Assessing the Regulatory Role of GMP audits for APIs

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Dissertation Supervisor: Dr. Alessandra Vecchi

Aayushi verma

09th May 2020

Candidate Declaration

Candidate Name: Aayushi Verma

I Aayushi Verma certify that the dissertation entitled: Assessing the regulatory role of Good Manufacturing Practices for Active Pharmaceutical Ingredients for the degree of MSc in Pharmaceutical Business and Technology is the result of my own work and that where reference is made to the work of others, due acknowledgement is given.

Candidate signature: 

Date: 06 May 2023

Supervisor Name: Dr. Alessandra Vecchi

Supervisor signature:

Dedication

I dedicate my work to my brother, my friends, and my loving family, especially my mother. A particular thanks to my partner, whose courage inspires me and who has supported me in all my endeavours, big and little.

Acknowledgements

My sincere thanks to God for His kindness and love in providing me with the knowledge and insight necessary for the completion of this work. I value Dr. Alessandra Vecchi, my supervisor, because she has been helpful at every stage of the process. I'm also appreciative of my family and friends' contributions to the completion of the dissertation through their moral support.

Abstract

The pharmaceutical sector is crucial to global economics as well as the preservation and advancement of human wellness. For people to live healthier and longer lives, the industry closes the gap among their health and lifespan. Good manufacturing practices audits have been implemented to direct the behaviour and operations of Active Pharmaceutical Ingredients to protect the public's health and safety from phony, illegal, or tampered APIs. This research study has attempted to analyse the restrictions for APIs that have emerged inside the GMP sector in the pharmaceutical business. After conducting a literature search, the research's objectives were informed by the shortcomings in the field. These gaps include the significance of GMP audits for APIs, challenges, and implications in ensuring API quality, the extent to which regulatory authorities mitigate these issues, and the creation of a framework for the role of various regulatory authorities in standardizing GMP audits for APIs. Six participants were chosen for the analysis using the convenience sample approach, which is a type of exploratory design used in qualitative research. Zoom was used to start semi-structured interviews with the participants to get their qualitative information. The gathered qualitative responses were analysed using the Gioia qualitative data evaluation method. The study concluded with 1. the goal of GMP audits is to make sure that a facility is producing pharmaceuticals with efficacy, compliance, and continuous improvement. 2. Audits and manufacturers are facing challenges with complex supply chain, regulatory complexity, and counterfeiting. 3. The biggest implication of non-compliant APIs is patient safety. 4. Participants made recommendations as continuous improvement, corrective actions, and revalidation. Results demonstrate that the regulatory role of GMP audits for API in the pharmaceutical industry has enhanced the sector, yet there still exists a need for advancement and further growth if the sector is to compete with its counterparts in other regions of the developed world, particularly in the context of higher utilization of technology and enforcing of the legal regulations governing the sector. Academia scholars, authorities, pharmaceutical products, producers, buyers, and government agencies will all profit from the present research's input.

Key words: Good Manufacturing Practice audits, pharmaceutical sector, Active Pharmaceutical ingredients, Regulations

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1 Introduction

1.1 Overview

There is limited chance for those giving or receiving prescriptions for medicines to determine whether they are defective. The doctor who issued the medication and the pharmacists who filled it are both trusted by those who use medications. The manufacturer is entrusted by the practitioner and pharmacist to ensure that the medication is appropriate for its intended use and secure for usage. Good Manufacturing Practice seeks to guarantee that the company and the production process are designed with quality in mind. More than just the production operations themselves are involved in producing quality. The products itself, the packaging, and the materials all require particular written requirements (Learoyd, 2005). Preparation and inspection, management, preservation, reception, and dispatching all be covered by written instructions and processes that are crystal clear. It is necessary to identify and make available suitable locations, equipment, and skilled personnel (Learoyd, 2005). Many consumers than ever take medications today. Adverse reactions are frequent, and several product lots that initially fulfilled criteria and were made available to the public were later recalled because of quality issues. Nonetheless, due to Good Manufacturing Practices systems, talented personnel, and the application of cutting-edge technology, the occurrence of security issues is quite low (Shadle, 2004).

The significance of the term active pharmaceutical ingredient used in this study is aligned with International Council Harmonization Q7 (CPMP and ICH, 2006) . According to the definition given in ICH Q7, an active pharmaceutical ingredient is any material or combination designed to be utilized in the production of a medicinal products and that, when used in the production of a drug, has become an active ingredient in the medicinal product. These chemicals are designed to provide pharmacological action or other immediate impacts in the identification, therapy, remission, or prevention of disease, or to influence the form and functioning of the body. Nowadays, Food and Drug Administration and industry also use different words to refer to an Active Pharmaceutical Ingredient. Bulk pharmaceutical chemical and Drug substance, respectively, are words that are frequently used to refer to Active Pharmaceutical Ingredient and inactive components for Bulk Pharmaceutical Chemical. These phrases may be regarded as being identical to API when used to define active components (APIC, *et al.* 2008).

According to Food and Drug Administration compliance program, the Adulteration Requirements of Section 501(a)(2)(B) of the Act, which mandates that all pharmaceuticals be produced in accordance with Current Good Manufacturing Practices, apply to Active Pharmaceutical Ingredients. The Act does not distinguish among an API and a finished pharmaceutical, and failing to adhere to Current Good Manufacturing Practices in either case is a breach of the Act. Food and Drug Administration has not released Current Good Manufacturing Practices guidelines that are unique to APIs or other medication constituents (APIC, *et al.* 2008).

The Qualified Person of the Manufacturing Authorisation Holder is accountable for the GMP conformity of produced pharmaceuticals in the European Union. As a result, in addition to his or her other obligations, the Qualified Person oversees ensuring that the APIs and particular active ingredients used in manufacturing comply with GMP. The need to supervise the GMP conformity of APIs is becoming more widely recognized, and the responsible health officials are increasingly verifying if the Market Authorization Holders or the relevant QPs are fulfilling it (Kettelhoit and Völler, 2012).

“Suppliers of active ingredients and some excipients regarded high risk compounds utilized as raw material must be frequently evaluated to ensure compliance with current GMP standards”(Kettelhoit and Völler, 2012).

There are still a lot of variances between various parts of the world, even though the Good Manufacturing Practices standards that apply globally are becoming more standardised. The International Council Harmonization Q7 Manual, "Good Manufacturing Practices Guidance for Active Pharmaceutical Ingredient," is the foundation upon which the GMP conformance of APIs is evaluated in International Council Harmonization member nations, particularly in North America, Japan, and Europe. For instance, the ICH Q7 Standard is immediately applicable in the United States; however, the EU GMP Guideline Part II, with a nearly similar form and phrasing, implements the regulation in Europe. The largest suppliers of pharmaceutical APIs, including China (SFDA GMP) and India (Drugs & Cosmetics Act, Schedule M), have substantially less comprehensive GMP regulations (Kettelhoit and Völler, 2012). Therefore, it is highly unlikely that a production batch that complies with Indian or Chinese Guidelines established will also meet EU requirements.

This study's focus will be on evaluating the regulatory role of Good Manufacturing Practices audits for APIs, with the involvement of different regulatory authorities. The motivation for choosing this subject is, the author has some experience conducting audits and operating in a

GMP-compliant injectable plant. Also, manufacturing of pharmaceuticals is changing from a style of art to one that is currently focused on engineering and science. The efficiency of both production and regulatory procedures can be significantly increased by applying this information efficiently in regulatory choices when creating specifications and assessing manufacturing operations.

1.2 Research Purpose

The production and quality management standards followed determine the safety of pharmaceuticals to a large extent. More than 80% of APIs are not produced in the United States. The Food and Drug Administration faces a significant difficulty because of their inability to effectively regulate overseas producers and their difficulties managing global logistics. From 2015 to 2018, the number of Food and Drug Administration warning letters grew fivefold, from 19 to 94 actions annually (White, 2020).

It was evident from the statements by European Union medicine agencies that they had no plans to investigate imported, off-patent API. The European Fine Chemicals Group is conscious that most off-patent APIs used in European Union medications are imported, primarily from China and India. It has also been observed aware that over the past ten years, the European Directorate for the Quality of Medicines has only introduced a very small amount of audits of non-EU API sites, and of the ones that were audited, the percentage of severe noncompliance cases was alarmingly high (Villax and Oldenhof, 2007).

A system of healthcare that is fiscally viable must include generic drugs. Although there are trustworthy generic producers, doctors have a right to be dubious in the absence of impartial verification. Due to a history of almost virtually non-existent quality inspection of foreign pharmaceuticals, the Food and Drug Administration permitted businesses to ship subpar goods into the country while still providing doctors and pharmacists with assurances (White, 2020).

According to the regulatory requirements and researchers' extensive experiences, the purpose of this research is to create a recommendation for just such a criterion for the inspection of GMP compliance for APIs. To get rid of the ambiguities and differences in this field that still exist today, it is aimed to aid to global building consensus and acceptability for such audit standards.

1.3 Significance of the Study

“It is obvious that any legal action needs to be supported by effective implementation and administration. Any law could only be completely successful if it is strictly implemented by the Member States' authorized agencies”.

“A comprehensive description of severely, purposely non-compliant APIs" is still missing”.

The term "deliberate" ought to be the core to this statement. To put it another way- This must apply if there are one or more entities involved that can be assumed to be completely knowledgeable of European Union GMP- and regulatory standards, but who are nevertheless delivering significantly non-compliant Active Pharma Ingredients into the supply chain for the Marketplace with knowledge of their actions.

It has been observed from the literature that the several counterfeit APIs come from producers in nations like China and India, wherein health regulators now operate with far weaker regulations than in the EU. The monitoring of APIs shipped from these nations to the EU by the local authorities is entirely absent, depending rather on the diligence and morals of the acquiring enterprise. Thus, appropriate EU-based methods for monitoring and enforcing the regulations all along full range of the worldwide supply chain are required for the safety of EU residents from counterfeit APIs.

It is an effort to evaluate and concentrate on the requirement for an enhanced, unified regulatory framework and enforcing laws to maximize the safety of the worldwide supply chain, which starts with the production of APIs intended for use in pharmaceutical products.

A gap has been identified from the literature reviewed concerning about various methods for conducting these audits, both in the scholarly literature and in actual practice. The quality of the audit reports that are produced as a result, which can vary substantially, also reflects this. Therefore, the suggestions for these audits are restricted to a few helpful hints, practical examples, or common anecdotes, like insufficient quality of raw materials and labelling, inadequate pharmaceutical water processing, inadequate dealing of change control procedures, or unsuitable utilization of the phrase "dedicated equipment."

This research is significant because it will establish the minimum standards for these kinds of audits and, as a result, will establish a foundation for a quality standard that is required and that permits a valid evaluation of the producer and the produced product as well as verifying the APIs quality.

1.4 Research Aim and Objectives

The comprehensive aim of the research is to evaluate the role and need for GMP audits for the compliance of Active Pharmaceutical Ingredients and to offer thorough Current Good Manufacturing Practices inspectional coverage. Two strategies will be used to accomplish the objectives and research questions of this research. The published work will first be critically appraised, then primary research will be conducted by interviewing specialists on the GMP audits.

The following is a list of the Research Objectives and Research Questions:

Table 1 **Research Objectives and Research Questions**

Research Objectives	Research Questions
• To evaluate the effectiveness of GMP audits in ensuring the quality of active pharmaceutical ingredients produced and supplied by manufacturers.	• What are GMP audits? • What are APIs? • Why there is a need to ensure the quality of APIs? • How GMP audits are responsible for the quality of APIs? • What is the role of manufacturers?
• To investigate the impact of GMP audit findings on the approval process of APIs.	• What are the implications with off-patent APIs?
• To create a framework of different actions taken by regulatory authorities.	• Do different actions taken by Regulatory authorities balanced or deterred the assurance of APIs and to which extent they mitigate the quality issues for APIs?

• To make recommendations to an API industry	• Centered on research led to this paper, what actions would be recommended to harmonize and coordinate non-compliant APIs?

1.5 Methodology

The research strategy for this proposed research topic is Qualitative. The reason this strategy has been chosen – it serves as a vehicle in combining prior information and connecting the research to the greater body of knowledge in the relevant field (Nenty, 2009).

The research starts with secondary sources, which entails a study of the literature to evaluate the documentation of the data provided and spot gaps in the literature. Key issues of attention that will serve as the basis for developing the initial structure of data analysis will be highlighted in the evaluation. The themes inferred from the literature will support the significance of GMP audits for APIs by various regulatory bodies, the consequences of API non-compliance, and the difficulties in mitigating API quality issues.

The methodology will be following the research approach, research philosophy, research design as a ladder. **Exploratory, interpretivist, deductive, and grounded** are all characteristics of this structure. To gather qualitative data, semi-structured interviews will be undertaken. This information will be used to create a framework for data analysis. Throughout the study, methodological restrictions won't be acknowledged, but it will be thought about looking at them as potential areas for future research.

In the second section of the research, primary research will be done using interviews with GMP audit specialists to produce fresh data. The semi-structured interviews are intended to shed light on the legal significance of GMP audits of Active Pharmaceutical Ingredients. The expert viewpoints will be both broad and specific, and interviewees frequently use personal examples that are relevant to their area of expertise—Good Manufacturing Practice inspections—to illustrate their points. While being person-specific, they are pertinent to add depth and valuable detail to the veracity of the data. Where possible, additional literature reviews have been done

to verify the experts' opinions. With the combination interviews with various specialists and the hypothesis deduced from the literature reviewed, data will be gathered.

A well-liked technique is used for analyzing qualitative data in qualitative studies is the **Gioia approach.** The first-order code phase, second-order code phase, and third-order code phase are the three phases that make up this process. The respondent's replies are compiled and placed in the initial column during the first-order code phase.

A discussion is used to highlight the pertinent connections between the findings and the study's objectives. It also compares the themes from the literature review with those that were emphasized in the data analysis.

1.6 Structure of the Study

The research begins with secondary research, which entails a review of the literature to evaluate the documentation of the data provided and spot gaps in the literature. Key issues of attention that will serve as the basis for developing the initial framework for data evaluation will be highlighted in the evaluation. The themes inferred from the literature review will confirm the need for exploring the required quality standard for GMP audits and that permits a valid evaluation of the producer and the produced product as well as verifying the APIs quality.

The primary research portion of the research, where new information will be produced using surveys of GMP audits professionals, was covered in the study's second section. Observations on the efficiency of GMP audits in assuring the quality of active pharmaceutical ingredients (APIs) manufactured and supplied by manufacturers are envisaged to be gained from the surveys and research on the API approval procedure. Where possible, additional literature reviews will be used to confirm the experts' predictions.

The study will be completed with a collection of details from surveys used to gather research data. A discussion will be used to highlight the pertinent connections between the findings and the study's objectives. It will also compare the themes from the literature review with the ones that were emphasized in the data analysis.

2 Literature Review

2.1 Overview

The relevant previous literature on the topic under research will be cited in this chapter. It looks at the keywords that constitute the dissertation's research topic, employs a concept or framework to analyze the research, and evaluates the empirical results of earlier studies in relation to the existing research. The challenge that this research is designed to address is partially caused by the gaps in the body of literature. Studying the prior literature and its conclusions in relation to this study is also crucial since it makes it simpler to compare the results of the existing study with those of the earlier studies as the research develops. This method will assist in contrasting and evaluating these results, which can be helpful for further study and for developing or increasing the body of literature on the issue.

Using this knowledge to the current research, the primary key terms for this study are Regulatory bodies, GMP audits, and GMP. The GMP audits and their role for the Active Pharmaceutical Ingredients will be explored to further contextualize this area and its extent.

2.2 Evolution of GMP in the pharmaceutical industry

Prior to adequate identification and action, the pharmaceutical industry's globalization may quickly disseminate subpar medications around the world. Substandard and falsified medications make up the two primary categories of subpar medications (Patel and Chotai, 2008). The idea of good manufacturing practice was formed when regulators realized that quality was defined during the production process rather than by the following quality control procedures implemented. After the Thalidomide controversy in Germany, in which newborns suffered birth abnormalities and even fatalities since their mothers had used the sleep aid while pregnancy, good manufacturing procedure traditionally became the holy grail for the creation of pharmaceuticals in the 1960s (Niggemann, 2019). While falsified are the "products" of thieves, subpar goods result from a lack of knowledge, bad manufacturing techniques, or inadequate infrastructure (Pezzola and Sweet, 2016). No active substance, improper components, or poisons may be included in counterfeit products. Proper manufacturing processes are adhered to so that quality is consistently obtained in the medication product. In brief, WHO GMP specifies that the manufacture and distribution of licensed pharmaceutical goods must only be carried out by licensed producers that have a manufacturing authorization

(Rantanen and Khinast, 2015). According to the WHO, GMP refers to the aspect of quality checks that ensures pharmaceuticals are continuously manufactured, monitored to accomplish quality norms appropriate for their destined need and as required by a regulator or authority responsible for marketing authorization (WHO, 2020). The efficient use of GMP results in improved and much more favorable overall healthcare outcomes, whereas its lack or inadequacy may provide a barrier to providing world citizens with access to high-quality healthcare (Steele and Subramanian, 2017)**.** Every leader and manager give regular, impactful GMP recalls, train and develop every staff, and actively take part in official, ongoing training courses to accomplish and sustain GMP compliance (Patel and Chotai, 2008).

2.3 Overview of Active Pharmaceutical Ingredients

The chemical-based substances known as active pharmaceutical ingredients (APIs) are mostly produced in the United States, Europe, China, and India. APIs contain pharmacological properties and are mostly combined with other compounds to cure, detect, and treat illness. Every single drug is made up of two primary parts: the API, which serves as the key element and is biologically active and must do the function in the body, and the excipients, which are inert substances like lactose or mineral oil in the tablet. To create an API, many chemical components and raw ingredients are used in a multi-step procedure (Kumar, *et al.* 2022).
In accordance with ICH Q7 (EMA, 2006), an active pharmaceutical ingredient is "any material or combination of substances designed for use in the creation of a drug product and which, when utilized in the manufacture of a drug, forms an active ingredient in the drug substance. These compounds are designed to provide pharmacological action or other relevant effects in the detection, treatment, mitigation, or suppression of illness, or to alter the form and operation of the body (CPMP and ICH, 2006).

2.4 Importance of GMP audits

GMP audits are conducted for several reasons, thus the auditor is adaptable in how they handle the audit's format and subject matter. Audits are carried out routinely in keeping with a predefined schedule, according to ICH Q7 (CPMP and ICH, 2006), to assure compliance with the GMP criteria for APIs. The audit's findings and suggested fixes are communicated to the firm’s management. Once decided upon, corrective actions are implemented promptly and effectively (Giralt, *et al.* 2020). This paper highlights a few of the conditions under which

audits are performed and how this influences the methodology used. Circumstances, the benefits of in-depth planning, checklists, and audit trails are discussed. Audits are targeted and preplanned to be effective, and when done correctly, they may be gratifying for both the auditor and the auditee (CPMP and ICH, 2006).

Self-inspection is also an important requirement of GMP itself. Self-inspections evaluates both the staff's compliance with existing processes and techniques as well as the compliance of the facilities and systems with GMP criteria. It is beneficial if representatives from the areas involved take part in this form of audit, which is often conducted with the consent of department or division being audited (Probitts, 2000).

2.5 Regulatory Role of Different Authorities

Through improved communication and the sharing of information on inspections planning, the GMP audit aims to promote collaboration and mutual confidence amongst participating regulators. On these bases, between Dec 2008 & Dec 2010, a pilot project on global cooperation on GMP audits of API manufacturers was carried out by competent agencies from Australia Therapeutic Goods Administration, Europe European Medicines Agency, European Directorate for the Quality of Medicines and Healthcare, French National Agency for Medicines and Health Products Safety, Agenzia Italiana del farmaco , Zentralstelle der Länder für Gesundheitsschutz, Medicines and Healthcare products Regulatory Agency, Health Product Regulatory Authority, and the US Food and Drug Administration (EMA, 2018) (Shaikh, *et al.* 2019).

Participating agencies worked together on inspection planning using various methods to prevent inspections from being repeated. These methods are Reliance upon inspections and Joint inspections which are different based on number of participating authorities involved (EMA, 2018).

GMP audit is a wide programme, it can be classified further. Most importantly, the evident contrast between audits from the perspective of an API manufacturer could be whether internal audits (a type of independent self-evaluation) or external audits (as may be performed on a critical raw material supplier).

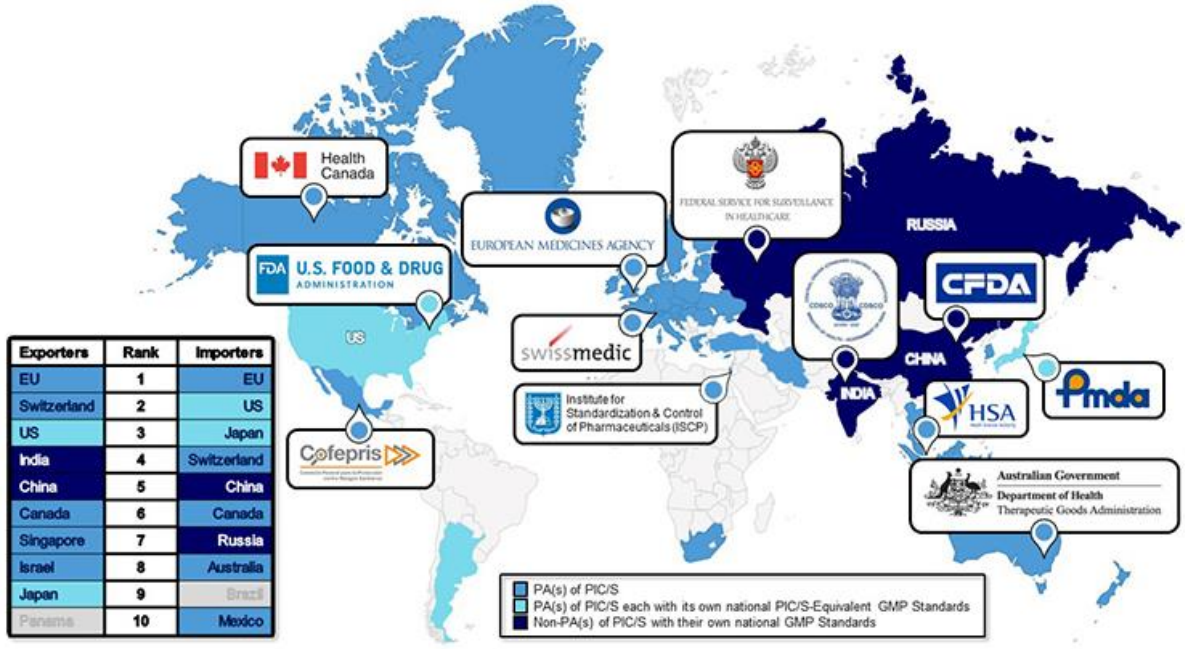
2.5.1 Additional program by Norgine

An additional concern by Norgine (A pharmaceutical business in the UK is called Norgine. In the fields of gastro, hepatology, and incontinence, the company creates solutions for both patients and healthcare professionals to cure, manage, and enhance the quality of life associated

with chronic as well as acute medical disorders) by starting a program to provide governance and oversight for GMP auditing procedures, including the creation and upkeep of a risk-based audit system, training, and ongoing professional development of GMP auditors within a matrix organization, and reporting on the GMP risks, trends, and efficiency of the quality systems (Director global quality governance, 2012). They used qualitative method to analyze the activities including discussing results, developing hazards, and steps to mitigate identified risks, making sure that top management receives formal input frequently. As regulatory changes affect the Norgine GMP audit program, provide quality direction to ensure ongoing adherence to rules and procedures (Director global quality governance, 2012).

2.6 Off-patent APIs

A directive passed in March 2004 established the legal framework for the need that APIs sold on the EU market be produced in accordance with Good Manufacturing Practices, which has been the case in the US since the 1970s (Villax and Oldenhof, 2007). The focus of European Fine Chemicals Group's was the trading, and use of off-patent APIs. Even today, Inspecting the use and manufacturing of off-patent APIs is a major concern (Villax and Oldenhof, 2007). European Fine Chemical Groups used a simple methodology to fill this gap of off-patent APIs (Kapoor, 2018). A targeted audit program of off-patent API manufacturers outside of the EU and at the intervening points inside the EU, favored whenever feasible by proof of questionable activities but also incorporating a random element, are seriously considered to ensure the security of EU medicines (Villax and Oldenhof, 2007)**.** For future fines and damages, a checklist for inspectors is provided to all the medical agencies by the EU-wide API program, which was launched by the European Agency for the Evaluation of Medicinal Products (Ubajaka, *et al.* 2016). According to European Agency for the Evaluation of Medicinal Products, this effort has two goals: to encourage and harmonize instruction on how to enforce and confirm API adherence when reviewing dosage form manufacturers and to acquire data in order to evaluate the API compliance issue (Villax and Oldenhof, 2007).



Exporters	Rank	Importers
EU	1	EU
Switzerland	2	US
US	3	Japan
India	4	Switzerland
China	5	China
Canada	6	Canada
Singapore	7	Russia
Israel	8	Australia
Japan	9	Brazil
Panama	10	Mexico

Figure 1 ***Lapses in Global GMP Compliance*** *(Chong Hock,* et al. *2018)*

2.6.1 Examples of Active Pharmaceutical Ingredient manufacturing issues

Zhejiang Huahai Pharmaceuticals, a business with a record of quality concerns, was one of the leading makers of valsartan and losartan API (Peters, 2019). When they were audited by the FDA in 2017, they discovered that they had documented passing grades rather than the fact that medicine batches had failed to fulfill US standards of quality in certified lab tests (Hackett, 2018). Chinese officials requested the business to retract any requests to market new products that contained inaccurate or missing data in 2016. The business withdrew applications for three medication classes (Peters, 2019) (Hackett, 2018). The first indication that there were problems with APIs in China was in 2008, when people getting heparin in the US instantly started having severe anaphylactoid responses, with more than 100 of those instances resulting in fatalities(Liu, *et al.* 2009). An anticoagulant contamination was purposefully but covertly introduced to heparin Active Pharmaceutical Ingredient in Asia as a substitute after a viral illness started ravaging the Asian pig herd. It's not really apparent where in the distribution chain this happened. Nevertheless, Changzhou SPL Corporation, a producer of the heparin API, was subject to an FDA inspection and was issued a legal notice after it was discovered that it had used raw materials (pig intestines) from unlicensed farmlands; the vessels used in manufacturing or storage had unknown material complying to them; and impurity testing had been carried out insufficiently (FDA, 2008)

2.7 Reasons for GMP Deviations

According to Max S. Lazar (Lazar, 2014) , addressing these five issues will significantly increase GMP compliance levels globally:

1. Companies either don't know what Active Pharmaceutical Ingredient GMP requires of them or don't bother to conform because they don't think it's necessary to comply to market their supplies nationally or export their goods.

2. If there is a major lack of management or staff comprehension of Active Pharmaceutical GMP, then severe training is required. These companies don't properly comprehend the API GMP's stated purpose. Anyone who has undergone training and is aware of ICH Q7's goals shouldn’t be flouting so many basic GMP requirements.

3. Financial and commercial concerns must be addressed to keep businesses on track if pride in the company and its culture are not strong enough to motivate them to follow Active Pharmaceutical Ingredient GMP. If this fails, those businesses must close their doors. Only if regulators forbid the import of their goods into nations is this possible.

4. Although regional variations can affect how businesses accept and implement regulatory standards from different nations, drug or products quality must not be compromised as a result. No matter where a substance is manufactured or evaluated, data validation with correct paperwork and operating procedures should always persist.

   Undoubtedly, there will inevitably be the occasional slip, but any employee actions that point to a culture that wants to conceal or erase data to utilize or deliver faulty materials or goods should never be accepted. The FDA and any company’s administration must guarantee data integrity.

5. The absence of supervision by authorities and companies buying API materials is a significant factor in GMP deviations. At some of the legal notices mentioned that it had been around six years before the next examination of a certain company. The notice states that the problem was identified six years ago and is still present. A serious failing to put "trust but verify" into practice! The patient care is undermined by this

refusal to verify and, as a result, permit shipping and sells into other nations, which also raises hazards for customers and the wider public.

	Total WL Issued	Total API WL (% of Total)	Countries	% by Country
YEAR2010	619	8 (1.3%)	China India Japan Canada UK	25% China 25% India 25% Japan 12.5% Canada 12.5% UK
YEAR2011	755	8 (1.1%)	China Mexico India Spain Italy/Switzerland	25% China 25% Mexico 25% India 12 1/2% Spain 12 1/2% Italy/Switzerland
YEAR2012	766	5 (0.7%)	Mexico Germany Poland Spain	40% Mexico 20% Germany 20% Poland 20% Spain
YEAR2013	671	6 (0.9%)	India Germany Japan	66 2/3% India 16 2/3% Germany 16 2/3% Japan
YEAR2014*	247	10 (4.1%)	India China Ireland Italy Germany Hong Kong	40% India 20% China 10% Ireland 10% Italy 10% Germany 10% Hong Kong
*Numbers based upon search results of FDA's Electronic Reading Room. Data from FDA Web site as of 8/24/2014[4]				

Figure 2 ***FDA warning letters (WL) issued to foreign firms by country (Lazar, 2014)***

2.8 Standardization of Good Manufacturing Inspections for APIs

The standardization of GMP inspections for Active Pharmaceutical Ingredients have been increased in last few years. Major industry groups and other authorities have come together and have already proposed audit standards. Active Pharmaceutical Ingredients Committee of the European Chemical Industry Council, recognized GMP audit provider blue inspection body GmbH; and Rx-360, an international pharmaceutical supply-chain collaboration, already have suggested audit criteria (Kettelhoit and Trieste, 2013). Food and Drug Administrator has published instructions for its inspectors that specifically address how to conduct Active Pharmaceutical Ingredient GMP inspections (Shaikh, *et al.* 2019). Similarly, an Aide Memoire for GMP-inspectors conducting audits of API producers has been released by the Pharmaceutical Auditing Agreement and the Pharmaceutical Inspection Co-operation Scheme **(PIC/S)** (Kettelhoit and Trieste, 2013). There is a methodology of performing fewer and better audits. It has been done by considering which API needs to be audited first according to Market Authorization Holder. A significant way to lessen the load on both MAHs and Active Pharmaceutical Ingredients suppliers is to share high quality audits conducted by impartial third parties with pharmaceutical manufacturers (Kettelhoit and Trieste, 2013).

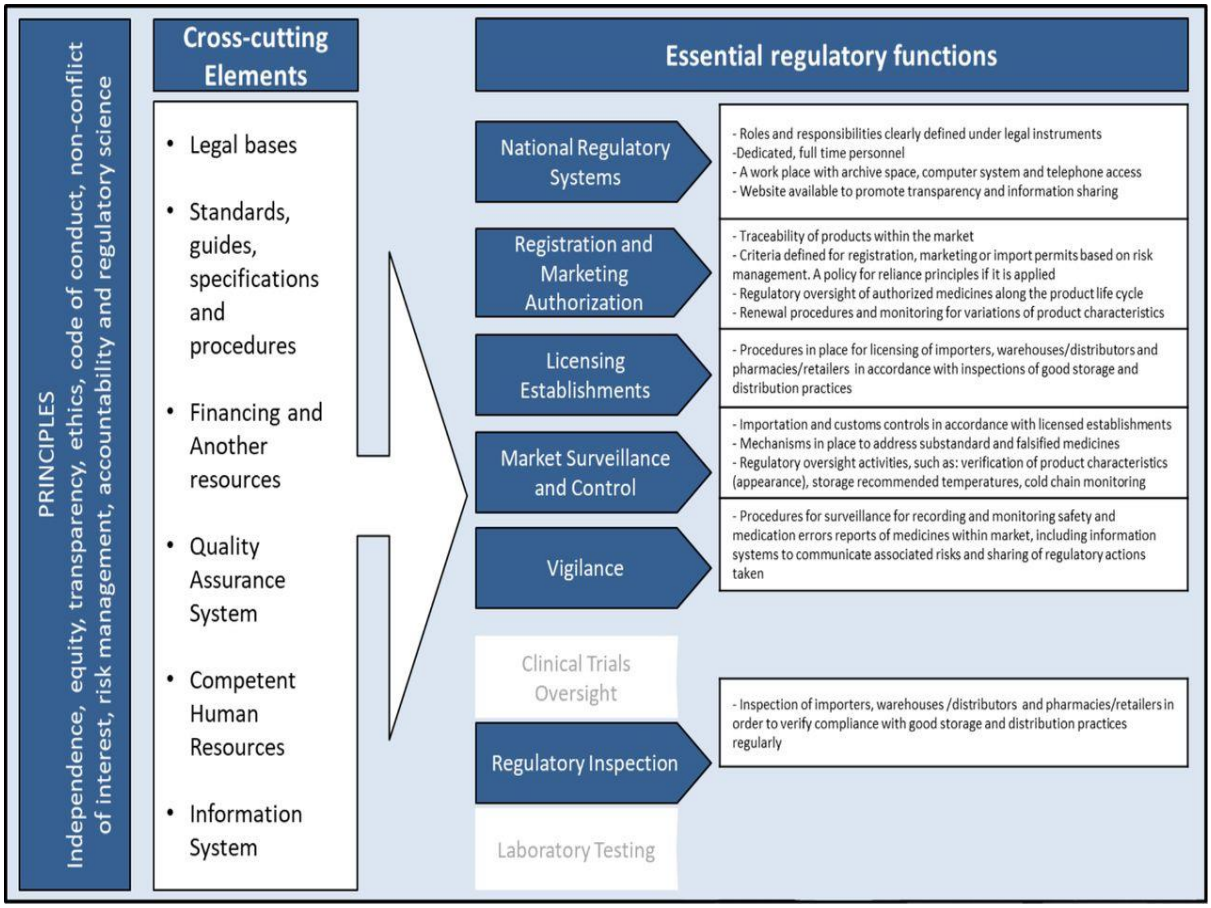


Figure 3 ***Essential functions recommended for small states*** *(Preston,* et al. *2020)*

2.8.1 Perspective of European Directorate for the Quality of Medicines and Healthcare in ensuring the quality of Active Pharmaceutical Ingredients

APIs used to create pharmaceutical goods should adhere to pharmacopoeia guidelines and other quality standards. The European Pharmacopoeia is the lawfully obligatory quality standard in the nations that have ratified the European Pharmacopoeia Agreement. If an API is covered by a suitable article in the European Pharmacopoeia, the producer of the API and the pharmaceuticals made with the API must adhere to its quality criteria. The regulatory agencies may ask the MAH for additional requirements in circumstances where a requirement in an article is inadequate to verify the quality of the substance (Haigney, 2022) (Jagun, 2018).

The goal of the ICH Q7 standard is to offer recommendations for the manufacture of APIs under a suitable quality management system. The GMP Part II regulation for the European Union has been established to include this regulation. The administrative structure, policies, practices, and assets, as well as the actions required to guarantee assurance that the API will achieve its planned criteria for quality and clarity, should all be included in the quality management system. All these requirements must be met by the Quality Management System

for APIs; if even one of these requirements is skipped, the effectiveness of the Quality Management System based on ICH Q7, and the safety of the APIs are both put at risk (Pavithra, *et al.* 2021).

While a pharmaceutical product is being developed, APIs are subjected to clinical and non-clinical tests to determine their safety and effectiveness. Data obtained in this way are included in applications for marketing authorizations, which are then examined by the appropriate regulatory bodies. If these investigations reveal an unfavorable benefit-risk ratio, the pharmaceutical product won't be given a marketing license and won't be sold (Haigney, 2022) Pharmaceuticals that have been given a marketing license are continually evaluated for their quality, security, and effectiveness. This approach is set up to identify any problems that could have a detrimental effect on the benefit-risk balance. MAHs must adhere to obligatory pharmacovigilance procedures to track the security of approved medicines and identify any changes to their relative risk. If there is a problem with the quality of APIs, the producers must take the necessary steps to fix it while authorities watch over them (Haigney, 2022)

2.8.2 Role of Active Pharmaceutical Ingredient Committee

Active Pharmaceutical Ingredient Committee has a major role in enhancing the regulatory framework of GMP compliance for Active Pharmaceutical Ingredients. The most significant venue for GMP inspections at APIs manufacturers and the pharmaceutical sector is APIC's annual Conference (June 18, 2018) on Active Pharmaceutical Ingredients. To discuss recent events, representatives from both industries and foreign authorities gathered there (Becker, 2019).

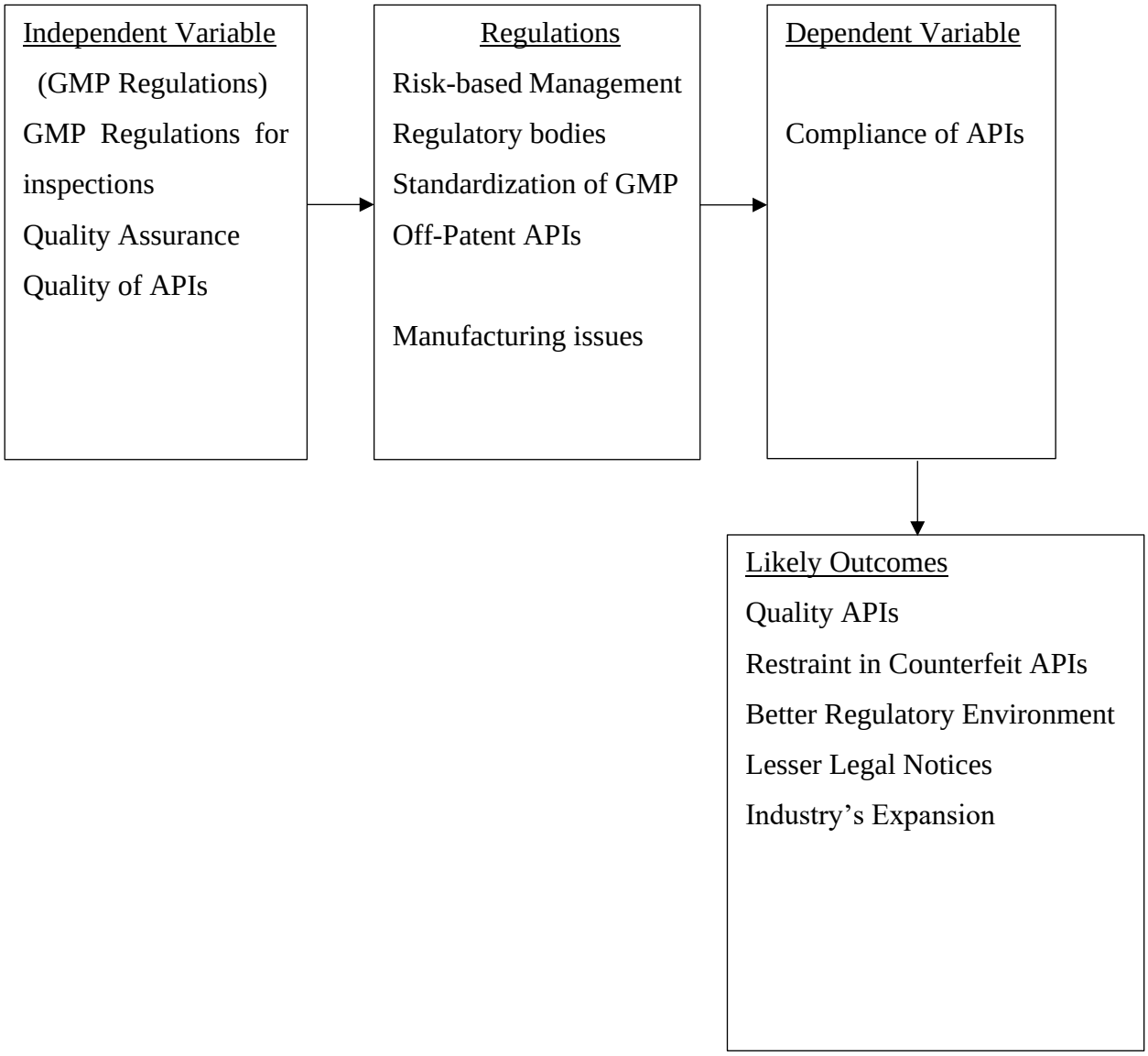
The conference was about the European Medicine Agency provides a summary of the status of the Mutual Recognition Agreement between the European Union and the USA as well as an explanation of some key elements of international cooperation in GMP inspections of Active Pharmaceutical Ingredient and pharmaceutical firms (Becker, 2019) (Angelino, *et al.* 2017). In the area of GMP inspections, the European Medicine Agency is primarily responsible for coordinative-administrative duties that are carried out by professionals with scientific technological skills. To foster trust between parties and harmonize GMP inspection procedures, the methodology involved worldwide collaboration with other monitoring authorities. On July 15, 2019, an important milestone was reached in the Mutual Recognition Agreement implementation process between the European Union and the USA. After this date, APIs batches produced in the USA and exported to the EU with the necessary certificate will no longer require the Qualified Person to conduct a fresh inspection (Becker, 2019).

2.9 Risk-based management

GMP inspection for Active Pharmaceutical Ingredients seems to be a wide and simple procedure but needs to have a risk-based management program. The quality of the purchased raw materials, particularly the APIs that enters the production process at an early level, contributes significantly to the quality of completed goods (Vesper, 1997). At the same moment, the influx of bogus APIs and counterfeit APIs into the European Union has increased. A well-defined risk management becomes more important for the supplier qualification to protect public health (Gerhard, 2009) . On one side, GMP audits are essential to determining the acceptability of suppliers and the areas that have the most room for development (Fujikawa and Ono, 2017). The agreed-upon remedial measures guarantee the quality of the relevant pharmaceutical items and safeguard the public's overall health, that is of course given priority (Batshon and Jones, 2006). On the other side, to ensure that the supply capability of both the parties is maintained, it is important to prevent an excessive overburden of the auditing business and the auditee (Tauqeer, *et al.* 2019). Thus, the pharmaceutical industry's quality management strategies must adapt to the challenges posed by globalization. By risk-based management, it is feasible to set realistic objectives within the parameters of the GMP auditing process and the audit plan of a pharmaceutical firm (Gerhard, 2009).

2.10 Conceptual Framework and Reasoning

According to (Sabel, *et al.* 2017) an examination of the interactions between external elements such as scaffolds and internal factors to support expected outcomes constitutes a conceptual framework.



Reasoning for Conceptual framework

Based on literature reviewed part 3.5, the production and shipping of APIs have taken place in a very globalized setting. The tempo of the globalization of the marketplace for APIs has prevented the growth and harmonization of networked government monitoring measures, which were needed in response to the possible risks posed by subpar or even fake drugs. Nevertheless, incidents like the heparin crisis have underlined the necessity for prompt global intervention. One of the numerous difficulties the auditors will have to face is an effort at fraud throughout the audit. Finding out if the audited organization purposefully withheld or fabricated its findings is a critical component of an audit's success. The risk situation that is produced by inaccuracies that are hidden, undetected but visible and apparent but not thoroughly probed was requested of auditors by regulatory organizations. Such errors occur in businesses due to the constraints of process planning or streamlining, as well as circumstances that increase the likelihood of error due to inadequate **Quality assurance (QA)** processes.

To summarize part 3.9 and 3.5 of the literature review, a **risk-based mechanism** should be used to prioritize global API inspections by **competent regulatory authorities**, with geographic location being a key factor in assessing risk. In addition, one of the primary criteria for taking on more risk should be the presence of mediators. All involved mediators should be the primary focus for **GMP inspections**. The correct supervision and training of inspectors is necessary to implement the suggested **risk-based strategy**, which might coordinate all **API inspections** to be conducted globally to ensure the successful and effective utilization of resources.

Based on the risk-based strategy, it is necessary to put in place a mechanism that will enable officials to stop known **counterfeit APIs** from entering other nations. All APIs coming from producers and intermediaries who have a track record of engaging in the counterfeit API trade should be prevented from entering the market by the system.

The **independent variable** is GMP regulations, and these builds of the explanatory variable are GMP Regulations for inspections, Quality Assurance and Quality of APIs. These are referred as independent variable since they are manipulated in the literature review, and they seem to have an influence of the **dependent variables** which is “compliance of APIs”. The independent variables make up the trends that effect the compliance of APIs. When in action, that is, when these trends such as Risk-based, Quality Assurance, Quality of APIs issues enhance the compliance of APIs GMP regulations, the likely outcomes would be Quality APIs, restraint in counterfeit APIs, lesser legal notices, and Industry's expansion.

2.11 Conclusion

This analysis of the literature has demonstrated that a variety of GMP inspection laws are changing how active pharmaceutical ingredients are produced and sold around the globe. There is agreement that GMP laws are fundamental requirements that are anticipated for Active Pharmaceutical Ingredient in any country to comply to, even though regulations may vary from country to country. The functioning of the businesses involved may be hampered by fines and other fees if these standards are not followed. This study is necessary to assess the impact of regulatory role GMP audits on Active pharmaceutical ingredients because most of the evaluated prior studies that explored GMP regulations concentrated on Europe and few for other countries, exposing the gaps that led to this study's inception. To strengthen the effort, the investigation will also investigate the effects of Off-patent APIs and the function of some of the biggest APIs committees. In a later section of this dissertation, conclusions from the primary qualitative data that will be gathered concerning these gaps will be covered. As outlined in the chapters previously, a variety of problems need to be resolved before fresh ideas may be incorporated into the rules governing GMP audits. It is intended that the expert opinions would offer advice on how to use the finest techniques to close the gap between the exploratory steps and a unified regulatory framework for APIs.

3 Methodology and Research Design

3.1 Overview

The subsequent sections will provide a brief explanation of the rationale for the selection of the research philosophy, research design, and methodology for this study.

The "onion" model, a study model created by Saunders, Lewis, and Thornhill, served as the foundation for the layout of this study (Saunders, *et al.* 2019) (Okesina, 2020). It describes how a research project should start with the outermost segments of the onion, which deal with research methodology and philosophy. The center of the onion, which includes the research approach, options, timelines, and eventually the methodologies and techniques, should then be considered (Okesina, 2020).

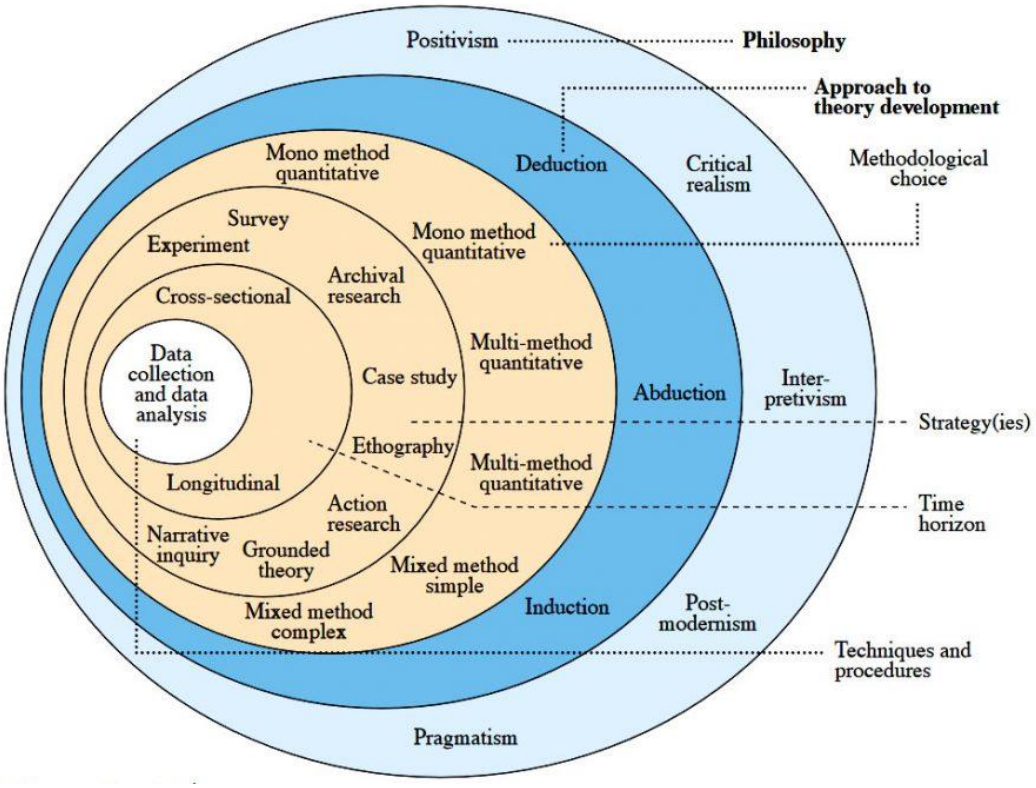


Figure 4 ***The Research Onion*** *(Saunders,* et al. *2019)*

The framework for creating a strong research technique is the "research onion," which enables you to make a series of choices that enable methodical study.

Following are the six layers of the onion:

1. Research Philosophy: This layer emphasizes the fundamental research methods. A given philosophical theory forms the foundation of a traditional research process. These include critical realism, interpretivism, and positivism. This research follows interpretivist philosophy. The goal of interpretivist research is to develop fresh, more in-depth perspectives on the world we live in (Puglisi, 2008). A method based on subjectivist ontological presumptions that since discourse makes up entities, only social creations like awareness or language may be used to study existing or socially produced reality. Since reality is socially constructed and continually changing, information and facts are arbitrary and contested (Myers, 2008).

2. Research Approach: Deduction, Induction, and Abduction are the three possibilities (Crotty, 2020).

Deduction is the process of using evidence to support or refute a theory that poses a question or makes an assertion. Inductive research begins with data collection and develops a theory through time.

To develop a theory, it is typically applied to fields with minimal investigation. The research on abduction eventually identifies an empirical phenomenon, progresses between inductive and deductive reasoning, and offers the most plausible conclusion. The methodology used in this dissertation is deductive.

3. Strategy: Saunders has categorized research methods into seven groups: experiment, survey, case study, action research, grounded theory, ethnography, and archive research. Experiments involves doing experiments to draw conclusions and may be carried out using some of the information from earlier types of research. The most popular data collection techniques for survey research are questionnaires and interviews. Individually or in a group, professionally conducted or self-administered, questionnaires normally contain several items that reflect the objectives of the research. This research follows grounded theory. Grounded theory aims to find or build a theory using data that has been methodically collected and examined via comparative analysis. Although grounded theory is a flexible methodology by nature, it is a complicated one. As a result, new researchers work hard to comprehend the debate and the actual use of grounded theory concepts and procedures.

4. Methodology: The employment of quantitative and qualitative research methodologies, as well as a straightforward or intricate combination of both, and the use of a single approach, are all examples of research choices according to Saunders. While qualitative approaches entail the collecting of a large amount of descriptive data, quantitative research methods utilize statistics and mathematical (Ramos, 2002) procedures. This study follows qualitative method. Expert semi-structured interviews are used to acquire the qualitative data for this dissertation.

5. Time horizon: In future studies, time horizons often relate to study intervals or an orderly horizon of different breadth. Kosow (Kosow and Gassner, 2007) identifies three fundamental time horizons: long-term - over 25 years; medium- - up to 10 years; and short-term - less than or equal to 10 years. In terms of time horizons, Saunders et al have recognised cross-sectional and longitudinal options for research projects. Overall, this is a cross-sectional, time-limited study.

6. Technique for Data Analysis: This is the onion's topmost layer. The decisions and results of each preceding layer influence the methods used for data collecting and analysis. Gioia approach is used for this research.

In order to defend and clarify the methodological research approach, this research strategy will be applied to the context of this research topic in greater detail in the next section.

3.2 Research Philosophy and Approach

The research onion begins with the outer layer, research philosophy. Saunders have classified philosophical approaches into four main categories; positivism; realism; interpretivism and pragmatism. This study follows an interpretivist philosophy (Saunders, *et al.* 2019).

The study's overarching goal is to investigate the role of GMP audits for active pharmaceutical ingredients through surveys and expert interviews. The author is aware that depending on their own backgrounds and experiences, individuals may have subjective opinions on the topic. To gain a perspective on the state of the GMP regulation for Active pharmaceutical Ingredients, surveys and interviews will be undertaken with specialists of various specialties in acknowledgment of this (Pervin and Mokhtar, 2022)

As a result of being formed by human views, "social reality" is neither objective nor dispassionate. To that end, the focus of this study is on the standard and breadth of the data acquired (Collis and Hussey, 2014).

Induction, deduction, and abduction are the three primary approaches used in theory construction. The method that is consistent with the interpretivist research philosophy of this research is the Deductive research method. The research approach placed a strong emphasis on the knowledge and opinions of professionals in the field of GMP audit requirements. Including an emphasis on qualitative, quantitative information and narrative material, the method supported the demand to examine and theorize the current position and potential futures of the emerging research within the regulatory world.

According to (Alase, 2017), for this study, an interpretative phenomenological analysis methodology has been used. According to its description, it is a "participant oriented" approach that looks to participants' "life experiences" to uncover and produce the study findings. The beauty of deduction is that it encourages different theories of truth instead of the strict cause-and-effect approach seen in inductive inquiry (Saunders, *et al.* 2019). This is the reason why the deductive technique is focused with the context wherein events occur and selects a limited sample of individuals from that setting to gather their perspectives on the study item being explored by the author.

According to (Saunders, *et al.* 2019) authors who adhere to this methodology or approach frequently use qualitative techniques, instruments, data, and data analysis to ascertain the various perspectives of study participants on the phenomena of interest (Okesina, 2020).

While the inclusion of dependent and independent variables and randomness, which are common in quantitative research, are not inevitably characteristics of the qualitative approach, studies using qualitative methods are anticipated to be solving research problems that may result in the development of theories or discovering knowledge through comprehending the trend that leads to it (Okesina, 2020). For this reason, convenient sampling, purposeful sampling, or additional nonprobability sampling methods are used in this type of research in order for researchers to be capable to choose subjects whose accurate responses, because of their familiarity with the subject, would result in more accurate or robust results (Okesina, 2020). This is why non-randomization approaches are used in the method of sampling in qualitative research, which also involves unstructured methods and tools to collect data, such as thorough-depth semi-structured interviews (Makombe, 2017).

3.3 Research Strategy and Time Horizon

Saunders has categorized research methods into seven groups: experiment, survey, case study, action research, grounded theory, ethnography, and archive research. This study used and grounded theory as its research strategy. Although the research concentrated on creating a framework to evaluate the regulatory role of GMP audits for APIs, the grounded theory method's predictive qualities are particularly relevant. Because the investigation was deductive, a theory was developed based on the perspectives of specialists. Both the structure of the framework and how it was used to the data gathered were crucial components in establishing the validity of the interview results. However, proper familiarity with the literature before the start of primary data gathering was a crucial aspect of the grounded theory strategy.

The research is based on qualitative data, the participants communicate to the researcher their views of the study's object through interviews or social contact. The researcher then creates or draws interpretations from the study's topic through one's own and participant experience.
Saunders have acknowledged cross-sectional and longitudinal alternatives for research studies across a variety of time periods. The timetables and due dates were established in advance because this research is being conducted for a dissertation. Surveys and interviews will be conducted around halfway through April 2023. The results only give a peek into the problem owing to time constraints. This study is cross-sectional and time-limited in all respects.

3.4 Research framework summary:

In summary, a deductive method, a cross-sectional temporal horizon, a semi structured interview data collection technique, and a review and categorization data analysis strategy were used to perform this exploratory study. In the parts that follow, the research framework's application will be explained.

3.5 Collection Primary Data

3.5.1 Sources

Examining the subject with professional viewpoints was a useful way to get the range of rich knowledge needed with the aid of the exploratory and deductive research methodologies. Interviews were chosen and sought for to gather information despite surveys being thought of as an alternate option.
According to evaluations, interviews would prefer detailed opinions from a smaller sample than the short responses that surveys typically get. A considerably bigger sample size would also be necessary for surveys.
The period allotted prevented surveys that ran the risk of receiving no or postponed responses. The use of the Delphi approach to design repeated surveys and elaborate on novel, intriguing results would not have been advantageous. Conversely, semi-structured interviews enable the pursuit of intriguing data discovered during the interviews (Wishkoski, 2020).
Since the research issue is somewhat specific, another issue was finding a large enough sample size of people who had the necessary competence. Moreover, considering the backgrounds of the random participants, the prospect of a low response rate had additional consequences to the

reliability of survey results. This risk was avoided by choosing to speak with a select group of well-known industry specialists (Hill and Shackelford, 2020).

In comparison to a structured framework, the semi-structured interview method was favored since it allowed for an adaptive examination of the intersection between studies on GMP audits and the pharmaceutical industry. Additionally, it allowed for unexpected data and pertinent aberrations. A desirable aspect was the ability to adapt interview questions to each interviewee's level of competence and, if necessary, make changes in-flight. A structured interview approach would not have allowed for this amount of freedom.

3.5.2 Sampling and Selection of participants

There is an objective in qualitative research Because qualitative research allows for the mindful or diligent choice of subjects who the researcher believes have knowledge about the area of study due to specific skills they have (their age, educational background, the exposure, status at work in the society and other factors), their opinions and viewpoints will be beneficial and could support solid study results (Wang, *et al.* 2020).

Although the method of sampling utilized in qualitative studies has been criticized as non-probabilistic and susceptible to skepticism, its usage is justified by the researcher's expectation of rich, well-informed information gathered from the participants. Due to the simplicity of obtaining them, their readiness to take part in the study, and the standard of remarks that can be anticipated of them due to their expertise, knowledge, and being subjected to GMP auditing, the present study will utilize semi-structured interviews and participants will be chosen based on sample convenience (Wang, *et al.* 2020).

Six participants who are experts in GMP auditing for Active Pharmaceutical Ingredients have been selected for interviews. Few of them run their own pharmaceutical companies and others are Global Lead GMP auditors. As saturation sets from the eight interview sessions, the selection of five individuals for an interview has been deemed sufficient.

Additionally, volunteers had to be experts in manufacturing, quality assurance, validation, and control. This is because these experts are probably familiar with GMP developments as they have an impact on the pharmaceutical business. Following are their profiles (All the participants are agreed to be recognized for their contribution in the research):

3.5.3 Sociodemographic details of Interviewees

Table 2 **Details of Interviewees**

Information	Interviewee 1	Interviewee 2	Interviewee 3	Interviewee 4	Interviewee 5	Interviewee 6
Name	Emilia Niekrasz	Vaibhav Dubey	Ibrahim Ghareeb Madian Mohammed	Giannis Fotopoulos	Gabor Mihalyi	Naresh Renikindi
Gender	Female	Male	Male	Male	Male	Male
Education	Master's Degree Holder	Master's Degree Holder	Bachelor's Degree Holder	Master's Degree Holder	Doctorate Degree Holder	Master's Degree Holder
Occupation	GMP auditor	GMP auditor	GMP auditor	GMP auditor	GMP auditor	GMP & GDP auditor
Position	Director of Moben Pharma	GMP/ Quality Consultant	Compliance Executive Consultant	Quality Manager/ Qualified Person	Qualified Person/ Quality Manager	Qualified Person
Experience	33 years	14 years	15 years	25 years	18 years	16 years
Nationality	Polish	Indian	Egyptian	Greek	Dutch	Indian

3.5.4 Interpretation of the semi-structured interviews

Online interviews were conducted using the Zoom platform. Due to the simplicity and widespread usage of video channels, the researchers have all shown an interest in conducting this interview over these methods. One participant, however, requested the usage of Skype because the Zoom application was unusable from their location. In addition to recording the interviews on video for simple playback and recording, notes will be taken throughout the discussions to record the respondents' opinions. Significant remarks provided by participants during the interviews were noted in a notepad. The researcher will be capable to

accurately translate responses from participants with video clip files and notepad annotations, which are going to be utilized for the data analysis.

3.5.5 Access and Ethical Issues

For participating in the study, a risk evaluation was done, but no dangers were found.
Risks to reliability and precision, however, were noted in that manner.

1. A challenge in reaching participants with the necessary competence
2. Poor research design; poorly crafted interviews; confusing or lead questions; inappropriate questions that fail to address the research goals
3. The researcher's absence of interviewing experience
4. Limitations of the literature; lack of relevant material, which lowers the interview capacity and increases the chance of missing essential points

The subsequent measures were taken to lessen the likelihood that the accuracy and veracity of the study might be compromised. The subsequent list of activities is organized numerically in relation to the dangers that were previously mentioned.
1. A big number of specialists were found early in the project to guarantee a sizeable sample for analysis. The questioning process and schedule were flexible, making it simple to reach a compromise with participants.
2. The researcher went over pertinent interview preparation guidelines. Through the application of prototype interviews, questions for interviews that directly addressed the study's goals were generated before being checked for ambiguous or undefined language.
3. The examiner had been trained for the interviews by becoming familiar with accepted concepts and practices for carrying out interviews. The researcher also practiced delivering the questions via a pilot study to assist predict any necessary consecutive questions.
4.A wide range of literary sources were investigated to find any pertinent information.

No ethical challenges or difficulties were found in the study's methodology or interview protocol after the study underwent an ethical evaluation, hence Griffith College's Research Ethics Committee assessment was not necessary. There were no susceptible participants in the trial, and there were no known dangers to the volunteers. All information gathered during the interview will be kept on the researcher's personal, encrypted laptop. Finally, no ethical issues with the data processing or publication of the study were brought up.

Prior to the start of the interviews, participants were given a Participation Information Letter and Participant Consent Form, which they carefully read and signed.

The letter made it abundantly clear that involvement was optional, consent could be withdrawn at any time, participants had the freedom to decline to respond any questions, and absolute secrecy and anonymity would be upheld throughout the research, along with the steps undertaken to guarantee this. There are duplicates of both forms in the appendix.

3.6 Approach to Data Analysis

Gioia Approach

A well-liked technique for analyzing qualitative data in qualitative studies is the **Gioia approach** (Gioia, *et al.* 2013) (Salamzadeh, 2020). The first-order code phase, second-order code phase, and third-order code phase are the three phases that make up this process. The respondent's replies are compiled and placed in the initial column during the first-order code phase (Gehman, *et al.* 2018).

The responses received from these individuals are then grouped into related themes in a different column for simple evaluation. In the third-order code phase, the second-order codes are purposefully condensed into a handful of thoughts or ideas that serve as the codes' representations. The result of the entire procedure is a document known as the code map, which resembles a quantitative analysis or classification of topics into codes that represent the participants' median ideas as shown by how they responded. This code map will be covered in more detail in the following chapter (Gioia, *et al.* 2013) (Langley and Abdallah, 2011).

4 Presentation and Discussion of the Findings

4.1 Overview

The interview findings regarding the regulatory function of API GMP audits are presented in this chapter. Participants in the interviews gave their knowledgeable opinions and knowledge about GMP audit trends in the pharmaceutical industry across several nations. The following research questions were addressed to the participants as part of the study's interview process:

1. What perceptions do professionals have on how GMP audits are important for APIs?

2. What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs?

3. What actions would the professionals recommend harmonizing and coordinate non-compliant APIs?

4. To which extent regulatory authorities mitigate the quality issues for APIs?

The study of the interview subjects' demographics opens this chapter. For easy understanding, participants will be identified as Aud_GMP1 or Auditor_GMP1 for participant number 1, Aud_GMP2 or Auditor_GMP2 for participant number 2, Aud_GMP3 or Auditor_GMP3 for participant number 3, Aud_GMP4 or Auditor_GMP4 for participant number 4, and Aud_GMP5 or Auditor_GMP5 for participant number 5. The examination of participant replies to the research questions and to demographic information will come next. The examination of the information or the interviewees' responses to the study questions will be done using the Gioia method of qualitative data analysis.

4.2 Analysis of participants responses

Table 3 **Responses from the participants**

Participant	Research Questions and Objectives	Responses
Aud_GMP1	**Research question 1** What perceptions do professionals have on how GMP audits are important for APIs? **Research objective 1** To evaluate the effectiveness of GMP audits in ensuring the quality of Active Pharmaceutical Ingredients produced and supplied by manufacturers.	• To evaluate GMP level if they pass all requirements. • This is a knowledge that everything that is included in the product is produce in accordance with the GMP. • Poor quality APIs can result in the failure of a drug to produce the intended therapeutic effect.
Aud_GMP1	**Research question 2** What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs? **Research objective 2** To investigate the impact of GMP audit findings on the approval process of APIs.	• We have different environment after Covid. • 90% of APIs synthesized are from India and China. • The biggest challenge is to transfer that what we need. • The hygiene aspects in India and China • If the batch of API is blocked and back to crystallization stage. The batch will have extra shelf life, but it will not be covered under stability test. • The drug products will be less effective with no expected potency.

Aud_GMP1	**Research question 3** What actions would the professionals recommend harmonizing and coordinate non-compliant APIs? **Research objective 3** To make recommendation to an API industry.	• Most companies have track wise system. • Many tools or systems let companies track all the incidents and close it in a defined period. • I recommend using these systems and it let all the employees to put what was happened. • Tracking should be performed in a standard way than in a paper way.
Aud_GMP1	**Research question 4** To which extent regulatory authorities mitigate the quality issues for APIs? **Research objective 4** To create a framework of different actions taken by regulatory authorities.	• Enforced submission of detailed data and documentation • Less resources sometimes results in less frequency of inspections and audits which limit the ability to detect potential quality issues.
Aud_GMP2	**Research question 1** What perception do professionals have on how GMP audits are important for APIs? **Research objective 1** To evaluate the effectiveness of GMP audits in ensuring the quality of Active Pharmaceutical Ingredients produced and supplied by manufacturers.	• APIs are the core ingredient of the medicine. • If API is not up to the specific quality which is maintained by respective pharmacopeia, the treatment will not be up to the mark. • Failure to comply with GMP regulations can result in regulatory actions.

Aud_GMP2	**Research question 2** What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs? **Research objective 2** To investigate the impact of GMP audit findings on the approval process of APIs.	• The regulatory norms are same, but the interpretation of the requirements and the regulatory guidelines is different with respect to the person-to-person audit and site to site. • If the APIs value is less than it is difficult for the site to maintain the compliance throughout the manufacturing part because to maintain the compliance throughout the manufacturing process. • Non-compliant API contains impurities which may be threatening to patients.
Aud_GMP2	**Research question 3** What actions would the professionals recommend harmonizing and coordinate non-compliant APIs? **Research objective 3** To make recommendation to an API industry.	• Because API synthesis is completely a chemical process, industries should reprocess the material till they get the expected quality of APIs. • There should be a proper requirement for investigation like different tools or mechanism to identify the root cause of non-compliant APIs and rectify that with the help of CAPA.
Aud_GMP2	**Research question 4** To which extent regulatory authorities mitigate the quality issues for APIs? **Research objective 4** To create a framework of different actions taken by regulatory authorities.	• The regulatory norm “ICH Q7” is widely accepted. • It is in generic form not in a descriptive form but some of the industries are not concerned about the gaps created by the inappropriate knowledge of the regulatory norms. • Also, after the pandemic, many people are entering into pharma and healthcare, so the consequences will be there if the person is properly educated.

Aud_GMP3	**Research question 1** What perception do professionals have on how GMP audits are important for APIs? **Research objective 1** To evaluate the effectiveness of GMP audits in ensuring the quality of Active Pharmaceutical Ingredients produced and supplied by manufacturers.	• The GMP audits covers all the aspects of API manufacturing process. • Because of GMP audits, it is assured that APIs produced are of good quality, regardless of when and where they are processed. • Gives assurance for compliance for regulatory authorities.
Aud_GMP3	**Research question 2** What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs? **Research objective 2** To investigate the impact of GMP audit findings on the approval process of APIs.	• Many African countries go for low grade raw material, this cause lot of problems in the formulations and manufacturing process. • One of the major challenges is that APIs need special storage and environmental conditions. • Besides potential hazards, it also causes issues during manufacturing process. • Low grade or non-compliant APIs can enter the black market which is a major concern.
Aud_GMP3	**Research question 3** What actions would the professionals recommend harmonizing and coordinate non-compliant APIs? **Research objective 3** To make recommendation to an API industry.	• Revalidation should be done after the change of supplier of the same API. • Analysis of the incoming material to avoid any black market.

Aud_GMP3	**Research question 4** To which extent regulatory authorities mitigate the quality issues for APIs? **Research objective 4** To create a framework of different actions taken by regulatory authorities.	• Sometimes it is difficult for the stakeholders to have the information about the compliance status of APIs. • It is also difficult for regulatory authorities to play along with rapidly growing industry.
Aud_GMP4	**Research question 1** What perception do professionals have on how GMP audits are important for APIs? **Research objective 1** To evaluate the effectiveness of GMP audits in ensuring the quality of Active Pharmaceutical Ingredients produced and supplied by manufacturers	• It is not only the regulatory requirement but also patient safety. • It cannot be replaced by other forms of evaluation like paper assessments. • Also, because it has the direct impact on the business, on quality and supply chain.
Aud_GMP4	**Research question 2** What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs? **Research objective 2** To investigate the impact of GMP audit findings on the approval process of APIs.	• Globalised supply chain because many API manufacturers have 2 or 3 intermediate API sites that are their supplier so production of APIs might not finish or start at the same site. • There might be a difference in local legislation like GMPs or other regulatory affair and active substance Master file requirements. • API manufacturing sites are large establishments, are not very easy to inspect because of their size.

		• Language and local conditions barriers between different regions. • Shortage of specific medicines in the market and eventually to the patient. • Business issues
Aud_GMP4	**Research question 3** What actions would the professionals recommend harmonizing and coordinate non-compliant APIs? **Research objective 3** To make recommendation to an API industry.	• So far after the pandemic, everything is smooth, but I would recommend the increase in the regulatory oversight. • Conduction of more frequent inspections.
Aud_GMP4	**Research question 4** To which extent regulatory authorities mitigate the quality issues for APIs? Research objective 4 To create a framework of different actions taken by regulatory authorities.	• It is connected to the oversight. There should be transparency between the regulatory authority and the stakeholders.
Aud_GMP5	**Research question 1** What perception do professionals have on how GMP audits are important for APIs? **Research objective 1** To evaluate the effectiveness of GMP audits in ensuring the quality of Active Pharmaceutical Ingredients produced and supplied by manufacturers	• It is important because we get to know about the whole process till the finished product. • It is a pathway to know all the aspects including manufacturing, source of raw material, tests, and the release of product.

Aud_GMP5	**Research question 2** What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs? **Research objective 2** To investigate the impact of GMP audit findings on the approval process of APIs.	• In the last 5-7 years I haven't seen that challenge. • Most of the industries especially in India and Europe, US, they have easily adopted the ICH Q7. • Still there are little bits and pieces where methodology is different when I see. It's down to the incorrect interpretation of the guidance. • There will be an issue if you find it in the finished product or even in the raw material. • The implications would be that you might end up consuming a product with low therapeutic value. • Implications are within quality, safety, and efficacy
Aud_GMP5	**Research question 3** What actions would the professionals recommend harmonizing and coordinate non-compliant APIs? **Research objective 3** To make recommendation to an API industry.	• To address some complex issues, stakeholders could come together to strengthen the supply chain. • This could lessen the risk of non-complaint APIs entering the supply chain.
Aud_GMP5	**Research question 4** To which extent regulatory authorities mitigate the quality issues for APIs? **Research objective 4** To create a framework of different actions taken by regulatory authorities.	• Majority of APIs are manufactured in China and India, so if we see the quality of the audits conducted by the competent authorities in India, it's at a different level to how it's conducted in the Europe. • Physically they are not forcing the challenges on the systems to be verifying the appropriate implementation of it.

		• So, in the regulatory norms, it is a big problem because of which, the manufacturers are easily getting the licences.
Aud_GMP6	**Research question 1** Describe your view on how GMP audits are important for APIs? **Research objective 1** To evaluate the effectiveness of GMP audits in ensuring the quality of Active Pharmaceutical Ingredients produced and supplied by manufacturers	• Indirectly, it's a tool that is required by the companies for the MAH and the for the QP to ensure that relevant parts of the supply chain are compliant and working towards the equivalent to regulation. • The audits are to ensure the companies are satisfied by the GMP compliance that is producing products for them.
Aud_GMP6	**Research question 2** What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs? **Research objective 2** To investigate the impact of GMP audit findings on the approval process of APIs.	• We always have certain amount of information about the manufacturing and the process, but we do not have the full visibility all the time. • It's limited and it's driven and controlled by someone else. • Implications would be safety risks to patients. • Loss of revenue in the pharmaceutical industry
Aud_GMP6	**Research question 3** What actions would the professionals recommend harmonizing and coordinate non-compliant APIs? **Research objective 3**	• The production of APIs involves different countries, therefore international cooperation is necessary. • Improvement in information exchange • The education of staff even if cost time and money

	To make recommendation to an API industry.	
Aud_GMP6	**Research question 4** To which extent regulatory authorities mitigate the quality issues for APIs? **Research objective 4** To create a framework of different actions taken by regulatory authorities.	• We still find companies which do not pragmatically apply the standards and they cannot translate it to their own organization. • It can't be proportional to the activities and the size that they have. • Sometimes the professional themselves cannot really translate these requirements into production, QC.

4.3 First order code generated from participants responses.

For this research study, first-order codes will be created based on the participants' responses. The compiled answers of interview subjects to the questions posed make up the first order of codes.

Table 4 **Generated First-order codes from the participants responses.**

Research questions	First-order codes
What perceptions do professionals have on how GMP audits are important for APIs?	1. APIs are the core ingredient of the medicine. 2. It's a tool that is required by the companies for the MAH and the for the QP to ensure that relevant parts of the supply chain are compliant and working towards the equivalent to regulation. 3. It is a pathway to know all the aspects including manufacturing, source of raw material, tests, and the release of product. 4. It has the direct impact on the business, on quality and supply chain.

	5. It cannot be replaced by other forms of evaluation like paper assessments. 6. It is assured that APIs produced are of good quality, regardless of when and where they are processed. 7. Failure to comply with GMP regulations can result in regulatory actions. 8. Poor quality APIs can result in the failure of a drug to produce the intended therapeutic effect.
What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs?	1. Having certain amount of information of the manufacturing but does not have full visibility all the time. 2. 90% of APIs synthesized are from India and China. The biggest challenge is to transfer that what we need. 3. Stability tests for the API batch with extra shelf life 4. The regulatory norms are same, but the interpretation of the requirements and the regulatory guidelines is different with respect to the person-to-person audit and site to site. 5. Non-compliant API contains impurities which may be threatening to patients. 6. Many African countries go for low grade raw material, this cause lot of problems in the formulations and manufacturing process. 7. One of the major challenges is that APIs need special storage and environmental conditions. 8. Globalised supply chain because many API manufacturers have 2 or 3 intermediate API sites that are their supplier so production of APIs might not finish or start at the same site. 9. There might be a difference in local legislation like GMPs or other regulatory affair and active substance Master file requirements. 10. API manufacturing sites are large establishments, are not very easy to inspect because of their size.

	11. Language and local conditions barriers between different regions.
What actions would the professionals recommend harmonizing and coordinate non-compliant APIs?	1. Most companies have track wise system. 2. Many tools or systems let companies track all the incidents and close it in a defined period. 3. Because API synthesis is completely a chemical process, industries should reprocess the material till they get the expected quality of APIs. 4. There should be a proper requirement for investigation like different tools or mechanism to identify the root cause of non-compliant APIs and rectify that with the help of CAPA. 5. Revalidation should be done after the change of supplier of the same API. 6. Analysis of the incoming material to avoid any black market. 7. The production of APIs involves different countries, therefore international cooperation is necessary.
To which extent regulatory authorities mitigate the quality issues for APIs?	1. Enforced submission of detailed data and documentation 2. The ICH Q7 is widely accepted. It is in generic form not in a descriptive form but some of the industries are not concerned about the gaps created by the inappropriate knowledge of the regulatory norms. 3. After the pandemic, many people are entering into pharma and healthcare, so the consequences will be there if the person is properly educated. 4. The connection between the authorities and the stakeholders is good but it should be more transparent. 5. Physically they are not forcing the challenges on the systems to be verifying the appropriate implementation of it. 6. We can still find companies which do not pragmatically apply the standards and they cannot translate it to their own organization.

	7. Sometimes the professional themselves cannot really translate these requirements into production, QC

4.4 Second order codes generated based on refining of First order codes.

The first-order codes, which are made up of the responses of the interviewers, are the second order of codes, which are common patterns that resonate with them.

Table 5 **Second order codes generated from first order codes.**

Research questions	Second order codes
What perceptions do professionals have on how GMP audits are important for APIs?	1. Compliance 2. Efficacy 3. Continuous Improvement
What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs?	1. Complex Supply chain 2. Regulatory Complexity 3. Counterfeiting 4. Patient safety
What actions would the professionals recommend harmonizing and coordinate non-compliant APIs?	1. Corrective actions 2. Revalidation 3. Continuous Monitoring
To which extent regulatory authorities mitigate the quality issues for APIs?	1. Inconsistent enforcement 2. Global variation

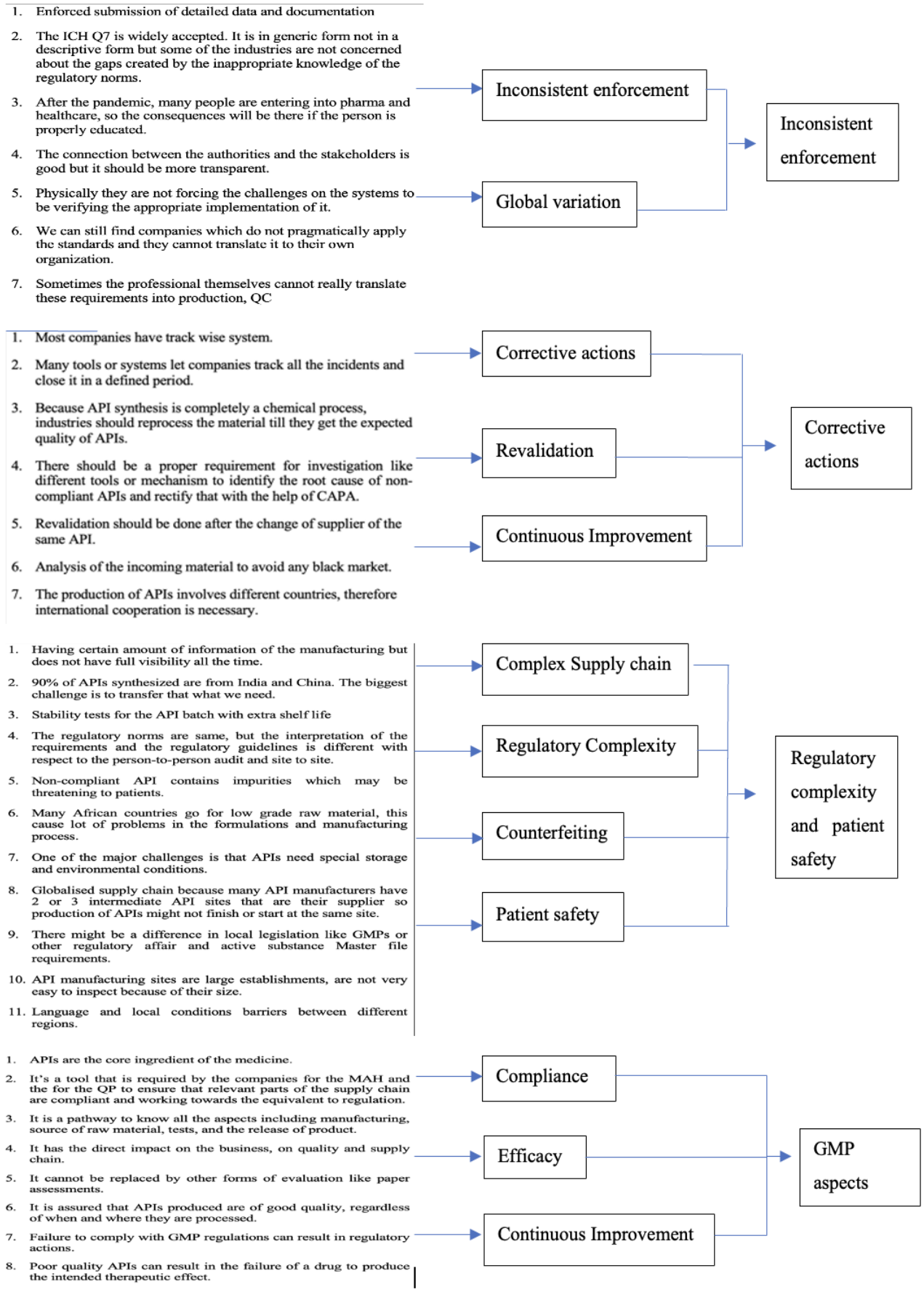
4.5 Third order codes based on refining of second order codes.

The themes are further condensed into individual thoughts or ideas in the third layer of codes. Based on the second-order codes, the third-order codes were chosen and displayed in the second column:

Table 6 **Third order codes generated from second order codes.**

Research questions	Third order codes
What perceptions do professionals have on how GMP audits are important for APIs?	GMP aspects
What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs?	Regulatory Complexity & patient safety
What actions would the professionals recommend harmonizing and coordinate non-compliant APIs?	Corrective actions
To which extent regulatory authorities mitigate the quality issues for APIs?	Inconsistent enforcement

4.7 Code Map of summary of results using Gioia method.



4.8 Discussion

Considering the findings of this review, which supports the literature's assertions on the regulatory importance of GMP audits for APIs. According to Max Lazar (Lazar, 2014) statement, companies don't properly comprehend the API GMP's stated purpose. Anyone who has undergone training and is aware of ICH Q7's goals shouldn't be flouting so many basic GMP requirements. This literature agrees to the perceptions of the GMP professionals from the interviews. They believe GMP audits support ensuring that the manufacture of API complies with legal specifications, including those outlined by the FDA and other governing organizations. Maintaining product safety and effectiveness depends on this. GMP audits can spot quality problems in the production of APIs and assist firms in resolving them before they worsen. This is considered very crucial to ensuring consistent product quality and avoiding recalls or batch failures. GMP audits show a manufacturer's dedication to quality and safety, which fosters consumer confidence. Increased sales and brand loyalty may result from this. In the long run, process improvements that are found during GMP audits may result in greater efficiency and lower costs.

Professional shared their real-life challenges in assuring the quality of APIs. According to (Lavelle, 2020), the difficulties in ensuring the caliber of APIs produced in emerging economies are covered in this study. The authors discovered that the main obstacles to assuring the quality of APIs produced in emerging economies included a lack of regulatory monitoring, inadequate quality control methods, and a lack of resources. Participants believe that depending on the source and supplier, the quality of the raw materials utilized to make APIs can change. It might be challenging to track down the source of raw materials and make sure they adhere to the necessary quality standards because of the complexity of the supply chain. It may be simpler for counterfeiters and unlicensed suppliers to bring contaminated or fake materials into the production process due to the intricacy of the supply chain. The effectiveness and security of APIs may be harmed by this. The rules governing API production can differ between nations and regions, which makes the supply chain more complicated. It can be quite difficult to make sure that all suppliers and intermediaries are adhering to these rules. Implementing and maintaining effective quality control procedures can be challenging due to supply chain complexity. It may be difficult for manufacturers to constantly monitor quality when they are unable to see all the steps involved in their suppliers' manufacturing processes.

Natural catastrophes and political unrest are two examples of events that can interrupt the supply chain and affect the quality and availability of raw materials and finished goods. To

guarantee supply continuity and uphold quality standards, manufacturers must be able to promptly adjust to these disturbances. In conclusion, ensuring the quality of APIs is significantly hampered by the complexity of the supply chain. It can influence the safety and quality of raw materials and finished goods, raise concerns about regulatory compliance, reduce visibility into production processes, and raise the possibility of supply chain interruptions. To overcome these obstacles, manufacturers must put in place strict quality control procedures and collaborate closely with their suppliers to guarantee that supply chain-wide quality requirements are met.

Concluding from the responses of the interviewees, regulatory complexity is regarded as another major obstacle to ensuring API quality. Manufacturers must adhere to numerous rules, norms, and regulations because the regulatory requirements for APIs are strict. Different nations and regions may have very different laws concerning APIs. To guarantee that their APIs are approved in various areas, manufacturers must be aware of and adhere to these variances.

Most of the participants elaborated their opinion on implications of non-compliant APIs which are ultimately related to patient safety. In "Contaminated heparin and adverse clinical events" by (Kishimoto, *et al.* 2008), authors discussed the effects of tainted heparin APIs are covered in this research. According to the authors', contaminated heparin was linked to serious adverse effects, including fatalities, and caused a global recall of heparin-related items. Additionally, the authors discovered that contamination could cause unfavorable outcomes and erode public confidence in the pharmaceutical sector. After summarizing the interviewees responses, non-compliant APIs may not have the desired therapeutic outcome, which could result in treatment failure and patient damage. This may be the result of insufficient potency, stability, or other superior qualities. It may become more challenging to treat infectious diseases because of the emergence of drug-resistant types of bacteria or viruses caused by non-compliant APIs.

The goal of this research is found if regulatory authorities mitigated the quality issues for APIs or how far they have come. Participants believe that regulations that are not consistently enforced may even make API quality problems worse. Manufacturers could be tempted to take short cuts to lower costs or boost profits when laws are not regularly enforced. This may result in the manufacturing of inferior or fake APIs, which may have detrimental effects on patients' health. Regulators and manufacturers may find it challenging to maintain consistent quality control throughout the supply chain because of inconsistent enforcement, which can also result in inconsistent quality standards across various markets. Due to this, different locations may produce APIs that may not satisfy the same quality standards, which could result in problems

with quality. In general, inconsistent enforcement can jeopardize patient safety and erode public confidence in the pharmaceutical sector. To maintain the integrity of the supply chain and safeguard public health, authorities must make sure that laws are consistently applied. One more major reason because of which we are still finding few cases of non-compliant APIs is Global variation.

If it is correctly handled, global variance can help API quality issues be mitigated. In “Global pharmaceutical regulation: the challenge of integration for developing states” by (Pezzola and Sweet, 2016), there is a discussion on the striking opposition to the adoption of international pharmaceutical standards for quality in underdeveloped countries and in regulatory infrastructure. In many developing nations, human capacity is still constrained. The vast differences between states are most notable. Leaders in developing international standards do not seem to have influenced their neighbors' development of local norms. The United States and the European Union, two major global standard-setters, appear to have remarkably little influence on standard setting across our sample, in contradiction to classic conceptions of the transmission of international standards. From the interviews, supply chain logistics, regulatory frameworks, and manufacturing methods diversity can make it difficult to maintain consistent quality control and legal compliance. Global variation can also be advantageous if it is correctly handled, since it can boost API access, reduce costs, and create chances for innovation.

The creation and execution of standardized regulatory standards that are accepted and upheld in many locations is one method for managing global diversity. Regardless of where they were produced, this can assist guarantee that APIs manufactured and marketed in various markets satisfy the same quality and safety criteria. Creating risk-based quality control strategies is another technique to reduce quality problems brought on by global variation. Focusing quality control efforts on high-risk areas, such as crucial production processes and potential sources of contamination or adulteration, is one way to do this. This strategy can save excessive expenditures and hassles on producers while ensuring that quality issues are quickly discovered and resolved.

Finally, a critical component of reducing quality difficulties brought on by global variance is good supply chain management. This entails collaborating closely with distributors, suppliers, and other stakeholders to guarantee that every component of the supply chain is adequately controlled and monitored and that any possible risks are recognized and handled pro-actively. To summarize, Global variance can create issues for maintaining consistent quality control and regulatory compliance, but it can also lead to opportunities for cost-cutting and innovative solutions. The pharmaceutical sector can contribute to ensuring the quality and safety of APIs

for patients all over the world by efficiently controlling these risks through harmonized laws, risk-based quality control systems, and effective supply chain management.

4.9 Interpretation of results

Four coding steps were developed according to the present study's research topics.

As a result, using the four coding processes, this section interprets an overview of responses provided by participants. Outcomes will be compared to the literature on the regulatory function of GMP audits for APIs in the following and final chapter.

4.9.1 Interpretation of coding outcomes of Research question one

Research question 1: What perceptions do professionals have on how GMP audits are important for APIs? Participants' replies to this topic produced three codes under the GMP features of compliance, efficacy, and continuous improvement.

4.9.1.1 Compliance

An overview of participants responses shows that since the goal of GMP audits is to make sure that a facility is producing pharmaceuticals or medical supplies in accordance with relevant regulations and guidelines, compliance is an important aspect of these audits. *According to Aud_GMP6, it's a tool that required for the companies for the MAH and the QP to ensure that relevant parts of the supply chain are compliant.* Aud_GMP6 further added *audits are there to ensure the companies are satisfied by the GMP compliance that is producing products for them.*

4.9.1.2 Efficacy

The participants have also affirmed efficacy as an important aspect of GMP audits. According to Aud_GMP4, *throughout a GMP audit, an auditor will examine the documentation and operating procedures of the facility as well as carry out facility inspections to determine the effectiveness of the manufacturing operations there. The auditor will search for proof that the establishment complies with the necessary quality control procedures, which include testing, validation, and calibration. To make sure that the necessary documentation is correct and comprehensive, they will also examine the facility's record-keeping procedures. The auditor*

will evaluate the effectiveness of the facility's quality management system as well as to the manufacturing procedures at the facility. Aud_GMP1 added, *this is a knowledge that everything what is included in the product is produce in accordance with the GMP.*

4.9.1.3 Continuous Improvement

Participants view continuous improvement as a key characteristic of GMP aspects and gave the opinion that a facility's production processes, policies, and systems will be examined by an auditor to find room for improvement. Typically, the auditor will give the facility suggestions for improvement based on industry best practices and standards.

Participants Aud_GMP4 affirmed, *all the audits should perform on site, remote audits should only be performed during pandemics. It is not only seen as improvement, but it is important for patient safety. It cannot be replaced by other forms of evaluation like paper assessments.* Aud_GMP2 added, *to find areas that need improvement and put remedial measures in place, the facility may also carry out its own internal audits.*

The participants' perceptions of GMP aspects are compliance with the GMP audits for APIs, according to the summary of their responses. As it continually strives to improve its processes and systems, effectiveness and continuous improvement are additional factors.

4.9.2 Interpretation of the coding outcomes for the research question two

Research question 2: What are the challenges in assuring the Quality of APIs and What are the implications of non-complaint APIs?

The second research question elicited the following four codes from participant opinions: Complex supply chain, regulatory complexity, counterfeiting and patient safety.

4.9.2.1 Complex supply chain

Participants emphasized their viewpoint that APIs are frequently purchased from suppliers all over the world, it is difficult to guarantee their quality all through the supply chain. Monitoring and managing these circumstances can be challenging, particularly if there are several parties engaged in the transportation and storage of the APIs. Aud_GMP4 added, *Globalised supply chain is the biggest challenge because many API manufacturers have 2 or 3 intermediate API sites that are their supplier so production of API might not finish or start at the same site. It might be challenging to verify that every supplier is producing the API in accordance with the*

requisite quality requirements when APIs are received from a variety of suppliers. Additionally, it may be difficult to guarantee quality consistency throughout the supply chain because some suppliers may be situated in nations with various regulatory frameworks.

4.9.2.2 Regulatory complexity

According to the participants opinion, another difficulty in ensuring the quality of Active Pharmaceutical Ingredients is regulatory complexity. Depending on the nation or area where they are produced or utilized, APIs are subject to a variety of regulatory standards and rules. Aud_GMP5 says, *methodologies are different between different continents when I see the challenge, it's down to the incorrect interpretation of the regulatory guidance.* Aud-GMP5 affirmed in an open discussion, *Majority of APIs are manufactured in China and India, so if you see the quality of the audits conducted by the competent authorities from India, it's at a different level to how it is conducted from the Europe. Physically they are not forcing the challenges on the system of verifying the appropriate implementation of it. So, from the regulatory perspective, it is a big problem because of which, the manufacturers are easily getting the licences.* Aud_GMP4 also see it as a challenge says, *there might be difference in local legislation like GMPs or other regulatory affair and active substance Master file requirements.* Aud_GMP2 also added, *the biggest challenge is that regulatory norms are same, but the interpretation of the requirements and the regulatory guidelines is different with respect to the person-to-person audit and site to site.*

4.9.2.3 Counterfeiting

Participants see counterfeiting as a major challenge since in their opinion, they may not contain the right active ingredient or may contain impurities that are dangerous, which can pose serious concerns to patient safety. Aud_GMP2 says on this, *API is the core ingredient of the medicine. If API is not up to the specific quality that maintained by respective pharmacopeia, the treatment will not be up to the mark.* Aud_GMP5 has an opinion saying, *the implications would be that you might end up consuming it and producing a finished product. So, if the API has low potency that means it will have a low therapeutic value that means the patient might not get the required therapeutic relief. So, if it is high potent, you might end up giving a high dose product which might produce adverse reaction. It might counteract. More level of API might be poisoning because your body will not be able to process.*

4.9.2.4 Patient safety

For patient safety, participants have an opinion that pharmaceutical products may not be safe or effective when using APIs that are generated outside of regulatory guidelines or that are fake. Patients who depend on these items for their health and well-being may be at risk because of this. Aud_GMP2 added, *the effect of the non-compliant API on patient could be life threatening and can generate carcinogenic impurities.* Aud_GMP2 and Aud_GMP4 mentioned the nitrosamine impurities. Aud_GMP4 affirmed, *it may cause a high risk to the patients because of cross contamination. Effective therapy may be delayed for patients, which may negatively affect their quality of life and overall health*.

From the above, it is concluded that auditors face major challenges as regulatory complexity, complex supply chain and counterfeiting while auditing. Most of the participants responded with their opinions on patient safety as an implication of the non-compliant APIs.

4.9.3 Interpretation of coding outcomes for research question three

Research question 3: What actions would the professionals recommend in harmonizing and coordinate non-compliant APIs? In discussing the actions recommended by the professionals, three codes are generated which are: corrective actions, revalidation, and continuous improvement.

4.9.3.1 Corrective actions

The participants provided their recommendations basically related to corrective certain actions that an industry should take, depending on the type of non-compliance and the seriousness of the risks involved. Aud_GMP2 says, *there should be a proper requirement for investigation like different tools for the non-compliant APIs and rectify that with the help of CAPA. Also, because API is completely a chemical process, so the industries can reprocess the material till they get the expected quality of API. The reprocessing is the biggest tool.* Aud_GMP1 suggested, *all companies should adopt track wise system and any other system which let them track all the incidents and close it in a defined time, so I recommend using these systems and it let all the employees to put what was happened so tracking is performed in a standard manner than in a paper assessment.*

4.9.3.2 Revalidation

Few participants considered revalidation as a great tool for coordinating non-compliant APIs. They believe that revalidation is a thorough examination of the manufacturing procedure to make sure it adheres to the necessary quality standards. If non-compliant APIs are found, revalidation can be used to reassess the manufacturing procedure, find the underlying cause, and put corrective measures in place to keep it from happening again. Aud_GMP3 says, *revalidation should be done after the change of supplier of the same API. Depending on the type of change and the risks involved, separate revalidation procedures will apply. To make sure the product is secure for patients, it is crucial to carry out a risk analysis, a gap analysis, a revalidation strategy, implement the plan, and monitor continuing quality. This could also help in analysis of incoming material to avoid any black market.*

4.9.3.3 Continuous Improvement

Based on participants responses, continuous improvement could be connected to corrective actions as well. Participants believe that to maximize productivity, cut costs, and enhance product quality, manufacturing processes must continually be reviewed and improved. This can be accomplished by putting best practices into practice, utilizing modern technologies, and utilizing creative problem-solving techniques. Aud_GMP1 says, *before covid everything was smooth but at the end of the day today we have a different environment means that we need in Europe to think about our future. 80% of intermediates to produce antibiotics and APIs and additionally 90% of chemicals synthesized APIs are from India and China. It means that if anything happens in Europe, we will be without APIs. We have lot of finished products manufactured but without API we can't do anything. The biggest challenge is to transfer what we need. Also, we need lot of additional activities for the environment protection in the production of APIs.* Aud_GMP6 suggested on educating the staff saying, *all of us are affected by the implied regulations. You still find companies which don't pragmatically apply the standards and they cannot translate it to their own organization. It can't be proportional to the activities and the size that they have. Sometimes the professionals themselves cannot really translate these requirements into the everyday life, into production and QC. What is to invest in educating your staff and to challenge the system even if it cost time and money.*

It's concluded that the participants shows that corrective actions, revalidation, and continuous improvement can contribute to a good pharmaceutical sector.

4.9.4 Interpretation of coding outcomes of research question 4

Research question 4: To which extent regulatory authorities mitigate the quality issues for APIs? Two codes are concluded from the participants responses on this research question which are: Inconsistent enforcement and global variation.

4.9.4.1 Inconsistent enforcement

Participants believe that regulations can be inconsistently enforced when regulatory agencies in several nations or regions interpret and apply laws in different ways, or when laws are inconsistently applied within one jurisdiction. As a result, the quality of APIs made by various manufacturers or even within the same manufacturing facility, may change. Aud_GMP2 says, *the biggest challenge is that regulatory norms are same, but the interpretation of the requirements and the regulatory guidelines is different with respect to the person-to-person audit and site to site. The quality of the raw materials utilized, the production procedures, the testing procedures, and the product standards can all vary. As a result of these changes, the potency, purity, and stability of the finished product can vary, which can have a substantial impact on the safety and effectiveness of APIs.*

4.9.4.2 Global variation

Participants responses reveal that the testing requirements, specs, and approval criteria for APIs may vary depending on local laws and quality standards. It's possible that one nation has stricter regulations for impurity or contaminant testing than another, or that it has different standards for stability testing or packaging materials. Because of these variations, it may be challenging for API producers to ensure that their goods satisfy all market criteria. Aud_GMP5 says, *not every competent authority recognizing problem with APIs in the same what Europe and USA has recognized. It is the reason why you are finding non-compliant APIs in some cases. For example, Majority of APIs are manufactured in China and India, so if you see the quality of the audits conducted by the competent authorities from India, it's at a different level to how it is conducted in Europe. Manufacturers of APIs must carefully assess the legal restrictions and quality criteria for each market in which they conduct business. This could entail creating numerous sets of product standards and testing procedures, or it could entail modifying already-used procedures to satisfy the demands of various markets.*

5 Concluding Thoughts on the Contribution of this Research, its Limitations and Suggestions for Further Research

5.1 Implications of Findings for the Research Questions

The objective of this study is to assess the regulatory value of GMP audits for Active Pharmaceutical Ingredients, with the participation of several regulatory authorities. this goal was accomplished, and the following conclusions are the consequence of this dissertation:

To maximize the safety of the global supply chain, which begins with the creation of APIs intended for use in pharmaceutical products, efforts are being made to assess and focus on the need for an improved, unified regulatory framework and enforcing laws.

It has been noted from the literature that several fake APIs originate from factories in countries like China and India, where health regulators now operate under much laxer rules than in the EU. Local authorities in these countries do not even remotely supervise API shipments to the EU; instead, this is left to the diligence and morals of the acquiring company. In order to protect EU citizens against fake APIs, adequate EU-based measures for monitoring and enforcing the laws along the entire global supply chain are necessary. APIs have been manufactured and shipped in a highly worldwide environment. Given the potential risks posed by poor or even phony medications, networked government monitoring systems were required, but their growth and harmonization have been hampered by the pace of the globalization of the API industry. However, situations like the heparin crisis have highlighted the need for quick international action. An attempt at fraud during the audit has caused the auditors numerous problems. A key factor in the success of an audit is determining whether the entity being audited purposely concealed or falsified its findings. Regulatory entities asked auditors to assess the risk posed by concealed, undetected, but evident, and apparent errors that are not fully investigated. These mistakes happen in enterprises because of the limitations imposed by process planning or streamlining, as well as conditions that make mistakes more likely due to insufficient Quality assurance systems.

The review of the literature has shown how different GMP inspection laws are affecting the production and distribution of active pharmaceutical ingredients globally. Even though legislation may differ from nation to country, it is generally agreed that GMP laws are fundamental standards that Active Pharmaceutical Ingredients are expected to adhere to in any country. Competent regulatory agencies should prioritize worldwide API inspections based on risk, with geographic location playing a significant role in risk assessment. The presence of

mediators should also be one of the main requirements for accepting increased risk. GMP inspections should concentrate primarily on all participating intermediaries. Implementing the suggested risk-based strategy, which could organize all API inspections to be undertaken globally to guarantee the effective and efficient utilization of resources, requires the proper supervision and training of inspectors.

Several additions to the literature on the regulatory role of GMP audits for Active Pharmaceutical Ingredients are made by the current research work.

First, it supports the argument made in the literature that GMP audits for APIs are essential for ensuring that pharmaceutical products fulfil regulatory criteria for **Compliance** and **Efficacy** and that manufacturers **continually improving** their procedures to meet the standards.

Second, the recent study also supports the challenges like **complex supply chain, regulatory complexity** and **counterfeiting** that manufacturers and auditors' experience in ensuring the quality of APIs. This finding is very important since it will be helpful since before being included in finished pharmaceutical goods, APIs are frequently purchased from several sources and may go through several production and distribution steps in a regulatory environment which is complicated and constantly changing, and it can differ greatly between different areas and nations.

Third, this research study additionally broadens understanding of how much regulatory bodies have reduced API quality issues by providing the major reasons as barriers which are inconsistent enforcement and global variation. This finding is also equally important since it tells that manufacturers may find it challenging to assure compliance because of variances in the interpretation and application of regulatory requirements. A lack of uniformity in API manufacturing procedures and quality standards may result from this, which may affect how well-made the final goods are. Also, numerous quality and safety problems, such as those relating to ingredient stability, purity, and contamination, might be introduced by the global variety. A thorough quality management system that includes supplier qualification, risk assessment, and continuing monitoring and control is necessary to ensure the quality of APIs in the face of worldwide diversity.

5.2 Contributions and Limitations of the Research

This study has shown that different GMP inspection regulations are altering the production and distribution of active medicinal ingredients globally. The regulatory authorities have made significant progress in addressing quality issues for APIs in their endeavour to evaluate the

regulatory function of GMP audits for APIs, but there are still a few niggling issues that require attention. The interview results are given in relation to API GMP audits' regulatory role. Participants in the interviews shared their insightful thoughts and familiarity with the developments in GMP auditing in the pharmaceutical business across different countries.

One potential limitation of this research is the small proportion of the sample information, which is a qualitative research design trait. It denotes that the study's participant pool is too small to represent the population under investigation. The inability to apply the study's findings to a larger population limits the study's capacity to generalize about its findings. The number of participants that is good for qualitative research designs will not be ideal for quantitative research, and this could seriously undermine the validity of the study's conclusions. However, this study offers an exploratory input that future researchers can use to carry out quantitative research inquiries.

The lack of quantitative data to supplement the qualitative data that was gathered for analysis. A qualitative study could investigate the experiences of the auditors in this study by looking at things like consequences, difficulties, and general satisfaction. The effectiveness or safety of a drug may not be quantified in this type of study, even though it can offer insightful information into the opinions of auditors and producers. The lack of quantitative data, which via statistical methods and analysis can provide more reliable results, is one shortcoming that the current inquiry might share with most qualitative investigations.

5.3 Recommendations for Practice

It is crucial to outline the audit's objectives in detail before beginning. This will make it easier for the auditors to analyse all pertinent elements of the production process and to focus their examination. Auditors should be knowledgeable about the requirements for APIs and have expertise performing GMP audits. They should also receive instruction in the pertinent laws and rules.

To pinpoint the parts of the production process that are most crucial to quality, auditors should take a risk-based approach. By using this strategy, the audit will be more likely to concentrate on the factors that will most likely affect the API's quality.

All pertinent documents, such as batch documents, quality control documents, and SOPs, should be thoroughly examined as part of the audit.

The whole manufacturing facility, including each section where API is produced, should be thoroughly inspected by auditors. The effectiveness of the QMS in ensuring the quality and safety of the API should be examined by auditors. Examining the QMS documentation, conducting employee interviews, and watching the QMS in action are all part of this process.

Auditors should follow up if any flaws are found during the audit to make sure that corrective measures have been adopted and are working.

The government should keep collaborating with the regulatory organizations to make pharmaceutical companies responsible for their actions regarding the prompt and efficient application of GMP requirements for APIs. Any corporate entity interested in medicine manufacture and distribution along any link in the value chain should be required to abide by the expected regulatory requirements, according to the government and regulators. Manufacturers that violate the law must be punished legally, and when regulators are compromised or corrupted agents are identified, they should not be given another day of employment.

As it comes to the criteria that direct their medication production processes, manufacturers themselves need to accept GMP principles. Pharmaceutical companies may stay current while advancing patient and public health and safety by investing in technological tools, quality assurance systems, and novel medication safety procedures. Although such investments may seem overwhelming at first, they will eventually pay dividends for compliance manufacturers when consumers become devoted clients and demand for their pharmaceuticals and healthcare services rises.

5.4 Recommendations for Future Research

Auditors should receive training on how to audit and validate these new technologies as they are used more and more in the production of APIs. This entails comprehending the technology, evaluating its efficacy, and confirming that it complies with GMP specifications.

GMP regulations varies between nations and regions, which might make it challenging to guarantee audit uniformity. Global GMP regulations should be standardized to ensure uniformity in audits across various geographic areas.

To guarantee that any issues are resolved as soon as possible, auditors should improve their interactions and coordination with manufacturers. Additionally, it is important to motivate manufacturers to share their best practices so that other manufacturers can enhance their own operations.

Audits should be seen as a continual improvement process rather than a one-time occurrence. Auditors should offer comments as well as encouragement to manufacturers to assist them in identifying and resolving any concerns, while manufacturers should be encouraged to regularly examine and enhance their procedures.

Auditors should broaden the scope of their audits to cover every link in the supply chain, from the suppliers of the raw materials to the manufacturers of the final goods. This will make it easier to spot any problems that might arise and affect the API's quality.

5.5 Final Conclusion and Reflections

The work contributes significantly to the literature on GMP audits for APIs, which facilitates their adoption in the pharmaceutical sector. Results demonstrate that the regulatory function of GMP audits for Active Pharmaceutical Ingredients has enhanced the industry, but there is still potential for development and additional growth if the industry is to compete with rivals in the rest of the developed world, particularly in higher adoption of technology and strengthening of the regulatory framework governing the industry. Future research can further investigate the conclusions or findings reached in this study by either using a mixed-methods approach to circumvent any potential drawbacks of the qualitative research method or by investigating the same subject matter in a new study environment.

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Appendices

Appendix A Director Moben Pharma/GMP auditor

Interview number – 1

Platform – Zoom

Aayushi verma: Provide your job title, highlighting your experience working in the area of GMP audits.

Emilia Niekrasz: I am GM p and GDP auditor. I have my own company which called mobile Pharma and I perform audit for my customer. This is mostly market authorization holder. What means they produce the product and they are interested in audits in API facilities. This business is almost 20 years. I started as a validation specialist in HASCO, one of the polish company. Next I change my job profile many times and at the end I was head of QA in herbal. It's also a polish company. Later I was IT validation lead in Russia and now I have my own company. That means that the audit was performed by me for a long time. 17 years for sure because I was permanent employee. Additionally, I perform a lot of ordered for my individual customers. So at the end of the day 3 years ago I decided to quit from the job and to develop my own company and work with my customers.

Aayushi verma: Describe your view on how GMP audits are important for Active Pharmaceutical Ingredients.

Emilia Niekrasz: In fact they are performed to get the knowledge how they are manufactured for sure and what is the GMP level and if they pass all requirements but additionally from the regulatory point of view declaration of QP required for a change and there is an information that the API manufacturer comply all the requirements concerning GMP an additional if they are required like agriculture practices. So more or less we have to options that this is the knowledge that everything what is included in the product produce accordance to the GMP and the second thing is the regulatory point of view just to have the background to fulfill the cupid declaration and put it into the product dossier

Aayushi verma: What are the challenges in assuring the quality of APIs?

Emilia Niekrasz: There are a lot of things we are in Europe so after the war in Ukraine started before COVID. Everything was smooth. But at the end of the day today we have a different environment means that we need in Europe to think about our future 80% of intermediates to

produce antibiotics and APIs additionally, 90% of chemicals synthesized API are from India and China. It means that if anything happen in Europe will be without APIs. We have lot of finished products manufactured but without API you can't do anything more or less. The biggest challenge is to transfer that what we need. Because everything is outside of Europe and we have blockers concerning this. The one of the blockers is environmental protection. Absolutely! I follow all the requirements concerning environmental protection, but there should be additional activities allowed to API manufacture in Europe just to additional lots of activities to let them fulfil all environmental protection requirements and to produce APIs. When we are going into the deep quality then for sure in India and in China there are the problem of hygiene aspects so they understand the requirements but this is But they don't have the ruling hygienic thinking about the production so this is the issue so this is the biggest challenge to keep the substance from cross contamination and from foreign bodies for example, we have a synthesis of API and they put the substance two final products let's say to the warehouse and at the end of the day somehow and at the end of the day they are in the stock and they are not able to sell it so it's blocked they made the decision to transfer it once again to the crystallization state then it once again and then give it additional 3 years for example of shelf life. Means that we have a substance with additional shelf life and this substance is not covered with stability test so we don't know how the substance will behave in the final formulation at the end of the day finish product manufacturing is stored into the warehouse for 3 years for example But we are not aware what happens between this time period. Because Indian and Chinese company they are aware of these requirements But they can perform additional activities.

Aayushi verma: What are the implications of non-compliant APIs?
Emilia Niekrasz: Normally it looks like that it's a standard situation that you find some non-conformities during an audit so if this is minor or major then okay you can expect the CAPA plan should cover all the deep diving thinking What happened should known by the manufacturer The issue is if there are critical find it was observed during the audit then at normal situation the substance is blocked means if I perform the audit for the manufacturer so during the audit I just inform and put the information that critical and non-conformities are observed and the substance should be blocked an additionally, risk assessment should be performed and in most of the cases, the final batch should be withhold later if the risk assessment showed it.

Aayushi verma: What actions would you recommend harmonizing and coordinate non-compliant APIs?

Emilia Niekarsz: Most companies have tracked by system and any other system which led them track all the incidents and close it in a defined time. Or to use the system which are already available on the market you can buy it. I know it's an additional cost but it let everyone just to follow all the CAPA incident and close it it lets all the employees to put the feedback. Tracking is performed much better in a standard way than in a paper way. So that's what I can recommend to the IT systems.

Appendix B – GMP auditor/GMP Quality Consultant

Interview number – 2

Platform – Zoom

Aayushi verma: Provide your job title, highlighting your experience working in the area of GMP audits.

Vaibhav Dubey: I have total 15 plus years of experience in pharmaceutical industry which is closing expensing the manufacturing plant core products like tablet, injectables and ointment manufacturers along with the auditing of all the formulation as well as API sites to assess the quality and the compliance part with respect to the regulatory requirements so after completion of my masters in pharmacy I started my career different pharmaceutical companies.

Aayushi verma: Describe your view on how GMP audits are important for Active Pharmaceutical Ingredients.

Vaibhav Dubey: This is a very important part of a pharmaceutical industry as we unload the API is the core ingredient of medicines like if we are taking the paracetamol tablet the paracetamol is the key ingredient or the raw material of the tablet if active pharmaceutical ingredient is not up to the specific quality that mentioned by respective pharmacopoeia the treatment will not be up to the mark it will sometimes cause the adverse effect to the patients

the situation will go worse if you heard about a nitrosamine impurities the API was not respect to the compliance so the quality was not suitable for the patients so it is very very important.

Aayushi verma: What are the challenges in assuring the quality of APIs?
Vaibhav Dubey: As I am auditing the different sites around the globe I have 300 plus audit experience in India as well as in the Europe so the biggest challenge is that regulatory norms are same but the interpretation of the requirements and the regulatory guidelines are different with respect to person to person audit and site to site so this is the biggest challenge and the second one according to me is the value of the product if the API is less. I am talking about the commercial point of view, if the API values less than it is difficult for the site to maintain the compliance throughout the manufacturing part because to maintain the compliance throughout the manufacturing process, it is a costly process. So if manufacturing don't have the margin in the product, it is difficult to sustain it in the market. So these are the biggest challenge the first one is the interpretations of the guidelines second one is for the commercial value

Aayushi verma: What are the implications of non-compliant APIs?
Vaibhav Dubey: This is also a very important question from your side so if the non-complaint API will be released in the market or to the client like manufacturing of injections if the product is taken by any patient as I said earlier also that effect of that non-quality APIs or non-compliant APIs will be adverse sometimes it also life threatening it may also generate some kind of impurities and these impurities are very harmful to the human beings sometime these impurities are carcinogenic

Aayushi verma: What actions would you recommend harmonizing and coordinate non-compliant APIs?
Vaibhav Dubey: Oh I can give this answer in two parts. In the manufacturing part, there is a proper requirement of the investigation there should be a proper requirement for investigation like different tools or mechanism to identify the root cause why this non-compliant API is happened there should be a proper requirement for investigation like different tools or mechanism to identify the root cause why this non-compliant API is happened. With the help of that procedure the industry identifies the non-compliant part and rectify that with the help of CAPA. What is CAPA. Corrective and preventive action so they can take the corrective and

preventive action and reprocess because API is completely a chemical process so you can reprocess the material till you get the quality of APIs so in the manufacturing part The reprocessing is the biggest tool to achieve the quality you can reprocess the material until you get the quality of the APIs second part is a few identify the non-compliant API after releasing the material in the market so ask for regulatory norms. You can recall that material that we have identified these impurities in our product and we are recalling our product. And then you can destroy the material or you can reprocess it

Appendix C – GMP auditor/Compliance Executive Consultant

Interview number – 3
Platform – Zoom

Aayushi verma: Provide your job title, highlighting your experience working in the area of GMP audits.
Ibrahim Ghareeb Madian Mohammed: So I work as a QA quality assurance officer so my role is primarily in manufacturing operations envy manufacturer flu vaccines around the globe and we send them to UK Europa America all over the world already so as the manufacturing taking place I'm on the line supervising the line any issues Any deviations Any problems Any non-GMP Anything runs through me reviewing all the bad records all the data documentation and send it to the QP for released market. So it's really good for me in terms of experience.

Aayushi verma: Describe your view on how GMP audits are important for Active Pharmaceutical Ingredients.

Ibrahim Ghareeb Madian Mohammed: I think it's crucially important for APIs because API is the active ingredient you need to have the active ingredient present it's going to form any

therapeutic response support the patient in any way and I think it's very very important in terms of audit because you trace how it was made where it was made if they follow the right standards follow the regulations and basically make sure that what they are making is correct and it's in the right concentration and quantity.

Aayushi verma: What are the challenges in assuring the quality of APIs?
Ibrahim Ghareeb Madian Mohammed: I think it depends on the API if it's like the powder stuff we get if it's manufactured by a GMP facility so just pharmaceutical company. They may have a division where they manufacturer as well. The challenge if it's not a pharma industry if it's a chemical industry they don't always follow the GMP obliged to follow GMP. They have their own kind of guidelines so we always have that kind of battle with them say is it correct. So I think the main challenge is that the drug is not manufactured in the GMP facility being able to trace the full manufacturing process for example, one company give it to other company for refining and then it comes to your company and you don't know if it's purely refined and about manufacturing processes and data because that's what GMP is all about to trace documents and processes. And again, especially if it's overseas we have used a lot of manufacturers from Asia South Asia China all these places can be quite difficult sometimes in the data integrity making sure that everything is compliant or it is corrupted like like my parents are from Bangladesh and it's so corruption there. So you doubt it if it's the right stuff and then we question the purity of it. And sometimes you also find shortages as well like war in Ukraine and Russia we have to think ahead and keep things stocked. Also many African countries go for low grade raw materials. This also cause lot of problems in the formulations and manufacturing. And for example, like GXP audits are all about storage conditions of APIs. Like some APIs need some special environmental conditions. We should assure both the storage and the distribution that all the environmental conditions should be up to their mark.

Aayushi verma: What are the implications of non-compliant APIs?
Ibrahim Ghareeb Madian Mohammed: According to me, the fundamental implication is a risk to the patients it can be a risk to the patient in many ways let's start with the worst case scenario if they get something very wrong or counterfeit it could potentially kill them before all that you have all the issues like the concentrations would be wrong so if a patient takes it, for example an inhaler for breathing and the API in that is not compliant and it doesn't pass all the specific tests and they are running around with shorten breath it's not going to work. Another thing is if they use non-compliant APIs in manufacturing, it may cause many problems there as well. It

may not get validated. It will give different readings all the way back from the patients if you keep moving it may cause many problems. Also, most of the non-compliant APIs enter into the black market.

Aayushi verma: What actions would you recommend harmonizing and coordinate non-compliant APIs?
Ibrahim Ghareeb Madian Mohammed: If you get involved early in API manufactur, Trace yourself back. And also when we have any regulatory updates Tell them of the changes. Tell them to update. Sometimes API manufacturers are not aware of updated regulatory norms. And the best case scenario would be to get these manufacturers on board with us to be compliant. The main thing should be considered communication an education really. So we can see things early on and we can take action to them. And revalidation should be done after the change of supplier of same API and again for the black market issue. Analysis of incoming material to avoid any black market should be done.

Appendix D – GMP auditor/Quality Manager/Qualified Person

Interview number – 4
Platform – Skype

Aayushi verma: Provide your job title, highlighting your experience working in the area of GMP audits.
Giannis Fotopoulos: My current title is quality Manager. I'm ahead of quality management in help pharmaceutical company situated in Greece I'm also a qualified person or finished dosage forms also, in particular of GMP compliance of APIs. I'm also qualified auditor with external companies providing third party GMP audits

Aayushi verma: Describe your view on how GMP audits are important for Active Pharmaceutical Ingredients.

Giannis Fotopoulos: Firstly, these audits are very important because it's for your safety and also a regulatory requirement. In Europe it is mandatory every manufacturing facility must be audited on site, remote audit should only be performed during pandemics. Now the authorities and also and companies starting expecting on site again and expectation is after every 3 years so the first one is a mandatory requirement for APIs. And secondly it is very important because API is the main raw material finished dosage form. The GMP requirements are quite similar to finished products. And also they are very important because they are directly related to the safety of the patients and also of the quality of the finished dosage form. So it's a regulatory compliance requirement and patient safe to requirement and also because it cannot be replaced with other means of evaluation like paper assessment or other type of assessments. Third one is because it's have a direct impact on business. Quality problems or supply chain problems due to poor API manufacturer performance can lead to major disruptions.

Aayushi verma: What are the challenges in assuring the quality of APIs?

Giannis Fotopoulos: The challenges are the globalized supply chain. Because many API manufacturers have two or three intermediates that are their suppliers so production of API might not start and finish at the same site. So this is one of the important factor. APIs are distributed globally and there might be differences in local legislation GMPs or other regulatory affairs active substance master file requirements. There are of course harmonization actions between USA and Australia or other regions however, these differences also complicates the specifications etc. Another challenge is a fact. Is that API manufacturing sites our large establishments and are not very easy to impact because of the size and the nature of the processes. So one must have good knowledge of the specific processes which are required are different from the finished product processes. The fourth challenge would be the language and the local conditions barriers between different regions because different regions have different have different way of doing things in everyday practice again they can have different GMP practices. There might be differences in different regions of the world in the way the things are implemented. Go finding conformance and compliance might be challenging in that aspect.

Aayushi verma: What are the implications of non-compliant APIs?

Giannis Fotopoulos: We have seen the relevant examples in the recent years. For example, like nitrosamine impurities, we have issues which showed the global disruption. The next implication will be the shortage of stock in the market of specific medicines for patient users. It can have risk to the patient because of the cross contamination issues. And like I said, according to the second question, it can be related to the business issues. So the companies because of the not well managed risks can face challenges in market sale and on their profits etc.

Aayushi verma: What actions would you recommend harmonizing and coordinate non-compliant APIs?

Giannis Fotopoulos: I would recommend in the case of major non-compliance cases, where there are critical non-conformances and critical compliant issues, so my opinion if it get identified by a regulatory authority, then it is a possibility that they can take any measures. If it's a client inspection then then there should be standard actions to escalate the issue. What would be beneficial according to me in the coordination, the issue should be approached more of a harmonized GMP level. I think it is the best way to assure the minimum level of coordination. So for example if there is a non-conformity issue on a local site in India so they should be communicated the issue to all the local authorities. They should alarm to their site. So my recommendation is to have a better coordination between the authorities and secondly regarding the customer audits, widely accepted third party organization, reduce the audits for the sites, so many customers can receive compliant and conformant third party audits to cover all customers.

Appendix E – GMP and GDP auditor/Qualified Person

Interview number – 5
Platform – Zoom

Aayushi verma: Provide your job title, highlighting your experience working in the area of GMP audits

Naresh Renikindi: I'm an owner of an Independent consulting company. My title is you can be a principal consultant or QA consultant. Basically I'm a pharmacist and did my masters in a pharmaceutical sciences from, Greenwich University and from last few years I spent time working in QC and QA, regulatory manufacturing commercial products, and spectrum of sterile and non-sterile. So it's a day-to-day requirement for me to verify your vendors. And the most important vendor is API. So I started conducting audits in 2012, then I started my auditing career. So since then I conducted nearly 260 audits. Of which roughly 100 audits are API audits.

Aayushi verma: Describe your view on how GMP audits are important for Active Pharmaceutical Ingredients.

Naresh Renikindi: Yes, definitely it is very important. So it's definitely just two or three days when you get to see to see the processes. Because all you see is the end product, and if then you realize the problem then it will be too late by then the product might have been consumed by the patient. It is a reason that you should periodically audit the importance of APIs to verify the continued compliance of the GMP.

Aayushi verma: What are the challenges in assuring the quality of APIs?

Naresh Renikindi: So in the early days it was pretty difficult because people were not able to interpret the guidance properly. But lately in last 7 to 5 years I haven't seen that challenge much most of the industries especially in India, Europe, US and they have easily adapted the ICH Q7. Still there are little bits and pieces where methodology are different between different continents. When I see the challenge, it's down to the incorrect interpretation of guidance.

Aayushi verma: What are the implications of non-compliant APIs?

Naresh Renikindi: So if you have a issue with your API unless you found it in your raw material testing at the finished product site, the implications would be that you might end up consuming it and producing a finish product. So if the API has low potency that means it will have a loop therapeutic value. That means the patient might not get the required therapeutic relief. So if it is high potent, you might end up giving a high dose product which might produce adverse reaction. It might counter act more level of API might be having be poisoning the patient because your liver will not be able to process it. And obviously because it impacting the safety the quality of the product will be impacted because you're not producing your product in line of specification. And efficacy again you know, The implications will be the quality, safety and efficacy will be impacted.

Aayushi verma: What actions would you recommend harmonizing and coordinate non-compliant APIs?

Naresh Renikindi: So if you're asking in a regulatory point of view, this problem is not in the existence. So across the world 95% of the population accepted the ICH guideline. So it's not virtually in the existence. In order we do not recommend but the action is based on the risk. I cannot give black and white answer because it all depends on the actions you find and it depends on the quality and safety of the particular API. And also I would like to say again about the interpretation of guidance because not every competent authority recognizing problem with APIs in the same what Europe and USA has recognized. It is the reason why you are finding non-compliant APIs in some cases, for example, majority of APIs are manufactured in China and India. So, if you see the quality of the audits conducted by the competent authorities from India, it's at a different level to how it is conducted in Europe. Physically they are not forcing the challenges on the system of verifying the appropriate implementation of it. So in the regulatory point of view, it is a big problem because of which the manufacturers are easily getting the licenses and they are making the product and it's adding a regulatory challenge in the Europe and US of the world, the API audits, etc. All all these were introduced because in the first stage the competent authorities in the local countries have not understood the regulatory requirement and not interpreted well and not made sure approved by the industry. So if they would have applied properly they would have not need for GMP audits.

Appendix F – GMP auditor/Qualified Person/Quality Manager

Interview number – 6

Platform - Zoom

Aayushi verma: Provide your job title, highlighting your experience working in the area of GMP audits

Gabor Mihalyi: I am director and the owner of my own pharmaceutical consultant company. But most of the time I go with the title of qualified person or QP for finished dosage forms. I'm also QA consultant or GMP and GDP auditor. And I have performed approximately 80 audits.

Aayushi verma: Describe your view on how GMP audits are important for Active Pharmaceutical Ingredients.

Gabor Mihalyi: So first of all, it is a requirement for GMP rules and regulations. And a GMP guideline which is very important. So indirectly it's a tool that required for the companies for the marketing authorization holder and also the QP to ensure that relevant parts of the supply chain are compliant and working towards the equivalent of regulation overall worldwide. If it comes to us or Asian markets like China and India or the others. Generally speaking that audits are there to ensure the company are satisfied by the GMP compliance that is producing products for them. So that is the main reason and of course you need GMP audits for QP declaration for commercial products but overall multiple stakeholders within the legal supply chain all relevance stakeholders ensure packaging facilities are compliant to the relevant GMP regulations.

Aayushi verma: What are the challenges in assuring the quality of APIs?

Gabor Mihalyi: So I will say the challenges are the audits are always like a glimpse or a snip or a screenshot kind of thing from the manufacturer's life. And this is in very controlled and in very driven environment and very much controlled by the auditee itself. And you only have a day or two days to evaluate whether you think if there any non-conformities which might be dangerous to the other facilities. So the challenge is that you have only certain amount of information of the manufacturing process and you don't have the full visibility all the time so

either you're lucky and good that you can see which is there and might affect the quality of the product. And obviously you are really lucky if the company is fully compliant and there are no issues. And if you're not lucky, you may never find the issues that exist there and in some time maybe you can get warning letters or something in non-conformance. Difficulty is that it's limited and it's driven by someone else.

Aayushi verma: What are the implications of non-compliant APIs?

Gabor Mihalyi: It could be very severe and it could be very minor you need to correct within your dossier or within your process. It could also ultimately result into the patient death. It could also lead to severe or Edwards events or huge quality issues within the industry and manufacturing processes. It is difficult to say because it mostly depends on the type of deficiency you found. And we have seen many examples in the history as well. That's why GMP came into action of course. But at the same time it can also be some minor issue be fixed at the same time. So if it's a systematic issue they can fix it right away. But if the humans are involved sooner or later it will go into happen. If you find anything related to cleaning validation so it can be severe. Those for example, if highly sensitizing product is compromised then it will lead to many severe issues.

Aayushi verma: What actions would you recommend harmonizing and coordinate non-compliant APIs?

Gabor Mihalyi: I think it's mostly related to challenge your own system at most of the companies say that they do. Like all of us are affected by the implied regulations. You still find companies who don't pragmatically apply these standards and they cannot translate it to their own organization. It can't be proportional to the activities and the size that they have. Sometimes even the professional themselves cannot really translate these requirements and regulations into the everyday life and processes into production and into quality control. What is to invest in educating your staff and your team and they're into challenge the system even if it cost time and money to you.