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# Developing new products in cystic fibrosis: Needs and obstacles for activities of small and middle-sized companies

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**Abstract**

Small and middle-sized enterprises (SMEs) can make important contributions to medical progress through the development of new safe and effective drugs that address the greatest unmet needs of patients. Regulatory inconsistencies across agencies in various countries, however, remain major challenges in cystic fibrosis (CF) drug development. Clear and consistent treatment guidelines, well educated clinical trial sites, a patient registry and grant funding for early development programs are important success-factors for an efficient development process.

SMEs developing products for CF need partners in the CF community to assist with disease education and awareness for ongoing clinical trials. SMEs should collaborate and communicate with the CF community in a legally compliant way to take a patient-centric approach to drug design, development and administration. Furthermore, they can help to develop educational tools and fund medical education activities to increase the understanding of the underlying defects and mechanisms of CF disease.


*Keywords:* Cystic fibrosis; SME, New product development; Drug development

## 1. Introduction

Cystic fibrosis (CF) is a rare disease that attracts only a limited number of companies to develop and market specifically designed products for diagnosis and treatment. Most of them are either small or middle-sized with little or no experience in the area of CF. For these companies, it is hard to find partners to co-operate with in academia and patient-organisations. In addition, they often have products under development that will be complementary to other products either marketed or under development. Academia in turn needs to co-operate with companies willing and able to take scientific findings to the market. It was the idea of EuroCareCF's workpackage 4 (WP-4) to provide a forum for these different stakeholders. WP-4 has managed to convene a group of small and middle-sized enterprises (SMEs) from both Europe and the US with a strong interest in drug development for CF. While most of the companies strictly met the definition applied by the EC for SMEs (for details, see Table 1), the workpackage decided at the beginning of its activities, to allow also companies to join the group that met the criteria within the past five years, but which had grown beyond the boundaries of the definition in the meantime. For the majority of companies included, CF was a major therapeutic area of interest with specific products under development. Development stages included clinical phases I to III. In the following we summarize what this group identified as needs and obstacles for SME activities in developing CF drugs.

Table 1
EU-definition of small- and middle-sized enterprises*

| Enterprise category | Headcount | Turnover | Balance sheet total |
|---|---|---|---|
| Medium-sized | <250 | ≤€ 50 million | ≤€ 43 million |
| Small | <50 | ≤€ 10 million | ≤€ 10 million |
| Micro | <10 | ≤€ 2 million | ≤€ 2 million |

* Recommendation 2003/361/EC.

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## 2. Methods

The bulk of information from participants was provided during four workshops held in Frankfurt, Germany and Anaheim, California, USA in 2007, in Prague, Czech Republic in 2008 and in Bad Nauheim, Germany in 2009. In addition, phone conferences were regularly held between participants of the group. To avoid any promotional flavour, the group decided not to disclose company names. The group addressed the needs of SMEs developing products for CF, identified areas of action for regulators and the CF community (not-for-profit research centers, clinical centers and patient-organizations) and discussed ways to drive further collaboration between industry, regulators and the CF-community.

The opinion of the group was developed along the following questions:

- What are the needs of companies developing products in the field of CF?
- What are the most critical issues that prevent more efficient development?
- How can the CF-community help tackle these critical issues?
- What do companies expect from governments dealing with these issues?
- What can companies do to make improvements in specific areas?

These questions were addressed in four sections covering pre-clinical development, clinical development, medical communication and business context.

## 3. Results:

### *3.1. Pre-clinical development*

#### *3.1.1. What are the needs of companies developing products in the field of CF?*

To define the most relevant topics for development in CF therapy, strong communication between SMEs and the CF-community, both physicians and patients, is needed at the international level. In doing so, not only yet unmet medical needs have to be discussed, but also areas of improvement over and above current therapy need to be identified and prioritized. In addition, medical needs emerging from the increased life-expectancy such as osteoporosis and CF-associated diabetes mellitus, but also secondary needs caused by side-effects of traditional CF-therapy should be anticipated by exchange of knowledge between academia, medical doctors, patients and SMEs.

First, companies identified a need to define which cell models are suitable for preclinical evaluation of different aspects of CF treatment. If the best *in vitro* models are primary cell cultures from human bronchi, such cells should be available in a bank of frozen human or nasal bronchial epithelial cells with multiple different CFTR genotypes. This cell bank would need to be established within the framework of applicable privacy regulations. A bio bank combining biomaterial with detailed, but anonymized patient characteristics should ideally be operated by the European Cystic Fibrosis Society (ECFS) and/or a consortium of national CF-organisations. Workpackage 7 of EuroCareCF made important progress towards developing a repository of primary cultures of human airway epithelial cells from control individuals as well as from CF-patients. While further work will be necessary to accomplish a bio-bank as described, this outcome of the EuroCareCF project is considered a significant step forward.

Furthermore, to afford target-based drug discovery strategies companies need clarification and prioritization of the molecular targets in the CFTR processing, trafficking and degradation pathways. Improved pharmacology models of CF pulmonary and non-pulmonary disease and *in vivo* models that replicate human lung physiology and key CF lung disease phenotypes are needed. Models designed to express the human form of CFTR would be preferred. Large animals requiring the costly and bothersome synthesis of large quantities of compound should ideally be avoided whenever possible.

#### *3.1.2. What are the most critical issues that prevent more efficient development?*

CF research could be accelerated with the availability of and standardization of culture conditions for human bronchial and/or nasal epithelia. This would allow for the profiling and prioritization of compounds and subsequent medicinal chemistry programs.

#### *3.1.3. How can the CF-community help tackle these critical issues?*

A discussion between CF-community experts and regulators on which cell models are suitable is needed. Workpackage 6 of EuroCareCF has established consensus guidelines on the application of mouse models [1] helping to improve their use during pre-clinical development. In addition, the ECFS could make a list of such models including information about how to access them available on a website. The CF community can help by organizing focused discussions between companies, clinical experts and research organizations to help identify common issues and solutions to these topics.

New animal models have been developed including CFTR knockout pigs and ferrets [2–4]. The developers of these models should contact the European Medicines Agencies (EMA) to discuss which animal models are suitable for translation research. Any research helping to make more suitable animal models available to the CF-community is very much welcome. The CF-community can also contribute by helping to develop a biomarker program that includes biomarker identification, assessment and validation.

#### *3.1.4. What do companies expect from governments dealing with these issues?*

First of all companies need clear and consistent guidance on the drug development process based on a thorough understanding of the disease and awareness of needs.

Companies would be aided by easier access to funding to support research activities in rare diseases like CF. Clearly,

there is a need for public funding to support research in all fields of CF. Grant funding for promising new ideas would help to bring new treatment to patients. Coordinated development programs should be funded.

Governments could also help to facilitate access to reagents or assays by providing a fee-for-service type arrangement or by minimizing restrictions based on intellectual property. Research grants to fund these activities should be available.

Companies expect greater transparency on how submission decisions are made. Some toxicological evaluations may not be relevant to some compounds in development. Moreover, they can be exceptionally burdensome for drug development in areas with very small patient populations (e.g. CF) when compared to diseases with large patient populations (e.g. asthma); nonetheless, the regulatory requirements between these therapeutic areas are common. It is appreciated, however, that patients' safety must not be compromised by omitting critical toxicological studies.

#### *3.1.5. What can companies do to make improvements in specific areas?*

Companies can develop their own *in vitro* models and can assess potential interesting pharmacodynamic markers in CF studies. The results of studies using these markers can then be submitted to regulatory agencies for adoption. Regular communication of progress and issues surrounding drug development plans within the constraints of what is legally and competitively feasible between companies and regulatory agencies might help to improve the situation.

### *3.2. Clinical development*

#### *3.2.1. What are the needs of companies developing products in the field of CF?*

Companies need a complete understanding of the regulatory environment and consistency in that environment for obtaining approval for novel therapeutics. In particular, SMEs require consistent guidance from regulatory agencies in the EU and the US. They need clarity on the expectations of regulatory agencies for the conduct of clinical studies in small patient populations. High levels of statistical significance are often not necessarily achievable due to small study size. It would be valuable for companies to know clearly which data are required and which are "nice to know".

A more efficient way for companies to accomplish small Phase I studies in CF patients to support formulation development and understand pharmacokinetics would be beneficial. The pharmacokinetic equivalence of inhaled drug products is very relevant to the development of new formulations. The scientific community together with regulators should define clear pathways to demonstrate and agree on the equivalence between inhalation devices.

For Phase II studies, it is essential to standardize (and implement across study sites) outcome measurement parameters (e.g. sweat chloride concentration, nasal potential difference (NPD) and intestinal current measurements). Standardized diagnostic procedures have to be operational at all clinical study sites that wish to participate in phase I and II clinical trials. Methods for studies, for example deposition studies, have to be standardized.

Acceptable endpoints should be agreed by all parties. It is generally accepted that the pulmonary endpoint $FEV_1$ is suboptimal. However, better alternatives remain to be proven. In addition, although there is CF-specific guidance from the EU, there is still a lack of clarity in understanding which ex-pulmonary endpoints can be measured and how this can be achieved. The transatlantic standardization of methodology is very much encouraged to facilitate parallel trial programs in both Europe and the USA.

SMEs require better access to the CF patient population. Improved epidemiological data are required for this purpose. Moreover, the recruitment of CF patients for clinical trials needs to be improved because in rare diseases, such as CF, the eligibly patient population is very limited. This is a bottleneck for the development of truly innovative therapeutic options. Patient registries exist in several European countries, but these registries vary widely in terms of quality and completeness. Comparison of aggregated data between registries is hampered by the different data structure and in particular by a diversity of definitions applied. Because of this, it is difficult to evaluate the patient population characteristics and medical needs. The group therefore very much welcomes the efforts of EuroCareCF Workpackage 2 and the ECFS Registry Working Group to develop a European CF Patient Registry, which collects high quality data from the national CF-registries and aggregates them. This new approach towards a really useful European CF patient registry is a major outcome of the EuroCareCF project.

A growing problem for Phase II/III studies is seen in the limited number of patients available within the study population who can be enrolled in clinical studies. Concurrent trials might force delays in other studies until those subjects again become available. To tackle a clinical study in an efficient manner, companies need to have access to CF subjects at experienced sites. Healthcare provider-mediated access to patients who satisfy the eligibility criteria of a given trial is a key success factor for the efficient development of new therapeutic options. A legally compliant centralized database of the CF patients treated at different clinics would help to identify potential patients in an efficient way. However, there is full consensus that companies must not be given access to individual non-anonymous patient data. In addition, it would be helpful to set up a referral program whereby CF patients from clinics not participating in clinical trials might be eligible for recruitment by clinics conducting clinical trials.

In Phase III studies regulators and companies should be innovative about how to deal with the small number of patients available for studies.

#### *3.2.2. What are the most critical issues that prevent more efficient development?*

Just recently, the EMA published a new version of the guidelines for the development of new therapies for CF

[5]. Those guidelines were subject to critical comment from both academia and industry and should be further developed in collaboration with patient organizations, investigators and industry to make them realistic and achievable. A harmonized approach between the EU (EMA) and the USA (FDA) is mandatory to avoid conflicting regulatory requirements.

The timing of feedback on the Pediatric Investigation Plan (PIP) from the EMA Pediatric Committee in relation to Scientific Advice from EMA and/or EU national agencies would also benefit from better coordination.

Considering the increased risks of drug development for rare diseases such as CF, there is often a lack of funding for creative approaches to research and development that might help to accelerate proof of concept studies for drug candidates. For example, by using parallel development strategies rather than the sequential approach of traditional drug development strategies.

SMEs also need to have access to CF subjects at experienced clinical sites capable of investigating a battery of specialized CF pharmacodynamic markers typically required for Phase I studies. Companies need access to patients who are motivated, available and qualified to participate in a clinical study. The operational efficiency of study-sites is also variable and can present a challenge to development. Information about who performs CF research, which centers have patients with specific CFTR genotype and details of the facilities, systems and processes at individual study sites is valuable, but difficult to obtain. For new therapies, universal genotyping for patient selection is necessary. Furthermore, the cost of conducting clinical studies in CF is extremely high because often many study centers have to be involved, each enrolling only a few subjects.

Diagnostic and treatment guidelines should be harmonized between countries to facilitate the design of internationally applied clinical trial protocols. For example, a control group receiving "standard care" is hard to define if no consensus exists about what the standards of care actually are. High quality diagnostic information, e.g. sweat-test values and genotyping, is indispensable for the development of new disease-modifying therapies. The group stresses that the genotyping of patients should be as complete as possible.

Change in $FEV_1$ is still used as the "gold-standard" primary clinical endpoint for lung function in CF clinical trials. However, there is broad consensus in the CF medical community that this endpoint is far from optimal. Hence, other clinical endpoints need to be developed and validated. This includes other lung function parameters such as Lung Clearance Index (LCI) as well as patient reported outcomes.

Larger observational studies helping to understand the quality of life and health-economic impact of CF and CF treatment for patients and payers should be initiated. This includes aspects such as resource-use of the healthcare system, absenteeism and the adherence to therapy.

#### *3.2.3. How can the CF-community help tackle these critical issues?*

The CF community can help to facilitate consistent guidance documents from global regulatory agencies. CF community experts should be regularly involved when the EMA handles CF applications. This includes the involvement of patient experts providing a unique view from a patient's perspective. Furthermore, the CF community can encourage the implementation of alternative, shorter-term endpoints for initial registration, while assessing long-term outcomes through post-approval commitments. The global CF community can advocate for the facilitation of the regulatory review processes, i.e. producing consolidated comments.

The CF community should also facilitate the education of physicians in the regulatory process and the relevant regulatory guidelines. If physicians better understand the regulatory process they will be able to contribute to the regulatory agencies as expert consultants in a beneficial way. The CF community can help to organize focus discussions between companies, clinical experts and research organizations aimed at helping to identify common issues and solutions to the challenges outlined above.

A worldwide database of CF clinics and research centers and a patient registry (including information about number of patients, genotypes, etc.) would help to facilitate identification and recruitment for clinical trials. It would therefore be very helpful if the patient registries of the CF Foundation and the ECFS used common definitions. Ultimately, a global registry of CF patients should be developed.

The CF community should also help to define protocols acceptable to patients and regulators thereby enhancing the feasibility of a clinical trial. The clinical trial networks in US and Europe should operate with consistent processes and have a central communication process to ensure messages are distributed to all centers.

Patient organizations should encourage patients to consider discussing participation in clinical trials with their physicians who can help to rapidly identify patients for clinical trials and provide information about clinical trials to patients. This would potentially accelerate the time-consuming and challenging task of recruitment. When recommending trials to patients, patient organizations need to select carefully those trials that are most promising in providing added value to the patient community. Challenges facing drug development can best be addressed by close and legally compliant collaboration across patient groups, healthcare providers and industry.

Patient organizations can also convey patient needs by providing input into development and implementation of international treatment guidelines.

#### *3.2.4. What do companies expect from governments dealing with these issues?*

Consistent feedback from regulatory bodies at local, national, regional and international levels would help to improve the efficiency of their development programs. This includes consistent guidance and review and timely approval of clinical trial applications for a given clinical study.

Unnecessary studies in developing novel therapies for an orphan disease should be avoided. Government agencies should be receptive to discussions about the challenges of studying pharmacodynamics in CF and creative ways to meet those challenges. It is of utmost importance in particular for SMEs to have full insight into the registration pathway for new drugs, to have an open dialogue between companies and regulators to address issues and concerns and the timely review of submitted questions and submission packages. A global review of documents by the CF community and government regulatory bodies (in particular EMA and FDA), with consolidated comments and a single timeline or unified review times would be ideal. Government agencies can provide advice on development programs and try to establish similar expectations about outcomes across countries.

#### *3.2.5. What can companies do to make improvements in specific areas?*

Companies should foster open communication with regulatory agencies to find mutually agreeable ways of developing CF drugs. They should have dialogue with all stakeholders including patients and physicians to achieve agreement for reasonable guidelines. Frequent communication between companies and regulatory agencies could facilitate understanding by agencies of the challenges faced by SMEs engaged in CF drug development and help to identify solutions to overcome these challenges.

Companies could support improved standardization of assessment tools, such as ambulatory lung-function monitoring, to support clinical trials. They can be more involved in discussions around the specific needs to facilitate drug development in CF.

### *3.3. Medical communication*

#### *3.3.1. What are the needs of companies developing products in the field of CF?*

Three target audiences for medical communication should be differentiated. Firstly the education of the general public through channels appropriate for the applicable legal framework. Informational about CF that is available for free would help to inform more people about CF. Importantly, such material should be non-promotional in nature and medically sound. Companies require balanced and objective advice when producing this kind of information. There was complete consensus, that any promotional material, whether specifically labeled as advertising or just as "information" should not be disseminated to patients.

The second audience is the CF medical community. For example a common definition and understanding of technical terms would facilitate drug development for CF. Better understanding of the natural history of CF, disease burden and outcomes would also be helpful. An understanding of the molecular basis of CF is required to understand new therapies.

Thirdly, companies developing and marketing products for CF would benefit from a better understanding of the healthcare systems in Europe. Sometimes uncertainty about the reimbursement policies in different countries prevents companies from entering the CF market. Reliable and up-to-date information as well as a regular exchange between companies about their experiences can help illuminate this issue.

#### *3.3.2. What are the most critical issues that prevent more efficient development?*

Improved documentation on the burden of illness and unmet medical need would help foster interest and funding for drug development in CF. A better understanding of the disease burden and outcomes in CF could also help regulators to gain deeper insight into the needs of CF patients.

#### *3.3.3. How can the CF-community help tackle these critical issues?*

CF clinics and patient organizations are best placed to recognize the educational needs of the CF community and the best avenues to address those educational needs. Close collaboration between the CF community and industry can optimize education by efforts to develop needs-appropriate educational tools and programs. However, transparency about the interrelationship between companies, patient organizations and healthcare providers is mandatory to allow the public a fair and balanced assessment of information provided through different channels.

#### *3.3.4. What do companies expect from governments dealing with these issues?*

Clear and consistent guidelines on the appropriate use and dissemination of educational tools and programs would make medical communication much easier among different countries and agencies. The group did not reach consensus about the current debate at the EU-level about whether or not to broaden the opportunities for companies to provide information on prescription-only drugs direct to patients.

#### *3.3.5. What can companies do to make improvements in specific areas?*

Industry can closely and compliantly collaborate with the CF community to ensure a diverse perspective on the assessment of educational needs and the development and dissemination of appropriate educational tools and programs. A policy of transparency and objectiveness is best applied by the involvement of all stakeholders, including healthcare providers, payers (public and private insurance), patient-organisations and regulators to the maximum extent possible.

### *3.4. Business context*

#### *3.4.1. What are the needs of companies developing products in the field of CF?*

One of the challenges facing companies in this field is to achieve the expected return on investment with a small patient population and fixed development costs. Clear guidance from regulatory authorities so as to avoid unnecessary studies

would help to accomplish development programs as efficiently as possible.

Another financial challenge due to the small patient population is the lack of economy of scale in clinical studies. Some of the startup costs for a clinical site are the same whether it enrolls 1 or 10 patients.

SMEs need a more transparent overview about regional or European sources of finance and conditions for obtaining public funding. SMEs would very much benefit from a harmonized funding policy of CF-non-profit-organizations across Europe as well as better insight into national and EU public funding programs.

Developing new medicinal products puts at risk significant amounts of money. A commitment from payers/government to reimburse the product once registered is therefore necessary. Differences in reimbursement policies across countries and sometimes even within a single country represent a major issue. Companies need to have their approved products listed on national reimbursement schemes in a timely fashion.

*3.4.2. What are the most critical issues that prevent more efficient development?*

If a company is unable to attain national reimbursement status, broad reimbursement of the cost of its products is unlikely until such agreement can be reached with national authorities. Otherwise patients may gain access to orphan products by public budget, private insurance, out of pocket funding, but none of these alternatives are optimal for the majority of eligible patients to gain access to much needed orphan drug products.

*3.4.3. How can the CF-community help tackle these critical issues?*

The community can also continue to have an open dialogue to identify issues and help clinical sites and companies to work together efficiently. It can also help to address some of these issues by supporting the creation of patient registries in each country. A database of clinical sites would also accelerate drug development.

The CF-community should continue to educate regulatory authorities on key aspects of CF. This will be important as regulatory authorities work with companies to develop and evaluate new CF drugs.

A better agreement on acceptable endpoints would help to manage CF drug development in an efficient way.

As a matter of fact, reimbursement policies vary widely across Europe. The CF-community should advocate ensuring that patients have easy access to state-of-the-art therapeutic options independent of their income and social status. The way to achieve this may differ from one country to another.

*3.4.4. What do companies expect from governments dealing with these issues?*

Companies expect governments to support the development of innovative CF drugs by helping to ensure that they have the appropriate financial incentives to discover and develop drugs. Companies also expect regulatory authorities to be well informed about CF and willing to work with companies in planning and executing a development plan in the most efficient way. They expect clear, fair and consistent regulation of reimbursement and ideally national reimbursement list status. They recognize however, that no pan-European policy about drug reimbursement is likely to be available in the near future.

*3.4.5. What can companies do to make improvements in specific areas?*

Companies should focus on developing drugs that have the best chance of providing substantial benefit to patients. They should design efficient clinical studies that take into account the limitations of the population and capabilities at the clinical sites. Ideally, companies will work proactively with clinical sites, patient groups, investigators, regulators and researchers from an early point of development onwards. This will eventually help to design development programs that are both meaningful and feasible for the CF community. Companies can work to develop novel therapeutic products with clear value. In countries with negotiation procedures, companies can accelerate inclusion into public reimbursement schemes by accepting the limits of pricing affordable for specific healthcare systems.

## 4. Conclusions

In conclusion, the following key areas of action have been identified:

Areas of action for the scientific community:
- Establish bio banks
- Prioritize molecular targets
- Transparency about the value and the availability of better cell culture and animal models
- Evaluate bio-markers
- Standardize outcome parameters
- Develop alternatives to $FEV_1$ as the primary pulmonary endpoint in clinical trials
- Establish (where not already available) and maintain reliable and comprehensive patient-registries
- Provide a worldwide database of CF care centers

Areas of action for the patient community:
- Contribute to acceptance in the patient community and support the performance of patient registries
- Encourage patients to become subjects in state-of-the-art clinical trials that are of significant therapeutic and/or scientific value
- Contribute to the design of clinical trial protocols early on to ensure acceptance within the patient community
- Help companies to better understand the reimbursement and healthcare policies of different countries in Europe
- Improve the documentation of the burden of illness and yet unmet medical needs
- Communicate this burden and needs appropriately to governments and regulatory bodies

Areas of action for governments and regulators:

- Clear and consistent guidance on pre-clinical and clinical prerequisites for marketing authorization
- Easier access to funding of development activities including on-time information about upcoming public funding opportunities
- Reasonable application of toxicological testing requirements
- Harmonization of regulatory requirements in the US and Europe
- Involve CF-patients and CF-experts when discussing a CF-related drug application
- Foster an open dialogue between all stakeholders including industry when revisiting treatment guidelines
- Reliable and consistent messages to SMEs during the entire application process
- Include orphan drugs indicated for CF quickly, reliably with reasonable conditions on national reimbursement programs/lists
- Provide access to state-of-the art treatment (not limited to pharmacotherapy) to all CF-patients independent of their social status or income

Areas of action for SMEs:

- Contribute to the development of cell and animal models for CF
- Involve all relevant stakeholders early on when making decisions on future development of projects and clinical trial protocols
- Apply a policy of transparency when communicating with physicians, patients and public bodies.

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## Conflict of interest

The authors state that there is no conflict of interest.

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