# Report on the European Ombudsman's telephone conference with the European Medicines Agency on the European Medicines Agency's allegedly delayed authorisation of the cystic fibrosis drug Kalydeco for the use in children with a specific gene mutation – non-confidential version (case 222/2020/EWM)

Correspondence - 03/03/2020
**Case** 222/2020/EWM - **Opened on** 21/02/2020 - **Decision on** 03/06/2020 - **Institution concerned** European Medicines Agency ( No maladministration found ) |

# REPORT ON THE EUROPEAN OMBUDSMAN'S TELEPHONE CONFERENCE WITH EUROPEAN MEDICINES AGENCY (EMA)

**COMPLAINT** : 222/2020/EWM

**Case title** : The European Medicines Agency's allegedly delayed authorisation of the cystic fibrosis medicinal product Kalydeco for use in children with the gene mutation R117H

**Date** : Tuesday, 03 March 2020

**Location** : European Ombudsman
Participants
*European Medicines Agency (EMA):*

2 Administrators from EMA's Stakeholders and Communication Division

3 Administrators from EMA's Office for Therapies for immune and inflammatory diseases, Human Division

2 Administrators, EMA's Legal Department

*European Ombudsman:*

Mr O' REGAN Fergal, Head of Unit

Ms WINTER-MES Elke, Case handler

A trainee case handler
Purpose of the inspection meeting
The purpose of the call was to request clarifications and more detailed information on the status of a request to authorise the use of Kalydeco in children with the gene mutation R117H.
Introduction and procedural information
The phone call took place on 3 March 2020 from 14:00h to 16:00h.

The Ombudsman's inquiry team members introduced themselves, thanked EMA's representatives for their availability and explained the purpose of the meeting.
Discussion with EMA's representatives
The Ombudsman's inquiry team clarified that the Ombudsman's inquiry does not cover the substantive medical/scientific assessment of the safety and efficacy of Kalydeco. Rather the aim of the inquiry is to clarify the status of the on-going assessment of a request to extend the indication of Kalydeco to cover use in children below 2 years of age with the gene mutation *R117H.*

*Background of the complaint*

Cystic fibrosis is a serious medical condition affecting the composition of sweat, functionality of respiratory tract, and digestive system. Cystic fibrosis is an inherited disease and a number of different genetic mutations can each give rise to cystic fibrosis. While the gene mutations that give rise to cystic fibrosis are present at birth, the persons with these gene mutations can, depending on which genetic mutation they have, be asymptomatic or present milder symptoms for a number of years.

The complainant is the father of a 3-year-old child who suffers from cystic fibrosis caused by the R117H gene mutation. Cystic fibrosis caused by the R117H gene mutation has been reported to be in some cases asymptomatic in early childhood (up to 11 years). However, there are cases, such as the case of the complainant's child, where symptoms appear earlier. These symptoms are very serious and can cause permanent health damage to sufferers.

Kalydeco (ivacaftor) is a medicine for which a marketing authorisation dossier was submitted to EMA by Vertex on 27 October 2011. Based on the its review of the data on quality, safety and efficacy, EMA's Committee for Medicinal Products for Human Use (CHMP) considered, on the basis of an Opinion adopted by consensus, that the risk-benefit balance of Kalydeco in the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene is favourable and therefore recommended the granting of the marketing authorisation. On 11 July 2014, Vertex submitted an extension of indication application (EMEA/H/C/002494/II/0027) to include the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an *R117H* mutation in the *CFTR* gene which was formally granted by CHMP on 24 September 2015. [1] Kalydeco is therefore not yet authorised in the

EU for the treatment of children or adolescents under the age of 18 years with cystic fibrosis who have this specific R117H mutation. Nevertheless, an application (EMEA/H/C/002494/II/0082) is currently under assessment by CHMP for the following indication:

· to extend the use of Kalydeco 150 mg tablets to patients with CF aged 6 years and older and weighing 25 kg or more who have an *R117H* mutation in the *CFTR* gene; and

· to extend the use of Kalydeco granules 75 mg and 50 mg to patients with CF aged 12 months and older and weighing 7 kg to less than 25 kg who have an *R117H* mutation in the *CFTR* gene.

The complainant wants EMA to authorise the use of Kalydeco for children with the R117H gene mutation and is concerned that EMA has incurred delays in this regard.

It bears noting that EMA exchanged correspondence with the complainant as regards the approval of Kalydeco between 3 December 2018 and 5 September 2019.

*Substance*

As regards the allegation that delays had occurred, EMA stated the following:

The above-mentioned application [CONFIDENTIAL] and the assessment thereof was initiated on 2 November 2019. The timeline of the assessment of a type II variation application is set out in Article 16(2) of Commission Regulation (EC) No 1234/2008. The assessment of a type II variation application may follow a 60- or 90-day timetable, depending of the complexity underlying the respective scientific assessment. [2] EMA informed the marketing authorisation holder that the assessment would follow a 90-day timetable, as the application sought the amendment of the indication of the medicinal product.

The actual time taken for the assessment varies on a case-by-case basis. The CHMP, which is in charge of the evaluation, may make a request for supplementary information, in which case the assessment can be placed in a default clock-stop. The marketing authorisation holder may also request the CHMP to stop the clock for a specific period of time if the marketing authorisation holder considers that it needs additional time to respond to a request for supplementary information issued by the CHMP. [3]

In the present case, a request for supplementary information was issued by the CHMP on 30 January 2020. Accordingly, the assessment was placed in a default clock-stop of 30 days [CONFIDENTIAL].

In this respect, EMA clarified that the adoption of a list of questions by the CHMP, requesting additional data, or information on the interpretation of the data, is a routine step in the context of assessments. [4] It occurs in most initial applications and extension of indication applications and constitutes an opportunity for the company seeking a marketing authorisation or an extension of the indication to provide additional explanations and data

when needed. Companies are familiar with this procedure.

EMA stated, in this regard, that it cannot pre-empt the outcome of the on-going CHMP assessment.

The Ombudsman's inquiry team asked EMA to provide an explanation as regards why the US authorities have approved the use of Kalydeco in children with this mutation based on similar data. As extrapolation from adults to children was a key issue and was one of the reasons for the decision of the US authorities to approve the use of Kalydeco in children who have this mutation, the Ombudsman's team also asked EMA to provide more information on the issue of extrapolation.

EMA noted that the main clinical study (VX-11-770-110) in patients with the R117H mutation, which the pharmaceutical company submitted to EMA as well as to the US authorities, was conducted mainly on adult patients. There were only 19 patients under 18 years (and no patients under the age of 6), and only 9 of them received Kalydeco. It contained no data on children who were between 6 months and 6 years old.

The US authorities granted the extension of indication in December 2014 to treat children 6 years of age and older with the R117H gene mutation based on extrapolation of data with support from population pharmacokinetic analysis showing similar drug exposure levels in adults and children. They granted a further extension in May 2017 to include children aged 2 years and older who have one mutation in the CFTR gene that is responsive to Kalydeco based on clinical and/or in vitro assay data. A further extension was granted to children aged 6 months and above in April 2019.

In the EU, this trial was assessed by EMA in 2015 in the context of the assessment of a type II variation application to include the treatment of patients with cystic fibrosis (CF) aged 18 years and above with R117H mutation in the CFTR gene. [5] In the context of that assessment, efficacy in children with R117H was also looked at and it was concluded that the data (in terms of lung function improvement, which was the main measure of efficacy measured in the trial) was very limited and inconclusive, as the children in the placebo group out-performed the group that received Kalydeco. Other test results showed some improvement (i.e. sweat chloride levels); however, this improvement does not always correlate with lung function improvement.

The CHMP had concerns that the extrapolation of conclusions, from adults to children, is not sufficient because the symptoms and signs of the illness, and the patterns of organ damage, can differ depending on age. [6]

EMA noted that it can authorise medicines or new uses for authorised medicines only if they are proven to be effective and safe. The possible authorisation of medicines or new uses for authorised medicines in third countries does not itself pre-empt or call into question the scientific assessment of the CHMP. [7]

The Ombudsman's team asked EMA to explain why there was limited clinical data on the

effects of Kalydeco on children with the R117H gene mutation.

EMA stated that no large-scale clinical trial has been submitted to EMA with very young children: in order to produce statistically reliable data, a trial must contain enough patients and cystic fibrosis being a rare disease makes it difficult to recruit enough patients. Moreover, the number of persons with the specific R117H gene mutation, is very low. Even among this group, the number of very young patients with symptoms is limited. Whereas some other gene mutations that cause cystic fibrosis are very symptomatic from birth onwards, this gene mutation is often asymptomatic until the age of 11.

EMA also noted that conducting trials on children is generally challenging since it not only involves administering the medicinal product, but also involves taking multiple regular tests, including blood tests and lung function assessments. Usually, a trial has a controlled group, which means that in placebo-controlled studies some children will go through the process of a study without being given the medicinal product.

While the assessment of an extension of indication formally commences only *once* the pharmaceutical company submits a request for an extension of indication EMA explained that it had previously been in contact with the pharmaceutical company to discuss what data could be provided to support the granting of the extension of indication. In a pre-submission meeting of 29 April 2019, EMA asked the company whether additional data (beyond the pivotal clinical study of Kalydeco) supporting the use of Kalydeco in children with R117H mutation, was now available and whether it could be submitted as part of an extension of indication application. EMA stated that this could include data from literature and real-life data from an ongoing US registry-based study.

The Ombudsman's inquiry team asked EMA about its correspondence with the patient and the company. The EMA representatives first pointed out that they fully understand the importance of the issue for the complainant. They agreed that the illness in question is very serious and that there is an unmet medical need.

EMA had emphasised to the company and the complainant the need for the company to make an application with additional data to support an approval in the paediatric population with the R117H mutation.

In addition, at the pre-submission meeting with the company referred to above, EMA encouraged the company to submit a new application since there may be more data from other regions, such as the US and Australia, where the medicine is now authorised for use in children. EMA clarified that, ultimately, it remains the responsibility of the marketing authorisation holder to submit a valid and comprehensive application.

The Ombudsman's inquiry team asked EMA to explain the length of the approval procedure at EMA compared to procedures at the US Food and Drug Administration (FDA) - the Ombudsman's team mentioned the complainant's concern that procedures are quicker in the US than in the EU. EMA stated that EMA and FDA approval procedures are different and that in the EU the length of an approval process depends on how quickly the company can

provide any additional information required by the regulator during the assessment. In any event, there has not been any delay that can possibly be attributed to EMA in respect of the ongoing assessment of the type II variation application for the extension of the indication of Kalydeco. As noted above, the assessment was placed in a 30-day clock-stop as additional information was needed for the purpose of the CHMP assessment. [CONFIDENTIAL].

The Ombudsman's inquiry team asked whether there is a way for a child to get access to Kalydeco despite the fact that it has not been approved for treating children with the R117H gene mutation. EMA explained that there are, generally speaking, different possibilities, such as 'off-label use' or consideration of enrolment in a clinical trial:
- EMA noted that, in its respective letters of 10 December 2018 and 14 June 2019, it had informed the complainant of the possibility of exploring with his son's doctor the possibility of off-label use. [8] The European Commission has published a study on off-label use of medicinal products in the European Union including country-specific information. [9]
- EMA noted that another pathway for gaining access to Kalydeco could be the enrolment in a clinical trial. EMA informed the complainant of this possibility in its respective letters of 10 December 2018 and 14 June 2019.

The Ombudsman's inquiry team asked whether the off-label use may imply that the patient has to bear the cost of the medicine (rather than a national medicine reimbursement system). On the basis of the above-mentioned study of the European Commission, [10] EMA explained that this is up to the Member States: depending on the Member State, the cost of the medicine may or may not be reimbursed.

Thus, there may already be mechanisms to make this medicinal product available to children prior to its approval by EMA. Indeed, EMA pointed out that these mechanisms (within the constraints of the applicable legislation) could be available for access to unauthorised medicinal products. EMA further explained that such mechanisms (within the constraints of the applicable legislation) may also generate data possibly supporting applications for the extension of the indication.

The Ombudsman's inquiry team asked about the possibility for the complainant to register his child for a suitable clinical trial. EMA explained that getting involved in a clinical trial on cystic fibrosis involves extensive blood testing for patients and potentially being treated with a comparator (or in some cases placebo). Moreover, EMA is currently not aware of any ongoing or planned clinical studies involving children with the R117H mutation.

The Ombudsman's team asked EMA if it can give any indication as to how long the on-going assessment of Kalydeco will take. EMA stated that it is not possible for EMA to predict how long the process is going to take. EMA explained that the assessment was placed in a 30-day clock-stop as a result of the request for supplementary information. Further to the adoption of a request for supplementary information, the marketing authorisation holder may submit a request for a longer clock-stop or for the extension thereof. [CONFIDENTIAL]. If and when the necessary information is provided, it must be assessed by the scientific committees which may decide to convene an expert meeting, if deemed necessary. The procedure could last a few more months or longer. With that said, EMA is bound by the timetable foreseen in

the applicable legislation. [11]
Conclusion of the phone call
The Ombudsman's inquiry team informed EMA that they would draft a detailed meeting report and send it to EMA to ensure accuracy. The Ombudsman's inquiry team also asked EMA to provide a non-confidential version of the report that could be shared with the complainant.

Brussels, 15 April 2020

Head of Inquiries, Unit 2 Case handler, Inquiries Unit 2

[1] The extension of the indication of an authorised medicinal product is possible further to the favourable assessment of an application for a type II variation. In this respect, see: Article 16 of Commission Regulation (EC) No 1234/2008. The term "extension of indication" should be distinguished from the term "extension of marketing authorisation". For the latter, see: Article 19 and Annex I of Commission Regulation (EC) No 1234/2008.

[2] In this respect, see: Article 16(2), second subparagraph, of Commission Regulation (EC) No 1234/2008, in conjunction with Annex V. At Day 90, the CHMP will adopt the Opinion on the type II variation application or issue a request for supplementary information; in this respect, see: Article 16(3) of Commission Regulation (EC) No 1234/2008 which states "Within the period referred to in paragraph 2, the Agency may request the holder to provide supplementary information within a time limit set by the Agency. The procedure shall be suspended until such time as the supplementary information has been provided. In this case the Agency may extend the period referred to in paragraph 2".

[3] For more information on the possibility for the so-called clock-stops, see: European Medicines Agency post-authorisation procedural advice for users of the centralised procedure, page 53; available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agenc
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[4] The CHMP is responsible for:

- conducting the initial assessment of EU-wide marketing authorisation applications;

- assessing modifications or extensions ('variations') to an existing marketing authorisation;

- considering the recommendations of the Agency's Pharmacovigilance Risk Assessment Committee on the safety of medicines on the market and when necessary, recommending to the European Commission changes to a medicine's marketing authorisation, or its suspension or withdrawal from the market.

The present case concerns a procedure for an extension of an existing marketing authorisation to cover also the treatment of children.

[5] https://www.ema.europa.eu/en/documents/variation-report/kalydeco-h-c-2494-ii-0027-epar-assessment

[6] EMA informed the Ombudsman's team that it published, in 2018, a reflection paper on the use of extrapolation in the development of medicines for paediatrics (available at: https://www.ema.europa.eu/en/extrapolation-efficacy-safety-paediatric-medicine-development#current- ). This document proposes a framework for extrapolation of data from adults to children which could serve as a basis for regulatory decision making in planning and developing paediatric developments, including paediatric investigation plans.

[7] In this respect, see: Judgment of the General Court of 19 December 2018 in *Vanda Pharmaceuticals v Commission* , T-211/18, EU:T:2019:892, paragraph 45, and the case-law cited therein.

[8] Off-label prescribing is the sole responsibility of the prescribing physician. In this respect, see: Judgment of the General Court of 11 June 2015 in *Laboratoires CTRS v Commission* , T-452/14, EU:T:2015:373, paragraph 82, and the case-law cited therein.

[9] https://ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_off-lab .

[10] Ibid. For country-specific information with regard to regulation of off-label use, see Annex H to this study.

[11] See Articles 16(2) and (3) of Commission Regulation (EC) No 1234/2008, available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02008R1234-20130804 .