28 September 2018
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Committee for Medicinal Products for Human Use (CHMP)

Review of comments submitted on the draft Qualification opinion - The European Cystic Fibrosis Society Patient Registry (ECFSPR)'

Procedure No.: EMEA/H/SAB/080/1/QA/2017

EMA/CHMP/SAWP/802259/2017

Product Development and Scientific Support Department

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1. General comments

Comment reference	Stake Holder number	General comment	Outcome	EMA comments
A	1	EAHP welcomes the draft qualification opinion that the ECFSPR may be allowed as a data source for regulatory purposes in the context of studies concerning medicines authorised for the treatment of cystic fibrosis.		Acknowledged.
B	2	As outcomes may be significantly influenced by access to care and local treatment standards which are different in some of the EU countries, we agree with ECFSPR consortium proposal to perform the analyses by countries having similar standards.		Acknowledged. Please note that the Opinion already makes reference to these issues with regards both to safety and efficacy. See lines 322-331, 546-548 and 631-636. In addition, ECFSPR has developed a model for comparison between groups of countries with similar socio-economic status, which is based on GNI (Gross National Income), number of doctors per region, and the percentage of income spent on healthcare.
C	2	Drug utilisation studies and efficacy/effectiveness studies will require accurate start and end dates of specific drugs – what measures are being proposed to document accuracy of such data (including drug discontinuations, interruption etc.)? For certain efficacy/effectiveness studies annual data may miss important information, it is likely that more frequent information 3-6 months) would be required.		Acknowledged. Please note that the opinion already makes reference to this start and stop dates in the *'Further recommendations for enhancement'* section. See lines 139-140, 381-382, 386-387, and 450-456 It is expected that ECFSPR will capture start dates in the future but this would not be possible on a retrospective basis. It appears that collecting this information on an encounter-based level could be more relevant. See also the EMA response to the comment on line 108-109, and agreed amendment to the draft opinion. The reasoning for annual outcome data is referenced in line 443-444, and 616-618, and 676-714 Again, if more frequent information is required a

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				possibility could be to contact those European National Registries with encounter-based data-collection. See lines 130-131 and 840 regarding the possibility to conduct single or multi-country studies.
D	2	Drug safety evaluation. From the document it is unclear how AEs will be defined in the registry. Will only drug-related AEs be reported (eg. possible, probably likelihood or any AEs)? Some clarity on solicited vs unsolicited AEs would be welcomed. Recommendation to have a clear distinction in the analyses between solicited vs unsolicited events. Given the complexity of safety data collection, considerations should be given to collect preferably SAE only rather than including also non-serious AEs. Propose that EMA provides guidance to the ECFSPR consortium on how drug-related AEs are expected to be distinguished from complications due to disease progression		Acknowledged. Please note that the opinion already makes reference to this issue. See lines 117-123, 137-138, and 585–643.
E	2	It is mentioned that there are pediatric patients included in this registry, and we'd like to ask for further clarification:		Acknowledged. Please note that the opinion already makes reference to the broad coverage of the CF population (lines 334-345), the widely established use of newborn screening in the EU (339-341) and highlights that these 'real world' populations are followed/assessed over extended periods of time (529-530). In page 15 of the latest version of the ECFSPR Annual Report with 2016 data (www.ecfs.eu/sites/default/files/general-content-images/working-groups/ecfs-patient-registry/ECFSPR_Report2016_06062018.pdf) it is

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		• How many of the 42000 patients are pediatric? Is data collected for pediatric patients in all the countries (including those in Eastern Europe with less coverage)? • Is the cut-off age at 16 or 18 years, literature claims there are different cut-offs in the individual national registries, how is it managed in the ECFSPR? • Does the SAWP also support pediatric PASS, PAES studies? Are additional measures for the pediatric population e.g. Tanner-scale available? (lines 235-265)		reported that 47.6% out of 44,719 patients are paediatric. The data is collected in 31 countries, and only Lithuania had no paediatric centre at that time. • As ECFSPR receives raw data from the national registries a cut-off age of ≥18 is used for adulthood. • Yes, pediatric PASS and PAES studies are supported. • Tanner-scale is not used. Where there would be specific hypothesis to be tested in that regard, it will need to be addressed in a specific study protocol.
F	3	Based on extensive experience collaborating with established, CF-specific patient registries to perform pharmacoepidemiological studies for regulatory purposes, we agree that such registries represent an invaluable tool to evaluate real world safety and effectiveness of CF medications. We also agree that the ECFSPR is evolving to become a suitable data source for pharmacoepidemiologic studies and should be evaluated as a potential data source at the time of feasibility assessments for future post-marketing safety and effectiveness evaluations, among other potentially suitable data sources, including large stand-alone mature country registries (e.g., UK, Germany). The following ECFSPR enhancements would be important to maximize its future use for regulatory purposes:		

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		1. Collection of detailed data on broad range of clinical outcomes (comparable to large mature national registries) In the past, ECFSPR collected a narrower subset of common variables compared to data available via some mature national registries (e.g. data on pulmonary exacerbations, hospitalizations, liver function test results, and pregnancies were not available in ECFSPR and the list of collected CF complications and pulmonary pathogens was narrower). Detailed collection of data on all these outcomes going forward would be important to allow for robust pharmacovigilance assessments and effectiveness evaluations using ECFSPR.		1. Clinical outcomes *Pulmonary exacerbations*: ECFSPR collects information on the number of days on IV (at home, in hospital and total) and an operational definition is under discussion in the International CF Registries (Global) Harmonisation Group. See attached the updated ECFSPR list of Variables and Definitions that will be collected, including additional pulmonary pathogens. *Liver toxicity:* cirrhosis with/without hypertension, and liver disease without cirrhosis are collected. For further investigation of suspected earlier liver toxicity, the potential for linkage or additional data collection should be discussed with ECFSPR. *Pregnancy:* The need for pregnancy data has already been raised in the '*Further recommendations for enhancement'* section. See lines 142-145, 365-368, 511-517 and 277-288 under Consortium's position.
		2. Broader and more detailed capture of medication use Collection of detailed medication use data, including medication start and stop dates, will be critically important for future pharmacoepidmiology studies. Further, the registry should have an ability to implement routine updates of data collection forms to collect data on newly approved medicines.		2. Start/stop dates: see the response to comment 'C' above.
		3. Standardization of collection of key clinical outcomes		3. All national registries have aligned their definition on FEV1 and are collecting the best of the year since 2016.

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		Consistency of the definitions of key clinical outcomes (e.g., lung function) across the countries contributing to ECFSPR will be critical for future pharmacoepidemiology studies. For instance, ECFSPR historically captured annual assessment values of $ppFEV_1$ for UK and Sweden as opposed to best available annual measures that were captured for the rest of the countries. Standardized definitions of lung function across all countries would allow for a consistent assessment of lung function evaluation across all patients in ECFSPR.		National registries are working towards alignment of their definitions with the ones used by ECFSPR and the International CF Registries (Global) Harmonisation Group.
		4. Consistency in data capture over time For long-term pharmacoepidemiological studies it would be important to ensure the consistent collection of the standardized data (as noted above) across the included countries over time going forward. If there are countries where data collection was not consistent over time during the long-term pharmacoepidemiologicla study period, such countries may need to be excluded from the analyses.		4. Agreed. Consistency over time is important and should be addressed in individual study protocols.
		5. Timely availability of ECFSPR data for analyses Due to the need to combine the data from over 20 countries, there is currently about 2 year lag reported for		5. The Annual Report is published within 18 months following the close of the data-collection year. Depending on the particular requirements single or multi-country studies could be considered. See lines 130-131 and 840.

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		the ECFSPR data (compared to under 1 year lag for some large mature country registries). For time-sensitive pharmacoepidemiological studies, in particular for pharmacovigilance purposes, shorter lag would be desirable. We would also like to note that although ECFSPR collects data on over 40,000 patients from almost 30 countries, the size of the effective data set for the potential future pharmacoepidemiological studies would need to be carefully examined and quantified as it could be affected by various factors, such as study research question, clinical data needs, geographic location of the indicated patient population, product approval and reimbursement timing in each country.		

2. Specific comments on text

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79-81	2	What is the reason to have clinical trial methodologies proposed for post approval pharmacoepidemiology studies rather than non-interventional study methodologies that does include propensity-scoring mechanisms?		As mentioned in the CHMP answer to question 6 (lines 886- 892), the most appropriate analysis method to be used will depend ultimately on the research question, patient population and outcomes for the specific study. In any case rigorous, pre-specified and well justified analysis methods should be used.
117-123	2	Are risk factors for adverse events eg. other co-medication, other comorbidities etc. available within this registry? It would be preferred to collect all SAEs rather than focusing on identified and potential risks only as this would restrict safety data collection to the risks of currently approved medications and would not allow detection of new risks.		See the response to comment 'D' above.
142-145	2	It would be also important to collect date of last menstrual period. The drop down list could contain the categories required as per table of Annex 3 of the EMA guidance on pregnancy reporting. In addition live births could be split in term and preterm live births: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf		See the response to comment 'F1' on pregnancy above. The suggestion to collect the date of last menstrual period is noted by the ECFSRR that will include this item in their discussions with the International CF Registries (Global) Harmonisation Group.
222	2	It would be preferable to include all CF patients no matter if treated or untreated to allow comparator cohorts to be available in the future.		The ECFSPR enrols patients irrespective of medicine use. In the context of pharmacoepidemiological studies which patients are included would depend on the study aim.
241	2	Is there a collection of dates and primary or underlying cause of death also provided? (according to appendix 2a it is collected)		See attached the updated ECFSPR list of Variables and Definitions: date and cause of death are recorded

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247	2	Comment: Sometimes it appears that the country of residence might be more important than country of origin		Country of residence is most relevant.
268	2	Comment: Is there a safety module to collect SAEs?		See the response to comment 'D' above.
272	2	With CF being an orphan, serious/ life-threatening disease is patient preference collected in any registry besides PRO since the perceived benefit-risk would be highly subjective to patient preferences? Are there plans to add this?		The ECFSPR do not plan to collect patient preferences in the near future.
273	2	Provided a consensus scoring system is used, imaging information may be valuable for long-term assessment of disease progression.		Not captured currently but the requirement has been passed to the ECFSPR. The ECFSPR will include this item in their discussions with the International CF Registries (Global) Harmonisation Group.
415-430	2	Recommendation to develop and use prospectively a consensus definition for PE at time of data collection. Analysis of PE collected retrospectively carries the bias of heterogeneity of PE definitions sued at different centres.		See the response to comment 'F1' above.
499-509	2	There may be interest in collection co-morbidities beyond CF complications, eg. hypertension, renal disease, osteoporosis, depression etc. This would allow looking into subsets of patients with specific needs and therefore to better understanding the outcomes (eg. depressive patients may be less adherent to CF medication and hence worse outcomes).		See the responses to comments 'C' and 'F' above.
868 ff.	2	Is the collected safety data sufficient for pragmatic trials in addition to post-marketing trials? Considering the disease area (orphan, serious/ life threatening) pragmatic trials		Outside the scope of the current qualification opinion.

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		would offer themselves.		
103-106	3	We agree that as ECFSPR matures, it may be used for regulatory purposes, and consider that a number of enhancements of ECFSPR are necessary in order to maximize such use (as described in the general comments). Proposed change: Suggest to add the following to line 103: "***with the expanded collection of data on pulmonary exacerbations, hospitalizations, start and stop date of CF medications, CF complications data, and standardization of lung function data,*** the status of ECFSPR (coverage, core dataset, governance, quality assurance approaches, and completeness of core variables), may allow its use …***"***		The current text is considered sufficiently clear.
108-109	3	In order to allow for the implementation of drug utilization studies, the registry needs to collect data on a range of CF medications, ideally including information on start and stop dates and doses. Drug utilization studies may also require retrospective analyses of drug utilization patterns in the past. We would also like to comment that as the collection of data on medication use via ECFSPR has been limited in the past, feasibility of some drug utilization studies, depending on the research question and time period of interest, may be affected. Proposed change: Suggest to add the following at the end of line 109: "***for medications with detailed information collected by ECFSPR consistently over time***"	Amend Opinion	It is agreed to add the following text at the end of line 109: "***for medications with detailed information collected by ECFSPR consistently over time***".

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111-116	3	We would like to comment that in the recent past, FEV_1 data collection was not entirely standardised across the ECFSPR contributing countries, CF complications data collection was relatively limited, and pulmonary exacerbations data have not been available. In addition, retrospective data (e.g., pre-2015) may be of insufficient completeness in ECFSPR and may not be sufficient for the purposes of historical comparison. Proposed change: Suggest to add the following to line 111: "***As the registry matures to expand the collection of pulmonary exacerbations, hospitalizations, CF complications data, and to standardize the lung function data***, ECFSPR could be used:…"		See the response to comment 'F' above. Based on EMA requirements, the ECFSPR has included new variables that will be collected with the upgraded software ECFSTracker 2.0 and included in the 2018 Annual Report and onwards. See attached the updated ECFSPR list of Variables and Definitions. The original text appears sufficiently clear, and the proposed change is not considered necessary.
129-131	3	We agree that early tripartite interactions with ECFSPR, regulators, and Applicants would be important, however it would be ideal if the framework for such interactions would be detailed. If, depending on the concrete study objectives and design/methodology, it is determined that single-country studies can be conducted, national CF registries (if available in the specific countries under consideration) may be an alternative data source.		The framework for tripartite interactions on individual studies is that of scientific advice/ protocol assistance. The ECFSPR is presented as a single point of contact for the handling of requests for PASS and PAES studies with the national CF registries, which includes the approach for a single country, multi-country or pan-European study.
132-134	3	We agree that in cases where additional data need to be collected outside of routine CF practice, additional patient consent would be needed. The feasibility of obtaining such consent across multiple countries contributing	Amend Opinion	It is agreed to add the following sentence at the end of line 134: ***"The feasibility of obtaining such consent should be assessed"***.

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		data to ECFSPR in a reasonable timeframe would need to be carefully assessed. Proposed change: Suggest adding the following sentence to line 134: ***"The feasibility of obtaining such consent across multiple countries contributing data to ECFSPR in a reasonable timeframe would need to be carefully assessed"***		
137-138	3	We would like to note that collection of adverse events and adverse event coding using MedDRA, while being a standard practice for clinical trials, is unlikely to be feasible for disease patient registries. We agree with the need of standardized data collection across all the ECFSPR contributing countries, and consider that pre-defining the variables of interest in the registry CRF (e.g., including a detailed list of CF complications routinely collected for all the patients in the registry) would be a more feasible and efficient approach. Proposed change : Consider the following sentence as an alternative: "***Strengthening of standardised collection of granular data on CF complications, relevant laboratory abnormalities, pregnancy outcomes across all contributing countries to facilitate unbiased safety assessments across all CF centres"***		See the responses to comments 'D' and 'F' above.
150	3	We note that registry linkages with prescription data may not be possible for many ECFSPR contributing countries.		The current text reflects the proposed recommendation adequately.

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		Proposed change : Suggest adding the following text to line 150: "Linkage with prescription data for further assessment on safety and effectiveness issues ***may be explored in select ECFSPR countries where high quality prescription databases are available***"		
312-316	3	We agree that it is not possible to provide a single answer if the target population and the collection of the data in ECFSPR are universally sufficient for pharmacoepidemiology studies. We are also in agreement with the recommendation that companies submit a study protocol or concept that discusses relevance and validity of ECFSPR data before the study is initiated. We would like to add that study feasibility assessments should also evaluate the relevance and validity of alternative available data sources, e.g. existing large country national registries. Proposed change: Suggest the following addition to the sentence in lines 314-316: "Therefore, we recommend that companies submit a study protocol that discusses the relevance and validity of the ECFSPR data ***versus other alternative data sources*** (including population) before a post authorization study is initiated."		For all studies based on observational data, the source and designs need to be appropriately justified.
415-430	3	We agree that data on pulmonary exacerbations that require IV antibiotic use therapy is critical for most pharmacoepidemiologic studies of CF medicines. ECFSPR did not collect these data in the past and the planned data collection is a		Acknowledged.

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		positive development. We would like to note where the study design requires analyses of historical data on pulmonary exacerbations, such analyses may not be possible using ECFSPR.		
432-447	3	We agree that FEV_1 is the main outcome to assess lung function in CF patients. The FEV_1 data collection across ECFSPR countries have not been standardized in the past (registry captured annual assessment values of FEV_1 for UK and Sweden as opposed to best available annual measures that were captured for the rest of the countries). Future standardization of lung function data collection across all registries would be a positive development, recording all available measures of FEV_1 would also be preferable. Proposed change: Suggest to add a sentence on the desired standardization of lung function data collection (e.g. best available) across all the ECFSPR contributing countries.		See the response to comment 'F3' above.
449-460	3	We agree that robust collection of medication data are critical for the future pharmacoepidemiology studies. ECFSPR should have an ability to routinely update data collection forms to allow the collection of data on newly approved medicines from the time of approval onward. Data on start and stop dates of medications would be important. Proposed change: Suggest the addition of the sentence to indicate that the ECFSPR should have an ability to routinely update data collection forms to		See the response to comment 'C' above, and to line 108-9.

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		allow the collection of data, including start and stop dates, on newly approved medicines from the time of approval onward.		
499-509	3	We agree with the importance of collection of detailed data on a broad range of CF complications across the organ systems for more robust pharmacovigilance evaluations. Moreover, it would be important to align on the definitions of the CF complication variables collected, e.g. for CFRD and CFLD, on a global level. Proposed change:		The comment on the importance of aligning the definitions for CF- complications is noted by the ECFSPR that will include this topic in their discussions with the International CF Registries (Global) Harmonisation Group.
511-517	3	We agree that pregnancy data collection in ECFSPR is currently limited and that standardized collection of pregnancy and pregnancy outcome data across all contributing countries would allow for more robust pharmacovigilance evaluations.		See the response to comment 'F1' on pregnancy above. The comment is noted by the ECFSPR that will explore pregnancy data collection opportunities and discuss them with the International CF Registries (Global) Harmonisation Group.
638-643	3	We agree that registry data could be used to monitor identified / potential safety risks (assuming the detailed high quality information on such events is collected in the registry). We also consider that if the registry systematically collects detailed data on a broad range of disease comorbidities and complications across organ systems, pulmonary microorganisms and laboratory abnormalities, statistical evaluations of such data could generate hypotheses about potential new safety concerns, not previously acknowledged and listed in the RMP. Proposed change: Suggest to add a clarification, that with the detailed systematic and high quality collection		See the response to comment 'D' above.

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		of data on a broad range of disease comorbidities and complications across organ systems, pulmonary microorganisms and laboratory abnormalities, ECFSPR data could be used to either monitor identified / potential safety risks listed in the RMPs or be used to generate hypotheses about potential new safety concerns.		
692-694	3	We agree with the importance of the timely post-approval study data analyses. Based on experience collaborating with the country national CF registries, it is feasible for the registry partners to perform analyses supporting post-approval studies 9 months after the reporting calendar year (after the data cleaning and QC is complete),). AN additional 3 months are required to prepare the regulatory-submission-ready reports in the appropriate templates (e.g. PASS). Therefore, the reports to can generally be EMA produced and submitted approximately 12 months after the reporting calendar year. Proposed change: Suggest to add that the report submission to the EMA may be expected approximately 12 months after the reporting calendar year.		The current text is considered sufficiently clear.
886-932	3	We agree that there is no universal statistical solution to cover every situation and that the most appropriate statistical procedure would need to be tailored on a case-by-case basis. For instance, depending on the study medicinal product and indicated population, identifying an appropriate untreated concurrent comparator may not be feasible and an		Acknowledged. The current text already covers the variety of potential study design options as included in your comment.

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		alternative approach, such as within-group pre- and post-treatment comparisons may be necessary. Similarly, we agree that whether the propensity score approach is valid and appropriate would depend on the research question, study population, and outcome(s) of interest. Proposed change : Suggest to consider adding text regarding the variety of study design options depending on research question, population and outcomes of interest, whereby study with a concurrent matched comparator is not the only appropriate option, and where alternative designs (such as within-group comparisons, or comparisons to historical data) may be warranted		