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Assessment of Regulatory Strategies for Orphan Drug Development and Approval Process in USA & EU

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ABSTRACT

Orphan medicines are pharmaceutical drugs or vaccines supposed to deal with, preventing or diagnose of a rare disease (viz., myoclonus ailment, Huntington's disease, Tourette syndrome, etc.). The meaning of rare sicknesses varies throughout some jurisdictions, however, generally contemplates the ailment of occurrence, severity, and life of alternate healing options. An uncommon ailment isn't worldwide and depends on the rules and guidelines officially adopted and approved via each region or U.S.A. The Orphan Drug Act, 1983 (ODA) has been recognized and adopted in numerous nations, international (United States of America (USA) and European Union (EU).) in the preceding 35 years, and has effectively advanced R and D ventures to widen new pharmaceuticals for the remedy of rare sickness. The rate of occurrences of such diseases were outpaced at an extra pace than the speed with which medicines are researched and developed to treat rare diseases. One of the main reasons is that the pharmaceutical industry is not interested in researching the enhancement of orphan medicines since they no longer have a significant large market. Despite the multiple incentives provided by the orphan drug act, this is the current reality. However, in this article, we've tried to concentrate on the current regulatory framework, current concepts of rare disease, regulatory challenges for rare disease drug development, and orphan drug approval in the United States & the European Union.

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INTRODUCTION

The definition of orphan and rare sickness is exceptional in one-of-a-kind nations based on the number of people that are affected by rare sickness (a typical picture is shown in Figure 1). In United States of America, The National Institutes of Health (NIH) says, 30 million Americans have one of the almost 7,000 sickness that are formally taken into consideration "rare" due to the fact every of these have an effect on much less than 200,000 human beings within the United States and affect more than the 200,000 humans, however in which healing of fee of improvement and market is very hard (Singh *et al.*, 2011). The orphan drug designation relying upon the ratio of the range of sufferers tormented by rare disorder that's 7.5 according to 10,000 individuals within the USA, five per 10,000 people within the EU, 4 according to 10,000 individuals. In the European Union at that time 5000 to 8000 special rare

diseases affecting 6% to eight% populace of it (European Medicine Agency, 2020). Most rare diseases are genetic; because symptoms do now not appear in advance, they exist at some stage in the individual's entire existence. The United States was the first country delivered an orphan drug act in 1983, after that range of different nations has observed the program, In Europe Union acts have been made plenty later than the us because its miles organization of 28 international locations and its talents concerning the fitness may be very an awful lot dispersed (Hall and Carlson, 2014). The incentives given by way of governments to the builders and producers of orphan pills have brought about growth of research on this subject.

Figure 1: Rare Disease

Objectives of the present work are as follows

1. To study the current principles of rare diseases & orphan drugs.

2. To study the assessment, challenges and regulatory framework of orphan drugs.

3. To study an all-encompassing strategy for the orphan drug development and approval process.

4. To carry out the study of globalization in orphan drug development strategies in the regulatory markets, USA (Food & Drug Administration (FDA)) and EU (European Medicine Agency (EMA)).

Orphan Drug Definition – According to USA - FDA Regulation

The orphan drug is a medication intended to treat a disease in the United States that affects less than 200,000 individuals. Examples of rare disease: Acromegaly, acute myeloid leukaemia (AML), Ovarian cancer, smallpox, Cushing's disease, Dravet syndrome, Fallopian tube carcinoma, ovarian cancer, cystic fibrosis (CF) (Evaluate, 2020).

Orphan Drug Designation in USA

The "Orphan Drug Designation Program" designates the status to drugs and biologic identified as those intended to diagnose, prophylaxis or prevent rare disease safely and effectively. A rare disease is a disorder affecting a small proportion of the population (Jyothi *et al.*, 2012).

So, called "Orphan drugs" are designed to treat diseases, so rare that marketers are hesitant to produce them under the normal conditions of advertising. Most rare diseases are hereditary and are therefore present throughout the whole life of the person, even if symptoms do not occur immediately. Rare disease examples: cystic fibrosis, Hamburger disease, Work syndrome, Gigantism.

Definition of orphan drugs – In the European Union (EU)

A disease is designated as rare when it affects less than 5 out of 10,000 people across the EU. In the European Union, 30 million people are in anguish because of a rare disease. Examples of rare disease: Ovarian cancer, Huntington's disease, Systemic sclerosis, Wilson's disease, Myasthenia gravies, Cystic fibrosis, Glioma. The European Medicine Agency (EMA) plays a central role in promoting the production and approval of rare disease drugs, known in the medical world as "orphan medicines," such as rare disease Mucoviscisis, haemophilia, Phenylketonuria, Marfan syndrome (Schieppati *et al.*, 2008). Most rare diseases are caused by genetic mutations, either inherited (even if the disorder has a late onset in the life of the patient), or caused by a new mutation (denova). A variety of opportunities in the EU will support the sponsors of approved orphan medicines (Marlene E. Haffner, 2006).

Regulation (EC) No 141/2000 (Orphan Regulation)

The European Parliament implemented Regulation (EC) No 141/2000 (Orphan Regulation) on 16 December 1999. This was written on 22 January 2000 in the Official Journal.

The Regulations

1. Lays down the EU procedure for designation of orphan drugs

2. Defines opportunities for the advancement in the development and marketing of orphan medicinal Products.

3. Establishes an Orphan Medicinal Goods Committee (COMP)

Current Regulatory principles of rare disease In United States of America (USA) – Food and Drug Administration (FDA)

1. The general principles that improve the utility of natural history research in the production of drugs for rare diseases include:

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2. Conduct a long-term experiment to identify clinically meaningful results and variance during the disease.

3. Select data elements based on disease characteristics, including patient-most important signs and symptoms (i.e., disease factors which can be maximum probably to be life-limiting or life-altering), potential prognostic physiognomies, and disease characteristics that can help articulate a complex clinical endpoint.

Collect data from the results of the clinical evaluation, laboratory tests, imaging, patient quality and feeling studies, 12 and other related sources. Data collection frequency is partly influenced by knowledge of disease characteristics, such as the

1. Level of a patient's condition worsening and the occurrence or absence of disease exacerbations.

2. Provide patients from a wide variety of disease incidence and phenotypes instead of concentrating on a subtype. Wide inclusion criteria may allow disease phenotypes to be recognized and better characterized for which design of therapy might be more feasible or necessary.

3. Using systematic methods of processing and scientific jargon to increase the value and usefulness of information from the study of natural history.

Current Regulatory principles of rare disease In European Union (EU) – European Medicine Agency (EMA)

Principle 1

Orphan Medicinal Products (OMP) assessment should take into account all applicable product value elements in an effective multi-dimensional context:

1. Decision-makers should consider the value of OMP from a client, health and wider societal perspective

2. While the collection of quality elements used to test OMPs should be country-specific, ORPH-VAL has suggested a set of core elements common to all health systems.

3. HTA agencies and payers should state clearly the value elements they consider, how the unusual nature of a disease affects their evaluation and how public expectations are integrated into their decisions.

Principle 2

Pricing and reimbursement decisions should be based on the OMP quality evaluation and adjusted to reflect certain factors beyond the value of the product.

Principle 3

Those who take P&R decisions on OMPs at national level will take into account all official regulatory and health technology assessments of OMPs carried out at European level.

Principle 4

The assessment and analysis of OMPs to guide national P&R decisions should include experience in rare diseases, including the views of both healthcare professionals (HCP) and patients.

Principle 5

All qualifying patients under the approved OMP mark should be taken into account in the national P&R decision, while different access decisions that apply to different sub-populations.

Regulatory Challenges for Rare Disease Drug Development in USA

1. Small populations also restrict the development and replication of research and the use of common inferential statistics.

2. Phenotypic variation within a disease, including genetic subsets, adds complexity.

3. Trial eligibility: It is particularly important for rare diseases that inclusion and exclusion requirements do not arbitrarily restrict patient eligibility not only for patient accrual, but for an adequate representation of security in the expected population of care. Sponsors will, however, allow enrichment approaches to minimize heterogeneity (Wästfelt et al., 2006).

4. Diseases tend to be progressive, serious, life-limiting and life-threatening.

5. There are often no well-defined and validated endpoints, outcome measures/tools and biomarkers.

6. Lack of precedent to produce drugs.

7. Ethical considerations in clinical trials for children.

8. Difficulty in medical care.

9. The disease's natural history has not been well understood.

10. Identify suitable biomarkers & endpoints.

11. Several, different regulatory standards world-wide.

Regulatory Challenges for Rare Disease Drug Development in EU

Challenge 1: Designation of orphan disease and control policy.

Challenge 2: Optimal production of pre-clinical and early drugs.

Challenge 3: Selection of appropriate care outcomes.

Challenge 4: Designing and reviewing criteria for clinical trials and collecting evidence from payers.

Regulatory Frame Work of Orphan Drugs in USA

Title 21: Food and Drugs

Part 316: Orphan drugs (cited in below Figure 2).

Technical overview of the proposed regulatory framework for orphan drugs in USA

1. Designation

2. Approval of New Drug Application (NDA)/Biological Licensing (BLA)

Orphan Drug Designation

In general, the Office of Orphan Products Creation may "designate" a drug / biologic for preventing, treating or diagnosing a disease/condition occurring in < 200,000 people in the U.S.

OrphanNDA/Orphan BLA Approval

OrphanNDA/Orphan BLA Marketing Approval of a new drug submitted pursuant to section 505 (b) of the Federal Food, Product and Cosmetic Act OR Marketing Approval of a license for biologic submitted pursuant to section 351 of the Public.

Orphan Drug Designation Request Form

In 21 CFR 316.20, the nature and structure of an orphan drug classification application are defined. This form (FDA 4035) is intended to assist sponsors in the full and succinct delivery of the required material.

Form 4035 Request for Orphan Drug Designation Form The content and format of an orphan-drug appointment application

1. Notice that the sponsor demands a rare disease or illness orphan drug status

2. Identify the source and the drug

3. Describe the genetic disease or condition, the suggested drug use, and the reasons for the need for such treatment.

4. Provide a detailed description of the drug and its use

5. If SAME Medication would be unacceptable as an already approved drug for the same genetic disease or condition, with or without the exclusivity of an orphan, clarify why it is medically superior.

6. Explain why some property of the drug or biologic will restrict the use of the product to the subset if the application is for an orphan subset of a common disease.

7. Description of regulatory status and experience of advertising.

8. Documentation: Prevalence < 200 K or No reasonable expectation that sales can recover the costs of research and drug development for indication.

Office of Orphan Products Development (OOPD)

The mission of the FDA Office for the Development of Orphan Products (OOPD) is to promote the evaluation and development of products (drugs, biologics, devices or medicinal foods) that show promise for the diagnosis and/or treatment of rare diseases or disorders. OOPD reviews sponsors' submissions of scientific and clinical data to identify and classify drugs that are promising for rare diseases and to further promote the scientific development of such promising medical products the office also works with the medical and research community, professional organizations, academia, government agencies, industry, and rare disease patient groups on rare disease issues. Orphan drug designation process and OOPD review division interaction is shown in below Figure 3 and Figure 4 respectively.

Drug Development and FDA Marketing Approval Process Steps is shown in below Figure 5. The review process of Orphan drug is shown in below Figure 6.

Regulatory Frame Work of Orphan Drugs in European Union

Legal framework: Orphan status in the European Union (EU)

This covers the key developments in EU legislation implemented since the first implementation of the Orphan Regulation in 1999. No 141/2000 of Regulation (EC) (Orphan Regulation).

Contents
Subpart A —General Provisions

316.1 – Scope of the medication in the orphan
316.2 – The orphan drug's intent
316.3 – Definitions
316.4 – Address for submission
Subpart B—Professional Recommendations for Orphan Drug Testing

316.10 Content and format of a written advice submission.
316.12 Providing advice in writing.
316.14 Refusal to make recommendations in writing.
Subpart C—Designation of an Orphan Drug

316.20 Material and structure of an orphan-drug classification submission.
316.21 Verification of the status of an orphan drug.
316.22 Global supporter permanent resident member.
316.23 Timing of requests for the classification of orphan drugs; designation of drugs already licensed.
316.24 Letters of failure and classification of orphaned drugs
316.25 Refusal of the classification for orphan drugs
316.26 Amendment to the classification of orphaned drugs
316.27 Shift of control of the class of orphan drugs
316.28 Publication of designations for orphan drugs
316.29 Revocation of the status of orphan drugs
316.30 Annual reports of the owner of the class for orphan drugs
Subpart D—Orphan-drug Exclusive Approval

316.31 Exclusive orphan-drug approval range
316.34 Exclusive approval from the FDA
316.36 Insufficient orphan drugs
Subpart E—Open Protocols for Investigations

316.40 Use of a drug known as an orphan
Subpart F—Availability of Information

316.50 Guidance reports
316.52 Transparency of requests and demands for public disclosure of data and information

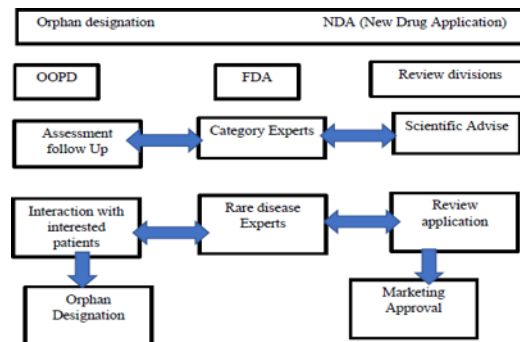**Figure 2: Regulatory Frame Work of Orphan Drugs in USA**

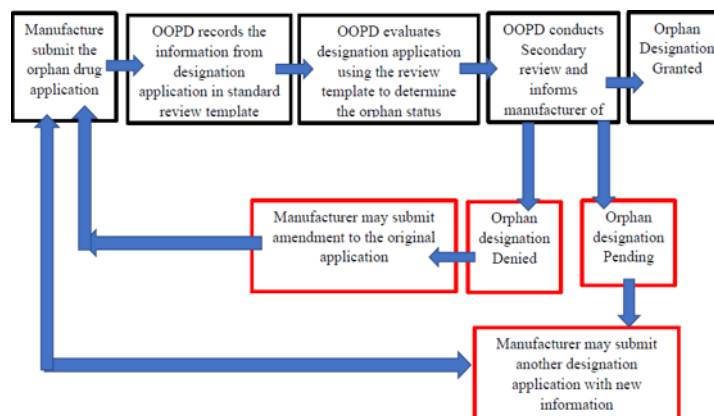

Figure 3: Orphan Designation Process

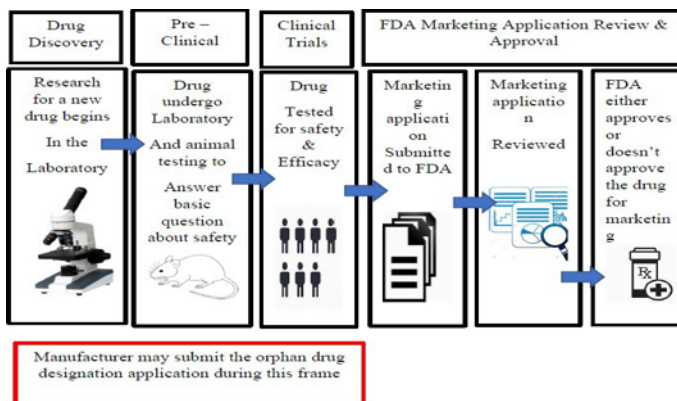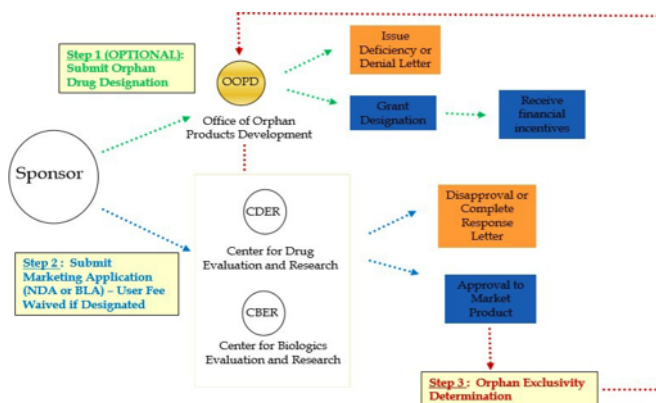**Figure 4: OOPD Review Division Interaction**

Figure 5: Orphan Drug Life Cycle in USA
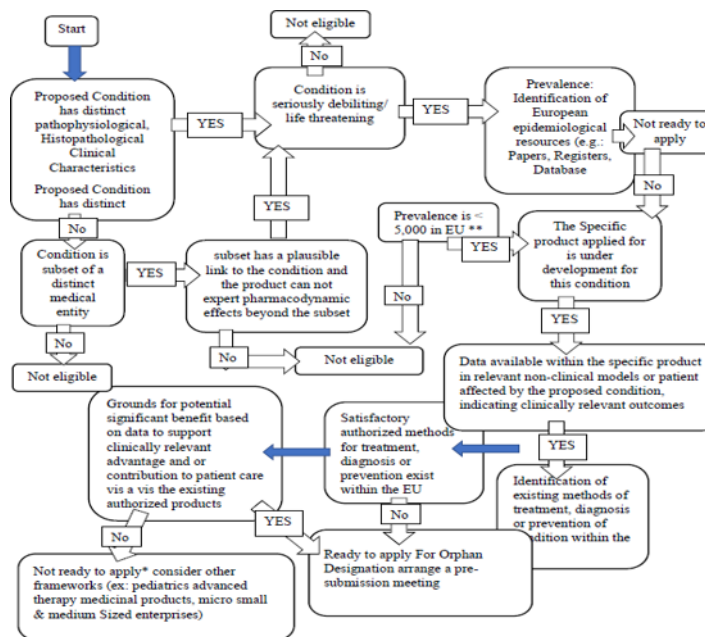

Figure 6: Orphan Drug Review Process in USA

Figure 7: Flowchart for the method of designating an orphan to potential sponsors

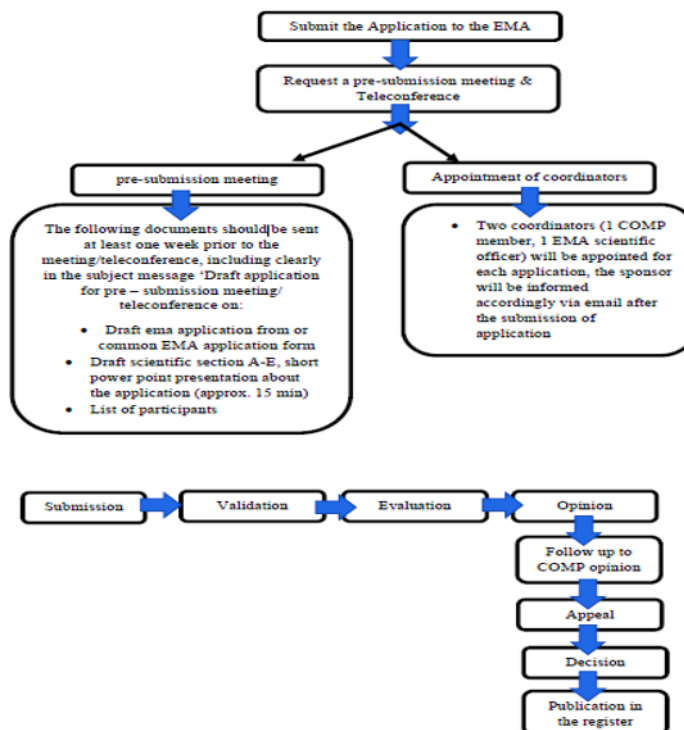**Figure 8: European Union orphan drug life cycle**

Figure 9: Orphan Drug Review Process in European Union

The European Parliament passed Regulation (EC) No141/2000 (the Orphan Law) on 16 December 1999. It was written on 22 January 2000 in the Official Journal of the European Communities.

The Regulation:

1. Defines the EU procedure for the classification of orphan medicinal products;

2. Creates requirements for the development and marketing of orphan medicinal products;

3. Establishes the Committee for Orphan Medicinal Products (COMP).

4. The European Commission adopted Regulation (EC) No 847/2000 on 27 April 2000, which:

5. Sets implementing rules;

6. Sets out criteria that are necessary for the implementation of the Orphan Regulation.

On 28 April 2000, this Regulation entered into force. Sponsors should begin sending applications to the European Medicines Agency for orphan classification on this date. No 726/2004 of Regulation (EC) On 31 March 2004, the European Parliament adopted Regulation (EC) No 726/2004 creating the European Medicines Agency (EMA) as the legal framework for regulated authorization and regulation of pharmaceutical products for human and veterinary use. This states that:

1. All advertising authorizations for orphan medicinal products in the EU will follow the centralized authorization procedure;

2. CHMP may provide guidance on compassionate use programs.

Orphan Designation

A rank assigned to a rare condition drug intended for use. The medicine must meet certain designation criteria as an orphan medicine so that once on the market it can benefit from incentives such as competition protection. Technical overview of the proposed regulatory framework applying for orphan status.

1. Apply using the service 'IRIS'

2. Access to IRIS

3. General principles

4. Compliance process

5. Review of applications

The European Medicines Agency (EMA) provides companies with information and advice on applying for a medicine's orphan status

Sponsors must use the secure online IRIS system of EMA from 19 September 2018 to submit applications for orphan designation and to coordinate pre- and post-designation activities:

IRIS is the secure online portal of the European Medicines Agency (EMA) where you can conduct such regulatory procedures with EMA

Orphan Designation

Using IRIS to apply for medication orphan designation and to control related activities for pre-and post-orphan designation.

To find out more about orphan designation and how to use IRIS for this purpose, see Applying for orphan designation on the Parallel distribution Using IRIS to send parallel distribution notifications and connect parallel distribution notifications to the public registry. The purpose of IRIS, IRIS is to make product-related regulatory procedures more efficient and user- friendly and to ensure better data quality through integration with other EMA systems such as the portal of substance, product, and organization and reference (SPOR).

IRIS is a key part of EMA's process of digital transformation. EMA plans to expand the network in the future to include new regulations and analysis procedures. MA launched IRIS for the first time in June 2018 and refined the program during a three-month pilot period based on user feedback. EMA expands the IRIS system to include other methods, including concurrent delivery. Sponsors will follow one of the two choices below to submit an orphan designation request:

Submit an application directly to EMA through the IRIS system: pre-submission meetings are not mandatory, and sponsors are welcome to submit an orphan drug designation application without warning. EMA would appreciate it, however, if sponsors could send the application a few days before any of the applications.

Application Process

To apply for orphan designation, sponsors should use the following forms:

1. Model for sections A to E for the scientific portion of the orphan designation application.

2. Translations required with the submission of an application for orphan medicinal product designation.

Documents to refer to:

1. Guidelines on the structure and content of requests for classification as orphan medicinal products and the transition of designations from one sponsor to another, 27 March 2014 (currently under review to reflect changes introduced by the IRIS system).

2. Recommendation on the elements needed to support the scientific plausibility and the conclusion that an orphan classification has a significant benefit.

3. Information providers and sources, identifying current pharmaceutical products Approved in the European Union and the European Economic Area.

Two coordinators are assigned to each application:

1. One member of the Committee for Orphan Medicinal Products (COMP);

2. One EMA Secretariat Scientific Administrator.

Requirements for the status of an orphan are available

1. EMA must verify the application and send a letter stating if the request is found to be invalid or incomplete with validity problems with the sponsor. After completion of the verification, the Company must give the sponsor a timetable for the assessment process.

2. EMA requires organizations implementing advanced therapies to apply to the Advanced Therapies Committee (CAT) separately to identify their medication as advanced therapy. For more info, see the list of medical items for advanced therapy.

Forward this for adoption of a decision to the European Commission

1. If the opinion of the COMP is negative, it may appeal to the sponsor.

2. Within 30 days of receipt, the European Commission must make a decision on a COMP opinion.

After a Decision,

1. EMA publishes information on the classification of orphan medicinal products;

2. The European Commission provides the designation of orphan medicinal products in the Community registry. EOLBREAK:

The European Medicines Agency (EMA) provides companies with information and advice on applying for a medicine's orphan status (Cited in Figure 7).

The European Union orphan drug life cycle and Orphan Drug Review Process in European Union is shown in above Figure 8 and Figure 9 respectively.

CONCLUSION

The orphan drug guidelines made via distinct countries have established as promoters in development of orphan drugs. The orphan drug regulation in the US and the EU has been a success in offering remedies to the patients with rare diseases.

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