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# Regulatory Stratergies For Repurposing Of Orphan Drug "Transtuzumab" For The Treatment Of Her2 Positive Gastric Cancer In United States And India

**Lakshmi Divya Munnangi[1]*, Koushik Yetukuri[2]**

*[1*] Department of Regulatory Affairs, Student of Masters of Pharmacy in Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh Mail ID: munnangilakshmidivya21@gmail.com Contact number: 9398243620*
*[2]Associate Professor Department of Regulatory Affairs, Faculty of Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh Mail ID: yetukurikoushik@gmail.com Contact number: 8500008019*

***Corresponding Author**: Lakshmi Divya Munnangi*
*[*]Department of Regulatory Affairs Chalapathi Institute of Pharmaceutical Sciences, Guntur, AP Masters of Pharmacy Mail ID: munnangilakshmidivya21@gmail.com Contact number: 9398243620*

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***Abstract***

There is a great need and opportunity for the development of medicines for rare orphan illnesses. In an increasing number of nations, it is projected that gastric cancer will become a rare disease. In recent years, the incidence of stomach cancer has continued to rise worldwide, accounting for 40% of all cases. The reality is that developing drugs for cancer is challenging, costly, and time-consuming, with only poor success rates. Due to the ineffectiveness of currently available treatments, their high cost, and the potential for therapy to lower quality of life, repurposing has become a crucial strategy in the development of anti-cancer medications. Repurposing that supports the alternate applications of existing medications is encouraged by regulatory bodies like the FDA. Trastuzumab is a repurposed orphan drug for the treatment of HER2 positive gastric cancer. Trastuzumab was added to standard chemotherapy in the ToGA study, which increased patient survival for those with HER2-positive advanced G/GEJ adenocarcinoma and moved these patients into a new era of HER2-targeted therapy. The importance of medication repurposing, as well as the regulatory procedure for repurposed drugs in the United States and India are summarized in this study.

***Key words: Trastuzumab, Gastric Cancer, Drug Repurposing, United States, Indi***

## INTRODUCTION

Stomach cancer is the fifth most common cancer in the world. It is the fourth most common type of cancer in men and the seventh most common type of cancer in women. In 2020, there will be over 1 million new cases of stomach cancer [1]. The majority of Gastric Cancer patients are in an advanced stage at the time of diagnosis, with a poor prognosis and outcome. Current Gastric Cancer treatment strategies include endoscopic detection, gastrectomy, and adjuvant or neo adjuvant chemotherapy or chemo radiotherapy. Drug development approaches demand extreme effort to identify molecular mechanisms of action of new drug candidates. The

research of new therapeutic indications for drugs approved for other pathologies is the foundation of drug repurposing [2].

**Gastric Cancer**

Cancer of the stomach or gastroesophageal junction can be further classified based on its genetic makeup, such as human epidermal growth factor receptor 2 (HER2)-positive and HER2-negative (sometimes referred to as "HER2-normal"). The HER2 testing process, including scoring and interpretation of results, differs between stomach and breast cancers, which may influence an accurate HER2-positive or HER2-negative diagnosis and treatment [3].

**HER2 overexpression/amplifcation**

The primary cause of HER2 overexpression is HER2 amplifcation, which results in constitutive expression of the ERBB signalling network. When HER2 is overexpressed, homodimers are created. These homodimers then cause ligand-independent signalling, which results in unregulated cell division, proliferation, differentiation, and death. Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) are frequently used to determine the expression of the HER2 gene, and the results are typically interpreted using the following scale: In contrast, IHC 2+ requires FISH and is HER2-positive if FISH amplifcation is observed and is HER2-negative if FISH amplifcation is not observed. IHC 3+ is HER2-positive while IHC 0/1+ is HER2-negative [4].

Therefore, IHC 3+ and IHC 2+/FISH+ are both indicators of HER2 overexpression. Lung cancer, BC, and other malignant tumours have been found to overexpress the HER2 gene. The prevalence of HER2 positive was higher in GEJ adenocarcinomas (32.2%) than in GC (21.4%) and in intestinal tumours (31.8%) than in diffuse tumours (6. 1%).In the most recent global report, HER2 overexpression in GC patients made up roughly 7.3-20.2% of all cases, while the country-specific expression rates varied [5].

**Molecular mechanism of HER2 blockade**

**Two main processes explain how HER2 blockage improves patients' prognoses when their malignancies are HER2-positive:**

1) HER2 blockade inhibits the downstream signalling pathways of the HER2 receptors by preventing the binding of ligands to the receptors and encouraging their internalisation and degradation, which controls cell survival, proliferation, and invasion [6].
2) By focusing on HER2 receptors, HER2 inhibition stimulates anticancer immunity through antibody-dependent cell-mediated cytotoxicity (ADCC) [7]. As a result, increasing patient survival might be possible through the development of HER2-targeted therapies.

**What is Transtuzumab**

A recombinant humanised monoclonal antibody directed against the human epidermal growth factor receptor 2. (HER2). Trastuzumab induces antibody-dependent cell-mediated cytotoxicity against HER2-overexpressed tumour cells after binding to HER2 on the tumour cell surface[8]

**Trastuzumab in USA for Gastric Cancer**

Trastuzumab is sold under the brand name of Herceptin

BUSINESS WIRE — SOUTH SAN FRANCISCO, Calif. — OCT. 20, 2010 - Genentech, a member of the Roche Group, announced today that the U.S. Food and Drug Administration (FDA) had approved Herceptin (trastuzumab) in combination with chemotherapy (cisplatin plus capecitabine or 5-fluorouracil [5-FU]) for HER2-positive metastatic (cancer that has spread) cancer of the stomach or gastroesophageal junction in both men and women who had not previously taken medications for their metastatic disease.

With the exception of those with HER2-positive disease who can be treated with Herceptin plus chemotherapy, persons with metastatic stomach cancer should have the HER2 status of their tumours established using FDA-approved diagnostic testing.

The company continued to research how the HER2 pathway contributes to the growth and spread of other cancers, such as stomach cancer, since Herceptin's approval in HER2-positive advanced breast cancer more than ten years ago," said Hal Barron, M.D., executive vice president, Product Development and chief medical officer. The approval of Herceptin in combination with chemotherapy today offers patients with this fatal condition, who now have few treatment alternatives, a crucial new, tailored drug.

The combination of Herceptin and chemotherapy for patients with metastatic stomach (gastric) cancer and tumours displaying high levels of HER2 was authorised by the European Commission in January 2010.
The success of the ToGA worldwide Phase III study, which shown that those who received Herceptin in addition to chemotherapy lived longer than those who only received chemotherapy, served as the foundation for the FDA's approval[3]

**Transtuzumab in India for Gastric Cancer**
In India transtuzumab is sold under the brand of herclon. Herclon is a monoclonal antibody. Its use for the treatment of HER 2 positive gastric cancer. Its works on the tumors known to overexpress the protein HER2/neu. The manufacturer of herclon is Roche Products India Pvt.Ltd [9].

**Mechanism of action**
Trastuzumab is a monoclonal antibody against human epidermal growth factor receptor 2 (HER2). Trastuzumab binds to an extracellular domain of this receptor and inhibits HER2 homodimerization, thereby preventing HER2-mediated signalling. It is also thought to facilitate antibody-dependent cellular cytotoxicity, leading to the death of cells that express HER2[10].

**When trastuzumab is used**
1. HER2 positive early-stage breast cancer after surgery, radiation therapy, and/or chemotherapy to lower the risk of the cancer
2. Metastatic breast cancer, an advanced form of breast cancer that is HER2 positive, should be treated to reduce the tumour's growth and prolong survival.
3. advanced stomach cancer that is HER2 positive and has metastasized outside of the stomach (metastatic stomach cancer)
4. Advanced gastro-oesophageal cancer that is HER2 positive that affects the area where the food pipe (oesophagus) enters the stomach[11]

**How trastuzumab is given**
via infusion, where the medication drips into your blood slowly. The duration of subsequent treatments is typically 30 minutes after the initial 90-minute session[11].

**Clinical Trial Results**
Herceptin was approved by the FDA for gastric cancer after an open-label, multi-center trial involving 594 patients with HER2 gene amplified or overexpressing cancer who had not previously received treatment for metastatic gastric or gastroesophageal junction adenocarcinoma. The participants were given Herceptin in combination with cisplatin and a fluoropyrimidine (FC+H) or chemotherapy alone (FC). The Herceptin arm received an IV infusion of 8 mg/kg initially, then 6 mg/kg every 3 weeks until disease progression.
Cisplatin was given at a dose of 80 mg/m2 every 3 weeks for 6 cycles as a 2-hour IV infusion in both study arms, and capecitabine was given orally twice daily at a dose of 1000 mg/m2 (total daily dose 2000 mg/m2) for 14 days of each 21-day cycle for 6 cycles. Alternatively, continuous intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m2/day from Day 1 to Day 5 every three weeks for six cycles.
Overall survival was the primary endpoint. Based on 351 deaths, the final overall survival analysis was statistically significant. In the FC arm, 62.2% of subjects passed compared to 56% in the FC+H arm (p=0.0193). One year after the initial analysis, a follow-up analysis was carried out. At this point, 76.7% of subjects in the FC arm had passed, compared to 74.2% in the FC+H arm[12].

**MATERIALS AND METHODS**:

This is study, where effort has been made to study, regulations and market scenario and provide recommendations on harmonization of the regulatory framework for the study of registration complexity &Post Marketing Surveillance of drug repurposing in United States and India. In this study, primary and secondary sources of data have been referred to which include the following:
- journal Articles published in peer-reviewed publications.
- Websites of various regulatory agencies and organizations.
- Guidelines and guidance documents issued by the regulatory authorities of the countries included in the study.

- Records and databases of various regulatory agencies.

## RESULTS AND DISCUSSION

### Repurposing of orphan drugs

There are currently 7000 maybe around rare diseases in the globe, and more than 95% of them don't have any FDA-approved treatments. Even though the theory underlying orphan diseases may differ, they all share the fact that only a small portion of the population is affected. Due to the small number of people who suffer from these diseases, it is incredibly difficult to discover new medications for their treatment[13]. Drug repurposing for orphan pharmaceuticals is the greatest solution because pharmaceutical corporations cannot afford to develop and then produce these medications[14]. Drug recycling is comparable to repurposing. It involves using well-known medicines for causes other than their intended usage[15]. Drug repurposing is a creative technique to find new applications for medicines that are already on the market. Drug repurposing has a number of benefits over traditional drug research, including a shorter development period, lower cost, quicker regulatory approval, higher success rates, and a quicker knowledge of disease causes[16].

### Regulations of Orphan Drugs in USA

In the United States, more than 30 million people are affected by more than 7,000 uncommon diseases [17]. The Orphan Drug Act, which was passed on January 4th, 1983, gave orphan medications legal status in the United States. This law provides pharmaceutical companies with incentives to create medicines that often save the lives of patients with uncommon diseases but only yield a small commercial return on investment.21 CFR Part 316 contains a codification of the Orphan Drug Act. Congress passed a number of amendments over time that described the prerequisites for a medicine to qualify as an orphan drug. In 1984, 1985, 1988, 1990, and 1992, the Orphan Drug Act was revised [18].

If a medication meets the following requirements, it will be accorded orphan drug designation.

- A medication that has not previously been approved,
- A medication that has been approved with a new orphan indication,
- A medication that has outperformed a medication in its category in terms of clinical trials, and so on [18].

### Orphan Designation Application Content

The sponsor must submit the information to the OOPD in order to be designated as an orphan drug product. The documentation for developing a product is rational for use in a specific disease, has a reasonable scientific basis, and has a prevalence criterion of fewer than 200,000 patients in the United States. A summary of the product's pre-clinical and clinical data, as well as the necessary documentation, should be provided. Clinical trial data is preferred, but in the absence of data, the scientific rationale can be sufficiently supported by 'compelling' pre-clinical data in the relevant animal model. The application must include prevalence criteria as well as a scientific rationale that establishes a plausible medical hypothesis [19].

According to 21 CFR 316.3(b), if the sponsor is submitting an application for the same drug that has already been approved, the sponsor must include information on the plausible hypothesis for clinical superiority in efficacy or safety or significant contribution to patient care. If the product is claimed to be unprofitable for seven years after marketing approval, an assessment of drug production and distribution costs, as well as an estimate of potential sales in the United States, must be made to confirm, in particular, the lack of economic viability of drug marketing. 21 CFR 316.20 specifies the content and format for orphan drug designation. The content of the designation application in the United States is provided in.

### Orphan Drug Designation Procedure in the USA

Prior to submitting the application for marketing authorization, the sponsor may contact the OOPD at any moment. A foreign sponsor must work with a US resident agent to submit an orphan drug designation application, which can now be done online. This portal was just opened in November 2020[20]. When OOPD receives an orphan drug designation request, it assigns it a designation request number, logs it into the database, and sends a letter of acknowledgement to the sponsor. When an application for an orphan medicine is received, the OOPD's scientific team evaluates it to determine. Whether a drug is an orphan medicinal product. The OOPD reviewer assigned to the submission must finish it, and this may involve consulting with the FDA centre. The review is then sent on to the Director of the Orphan Drug Designation Program for a second-level review and approval [21]. The result is either a designation letter, a letter requesting more details, or a letter of

rejection. The sponsors' names, the drug's name, and the suggested indications are made public after a favourable ruling. An average review cycle lasts 90 days [22].
The approval of an orphan designation request does not alter the standard regulatory requirements for obtaining marketing approval in the United States. To market a new drug, the applicant must submit an NDA or BLA to the FDA, regardless of orphan drug status. Because orphan medicines are mostly developed to treat patients with unmet medical needs, they may be eligible for one or more FDA expedited programmes. The FDA's four expedited programmes are accelerated approval, breakthrough therapy designation, fast track designation, and priority review. These programmes are intended to facilitate and expedite the development and review of new drugs to address unmet medical needs in the treatment of severe diseases [20].

**Drug Repurposing in Unites States**

As outlined in the Food, Drug, and Cosmetics Act, there are three separate regulatory approval pathways in the United States that allow for the registration of distinct classifications of drugs, though only one of these [i.e., "505(b)(2)"] is relevant to drug repurposing. All drug candidates for repurposing must be submitted via Section 505(b)(2), regardless of whether they are for cancer therapeutics or other diseases. Figure 1 explains the approval process for 505(b)(2).
Section 505(b)(2) became available in 1984 under the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), but applications to this pathway have only recently grown in popularity. Data show that approximately twice as many products receive FDA approval through 505(b)(2) as through the novel drug route [i.e. "505(b)(1), indicating that companies are looking to generate new revenue and exclusivity from short-term product [23]. Some of the examples of repurposed drugs mentioned in table 1 and also some of the examples of reurposed drugs in gastric cancer mentioned in table 2.

A 505(b)(2) submission is a type of the US New Drug Application (NDA) that includes comprehensive documents of efficacy and safety research, with part of the material required for acceptance lacking a point of reference and relying on previously authorized evidence. 505(b)(2) application is intended to ratify innovation by eradicating recurrence of clinical trials for accommodating new indications, variations in dosage form, strength, formulation, dosing regimen or route of administration, new combination products, new active ingredients, pro drug of an existing drug. Exploitation of this regulatory strategy will merely help to enter into market with less investment. The section 505(b)(2) and 505 (j) of the Federal Food, Drug, and Cosmetic Act (FFDC) and Patent Term Restoration Act of 1984 reflects congressional efforts to "expand the low-cost generic drug products by establishing a generic drug approval system with new impetus for drug development with exclusivities and patent extensions." Additionally, the section 505(b)(2) was incorporated into the FFDC Act by the Drug Price Competition and the Patent Term Restoration Act of 1984 (Hatch Waxman Amendments) [24]. Regulations of Repurposing of Orphan drugs in USA summarized in table 3.

**Table 1:** Some of the examples of repurposed drugs in cancer [25]

| S.no | Drugs | Original indication | Repurposed indication |
|---|---|---|---|
| 1. 1. | Thalidomide | Nausea, vomiting of pregnant woman (banned now) | Multiple myeloma by targeting TNF-α |
| 2. 2 | Trastuzumab | HER2-positive breast cancer | For HER2-positive metastatic gastric cancer |
| 3. 3 | Artemisinins | Anti-malarial | Anti-proliferative, pro-apoptotic effects |
| 4. 4 | Raloxifene | Osteoporosis | Breast cancer prevention |

**Table 2.** Some of the examples of Repurposed Drugs in Gastric Cancer [2]

| S.No | Drug | Clinical Use | GC Cell Lines | Effects In Vitro | Effects In Vivo |
|---|---|---|---|---|---|
| **1. 1.** | Metformin | Type 2 diabetes | MKN1 MKN-45 MKN-74 MKN-28 SGC-7901 BGC-823 AGS HR TSGH HGC27 SGC7901 N87 SNU216 MGC803 KATO-III SNU-1 HGC-27 | Inhibits cell proliferation through cell cycle arrest in G0-G1 or G2/M phase; inhibits migration and stemness; induces apoptosis | Suppresses tumour growth and reduces the self-renewal ability of cancer stem cells |

| | | | | | |
|---|---|---|---|---|---|
| **2.** | **2** | Disulfiram | Alcohol use disorder | MKN-45 SGC 7901 BGC-823 HGC-27 SGC-7901 | Inhibits cell proliferation, migration and invasion | Induces autophagy |
| **3.** | **3** | Propranolol | Hypertension, angina pectoris, arrhythmias, migraine, hyperthyroidism, anxiety, tremor, infantile haemangiomas and angiosarcoma | SGC-7901 BGC-823 MKN-45 NUGC3 | Inhibits cell proliferation, induces apoptosis and cell cycle arrest in the G1 or G2/M phase | Suppresses cell proliferation and induces apoptosis |
| **4.** | **4** | Levobupivacaine | Pain control during labour, postoperative periods and in patients with chronic pain | HGC27 SGC7901 | Inhibits cell proliferation | Inhibits cell proliferation |

**Regulatory Approval Pathway for 505b (2)**

**1. Start**

**Candidate identification**

Although the 505(b)(2) pathway presents a special chance for rapid authorization, success depends on finding goods with proven market difference, minimal development risk, and great profit potential.

**Ideal 505(b)(2) candidates consist of:**

- Already approved drugs with novel indications
- drugs that have modifications to their dosage form, potency, formulation, dosing regimen, or method of administration
- New combination products
- Prodrugs of an existing drug
- In some circumstances, medicines contain novel active components

**2. Feasibility**

**a) Assessment of Candidate:** To clarify a product concept's value proposition for investors and lower the likelihood of expensive mistakes, predevelopment assessment of candidates is crucial. The following issues must be taken into account while constructing the case for a product's prospective value:

**b) Scientific Viability:** Is the science logical? Is the formulation, for instance, stable and simple to prepare? Can you scale up manufacturing? Are both active and inactive substances accessible and reasonably priced?

**c) Medical Viability:** Does the product fit neatly into a certain medical niche? Is it successful in solving unique problems or solving them in novel ways? Is the risk/benefit ratio reasonable? Is there evidence that the product would appeal to the target patient group?

**d) Regulatory Viability:** What clinical studies or additional information will be needed to obtain approval? Can progress be accelerated? Will there be an option for exclusive marketing rights (exclusivity)? What distinctive information can be displayed on the labels for upcoming marketing campaigns?

**e) Commercial Viability:** Does the product have a strong market? What chance do you see for future competition or replacement? What is required to guarantee payment? What is the best price to charge?

**Product Planning**

According to the guidelines of section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, "traditional" new drug development and approval—generally necessary for a new chemical entity drug that has not yet been approved or that doesn't have a significant marketing history in the U.S. or elsewhere—occurs. The transition from "promising chemical" to "approved drug" in terms of 505(b)(1) is one that is protracted, challenging, hazardous, and expensive. It typically takes the sponsor up to 15 years and a billion dollars to get a medicine approved through the 505(b)(1) pathway, which necessitates the completion of new studies to prove the treatment's safety and effectiveness in a specific disease or condition. A potential developer of a 505(b)(2) should look for ways to incorporate such existing data into the product's development strategy at this stage of

product planning because a 505(b)(2) product can rely in part on the FDA's prior findings regarding the safety and efficacy of an active ingredient as well as data in the public domain. This will help to reduce the product's size, scope, timeline, and consequently cost. Products approved under the 505(b)(2) pathway not only provide a quicker and more affordable route to market, but they may also occasionally be eligible for different types of market exclusivity, such as orphan drug exclusivity (seven years), new chemical entity exclusivity (five years), "other" exclusivity (three years for a "change" if certain criteria are met), and paediatric exclusivity (six months added to current patents/exclusivity). 505(b)(2) development is a cost-effective and commercially appealing alternative to typical 505(b)(1) development, but it has important distinctions due to the expedited pathway to approval and potential for exclusivity.

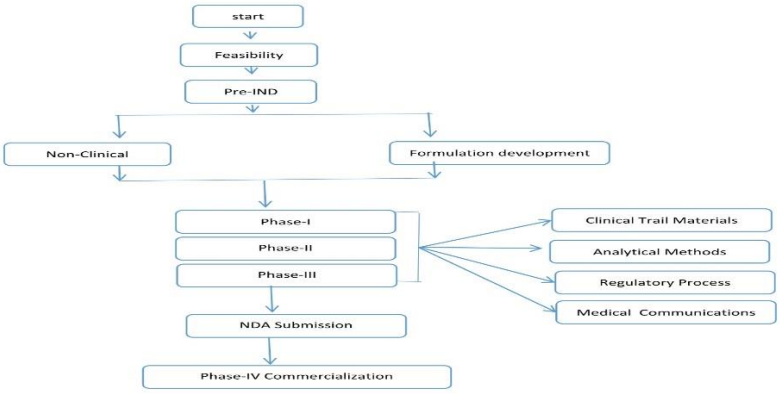


**Figure 1.** Approval Process for 505(b)(2) [26].

## 3. Pre-IND

The 505(b)(1) pre-IND development process is fairly straightforward:

a) conduct necessary pharmacology, pharmacokinetics, and toxicity investigations on animals; conduct preliminary pre-formulation research and decide on a lead formulation for advancement; create adequate analytical techniques; construct a proposed clinical procedure and acquire stability information on the active ingredient and dosage form;
b) complete a pre-IND consultation with the FDA in which the sponsor discusses the results of its nonclinical studies, manufacturing and analytical data, as well as a projected clinical trial, in order to get approval from the FDA to proceed with human testing; and
c) submission of the investigational new drug (IND) application [26].

### Regulations of Orphan drugs in India

India, like many other developing countries, lacks data on the prevalence of rare diseases as well as a consistent definition of what constitutes one. The number of people in India who are affected by rare diseases is estimated to be 72 to 96 million, which is a significant number if we take the international estimate of 6% to 8% of the population being plagued by uncommon diseases. This is just a ballpark estimate though, and India will need to develop its own estimate and definition of uncommon diseases.

The government of India has recently tackled the problem of rare diseases after realising the urgent need of the scenario. The National Health Policy of 2017 was the first initiative, and it dealt with the treatment of rare diseases to address public service shortcomings through a public-private collaboration. After that, in July 2017, a draught of the National Policy for the Treatment of Rare Diseases (NPTRD) was created, which was then revised by an expert committee in 2018 due to, among other things, implementation problems.

The Delhi High Court ordered the Centre to establish a "Rare Diseases Committee, a Rare Diseases Fund, and to finalise and notify the National Health Policy for Rare Disorders" on or before March 31, 2021, in the case of Master Arnesh Shaw vs. UOI in March 2021. A comprehensive "National Policy for Rare Diseases 2021" was approved by the Ministry of Health and Family Welfare in accordance with this order. Furthermore, "the Indian Council of Medical Research (ICMR) created a hospital-based "National Registry for Rare Diseases", integrating establishments across the nation that specialise in the identification and treatment of uncommon diseases.

Orphan Medicines are classified as "drugs intended to cure a condition which affects not more than five lakhs (500,000) persons in India" under "the New Drugs and Clinical Trial Regulations 2019". With the exception of the exemptions granted to orphan drugs, the regulatory framework for a clinical trial involving an orphan drug is the same as that for other medications.

- The Central Drugs Control Standards Organization (CDSCO), India's primary drug regulatory body, has the authority to waive the requirement for conducting local clinical trials in the case of orphan pharmaceuticals.
- The CDSCO may be urged to accelerate the approval process for a drug by the sponsor of a clinical trial for an orphan drug.
- There is no application cost necessary for an orphan drug clinical trial.

**The National Rare Disease Policy 2021**

The "National Rare Disease Policy 2021" was authorised by the Ministry of Health and Family Welfare with the following objectives:

- The goal of the programme is to minimise the cost of treating rare diseases while increasing emphasis on domestic research and local pharmaceutical manufacturing.
- The RashtriyaArogyaNidhi umbrella plan will provide "financial support of up to Rs20 lakh under the RashtriyaArogyaNidhi umbrella plan" to those with rare diseases (diseases listed in Group of the rare disease policy) who need one-time treatment. It will cover "almost 40% of people who are eligible under the Pradhan Mantri Jan ArogyaYojana".
- The policy will use a crowdsourcing approach to pay for the cost of treating rare diseases. Via a robust IT infrastructure, businesses and individuals will be urged to make financial contributions.
- To ensure that researchers and developers have access to sufficient data and comprehensive information about such conditions, a national registry for rare diseases based in hospitals will be established.
- With the assistance of Health and Wellness Centers, District Early Intervention Centers, and counselling, the plan aims to screen for and identify rare disorders at an early stage, which will help in their prevention.

**Latest developments**

The National Policy for Rare Diseases, 2021, from RS 20 lakhs to 50 lakhs under the umbrella schecme of Rashtriya Arogya Nidhi. The Union Health Ministry issued an office of Memorandum on May 19 20222 increasing the financial aids to patients who are suffering from rare diseases [27].

**Repurposing of Orphan drugs in India**

India, the world's largest producer of generic medications, has a huge potential for using repurposed orphan pharmaceuticals (RODs). It's possible that many RODs are produced, offered, and used for different ailments outside of the exclusivity period in India. Additionally, India's patent law forbids pharmaceutical product patents from being "ever greened," which would have protected minor adjustments to previously approved pharmaceuticals. As a result, India will be able to produce various RODs on a generic basis.

Additionally, there is a provision that allows for the approval of a "Subsequent New Drug Application" for a previously approved new medicine (within 4 years), with additional claims about indications, dosage, dosage form, and route of administration. *Figure 2 explains the approval process for drug product already approved by DCG(I) which isnow proposed to be marketed with modified or new claims. The NPRD promotes study into drug repurposing. Furthermore, the Government of India's Department of Science and Technology has just released a request for milestone-driven ideas to create off-patent generic medicines for the specified rare diseases.

Nevertheless, India does not have a specific system or information site for the clearance of orphan drugs. As a result, it can be challenging to find out where to buy these medications. There hasn't been any research to evaluate the accessibility of ODs in India. To make it simple to manage chronic disorders, this knowledge is

crucial for doctors, pharmacists, researchers, and patients. The industry and researchers will use this information to help them find potential medicine candidates that can be released as generics in India [28]. Regulations of Repurposing of Orphan drugs in India summarized in table 3

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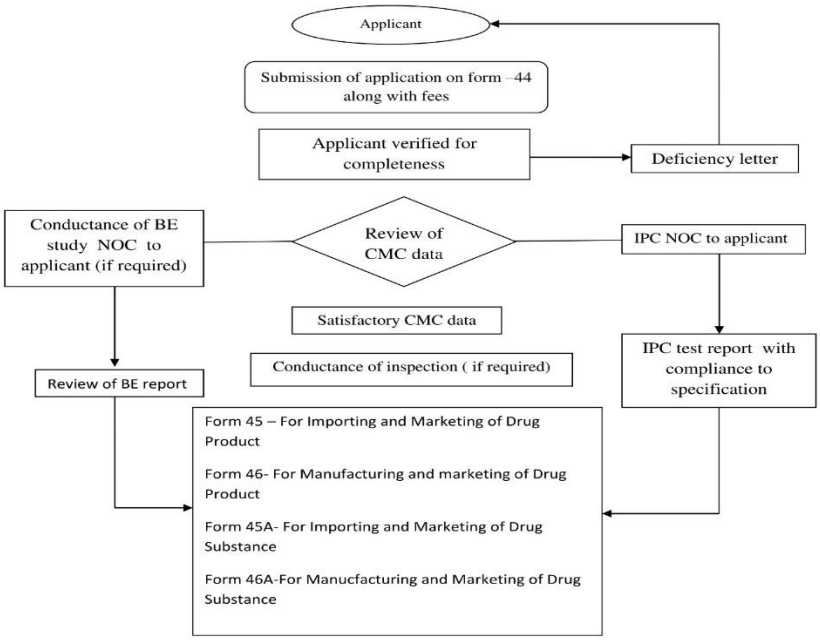


**Figure 2.** Approval process for Drug product already approved by DCG(I) which isnow proposed to be marketed with modified or new claims [29].

**A drug already approved and proposed to be marketed with new indication**
**Documents to be submitted include:**

1. Application for permission to Manufacture /Import: (Purpose should be mentioned clearly)
2. Name of the applicant and address
3. Information related to the new drug including name, Composition, Dosage Form, Proposed indication and therapeutic rational for proposed dosage form
4. Details of the approval of the New Drug in the country including approved Dosage Form, composition and indication
5. Application signed and stamped by authorized personal
6. Treasury challan of fees paid
7. Copy of valid manufacturing license
8. Copy of valid Test license
9. Source of bulk drugs along with current regulatory status of the source
10. Regulatory status in other countries, as appropriate.
11. Bio Equivalence/Bioavailability study Protocol
12. Justification on Bio equivalence study waiver, if requested
13. In case of parenteral formulation, Sub-acute toxicity data conducted with the proposed drug formulation.
14. Submit 11 sets of technical literature (whenever applicable) (10 soft copy and one hard copy) for expert opinion [30]

**Table 3.** Comparison of regulatory requirement for repurposing of orphan drugs in USA and India **[**3,9,18,26,27,29, 30]

| S.No | Requirements | USA | India |
|---|---|---|---|
| 1. | Regulatory Agency | USFDA | CDSCO |
| 2. | Orphan drug definition | a medication used to diagnose, treat, or prevent an orphan disease. A rare disease or condition that affects fewer than 200,000 people in the US is known as an orphan disease. | Orphan Medicines have been defined in the New Drugs & Clinical Trial Regulations 2019 ("New Drugs & CT Rules") as a drug "designed to treat a condition which affects not more than five lakh (500,000) persons in India". |
| 3. | Orphan drug legislation/policy | ODA (Orphan Drug Act) | In July 2017, India's Ministry of Health and Family Welfare created the National Policy for Treatment of Rare Diseases (NPTRD).<br>Later it was amended in 2021 National Policy for rare diseases |
| 4. | Regulatory Guideline for repurposing of drugs | 505 b(2) | Subsequent new drug application<br>Form 44 |
| 5. | Clinical studies | Not required<br>Previous clinical studies data should be submitted. | Not required<br>Previous clinical data should be submitted. |
| 6. | Fees | Less fees than 505(b)(1) NDA Companies with < 500 employees have the option to request to wavier the fees. Prescription Drug User Fee Act annual program **$393,933** as per 2023 | Application for permission to import approved new drug for new claims, new indication or new dosage form or new route of administration or new strength for marketing Rupees **3,00,000**<br>Application for permission to manufacture approved new drug for new claims, new indication or new dosage form or new route of administration or new strength for sale or distribution Rupees **3,00,000** |
| 7. | Exclusivity | 7yrs for orphan drug | 4years |
| 8. | Circumstances allowed for 505 b(2) and subsequent new drug application | • Already approved drugs with novel indications<br>• drugs that have modifications to their dosage form, potency, formulation, dosing regimen, or method of administration<br>• New combination products<br>• Prodrugs of an existing drug<br>• In some circumstances, medicines contain novel active components | • The nation has already approved bulk drugs (approved within 4 years).<br>• Formulation, a brand-new medication, has already received national approval (approved within 4 years).<br>• an already-approved medicine that is being considered for marketing with a new indication.<br>• A medicine previously licenced and planned to be marketed as a 'New Dosage Form/ New Method of Administration'.<br>• A medicine already licenced and proposed to be marketed as a 'Modified release dosage form'.<br>a medicine that has previously received approval but is being marketed with more strength |
| 9. | Data required for repurposed drugs | 1. Number and date of permission or license already granted for the approved new drug | 1. Number and date of permission or license already granted for the approved new drug<br>2. Therapeutic justification for new claim- New indication or modified |

| | | | |
|---|---|---|---|
| | | 2. Therapeutic justification for new claim- New indication or modified dosage form/new route of administration<br>3. Chemical and Pharmaceutical information<br>• Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; physicochemical properties<br>• Dosage form and its composition<br>• Test specifications (a) active ingredients (b) inactive ingredients<br>• Tests for identification of the active ingredients and method of its assay<br>• Specifications of finished product<br>• Outline of the method of manufacture of active ingredient and finished product<br>• Stability data<br>4. Therapeutic justification for new claim or modified dosage form<br>5. Animal pharmacological and toxicological data<br>6. Clinical trial data<br>7. Regulatory status in other countries<br>8. Marketing information | dosage form/new route of administration<br>3. Chemical and Pharmaceutical information<br>• Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; physicochemical properties<br>• Dosage form and its composition<br>• Test specifications (a) active ingredients (b) inactive ingredients<br>• Tests for identification of the active ingredients and method of its assay<br>• Specifications of finished product<br>• Outline of the method of manufacture of active ingredient and finished product<br>• Stability data<br>4. Therapeutic justification for new claim or modified dosage form<br>5. Animal pharmacological and toxicological data<br>6. Clinical trial data<br>7. Regulatory status in USFDA<br>8. Marketing information |
| 10. | Transtuzumab initial approval | 1998 | 2000 |
| 11. | Trastuzumab approval for gastric cancer | 2010 | 2010 |
| 12. | Manufactured by | Gnenentech Inc | Roche Products India |
| 13. | Dosage form and strengths | 440 mg lyophilized powder per multi-use vial. | 440 mg lyophilized powder per multi-use vial. |

## CONCLUSION

Gastric cancer is a rare disease in the United States, but it is a leading cause of cancer death worldwide. The need for an opportunity to discover medicines for rare diseases is enormous. the fact that novel drugs are expensive and out of reach for most patients. Repurposing drugs can be considered an essential alternative for rare diseases due to their cost effectiveness and reduced timeline, resulting in a higher success rate than novel drugs. Orphan drug policies and the repurposing of drugs have been fruitful in the USA. However, information on the availability of repurposed orphan drugs is limited and also, there is no portal for information on orphan drugs in India because there is no separate orphan drug designation there. So that's why India considers USFDA-approved orphan drug products as a reference. There is a backward step in regulation and advancement of orphan disease research because India is still in the developmental stage. India's research on uncommon diseases has recently begun to focus on mobility. Policies and successful implementation will be

difficult to achieve without a precise definition of rare diseases and their specifications Strong policies and activities from the government, as well as academic and corporate organizations, are required for orphan drug development.

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