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A REVIEW ON ADVACEMENT IN QUALITY ASSURANCE PRACTICES IN PHARMACEUTICAL MANUFACTURING

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ABSTRACT

The Pharmaceutical industry continually evolves, with QA playing a pivotal role in ensuring the safety, efficacy and compliance of drug product. This review article explores the latest advancement in quality assurance practices within pharmaceutical manufacturing focusing on regulatory compliance, process optimization and emerging technologies. This abstract delves into the evolving realm of quality assurance practices, spotlighting the latest advancement that are reshaping the industry. As pharmaceutical manufacturer navigates increasingly stringent regulations, heightened consumer expectation and the constant drive for innovation, this abstract also elucidates how cutting-edge technologies, data analytics, and regulatory strategies propelling quality assurance to new heights. From the implementation of real-time monitoring system to utilization of artificial intelligence in quality control processes, it is also exploring the innovative tools and methodologies that are redefining quality assurance protocols. It discusses the role of industry 4.0 concepts, such as the internet of things (IoT) and blockchain in ensuring transparency, traceability and overall product integrity throughout the pharmaceutical supply chain. This abstract also examine the critical intersection between quality assurance and regulatory compliance. It sheds light on how global regulatory bodies are adapting to the rapidly changing landscape, emphasizing collaborative approaches that foster continuous improvement in pharmaceutical manufacturing. Moreover, it highlights the

significance of risk- based approaches in quality assurance, enabling manufacturer to allocate resources effectively while maintaining product quality and safety.

KEYWORDS: Quality Assurance, QbD, 4.0 Concept, Pharmaceutical Manufacturing, PAT.

1. INTRODUCTION

Quality may be abroad concept for every article or item which is use, it also be a house hold-product, household appliance and any aid yield, machinery bought from the market, vehicle for personal uses or industrial use, food and food commodities or medicine for human and animal consumption.

Nobody needs to compromise in any product quality, QA is the method or trick of method for the integrity of the product to comply the quality.[1]

The evolving awareness is the improvement in the pharmaceutical product quality and services. Together ‘quality assurance’ and ‘quality control’ created in manufacturing. In fact, both of the thoughts remained in use as early as the Mid Ages. Back then, skills Guilds were accountable for safeguarding the quality of facilities and goods. The Associations set the product quality standards a cobbler or blacksmith would follow in order to be a Guild member. Subsequently Guild association group business to their doors, craftsman was satisfied to promote that they met Guild standards.

Fast onward to WW1 and the Industrial Revolt. We can touch the idea development to this time as mechanization replaced handmade goods. As an alternative of the cobbler or blacksmith reviewing their own makings, constructers needed the capability to verify large numbers of appliance crafted goods, on this way to develop the criteria these goods would be adjudicated by. Silent, production is a linear process. A widget manufacturer will do QA pre-and-during construction, then do QC after creation.

In the trade perfect, QA deals with manufacturing procedures by placing out the “plan-of-attack”. The plan-of-attack strength comprise creation design and specification, manufacturing procedures, and all the added details that go into making a widget for customer use. QC, on the additional hand, would be accountable for inspecting the product to verify it meet specification. Fundamentally, in the direct manufacturing atmosphere, QA quantified the procedures used to plan and manufacture a product, and QC stated how goods would be checked to confirm quantified standards were met.

Some aspect of quality assurance are standardized in the ISO 9000, addition to these standards manufacturer are attract to further develop and employ their own internal practice for standardization, they reduce variability using (SOPs), keep equipment's in good condition by effective maintenance strategy, by using of 5S or 6S and document using up-to-date formulas for production.[3]

SOFTWARE QC

The software development life cycle (SDLC) is reiterative; investigation, design, and application are is not constantly linear. It is not rare to see an app go through QC for lapse or examining testing then be directed back to growth for code solutions. This reiterative shape course is one of the explanations considerate the true nature of Software Quality Assurance (SQA) is vital to product achievement.

Software quality assurance is the big-picture canopy managerial your build to an end creation that encounters together commercial and user requirements. In the software world, QA includes the whole growth process, including: necessities explanation, software design, coding, source code regulator, code evaluations, configuration organization, testing, release organization, and product addition. SQA regulates the goals, promises, capabilities, actions, capacities, and confirmations of the software development process.

To remove misperception, and the possible for expensive miscommunication, it helps to reason of QA, QC, and testing as a hierarchy of procedures. QA founds the methods by which product are made and quality is assessed. QC confirms QA is applied correctly, and testing is a portion of the QC procedure.[2]

QUALITY ASSURANCE

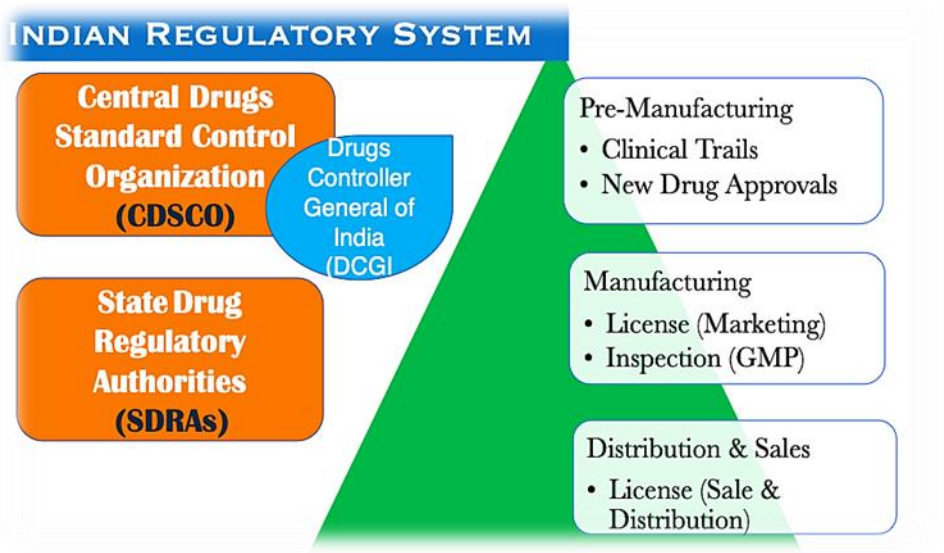
Quality assurance is a anticipatory and proactive procedure. It highlights planning, documenting, and finalizing the rules essential to promise the software's excellence. This process starts at the launch of the SDLC to recognize the product's necessities and prospects from both the corporate and user viewpoints. Once necessities and hopes are recognized, a test plan is established to meet recognized standards. Quality assurance is about making sure the correct steps are taken at the correct time through the SDLC.

Benefits of Quality Assurance

1. High efficacy
2. Cost Efficient
3. Improvement in Customer satisfaction

2. REGULATORY COMPLIANCE

Pharmaceutical compliance means that pharmaceutical companies always cleave to all applicable nonsupervisory condition. Pharma industries must production according to Good Manufacturing Practices (GMPs), Good Distribution Practices (GDPs), and other applicable regulations.



INDIAN REGULATION AND GUIDELINES

CDSCO

Ministry of Health and family Welfare, Government of India provides general information about medicine nonsupervisory condition in India.

NPPA

The Drug price control order 1995 and other orders executed by National Pharmaceutical Pricing Authority (NPPA), government of India.

D&C Act, 1940

The Drug and Cosmetics Act, 1940 regulates the import, manufacture, distribution and trade of drugs in India.

Schedule M

Schedule M of the Drug and Cosmetics Act specifies the general and specific conditions for industry demesne and resources, factory and equipment and least optional areas for introductory installation for some group of medicines.

Schedule T

Schedule T of the D&C Act prescribes the GMP specifications for manufacturing of Ayurvedic, Siddha and Unani drugs.

Schedule Y

The clinical trials statutory requirements are guided by specifications of schedule Y of the D&C Act.

GCP Guidelines

The ministry of Health along with **Drug Controller General of India (DGCI**) and **Indian Council for Medical Research (ICMR)** has originate out with draft recommendation for research in humanoid subjects. These GCP guideline are basically grounded on protestation of Helsinki, WHO guideline and ICH necessities for good clinical practice.

The Pharmacy Act, 1948

This Act is meant to regulate the profession of pharma in India.

The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954

The Drugs and Magic Remedies Act,1954 delivers to control the announcement regarding medicines; it prohibits the advertising of remedies contented to possess magic talents.

The NDPS Act, 1985 is concerned with control and regulation of operations relating to Narcotic Drugs and Psychotropic Substances.

WHO

WHO guideline on drug policy, Intellectual property Rights, funding and supply organization, quality and safety, selection and rational use of drugs, specialized co-operation and traditional drugs.

ICH

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceutical for Human use (ICH**)** standard defining excellence, efficacy, safety and

related features for growth and registering new therapeutic goods in Europe, Japan and the United States.

OECD

Organization for Economic Collaboration and Development including 30 fellow countries covers financial and communal issues in zones of health care.

EMEA

European Medical Agency (EMEA) a decentralized body of the European union headquarter in London, recommends recommendation for examination and general reporting and all aspects of mortal and veterinary drugs.

US FDA

The Regulation, Rules, announcements, news and communication from US Food and Drug Administration.

TGA

Specification regulating drugs, medical equipment, blood, muscle and chemicals, issued by Therapeutic Good Administration, the Australian supervisory body.

3. QUALITY by DESIGN (QbD)

QbD (Quality by Design) is an imprint initially developed by Pioneer Dr. Joseph M. Juran[4], Dr. Juran appreciate that quality should be designed into a product and utmost quality eventuality and complications related to the way in which a product designed in the first place.

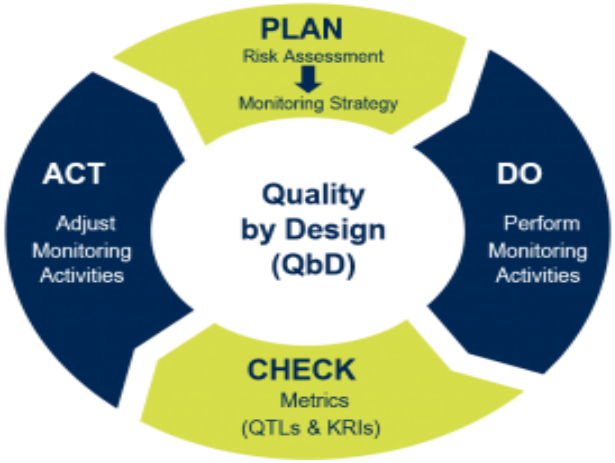
Woodcock defines excellent quality drug product free from any adulteration and faithfully delivering the health benefits confident in the label to the consumers.[5]

AIM OF QUALITY BY DESIGN

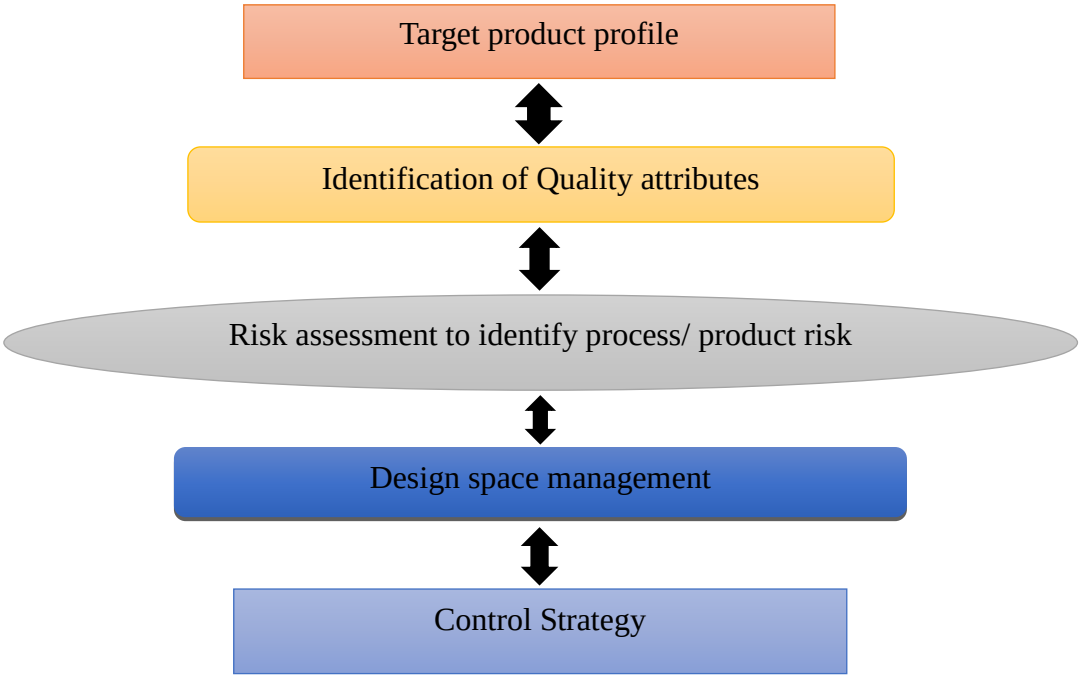
QbD is a systematized approach to development that starts with predefined objectives and concentrated product and procedure considerations and control grounded on quality hazard management.

The goals of QbD include

a. To achieve expressive product quality specifications.
b. Growth process competence and low product changeability.
c. Increase product development and manufacturing efficacies.
d. Improved root cause study.



Elements of QBD



Life Cycle Management

ROLE OF QbD FOR ENSURING PRODUCT QUALITY

- Better thoughtful of the procedure.
- Fewer batch failure.
- More efficient and actual control of change.
- Reoccurrence on investment / cost savings.

Case Studies

The authors' aim with this document is to deliver, in the form of a case study, a brief summary of the steps involved in the application of the QbD procedure in the development of a medicinal product.

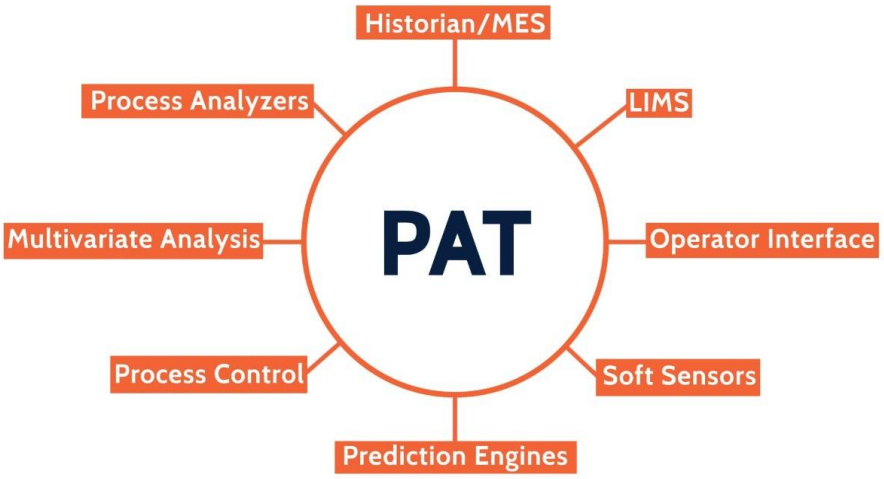
Methodology features related with design of trials, multivariate analysis, modelling, and quality risk management are given, as obligatory for the drive of this work, along the "5" section, though going through the case study.[7]

4. PROCESS ANALYTICAL TECHNOLOGY (PAT)

Process analytical technology is a system for scheming, analysing and monitoring manufacturing processes through timely dimension during processing. With the goal of confirming final product quality, it analyses raw and in-process resources. The PAT is now being installed in the pharmaceutical industry, where it is seen as skill that can help companies to progress their conformity with manufacturing guidelines. The emphasis in PAT is in the manufacturing process to growth the basic principle of the present drug quality system since quality can't be tested into products, it should be erected in or should be by design.

PAT particularly emphases on enhancing the considerate and control of the manufacturing process to achieve Quality-by-Design (QbD), quality should be built into a product with an understanding of the product itself and the process by which it is advanced and manufactured along with a information of the dangers involved in the industrial process and how best to mitigate those risks.

Quality-by-Design starts with the identification of Critical Quality Attributes (CQAs) that ensure a high performing pharmaceutical product. Next, Process Analytical Technology tools are link and enforced to control Critical Process Parameters (CPPs) and Key Performance Indicators (KPIs) to expand process quality and yield. These tools, in mixture with a formal design of trials methodology, are crucial in determining an ideal design space for product development and optimization.



Benefits of implementing PAT

- Reduce product cost
- Improved quality
- Provides product uniformity
- Reduce product change over time
- Meets all kinds of regulatory requirements
- Increase robotization to better operator’s safety and reduce mortal errors
- Prevents rejects and re-processing

PAT real time monitoring and control enhance product quality

Successful implementation of PAT technology meaningfully enhanced procedure considerate the growth periods and can be used as a tool for actual time assurance in the manufacturing process.

It signalled and abnormal batch and can be possibly used for real time interference for RTA. Online mass spectrometry successful monitored a biphasic vacuum distillation process and

ensured the removal of water in real time to ensure the final product quality. PAT is proficient of RTM and RTA in the chemical development stages as well as the manufacturing stage.[12]

5. Risk based approaches

A risk-based approach to QMS procedures is an method that prioritizes the managing of potential risks allied with medical devices throughout the product life cycle. It involves recognizing, evaluating, and managing risks associated with the design, development, production, supply, and post-market surveillance of medical devices.[13]

FMEA

Failure Modes and Effects Analysis (FMEA) is a systematic, proactive method for evaluating a process to identify where and how it might fail and to assess the relative impact of different failures, in order to identify the parts of the process that are most in need of change.

FMEA reviews of the following

- Failure modes
- Failure causes
- Failure effects

Teams use FMEA to evaluate processes for possible failures and to prevent them by correcting the processes proactively rather than reacting to adverse events after failures have occurred. This emphasis on prevention may reduce risk of harm to both patients and staff. FMEA is particularly useful in evaluating a new process prior to implementation and in assessing the impact of a proposed change to an existing process.

6. Data Integrity and Digitalization

Data integrity testing is the process of validating the accuracy, consistency, and reliability of data in a database or information system. It ensures that the data is not lost, altered, or corrupted during storage, processing, or transmission.

Data integrity testing verifies the completeness of data, confirms that the data is consistent with business rules and requirements, and identifies any anomalies or errors.

Impact of Digitalization

Historically, batches have been recorded on paper, generating endless pages that must be manually filled out and stored. This puts a large burden on the factory staff, who are plagued with multiple hours of paperwork each week.

As the era of digitalisation arrived, many companies evolved their batch records into the 'paper on glass' concept by duplicating the current paper records into an electronic environment. The benefit is the creation of digital records, which are much easier to review and access for audits.

This didn't solve the root of the problem though, as production data was still being taken down on paper first. Any error in that record, caused by a simple mistake or some sloppy handwriting, and the inaccuracy will find its way into the digital version too, compromising the integrity of the data. Fortunately, today there exists a true solution.

Across the manufacturing industries, software-based digital alternatives to the labour-intensive manual ones are constantly being developed. As companies implement them one by one, their digital transformations commence. For the pharmaceutical industry, the adoption of electronic batch records (EBR), where data is extracted from process equipment and automatically entered in a computerised document, is a vital step in this digitalisation.

7. Advancement in analytical technique used for quality control

Although old-style analytical tools such as HPLC or NMR spectroscopy typically require dimension times in the order of several minutes per sample, suitable high quantity analytical (HTA) techniques that are capable of generating datasets in timeframes of less than a minute or seconds are important for HTE systems. In many industries, THE has been followed in many areas such s the discovery of biomarkers and new drug discovery and small molecule process development, in biotherapeutic analysis, forced degradation studies of peptides and analytical method qualification.[14]

Now highly automated platforms are available

- Thin Layer Chromatography
- Liquid Chromatography
- Supercritical Liquid Chromatography
- Multiple Injections in a Single Experimental Run

- ❖ On-Chip Chromatography
- ❖ Gas Chromatography
- ❖ Mass Spectrometry
- ❖ Microfluidics

8. Good manufacturing practices (GMP)

Good manufacturing practice (GMP) is a system for certifying that products are reliably formed and meticulous according to quality standards. It is intended to diminish the risks involved in any pharmaceutical production that cannot be removed through testing the final product.

Latest updates in GMP guideline

FDA issued a new draft guidance document on the potential use of alternative tools in preparation for, or in lieu of, inspection in pending applications: "Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications".

In the beginning of September, the stimuli document "Proposed Definitions of Excipient Components- Revisions to 2018 Definitions- PF 49(5)" was published for comment on the website of the Pharmacopeial Forum of the USP. Comments on this draft can be submitted until 30 November 2023.

The pharmaceutical industry is witnessing a massive revamp. Traditionally slow in the adoption of technology, the industry is now undergoing rapid changes due to the development of several technologies. The top trends in the pharmaceutical industry include artificial intelligence (AI), additive manufacturing, blockchain, and other Industry 4.0 technologies.

The EU GMP Annex 1 “Manufacture of Sterile Medicinal Products” was revised in 2022 with the aim of eliminating ambiguities and inconsistencies and taking into account technological advances. The revised version is now better structured, with **11 clear sections**:

- Scope
- Principle
- Pharmaceutical Quality System
- Premises
- Equipment
- Utilities

- Personnel
- Production and specific technologies
- Environmental and process monitoring
- Quality control
- Glossary

Importance of GMP Compliance Audits

- GMP audits help ensure products are made and controlled in accordance with appropriate quality standards.
- Current industry best practises, and that they comply with applicable health authority regulatory requirements and guidance documents.

9. Future trends and Challenges

The Evolution of Compliance management in the pharma industry has undergone significant changes over the years. Traditionally, compliance processes relied heavily on manual documentation, spreadsheets, and reactive approaches to address compliance issues.

The future of pharma quality assurance lies in the integration of technology to streamline compliance processes. Automation tools, such as electronic document management systems, facilitate efficient documentation and version control, reducing the risk of human errors and enhancing compliance.

Additionally, the adoption of cloud-based solutions enables real-time collaboration, secure data storage, and accessibility from anywhere, providing seamless workflows and enhancing data integrity.

Effect of industry 4.0 and artificial intelligence

This world simultaneously also desires the technology to have access to higher productivity, upgraded efficiency and enhanced competition among various industries involving products associated with artificial intelligence and industry 4.0.[15]

Implementation of artificial intelligence has widely spread in all domain ranging from engineering to management as these devices furnish efficient outputs with minimum number of inputs.

The current trends depict a considerable rise among interaction between artificial intelligence and human beings.

Industry 4.0 or the fourth industrial revolution (4IR) is gaining a lot of attention particularly on its potential impact on humanity[16], Schwab[16] argued that 4IR will change how human beings live, work and how the economies work as well as how we are governed.

It is also believed that the industrial revolutions began as far as the 17th century with Britain being the major player with what came to be known as the first industrial revolution.[17]

Major challenges in industry 4.0

The growing demand for automation of information and data interchange in industrial technology is known as Industry 4.0 (industry 4.0 technologies,). Cyber-physical systems, the Internet of Things (IoT), and cloud computing are all part of the concept. It is rapidly approaching, and IT businesses must adapt to compete in tomorrow's world and beyond.

Some of the most common challenges found in Industry 4.0(digital factory industry 4.0):

- Data
- Security
- Network misconfigurations
- Testability
- Operations
- Device management

How to overcome

1. Ditch Legacy Software

Legacy software poses one of the biggest challenges to Industry 4.0 projects. Too many businesses rely on outdated applications that can’t keep up with growing demands. Furthermore, these legacy platforms are unable to integrate with new software systems or support cutting-edge technology.

2. Develop a Roadmap

A successful journey to become an Industry 4.0 enterprise starts with a roadmap that lays out this strategy, and every roadmap looks a little different.

3. Work with experts

Frankly, many businesses don't think they have the time to worry about new technology. Other goals are higher on their priorities. Plus, small manufacturers and distributors often lack the internal expertise to execute these projects.

4. Wrap Up

The end goal of digital transformation is not to plant robots across your factory or incorporate AI tools into your customer service protocols.

10. CONCLUSION

It concluded that, this review highlights the significant advancements in quality assurance practices within the pharmaceutical manufacturing industry. These advancements have not only improved the overall quality and safety of pharmaceutical products but have also enhanced regulatory compliance. The integration of technologies such as data analytics, automation, and continuous monitoring has played a pivotal role in achieving these improvements. However, it is essential for pharmaceutical companies to remain vigilant, adapt to evolving regulations, and continue investing in innovative quality assurance methods to ensure the consistent delivery of safe and effective medicines to patients."

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