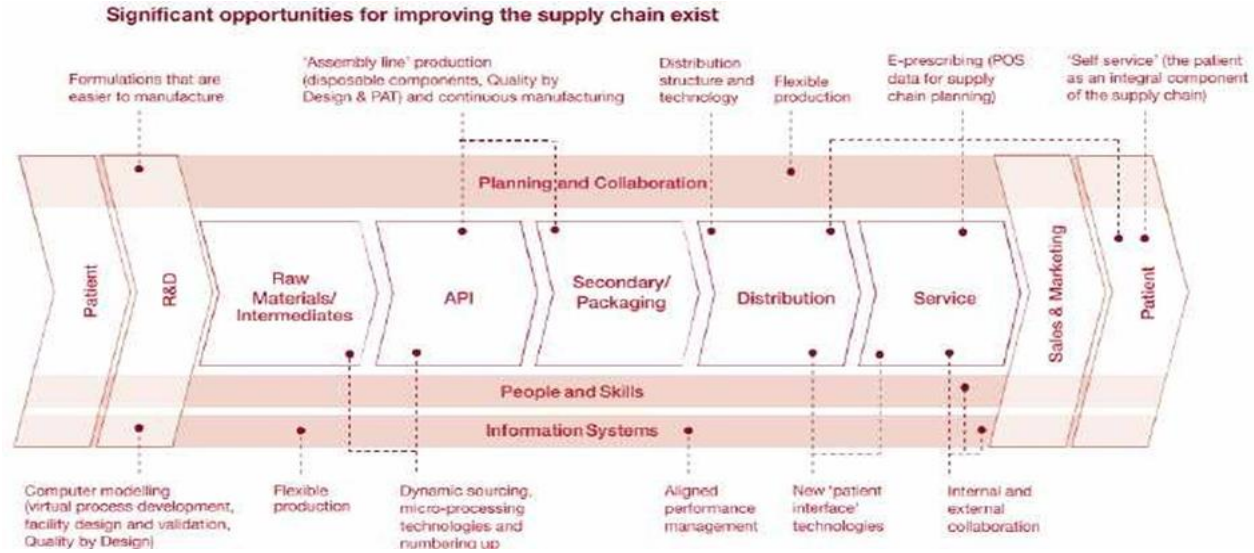

Figure 3. Opportunities for improving the supply chain

Traditional generic drug companies are looking toward china for the supply of Active Pharmaceutical Ingredients (API) drugs. China is also a viable source for key intermediates and active ingredients as well. Today, there is also collaboration between India and China, as China is sufficient in supplying API and other intermediates for the key drugs. As indicated earlier India is well-versed in the field of generic drugs manufacturing. As the number of companies and intermediaries in the Chinese pharmaceutical industry continue to expand at an unprecedented rate, there are mounting concerns about the threat of counterfeit API‟s emanating from this country on the global pharmaceutical market.[[25]]

VI HOW TO DEALS WITH SUCH CHALLENGES: INTELLECTUAL AND PRACTICAL OUTCOME

Four steps to a better supply chain-

To create a harmonized and integrated supply chain, it's critical to:

a) Implement a strong and uniform quality system-

Apply it, too, with regular audits at your suppliers. Measure performance with strict KPIs such as right first time (RFT). With a small, stable network of quality suppliers, a harmonized system can be achieved with several measurable benefits:

- Safety margins in ordering lead times can be substantially reduced or eliminated. As soon as the network is qualified, and regular auditing established, there will be no returns for re-work. This will create stability in the supply chain. In our example, at least two months were recaptured.
- The manufacturing process becomes transparent. A strong quality management process with quality leaders at the raw material suppliers allows for quality agreements that can be enforced. With such a system, suppliers‟ certificates of analysis (COAs) can be trusted, and time savings achieved. In our example, this removed at least a month from the timeline.
- Network partners can provide capacity flexibility. With harmonized process validation for chemical APIs, a network partner can serve as an extension of internal manufacturing to accommodate unforeseen demand. A strong and enforced quality system is the foundation of this capability.

b) Reduce the number of interfaces, and standardize operational models-

Standardize project management internally, and with suppliers, to allow for direct and clear communication. Share data with a collaboration tool such as SharePoint. With such a system:

- Important information can be communicated quickly and reliably. For example, toxicology classifications of raw materials can be exchanged immediately and special handling requirements consistently conveyed. This will prevent lengthy reworks of intermediates or DS, or last minute changes to plant configurations.
- Supply chain breakdowns can be avoided. Real time and transparent information means fewer disruptions due to miscommunication. Also, where a problem needs to be addressed by changes to the upstream system, it can be recognized and the changes initiated without delay.

c) Optimize intermediate inventories-

Identify the bottlenecks and add safety stocks on the downstream side. Bottlenecks usually appear in API production rather than DP due to the latter's shorter manufacturing cycles and faster change-over times. You can add safety stock appropriately if you have a view of demand and of the whole supply chain, and if suppliers and API manufacturers collaborate. With safety stocks rationalized:

Large and expensive API safety stocks may be eliminated. Safety stocks of precursors or starting materials may obviate the need to hold stocks of API. In our example, a stockpile of one intermediate significantly reduces lead time.

• Demand responsiveness may be increased without holding excess DP. Inventories of intermediates for API synthesis can provide flexibility to demand changes without the need to hold expensive excess stocks of DP.

d) Validate more than one production site-

Validate two production sites, ideally within the same company network, and file for them both during the initial set-up. Harmonized quality systems, manufacturing, and QC setups will simplify such an approach. For biologic APIs, it is also possible to crossvalidate two production sites. Harmonized operations and quality systems will make this substantially simpler. With more than one production site, a company has the flexibility to respond to

unanticipated demand. With biologics, for instance, single use fermenters can be quickly added to expand capacity if enough downstream process capacity is available.

Transparency in supply chain-

Many small local final formulation firms who procure APIs in the global market, mainly from the API manufacturing firms located either in India or China sometimes find that navigating the market is challenging, especially when procuring the non-WHO GMP or SRA approved APIs. Furthermore some API manufacturers who could not directly export their goods had to go through a state-owned trading company; many Chinese API manufacturers still use such trading companies. These traders may have a tendency towards non transparency. Moreover there is no public database that can track the API manufacturers and quality assessments.

Usually when a final formulator procures APIs from global merchant market he should use USFDA audits along with internal audits aiming on the supply chain, technical processes and facilities in order to validate the quality of the API manufacturer directly. The direct contact of the final formulator with the API manufacturer provides the necessary transparency to the supply chain. A manufacturer would know the process better and would be able to do necessary quality control checks directly, provide any requested certification. Many smaller final formulators without the resources and experience rely on a trader to source the APIs.[[26]]

Particulars	United states	Europe	India	China	Canada
Guidelines	Food and Drug Administration (USFDA)	European Medicines Agency (EMA)	Central Drugs Standard Control Organization (CDCSO)	Chinese Food and Drug Authority (CFDA)	Canadian Food and Drug Act (CFDA)
Pharmacopoeia	United States Pharmacopoeia (USP)	European Pharmacopoeia (EP)	Indian Pharmacopoeia (IP)	Chinese pharmacopoeia (CP)	-
Federal Regulators	Review authorizes, new Drugs brand and generic under Food and Drug Administration (USFDA)	Review authorizes, new Drugs brand and generic under European Medicines Agency (EMA)	Review authorizes, new Drugs brand and generic under the Food and Drugs and Acts (FDA) & European Medicines Agency (EMA)	Review authorizes, new Drugs brand and generic under the Food and Drugs and Acts (FDA) European Medicines Agency (EMA)	Review authorizes, new Drugs brand and generic under the Food and Drugs and Acts (FDA)
Guidelines followed for API (Active Pharmaceutical Ingredients)	ICH Topic Q 10	ICH Topic Q 7 (European Medicines Agency)	ICH Topic Q 7	ICH Topic Q 7	ICH Topic Q 7
International fora	World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD)	World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD)	World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD)	World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD)	World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD)
API Exporting	Less	Less	More	More	More
Manufacturer Guidelines	GMP	GMP	GMP	GMP	GMP
Extent of Price Controls	-	-	High	High	Moderate
Cost of API Production	High	High	Low	Very Low	Medium
Regulatory of API	Stringent	Stringent	Medium	Low	Medium
Cost of API Production	High	High	Low	Low	Medium
Quality of API	High	High	Medium	Very Low	Medium

Table 1. Compression Study of Active Pharmaceutical Ingredients supply chain of United States, Europe, India, China, and Canada.

VII. IMPORTANCE OF DATA INTEGRITY & ITS REGULATION IN PHARMACEUTICAL INDUSTRY

Data integrity is the issue of maintaining and ensuring the accuracy and consistency of data over its lifecycle. This includes good documentation practice, good data management practices, such as preventing data from being altered each time it is copied or moved. Data integrity applies to both paper records and electronic records. Processes and procedures are put in place for companies to maintain data integrity during normal operation.[[27]]

Before a pharmaceutical product available for a patient, the manufacturing company has to present evidence of efficacy and safety. For this, they have to run trial studies and lab testing. ALCOA in pharmaceuticals is used to ensure that the quality of the evidence collected is maintained as per regulatory guidelines. Many regulatory bodies as the FDA, Health Canada and the EMEA recommend the use of ALCOA to ensure good documentation practices in pharmaceuticals.[[28]]

ALCOA- ALCOA is defined by US FDA guidance as Attributable, Legible, Contemporaneous, Original and Accurate. It relates to data, whether paper or electronic and these simple principles should be part of your data lifecycle, GDP, and data integrity initiatives[.[28]] It helps in developing strategies so that the integrity of the evidence is maintained both in research and manufacturing. The aspects of ALCOA in pharmaceuticals have been discussed below:

Attributable: Attributable means that the evidence or every piece of data entered into the record must be capable of being traced back to the person collecting it. This ensures accountability. This contains a record of who performed an action and when. This could be a paper or electronic record[.[28]] It requires the use of secure and unique user logins and electronic signatures. Using generic login IDs or sharing credentials must always be avoided. Unique user logons allow for individuals to be linked to the creation, modification, or deletion of data within the record. [[29]] It should be possible to demonstrate that the function was performed by trained and qualified personnel. This applies to changes made to records as well: corrections, deletions, changes, etc .[[27]]

Legible: The record created, especially the paper-based records should be legible. The records should be permanent and not erasable so that they are reliable throughout the data lifecycle.[[28]] The terms legible and traceable and permanent refer to the requirements that data are readable, understandable, and allow a clear picture of the sequencing of steps or events in the record.[[30]] This is very important in the pharmaceutical industry as a mistaken spelling could result in the administering of a completely different drug.[[28]] For an electronic record to be considered legible , traceable and permanent.[[29]]

Contemporaneous: Contemporaneous is the evidence of actions, events or decisions should be recorded as they take place or generated.[[30]] This documentation should serve as an accurate attestation of what was done, or what was decided and why i.e. what influenced the decision at that time.[[31]] If executing a validation protocol, tests should be performed and their results recorded as they happen on the approved protocol[.[30]]

Original: The original data sometimes referred to as source data or primary data whether recorded on paper (static) or electronically. Information that is originally captured in a dynamic state should remain available in that state.[[27]] This could be a database, an approved protocol or form, or a dedicated notebook. It is important where your original data will be generated so that its content and meaning are preserved.

Accurate: The recorded data should be correct, truthful, complete, valid, reliable, free from errors and reflective of the observation.[[32]] Editing should not be performed without documenting and annotating the amendments. ALCOA in pharmaceuticals helps both the companies and the users making it sure that there are no record-keeping errors due to which some sub-standard product is released onto the market. Therefore, ALCOA is a necessity for maintaining quality in the pharmaceutical field. [[28]]

VIII. FUTURE PERSPECTIVES

The future of quality control and regulatory compliance in Active Pharmaceutical Ingredients (APIs) is likely to involve advanced technologies such as artificial intelligence and blockchain to enhance

precision, traceability, and efficiency in manufacturing processes. Additionally, increased emphasis on real-time monitoring and data analytics will play a crucial role in ensuring product quality and meeting evolving regulatory standards. Continuous improvement strategies and global collaboration are anticipated to further shape the landscape for API quality control and regulatory compliance. The future of quality control in active pharmaceutical ingredients (APIs) is likely to see increased integration of advanced technologies such as artificial intelligence, machine learning, and automation. Continuous monitoring and real-time data analytics may become more prevalent, contributing to a proactive approach in identifying and addressing potential quality issues. Additionally, advancements in spectroscopy, chromatography, and other analytical techniques will likely play a crucial role in improving the accuracy and speed of quality assessments in API production. Additionally, regulatory agencies are expected to focus on risk-based approaches, incorporating data analytics to identify potential issues and streamline inspections. Continuous adaptation to evolving global standards and the integration of digital tools are key aspects in shaping the future landscape of API regulatory compliance.

IX. CONCLUSION

In conclusion, maintaining stringent quality control measures and adhering to regulatory compliance is imperative in the production of active pharmaceutical ingredients (APIs). This ensures the safety, efficacy, and consistency of pharmaceutical products, meeting global standards and safeguarding public health. Continuous vigilance and adaptation to evolving regulations are essential for the pharmaceutical industry to uphold quality and compliance in the dynamic landscape of API manufacturing. Ensuring regulatory compliance in active pharmaceutical ingredients (APIs) is vital for maintaining product quality and safety. Stringent adherence to regulatory standards, such as Good Manufacturing Practice (GMP), facilitates consistency in API production. This commitment helps pharmaceutical companies meet regulatory requirements set by health authorities, ensuring the reliability and efficacy of pharmaceutical products. Continuous monitoring, documentation, and adaptation to evolving regulatory frameworks are essential for sustained compliance in the dynamic pharmaceutical industry.

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