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## Original Article

## Traits, trends and hits of orphan drug designations in cystic fibrosis

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## ABSTRACT

**Background:** In the United States (US) and in Europe, cystic fibrosis (CF) qualifies as a rare disease, thus positioning the field to benefit from regulatory incentives provided by orphan drug designation (ODD) to boost pharmaceutical research and development.

In this study, we analyzed the pool of products for the treatment of CF that received such incentives from the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) over the past two decades. We describe the characteristics and trends in ODDs over time and explore factors that might be determinants of successful drug development.

**Methods:** We collected the products that received the ODD from the registries of the FDA and the EMA from 2000 to 2021, characterizing their nature, development stage, and type of sponsor. We categorized the study drugs according to the therapeutic target addressed and described trends of drug development over the study period. A logistic regression analysis was done to assess how ODD characteristics were associated with the approval for market authorization.

**Results:** From 2000–2021, 107 ODDs were collectively granted by the FDA and the EMA for products developed for the treatment of CF. Although the trends of the number of ODDs granted remained stable over time, those targeting the CF basic protein defect increased from 6 out of 54 (11.1%) in the first half of the study period up to 20 out of 54 (37.7%) in the second half, while those treating symptoms decreased from 48/54 (88.9%) to 33/53 (62.3%).

Overall, 10 products obtained marketing approval: 7 in both the US and Europe, 3 only in Europe. All the approved ODDs were chemical products for chronic use. No statistically significant difference was found across the examined variables, but we observed possible drivers of successful drug development for ODDs targeting CFTR, as well as for those with active substances previously marketed, and for those developed by large companies and companies with experience in developing orphan drugs. By contrast, our findings suggest that financial issues most hamper the development of ODDs sponsored by small-medium enterprises.

**Conclusions:** Although ODDs for treating infection and other CF sequelae accounted for the majority, we observed a shift of ODDs toward mechanism-based products over the study period.

In line with other rare diseases, we found that approximately 1/10 ODDs for CF reached the status of marketing approval.

Advances in disease genetics paved the way for a shift in CF drug development; however, we described how the convergence of pharmaceutical technology, the financial environment, and the regulatory ecosystem played a crucial role in successful marketing authorization in CF.

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## 1. Background

Cystic fibrosis (CF) is an autosomal recessive genetic disease whereby the accumulation of thick viscous mucus severely impairs the function of the lungs, pancreas, and other organs [1]. Since its description, the management of CF has been symptom-based, targeting secretory obstruction, inflammation, infection, and the consequences of pancreatic dysfunction [2].

The discovery of the genetic cause of CF and understanding of the variant-based dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, enabled the development of variant-targeted therapies. This class of therapeutic agents, termed, “CFTR modulators”, improve clinical and patient-reported outcomes for people with CF (pwCF) [3–7].

However, despite the remarkable advances, these new treatments are effective only for people with specific CF variants, and – more importantly – they cannot completely recover the irreversible damage and chronic infections in those with well-established disease [8–13]. Furthermore, not all of those eligible are able to tolerate these medications. Thus, the availability of symptom-based treatments remains necessary to target the wide spectrum of CF clinical manifestations [14].

Over 160,000 people live with CF worldwide, but most of the known burden is borne in the United States (US) and the European Union (EU) where, based on its prevalence (i.e., < 200,000 individuals and a prevalence < 5/10,000 respectively), it is considered a rare disease. Therefore, according to the US Orphan drug act of 1983 and the EU Regulation 141/2000, medicinal products intended for its treatment are potentially eligible for Orphan Drug Designation (ODD). ODD is a special regulatory status that qualifies sponsors for incentives to develop therapies in areas characterized by a limited size of market shares, such as rare diseases [15,16].

Although the two orphan drug legislations have a similar framework, substantial differences exist in eligibility criteria, regulatory procedures, and benefits provided. For example, in the US, after obtaining ODD, tax credits of up to 50% are provided to sponsors for expenses incurred in conducting clinical trials, as well as fee waivers, and technical assistance for the overall drug development plan by the US Food and Drug Administration (FDA). Once the product is marketed, a period of 7 years of market exclusivity is guaranteed [15,16]. On the other hand, in the

EU, no tax waivers are provided with ODD status, but sponsors can obtain fee reductions or exemptions, and protocol assistance from the European Medicines Agency (EMA). Unlike in the US, in the EU an initial ODD must be confirmed at the time of marketing authorization (MA), and – most importantly – when satisfactory methods are available, the new product must provide evidence that it confers significant benefit for patients over existing treatments. Ten years of market exclusivity is granted once the product is marketed [16].

ODD is an indication-driven process that can be requested at any time during development for a new or a repurposed drug, but – in any case – before the submission of the application for MA. ODDs have been acknowledged as a proxy of drug development in the field of rare diseases, and have already been used to monitor the progress of drug development in many orphan drug areas [17,18]. In this study, we described the characteristics and trends in ODDs granted by the FDA and EMA for CF from 2000 to 2021 and explored factors that might be determinants of a positive decision on market authorization.

## 2. Methods

### 2.1. Data collection

We collected and matched the data of ODDs for CF granted by the FDA and the EMA from 1 January 2000 to 31 December 2021 following the methodology reported in Box 1.

### 2.2. Data analysis

We categorized ODDs according to the leading therapeutic target for which the sponsor intended them to qualify and sorted them into five main therapeutic targets: CFTR, infection, inflammation, mucus clearance, and gastrointestinal. We analyzed trends over time in these respective categories. We considered an ODD as a ‘new entity’ when its active pharmaceutical ingredient (API) was not previously licensed in the US or the EU as medicinal products at the time of ODD for CF.

The development of each ODD was followed up to December 2022, i.e. 1 year after the last designation was granted, and considered as a) ‘approved’ when the ODD was licensed either by the FDA or by the EMA

### Box 1 Search strategy and matching

**Orphan Drug Designations (ODDs):** data on active pharmaceutical ingredients (APIs), date of designation, and sponsors that received ODD for CF were retrieved from publicly available databases of the FDA and the EU Community [25,26].

**Clinical trials (CTs):** data on phase, status (ongoing, terminated, completed), outcomes, and last update were retrieved through the following search strategy:

- 1) <https://clinicaltrials.gov> and <https://www.clinicaltrialsregister.eu>: <Cystic Fibrosis> AND <ODD description or acronyms or active pharmaceutical ingredient (API)>;
- 2) Pubmed: [Advanced search: all fields <Cystic Fibrosis> AND < ODD description or acronyms or API> OR <clinical trial number (NTC number or EudraCT Number)>]. Filter: Article type <clinical trial>].
- 3) Sponsors’ websites: search: API or Cystic Fibrosis

**Categorization of the Active Pharmaceutical Ingredient (API):** ODDs were categorized as chemical, biological, and gene therapy by comparison with the freely accessible database <https://go.drugbank.com> or the sponsor’s website.

**Sponsors’ profiles:** sponsors’ sizes were collected from companies’ official websites, and Dun & Bradstreet (<http://www.dnb.com/>), and clustered as large enterprises (>250 employees or >50 million (M) annual turnover in USD or euro as appropriate), and small-medium enterprises – SMEs (<250 employees or <50M turnover). For ODDs granted by both the FDA and EMA, we considered the sponsor to be the entity who first received the designation either in the US or in the EU.

Each item was reviewed by two authors (EC, SG), and a pilot-tested MS Excel database was developed to double-check for inconsistencies. Discrepancies were discussed and overcome by involving a third author (JLTC, CKvde, MC) (see supplementary material).

or by both agencies; b) ‘in development’ when preclinical or clinical testing were ongoing or the ODD was reported as active in the sponsor’s pipeline; c) ‘discontinued’ when the development process failed or the ODD was abandoned by the sponsor, i.e. no update was reported in the last 3 years, or if the information was published, but the development was either declared terminated, or the sponsor was determined to be inactive/in bankruptcy [19].

We considered a sponsor to be experienced in the field of rare diseases when at the time of granting ODD for CF it was granted one or more ODDs for CF or any other rare disease.

Reasons for discontinuation of ODDs were categorized as research and development (R&D) when related to lack of efficacy, safety concerns, and enrollment issues, or as sponsors’ issues in reference to the sponsor’s portfolio prioritization or financial issues.

We used the ‘Rate of Approval’ (ROA) as the main metric to measure drug development success, measured as the number of approved ODDs over the approved plus the discontinued ones [20]. This rate was stratified by potential drivers for MA, including regulatory authority that granted ODD and its approval, disease targets, and drug- and sponsor-related factors.

Univariate odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for each independent variable using logistic regression analysis. Adjusted odds ratios (OR<sub>adj.</sub>) were calculated using a multivariate logistic regression model. Variables that had a p-value of <0.20 in the univariate analysis were included in the final model. The analyses were performed using SPSS software version 28.0.1.1.

In addition, we investigated the ‘phase success rate’, expressed as the number of ODDs that moved from one phase of the drug development to the next divided by the sum of the number of ODDs that progressed and the number of drugs that were discontinued [21].

### 3. Results

#### 3.1. Features of orphan drug designations

From 2000–2021, 107 ODDs were collectively granted by the FDA and the EMA for products developed for the treatment of CF (4.9 ODDs/year). As shown in Table 1, 26/107 (24.3%) were treatments targeting

**Table 1**

Characteristics of Orphan Drug Designations granted by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to pharmaceutical products for the treatment of Cystic Fibrosis in the period 2000–2021.

	ODDs (N=107)	%
<b>Target</b>		
CFTR	26	24.3%
Infection	38	35.5%
Inflammation	18	16.8%
Mucus clearance	22	20.6%
Gastrointestinal	3	2.8%
<b>Type of product</b>		
Chemical	84	78.5%
Biotech	19	17.8%
Gene therapy	4	3.7%
<b>Route of administration</b>		
Oral	29	27.1%
Inhalation	65	60.7%
Parenteral	10	9.3%
N.A.	3	2.8%
<b>Previously marketed</b>		
No	66	61.7%
Yes	41	38.3%
<b>Sponsor size</b>		
SME	82	76.6%
Large	25	23.4%
<b>Regulator</b>		
FDA	84	78.5%
EMA	74	69.2%
In common	51	47.7%

the CFTR defect while 81/107 (75.7%) addressed the symptomatic consequences associated with CF: infection 38/107 (35.5%), inflammation 18/107 (16.8%), mucus clearance 22/107 (20.6%), and gastrointestinal complications 3/107 (2.8%).

ODDs targeting CFTR were mainly designed for oral administration (16/26; 61.5%), whereas those dealing with consequences were principally developed for inhalation delivery (57/81; 70.4%), mainly based on therapies for airway inflammation, infection, and mucus clearance (Table 1).

Analyzing the therapeutic classes in more detail, we found that 17/26 (65.4%) of the ODDs targeting CFTR aimed to enhance the function of the protein, whereby CFTR modulators accounted for 14/17 (82.3%) of this group; the remaining three consisted of one CFTR amplifier and two CFTR stabilizers. On the other hand, 9/26 (34.6%) ODDs were designed to increase CFTR expression through gene therapy, messenger ribonucleic acid (mRNA) delivery, or correction of deoxyribonucleic acid (DNA) transcription, i.e., antisense oligonucleotides (ASOs) or read-through agents (see supplementary material).

Most of the ODDs addressing infection were developed for chronic suppression (31/38; 81.6%) - of which there were 17 antibiotics for inhalation - while the remaining 7/38 (18.4%) were for treatment of pulmonary exacerbations.

Eventually, reflecting the complexity and multisystem pathophysiology of the disease, ODDs addressing inflammation, mucus clearance, and gastrointestinal complications address a wider range of function and targets as shown in Fig. 1.

#### 3.2. Trends and development of orphan drug designations

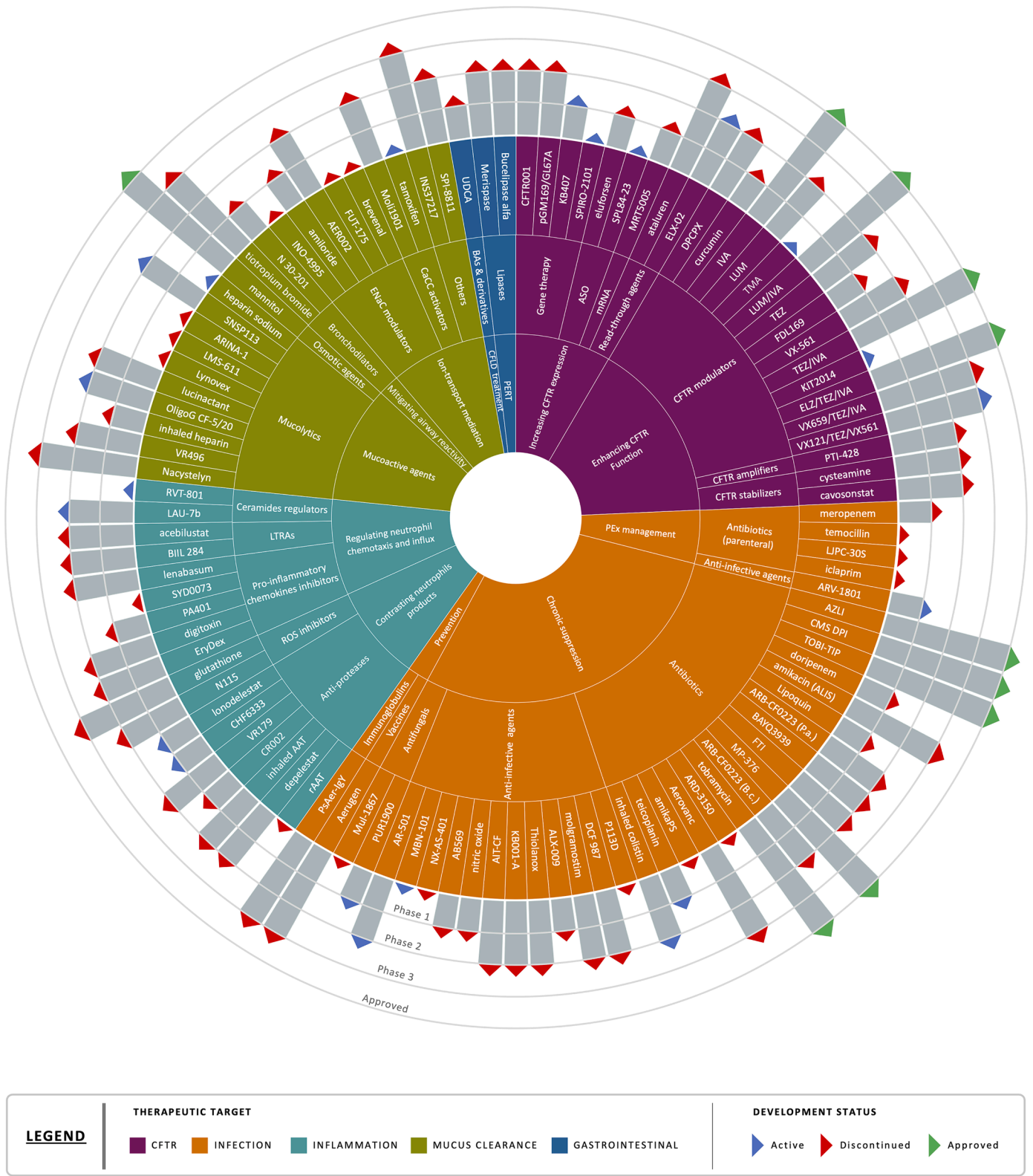
Fig. 2 shows the overall trends of ODDs for CF, supporting changes that occurred amongst the therapeutic targets addressed. ODDs targeting CFTR increased from 6 out of 54 (11.1%) in the first half of the study period to 20 out of 53 (37.7%) in the second half. By contrast, those not targeting CFTR expression or function decreased from 48/54 (88.9%) to 33/53 (62.3%), with a marked reduction of drugs targeting mucus clearance and the near disappearance of the already marginal contribution of gastrointestinal ODDs.

At the time of the analysis, 19/107 (17.8%) ODDs were ongoing (of which 7 are targeting CFTR) 10/107 (9.3%) reached MA either in the US or the EU, 78/107 (72.9%) were discontinued, of which 27 were formally withdrawn by the sponsor (Fig. 1).

Of the 10 ODD products that reached the market, 7 were approved in both the US and EU, but only five were licensed as orphan drugs by both the FDA and EMA. Developed as either a monotherapy or a combination, 4/14 (28.6%) of CFTR modulators were approved by both regulators, but for one (lumacaftor/ivacaftor) the designation was not confirmed at the time of MA in the EU. Tobramycin inhalation powder was approved in the EU as an orphan drug, but in the US, it was developed and approved outside the scope of orphan legislation.

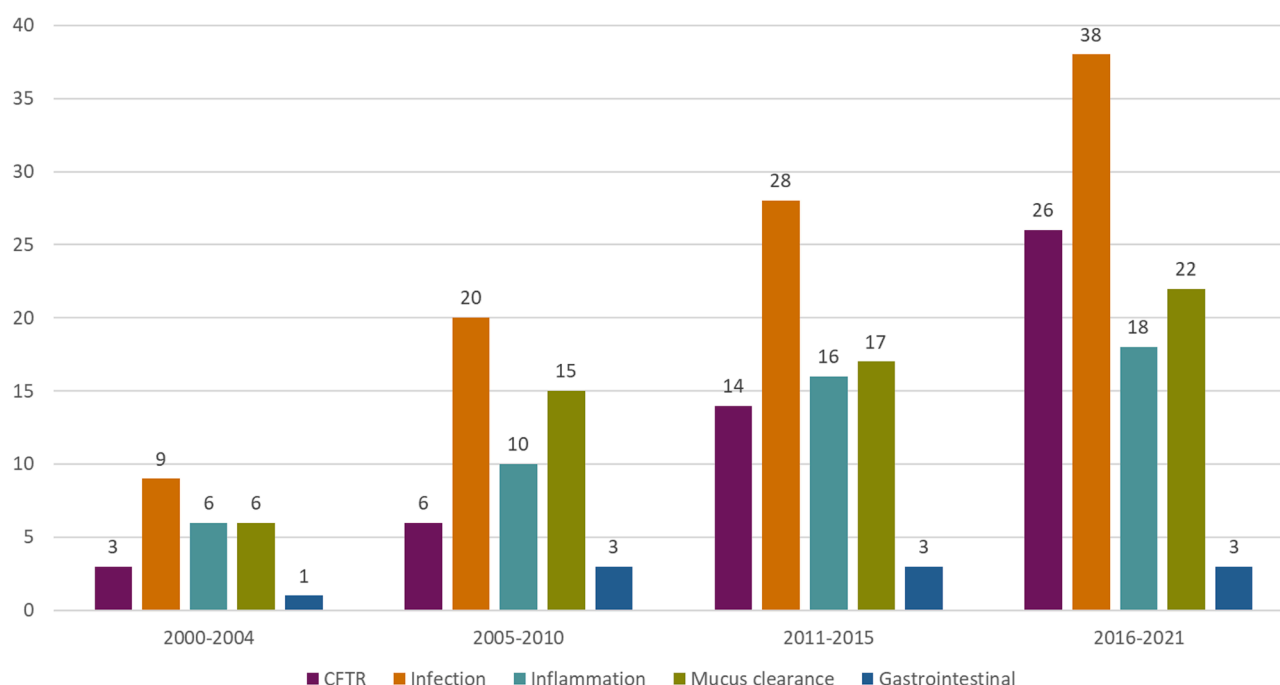
With respect to 5/38 (13.2%) ODDs targeting infection that gained market approval, all of them were products of preexisting active substances reformulated for inhalation. Remarkably, 3 of these products were licensed only in the EU, where, however, all these orphan designations were withdrawn by the sponsors at the time of MA because the EMA Committee for Orphan Medicinal Products (COMP) questioned the significant benefit of such products. When the outcome of a designation is negative, the sponsor can withdraw the application before the COMP adopts an opinion; explanation of the motivation for withdrawal is not requested by the EMA, and no information on the application is made public [22].

Levofloxacin, the first inhaled fluoroquinolone approved in Europe for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in pwCF, was not approved in the US because its risk-benefit profile was not considered favorable. Due to the limited detailed pharmacokinetic data, lack of standardized dosing, and lack of demonstration of efficacy versus standard-of-care therapy, inhaled colistin has



**Fig. 1.** Development of Orphan Drug Designations (ODDs) granted by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) to pharmaceutical products for the treatment of Cystic Fibrosis in the period 2000–2021. Within each therapeutic class, ODDs have been displayed by date of granting in clockwise order. The correspondence between acronyms of ODDs and the relevant active substance is reported in the **supplementary material**. Abbreviations: BAs = Bile acids, CFLD = Cystic fibrosis-associated liver disease, DPI = dry powder inhalation, LTRAs = leukotriene receptor antagonists, PERT = Pancreatic enzyme replacement therapy, PEx = pulmonary exacerbations.





**Fig. 2.** Trend of Orphan Drug Designations granted by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to pharmaceutical products for the treatment of Cystic Fibrosis in the period 2000–2021.

not been FDA-approved. Further, tobramycin, approved through a simplified procedure by the EMA as hybrid tobramycin - i.e. similar to an authorized medicine containing the same API, but with differences in their strength, indication, or pharmaceutical form. - has not been approved in the US as the FDA requested data from clinical trials, which are still being conducted [23].

ODDs addressing inflammation, mucus clearance, and gastrointestinal consequences had a minimal impact in terms of regulatory approval: only mannitol out of the 22 (4.5%) ODDs for mucus clearance was approved in both the US and the EU at the time of the analysis (Fig. 1).

### 3.3. Rates and determinants of successful marketing approval

By excluding the ODDs still in development, we found that the overall ROA was 11.6% (10/86 ODDs); for ODDs granted by the FDA, the ROA was 8.8% (6/68), for those granted by the EMA 16.9% (10/59), while for ODDs commonly granted by both regulators the ROA was 14.6% (6/41).

Although 6 out of the overall 10 approved ODDs did not directly target CFTR function, those targeting CFTR showed a higher ROA: 21.1% (4/19) vs 9.0% (6/67).

Stratifying for product- and sponsor-related factors, we explored the association between determinants and approval for MA. Although no statistical significance was found across the different variables, the multivariate analysis confirmed a positive association for mechanism-based ODDs when compared with all the symptom-based ODDs, for ODDs containing active substances previously marketed, developed by large companies, and with experience in the development of orphan drugs (Table 2).

We found that 83.8% of ODDs entered the clinical phases, where the lowest phase-success rate was from phase 2 to phase 3 (38.2%). These trends were consistent across all the therapeutic groups investigated (Fig. 3).

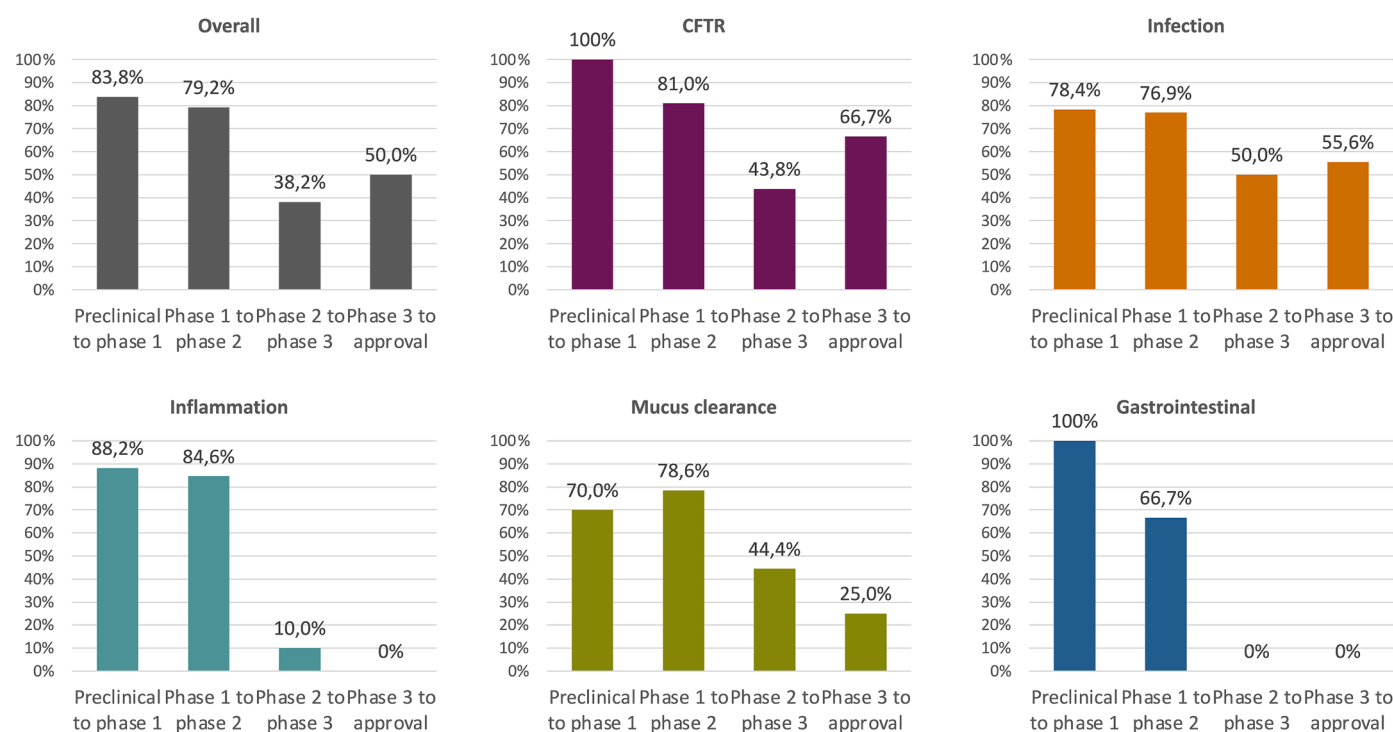
In depth evaluation of the reasons for discontinuations revealed that 44/76 (57.9%) ODDs were discontinued for a failure in the R&D process, while 32/76 (42.1%) were for sponsors' issues, a ratio consistent across all the therapeutic groups investigated.

**Table 2**

**Association between determinants and approval for marketing authorization of orphan drug designations (ODDs) for Cystic Fibrosis in the US and the EU in 2000–2021.** The multivariate analysis was adjusted for target, a substance previously marketed, sponsor size, and sponsor experience in the development of orphan drugs.

Variables	Total (N=86)	Approved (N=10)	%	Univariate OR (95% CI)	Multivariate OR (95% CI)
<b>Target</b>					
Symptoms-based	67	6	9.0	1	1
CFTR-based	19	4	21.1	2.7 (0.7–10.8)	5.6 (0.7–48.9)
<b>Route of Administration</b>					
Oral	25	4	16.0	1	
Other	61	6	9.8	0.6 (0.2–2.2)	NA
<b>Type of product</b>					
Chemical	67	10	14.9	1	
Other	19	0	0.0	NA	NA
<b>ODDs previously granted for other indications</b>					
No	57	8	14.0	1	
Yes	29	2	6.9	0.5 (0.1–2.3)	NA
<b>Active substances previously marketed</b>					
No	51	4	7.8	1	1
Yes	35	6	17.1	2.4 (0.6–9.4)	8.0 (0.9–68.7)
<b>Sponsor Size</b>					
SME	65	4	6.2	1	1
Large	21	6	28.6	6.1 (1.5–24.4)	3.2 (0.5–19.1)
<b>Sponsor's Experience in ODD development</b>					
No	53	3	5.7	1	1
Yes	33	7	21.2	4.5 (1.1–18.8)	2.6 (0.5–16.0)
<b>Regulator</b>					
FDA - EMA	41	7	17.1	1	
Only EMA	18	3	16.7	1.0 (0.2–4.3)	
Only FDA	27	0	0.0	NA	NA

Among the 44 ODDs discontinued for lack of efficacy and safety issues, 13 (29.5%) were sponsored by large companies while 31 (70.5%) were by SMEs. On the other hand, out of the 32 ODDs discontinued for sponsors' issues, 30 (93.7%) occurred for SMEs: 7 for financial issues, 7



**Fig. 3.** Success Rate from one phase to the next one (Phase Success Rate) of Orphan Drug Designations granted by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) to pharmaceutical products for the treatment of Cystic Fibrosis in the period 2000–2021.

for portfolio prioritization, and 16 were abandoned (no updates > 3 years); 2 (6.3%) from large companies were both discontinued for portfolio prioritization (see supplementary material).

#### 4. Discussion

In this study, we analyzed drug development for CF over the past two decades through the lens of orphan drug legislation in the US and Europe. Our analysis focused on 107 ODD therapies, describing factors that might have influenced the successful development of ODDs for CF by the FDA and EMA - which include the therapeutic targets addressed, the type of sponsor, and the regulatory ecosystem – as well as those accountable for R&D discontinuation. In line with other studies carried out in the area of rare diseases, we found that approximately 1/10 ODDs for CF reached the status of MA, with remarkable differences across the analyzed variables [18,24].

Despite the relatively high amount of ODDs granted for CF when compared with other rare diseases [25,26], no statistically significant associations were found between the selected variables and marketing approval, likely because of the limited overall number of studies. However, our results suggest some possible drivers in the drug development and approval of ODD for CF. For example, although initially, airway infections were a major therapeutic target of CF drug development, over the study period and as scientific advances enabled the development of therapies directed at the basic CF defect there was a shift of ODDs towards CFTR mechanism-based treatments, an approach that showed a higher rate of reaching MA when compared to all the symptom-based treatments. While there is a relative paucity of data in the literature regarding the contribution of ODDs to therapeutic success in other rare genetic diseases [18,27], a similar shift of the therapeutic paradigm from addressing purely symptoms to underlying mechanisms has had a meaningful clinical impact in other genetic disorders, with an increasing number of ODDs brought into the regulatory space over time [28,29].

##### 4.1. Inhaled antibiotics and symptom-based treatments

Inhaled antibiotics, most often developed as new formulations of previously marketed antibacterial substances that have been modified to deliver an effective concentration of the drug directly into the lungs in order to avoid systemic toxicity, represented in absolute terms the largest group of products that reached the clinic [30]. As soon as the antipseudomonal treatment paradigm expanded from the use of tobramycin towards strategies to reduce the risk of tobramycin resistance [30], new nanotechnology platforms have been embraced in CF to improve airway and mucus clearance [31].

However, we also observed a marked relative reduction of therapies targeting inflammation, mucus clearance, and gastrointestinal consequences of CF, a trend that is likely explained by the decreased interest of sponsors to develop symptom-based therapies for those on CFTR-based products that may obviate the need for symptom-based therapies in many pwCF, as well as the decreased population size of people in need of numerous medications for managing symptoms (e.g. pwCF who are ineligible for or do not tolerate CFTR modulators) [32]. Since the licensing of dornase alfa in 1993, i.e. the first regulatory approval for a drug specifically developed for CF, drug development has progressively become more challenging [33]. The multiple drug development failures in the CF therapeutic space are likely related to the lack of discovery of antibiotics with novel mechanisms for gram negative infections, testing of anti-inflammatories with insufficient versus over-suppression of the immune system, gastrointestinal-directed therapies that do not offer substantial benefit over approved therapies. We cannot exclude that repeated failures may also discourage additional companies to pursue development in this area with the concomitant flourishing of drugs targeting the CFTR protein.

##### 4.2. Small molecules, variant eligibility, and theratyping

The identification of the CFTR gene in 1989 represented the watershed in the R&D approach to CF, ultimately leading to the approval of the first CFTR modulator (ivacaftor) in 2012. Since then, three other

modulators have been approved as dual or triple combinations to target a wider range of CFTR variants. Following a decade of development, today approximately 80–90% of all pwCF could potentially be variant-eligible for CFTR modulators [34,35]. In contrast to other disease areas, in which peptides, proteins, or monoclonal antibodies have been developed through biotechnology platforms, for CF virtually all the innovations over the last two decades were small chemical-based molecules [32]. Unlike many other rare diseases in which even early phase clinical trials of orphan drugs are less feasible based on potential participant recruitment, –the CF community benefits from a well-established network of specialized centers that ensures clinical research infrastructure as well as patient access to diagnosis and relevant treatment [36].

#### 4.3. Nucleic acid therapy development

Following the identification of the CFTR gene, in the early 1990s, the first attempts to correct the genetic defect by gene therapy through adeno-associated viruses (AAVs) failed [37,38]. For CF, the design of a proper vector, the physiological barriers to transferring the gene into the lungs, and the rapid renewal of the airway epithelium, hampered the development of such approaches [39].

Based on patient need, our data not surprisingly also showed a rising interest in drug development for genotypes not addressed by currently approved CFTR modulators, i.e., variant-specific approaches such as ASOs, nonsense-mediated mRNA decay (NMD) inhibitors, and read-through agents. In recent years, new vectors for gene therapy delivery beyond AAVs have been explored to overcome the historically well-known efficacy barriers. Therefore, alternative approaches are progressing for pwCF who are not suitable for- or do not have access to CFTR modulators [40]. However, unlike with other monogenic disorders e.g. Sickle Cell Disease and Beta Thalassaemia - for which gene therapies have already reached the market - for CF all the potentially curative ODDs currently listed are still at an early stage of development [18,27].

#### 4.4. Regulatory decision-making and the ecosystem

Although the US and the EU orphan drug legislations have been widely acknowledged as powerful regulatory tools that have facilitated unprecedented success in pharmaceutical development history, we must acknowledge that they have different legal and socio-political obligations and viewpoints. These differences influence their perceptions regarding the weight of the evidence for both safety and efficacy. For example, CFTR modulators have been granted ODD by both the FDA and the EMA, there are differences in the way each agency approached the approval of CFTR modulators and the relevant impact on patients' eligibility for and access to treatments [41]. Importantly, in the US, the expansion of eligible genotypes for CFTR modulators was primarily based on *in vitro* efficacy, whereas in the EU data from clinical trials is required [41].

In addition to differential approaches to CFTR modulator approval, regulators handled the development and approval of inhaled antibiotics with contrasting perspectives. While in the US, ODD is granted on the basis of prevalence and disease characteristics, in the EU, sponsors for a new therapy are requested to provide evidence of significant benefit for patients over existing treatments. This expectation is particularly challenging in a disease area in which multiple options for similar signs or symptoms are approved. We noted that applications for such therapies were withdrawn by the sponsor before a negative opinion was rendered by the agency. Amendments to EMA's Guidance have been proposed, requiring sponsors to include a valid motivation for withdrawals, with speculation that in most cases withdrawals are based only on the predicted lack of adequate potential for marketing success [42]. However, this agreement was established with the view that there is value in fostering drug development in rare diseases. Therefore it would be

counterproductive to enact policies that would disincentivize potential sponsors. To the best of our knowledge, apart from pancreatic enzymes, all drugs developed for CF sought ODD at some time point in development. The wide adoption of this approach by sponsors in the rare disease space is expected given the benefits provided by the incentives, not to mention the indirect encouragements.

#### 4.5. Financial considerations

Consistent with other analyses on pharmaceutical R&D, our findings showed that the success rate of drugs evaluated in Phase 2 was far lower than those evaluated in any other phase [21]. In other words, although an agent may show safety in Phase 1, lack of safety or early signs of efficacy during Phase 2 evaluation precludes the agent from conclusive efficacy evaluation in a Phase 3 study. For pharmaceutical investors, it remains important that the sooner R&D discontinuation occurs in the setting of an agent without future potential, the smaller the financial loss [43]. We saw that this motivation was mainly relevant to the early stage of drug development, whereas clinical reasons, i.e. lack of efficacy and safety concerns, dictated discontinuation in the later phases.

With the advent of molecular medicine and orphan legislation, pharmaceutical companies have actively looked toward rare diseases as revenue drivers for their investments. In our analyses, we saw that SMEs accounted for the majority of ODDs, and were the primary originators of innovation. However, large companies, particularly those with previous successful experience in OD development, had the highest rate of final drug approval. Almost all the ODDs sponsored by SMEs were discontinued for sponsors' issues; despite apparently promising results, the majority of ODDs were abandoned by the sponsor based on decreased product interest, presumably by investors. This phenomenon is not exclusively seen in rare diseases but is a broader characteristic of the current landscape of pharmaceutical research, as bringing a product to approval requires experience in the regulatory framework as well as a strong organization and financial solidity to overcome the difficulties in the long journey from drug conceptualization to market approval [44]. At present, one large company owns the entire CFTR modulators market and, according to our data, it is expected to remain the market leader in the upcoming years because agents being developed by other sponsors are still in the early phase of evaluation. Whether this will drive or hamper access for pwCF to new beneficial products is relevant to future study. Based on our data, we saw that in some cases the availability of this highly effective approach has impacted the portfolio prioritization of some companies.

#### 4.6. Limitations

Through evaluation of the impact of ODDs in R&D trajectories, we acknowledge that we may be overestimating the success of this process as some molecules might have been discontinued before seeking ODD. On the other hand, the development of products with ODDs abandoned for financial issues can potentially be acquired and the process resumed by other drug developers, particularly after patents or other protections have expired. This information, not captured in our analyses, would have been useful to gain additional insights into the success rate of ODDs for CF.

Furthermore, our analysis did not assess at which stage of development the ODDs were granted the data upon which decisions were made, nor data for rejected or withdrawn applications as this information is not always accessible. Finally, there undoubtedly are other factors beyond ODD that contribute to successful drug development, including basic scientific progress, the high prices at which the market accepts new therapies, and the expected length of life-time use of a new therapy; such factors are beyond the scope of ODDs and were not included in the analysis.

## 5. Conclusion

Overcoming the biology of CF has been the key to developing effective treatments able to restore CFTR function and enable precision medicine in this rare disease [45]. Our findings illustrate CF as an intriguing drug development space in which both symptom-based and mechanism-based approaches in parallel have paved the way for new therapies.

However, successful drug development is a long journey for a candidate in a strictly regulated regulatory environment; its success requires the convergence of several factors: the biological rationale confirmed in the clinical setting, financial strength to overcome R&D hurdles, and an attractive regulatory ecosystem.

The scientific and clinical accomplishments gained in CF are not without concerns. Although many pwCF today are experiencing far better health outcomes than those at a similar disease stage a few decades ago, and certainly better than the majority of other individuals with rare life-limiting diseases, the substantial disparities in health outcomes for those eligible and ineligible or without access to new therapies have made it critical to create regulatory alignment on use of novel trial designs and endpoints to ensure the success of future drug development in CF [45]. Furthermore, the monopoly by one sponsor in a new therapeutic category, which represents an attractive incentive for developers, paradoxically introduces serious challenges in terms of affordability and disincentives for investors of other sponsors. Nonetheless, the future therapeutic horizon for pwCF as measured by current ODDs looks promising.

## Disclosure / competing of interest

**Enrico Costa** - Member of the Committee for Orphan Medicinal Products (COMP) at the EMA. The views expressed in this article are personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA.

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Hubert G. M. Leufkens - none

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jcf.2023.07.006](https://doi.org/10.1016/j.jcf.2023.07.006).

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