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# The impact of the rare disease and Orphan Drug Act in Taiwan

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## Abstract

The Rare Disease and Orphan Drug Act (the Act) was enacted in 2000 in Taiwan for the facilitation of the research, development, and accessibility of orphan drugs and special nutritional foods; for the prevention and early diagnosis of rare diseases; and for providing intensive care for patients with rare diseases. The aim was to investigate the impact of the Act on the availability and use of orphan drugs in Taiwan in the hope of identifying the remaining challenges and possible solutions to assist future policy making, which may be applicable in other countries as well. The information and statistics for rare diseases and orphan drugs retrieved from the official annual reports and documents were analyzed. There were 225 diseases recognized as rare diseases, and one-third (75/225) of them were congenital metabolic disorders. Among the 110 designated orphan drugs that could apply for listing in the National Health Insurance (NHI) Pharmaceutical Benefits and Reimbursement Scheme, approximately half (62/110) of them were granted marketing authorization. While the NHI program compulsory for all citizens increased patient accessibility to orphan drugs, the rapidly increasing economic burden became an urgent issue for the government. Emerging gene therapies may be the solution to unmet medical needs and also a financial obstacle to tackle. The Act increased the availability of orphan drugs while the NHI system facilitated patient access, which benefited many patients with rare diseases in Taiwan. However, the soaring economic burden was noticed and was anticipated to aggravate. More communication and cooperation between stakeholders is critical in finding solutions for the long-term sustainability of the NHI system.

**Keywords:** Orphan drugs, Regulation, Reimbursement, Taiwan

## 1. Introduction

Rare diseases, as suggested by the term, are diseases affecting limited patient populations [1–6]. Although the terminology was not harmonized internationally, rare diseases are often serious, mostly genetically based, and can be life-threatening [1–3]. Many patients with rare diseases suffer from a lack of available treatment while some of them may even be undiagnosed [2,3]. In view of this, the Orphan Drug Act was passed in 1983 in the United States (US), and related legislations have been established worldwide [2–6]. In Taiwan, The Rare Disease and Orphan Drug Act (the Act) was

enacted in 2000 for the facilitation of the research, development, and accessibility of orphan drugs and special nutritional foods; for the prevention and early diagnosis of rare diseases; and for providing intensive care for patients with rare diseases [7]. The Act defined the term “rare diseases” as “diseases with a prevalence rate lower than the standard announced by the central competent authority (Ministry of Health and Welfare, MOHW); or diseases recognized through review by the Review Committee specified in Article 4 of this Act, and designated and publicly announced by the central competent authority under special circumstances” [7]. The current standard for the prevalence rate is 1

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per 10,000, and the recognition also involves considerations regarding heredity, the difficulties in diagnosis and treatment, and the exclusion of diseases/harm due to external or acquired factors and cancers [8,9].

In Taiwan, the National Health Insurance (NHI) program is a system of universal health coverage launched in 1995 and is compulsory for all citizens [10]. According to the National Health Insurance Act [11], “in case the beneficiaries encounter illness, injury, or maternity, the contracted medical care institutions shall provide medical services.” Then, “the contracted medical care institutions shall declare to the Insurer (NHIA, MOHW) the points of the medical services rendered and expense of drugs, based on the Fee Schedule and Reference List for Medical Services and the Reference List for Drugs.” For patients with rare diseases, the copayment for the treatment related to rare diseases is exempted so as to reduce patients’ financial burdens [12]. Since 2009, a specified proportion of the tobacco health and welfare surcharge has been utilized for the treatment of rare diseases [13].

According to the Act, the designation of orphan drugs is reviewed by the Review Committee and then announced by the central competent authority. These orphan drugs could apply for listing in the NHI Pharmaceutical Benefits and Reimbursement Scheme after obtaining approval through the registration process or specific permission to import; within ten years from the market approval, the central competent authority shall not accept applications for registration of pharmaceuticals of the same kind. In addition to the aforementioned incentive, the central competent authority should provide funding support to encourage research related to the prevention and control of rare diseases [7]. Moreover, the application fees for marketing registration and related processes were reduced [14,15]. For example, the application fee for the registration of a new orphan drug is approximately US\$341, in contrast to US\$51181 for that of a nonorphan new chemical entity based on the exchange rate (29.308) announced on September 16, 2020 by the Central Bank of the Republic of China (Taiwan) [14–16]. Sponsors can also apply for priority review and the accelerated approval pathway based on the surrogate endpoint for applications of new orphan drugs, and scientific advice is also available [17,18].

The implementation of the Act and related regulations at the government level is mainly achieved by the cooperation of three administrative agencies in the MOHW, including the Health Promotion Administration (HPA), the Food and Drug

Administration (FDA), and the National Health Insurance Administration (NHIA) [19–21]. For example, the recognition of rare diseases and regular reviews of the qualifications of designated institutions for genetic and rare diseases are governed by the HPA [19]. A rare disease special nutritional food and drug logistic center was initiated to store and supply special nutritional foods essential for the maintenance of life and emergency drugs for patients with rare diseases [19]. Moreover, the HPA also provides medical subsidies for rare diseases not covered by the NHI; subsidies for programs related to the prevention, control, and advocacy of rare diseases; and care assistance to patients and their families through commissioned institutions [19]. In addition, the designation of orphan drugs, the approval for the marketing authorization applications of orphan drugs, and the compilation of the annual reports for drugs to which the Act is applicable are conducted by the Taiwan FDA [20]. The NHIA is responsible for managing health insurance affairs, including but not limited to the determination of the reimbursement prices for the designated/approved orphan drugs, while the NHI covers most of the medical expense for patients with rare diseases [21].

Similar to the situations in other countries worldwide, patient advocacy groups in Taiwan also play important roles in making rare diseases a priority for health policy [6,22]. For example, the Taiwan Foundation for Rare Disorders, founded in 1999, actively promoted the adoption of the Act and is continually devoted to the improvement of the lives of patients with rare diseases through various activities [22]. To date, it has been 20 years since the enactment of the Act [7]. The aim of the present study was to investigate the impact of the implementation of the Act on the availability of orphan drugs in Taiwan through the study of available orphan drugs, their utilization, and the associated economic burden in the hope of identifying the remaining challenges and possible solutions to assist future policy making, which may be applicable in other countries as well.

## 2. Methods

The information and statistics for rare diseases and orphan drugs were retrieved from the annual reports and documents announced and/or published by the MOHW, Taiwan, which are publicly available on official websites (last accessed September 16, 2020) [7,9–15,17–21,23–30]. Based on the Act [7], “when there are difficulties in manufacturing or importing nonorphan drugs in

accordance with the provisions of the Pharmaceutical Affairs Act, and said drugs are reviewed by the Review Committee and determined to be beneficial for the treatment of specific diseases, provisions in this Act regarding registration, market approval and ad hoc application may be applied". These drugs were classified as drugs that were "difficult to obtain". Therefore, in the present study, these drugs were included unless stated otherwise. Drugs with the same active pharmaceutical ingredient(s) were regarded as the same drug despite differences in unit doses (strengths) and/or dosage forms. If a drug had more than one unit dose (strength)/dosage form, the earliest time for designation and/or approval for marketing authorization was recorded. The drug Cholbam (cholic acid) is indicated for (1) treatment of bile acid synthesis disorders due to single enzyme defects; (2) adjunctive treatment of peroxisomal disorders including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat-soluble vitamin absorption [28]. Herein, only the first indication is included in the calculation of the number of the orphan drugs. The estimation of the evolution of annual NHI expenditures on specific drugs was calculated using the amounts of the drugs used stated in the annual report [20] multiplied by the unit prices announced by the NHIA in the same year [25]. If there was a change in a reimbursement price within the year of interest, the highest price was used for the estimation. The total NHI expenditures for orphan drugs, the total amounts from the subsidies from the tobacco health and welfare surcharge, and the numbers of patients suffering from rare diseases from 2009 to 2018 were collected from the public document released by the NHIA [13]. The conversion of New Taiwan dollars to US dollars was based on the 2016 exchange rate (32.3180) obtained from the Central Bank of the Republic of China (Taiwan) [31] and the data were adjusted using the annual consumer price index - medicines & health food (base: 2016 = 100) collected from the AREMOS Taiwan Economic Statistical Databanks for inflation unless stated otherwise [32]. Microsoft Excel 2016 was utilized for the analysis and the preparation of the table and figures.

### 3. Results

#### 3.1. Characteristics of the rare diseases and the orphan drugs currently available in Taiwan

Currently, there are 225 diseases recognized as rare diseases; and there are 110 available designated

orphan drugs, including 29 drugs classified as "difficult to obtain" [20,23,24]. The top three types of these 110 orphan drugs classified by the Anatomical Therapeutic Chemical (ATC) classification [33] include drugs for alimentary tract and metabolism (A, 30 drugs), antineoplastic and immunomodulating agents (L, 18 drugs), and drugs for blood and blood forming organs (B, 14 drugs). The categories of rare diseases classified in the annual report and the distribution of currently available orphan drugs excluding 29 "difficult to obtain" drugs are collectively displayed in Table 1. One-third (75/225) of recognized rare diseases were congenital metabolic disorders, and there were approximately half of orphan drugs excluding those classified as "difficult to obtain" (35/81) indicated for treating patients with these diseases. Among 225 rare diseases, multiple sclerosis had the highest number (11) of available drugs, followed by idiopathic or heritable pulmonary arterial hypertension (IPAH or HPAH) with nine designated orphan drugs. Nonetheless, there were still many rare diseases without available drugs, such as those classified as kidney and urinary system disorders, muscle disorders, connective tissue disorders, congenital malformation syndromes, and other unclassified diseases or diseases due to unknown causes.

Among the 110 designated orphan drugs, 56% (62/110) were granted marketing authorization, including 14 "difficult to obtain" drugs. Among the 62 drugs with marketing authorization, 23% (14/62) involved at least one manufacturer in Taiwan. Except for one "difficult to obtain" drug for which the date for authorization was earlier than the date for designation, the average time from designation to approval for 13 "difficult to obtain" drugs was 1887 days (Fig. 1a). Similarly, except for two drugs for which the dates for authorization were earlier than the dates for designation, the average time from designation to approval for 46 orphan drugs not including "difficult to obtain" drugs was 1621 days (Fig. 1b). There were 11 orphan drugs with more than one dosage form, including one "difficult to obtain" drug. Thirty-two drugs had more than one unit dose, including four "difficult to obtain" drugs.

#### 3.2. Evolution of the utilization pattern

The top three most commonly used orphan drugs from 2001 to 2018 is shown in Fig. 2. Herein, drugs classified as orphan drugs including those listed as "difficult to obtain" to which the Act could be applied for the respective year were included. Except for 2007, the data for the amount of drugs

Table 1. Categories of rare diseases and the distribution of currently available orphan drugs.

Category of rare diseases	Number of rare diseases	(%)	Number of orphan drugs <sup>a</sup>	(%)
Congenital metabolic disorders	75	33.3	35	43.2
Brain and nervous system disorders	26	11.6	19	23.5
Respiratory and circulatory system disorders	8	3.6	10	12.3
Digestive system disorders	5	2.2	2	2.5
Kidney and urinary system disorders	3	1.3	0	0.0
Skin disorders	12	5.3	1	1.2
Muscle disorders	15	6.7	0	0.0
Bone and cartilage disorders	9	4.0	1	1.2
Connective tissue disorders	1	0.4	0	0.0
Blood disorders	5	2.2	3	3.7
Immune system disorders	10	4.4	3	3.7
Endocrine disorders	15	6.7	6	7.4
Congenital malformation syndromes	27	12.0	0	0.0
Chromosomal abnormalities	9	4.0	1	1.2
Other unclassified or unknown causes	5	2.2	0	0.0

<sup>a</sup> These orphan drugs did not include “difficult to obtain” drugs. Drugs with the same active pharmaceutical ingredient(s) were regarded as the same drug despite differences in unit doses (strengths) and/or dosage forms. The drug Cholbam (cholic acid) is indicated for (1) treatment of bile acid synthesis disorders due to single enzyme defects; (2) adjunctive treatment of peroxisomal disorders including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat-soluble vitamin absorption [28]. Herein, only the first indication is included in the calculation of the number of the orphan drugs.

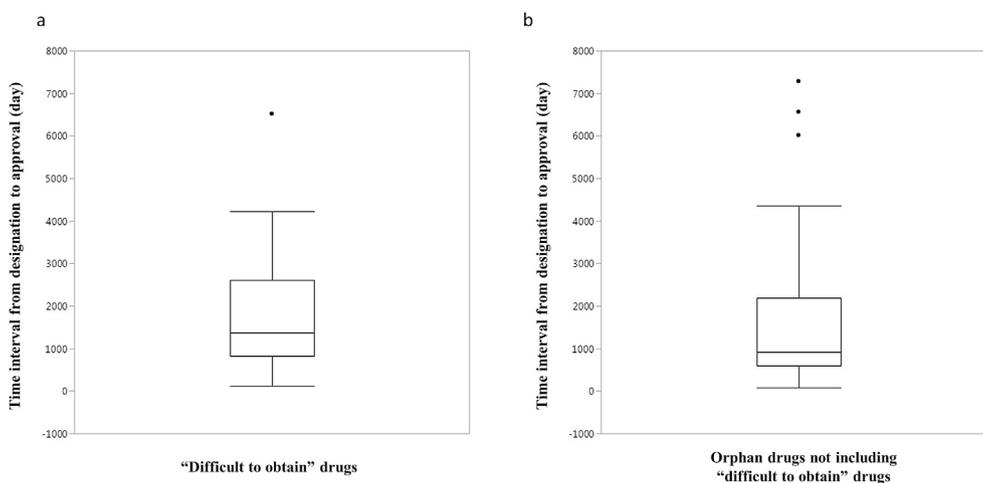


Fig. 1. The distribution of the time intervals (days) from designation to approval for (a) “difficult to obtain” drugs except for one drug for which the date for authorization was earlier than the date for designation or (b) orphan drugs not including “difficult to obtain” drugs except for two drugs for which the dates for authorization were earlier than the dates for designation.

used were available in the annual reports [20] from 2001 to 2018 (Fig. 2). Among these commonly used orphan drugs defined by the amount of drugs used each year (Fig. 2a), the “difficult to obtain” drug containing anagrelide (anagrelide hydrochloride monohydrate), a platelet reducing agent used to treat essential thrombocythemia, ranked as the top drug in 2004, in 2006, and from 2008 to 2018. Considering the number of patients using the drugs, data were available in the annual reports [20] from 2001 to 2018 except 2007 (Fig. 2b). A drug containing anagrelide also ranked as the top drug in 2004 and from 2008 to 2014.

Orphan drugs including those classified as “difficult to obtain” with the top three highest annual NHI expenditures from 2001 to 2018 except 2007 (data not available in the annual reports [20]) are shown in Fig. 3. Among these 12 drugs, half are enzyme replacement therapies. For example, imiglucerase for Gaucher disease type 1 was ranked as the top drug from 2001 to 2006 and third in 2010. Agalsidase alfa for Fabry disease ranked as the top drug from 2011 to 2018. A similar drug for Fabry disease, agalsidase beta, ranked second in 2002, from 2004 to 2006, and in 2009 and third in 2003, 2008, 2017, and 2018. Another two drugs that once

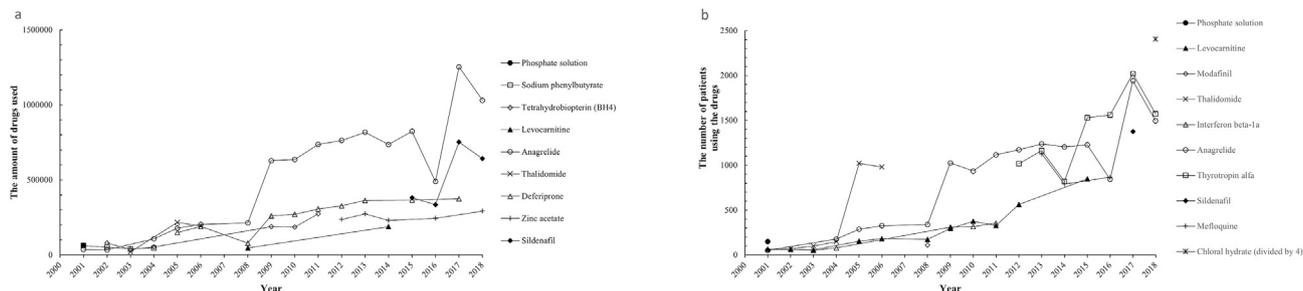


Fig. 2. The top three most commonly used orphan drugs defined by (a) the amount of drugs used or (b) the number of patients using the drugs each year from 2001 to 2018 except for 2007 for which data were not available. Drugs with the same active pharmaceutical ingredient(s) were regarded as the same drug despite differences in unit doses (strengths) and/or dosage forms. The amount of drugs was calculated by the number of dosage units except that the amount of phosphate solution was calculated in “milliliters”.

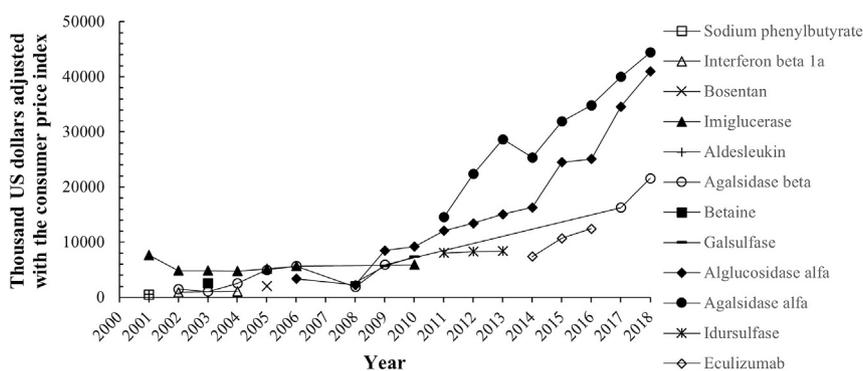


Fig. 3. The top three most costly orphan drugs defined by the annual National Health Insurance (NHI) expenditures from 2001 to 2018 except for 2007 for which data were not available. The conversion of New Taiwan dollars to US dollars was based on the 2016 exchange rate (32.3180) obtained from the Central Bank of the Republic of China (Taiwan) [31] and the data were adjusted with the annual consumer price index - medicines & health food (base: 2016 = 100) collected from the AREMOS Taiwan Economic Statistical Databanks for inflation [32]. Drugs with the same active pharmaceutical ingredient(s) were regarded as the same drug despite differences in unit doses (strengths) and/or dosage forms.

ranked at the top, galsulfase and alglucosidase alfa, were also enzyme replacement therapies indicated for use in patients with mucopolysaccharidosis VI and Pompe disease, respectively. Furthermore, idursulfase for Hunter syndrome (mucopolysaccharidosis II, MPS II) ranked third from 2011 to 2013. Among the drugs included in Figs. 2 and 3, no drug was removed from the orphan drug list except aldesleukin, which was no longer classified as an orphan drug in August, 2002.

### 3.3. Economic burden

The total NHI expenditures for orphan drugs, the total amounts of the subsidies from the tobacco health and welfare surcharge, and the numbers of patients suffering from rare diseases from 2009 to 2018 are collectively shown in Fig. 4 [13]. As the total NHI expenditures for orphan drugs grow rapidly, the allocation of resources becomes an increasingly important issue for the government. For example, the recent total expenditures for orphan drugs

accounted for 2.7%, 2.9%, and 3.0% of the total NHI expenditures for drugs in 2016, 2017, and 2018, respectively [26]. However, the numbers of patients with rare diseases accounted for 0.034%, 0.035%, and 0.037% of the total beneficiaries including the insured and his/her dependents, respectively [26,27]. The average drug expenditures per patient with a rare disease was thus unproportionally high, which remains an issue vigorously debated [34].

The economic challenges could be further aggravated by the emergence of expensive innovative therapies. For example, nusinersen (Spinraza®) is an antisense oligonucleotide, an orphan drug designated in 2018 and approved in 2019 for treating specific types of patients with spinal muscular atrophy (SMA) [20,24,28]. The tentative reimbursement price is US\$82764 per vial based on the exchange rate (29.612) announced by the Central Bank of the Republic of China (Taiwan) on July 1, 2020, the effective date of the price [16,30]. There are restrictions on the age of patients and the detection method for the genetic mutation for the

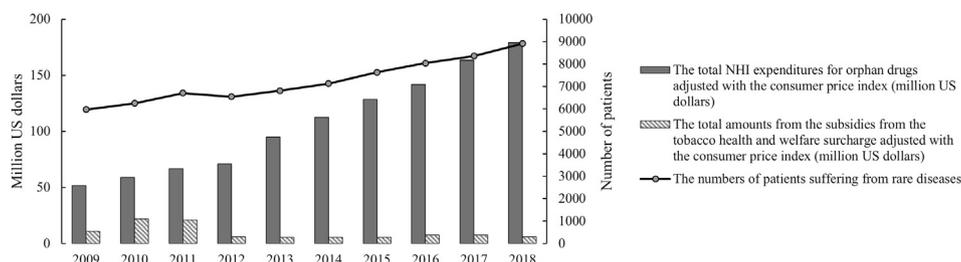


Fig. 4. The total National Health Insurance (NHI) expenditures for orphan drugs, the total amounts of the subsidies from the tobacco health and welfare surcharge, and the numbers of patients suffering from rare diseases from 2009 to 2018. The conversion of New Taiwan dollars to US dollars was based on the 2016 exchange rate (32.3180) obtained from the Central Bank of the Republic of China (Taiwan) [31] and the data were adjusted with the annual consumer price index - medicines & health food (base: 2016 = 100) collected from the AREMOS Taiwan Economic Statistical Databanks for inflation [32].

reimbursement [30]. In addition, the effectiveness of the treatment should be evaluated and confirmed or the payment should be discontinued [30]. Despite these restrictions, the huge impact on the budget is foreseeable and requires further observation.

#### 4. Discussion

Despite the similarity in the purpose of the enactment of the law related to orphan drugs, the details and measures varied among countries. The number of rare diseases recognized in Taiwan (225) was relatively low in comparison with those in the EU and the US with thousands of rare diseases, which could be related to different definitions applied, varied epidemiology, and disparities in the framework of the reimbursement system [1]. For example, cancers were excluded from being recognized as rare diseases in Taiwan [8,9] while drugs for rare cancers could be categorized as orphan drugs in both the EU and the US [2,35]. The enactment of the law greatly improved the care for patients with rare diseases, enhanced the research and development of orphan drugs in Taiwan, and increased the availability of orphan drugs in Taiwan. However, a relatively large proportion of rare diseases recognized still lack effective treatments (Table 1). More research and development are needed. To expedite patient access to orphan drugs, the designated orphan drugs could apply for listing in the NHI Pharmaceutical Benefits and Reimbursement Scheme after obtaining specific permission to import [7]. However, since the drugs would be administered to patients, the criteria for designation of these orphan drugs were largely different from and much stricter than those designed for facilitating the development process of the potential orphan drugs in the EU and the US [5]. In order to promote progress in developing orphan drugs, the Taiwan FDA announced the Directions for Applications for Recognition of Orphan Drugs in

Development in 2018 in which the purpose of recognition resembles that of the designations in the EU and the US [36]. In addition, in the past, as mentioned earlier, the application for marketing authorization was not required for reimbursement [7]. The results demonstrated that among the 110 designated orphan drugs, only 56% (62/110) were granted marketing authorization. In order to urge sponsors to proceed with the application process for marketing authorization, the “Regulations for National Health Insurance Pharmaceutical Benefits and Reimbursement Scheme” was amended in 2016 [37]. The designated orphan drugs listed in the NHI Pharmaceutical Benefits and Reimbursement Scheme without being granted marketing authorization should apply for marketing authorization within three years [37]. Although the designated orphan drugs approved by the US or the EU could be exempted from this requirement, the amounts to be paid for these drugs would be reduced annually [37]. The trends of the research and development of orphan drugs after the implementation of the aforementioned measures are worth further observation.

While the utilization of drugs may be related to the number of patients with the diseases and the dosage and administration pattern depending on the drugs and the conditions of patients, the results (Fig. 2) suggested that in certain years, some drugs, such as phosphate solution, levocarnitine, anagrelide, thalidomide, and sildenafil, with the top three largest amounts of drugs used were also those with the top three highest numbers of patients using the drugs. However, the top three most commonly used orphan drugs defined by the amount of drugs used and the number of patients using the drug were seldom the drugs with the top three highest NHI expenditures (Figs. 2 and 3). Only sodium phenylbutyrate and interferon beta-1a could be found simultaneously in both Figs. 2 and 3. The drugs with the top three highest NHI expenditures

were more often associated with higher unit prices. For example, imiglucerase (2001–2006), agalsidase beta (2002–2006, 2008, 2009, 2017, and 2018), agalsidase alfa (2011) and eculizumab (2014–2016) were the drugs with the top three highest unit prices and annual NHI expenditures simultaneously in the respective years stated above.

While the marketing approval of orphan drugs does not assure affordability for patients [38], the NHI program in Taiwan [10] significantly lowers the barriers to patient access. The total NHI expenditures for orphan drugs was found to be unproportionally high and rapidly increasing. Hsu et al. [39] demonstrated similar findings utilizing rare disease-related claims data from 2003 to 2014 from the National Health Insurance Research Database in Taiwan. They also found an increasing trend of the related economic burden [39]. Considering the economic challenges, in addition to the aforementioned nusinersen (Spinraza®), patisiran (Onpattro®) and onasemnogene abeparvovec (Zolgensma®) are also worth special attention due to the anticipated high price [40]. Onasemnogene abeparvovec, a gene therapy, was designated in 2020 for specific types of patients with SMA [24,40]. SMA affected 497 patients in Taiwan as of August 31, 2020, and 82 patients with SMA died as of June 30, 2020 [29]. Patisiran, a targeted RNA-based therapy, was designated in 2019 for specific groups of patients with familial amyloidotic polyneuropathy (FAP) [20]. FAP affected 166 patients in Taiwan as of August 31, 2020, and 59 of these patients died as of June 30, 2020 [29]. As mentioned earlier, in Taiwan, the recognition of rare diseases involves considerations regarding heredity [8,9], while approximately 80% of rare diseases in the US was related to a single-gene defect [41]. While gene therapies bring hope of curing diseases that were managed chronically in the past, their extremely high costs would have large impacts on the health care system, which is a worldwide concern [42,43].

For these innovative therapies including but not limited to gene therapies, uncertainty of the clinical benefits is another issue further complicating the problem of the economic impact [42,43]. To reduce the budget impact and increase the early accessibility of these innovative drugs in Taiwan, the “Regulations for National Health Insurance Pharmaceutical Benefits and Reimbursement Scheme” was amended in 2018 to introduce the risk-sharing approach [37]. In addition to the original price-volume agreements, other agreements such as outcome-based and finance-based agreements were incorporated [37]. Therefore, the reimbursement would be linked to the clinical outcome or financial

status, and the manufacturer would be more involved and share the risk of the use of these highly innovative therapies with extremely high costs [37,43]. Whether the approach would be a long-term solution for the upcoming challenges of orphan drugs remains an issue to be closely monitored. The success and sustainability of the framework and the NHI system require more communication and cooperation between all stakeholders.

## 5. Conclusions

The present study demonstrated that the implementation of the Act and the establishment of the related regulatory framework increased the availability of orphan drugs. Meanwhile, the NHI program compulsory for all citizens increased patient accessibility to orphan drugs. The aforementioned frameworks benefited many patients with rare diseases in Taiwan. Nonetheless, the results also revealed the need to promote the research and development of orphan drugs for treating those diseases without effective treatments and the upcoming challenges posed by the rapidly increasing economic burden. Emerging gene therapies may serve as both a solution to unmet medical needs and a financial obstacle to tackle. More communication and cooperation between stakeholders would be critical in finding solutions for the long-term sustainability of the NHI system.

## Conflict of interest

All authors declare no competing interests.

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