# MEDICINE VALIDATION AND IMPLEMENTATION OF STEM CELL THERAPY REGULATORY APPROVAL STATUS

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**Abstract**

The stem cell therapy has a developing emerging field in the world and market rate in around 145.8 in 2021. As well Compound Annual Growth Rate (CAGR) has in 11.0%. Stem cell growing awareness, stem cell diseases application, screening via genome, therapeutic application and investment on stem cell research, identification of infrastructure stem cell banking and new stem cell identification has significantly increased day-by-day. An official notification has been published by several Indian government bodies, including the CDSCO (Central Drugs Standard Control Organization), Ministry of Health and Family Welfare, Department of Biotechnology, and Ministry of Science and Technology. In addition, 2019 NDCT has developed rules on Drugs and Cosmetics Act and Rules and National Guidelines (2017) for Stem Cell Research products supports to the applicant guidelines. Parley, stem cell regulatory guidelines have support to the stem cell research development and product commercialization and socio-ethical clearance related to Human Embryonic Stem Cells (HESC) utilization has the major factors for the stem market growth significantly. Hence, the common society people have unawareness on the stem cell research and the regulatory approaches. The present articles has focus on i) the stem cell mechanism with regulatory approach pathways and clinical research; ii) Stem cell derived products are future precision therapy for biopharmaceutical companies but also for the patients, who can now have access to disease specific treatment. In addition, the government enhances newer and modern technology with future medicines. The present article completely described the stem cell derived products.

**Keywords:** CDSCO, safety, efficacy, stem cell, DBT.

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**Introduction**

Stem cell research is a vital field in the biomedical science. In the global markets of stem cell research and different applications that includes stem cell developmental biology, modeling diseases, bioengineering model tissues, drug screening and toxicity testing as well (Chengyi et al., 2021). Hence, the available regenerative medicines stem cells that have the promise to improving the health of human and restoring function degeneration and injury. Few other medical innovations research with the translational studies and scientific sound rationale (Wei et al., 2023).

Stem cell studies has an established via therapies cell-based for the cure of many diseases; that which are not many times recovered through medicine with the conventional methods. Degenerative diseases have a mainly focus on functional cells that were severely affected and has used in certain cell types. Many of the identified degenerative diseases have cured by the stem cell treatment; that can support and re-modified the dead cells and make a new cell. The stem cells supported by the regenerative medicine and has developing health of human holds promise to improve the health of human. In addition to scientific rationale, medical innovations and basic and translational research must also consider ethical, legal, and social considerations. There are few challenges shown in excision of the respective gene as well as the modification through human cell-line engineering and cloning reproductive system. At the same time modern technologies that are being improved the deriving pluripotent of stem cells through variety of resources that is simply available for the clinical development, often lacking motivation. It is potential form of danger of the tumorigenicity of developed stem cells, that has considering with the significance capacity for contains unlimited development; it has possible risk of biological contamination and also the genomic development via the *in vitro* process of the development. It has the boundaries related to immunological form of tissue mismatch and also amid people with the areas of serious concern (Jun et al., 2014).

There is an independent exploitation of the individual of stem cell experiment that has an inherent risk of exploitation and also belonging to the under privileged form of groups. However, the many stem cell stake holders have an significantly involved the research as well as follow the guidance, legislation commercialization after the clinical trials (Shahani et al., 2021).

However, utilization of therapeutic potential of stem cells has been significantly increases and the disease screening as well as the development on the particular genome-based cell screening techniques. In addition, the role of public-private has been increasing the investments for the research and the growth of this segment. The stem cell regulatory guidelines and the endorsement of commercializing stem cell therapy, along with the social and ethical considerations surrounding the utilization of embryonic stem cells (ESCs) in treating diseases, play crucial roles in limiting the expansion of the stem cell product market.

The North American region is likely to facility the largest chunk of the stem cell therapy market in 2016. There are numerous factors driving the growth of the stem cell therapy market in this region, including increasing public awareness regarding the therapeutic potency of stem cells in disease therapy, an increase in clinical trials for stem cell-based products, an increase in public-private funding & research grants. The demand for stem cell therapy products that are both safe and effective is increasing, driven by a growing number of patients seeking treatment for specific diseases. (Xue et al., 2023).

Furthermore, to estimate the stem cell global growth via stem cell therapy market grow at lower CAGR status in developed countries and as compared to growing countries like China, India & Korea that has offer new stem cell growth opportunities in the global market (Rasaei et al., 2022).

In India, the stem cells developmental market has been significantly segmented two varieties such as stem cell storage banking and stem cell advanced research. However, the stem cell research that conquered in 2014 that account and has supremacy in the year of 2015-2020 (Figure 1). The discourse surrounding commercialization in both public and private research has been accompanied by an increasing number of research groups dedicated to stem cells, as well as the escalating costs associated with traditional drug development. In 2014, the Indian market for stem cells was largely driven by the promotion of adult stem cells due to the substantial volume of research conducted on them. In terms of regional distribution, the South Indian market emerged as a dominant player in the field of stem cells. (Ray and Kaz, 2022).

In the present scenario the development of private stem cell banks that significantly adopting different marketing methodologies supported for the production of increasing strategies for their product visibility in the country. A significant portion of the firms' product sales come from visiting consumers

as well as educating them about stem cell banking. The developed stem cell industry in India is a observing the rising level of market associations between the different shareholders, that has positively developing the stem cells market in around the country. At the same time, development growth of the market is on account of the rising government investment and the various part of the private organization, growing industry significantly focuses on the stem cell research and significantly raising the awareness in stem cell banking and research stem cell research. In the rise of the induced pluripotent stem (iPS) cells has an substitute form of the ESCs, and therapies of the new stem cell evolution that could be anticipated for the growth of stem cells developmental market in India on the subsequent five years (Rosemann et al., 2016).

**Explanation of stem cells**

The studies stem cells have an amazing as well as the significantly potential for to develop into the different cell types of the body stage during the early life as well as the growth. According to specific studies, many tissues have a self-repairing mechanism as well as a dividing and replenishing system that is essentially unrestrained for the person and animal. Stem cells undergo frequent divisions, where each newly formed cell possesses the ability to either maintain its stem cell characteristics or differentiate into various specialized cell types, such as muscle cells, red blood cells, or brain cells.

Stem cells varies and differentiated from the other type of cell determine through different characteristics. First, the stem cell developed an unspecialized part of cells that are able to re new themselves under the cell division, occasionally and make inactivity after extended periods. Certain investigative conditions and studies have shown promising results in the production of tissue- or organ-specific cells that possess specialized functions. Stem cells play a vital role in repairing and regenerating damaged or deteriorated tissues in various organs. (Lang et al., 2023).

In general, scientist has concentrated on 2 types of stem cells derived from humans as well as the animals: those are non-embryonic form of “somatic" or "adult" stem cells and embryonic form of stem cells. The cells are called human embryonic stem cells. The developed embryos were used and created for the reproductive application via *in vitro* fertilization process. It has no more regulated required for the specific purpose as well as supported for the research and informed consent donor respectively. In 2006, research make another break through identifying significantly conditions as well as let some specialized adult cells could be "reprogrammed" genetically determine stem cell-like structure. However, the new formation of stem cell that could induce pluripotent stem cells (iPSCs) (Golhani et al., 2022).

The development of stem cells is a crucial process for living organisms. During the early stage of embryo development, typically between 3 to 5 days, the embryo forms a structure called a blastocyst. At this stage, the inner cells undergo extensive migration throughout the developing organism, giving rise to a wide range of cell types and organs, including the heart, lungs, skin, as well as reproductive cells like sperm and eggs. As the organism matures, certain adult tissues such as the bone marrow, muscles, and brain harbor distinct populations of stem cells. These adult stem cells play a vital role in replenishing lost cells due to normal wear and tear or injury caused by diseases. (Ding et al., 2022).

The stem cells regenerative potential significantly treating for many diseases of diabetes as well as the heart disease. The stem cell laboratory studies and the clinic complications could be understood; the stem cells a based therapy has utilize in various diseases, the field referred as a regenerative medicine or medicine of reparative. Scientists are employing stem cells for drug screening purposes and to create model systems that simulate normal growth and investigate the underlying causes of birth defects.

Stem cell research contributes to expanding our knowledge and has the potential to replace damaged cells with healthy ones in adult organisms. Stem cell research has an advanced of the molecular medicine and creates the significant discoveries (Golhani et al., 2022). The subject was classified into two categories; stem cell embryonic that separated the inner cell of blastocysts and the adult stem cells of various tissues. However, progenitor stems cells that replace the body as well as the replenishing the stem adult tissues respectively.

The embryonic stem cells develop embryos from storage embryos and have the capacity to produce all the cells of the adult body. As ESCs have infinite self-renewal capacity, they can naturally form tumors. They present various dangers when used in cell therapy and are primarily employed for research purposes. On the other hand, adult stem cells come in different types, including hematopoietic stem cells (HSC), which are located in bone marrow and cord blood. Hematopoietic stem cells are responsible for producing diverse blood cell types. Additionally, adult tissues harbor

specific stem cells tailored to their respective organs, such as cardiac stem cells, neural stem cells, and pancreatic stem cells, among others. These committed precursor cells are vital for organ repair and maintenance. Another type of stem cell, called mesenchymal stromal cells (MSC), can be found in various postnatal organs like bone marrow stroma, fat tissue, umbilical cord, and placenta. MSCs are considered multipotent as they can differentiate into multiple cell types. Unlike embryonic stem cells (ESCs), MSCs have limited self-renewal capacity, which ensures their safety and non-tumorigenic nature in cell therapy applications. (Nakanishi et al., 2022).

Pluripotent embryonic stem cells are obtained from the inner cell mass (ICM) of a blastocyst. These adaptable cells have the remarkable capability to differentiate into various tissue types throughout the body, excluding the placenta. It is worth mentioning that totipotent cells, present in the morula stage of embryo development, possess the extraordinary ability to differentiate into all body tissues, including the extraembryonic placenta. (De and Flores, 2021). Stem cells are like a seed of a plant that give rise to branches, leaves, stems and fruits, these varieties of stems cells have the potential to screen the hematopoietic cells followed that brain cells, muscle cells etc. of individual body (Ahmed et al., 2022).

However, the global market for stem cell therapy is facing several challenges that hinder its growth, including high manufacturing complexities and costs, stringent regulatory requirements in various countries, and the need for innovative strategies. In this market, notable companies such as JCR Pharmaceuticals, Holostem Advanced Therapies, Osiris Therapeutics, Organogenesis, and Vericel hold prominent positions. Other significant vendors in the stem cell therapy market include AbbVie, Astellas Pharma, Athersys, Promethera Biosciences, Beike Biotechnology, Sangamo Therapeutics, Bristol-Myers Squibb, GlaxoSmithKline, Pharmicell, Histocell, International Stem Cell, Taiwan Bio Therapeutics, Ivy Institute of Stem Cells, Takeda Pharmaceutical, Japan Regenerative Medicine, Laboratorios Salvat, MEDIPOST, Mesoblast, Nuo Therapeutics, Opsis Therapeutics, Pluristem Therapeutics, RHEACELL, Salus Medical Solutions, TWO CELLS, Kangstem Biotech, Shire, Steminent Biotherapeutics, Sumitomo Dainippon Pharma, Teva Pharmaceutical Industries, Thoratec Corporation, Translational Biosciences, U.S. Stem Cell, ViaCyte, and VistaGen Therapeutics. (Mannino et al., 2022).

On the above description and modern challenges with stem cell therapy has a promising future. It is a study that an imperative form to explore the solutions working against the challenges of stem cell research. However the manuscript clearly expressed research as well as the regulatory requirement from conceptualisation to commercialisation of stem cells modern therapy in India.

**Materials and Methods**

For this study the regulatory aspects to assess and support the deliberations and information with the current status of Stem cells in India. We have successfully first conducted online data of bases of searches using Google and PubMed data of bases. All information describes the strategy of the secondary date of base resources such as technical finding reports, review of literature articles, reputed international journals, and government approved documents. Above data of bases support for the depth knowledge, regulatory regimen status and current approval status of the similar biologics in India. In addition, the Information data of bases search was conducted via WHO organization website, Food and Drug Administration of the United States (FDA), CDSCO, and DBT etc. All the information of the stem cell market, regulatory approval, was support and carried out the regulatory approval and better understanding on the current regulatory approval process respectively.

**Results and discussion**

Regulatory approval guidelines were an important and to conclude the strategists approval respectively. In 2007, ICMR and Department of Biotechnology (DBT) Government bodies were conjointly delivered a set of approval Rules for Stem Cell Research and Therapy (ICMR-DBT 2007) and subsequently, the board of National Guidelines for Stem Cell Research 2017, the Apex Committee of CDSCO has strongly suggested on the special IND approval applications that are assessed by CBBTDEC and directly recommended before the Apex Committee without going over the Technical Committee as was needed earlier. Furthermore, a significant milestone has been the introduction of conditional approval for cell-based products that address unmet needs. This approval is granted if the developmental approach or the proposed products show substantial trends of safety and efficacy in stem cell therapeutics. (Lang et al., 2023).

Efficacious and significantly safe stem cell treatments have been committed by the government in the past. The regulatory guidelines for Stem Cell Research and Therapy were first established in

2007. Following extensive public consultations, these guidelines were later revised and released as the National Guidelines for Stem Cell Research (NGSCR-2013). This revision showcases a dedication to the progress and development of stem cell research and therapy. The formulation of the National Guidelines for Stem Cell Research in 2017 was the result of collaborative efforts from various stakeholders. The guidelines were meticulously crafted, incorporating the most recent scientific progress, technical considerations, and anticipated obstacles in the field. A collaborative effort was made to bring together relevant ministries and agencies to devise strategies and tackle unethical practices associated with stem cell banking and therapeutic applications. The guidelines were meticulously crafted, incorporating the most recent scientific progress, technical considerations, and anticipated obstacles in the field. A collaborative effort was made to bring together relevant ministries and agencies to devise strategies and tackle unethical practices associated with stem cell banking and therapeutic applications.

The stem cell therapy recommendation has given by the Inter-Ministerial/Inter-Agency meetings to form rules after careful examination of the document. In addition, the detailed and the extensive consultation of the stem cell shareholders were given and their propositions were taken into consideration before completion of the products. These rules play a crucial role in aligning with present rules and regulations, highlighting the comprehensive nature of the document. (Mannino et al., 2022).

The 2017 guidelines reaffirm that the usage of stem cells in patients, except for HSC reconstitution for approved indications and investigational purposes, should be subject to careful review. It emphasizes that any administration of stem cells to patients must strictly adhere to approved and monitored clinical trials aimed at advancing scientific knowledge and medical practices, rather than being offered as a standard therapy. It is considered unethical and deemed as malpractice to provide stem cell treatments to patients external to approved and reputable clinical trials. However, the provided document shown and elaborates levels of manipulation as well as research category followed that manufacturing process; release of criteria and others. The HSCT has been provided with the special approved indication. In addition, review mechanism of the stem cell research depends on clinical research strengthened depends on CDSCO approvals. The Government has implemented various amendments to ensure regulatory compliance in stem cell research and therapy. These include mandatory registration of Institutional Ethics Committee (IEC) and Institutional Committee for Stem Cell Research (ICSCR) with the CDSCO board and National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT). Additionally, clinical trials are only allowed to be conducted at institutes with registered IEC and IC-SCR, as well as at facilities certified with GLP and GMP standards. Furthermore, the research is carried out by medical professionals who are registered with the Medical Council of India (MCI) and hold an MCI-approved postgraduate qualification relevant to the specific trial. (Ciccocippo et al., 2021).

India has a considerable demand for medical solutions that are currently unmet, necessitating the support of safe and regulated translational and clinical stem cell research. The development of this guidance has prioritized both the advancement of stem cell research and the protection of patient safety and the well-being of vulnerable individuals.Furthermore, there have been continuous and proactive efforts to engage all stakeholders and incorporate necessary revisions in a timely manner to meet the evolving requirements in this field of research. However, the social science literature reveals a complex landscape in India's stem cell industry, which is similarly reflected in the intricate nature of the associated laws and regulations. (Jun et al., 2014).

According to the New Drugs and Clinical Trial Rules 2019, a review of drug formulation records indicates that a new drug can be classified as a vaccine, a product derived from recombinant Deoxyribonucleic Acid (r-DNA), a monoclonal antibody, a product derived from stem cells, a living modified organism, a gene therapeutic product, or a xenograft model intended for use as a drug. However, Indian regulatory approval agency CDSCO has granted first limited approval to market Stempeucel® product for treating Critical Limb Ischemia due to Buerger’s disease in 2016 and after that many stem cell derived products have been undergone clinical trials and marketing authorization (Ruhela et al., 2021; Suresh et al., 2014).

In India, individuals who wish to obtain permission for importing or manufacturing new drug substances and their preparations for marketing purposes, or for conducting clinical trials, are required to submit an application using specific forms (Form CT-18/21 for import/manufacturing and Form CT-04 for clinical trials) along with the

prescribed fees mentioned in the Sixth Schedule. These fees need to be paid through a treasury challan. Additionally, applicants must provide all the relevant data as outlined in Table 1 of the Second Schedule of the NDCT Rule 2019 of Drugs and Cosmetics Rules. The required documents include information about the chemical and pharmaceutical aspects of the drug, animal testing data related to pharmacology and toxicity, clinical data demonstrating safety and efficacy. It is mandatory to submit these documents through the SUGAM online portal. Local clinical trial may be waived off in certain conditions on case to case basis, the use of such drugs is indicated for life-threatening or serious diseases, as well as for conditions that are particularly relevant to the healthcare scenario in India. These may include diseases like XDR tuberculosis, hepatitis C, H1N1, dengue, malaria, and HIV, among others. Additionally, these drugs may be employed for rare diseases where treatment options are not available or come at a high cost, or if they fall under the category of orphan drugs.

**Import of drugs for examination, test or analysis in Form CT-16**

The Form CT-17 license, known as an Import Test license, is acquired for importing small quantities of new drugs or any substance classified as a drug under the Drugs and Cosmetics Act and Rules, 1945. This license is specifically used for conducting clinical trials, bioavailability or bioequivalence studies, and for examination, testing, and analysis purposes.To seek approval, candidates are required to submit their application in Form CT-16 along with the prescribed fee of Rs. 5000/- (equivalent to 70 USD) for each drug, and the necessary supporting documents. These documents should be submitted through the SUGAM portal for the approval process in Form CT-17. (Ruhela et al., 2021; Suresh et al., 2014).

**Manufacture of drugs for examination, test or analysis in Form 29 and Form CT-11**

Form 29 is an important role in the drug development for the new applicant license from State Licensing authority form CT-11 available in the portal of CDSCO. Whereas, the application form CT-10 and information to be submitted through SUGAM in the given format which includes the product data, manufacturing procedure, facility details, technical staff information should be specified in the Fourth schedule as per the Rule 52 of GSR 227 E, 19.03.2019.

Form 29 is an application used for obtaining a license for the manufacturing of drugs intended for examination, drug testing, and analysis. This license application, submitted in Form 30, must be presented to the Licensing Authority designated by the State Government. The application should be endorsed by the head of the institution and the director of the manufacturing firm or company responsible for producing the specific substance. The Form 29 license is valid for three years from the date of issuance and can be renewed for subsequent three-year periods, unless it is cancelled prior to its expiration. (Ruhela et al., 2021; Suresh et al., 2014).

**Drug Clinical trial approval in India**

Drug clinical trial has a vital role for the drug approval. In the application for clinical trials, it is required to submit the findings data online with prescribed format in the Form CT-04/04A along with pre-requisite fee as well as the supportive documents for clinical trials should include essential information such as pharmaceutical data, chemical and generic names, product composition, results of animal experiments, acute toxicity reports, evidence of animal toxicology screening, and clinical data. It is also important to provide phase I, II, III, and IV data to the Drug Controller General of India (DCGI) to ensure the accuracy and integrity of the submission. The submission should also include the experimental study protocol along with supporting evidence of the clinical trial, including a consent form. The evaluating team members were examined properly with the regulatory board status and respective development of pharmaceutical drug in the varies countries, as well as names of countries and approved catalog respectively. Moreover, the international package insert in the catalog for the Investigational New Drug (IND) application is included. Furthermore, an affidavit must be submitted stating that neither the sponsor nor the respective study has been terminated in any country. In the event of study discontinuation, appropriate explanations are to be communicated to the board of the Drug Controller General of India (DCGI). Moreover studies, a letter of undertaking in the recompence reported by the NDCT Rules 2019; in addition the pharmaceutical and marketing approval of the application submission done by CSDCO accepted in country of respective origin (Ruhela et al., 2021; Suresh et al., 2014).

Post application submission shall be reviewed by CDSCO as well as the pharmaceutical drug experts of country and issuance approval through CT-06 Form. In addition, the supportive clinical trials done by pharmaceutical research team and analysis by the respective CDSCO committee with proper

ethical records maintained by the committee through ethics. The ICMR made it mandatory for clinical trials to begin from June 2009 with proper initiation processes. (Lang et al., 2023).

**New Drug Approval Process**

The NDCT Rules and replaced by the Part of Schedule Y and XA with the D&C Rules implemented. Furthermore, the NDA process in India follows specific regulations and requirements for clinical evaluation trials, importation, manufacturing, and marketing approval. These guidelines ensure proper procedures and support the development of new drugs in the country. In studies observation; demonstration of safety as well as the drug efficacy of the particular drug evaluation has an important and human important drug product manufacturing and marketing in the country. In currently, there are various form are available online in Form CT-18 / CT-21. However, after a thorough review by the CDSCO officials, the SEC (Subject Expert Committee) and the DCGI will grant approval for the new drugs. This approval process involves the issuance of CT-22 for Active Pharmaceutical Ingredients (API), CT-23 for the drug, and consent for the production the new drugs, accordingly new candidate needs to develop manufacturing license from SLA. Additionally, if the agreement includes importing the drugs, the applicant needs to obtain Form CT-19 for API and Form CT-20 for the new drug product to initiate the import permission and registration process. (Ruhela et al., 2021; Suresh et al., 2014).

**Registration and license direction of drug**

The CDSCO recommended drugs must have proper registration before import process in India. However, foreign manufacturers drugs must have to submit the registration certificate and individual drugs respectively. Applicant submits the application through respective agents in India via SUGAM portal. In case of the new legislation, licences import must be all types of drugs, import license requirements schedule C and C (1) as well as schedule X drugs only. FORM 40 has considered as Import license applications and challan treasury value 10,000/- USD in the website registration as well as the 5000/- USD need to pay the respective product registration. Furthermore, the application must include the necessary information and commitments specified in Schedule D(I) and Schedule D(II), which should be appropriately signed by the manufacturer. Schedule D(I) and D(II) should accurately present data on the manufacturing facility and the drug, including the plant master file, demonstrating adherence to the manufacturing standards of the respective country in order to obtain the manufacturing license. The application should also include the GMP certificate, a Certificate of Pharmaceutical Products (CPP) issued by the regulatory authority of the country of origin, as well as comprehensive documentation regarding the drug substance, finished formulation, clinical evidence, and packaging and labeling details. The import registration for a specific drug remains valid for three years. Additionally, applicants can apply for commercial import licenses for product development using FORM 8 or FORM 8A, accompanied by a fee of Rs. 10,000/- for the first drug and an additional Rs. 1,000/- for each additional drug. The marketability and value of imported pharmaceutical products can be enhanced by obtaining marketing approval within the Indian territory. (Ruhela et al., 2021; Suresh et al., 2014).

**Conclusions**

Precision therapy studies recommended for the stem cell products and has significantly used in biopharmaceutical companies. The specific treatment has a used in the disease developmental patient and have an enhance modern new technology recommended for the future advance technology. We have noted the stem cell derived products and has recommended for the pharmaceutical industry market. However, the necessary for promulgate followed that harmonize with standard regulatory approval for the stem cells.

The specific advantage of stem cell derived for the product developer, stem cell manufactures as well as the cost reduction. Whereas, the applicant need to be submit the regulatory pathways developed products of the stem cells followed that continue as well as the evolve, clearer, concise, with the specific and more specific experience in these registry products followed that harmonization have been realized.

India has rigorous countries format and pair regulatory approval requirements for the new drug. The regulatory approval has done in the single drug application with marketing authorization application (MAA) for the new drug development respectively. However, the various boards in India recommend to categories of the new drug development in NCE, Biologicals /Similar biologics Controlled Drugs etc.) and has not feasible as well as challenging respectively. Therefore above described studies were understand with the accurate registration information followed that revised the regulatory procedure for MAA in

the different categories of drugs and should be developed suitable as well as follows advance regulatory approach for the commercial launch respectively.

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