International Journal of Innovative Research and Advanced Studies (IJIRAS)
Volume 12 Issue 4, April 2025

ISSN: 2394-4404

Navigating The Landscape Of Rare Diseases: The Role And Impact Of Orphan Drugs As Well As Challenges, Progress, And Future Directions

Mr. Pathan Ayaj S

Mr. Shinde Nilesh N

Assistant Professor, Department of Pharmacy at Godavari Institute of Pharmacy Kolpa, Latur, Maharashtra, India

Ms. Swami Vaishnavi B

Ms. Samiksha S. Dhaware

Mr. Suryawanshi Vishal V

Mr. Patharkar Dnyaneshwar B

Student, Department of Pharmacy at Godavari Institute of Pharmacy Kolpa, Latur, Maharashtra, India

Abstract: *Globally, millions of lives are lost annually due to health-related challenges. Among these, malnutrition and hunger are the leading causes, contributing to 36 of the 62 million deaths. In wealthier nations, non-communicable diseases such as heart disease and cancer account for about 5.44 of the 13.43 million deaths. Conversely, in lower-income countries, infectious diseases including pneumonia, HIV/AIDS, malaria, tuberculosis, and diarrheal diseases result in approximately 10.88 million deaths, with children comprising a significant portion of these fatalities. Additionally, around 800 million individuals suffer from rare diseases, many of whom receive little to no treatment. For instance, an estimated 100,000 children are born with thalassemia each year, yet most lack access to adequate care. Addressing health disparities tied to poverty and rare diseases raises numerous ethical dilemmas.*

Rare diseases, often referred to as "orphan diseases," individually affect a small segment of the population but collectively impact millions worldwide. To address the limited availability of treatments, legislation such as the Orphan Drug Act (ODA) of 1983 was enacted to encourage the development of orphan drugs. This paper reviews the complex landscape of rare diseases and orphan drug development, including regulatory efforts, treatment innovations, and ethical considerations related to drug pricing and accessibility.

Of the approximately 50,000 available medications, only 10% target rare diseases, yet orphan drugs collectively generate close to $100 billion annually. In 2009, the 12 largest pharmaceutical companies in the West earned $445 billion, with atorvastatin alone contributing $100 billion. That same year, total healthcare expenditure in developing nations was $410 billion, only 6–7% of which came from international aid.

In the UK, the National Health Service (NHS) allocates over $20 billion annually for medicines, which constitutes about 10% of its healthcare budget. High drug prices and aggressive marketing campaigns have significantly driven up healthcare costs and posed risks to patient safety. Recent legal actions in the U.S. resulted in $5.3 billion in fines for pharmaceutical misconduct, while regulatory authorities in France underwent restructuring due to related issues.

Marketing expenses in drug development often overshadow research investments. For example, the development of deferiprone (L1), a treatment for thalassemia, cost only $2 million through extensive clinical trials. There is an urgent need to reassess global pharmaceutical development, pricing models, and distribution to make medications safer and more affordable. Equitable global health policies prioritizing cost-effective treatments could dramatically improve the lives of millions suffering from rare diseases.

Rare diseases encompass a wide array of conditions that occur infrequently in the general population. Most are genetic in origin, though environmental factors can also play a role. Roughly half manifest at birth or during childhood, while others emerge later in life. These conditions often result in early mortality or severe, lifelong disabilities.

Despite their diversity, rare diseases present common challenges: delayed or incorrect diagnoses due to limited awareness, insufficient research funding, a scarcity of clinical trials, and low commercial interest due to the limited patient population. Consequently, affected individuals frequently struggle to access timely and effective care.

I. INTRODUCTION

Rare diseases are defined in the United States as conditions affecting fewer than 200,000 individuals. While each disease is rare, their cumulative impact is significant. Historically, the limited commercial interest in developing treatments for such diseases stemmed from the small patient

ISSN: 2394-4404

populations. The Orphan Drug Act (ODA) of 1983 was a landmark legislative effort designed to address this gap.

Global organizations such as the World Health Organization (WHO), UNICEF, and various governmental and non-governmental entities continue working to improve global healthcare outcomes. While notable progress has been made, persistent issues such as ethical dilemmas and healthcare policy challenges remain, especially regarding treatment access in low-income regions and support for rare disease patients.

A key concern is the disparity in healthcare resources. While medical science has advanced considerably, many in developing nations continue to face barriers such as poverty, hunger, lack of healthcare infrastructure, and limited access to essential medicines. In contrast, affluent countries grapple with health issues stemming from aging populations, lifestyle diseases, and environmental factors.

Financial considerations heavily influence healthcare delivery. In under-resourced settings, the lack of funds raises questions about prioritizing diseases and treatment options. This situation exacerbates existing inequities, with diseases like malnutrition, malaria, and HIV/AIDS dominating public health concerns in poorer nations, while cancers and cardiovascular disorders prevail in wealthier ones.

The Orphan Drug Act of 1983:

The ODA offers several incentives to promote the development of treatments for rare diseases:

- ✓ Tax Credits: Provided for costs associated with clinical trials of orphan drugs.
- ✓ Market Exclusivity: Grants seven years of market exclusivity following approval, preventing competition for the same drug and indication.
- ✓ User Fee Waivers: Exempts companies from certain FDA application fees.
- ✓ Grant Funding: Offers financial support for the research and development of orphan drugs.

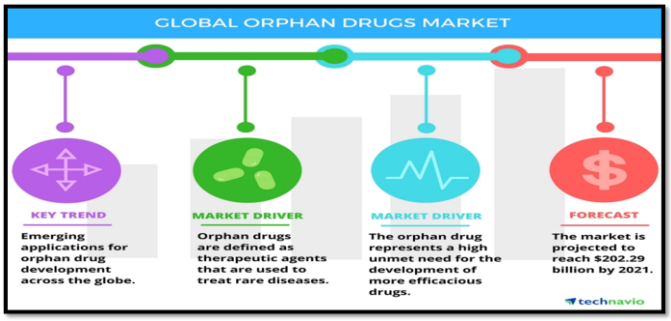
These incentives have significantly increased the number of approved orphan drugs since the Act's passage.

Global Health Challenges Contributing to Illness and Mortality:

Global health is shaped by numerous dynamic factors and involves the collaboration of entities like the WHO, national governments, and local health departments. Determinants include financial resources, disease severity and prevalence, transmission patterns, and demographic factors such as age and gender.

Human actions—including governmental fiscal policies, armed conflicts, industrial accidents, food security, and access to medicines—profoundly influence health outcomes. A wide spectrum of health challenges, from infectious to chronic and genetic diseases, affects communities worldwide.

To improve health outcomes, researchers have devised models for classifying diseases and strategizing interventions. However, limited healthcare funding remains a major obstacle. Consequently, health systems strive to prioritize conditions based on severity and burden, aiming to optimize resource allocation and reduce morbidity and mortality globally.



(Fig- Global Orphan Drugs Market)

II. PRIORITIZING DISEASES AND TREATMENTS: HEALTH ECONOMICS TOOLS

In order to determine which diseases and treatments should be prioritized—especially in developed countries—various health economic tools are employed. These tools help in assessing both the burden of disease and the value of medical interventions:

- ✓ *QALY (Quality-Adjusted Life Year):* This metric evaluates the benefit of medical treatments by combining life expectancy with the quality of life. One year in perfect health equates to 1 QALY, while time spent in less than optimal health is valued proportionally lower. A QALY of 0 represents death.
- ✓ *DALY (Disability-Adjusted Life Year):* This concept measures the total number of years lost due to illness, disability, or early death, highlighting the overall burden of disease.
- ✓ *YLD (Years Lived with Disability):* This indicator focuses specifically on the years an individual lives with a disease, accounting for the severity of the disability.

These models are crucial in comparing the impact of different diseases and determining how to allocate healthcare resources efficiently. For instance, the cost per QALY gained is a commonly used metric to assess the cost-effectiveness of a treatment, although this figure varies greatly depending on the condition and the therapy involved.

III. THE CONCEPT OF ORPHAN DISEASES AND ORPHAN DRUGS

As global efforts toward universal health coverage intensify, the development of novel drugs remains a cornerstone of these initiatives. Much of this innovation originates from pharmaceutical industries based in high-income countries, where there are greater financial resources and stronger market incentives.

A major challenge in this arena is the development of treatments for rare, or "orphan," diseases. These conditions affect a relatively small percentage of the population and often lack effective treatment options. To address this, the concept of "orphan drugs" was introduced—specialized medications developed specifically for rare diseases. Since these drugs are not typically profitable due to the limited number of patients, governments in wealthier nations offer incentives to stimulate

ISSN: 2394-4404

their development. These incentives include financial grants, tax relief, and accelerated regulatory pathways.

The introduction of orphan drug legislation began with the United States' Orphan Drug Act in 1983, followed by similar frameworks in Singapore (1991), Japan (1993), Australia (1997), and the European Union (2000). According to the EU, a disease is considered rare if it affects fewer than 5 in 10,000 individuals. In the U.S., the threshold is fewer than 200,000 affected individuals. Notably, even some subtypes of more common diseases—such as esophageal Crohn's disease—can be classified as orphan diseases if they meet the rarity criteria.

Since the enactment of the U.S. Orphan Drug Act, there has been a dramatic increase in the number of orphan drugs developed. Prior to the legislation, fewer than 40 such drugs existed. Between 1983 and 2009, the U.S. Food and Drug Administration (FDA) approved approximately 275 orphan drugs for 337 rare conditions. Today, orphan drugs represent around 22% of all new drug approvals.

Pharmaceutical companies developing orphan drugs in the U.S. benefit from:

- ✓ Seven years of market exclusivity
- ✓ Up to $30 million in research grants
- ✓ Waivers for FDA application fees (typically over $1 million)
- ✓ Tax credits for clinical research

In the European Union, similar benefits are available, with a longer exclusivity period of ten years. Between 2005 and 2011, global sales of orphan drugs increased by approximately 10% annually, reaching nearly $100 billion per year.

Initially, most research into orphan diseases was conducted by academic institutions, niche biotechnology firms, and small pharmaceutical companies. More recently, large pharmaceutical corporations have entered the field, partly drawn by the incentives and the opportunity to target rare subtypes within broader disease categories.

Examples of orphan-designated drug products with at least one marketing approval in the United States for a rare disease indication:

Drug Product Name	Orphan Indications
Alglucerase injection	Replacement therapy in Gaucher's disease
Alitretinoin	Acute promyelocytic leukemia
4-Aminosalicylic acid	Crohn's disease
Anagrelide	Polycythemia vera
Amifostine	Chemoprotective agent in cancer
Azacitidine	Acute myeloid leukemia
Beractant	Newborn infants with pneumonia
Busulfan	Primary brain malignancies
Calfactant	Acute respiratory distress syndrome
Canakinumab	Juvenile idiopathic arthritis
Cladribine	Non-Hodgkin's lymphoma, CLL, AML
Clofarabine	Acute myelogenous leukemia
Coagulation factor VIIa	Bleeding in Glanzmann thrombasthenia
Cysteamine hydrochloride	Huntington's disease
Cytarabine	Gliomas
Decitabine	Sickle cell anemia, CML, AML
Daunorubicin liposomal	Acute myeloid leukemia
Eculizumab	Dermatomyositis
Epoprostenol	Replacement of heparin in hemodialysis
Filgrastim	Myelodysplastic syndrome and AIDS
Fludarabine phosphate	Non-Hodgkins lymphoma
Idarubicin	AML in pediatrics, MDS and CML
Indium111 pentetreotide	Neuroendocrine tumors
Interferon gamma-1b	Idiopathic pulmonary fibrosis
Levocarnitine	Pediatric cardiomyopathy
Melphalan	Cutaneous melanom
Mesna	Inhibition of the urotoxic effects
Mitomycin-C	Refractory glaucoma
Nitazoxanide	Intestinal amebiasis
Nitric oxide	Acute respiratory distress syndrome
Procarbazine hydrochloride	Malignant glioma
Rapamycin (mTOR) inhibitor	Tuberous sclerosis complex
Rifabutin	Mycobacterium avium disease
Sodium thiosulfate	Platinum-induced ototoxicity
Somatropin	Induction of ovulation in women with infertility
Succimer	Mercury toxicity and kidney stones
Temozolomide	Advanced metastatic melanoma
Topotecan HCl liposomal	Gliomas

IV. THE ETHICS OF CARE: ADDRESSING DILEMMAS IN TREATING ORPHAN PATIENTS

Modern healthcare systems, particularly in the West, are heavily influenced by economic considerations. This emphasis on profit often shapes healthcare delivery both domestically and globally. A stark example lies in global food production—although sufficient food is produced to feed everyone, significant quantities go to waste due to market inefficiencies and economic barriers. Similarly, these market-driven dynamics create obstacles in preventing and treating diseases, especially in low-income countries, where access to even basic medical care is largely dictated by financial capacity.

Even in wealthier nations, access to healthcare technologies such as organ transplants or high-cost procedures like hip replacements can be restricted by budgetary limits. The ethical dilemma becomes more pronounced when considering treatments involving expensive technologies such as dialysis machines or novel cancer therapies. Many "orphan

patients"—individuals lacking familial or social support—reside in poorer regions of the world, though they are also found in wealthier countries, where treatment exists but is inaccessible due to funding gaps or systemic inequities.

Healthcare policy is influenced by a diverse array of stakeholders, including governments, pharmaceutical corporations, advocacy groups, and civil society. Broadly, two ideologies shape national health policy:

- ✓ Capitalist Viewpoint: Health is treated as a commodity—those who can afford care receive it.
- ✓ Socialist Perspective: Healthcare is viewed as a fundamental human right—everyone deserves equal access.

In many high-income countries, healthcare decisions are often guided by utilitarian principles, aiming to maximize benefits across the population. Tools such as Quality-Adjusted Life Years (QALYs) are used to evaluate the cost-effectiveness of treatments. However, QALYs are not without criticism—they offer a limited view of what constitutes a "quality" life and raise complex ethical questions:

- ✓ Should younger individuals be prioritized because they potentially have more life years ahead?
- ✓ Should societal contribution influence access to treatment?
- ✓ Should lifestyle choices that contribute to illness (e.g., smoking, obesity) impact treatment eligibility?

The increasing role of economics in medicine has shifted the focus toward optimizing the use of limited healthcare resources. Most national healthcare systems, funded by taxation and public resources, face the challenge of delivering equitable care amidst growing financial constraints and healthcare worker shortages. For example, in 2010, the UK's National Health Service (NHS) allocated over £13 billion—around 10% of its total budget—solely for medications.

V. THE INFLUENCE OF LARGE PHARMACEUTICAL CORPORATIONS IN DRUG DEVELOPMENT

The pharmaceutical industry is one of the most lucrative sectors globally and significantly impacts the economies of developed countries. In 2009, the combined revenue of the world's twelve largest pharmaceutical firms exceeded $445 billion. By contrast, the total healthcare expenditure of all developing countries combined was approximately $410 billion, with only 6–7% of that funded by international aid. Between 2009 and 2014, the United States contributed about $63 billion to global health initiatives.

One notable example of pharmaceutical success is Lipitor (atorvastatin), produced by Pfizer in the U.S., which generated roughly $100 billion in revenue before its patent expired in 2011. Among the top twelve pharmaceutical firms, six are headquartered in the United States, with others based in Switzerland, the UK (including a UK-Sweden collaboration), France, and Germany.

These large corporations typically prioritize the development of drugs that promise significant financial returns. Consequently, they often hesitate to invest in orphan drugs—medications for rare diseases—unless the expected revenue is comparable to that of mainstream therapies. An example of an orphan drug that reached commercial success is deferasirox (DFRA), used to manage iron overload in patients with thalassemia. It is marketed by Novartis, one of the industry's major players.

Though regulatory frameworks for drug approval differ slightly between agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), both follow rigorous, multi-phase processes. These include preclinical laboratory testing and four sequential phases of clinical trials, often spanning several years before final approval is granted.

Most drug development happens in developed countries because it's expensive. On average, it takes about 10 years to discover a new drug. This process involves testing many different chemical compounds. Today, computers help design new drugs by copying existing ones and changing their structures to improve effectiveness and reduce side effects. However, these methods are still limited because the human body is very complex.

After selecting promising compounds, researchers make and test them in the lab. This screening process is slow and often unsuccessful. For example, the company Hoechst tested 120,000 compounds between 1972 and 1985, but only 15 became new drugs. The early testing (preclinical stage) and safety checks can take 2 to 6 years. Human trials (clinical stages) can take another 6 to 10 years. Orphan drugs usually take less time to test and approve, and the rules for them are different in each country. For example, the iron-chelating drug L1 was approved in India in 1994, in Europe in 1999, and in the U.S. only in 2011.

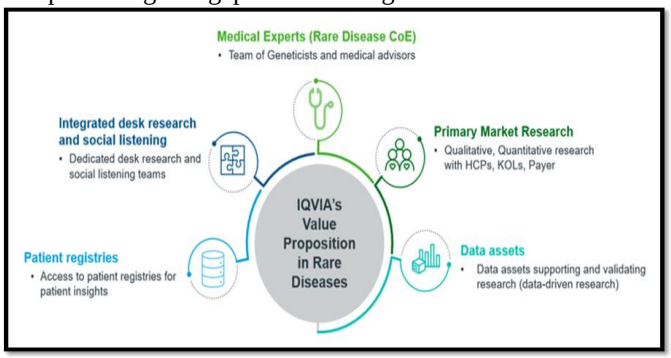
Preclinical testing involves lab (in vitro) and animal (in vivo) experiments. In vitro tests include chemical and cell studies, like checking for mutations. In vivo tests use different mammals and study how the drug works in the body—its effects, how it is absorbed and broken down, and if it's safe. After this stage, if the drug looks promising, it can move forward as an "investigational new drug" (IND) for further testing.

Orphan diseases with the most orphan drug approvals:

Disease	Drug Approved
AIDS	8
Acute myeloid leukemia	5
Ovarian cancer	4
Multiple myeloma	6
Glioma	4
Chronic myelogenous leukemia	4
Acute lymphoblastic leukemia	5
Pneumocystis carinii pneumonia	6
Respiratory distress syndrome	5
Growth hormone deficiency	9
Multiple sclerosis	4
Kaposi's sarcom	5
Malaria	4

DELIVERING VALUE VIA TECHNOLOGY AND EXPERTISE

IQVIA has multiple touchpoints in primary market research, including physicians, patients/caregivers, payers, and patient advocacy groups, conveying challenges and perspectives that help generate strategic insights. IQVIA has dedicated teams that work with customers on their requirements, identifying unmet needs and opportunities for customers by establishing the rare disease patient journey, market dynamics, demands and access to therapies. These assessments empower customers to formulate their strategy, thus making sound investment decisions. With rare diseases, it is particularly important to strategize due to many grey areas still prevailing and gaps still needing to be filled.



IQVIA is committed to contributing to the advancement of the rare disease clinical trial landscape to facilitate better diagnosis and treatment for patients who, too often, live with limited therapeutic options. As highlighted in this blog, IQVIA provides unparalleled market research alongside our scientific expertise to provide any rare disease stakeholder with customized, fit-for-purpose solutions. Please contact us to learn more about how we can help you advance and manage the rare disease product and brand lifecycles.

VI. NEW POLICIES FOR IMPROVING WITH RARE DISEASES AND ORPHAN DRUGS

A. FASTER REGULATORY PATHWAYS

Adaptive Licensing: Allow conditional approval for orphan drugs based on early clinical evidence, with ongoing data collection.

Harmonized Global Approvals: Streamline international regulatory processes (e.g., FDA, EMA, PMDA) for rare disease treatments to avoid duplication.

B. INCENTIVES FOR DEVELOPMENT

Tax Credits: Expand R&D tax credits specifically for rare disease drug development.

Public-Private Partnerships: Encourage joint funding models for early-stage research.

Extended Market Exclusivity: Provide longer exclusivity for truly innovative orphan drugs.

C. IMPROVED ACCESS AND AFFORDABILITY

Price Caps or Risk-Based Pricing: Link pricing to treatment outcomes and patient benefit.

National Rare Disease Funds: Create centralized funding pools to subsidize high-cost orphan drugs.

Expanded Newborn Screening Programs: Catch rare diseases early for better treatment outcomes.

D. DATA & RESEARCH INFRASTRUCTURE

Global Patient Registries: Fund interoperable databases for rare diseases to collect clinical, genetic, and outcome data.

Real-World Evidence Use: Incentivize the use of real-world data in clinical trial design and drug approval.

E. SUPPORT FOR PATIENTS AND FAMILIES

Care Coordination Services: Offer dedicated case managers for rare disease patients.

Mental Health & Counseling Support: Recognize the psychological burden and offer ongoing care.

Travel & Accommodation Grants: Support patients who must travel for specialized treatment.

F. EQUITY IN RESEARCH AND ACCESS

Rare Disease Research in LMICs: Fund research and capacity building for rare disease care in low- and middle-income countries.

Inclusive Trial Design: Require demographic and geographic diversity in orphan drug trials.

VII. FUTURE DIRECTIONS OF RARE DISEASES AND ORPHAN DRUGS

A. PRECISION MEDICINE AND GENOMICS

Genetic Therapies: Increasing use of gene therapy, gene editing (e.g., CRISPR), and RNA-based treatments.

Personalized Treatments: Tailoring therapies to individual genetic profiles will become more prevalent, especially as sequencing costs drop.

B. REGULATORY AND POLICY ADVANCES

Global Harmonization: Regulatory bodies like the FDA, EMA, and PMDA are working toward more aligned approval processes.

Expanded Designations: More flexible criteria for orphan designation and accelerated pathways are encouraging development.

C. ARTIFICIAL INTELLIGENCE AND DIGITAL HEALTH

AI for Drug Discovery: Using machine learning to identify drug candidates and predict responses.

Digital Biomarkers: Wearables and health apps will track rare disease progression and treatment efficacy in real time.

D. INNOVATIVE CLINICAL TRIAL MODELS

Decentralized Trials: Remote monitoring and telemedicine reduce the burden on patients.

Adaptive and Basket Trials: More efficient designs allow testing of multiple diseases or therapies simultaneously.

E. MANUFACTURING AND ACCESSIBILITY

Scalable Gene Therapy Production: New platforms to reduce the cost and time of manufacturing personalized therapies.

Global Access Strategies: Efforts to make orphan drugs more available in low- and middle-income countries.

F. STRONGER PATIENT AND ADVOCACY GROUP INVOLVEMENT

Patients are increasingly involved in:
Trial Design
Regulatory Decisions
Post-market Surveillance

Advocacy groups are also driving fundraising, awareness, and policy changes.

G. MULTI-STAKEHOLDER COLLABORATION

Public-private partnerships, consortia, and cross-sector collaboration are essential to share risks and knowledge.

VIII. CONCLUSION

World health developments including morbidity and mortality outcomes reflect many factors which are affected by health policies in individual countries and globally. Food availability, health provision and education, family planning, disease prevention, nutrition, environmental and monetary influences, genomic and psychological aspects are some of the factors which are in dynamic equilibrium and can influence health levels and outcomes in each country. There is scope for substantial improvements in world health policies and many ethical dilemmas and issues related to health strategies need to be prioritised, readdressed and resolved in each country and globally. The disease profile and health policies between developed and developing countries are different, with profound financial resource insufficiencies in the latter The availability and cost of generic and new medicinal drugs are among the major areas affecting the level of global health care. Monetary, ethical, and other issues affect the supply of medicinal drugs for different categories of patients in each country. Health policies, regulatory and marketing procedures can variably influence the risk/benefit assessment, patient safety, drug availability and drug treatment outcomes in each country. Public health and overall national spending are also influenced by such procedures. Reassessment of drug pricing and of regulatory procedures with major emphasis on the development of orphan drugs based on a risk/benefit assessment may help in the treatment of many categories of orphan and Rds and millions of orphan patients globally. The criteria for drug development and use and of price levels in each condition should be readdressed and modified to improve patient treatments, drug safety and minimise costs. The implementation of improved policies on health resource allocation and drug development can lead to the realisation of many major health aims such as the introduction of worldwide and universal health care. Similarly, advances in medical research can lead to the elimination and improved treatment of many diseases, to an overall reduction in the morbidity and mortality rates and an increase in the quality of life for patients worldwide.

REFERENCES

[1] Frenk J, de Ferranti D. Universal health coverage: good health, good economics. Lancet. 2012;380(9850):862-864. doi:10.1016/S0140-6736(12)61341-5.
[2] Marais B, Crawford J, Iredell J, Ward M, Simpson S, Gilbert L, Griffiths P, Kamradt-Scott A, Colagiuri R, Jones C, Sorrell T. One world, one health: beyond the Millennium Development Goals. Lancet. 2012;380(9850):805-806. doi:10.1016/S0140-6736(12)61450-0.
[3] Bishai D, O'Neil J. Economic growth and better health: the UK's surprising progress. Lancet. 2012;380(9850):649. doi:10.1016/S0140-6736(12)61370-1.
[4] Weiss HB. Adolescent health and ecological determinants. Lancet. 2012;380(9850):645. doi:10.1016/S0140-6736(12)61363-4.
[5] Walley T. Drugs, money and society (Part II). Br J Clin Pharmacol. 2010;70(3):342-345. doi:10.1111/j.1365-2125.2009.03569.x.
[6] Caplan AL. Clinical trials of drugs and vaccines among the desperately poor in poor nations: ethical challenges and ethical solutions. Clin Pharmacol Ther. 2010;88(6):583-584. doi:10.1038/clpt.2010.208.
[7] Rezaie R, Singer PA. Global health or global wealth? Nat Biotechnol. 2010;28(9):907-909. doi:10.1038/nbt0910-907.
[8] Woodcock J. Assessing the clinical utility of diagnostics used in drug therapy. Clin Pharmacol Ther. 2010;88(6):765-773. doi:10.1038/clpt.2010.230.
[9] Smith RD, Lee K, Drager N. Trade and health: an agenda for action. Lancet. 2009;373(9670):768-773. doi:10.1016/S0140-6736(08)61780-8.
[10] Orenstein WA, Hinman AR. Measles: the burden of preventable deaths. Lancet. 2012;379(9830):2130-2131. doi:10.1016/S0140-6736(12)60638-2.
[11] Phillips IM. Big Pharma's new model on orphan drugs and rare diseases. Expert Opin Orphan Drugs. 2013;1(1):1-3.
[12] Howitt P, Darzi A, Yang GZ, Ashrafian H, Atun R, Barlow J, Blakemore A, Bull AM, Car J, Conteh L, Cooke GS, Ford N, Gregson SA, Kerr K, King D, Kulendran M, Malkin RA, Majeed A, Matlin S,

Merrifield R, Penfold HA, Reid SD, Smith PC, Stevens MM, Templeton MR, Vincent C, Wilson E. Technologies for global health. Lancet. 2012;380(9850):507-535. doi:10.1016/S0140-6736(12)61127-1.

[13] Cohen J, Milne C-P. Is the increasing cost of treating rare diseases sustainable? Expert Opin Orphan Drugs. 2013;1(9):581-583.

[14] Smith RD, Correa C, Oh C. Trade, TRIPS, and pharmaceuticals. Lancet. 2009;373(9670):684-691. doi:10.1016/S0140-6736(08)61779-1.

[15] Ekins S, Williams AJ. Finding promiscuous old drugs for new uses. Pharm Res. 2011;28(8):1785-1791. doi:10.1007/s11095-011-0486-6.

[16] Kontoghiorghes GJ. Design, properties, and effective use of the oral chelator L1 and other alpha-ketohydroxypyridines in the treatment of transfusional iron overload in thalassemia. Ann N Y Acad Sci. 1990;612:339-350.

[17] Kontoghiorghes GJ, Pattichis K, Neocleous K, Kolnagou A. The design and development of deferiprone (L1) and other iron chelators for clinical use: targeting methods and application prospects. Curr Med Chem. 2004;11(16):2161-2183. doi:10.2174/0929867043388785.

[18] Kontoghiorghes GJ, Barr J, Nortey P, Sheppard L. Selection of a new generation of orally active alpha-ketohydroxypyridine iron chelators intended for use in the treatment of iron overload. Am J Hematol. 1993;42(4):340-349.

[19] Davidoff F, DeAngelis CD, Drazen JM, Hoey J, Højgaard L, Horton R, Kotzin S, Nicholls MG, Nylenna M, Overbeke AJ, Sox HC, Van Der Weyden MB, Wilkes MS. Sponsorship, authorship, and accountability. JAMA. 2001;286(9):1232-1234. doi:10.1001/jama.286.9.1232.

[20] Kontoghiorghes GJ. A record number of fatalities in many categories of patients treated with deferasirox: loopholes in regulatory and marketing procedures undermine patient safety and misguide public funds? Expert Opin Drug Saf. 2013;12(5):605-609. doi:10.1517/14740338.2013.799664.

[21] Kates J, Morrison JS, Lief E. Global health funding: a glass half full? Lancet. 2006;368(9538):187-188. doi:10.1016/S0140-6736(06)69081-7.

[22] Stuckler D. Population causes and consequences of leading chronic diseases: A comparative analysis of prevailing explanations. Milbank Q. 2008;86(2):273-326. doi:10.1111/j.1468-0009.2008.00522.x.

[23] Kontoghiorghes GJ. Deferasirox: uncertain future following renal failure fatalities, agranulocytosis, and other toxicities. Expert Opin Drug Saf. 2007;6(3):235-239. doi:10.1517/14740338.6.3.235.

[24] Kontoghiorghes GJ. A record of 1,320 suspected deferasirox-related patient deaths reported in 2009: insufficient toxicity testing, low efficacy, and lack of transparency may endanger the lives of iron-loaded patients. Hemoglobin. 2011;35(3):301–311. doi:10.3109/03630269.2011.576906.

[25] Robins-Browne RM, Prpic JK. Desferrioxamine and systemic yersiniosis. Lancet. 1983;2(8352):1372.

[26] Braillon A, Bewley S, Herxheimer A, Mansfield P, Lexchin J, Menkes DB, Ziganshina LE, Montastruc JL. Marketing versus evidence-based medicine. Lancet. 2012;380(9833):340. doi:10.1016/S0140-6736(12)61250-1.

[27] Lochouarn M. France launches new drug regulatory agency. Lancet. 2012;379(9833):2136.

[28] Uhlemann AC, Fidock DA. Loss of malarial susceptibility to artemisinin in Thailand. Lancet. 2012;379(9830):1928-1930. doi:10.1016/S0140-6736(12)60488-7.

[29] Lynch M, Korenromp E, Eisele T, Newby H, Steketee R, Kachur SP, Nahlen B, Bhattarai A, Yoon S, MacArthur J, Newman R, Cibulskis R. New global estimates of malaria deaths. Lancet. 2012;380(9841):559. doi:10.1016/S0140-6736(12)61320-8.

[30] Schubert D, Maher P. An alternative approach to drug discovery for Alzheimer's disease dementia. Future Med Chem. 2012;4(13):1681–1688. doi:10.4155/fmc.12.109.