

# Medical needs of cystic fibrosis patients and policies for fair co-operation between small and middle-sized companies and patient organizations

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## Abstract

*Background and methods:* Workpackage 4 of EuroCareCF brought together a group of small and middle-size companies (SMEs) with strong interest in drug development for cystic fibrosis (CF). The common interest of SMEs and patient organizations (PO) in mutually beneficial cooperation was assessed. This was achieved by identifying critical unmet medical needs of CF patients and by analyzing fields of cooperation between SMEs and POs.

*Results:* Over and above all, finding a cure for the disease is considered the most important unmet medical need by POs. However, preventing or slowing down any further deterioration of health and the alleviation of symptoms are also considered valuable objectives. Areas of co-operation with SMEs include the preparation and conduct of clinical trials and co-operation in the post-marketing authorization period.

*Conclusions:* If a policy of transparency and respect for the independence of POs is applied, SMEs and POs can develop mutually beneficial and sustainable co-operation.

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*Keywords:* Cystic fibrosis; SME; Patient organizations; Transparency; Drug development; Drug marketing

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## 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 co-operation partners in academia and patient-organizations. It was the idea of workpackage 4 (WP-4) of the EuroCareCF project to provide a forum for these different stakeholders. WP-4 managed to convene a group of small and middle-size enterprises (SMEs) from both Europe and the US with a strong interest in drug development for CF. For the majority of companies involved, CF was a major therapeutic area of interest with specific products under development. Development stages included clinical trial phases I to III.

Patient organizations (POs) traditionally play a strong role in fostering research and therapy development in CF. Strong national organizations such as the Cystic Fibrosis Foundation (CFF) in the USA, the Canadian Cystic Fibrosis Foundation (Canada), the Cystic Fibrosis Trust (UK), Vaincre La Mucoviscidose (France) and Mukoviszidose e.V. (Germany) are the core of a world-wide community to which not only patients and their relatives, but also physicians, healthcare professionals and researchers belong. In the meantime, CF POs have been established in almost all European countries.

The co-operation of POs and the healthcare related industry in general is a highly controversial subject due to various instances where companies tried to influence the opinion and policies of POs to support marketing activities. Today, it is generally accepted that lack of transparency and behaviour close to corruption is a major threat to the credibility of both POs and industry and is not acceptable at all. However, in particular in a rare disease, both POs and companies can mutually benefit from exchanging views and experiences. Therapy for CF has benefited critically from the input of POs into developing companies, most of them fitting into the definition of SMEs.

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## 2. Methods

This report summarizes the results of a workshop held in Bad Nauheim, Germany, 20–21 April 2009, which convened representatives of SMEs participating in WP-4 of EuroCareCF and delegates from European CF POs. The discussions at this workshop focused on the needs and obstacles for SME activities in developing drugs for CF patients.

## 3. Results

### 3.1. Patient organizations in Europe

CF POs have been established in various European countries during the past four decades. However, big differences exist between well established POs (e.g. Vaincre La Mukoviscidose (France), the UK CF Trust and the German Mukoviszidose e.V.), which have been in existence for more than 40 years and relatively young POs such as those in most countries of Eastern Europe. All these POs share the common objective to improve and prolong the life expectancy of CF patients by fighting for access to state-of-the art care and by promoting research to conquer CF. Nevertheless, the means to achieve these objectives are dissimilar between different CF POs because their financial resources vary widely. Annual income per organization ranges from less than €1,000 up to €20 million. Hence, only a few CF POs have full-time staff providing professional services. Most CF POs must rely solely on the commitment of volunteers. Also membership structure is different. While some POs focus only on CF-patients and their relatives, most are open to membership by CF team members, i.e. physicians and allied healthcare professionals. Finally, the role of the national organization when compared to that of regional and local organizations differs across Europe. Again, national traditions (e.g. centralism in France and regionalism in Italy) influence strongly the culture of different CF POs.

These different cultures also shape the strategic focus of POs, including research promotion, lobbying, public-relations and social services. Professional fundraising, an important supporting function, is available in only a few organizations.

Because of the increasing importance of European legislation and to strengthen interactions between European CF POs, Cystic Fibrosis Europe e.V. (CFE) was established in 2003. CFE now has a membership of 34 European CF POs (Albania, Armenia, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Georgia, Greece, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, FYR Macedonia, Netherlands, Norway, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland and Ukraine). CFE is a part of CF worldwide (CF-WW), the global umbrella organization for CF POs. The objectives of CFE are to improve the quality of life and longevity of CF patients and support their families, to represent CF patients and defend their interests, to raise awareness and understanding about CF, to promote optimal diagnosis and treatment and to provide a forum for discussion and exchange.

As *pars pro toto* some national CF POs with diverse national, historical and organizational background introduced their work. The Belgian CF association (Association Belge de Lutte Contre La Mucoviscidose (ABLM)) was established in 1966. Today, it represents 1,100 CF patients and their relatives. ABLM's activities include social work, patient education and research funding.

The French CF association Vaincre la Mucoviscidose (VLM) takes care of CF patients and their families. VLM was established in 1965 by parents of children with CF. The Association annually funds up to 80 research projects and organizes regular young investigator meetings for French and European CF researchers. It funds more than 90 medical positions in 49 specialized CF centres. VLM offers continuous help to CF patients and their families by being attentive to their needs and difficulties. Traditionally, strong co-operation exists between VLM and the German association, Mukoviszidose e.V.

Mukoviszidose e.V. was also established in 1965. The Association brings together adult patients, relatives and medical professionals. Its main activities are the funding of research projects, the support of patients and their families by supporting regional groups as well as the provision of psychosocial and legal advice to individuals. Furthermore, it supports therapy by organizing and financing a comprehensive quality management system and arranges actions to increase public awareness.

The German CF Institute (Mukoviszidose Institute, MI) is a non-profit organization, 100% subsidiary of the German Cystic Fibrosis Association. MI supports the CF Clinical Trial Network (CF-CTN) in Germany. The MI is a sponsor according to German Drug Law and provides operative and specialist support with planning, implementation and evaluation of clinical trials (phases I–IV).

Founded in 2008, the Romanian CF Association has 30 members (parents and patients) and a small annual budget of €2,500. In Romania, 300 CF patients are treated in 7 CF centers. The main activities of the Association are lobbying and patient advocacy (e.g. drug reimbursement for basic therapy), educating parents and physicians (meetings, conferences, workshops) and raising awareness of CF through campaigning (e.g. media and a website).

### 3.2. Unmet medical needs

Representatives of POs stated clearly that for CF patients and their families the main unmet medical need is to *cure the disease*. Therapeutic strategies currently under development (e.g. small molecule CFTR correctors, CFTR potentiators and activators of alternative channels) raise the possibility that disease symptoms will be attenuated markedly or even abolished. CF should no longer have a severe impact on the lives of individuals. This was put in the short message “dying with, but not of CF”.

As long as this overall objective is not achievable, the *alleviation of symptoms and the slowing of disease progression* was identified as a second need. The prevention and treatment

of lung disease is critical for the quality of life of CF patients. This includes prevention and effective treatment of first infection, acute infection, chronic infection and the eradication of multi-resistant bacteria. Any breakthroughs in the field of vaccines, agents preventing biofilm formation, antibodies, anti-inflammation drugs and new antibiotics are of great interest to CF patients of all ages. In particular, parents of young children and patients without chronic infection seek vaccines against *Pseudomonas aeruginosa* because the initial and/or chronic infection has a major impact on the quality of life.

The prevention and treatment of gastro-intestinal problems is a medical need that has until now not always been sufficiently well addressed. Representatives of POs expressed their disappointment that they face a lack of interest by researchers in the gastrointestinal manifestations of CF. This contrasts markedly with the experience of most CF patients who experience a range of gastrointestinal problems (e.g. recurrent abdominal pain, reflux and liver disease). Even with pancreatic enzymes, there are frequent problems with the digestion and absorption of food, including malnutrition, diarrhoea and constipation. Most CF patients must take high doses of enzymes, which decreases their quality of life. More effective and compact enzymes requiring lower daily doses would be very welcome.

CF-associated liver disease may not cause symptoms for the majority of patients. However, there is as yet no real effective treatment available for this condition. European Reference centers for CF-associated liver disease are an important medical need.

Patient representatives stressed the importance of user friendly drugs and devices. Therapy should require little time, be painless and not intrusive. Ranked-preference for drug-delivery devices for CF patients is oral use, puffs, nebulizers and intravenous applications. For oral use, any substance is preferred that can be easily swallowed. For young children, syrup is probably the easiest method of application because of their inability to swallow. Older children prefer tablets with good taste and smell being of added value.

In more general terms, not necessarily related to medicinal products exclusively, POs stressed the need for specialized care for adult CF patients. The increasing number of patients over 18 mandate a change in care structures that are until now predominantly organized in pediatric out-patient clinics and hospitals.

It was generally agreed that there is a need to follow up EU and US orphan drug designations for CF to ensure that no opportunity is missed simply because the sponsor is no longer in the position to foster drug development until marketing authorization.

The CF POs also highlighted the fact that in several Central and Eastern European countries access to care is limited. Often drugs and devices are not available in their country at all or only affordable by a few families. This is because many drugs are either not registered in their region or are not reimbursed by the general health-care system.

### 3.3. Co-operation between POs and SMEs

Mutual co-operation between POs and SMEs might comprise both the pre- and post marketing authorization period.

#### 3.3.1. Involvement of PO in planning phase of clinical studies

POs can help SMEs design clinical trials to maximize their acceptance by families and patients which in turn is a prerequisite for rapid and successful patient recruitment. While POs fully acknowledge the need of companies to comply with regulatory stipulations, they emphasized strongly that it is unacceptable for the design of clinical trials to impact severely on patient routine and lifestyle.

Representatives of POs may be requested by regulatory agencies to participate in protocol review meetings prior to the start of a study in a specific country and as part of the drug development program. The identification of qualified CF patients capable of participating in these meetings is the task of the PO. CF patients should comment on feasibility of study protocols from the patient's perspective.

Patient registries are instrumental to identify patients with specific mutations or other eligibility criteria for clinical trials. Steering and organizing patient registries has become an increasingly important task for POs. They need to provide proper information to patients before patients consent to participate in patient registries. Moreover, POs need to guarantee to protect patient privacy. By setting up and maintaining a patient registry, POs and the CF scientific community provide valuable tools to companies developing CF products. SMEs are best advised to make use of these anonymised data early on when planning clinical trials. POs are prepared to share information from the registries with industry provided the legal framework is properly defined in the best interest of patients.

#### 3.3.2. Co-operation during the conduct of clinical trials

The motivation of CF patients to participate in clinical trials is uncertain. To overcome their hesitancy and to motivate CF patients to participate in clinical trials, POs may offer general information in local language about clinical studies and information about upcoming specific clinical trials. General information about studies may be developed by CFE and provided to all POs for further translation. It is up to the sponsor of the trial to provide study related information such as a study synopsis or additional material relevant for patients. The main task of POs is to review, to sort out and to rank information in order not to bias patients. Guidelines on how to score such information are required. POs should consider encouraging patients to participate in a specific trial only, if the PO considers after thorough review of the trial documents that the objectives and the design of the clinical trial will help to address yet unmet medical needs and the potential benefits outweigh the risks. However, it is not in the interest of patients if a clinical trial with high potential scientific and medical value fails because of poor recruitment. POs must therefore be mindful of their responsibility to patients when making recommendations about patient participation in a given clinical

protocol. Promoting participation in clinical trials must never be associated with or even driven by financial contributions offered by industry to POs.

POs should be involved early on in the preparation of communications about the results of clinical trials. POs expect reliable data on the trial outcome to be posted on an acknowledged clinical trial database (e.g. [www.clinicaltrials.gov](http://www.clinicaltrials.gov)) within one year of the last patient leaving the clinical trial. Full peer-reviewed publications should be available as soon as possible. POs consider withholding trial results from patients and the general public an unacceptable policy. Communication of results is critical to respect the involvement of patients in a trial and to motivate them to participate in forthcoming trials.

### 3.3.3. Co-operation in the post marketing-authorization period

There is general demand to include patient and parents representatives in the development of guidelines. It would be useful to have a standing committee to form and update guidelines on CF care at a European level with participants from POs. Currently ECFS, CFF and CFW are working on consensus guidelines that may be reviewed by POs. These international guidelines might be implemented into national guidelines with the support of POs. The Standards of Care consensus produced by the ECFS [1] helped to communicate the concept of CF care centers to health authorities in EU member states.

Codes of conduct for co-operation between POs and pharmaceutical industry have already been established in both the US and various European countries. There was broad consensus about respecting the independence of each partner. Moreover, full transparency about relationships between POs and SMEs is mandatory to ensure sustained co-operation. In some countries, independent monitoring processes have been developed to oversee PO-industry co-operation with codes of conduct elaborated to govern the relationship.

SMEs may play an important role in contributing to better patient satisfaction. Treatment adherence may be raised by providing safe and efficacious products. Motivation can also

be raised by providing useful add on equipment such as pill boxes for enzymes etc.

Eventually, general information about CF should be provided to the general public for educational purposes. For example, such information might help students living with CF to explain the disease and its impact on daily life to classmates. POs and SMEs might collaborate to develop this material.

## 4. Conclusions

If a policy of transparency and respect for the independence of POs is applied, SMEs and POs can develop mutually beneficial and sustainable co-operation to address the yet unmet medical needs of CF patients. Areas of co-operation include both the development and the post-marketing authorization phase of drug development. Based on their capabilities and resources, CF POs should decide carefully the depth of co-operation with industry that is in the best interests of patients in specific European countries.

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## Conflict of interest

The authors state that there is no conflict of interest.

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