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Decision of the European Ombudsman closing his inquiry into complaint 2575/2009/(TS)(TN)RA against the European Medicines Agency

Available languages: en

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Case: 2575/2009/(TS)(TN)RA

Opened on **19 Jan 2010** - Draft recommendation on **11 May 2012** - Decision on **22 Jul 2013**

- Institution(s) concerned: **European Medicines Agency**
- Field(s) of law: **Environment, consumers and health protection**
- Types of maladministration alleged – (i) breach of, or (ii) breach of duties relating to: **Lawfulness (incorrect application of substantive and/or procedural rules) [Article 4 ECGAB]**,**Absence of discrimination [Article 5 ECGAB]**,**Duty to state the grounds of decisions and the possibilities of appeal [Articles 18 and 19 ECGAB]**
- Subject matter(s): **Institutional and policy matters**

The background to the complaint

1. The complaint concerns a decision of the European Medicines Agency (hereinafter, 'the Agency') to refuse a request from two pharmaceutical companies for a waiver from the obligation to test how a medicinal product they developed can be used with children. The obligation involves submitting a paediatric investigation plan (hereinafter, a 'PIP'), which is a research and development programme aimed at ensuring that the necessary data are generated to determine the conditions in which a medicinal product can be used to treat children.

2. The complaint was submitted by Arnold & Porter UK LLP on behalf of the two pharmaceutical companies (hereinafter, 'the complainants'), Takeda Global Research & Development Centre and Astrazeneca AB. The complainants co-developed candesartan cilexetil (hereinafter, 'candesartan'[1]), a medicinal product used to treat hypertension and heart failure. Candesartan is an "angiotensin II type 1 receptor blocker" (hereinafter, an 'ARB'). There are two other ARBs on the market, namely, losartan and valsartan. According to the complainants, the Agency wrongly treated an application for a waiver for candesartan, given that it treated that waiver application differently from waiver applications for losartan and valsartan.

3. Regulation 1901/2006 on medicinal products for paediatric use[2] (hereinafter, 'the Paediatric Regulation') aims to facilitate the development of, and access to, medicinal products for use in the paediatric population, whilst ensuring that medicinal products used to treat the paediatric population are subject to ethical research of high quality[3]. The Paediatric Regulation requires pharmaceutical companies to examine the possibility of using their medicinal products to treat children. In this respect, the Paediatric Regulation creates an obligation for pharmaceutical companies to carry out studies in accordance with an agreed PIP[4]. In accordance with this obligation, (i) applications submitted to the European Medicines Agency for a marketing authorisation, or (ii) applications to the Agency to alter a marketing authorisation (for example, in order to extend the marketing authorisation to cover a new indication), to authorise a new pharmaceutical form, or to authorise a new route of administration, now have to include the results of studies conducted in the paediatric population, in compliance with an agreed PIP[5].

4. The Paediatric Regulation, however, warns against subjecting the paediatric population to unnecessary clinical, or other, trials[6]. In this context, the Paediatric Regulation provides that the Agency[7] can waive the requirement to carry out a PIP[8] if there is evidence showing:

(a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;

(b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations;

(c) that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients[9].

5. On 12 July 2007, the complainants submitted to the Agency identical applications for a PIP for their product (candesartan). The applications included a request for a product-specific waiver which would have allowed them not to carry out studies on the effects of candesartan on heart failure in children[10]. They argued that candesartan is likely to be ineffective or unsafe in part or all of the paediatric population and that candesartan does not represent a significant therapeutic benefit over existing heart failure treatments for children (the complainants argued that angiotensin converting enzyme inhibitors (ACEIs)[11] constitute established, recommended, and effective existing therapy for children with chronic heart failure). The complainants also gave detailed reasons as to why a clinical trial to establish a significant therapeutic benefit over existing treatment was not feasible.

6. On 12 December 2008, the Agency's Paediatric Committee refused the submitted PIP and turned down the request for a waiver. The complainants were thus requested to carry out a limited PIP on candesartan with respect to the condition heart failure[12]. When justifying its decision, the Paediatric Committee stated that there is an unmet therapeutic need for the

development of medicinal products for the treatment of heart failure in children. It noted that no medicinal product is currently authorised for this indication. Because no alternative exists, ACEIs and ARBs are currently used "off-label"[13], without appropriate data on safety and efficacy. The Paediatric Committee considered that conducting a clinical study to attempt to define risks and benefits would be a more appropriate option than off-label use, especially when ethical requirements are taken into account.

7. As regards the fact that it denied a waiver for candesartan, while granting a waiver for losartan and valsartan, the Paediatric Committee stated that there was a limited number of patients in the target population (thus making it difficult to carry out testing on numerous products) and that candesartan had the most favourable taste of all available ARBs. This made it the best candidate drug for paediatric development.

8. On 14 January 2009, the complainants requested a re-examination of the Paediatric Committee's opinion, specifically with regard to the requirement to undertake a "limited development plan" and, more particularly, to conduct a paediatric study for candesartan related to the treatment of heart failure. They argued that a product-specific waiver for candesartan for the condition of heart failure in children was justified given the expected lack of a significant therapeutic benefit over existing treatments (namely, Article 11(1)(c) of the Paediatric Regulation). They also argued that there were inconsistencies in how the Agency dealt with the waiver applications for the various ARBs (candesartan, losartan, and valsartan)[14]. In sum, in light of the principle of equal treatment, the complainants requested that the same waiver be granted to candesartan as had already been granted to losartan and valsartan. They contested the argument that potential differences in taste could constitute a sufficiently compelling justification to designate candesartan as the only product required to undergo a paediatric study related to heart failure. The complainants further argued that, in light of EU law requirements, the Paediatric Committee's request for an uncontrolled, exploratory study to be conducted, in the full expectation that it would not be clinically interpretable, would not be appropriate.

9. The re-examination procedure commenced on 15 January 2009. Having assessed the detailed grounds for re-examination, the Paediatric Committee maintained its opinion and rejected the request for a product-specific waiver for candesartan. The Agency adopted its decision refusing a PIP and a waiver for candesartan on 20 February 2009[15]. The complainants then turned to the Ombudsman.

The subject matter of the inquiry

10. The complainants contest the Agency's refusal to grant a waiver in respect of the condition of heart failure and to approve the PIP for a medicinal product containing candesartan as the active ingredient.

11. The complainants allege that the Agency failed:

(i) to comply with the principle of equal treatment and to base its decision on an objective and fair assessment; and

(ii) to comply with the obligation to state reasons for the decision.

12. The complainants have made no express claim. The Ombudsman understands, however, that they implicitly claim that the Agency should replace the contested decision by a new one which meets the requirements of equal treatment, objective and fair assessment, and adequate reasoning.

The inquiry

13. The complaint was submitted to the Ombudsman on 8 October 2009. On 19 January 2010, the Ombudsman opened an inquiry and sent the complaint to the Agency with a request for an opinion. This correspondence also contained a request to inspect documents that the Ombudsman considered to be relevant to the inquiry[16]. That inspection took place on 24 and 25 March 2010. On 29 April 2010, the Agency sent its opinion, which was forwarded to the complainants with an invitation to submit observations. The complainants submitted observations on 28 May 2010 and followed up with additional observations on 16 May 2011. On 11 May 2012, the Ombudsman issued a draft recommendation to the Agency and asked it to send a detailed opinion. The Agency's detailed opinion was forwarded to the complainants, who sent their observations on 26 November 2012.

The Ombudsman's analysis and conclusions

Preliminary remarks

14. In its opinion, the Agency questioned whether the current complaint fell within the Ombudsman's mandate. The Agency maintained that the issues that arise in the present complaint do not fall within the scope of "maladministration".

15. The Ombudsman recalls that maladministration encompasses failure to respect the law, failure to respect fundamental rights, and failure to respect the principles of good administration. The Ombudsman noted that the allegations put forward by the complainants, namely, failure to comply with the principle of equal treatment, with the principles of fairness and objectivity, and with the obligation to state reasons for the decision, would, if shown to be well grounded, certainly constitute maladministration.

16. The Agency also argued that the complainants could have lodged an action for annulment before the EU Courts if they were unhappy with the refusal of their waiver application. The Ombudsman stresses that the possibility to complain to him about maladministration constitutes an alternative remedy alongside the right to go to court[17]. He further underlines that this right is laid down in Article 24 of the Treaty on the functioning of the European Union (TFEU) and, according to Article 43 of the Charter of Fundamental Rights of the European Union, is a fundamental right.

A. Allegation of failure to comply with the principle of equal treatment and to base the decision on an objective and fair assessment and related claim

Arguments presented to the Ombudsman

17. The complainants stated that, on 29 February 2008, losartan was granted a product-specific waiver in respect of the condition of heart failure[18]. Valsartan was granted a product-specific waiver in respect of the condition of heart failure on 14 October 2008[19] (the position of the Agency in respect of valsartan was subsequently reinforced with respect to the condition of heart failure by its decision adopted on 26 June 2009[20]). In the complainants' view, the Agency then wrongly treated an application for a product-specific waiver for candesartan differently from waiver applications for losartan and valsartan, notwithstanding the fact that all three drugs belong to the same therapeutic class of medicinal substances (they are all ARBs) which are approved for the indication of heart failure in adults.

18. The complainants argued that, on the basis of internationally recognised drug classifications (the WHO INN system[21] and the ATC classification[22]), there is a strong presumption that, by virtue of the fact that they mediate their primary mode of action through the same angiotensin II receptor to bring about a therapeutic effect, these substances exhibit essentially the same pharmacological properties. The complainants argued that they therefore had a legitimate expectation that the manner in which the waiver application for candesartan was examined would be consistent with the manner in which the waiver applications for losartan and valsartan were examined. The complainants pointed out that the applications for waivers for losartan and valsartan were made on exactly the same grounds as the complainants' application. However, losartan and valsartan were granted product-specific waivers in relation to the need to conduct a paediatric study in heart failure, whereas candesartan was not. The complainants contended that the position taken by the Paediatric Committee (according to which ARBs, while similar to each other, are not identical to each other, thus implying that it is possible to have different options for the different products) is contrary to the established position of the WHO INN system and the ATC classification.

19. The complainants pointed out that, in compliance with the Commission's PIP Guideline[23], the Agency ought to have applied the same reasoning to the PIP application for candesartan, as had been applied to the PIP applications for the other ARBs, unless a distinction between candesartan, losartan, and valsartan could be objectively justified. In their view, nothing in the Agency's original assessment, or in the re-examination assessment, provided any clarity on the objectively defined and relevant features that could be used to justify its decision to treat candesartan differently from losartan and valsartan. They pointed out that the applications for product-specific waivers for candesartan, losartan, and valsartan were submitted by the respective companies broadly at the same time[24]. They therefore assumed that the Paediatric Committee's discussions took into account substantially the same state of scientific and medical knowledge. The Paediatric Committee did not, however, provide them with scientific justification, based on safety and/or efficacy, as to why only candesartan should be studied in paediatric patients with heart failure.

20. With regard to the Agency's failure to base its decision on an objective and fair assessment (Articles 9[25] and 11[26] of the European Code of Good Administrative Behaviour), the complainants submitted first, that the assessment conducted by the Agency attached undue weight to therapeutic need for an ARB to be tested, in order to determine if and how it could be used for heart failure in children. EU law requires an assessment of whether a given product is likely to improve the risk/benefit balance as compared with the existing treatment regimes[27]. Therapeutic need is not *per se* decisive. It is the complainants' firm opinion that the risk/benefit balance of ARBs is unlikely to confer a significant therapeutic advantage over the existing treatment modalities.

21. The complainants insisted, moreover, that the Paediatric Committee fully acknowledged that ACEIs constitute existing effective treatment. With regard to the comparison between ARBs and ACEIs, they noted, referring to peer-reviewed published literature, that, while there are mechanistic differences by which ACEIs and ARBs intervene on the angiotensin II effects, pre-

clinical studies indicate that neither mechanism is clearly superior. Consistent with these experimental data, clinical trials in adults have established that both ACEIs and ARBs effectively treat heart failure due to left ventricular systolic dysfunction. However, none of the trials has directly compared these agents. Expert groups recommend ACEIs as first-line therapy in heart failure and only suggest ARBs for subjects intolerant to ACEIs. Accordingly, studies with an ARB would need to establish a significant therapeutic benefit relative to ACEI treatment.

22. The complainants argued that taste characteristics of candesartan (which were referred to by the Agency as a differentiating factor) could not be viewed as a decisive factor to require the complainants alone to conduct a paediatric study in heart failure. This was because, before commencing a paediatric study, there is a need to develop a suitable paediatric dosage form and a formulation suitable for use in children. This prerequisite applies with equal force to all the ARBs.

23. The complainants went on to say that the decision to choose candesartan was not evidence-based, because the Agency could equally have suggested valsartan as a suitable drug candidate for testing in a paediatric population for heart failure. In the absence of any objectively justified reasons, the decision to require the complainants to undertake paediatric clinical studies in heart failure is arbitrary and lacks objectivity.

24. Finally, the complainants argued that the Paediatric Committee's request to conduct an uncontrolled, exploratory study for candesartan with the full expectation that it would not be clinically interpretable is not appropriate. They quote the draft version of the PIP Guideline to describe the Commission's criteria for assessing the significance of studies. Implicit in the PIP Guideline, they argued, is that the data generated from paediatric studies should be clinically meaningful and interpretable because such study results should be included in the Summary of Product Characteristics for candesartan. According to the Commission's Guidelines on Summary of Product Characteristics, information included in an approved Summary of Product Characteristics[28] forms *"the basis of information for healthcare professionals on how to use the medicinal product safely and effectively"*. The complainants insisted that the Paediatric Committee's request failed to meet the above regulatory standard and threshold as regards clinical significance and relevance.

25. In its opinion, the Agency argued that the concept of maladministration cannot be used to call into question the margin of discretion enjoyed by its Paediatric Committee in assessing scientific issues.

26. The Agency then repeated the points made by its Paediatric Committee during the course of the administrative proceeding, as these are set out in the Summary Report on candesartan[29]. First, the Agency stated that, from the beginning of the procedure for candesartan, the rapporteur and peer-reviewer identified a clear therapeutic need for the development of medical products with regard to heart failure in children and the good "*potential for ARB*" in this area. Recognising that the conduct of a clinical study in paediatric heart failure would be scientifically challenging and acknowledging the safety concerns raised by the complainants in their application, the Paediatric Committee went on to state that the unmet therapeutic need had to be taken into account. The Paediatric Committee thus considered whether "off-label use" without appropriate data on safety and efficacy is more ethical than conducting a clinical study trying to define the risks and benefits with all available and necessary precautions and measures in place in order to minimise the risks of participating subjects. This aspect is addressed in Recital 7 of the Paediatric Regulation, it said. The conduct of clinical studies would, in any event, be subject to the specific requirements for the protection of the paediatric population laid down in Directive 2001/20/EC[30].

27. According to the Paediatric Committee, the need to conduct clinical trials (also between different applicants) has to be balanced against the ethical imperatives laid down in Recitals 4 and 7 of the Paediatric Regulation, which mandate against requesting many applicants to conduct the same clinical trials in the same population when the number of patients in the target population for enrolment and the feasibility of a clinical trial conducted according to Directive 2001/20/EC is limited. The different approach taken to products belonging to the same class is therefore justified from (i) a scientific point of view (there are a limited number of patients in the target population and candesartan has the most favourable taste of all available ARBs, thus rendering it as candidate drug for paediatric development) and also (ii) an ethical point of view.

28. The Agency then went on to refer to the assessment carried out by its Paediatric Committee following the complainants' request for re-examination. It acknowledged the complainants' argument that the current standard of care is ACEIs and ARBs, but recalled that their use in children is not evidence-based and is "off-label". No alternatives exist. It repeated the argument that conducting a clinical study is more ethical than allowing off-label use to continue to occur without appropriate data on safety and efficacy.

29. According to the Agency, the Paediatric Committee refused to recommend a waiver not only on grounds relating to therapeutic need for candesartan in treatment of heart failure in children, but also having assessed whether the product is likely to improve the benefit/risk balance as compared with the existing treatment regimes.

30. With regard to the complainants' argument that there was a lack of significant therapeutic benefit for ARBs in the condition of heart failure, the Agency again stated that the Paediatric Committee did not find that ARBs did not have a significant therapeutic benefit in the condition

of heart failure. This can be indirectly illustrated, it says, by the lack of class waiver for ARBs in the condition of heart failure. Moreover, the therapeutic need for each specific product (that is, in this case, each ARB) is assessed on several criteria related to the product characteristics and to the targeted clinical condition. It went on to say that this assessment is to some extent made case-by-case, but with similar common grounds applied across the conditions and the products.

31. The Agency pointed out that the Paediatric Committee did not find that the fact that ACEIs constitute established, recommended, and effective existing therapy in the condition of heart failure was sufficient to disregard the potential therapeutic need for ARBs as a whole class and candesartan in this particular condition. There is, it said, definitely a therapeutic interest for different products with different features, and adequate dosing data, pharmacokinetic data, efficacy data, and safety data in children with heart failure. It went on to argue that it fully endorses the possible different positioning of ARBs over ACEIs between adults and children but that this actually applies to any other product, justifying the need for a PIP as outlined by the Paediatric Regulation.

32. The Agency further stated that the argument that candesartan, or other ARBs, do not represent a significant or potential therapeutic benefit for the paediatric population is not acceptable and is even quite surprising given that the complainants applied for a PIP for candesartan concerning the condition of hypertension without putting forth a different rationale.

33. The Agency went on to cite the Paediatric Committee's comparison of candesartan with ACEIs for the condition of heart failure and in the paediatric population, which, it adds, is the purpose of any PIP. Candesartan, it said, could display the following benefits for children: (i) age-appropriate formulation for very young children; (ii) oral formulation with good taste for young children; and (iii) possibility of once-a-day doses for all age categories. These specific features plus appropriate pharmacokinetic/pharmacodynamicdata, dosing recommendations, efficacy, and safety data would constitute very valuable and necessary clinical information.

34. As far as the alleged inconsistency in treatment between ARBs is concerned, the Agency pointed out that the Summary Report for candesartan is unambiguous as to the fact that the argument of better taste was not the main justification in deciding to designate candesartan as the only agent required to undergo evaluation in the condition of heart failure. It quoted the Summary Report as follows: "*In our opinion taste represents an important aspect of a medicinal product, as it not only influences patient adherence, but also will have an impact on the formulation (no need for additional excipients to mask a bad taste). Additionally, the PK characteristics and the currently available data in adults make candesartan a better notion than the two other mentioned. Valsartan is more susceptible to a food effect (decrease of bioavailability in the presence of food) and losartan has the highest potential for drug interactions; besides, in light of ELITE II data, losartan could not have been chosen as an appropriate candidate for this indication. One could also argue that although Val-HeFT and CHARM trials supported the use of both valsartan and candesartan in HF, in light of the results, if a single candidate had to be chosen, it would be candesartan (although it is not clear to what extent the differences seen in those trials were due to the products or chance)*".

35. The Agency finally stated that the Paediatric Committee evaluates each PIP application on its own merits, on the basis of the data provided by the applicant and taking into account the paediatric population to be studied.

36. In their observations on the Agency's opinion, the complainants maintained that there is no proper basis for the Agency to refuse to grant a product-specific waiver in their case and that the Agency's decision is defective. In support of their position, they argued that (i) the Agency did not apply the rationale for granting a product-specific waiver consistently to similar cases, thereby infringing the principle of equal treatment; (ii) the Agency introduced an arbitrary consideration, which was inconsistent with the Paediatric Regulation, as the sole basis for requiring the complainants to carry out a paediatric study; and (iii) the Agency failed to provide proper reasoning to justify the differential treatment. As a result, the decision not to grant the requested waiver does not comply with the principle of fairness.

37. The complainants referred, in particular, to the Agency's position that the use of ACEIs and ARBs is not evidence-based. This position is, they said, not consistent with the existing clinical guidelines (based on the available clinical evidence) that support the view that ACEIs are effective therapies.

38. The complainants repeated the argument that, as a matter of EU law, an unmet medical need *per se* could not be the proper basis for justifying differential treatment. Nor could this be properly deployed as the basis for the Agency to refuse to grant a product-specific waiver.

39. The complainants contested the Agency's justification of a case-by-case approach to evaluating the therapeutic need for each specific product in heart failure against several criteria. The reasoning for this approach is, they stated, lacking throughout the entire assessment and re-examination process.

40. The complainants submitted that none of the scientific arguments made by the Agency as to why losartan and valsartan could not equally be chosen as suitable candidates for paediatric development is scientifically compelling, considering that both of these products have now been approved for use in the paediatric population[31]. They went on to contest, in detail, the scientific arguments advanced by the Agency in their choice of candesartan. They repeated their argument that taste is an irrelevant consideration and insisted that the three specific beneficial

features of candesartan listed by the Agency (see paragraph 33 above) are not unique to it, but are equally relevant to paediatric medicine development for the entire class of ARBs. They argued that, based on the pharmacokinetics of candesartan, losartan, and valsartan, it cannot be predicted with any degree of certainty that any one of the ARBs would be more beneficial than another for the treatment of heart failure in children. They also referred to the admission that the data extrapolated from adult studies with regard to candesartan and valsartan is not conclusive and could constitute a chance-finding.

41. With regard to the Agency's acknowledgment that the conduct of a paediatric study would be *"scientifically challenging"* and that the complainants had raised safety concerns arising from the conduct of such a study, the complainants argued that, ordinarily, such considerations would form the basis for granting a product-specific waiver pursuant to Article 11 of the Paediatric Regulation.

42. Finally, the complainants insisted that it would be manifestly wrong for the Agency, in light of ethical principles[32], to require the complainants to carry out a paediatric clinical study which, they argued, will not lead to a clinically meaningful and interpretable conclusion.

43. In their additional observations, the complainants submitted a report arising from the Expert Group Meeting of Paediatric Heart Failure that was organised by the Agency on 29 November 2010 to discuss clinical trials in paediatric heart failure. According to the complainants, key considerations arising from the Report include that ACEIs remain the first line treatment for heart failure and that ARBs *"have little beneficial effect over ACEI in adults, but pharmacokinetic/pharmacodynamic (PK/PD) and safety data are needed anyway. It is possible to obtain PK data from hypertension trials with ARBs"*. In the complainants' view, the Report supports the granting of a product-specific waiver for candesartan, consistent with the Agency's prior decisions in respect of two similar ARBs, for the reasons that any paediatric study for treating heart failure with an ARB would be unlikely to generate any clinically meaningful results.

The Ombudsman's assessment leading to a draft recommendation

Preliminary Remark

44. The Ombudsman's services carried out an inspection in the present case in which access was obtained to, notably, the Agency's documents concerning the PIP and waiver applications submitted for losartan and valsartan[33]. In the context of the inspection, the Agency stated that the documents inspected by the Ombudsman's services were confidential. In accordance with Article 4(1) of the Ombudsman's Statute[34] and Articles 5(2), 13(3), and 14(2) of the implementing provisions adopted by the Ombudsman and last amended on 3 December 2008[35], the Ombudsman's inspection will not result in the complainant's or any other person's obtaining access to any documents which the Agency identified as confidential during the inspection, or to any information contained in such documents. While the Ombudsman will not reveal documents which the Agency identified as confidential, or any information contained in such documents, the Ombudsman's analysis will clearly take account of, and draw the appropriate conclusions from, the information contained in these documents.

The legal framework

45. The Ombudsman will set out his analysis of the legal framework and examine whether the Agency applied that legal framework correctly.

46. The Ombudsman recalls that the aim of the Paediatric Regulation is to improve the availability of medicinal products tested for paediatric use. Pharmaceutical companies that wish to obtain a marketing authorisation through the EU central authorisation system are therefore required to consider, as part of product development, the possible paediatric use of their products. In this context, the Paediatric Regulation requires pharmaceutical companies to propose PIPs. Article 2(2) of the Paediatric Regulation defines a PIP as a research and development programme aimed at ensuring that the necessary data, determining the conditions in which a medicinal product may be authorised to treat children, are generated.

47. The Agency's Paediatric Committee is responsible for assessing the content of any PIP submitted to it, as well as requests for a waiver or a deferral of the obligation to carry out a PIP. In carrying out these tasks, the Paediatric Committee performs a careful balancing act, reflecting the considerations laid down in Recitals 4 and 7 of the Paediatric Regulation, according to which, respectively (i) the objectives of the Paediatric Regulation should be achieved without subjecting children to unnecessary clinical trials[36], and (ii) any concerns about conducting trials should, in turn, be balanced by the ethical concerns related to giving untested medicinal products to children[37].

Grounds for granting a waiver

48. As will be explained in detail below, the Ombudsman finds that the structure of analysis that should be applied in the case of waiver applications[38], is as follows.

- Stage 1[39]: Determine whether the applicant has demonstrated that Article 11(1) (b) of the

Paediatric Regulation applies, namely, whether the applicant has demonstrated that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations;

If the applicant has not demonstrated the above, the Agency should move to Stage 2.

- Stage 2: Determine whether the applicant has demonstrated that Article 11(1) (a) of the Paediatric Regulation applies, namely, whether the applicant has demonstrated that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;

If the applicant has not demonstrated the above, the Agency should move to Stage 3.

- Determine whether the applicant has demonstrated that Article 11(1) (c) of the Paediatric Regulation applies, namely, whether the applicant has demonstrated that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

If the applicant has not demonstrated the above, the Agency should move to Stage 4.

- Stage 4: Determine whether the applicant has demonstrated that it is impossible (because, for example, the patient population is too small) to design studies in relation to a medicinal product which create the necessary therapeutic benefits in terms of quality, safety, and efficacy[40];

If the applicant has not demonstrated the above, the Agency should move to Stage 5.

- Stage 5: If there are two or more products in the product class that are suitable for a PIP, and if the relevant patient population is too small to allow for the PIP to be carried out on all the relevant products in the product class, a waiver should be granted to the applicant that has demonstrated that its product is sub-optimal, as far as the PIP is concerned, when compared with the alternative candidate product(s).

Stage 1

49. Stage 1 of the analysis requires little explanation. Certain diseases or conditions, such as many occupational diseases, only occur in adult populations. If the specific medicinal product or class is intended to treat such diseases or conditions, it serves no purpose to do a PIP in relation thereto.

Stage 2 and Stage 3

50. Stages 2 and 3 are closely linked. If a product (or a class of product to which it belongs) is deemed to be ineffective or unsafe for paediatric patients under Stage 2, it is clear that the product will not have, under Stage 3, a "significant therapeutic benefit" over existing treatments for paediatric patients (assuming that no existing treatments are ineffective or unsafe). However, it could be the case that a product passes Stage 2, because it is deemed to be effective and safe for paediatric patients, but fails to pass Stage 3, because it does not provide a "significant therapeutic benefit" over existing treatments for paediatric patients.

51. With regard to Stage 3, concerning Article 11(1)(c) of the Paediatric Regulation, the Commission's PIP Guideline[41] states that, when considering the question of whether a specific medicinal product constitutes a "significant therapeutic benefit" over existing treatments for paediatric patients, the Paediatric Committee will take into account the nature of the condition to be treated and the available data on the medicinal product concerned. The Guideline also lists the elements on the basis of which a finding of "significant therapeutic benefit" might be made. For example, the Paediatric Committee may determine that there is a significant therapeutic benefit where existing treatments are not satisfactory and alternative methods with an improved expected benefit-risk balance are needed, or where the product in question offers an improved dosing scheme or method of administration (number of doses per day, oral compared to intravenous administration, reduced treatment duration), or makes a new clinically relevant age-appropriate formulation available[42]. The assessment carried out by the Paediatric Committee is clearly comparative in relation to alternative treatments.

52. Since the benchmark for determining whether Article 11(1)(c) of the Paediatric Regulation applies is the efficacy of **alternative existing treatments** for paediatric patients, this means that, as regards the application of Article 11(1)(c) of the Paediatric Regulation to the present case, the relevant question is: does candesartan represent a "significant therapeutic benefit" for paediatric patients when compared with ACEIs.

Stage 4

53. The Ombudsman notes that the grounds for granting a waiver laid down in Article 11(1) of the Paediatric Regulation are not exhaustive. An additional implicit reason for granting, or not granting, a waiver can be derived from Article 6(2) of the Paediatric Regulation[43], according to which, when carrying out its tasks, the Paediatric Committee shall consider whether or not any proposed studies can be expected to be of significant therapeutic benefit to the paediatric population and/or to fulfil a therapeutic need[44] of the paediatric population[45].

54. The determination as to whether or not any studies proposed under a PIP can be expected to be of significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population, must be measured against the following benchmarks:

- First, the "therapeutic benefits" resulting from a PIP must be measured against the present day level of knowledge concerning the medicinal product in question in order to determine if the "therapeutic benefits" of a PIP are indeed "significant". For instance, if the present-day level of knowledge concerning the use of candesartan for paediatric patients were very low, even a modest PIP (for example, a PIP relating to a limited number of patients and relating to only one field of study, such as dosage) could bring "significant therapeutic benefits". In contrast, if the level of existing knowledge in relation to a product were already extensive, it might be necessary to carry out very wide-ranging studies to ensure that they gave rise to significant therapeutic benefits.

- Second, the "therapeutic benefits" resulting from a PIP must be measured against the possible consequences of carrying out tests on paediatric patients in order to determine if the expected therapeutic benefits justify the studies proposed[46]. In sum, even if the test set out immediately above leads to the conclusion that a PIP would bring "therapeutic benefits", it might still be the case that these "therapeutic benefits" are not sufficient to outweigh the concerns inherent in the testing of the medicinal product in question on paediatric patients.

55. In relation to the above, the Ombudsman notes that it may be impossible, in certain circumstances, to carry out an extensive PIP (for example, where the paediatric patient population is not sufficiently numerous to permit extensive assessments). In such circumstances, it is consistent with the purpose of the Paediatric Regulation, and the wording of Article 6(2) of the Paediatric Regulation in combination with Articles 15 and 17 of the Paediatric Regulation, to require the applicant to carry out at least a limited PIP, provided that limited PIP can be reasonably expected to give rise to "significant therapeutic benefits". As noted above, the relative present-day lack of knowledge in relation to the paediatric use of a product will be a relevant factor when determining if a limited PIP can produce "significant therapeutic benefits". If very little is currently known in relation to the paediatric use of the product, it will be more likely that even limited studies will provide therapeutic benefits which are "significant"[47].

56. In sum, the fact that large scale studies cannot be carried out does not imply that no studies should be carried out. In other words, this aspect of the Paediatric Regulation reflects the popular adage that the best should not be the enemy of the good.

57. Furthermore, and of particular relevance to the case at hand, where the Paediatric Committee concludes that a waiver should not be granted on the basis of Article 11(1)(c) — in other words, where there **is** a potential significant therapeutic benefit of the product compared to existing treatments — there would need to be particularly compelling reasons put forward by the applicant as to why studies could not be carried out in that particular case and why, therefore, it believes that a waiver should be granted[48].

Stage 5

58. While the limited size of a patient population will have an impact on the extent and nature of a PIP (a large scale PIP may be impossible if the paediatric patient population is small), it will also have an impact on which product(s) within a particular product class should be required to carry out a PIP. If the paediatric patient population is so small as to make it impossible to carry out (even a small scale) PIP **in relation to more than one product**, it will be necessary, first, to conclude that only one product be required to undergo tests in the paediatric population[49], and second, to carry out a comparative assessment of the various candidate products in order to ascertain which product should be chosen to undergo testing. Where there is a limited patient population for testing, it is important that testing is not carried out using a sub-optimal product. This latter assessment will therefore involve a comparative examination of the various products in a product class (in this case, the relevant ARBs) to determine which product is the most appropriate candidate. The comparative examination will be based on a number of criteria, such as amenability to testing and the relevant specific potential therapeutic benefits of each product.

59. As the Agency has correctly pointed out (see paragraph 27 above), the need to conduct clinical trials has to be balanced against the ethical imperatives laid down in Recitals 4 and 7 of the Paediatric Regulation, which mandate against requesting many applicants to conduct the same clinical trials in the same population when the number of patients in the target population for enrolment and the feasibility of a clinical trial conducted according to Directive 2001/20/EC is limited[50]. In such circumstances, even if more than one product might be suitable for a PIP, it will be necessary to choose, from amongst the products suitable for a PIP, the product which is the most suitable for a PIP.

60. A waiver may therefore be granted, even if the four tests for granting a waiver described above are not met (the three tests set out in Article 11(1) of the Paediatric Regulation, and the additional test derived from Article 6(2) of the Paediatric Regulation in combination with Articles 15 and 17 of the Paediatric Regulation). Such a situation would arise, if the Agency concludes that: (i) the relevant patient population is too small to allow for a PIP to be carried out on all relevant products in the product class, and (ii) the product in question is a less suitable candidate (in terms of, for example, amenability to testing and relevant specific potential

therapeutic benefits) than (an) alternative product(s) in that product class.

61. The Ombudsman underlines that if Stage 5 of the analysis is arrived at, it is only necessary to find that a product has **some therapeutic benefit when compared with other products in that product class**. That comparative therapeutic benefit taken into account could, indeed, be minimal.

Rationale for differences between the different stages of analysis

62. To recall, under Stage 3 of the analysis the applicant will seek to demonstrate that its product has no **significant** therapeutic benefit when compared to existing treatments for paediatric patients. If Stage 5 of the analysis is arrived at, the applicant will seek to show that its product has less therapeutic benefit when compared with other candidate products in that product class. The comparative therapeutic benefit taken into account under Stage 5 could, indeed, be **minimal**. The reasons for the difference between Stage 3 and Stage 5 are as follows. The purpose under Stage 3 is **to determine if testing should be carried out at all**. When analyzing this question, account is taken of whether the product could provide a **significant therapeutic benefit compared to existing treatments**. In contrast, the purpose under Stage 5 is not to decide whether testing should be carried out (that question will already have been answered in the affirmative if Stage 5 is reached), but rather **to identify the most suitable product(s) to test in a situation where it is not possible to test all products** (for example, due to the limited size of the patient population). If a candidate product is deemed to be more suitable for testing at Stage 5 of the analysis because it has **some therapeutic benefit when compared with other products in that product class**, a waiver can be validly withheld for the more suitable candidate product. The fact that the comparative therapeutic benefit between one candidate product and another might be minimal is not problematic under Stage 5[51].

Overall consistency of the analysis under the Paediatric Regulation

63. The Ombudsman also finds it important to note that his suggested structure of analysis is consistent with the analysis of proposed PIPs carried out by the Paediatric Committee in contexts other than waiver applications[52].

64. As regards Stage 4 of his suggested structure of analysis, the Ombudsman notes that such consistency is a legal requirement. In sum, Article 6(2) of the Paediatric Regulation states that when carrying out (all) its tasks, the Paediatric Committee shall consider whether or not any proposed studies can be expected to be of "significant therapeutic benefit" to and/or fulfil a "therapeutic need" of the paediatric population. In sum, a single benchmark is set for all such tasks.

65. Article 6(1) of the Paediatric Regulation states that the tasks of the Paediatric Committee include the tasks of (a) assessing the content of any paediatric investigation plan for a medicinal product submitted to the Paediatric Committee in accordance with the Regulation and formulating an opinion thereon (the Ombudsman refers to this procedure as the "agreement procedure")[53], and of (b) assessing waivers and deferrals and formulating an opinion thereon (the Ombudsman refers to this procedure as the "waiver procedure").

66. The Ombudsman underlines that the benchmarks that apply with respect to obtaining an "agreement" in relation to a proposed PIP by using the “agreement procedure” under Articles 15 to 19 of the Paediatric Regulation (in sum, the process by which a "proposed PIP" becomes an "agreed PIP") are substantively identical to the benchmarks that apply in relation to a waiver procedure under Articles 11 to 14 of the Paediatric Regulation. In sum, in both the "agreement procedure" and the "waiver procedure", if it is excluded that one of the exceptions set out in Article 11(1)(a), (b), or (c) applies (Stages 1 to 3 of the analysis), the Paediatric Committee must examine whether a PIP brings "significant therapeutic benefits" (Stage 4 of the analysis). Under the "agreement procedure", the issue will be approached by asking whether the applicant has proposed studies which bring "significant therapeutic benefits"[54]. In such a context, the Paediatric Committee may take the view that the proposed PIP is not sufficiently extensive and may, through dialogue with the applicant, seek to identify a more appropriate, broader PIP. Under the "waiver procedure", the issue will be approached by asking whether the applicant has put forward objective reasons as to why it is not possible to carry out studies which bring "significant therapeutic benefits". If the Paediatric Committee finds that it is possible to undertake a PIP which gives rise to "significant therapeutic benefits", a waiver will not be granted[55]. In sum, while the manner in which the issue is approached differs between the "agreement procedure" and the "waiver procedure", the benchmarks used in both procedures are identical.

67. It must be underlined, in relation to the above, that the practical outcome for an applicant, in terms of the extent of a PIP that it will be required to carry out, should thus be identical if an application is made under the "agreement procedure" or under the "waiver procedure". If, under the "waiver procedure", a waiver is refused under Stage 4 of the analysis because the Paediatric Committee finds that a PIP generating "significant therapeutic benefits" is feasible, and following that finding a relevant PIP is agreed, it would have to be the case that the same PIP would have been accepted by the Paediatric Committee if no waiver application were ever made and the PIP had been submitted directly through the "agreement procedure"[56].

Principle of equal treatment[57]

68. The principle of equal treatment prohibits, among others, comparable cases from being treated differently, thereby subjecting to disadvantages some as opposed to others, unless such treatment can be objectively justified[58]. The principle of equal treatment is a fundamental right protected by the Charter of Fundamental Rights of the European Union[59].

69. Losartan, valsartan, and candesartan form part of the same product class (they are all ARBs) and they were all subject to the same waiver procedure over the same period of time. The companies submitting the waiver applications to the Paediatric Committee were thus in a comparable situation. The principle of equal treatment should therefore have applied as regards all three waiver applications. As such, any difference in treatment between these three waiver applications must be objectively justified.

The losartan and valsartan decisions

70. At the time their application for a waiver was being examined, the complainants only had access to the limited information concerning the waivers for losartan and valsartan which the Agency had provided in the public versions of those waiver decisions[60]. The candesartan, losartan, and valsartan decisions refer to the fact that the Summary Reports of the Paediatric Committee are appended to all three decisions. Those Summary Reports are not, however, publicly available. This is because the full decisions, including all the annexes and appendices, are only sent to the applicants (that is, the companies that, respectively, submitted the candesartan, losartan, and valsartan waiver requests). While the Summary Reports for PIP and waiver applications set out in detail the analysis of the Paediatric Committee (for example, the Summary Report relating to candesartan contains 126 pages), the publicly available decisions for PIP and waiver applications are very brief (the publicly available decision relating to candesartan contains only 7 pages).

71. The relevant sections of the **publicly available version**[61] of the Agency's decision of 29 February 2008 concerning losartan read as follows:

"Article 1

A Paediatric Investigation Plan for Cozaar and associated names, losartan potassium, 12.5, 25, 50 and 100 mg, film-coated tablets, oral use, the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby agreed.

Article 2

A waiver for Cozaar and associated names, losartan potassium, 12.5, 25, 50 and 100 mg, film-coated tablets, oral use, the details of which are set out in the Opinion of the Paediatric Committee the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

(...)

Opinion [of the Paediatric Committee]

1. The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

- to agree the paediatric investigation plan in accordance with Article 18 of Regulation (EC) No 1901/2006 as amended,

- to grant a deferral in accordance with Article 21 of Regulation (EC) No 1901/2006 as amended

- to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of Regulation (EC) No 1901/2006 as amended and concluded in accordance with

Article 11(1)(a) of Regulation (EC) No 1901/2006 as amended, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population

Article 11(1)(c) of Regulation (EC) No 1901/2006 as amended, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

(...)

B. WAIVER

Condition

(...)

Heart failure

Subset(s) of the paediatric population, pharmaceutical form(s) and route(s) of administration covered

The waiver applies to

All subsets of the paediatric population for tablets and age appropriate, commercial liquid formulation for oral use

(...)"

72. The relevant sections of the **publicly available version**[62] of the Agency's decision of 14 October 2008 concerning valsartan read as follows:

"Article 1

A Paediatric Investigation Plan for Valsartan (Diovan), film-coated tablet, hard gelatin capsule; age appropriate formulation: liquid formulation, oral use, the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby agreed.

Article 2

A waiver for Valsartan (Diovan), film-coated tablet, hard gelatin capsule; age appropriate formulation: liquid formulation, oral use, the details of which are set out in the Opinion of the Paediatric Committee the European Medicines Agency annexed hereto, together with its appendices, is hereby granted

(...)

Opinion [of the Paediatric Committee]

The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

- to agree the paediatric investigation plan in accordance with Article 18 of Regulation (EC) No 1901/2006 as amended,

- to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of Regulation (EC) No 1901/2006 as amended and concluded in accordance with:

Article 11(1)(a) of Regulation (EC) No 1901/2006 as amended, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population

Article 11(1)(b) of Regulation (EC) No 1901/2006 as amended, on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in adult populations

Article 11(1)(c) of Regulation (EC) No 1901/2006 as amended, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

(...)

B. WAIVER

Condition

(...)

Heart failure

Subset(s) of the paediatric population, pharmaceutical form(s) and route(s) of administration covered

The waiver applies to

All paediatric age groups (0 to less than 18 years) for film-coated tablet, hard gelatin capsule for oral use

(...)"

73. The Ombudsman notes that the publicly available versions of the Agency's decisions for PIP and waiver applications **do not set out specifically why a waiver is granted for a particular indication** (for example, the publicly available versions make no distinction between the waivers granted for hypertension and heart failure). As can be seen from paragraphs 71 and 72 above, they generically and formalistically refer to the relevant grounds of Article 11(1), but without specifying which ground justified a waiver for which particular indication. For example, the decision of 14 October 2008 relating to valsartan states that the Paediatric Committee recommended the granting of a waiver "for one or more subsets of the paediatric population" in accordance with:

- Article 11(1)(a) of the Paediatric Regulation, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population

- Article 11(1)(b) of the Paediatric Regulation on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in adult populations

- Article 11(1)(c) of the Paediatric Regulation on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

The above information does not clarify which grounds for a waiver are relevant for which indication. We cannot, for example, decipher from this information which grounds for a waiver applied to hypertension and which to heart failure[63].

74. As is explained in further detail below, a person reading only the publicly available version of the valsartan decision would have wrongly assumed that a waiver was granted to valsartan under Stages 1 to 3 of the structure of analysis suggested by the Ombudsman for the indication of heart failure in children.

Comparative assessment between valsartan and candesartan

75. The comparison between candesartan and valsartan is a key issue in this case (see paragraphs 117 to 121 below). The Ombudsman notes that, in response to a request from the complainants to explain why candesartan was treated differently from the two other products in the same product class, namely, losartan and valsartan, the Agency maintained that it did carry out a **comparative assessment between valsartan and candesartan**. In this context, it stated in the Summary Report concerning candesartan, that *"(...) (ii) the PK characteristics and the currently available data in adults make candesartan a better candidate than the two other ARBs (valsartan is more susceptible to a food effect and losartan has the highest potential for drug interactions); (iii) in light of ELITE II data, losartan could not have been chosen as an appropriate candidate for this indication; (iv) while trials supported the use of both valsartan and candesartan in heart failure, in light of the results, if a single candidate had to be chosen, it would be candesartan (although it is not clear to what extent the differences seen in those trials were due to the products or chance)."*

76. It must be recalled (see paragraph 58 above) that it is only necessary to carry out the comparative assessment under Stage 5 of the structure of analysis put forward by the Ombudsman, if at least two candidate products have passed Stage 1 to Stage 4 of the analysis. If it actually were the case that both losartan and valsartan were granted a waiver at Stage 1 to Stage 3 of the analysis, it would have to be concluded that candesartan could not be dealt with under Stage 5. In sum, it would not be possible to carry out a comparative assessment involving candesartan under Stage 5, given that a Stage 5 comparative assessment would necessarily have to concern candesartan and at least one other ARB. A review of the full candesartan decision (in particular the citation in the preceding paragraph) indicates, however, that candesartan was subjected to a comparative assessment under Stage 5 (see further below)[64].

77. It should also be noted that, if losartan and valsartan were in fact granted a waiver on the basis of Article 11(1)(c) (that is, at Stage 3), one would have expected the Agency to limit itself, in its candesartan decision, to indicating why losartan and valsartan did not represent a significant therapeutic benefit over existing treatments for paediatric patients, that is, over ACEIs. It would then, in the candesartan decision, have stopped its analysis after Stage 4, since no comparative analysis between candesartan and another ARB would have been necessary under Stage 5. However, this is not what occurred in the candesartan decision. In its decision concerning candesartan, the Agency does indicate why losartan did not represent a significant therapeutic benefit over existing treatments for paediatric patients. It does so by stating that "*in light of ELITE II data, losartan could not have been chosen as an appropriate candidate for this indication*" -- a conclusion which shows that losartan was granted a waiver at Stage 3. The same, however, cannot be said for valsartan. Indeed, the reasons which the Paediatric Committee put forward in the candesartan decision to justify the difference in treatment between valsartan and candesartan show that valsartan could also have been chosen to undergo a PIP for heart failure. The only reason it was not chosen was because the comparative analysis undertaken under Stage 5 of the Ombudsman's structure of analysis led to the conclusion that valsartan constituted a sub-optimal choice when compared to candesartan. It was, in this context, entirely understandable that the complainants, having only had access to the publicly available versions of the losartan and valsartan waiver decisions, would take the view that they were the victims of a breach of the principle of equal treatment in relation to their waiver application. It was thus entirely understandable that they made a complaint to the Ombudsman in relation thereto.

78. Before drawing the necessary conclusions from this finding, the Ombudsman will now set out his analysis of the substance of the candesartan decision.

Assessment of the Agency's position in relation to candesartan

79. The Ombudsman will now examine in detail how the Agency dealt with the waiver request for candesartan. In doing so, he will also examine a number of the arguments put forward by the complainants in relation to the Agency's assessment. The arguments the Ombudsman will focus on relate to Stages 3, 4, and 5[65] of his structure of analysis.

Stage 3

80. With regard to Stage 3, the complainants make a range of arguments. First, they argue that therapeutic need is not, *per se*, decisive. The Ombudsman cannot agree with that argument. The very purpose of the Paediatric Regulation, according to Article 1 thereof, is to lay down

rules concerning the development of medicinal products "*(...) in order* ***to meet the specific therapeutic needs of the paediatric population*** *(...)*". (emphasis added)

81. The complainants then point out that, as far as Article 11(1)(c) of the Paediatric Regulation is concerned, EU law requires an assessment of whether the product is "likely" to improve the risk/benefit balance as compared with the existing treatment regimes[66]. They point out that the risk/benefit balance of ARBs is *unlikely* to confer a significant therapeutic advantage over the existing treatment modalities. Moreover, in their re-examination request, they state that candesartan is *unlikely* to provide a significant therapeutic benefit over existing treatment modalities.

82. The Ombudsman notes that, while both Article 11(1)(a) and Article 11(1)(c) are based on assessments of the possible outcomes resulting from the use of the product under examination (in this sense, both assessments are prospective), there is an important difference between the two assessments. Whereas Article 11(1)(a) speaks of "likelihood" (of a product being ineffective or unsafe), Article 11(1)(c) does not speak of "likelihood". It does not suffice, under Article 11(1)(c), to show that a product is *unlikely* to provide a significant therapeutic benefit. Rather, it must be argued that the product does not provide a significant therapeutic benefit. In sum, a stricter standard of proof applies to Article 11(1)(c) when compared to Article 11(1)(a)[67]. The complainants do not appear to have met this higher standard of proof.

83. As regards the Agency's substantive scientific assessment that ARBs constitute a significant therapeutic benefit over existing treatments (that is, over ACEIs), the Ombudsman also underlines that the Paediatric Committee's scientific view that ARBs could constitute a significant therapeutic benefit over existing treatment modalities is a scientific assessment which could only be called into question in the event it were shown that there was a manifest error of assessment by the Paediatric Committee[68]. The complainants have not put forward arguments which show that there was a manifest error of assessment by the Paediatric Committee.

84. The Ombudsman notes that all the above points in paragraphs 80 to 83 apply to all ARBs, namely, to candesartan, losartan, and valsartan. The Ombudsman notes, indeed, that the conclusion of the Paediatric Committee that "there could be a perceived benefit of ARBs" and that "ARBs could play a role in this indication" underscores the need for the Agency to explain to the complainants why **their particular ARB** was seen to be of significant therapeutic benefit compared to ACEIs, **while the other two ARBs were not**.

85. The Ombudsman notes that, to support its conclusion that candesartan may have a significant therapeutic benefit over ACEIs, the Paediatric Committee went on to point to what it considered to be specific characteristics of candesartan. These benefits were (i) age appropriate formulation for very young children; (ii) oral formulation with a good taste for young children; (iii) possible once-a-day use for all age categories. The complainants state that these three characteristics are not unique to candesartan but are *"equally relevant to paediatric medicine development for the entire class of ARBs"*. The complainants go on to argue that they cannot be forced to carry out a PIP solely because their product is **already available** in a suitable paediatric dosage form and a formulation suitable for use in children. The Ombudsman agrees. He notes that, **as part of the requirement relating to PIPs**, the Paediatric Regulation imposes an obligation to develop a suitable paediatric dosage form and a formulation suitable for use in children **before** commencing a paediatric study. If these are requirements **resulting from the general obligation to carry out a PIP**, the absence of a suitable paediatric dosage form and a formulation suitable for use in children, prior to a waiver application, cannot be a reason for granting a waiver (if this were not the case, any waiver applicant (in relation to any product) would be successful by simply arguing that it has not yet developed a suitable paediatric dosage form and a formulation suitable for use in children[69]). In sum, absent other reasons for granting a waiver to a particular ARB, **all ARBs would be required to create a suitable paediatric dosage form and a formulation suitable for use in children**.

86. It follows from the previous paragraph that the Agency would not be empowered to penalise the complainants, in denying them a waiver, for having already developed a paediatric formulation/dosage.

87. The Ombudsman underlines that the only correct justification for granting waivers under Article 11(1)(c) of the Paediatric Regulation, that is, under Stage 3, to losartan and valsartan, but not to candesartan, would be if the Agency identified specific characteristics of losartan and valsartan, which were not shared by candesartan, and which proved why losartan and valsartan did not represent a significant therapeutic benefit compared to ACEIs.

88. The Agency did indeed show, in its candesartan decision, that losartan did not represent a significant therapeutic benefit compared to ACEIs (the candesartan decision states that "*in light of ELITE II data, losartan could not have been chosen as an appropriate candidate for this indication*"[70]). However, it did not do so for valsartan. This deficiency further suggests that, as identified by the Ombudsman in paragraph 77 above, valsartan was not, after all, granted a waiver on the basis of any of the reasons set out in Article 11(1) of the Paediatric Regulation.

Stage 4

89. Having discounted the possibility of granting a waiver to candesartan on the grounds of Article 11(1)(c) of the Paediatric Regulation (Stage 3 of the Ombudsman's structure of analysis),

the Paediatric Committee dealt in detail with the complainants' concerns that the requested dose exploratory study in 50 children with heart failure is neither ethically acceptable nor feasible and will not yield interpretable, useful results. In line with Stage 4 of the structure of analysis outlined above, the Paediatric Committee examined whether it would be possible to carry out studies in relation to candesartan which create "therapeutic benefits" in terms of quality, safety, and efficacy.

90. The Paediatric Committee recognised, inter alia, that (i) the relevant patient population was not numerous, (ii) a study would be *"scientifically challenging"*, and (iii) the applicant had raised safety concerns arising from the conduct of such a study.

91. The complainants argue that, ordinarily, such considerations would form the basis for granting a product-specific waiver pursuant to Article 11 of the Paediatric Regulation[71].

92. In their complaint to the Ombudsman, the complainants also argue that, in light of ethical principles, it was manifestly wrong for the Agency to require them to carry out a paediatric clinical study which will not lead to a "clinically meaningful and interpretable conclusion". They argue that the Paediatric Committee's request for them to carry out a dose exploratory study in 50 children with heart failure failed to meet the regulatory standard and threshold as regards clinical significance and relevance.

93. The Ombudsman does not agree with the complainants' arguments. As outlined in detail above, the considerations set out in paragraph 54 will be relevant in determining the nature and extent of the eventual PIP(s), but, unless they were to lead to the conclusion that it is not technically possible to carry out a PIP, they do not necessarily imply that a waiver should have been granted.

94. The Ombudsman further recalls that, as outlined in Article 6(2) of the Paediatric Regulation, a PIP should be approved if it can be expected to be of "significant therapeutic benefit" to and/or fulfil a "therapeutic need" of the paediatric population. It is for the Agency to determine, on the basis of the available scientific evidence, what studies are useful[72]. This determination will, moreover, be guided by **the present day level of knowledge concerning the medicinal product**. A PIP should be deemed valid if it seeks to obtain information concerning the correct use of a medicinal product for the paediatric population. Given that the use of ARBs in the treatment of heart failure in children is, according to the Agency, currently not "evidence-based", even a modest PIP in this specific instance could bring, relative to the present limited level of knowledge on the use of ARBs in children, "significant therapeutic benefits". It should be recalled, after all, that medical practitioners currently use these products to treat children with heart failure, despite the fact that little or no scientific data are available as regards their use in children.

95. The Ombudsman notes, moreover, that it is for the complainants, who shoulder the burden of proof, to show that **no possible studies** that would potentially lead to an improvement in the level of knowledge could be carried out. He notes that they have not done so. The complainants insist, instead, that the data generated from the studies should be clinically meaningful and interpretable. They argue that they should only be required to carry out studies if the study results can be included in the Summary of Product Characteristics. The Ombudsman notes that the Paediatric Committee recognises in this case that while the study "will probably not lead" to a marketing authorisation for the indication of heart failure in children, it "may generate relevant data to be included in the Summary of Product Characteristics".

96. The fact that the complainants do not share the Paediatric Committee's view that the PIP may generate relevant data to be included in the Summary of Product Characteristics is a question of scientific opinion. As outlined above, the Ombudsman could only call into question the scientific assessment of the Paediatric Committee if evidence were provided of a manifest error of assessment by that Committee[73]. In such circumstances, the Ombudsman would not second guess the Paediatric Committee, but would ask it for a further review in order to allow the Agency to clarify the issue.

97. The Paediatric Committee has taken the view that the PIP study "will probably not lead" to a marketing authorisation for the indication of heart failure in children, but "may generate relevant data to be included in the Summary of Product Characteristics". As regards this point, the Ombudsman notes that, even if the use of candesartan would, subsequent to the envisaged limited PIP, remain “off-label” for the indication of heart failure in children (because the PIP would not generate the very significant data required to justify the granting of a marketing authorisation), that off-label use could be made more effective and/or safer, given that at least **some** relevant data could be generated concerning the indication of heart failure in children. As such, while not sufficient to lead to a marketing authorisation for the indication of heart failure in children, the PIP could still give rise to "significant therapeutic benefits". It must, once again, be underlined that ARBs are already used "off-label" to treat children.

98. With regard to the arguments put forward by the complainants in their additional observations, the Ombudsman notes the specific argument made therein that ARBs "*have little beneficial effect over ACEI in adults, but pharmacokinetic/pharmacodynamic (PK/PD) and safety data are needed anyway. (...)"*. He finds that this can only argue in favour of conducting studies.

99. Similarly, while the Paediatric Committee appears to acknowledge that there might be safety concerns arising from the conduct of a study, it concludes that a study is necessary in this case, as (i) there is a clear unmet therapeutic need; (ii) ACEIs and ARBs are currently used off-label,

raising the issue of whether such use without appropriate data on safety and efficacy is more ethical than a clinical study which tries to define the risks and benefits of using the product and is undertaken with all the necessary precautions and measures to try to minimise the risks to participating subjects. In sum, while there are acknowledged risks in carrying out the PIP, these are outweighed by the risks resulting from the fact that ARBs are currently in use in children (off-label) despite the lack of appropriate data on safety and efficacy.

100. The Ombudsman therefore finds that the Paediatric Committee gave detailed reasons as to why it concluded, in relation to Stage 4 of the structure of analysis, that even a limited PIP would bring significant therapeutic benefits in this specific instance.

Stage 5

101. Having therefore further discounted the possibility of granting a waiver to candesartan in line with Stage 4 of the structure of analysis outlined by the Ombudsman above, the Paediatric Committee went on to carry out the comparative assessment referred to in Stage 5 of the said structure. Specifically, it examined whether, when compared to other candidate ARBs, candesartan is sub-optimal as far as testing is concerned. The Paediatric Committee found, for a number of reasons, that candesartan is the most appropriate product out of the three ARBs[74].

102. The complainants develop in detail the point that the substances candesartan, losartan, and valsartan, which belong to the same therapeutic class (ARBs), exhibit essentially the same pharmacological properties and that there is no substantial difference between them. The Ombudsman notes that it is not contested that the ARBs, which belong to the same therapeutic class, exhibit essentially the same pharmacological properties. However, the fact that all ARBs essentially have the same pharmacological properties does not imply that all ARBs are identical.

103. In order to justify differential treatment, the Ombudsman notes that the Agency should be able to point to objective evidence allowing it to differentiate the products[75].

104. As far as the justification for differential treatment is concerned, the Ombudsman notes that, in its opinion on this complaint, the Agency repeats the arguments put forward by the Paediatric Committee in its re-examination assessment. More specifically, it takes the view that (i) taste represents an important aspect, as it not only influences patient adherence, but also will have an impact on the formulation (if taste is not an issue there is no need for additional excipients to mask a bad taste)[76]; (ii) the PK characteristics and the currently available data in adults make candesartan a better candidate than the two other ARBs (valsartan is more susceptible to a food effect and losartan has the highest potential for drug interactions); (iii) in light of ELITE II data, losartan could not have been chosen as an appropriate candidate for this indication; and (iv) while trials supported the use of both valsartan and candesartan in heart failure, in light of the results, if a single candidate had to be chosen, it would be candesartan (although it is not clear to what extent the differences seen in those trials were due to the products or chance).

105. The complainants insist that none of these points is scientifically compelling as regards the reasons why losartan and valsartan could not be equally chosen as suitable candidates for paediatric development. In their view, this is so given that both of these products have by now been approved for use in the paediatric population[77].

106. Further, they argue that it cannot be predicted with any degree of certainty, on the basis of the pharmacokinetics of candesartan, losartan, and valsartan, that any one of the ARBs would be more beneficial than another for the treatment of heart failure in children. Nor was the decision evidence-based, they say, because the Agency could equally suggest valsartan as a suitable drug candidate for testing in a paediatric population for heart failure.

107. The Ombudsman first recalls that the candesartan decision indicates that, in light of ELITE II data, losartan could not have been chosen as an appropriate candidate for this indication. In sum, it can be deduced from the candesartan decision that the reason losartan was granted a waiver was indeed based on Stage 3 of the analysis, namely, that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients (Article 11(1)(c) of the Paediatric Regulation). This implies that it was not even necessary to carry out a comparison, under Stage 5, of the relative benefits of candesartan compared to losartan. With regard to this point, the Ombudsman points out that, despite the fact that it was not necessary to carry out a comparison, under Stage 5, concerning losartan, the Agency nevertheless stated, in the candesartan decision, that "losartan has the **highest** potential for drug interactions" (emphasis added), thus implying that it did undertake at least some comparative assessment concerning losartan.

108. With regard to valsartan, the Ombudsman notes the statement in the candesartan decision that trials supported the use of both valsartan and candesartan in heart failure[78]. This implies that a comparison **must** have been carried out under Stage 5 as to the relative benefits of candesartan when compared to valsartan. In this regard, the candesartan decision states that the pharmacokinetic characteristics and the currently available data in adults make candesartan a better candidate, since valsartan is more susceptible to a food effect[79]. Thus, it concludes that, in light of the results of these characteristics and other studies, if a single candidate had to be chosen, it would be candesartan.

109. The Ombudsman notes that, given the Agency's admission that it is not clear to what extent the differences seen in the trials were due to the products or to chance, *"it cannot be*

predicted with any degree of certainty" that candesartan would be a better candidate than valsartan. However, he also notes that the decision as to which product to choose must not necessarily be based on certainty[80]. Rather, it suffices that the Agency shows that it carried out its assessment on the basis of the available scientific evidence and that it reasoned its choice of product on the basis of the available scientific evidence. The Agency has done so.

110. Moreover, the Ombudsman notes that a PIP waiver analysis is always prospective. A PIP seeks to generate information about a product's use in children. If there was absolute certainty surrounding the use of a product in children, it would not be necessary to carry out a PIP. Thus, in order to decide on Stage 5 of a waiver application, it should be sufficient to examine if a product is *likely* to constitute a more appropriate choice than another product in the same product class. That assessment must be based on the present day available information on the use of the product in children, which will necessarily be limited before a PIP is carried out.

111. The Ombudsman also underlines, as already stated in paragraph 61 above, that, while at Stage 3 of the analysis a given product's **significant therapeutic benefit for paediatric patients** must be demonstrated **when compared to existing treatments**, if Stage 5 of the analysis is arrived at, it is only necessary to find that a product has **some therapeutic benefit when compared with other products in that product class**. The comparative therapeutic benefit taken into account if Stage 5 of the analysis is arrived at could, indeed, be minimal. As such, the Agency's conclusion that candesartan was the most appropriate ARB for which studies should be requested does not appear to be manifestly unreasonable.

112. The Ombudsman finds, therefore, that, as far as the examination of the candesartan decision itself is concerned, the Agency adhered to the structure of analysis outlined above. Specifically with regard to Stage 5, it carried out a comparative assessment and identified objective, scientific evidence to differentiate candesartan from valsartan (losartan already having been excluded under Stage 3 "in light of ELITE II data").

Treatment of candesartan when compared to losartan and valsartan

113. The Ombudsman notes that the candesartan, losartan, and valsartan decisions are necessarily interlinked. They all deal with the same class of product and the same indications. In order to show that the waiver applications were dealt with fairly and correctly, it is necessary that the reasoning set out in all three decisions be consistent and that the principle of equal treatment be respected. Having already identified potential inconsistencies, the Ombudsman will now examine this issue in greater detail.

114. The candesartan decision indicates that this product was refused a waiver because (i) none of the exceptions under Article 11 was found to apply; (ii) the Agency considered that it was possible to carry out at least a limited PIP; and (iii) given the limited patient population, it was appropriate to choose one ARB. Furthermore, on the basis of a comparative assessment with valsartan and given that losartan was not an appropriate candidate for testing, candesartan was deemed to be the most appropriate of the ARBs to carry out that PIP.

115. It is thus necessary for the Ombudsman to determine whether the correct structure of analysis was adhered to in all three waiver decisions and whether the factual findings were consistent[81].

116. With regard to losartan, the Ombudsman notes that the Summary Report on candesartan states that *"in the light of ELITE II data, losartan could not have been chosen"*. The Ombudsman finds, therefore, that the Paediatric Committee granted a waiver to losartan on the basis of Article 11(1)(c) of the Paediatric Regulation and was therefore entitled to halt its analysis at Stage 3 of the structure of analysis referred to above. He notes, however, that further argumentation and reasoning is put forward in the Summary Report on losartan and that it would be useful for the complainants to have access to that information in order to understand fully the contested decision. The Ombudsman deals with this issue in section B below.

117. With regard to valsartan, the relevant decision, much like the decision concerning candesartan, identified a clear unmet therapeutic need which could be met by ARBs[82]. On this basis, the Paediatric Committee did not immediately proceed to agree to a waiver for valsartan on the basis of Article 11(1)(c) of the Paediatric Regulation. Put somewhat differently, the impression created by the limited publicly available version of the valsartan decision (see paragraph 72 above) is misleading. In fact, the **full** valsartan decision was consistent with the candesartan decision as regards Stages 1 to 3 of the analysis.

118. The Paediatric Committee was therefore obliged to move on to Stage 4 for valsartan. In line with Stage 4, the Paediatric Committee identified, in the **full** valsartan decision, trial difficulties with all ARBs but did not conclude that trials were impossible[83]. Again, as regards Stage 4 of the analysis, the valsartan decision was consistent with the candesartan decision.

119. The Paediatric Committee should then have moved on to the comparative analysis under Stage 5 between valsartan and candesartan. However, it was not shown in the Summary Report of the valsartan decision, or in any other part of the valsartan decision, that **any** comparative analysis under Stage 5 was actually carried out. A waiver in relation to a PIP was, nevertheless, granted to valsartan.

120. In light of the foregoing, the Ombudsman finds that the Agency failed to document that it

carried out a complete comparative assessment in the case of valsartan under Stage 5 of the structure of analysis referred to above. The Agency should have documented that comparative assessment in order to provide a complete and consistent valsartan decision. In line with the structure of analysis set out above, it should have set out expressly in the valsartan decision why valsartan would constitute a sub-optimal choice for a PIP when compared to candesartan.

121. In light of the above, the Ombudsman made the finding that, by not documenting a full comparative assessment of valsartan and candesartan in its Summary Report concerning a waiver request for valsartan, the Agency failed to ensure adequate transparency of the process through which it reached its decisions. This was an instance of maladministration.

122. In light of this finding, the Ombudsman considered the possibility of proposing a friendly solution[84]. As noted in paragraph 12 above, the complainants made no express claim in their complaint to the Ombudsman. The Ombudsman understood that they implicitly claimed that the Agency should replace the contested decision by a decision meeting the requirements of equal treatment, objective and fair assessment, and adequate reasoning. The Ombudsman notes, however, that the defect in this case relates to the valsartan decision and not to the decision contested by the complainants. Moreover, the above procedural error did not imply that the eventual end result achieved was wrong in substance, since it did not call into question the substantive finding in the candesartan decision that, when compared to valsartan, candesartan was the optimal choice for a PIP. In this context, the Ombudsman concluded that no useful purpose would be served by proposing a friendly solution to the complainants.

123. However, the Ombudsman underlined that the potential for serious errors occurring if proper procedures are not followed is obvious. In the case at hand, the fact that the Agency did not fully document the comparative assessment of valsartan and candesartan in its Summary Report on valsartan meant that it is impossible to confirm that the elements the Agency took into account in that assessment were consistent with the elements it took into account in its comparative assessment of valsartan and candesartan during its examination of the candesartan waiver application[85].

124. As the Ombudsman concluded above, the Agency failed to ensure adequate transparency of the process through which it reached its decisions. He underlines that transparency is a vital means by which the Agency can ensure the accuracy of its decisions. By making its fully documented opinions available to those with expert, scientific knowledge, such as the complainants in the current case and the other waiver applicants, the Agency can ensure that all its work stands up to scrutiny and is, ultimately, correct.

125. The importance of ensuring that the Agency's decisions are based on accurate and comprehensive information is evident. It is vital, for the public, that the Agency take correct decisions. Correct decisions can only be taken when the Agency obtains all relevant information and arguments. Ensuring that waiver decisions concerning products in the same product class are made known to other waiver applicants empowers those waiver applicants to make known to the Agency all relevant counter arguments and facts. If such counter arguments and facts call into question the facts and arguments already taken into consideration in the previous waiver procedures, and thus further the Agency's understanding of the issues[86], the public's interest will be served.

126. In light of the above, the Ombudsman made a draft recommendation, in accordance with Article 3(6) of the Statute of the European Ombudsman. In making his draft recommendation (see paragraph 147 below), the Ombudsman sought to ensure that the Agency avoids similar errors in all future cases.

B. Allegation of failure to comply with the obligation to state reasons for the decision and related claim

Arguments presented to the Ombudsman

127. The complainants alleged that the Agency failed to comply with the obligation to state reasons for the decision (Article 18 of the European Code of Good Administrative Behaviour[87]). They argued that the Agency's decision, according to which candesartan could be treated differently from losartan and valsartan, was not made in a transparent manner, because it did not identify and explain what relevant facts and factors had been taken into account in treating PIP applications for products in the same therapeutic class differently from each other.

128. More specifically, in its response to the complainants' argument relating to the principle of equal treatment, the Paediatric Committee stated that, for confidentiality reasons, not all requirements included in its opinion are publicly available. As a result, the complainants should not base their claim of an unjustified different approach on the limited information published on the relevant webpage. The Paediatric Committee stated that, in the interest of applicants, it will not discuss the content of PIPs of the complainants' competitors.

129. The complainants do not agree with the Agency's assessment, according to which a breach of confidentiality would arise if it were to provide proper reasoning by identifying the relevant factors which were relied upon to justify differential treatment. In their view, the relevant facts are

largely related to the pharmacological properties of the active substances. This information is contained in a Summary of Product Characteristics, which is a publicly available document describing the characteristics of an approved medicinal product.

130. The complainants support this contention by referring to the Agency's transparency policy as described in its guidance relating to the principles to be applied for the deletion of commercially confidential information for the disclosure of Agency documents[88]. This states that commercially confidential information is generally considered to fall broadly into two categories: (i) confidential intellectual property, "know-how" and trade secrets (including e.g., formulas, programmes, process or information contained or embodied in a product, unpublished aspects of trade marks, patents, etc.); and (ii) commercial confidences (e.g., structures and development plans of a company).

131. Furthermore, the complainants note that the above-mentioned guidance goes on to say that non-clinical and clinical development of the medicinal product is not commercially confidential. They also note that they did not request the Agency to disclose the entire development programme for the other ARBs, for which waivers were granted. Instead, they requested that the Agency provide proper reasoning by identifying what differentiating pharmacological properties exhibited by losartan and valsartan could properly be relied upon to justify differential treatment. The complainants take the view that such information cannot be viewed as commercially confidential, as the basic information for such an analysis is already in the public domain. The Agency could simply identify those aspects of the pharmacodynamic and/or pharmacokinetic properties, fully described in the published Summary of Product Characteristics, which the Agency relied upon to justify differential treatment.

132. In its opinion on the complaint, the Agency remarks that it has difficulties in understanding the complainants' arguments regarding confidentiality. It insists that the fact that the Paediatric Committee has refused to discuss the content of PIPs of other applicants is in the interest of applicants and is in accordance with a general principle recognised under the applicable EU legislation. This cannot be challenged by the complainants, it says.

133. In any event, the Agency continues, the complainants could have, and still can, file a request for access to documents that will be dealt with in accordance with the principles set out in Regulation (EC) No 1049/2001[89] and the Agency's implementing rules.

134. In their observations on the Agency's opinion, the complainants inform the Ombudsman that a request was made to the Agency for public access to documents pertaining to the losartan PIP. The request was made in order to understand the scientific basis upon which a product-specific waiver was granted to losartan but not to candesartan. The Agency denied the request.

The Ombudsman's assessment leading to a draft recommendation

135. The obligation to state reasons is laid down in Article 296 TFEU, and Article 41 of the Charter of Fundamental Rights of the European Union. It forms an essential aspect of the right to good administration[90].

136. Article 25 of the Paediatric Regulation provides that the opinion of the Paediatric Committee delivered in response to a request by the applicant for re-examination shall be duly reasoned, and a statement of reasons will be annexed to the Paediatric Committee's opinion[91]. This opinion will then be annexed to the Agency's decision[92].

137. Article 25(7) of the Paediatric Regulation provides that the Agency's decisions shall be made public after deletion of any information of a commercially confidential nature.

138. The Ombudsman notes that there are two distinct issues to be examined here. The first concerns the provision of a sufficiently detailed statement of reasons to the interested party, in this case the complainants, in accordance with Article 27(3) of the Paediatric Regulation and, more generally, the obligation as described in paragraph 135 above. The second concerns the extent to which the Agency's decisions are made public, under Article 25(7) of the Paediatric Regulation.

139. With regard to the first issue, the Ombudsman's analysis under Section A above has shown (i) that the complainants would have needed further information in order to understand fully the basis of the decision taken as regards their own product and (ii) that the opinions of the Paediatric Committee concerning the two other products contained information which would further the complainants' understanding of the Agency's position. This is so because, given that the Agency's position concerning ARBs involves a comparative assessment, it is necessary, in order to understand its position fully, for the complainants to be aware of the reasoning relating to all three decisions.

140. In relation to point (i) of the previous paragraph, the Ombudsman is of the view that, as a minimum, the Agency could have confirmed expressly in the candesartan decision that the same comparative assessment between candesartan and valsartan was carried out as part of the procedure concerning the valsartan waiver application. Such a statement in the candesartan decision would have gone some way in reassuring the complainants that candesartan was being treated consistently with other similar products.

141. However, while making such a statement in the candesartan decision is necessary, it may not be sufficient. In relation to point (ii) of paragraph 139 above, it would further reassure the complainants that the position of the Agency is correct, if the Agency were to give appropriate access to all three waiver decisions. The Ombudsman notes in this respect that, if the detailed analysis in the valsartan and losartan decisions were publicly available, the Agency could make relevant cross references in the candesartan decision to the analysis set out in those decisions, thus enabling the complainants to verify the consistency of its analysis for all three waiver applications.

142. The Agency's failure to provide the complainants with the requisite access to the valsartan and losartan decisions, and to make the necessary cross references to those decisions in the candesartan decision, meant that the complainants were not provided with an adequate statement of reasons. This constituted an instance of maladministration and the Ombudsman made a corresponding draft recommendation (see paragraph 147 below).

143. When making his draft recommendation, the Ombudsman took into account, that the Agency must, as a general rule, conduct its work **as transparently as possible**[93]. Making decisions public in an appropriate manner enables stakeholders to understand on exactly what grounds decisions, such as those concerning the waivers granted to losartan and valsartan for the condition of heart failure, are taken[94]. Certainly, public access to decisions should take due account of information of a commercially confidential nature. However, having inspected all the relevant documents in the present case, the Ombudsman notes that these decisions contain much information, in particular the Agency's analysis, which is clearly not commercially confidential[95]. It must, moreover, be noted that the redaction of any commercially sensitive information from such decisions should be balanced with any overriding public interest in disclosure. It should also be noted that, in accordance with the principles underpinning Regulation 1049/2001, any potentially affected party can be consulted for the purposes of obtaining its views before a document which might contain commercially sensitive information relating to it is released[96].

144. In line with the considerations laid out in paragraph 122 above, the Ombudsman noted that a proposal for a friendly solution in this case would not be appropriate. Given the important issue of public interest raised by the foregoing, his draft recommendation also reflected his findings concerning this aspect of the case.

C. Draft Recommendation

145. In making this draft recommendation, the Ombudsman outlined that he is fully aware of the important role the Agency is playing in ensuring the protection of public health. Given that children are, in terms of the secure availability of medicines, a vulnerable group, the Agency's role in the area of the application of the Paediatric Regulation is of particular importance.

146. In this context, the present complaint cannot only be viewed from the perspective of the rights of the complainants to a fair and effective procedure in relation to their application for a waiver. It must also be examined in terms of ensuring, for society, that the correct end result is achieved in waiver applications. If a waiver application is wrongly refused, or wrongly granted, society, and in particular some of its weakest members, suffer.

147. Accordingly, and on the basis of his inquiries into this complaint, the Ombudsman made the following draft recommendation to the Agency:

The Agency should, in future, document fully its assessment of all waiver applications, with a view to ensuring consistent and complete reasoning in its decisions.

The Agency should commit to drafting guidelines aimed at assisting its Paediatric Committee to follow a coherent structure of analysis in future cases.

The Agency should provide the complainants with an adequate statement of reasons concerning the decision not to grant a waiver to candesartan. Such a statement would confirm to the complainants that its Paediatric Committee carried out a comparative assessment in the context of its examination of the valsartan waiver application, which was consistent with the comparative assessment it carried out in the context of its examination of the candesartan waiver application.

The Agency **should, (a) in accordance with its existing commitments regarding a proactive transparency policy, (b) with a view to assisting interested parties fully to understand its decisions, and (c) taking due account of the need to protect legitimate public and private interests,** disclose decisions and their annexes resulting from the application of the Paediatric Regulation, including those related to the losartan, valsartan, and candesartan waiver applications.

The Ombudsman underlined that he would consider his draft recommendation accepted if the Agency agreed to implement the measures set out therein. He recognised that the actual implementation of the commitments may take a certain period of time.

The arguments presented to the Ombudsman after his draft recommendation[97]

148. The Agency first stated that it agreed with the Ombudsman's draft recommendation. It

added that the draft recommendation sought to further enhance the transparency measures the Agency has already taken, or intends to put in place.

149. With regard to the first part of the Ombudsman's draft recommendation, namely, that the Agency *"document fully its assessment of all waiver applications"*, the Agency explained that it is working on a new document to be published on its website. The new document will take the form of a lay language summary of the procedure and its outcome, as adopted by the Paediatric Committee. This summary will be published on the Agency's website, at the same time as the Agency's decision. According to the Agency, this summary will ensure the same level of transparency across procedures and will help stakeholders understand the overall reasoning of the Paediatric Committee. However, it will not replace the scientific grounds detailed in the Paediatric Committee's Summary Report, the latter being part of the formal Paediatric Committee opinion. The Agency further explained that the Summary Report is made public after the Commission has decided on a product's marketing authorisation[98].

150. With regard to the second part of the Ombudsman's draft recommendation, that the Agency *"should commit to drafting guidelines aimed at assisting its Paediatric Committee to follow a coherent structure of analysis in future cases"*, the Agency replied that, in 2008, it published guidelines[99] for the preparation of the Summary Report, which guides the Paediatric Committee in its assessment of applications, and addresses in detail the issue of proper justification of opinions. The Agency further explained that it is working on improving the guidance for the Paediatric Committee, with a view to ensuring that the agreement or refusal of PIPs, waivers, and deferrals are better justified. The updated guidelines will be published on the Agency's website, once they have been adopted by the Paediatric Committee, it said.

151. With regard to the fourth part of the Ombudsman's draft recommendation, namely, that the Agency should *"disclose decisions and their annexes resulting from the application of the Paediatric Regulation, including those related to the losartan, valsartan, and candesartan waiver applications"*, the Agency stated that it fully accepted it, while adding that it will have to further reflect on how to continue to protect commercially confidential information, in line with Regulation 1049/2001 and the evolving case-law. The Agency explained, in this regard, that it has decided to publish the complete content of the Paediatric Committee opinion, including the individual key elements of each measure in the PIP (such as formulation development, nonclinical studies, clinical trials, etc) in Annex I, instead of a summarised version as it has done to date. Almost all of these key elements represent a subset of the information that is now recorded in EudraCT, which will be made public via the EU Clinical Trials Register, it said.

152. The Agency further explained that it has modified the content of the opinions of its Paediatric Committee so that the published opinion now includes more detailed explanations on the grounds for granting or refusing a waiver, particularly in the case of lack of significant therapeutic benefit, and on the grounds for refusing a deferral. In addition, Annex I of the opinion now specifies the individual grounds for granting a waiver for each separate condition in the PIP and, where applicable, for the different paediatric subsets within a condition.

153. More generally on the subject of the transparency of its proceedings, the Agency explained that, since July 2012, the agendas and minutes of the meetings of its Paediatric Committee concerning non-confidential topics, have been published on the Agency's website.

154. Finally, the Agency provided a detailed reply in relation to the third part of the Ombudsman's draft recommendation, namely, that the Agency should *"provide the complainants with an adequate statement of reasons concerning the decision not to grant a waiver to candesartan. Such a statement would confirm to the complainants that its Paediatric Committee carried out a comparative assessment in the context of its examination of the valsartan waiver application, which was consistent with the comparative assessment it carried out in the context of its examination of the candesartan waiver application"*.

155. The Agency, first, argued that it has already provided the complainants with an adequate statement of reasons as the complainants received the Agency's Decision refusing a waiver, including the Summary Report. The latter contains the minutes of the Paediatric Committee's discussion, as well as the reasoning and the justification behind its opinion, including an assessment of the known specificities of candesartan based on the data for this medicinal product, and other medicinal products in the same class that are authorised for use in adults.

156. With regard, second, to the Ombudsman's reference to a comparative assessment across PIPs for medicinal products of the same therapeutic class, the Agency argued that it cannot carry out a comparative assessment, as this would restrict the Paediatric Committee's scope of responsibility and could lead to inappropriate evaluation of the products that may treat children, as well as to delays in procedures. More generally, the Agency explained that it always assesses medicinal products on their own merit. This not only applies to paediatric assessments, but also to assessments of marketing authorisation applications[100].

157. The Agency further explained, in this regard, that when the Paediatric Committee is carrying out its work, there are still many uncertainties regarding the quality, safety, and efficacy of a medicinal product. Without having study results, it is not possible to prejudge the safety and efficacy profiles of various medicinal products and thus to perform a comparative assessment vis-à-vis other products to identify the most suitable candidate. In the case at hand, a development for candesartan was discussed as (i) there was no medicinal product authorised for heart failure in children (which was thus an unmet paediatric need), (ii) there was a potential

paediatric use for candesartan (based on candesartan's mechanism of action) and, in this case, (iii) existing data showed that the product was well-accepted by children (palatability), and (iv) none of the waiver exceptions applied. Although medicinal products belonging to the same therapeutic class may share a similar mechanism of action, their properties may differ and could lead to different dosages, risks of adverse reactions, or ineffective treatment. It is therefore essential to establish their safety and efficacy in children, except where a waiver is justified as per Article 11 of the Paediatric Regulation. The Paediatric Committee may consider the available data, including information related to other products belonging to the same class, and to comparative studies if they exist, to define the extent and type of paediatric measures that need to be performed for a specific medicinal product.

158. Additionally, the Agency explained that, from a practical perspective, a comparative assessment would require the Agency to have similar information for each product of a class and at the same time. The Agency does not have the mandate to require such data. Moreover, pharmaceutical companies follow their own schedules when submitting applications with the result that there are often months, or years, between applications for products of the same class. In addition, the Agency does not have the mandate to initiate the modification of an agreed PIP. Such a revision would, moreover, result in significant difficulties for applicants who would have to change their ongoing clinical programmes to take account of new Paediatric Committee requirements following comparative assessments at the time of a subsequent application.

159. Finally, in this regard, the Agency stated that it cannot agree with the Ombudsman's statement relating to the comparative assessment of products for the purpose of evaluating waiver applications. The Agency first noted, in this respect, that no ARB (and indeed no ACEI) was authorised to treat heart failure in children (all such products were used off-label).

160. The Agency then made three additional points in its opinion on the Ombudsman's draft recommendation. First, it addressed the five-stage structure of analysis proposed by the Ombudsman for assessing waiver applications. In the Agency's view, since a waiver is an exception, the starting point should not be Article 11 of the Paediatric Regulation, as suggested by the Ombudsman, but rather, as laid down in Article 1 of the Paediatric Regulation, whether the development of the medicinal product in question could meet the specific therapeutic needs of the paediatric population. Whether it is assessing a request for a PIP, a waiver, or a deferral, the Paediatric Committee first determines whether there is an unmet paediatric need and, second, whether a PIP should be agreed for a medicinal product, if the latter brings significant therapeutic benefit in the related condition(s). It is then that the Paediatric Committee assesses whether one of the three grounds for a waiver, as laid down in Article 11 of the Paediatric Regulation, applies to the condition and/or the characteristics of the medicinal product.

161. Second, with regard to the additional ground for a waiver outlined by the Ombudsman, the Agency's view is that this interpretation does not seem to derive from either the Regulation or the Commission Communication on the Paediatric Regulation. The grounds for granting a waiver are explicit, and stated exclusively in Article 11 of the Paediatric Regulation, it said. An approach such as that espoused by the Ombudsman and departing from a literal reading of Article 11 would lead to legal uncertainty.

162. Finally, with regard to the Ombudsman's finding of maladministration, the Agency insisted that, in the case at hand, it followed all the rules and timelines applicable to the procedure at stake. The complainants received an adequate statement of reasons and the Agency cannot at this stage modify the Paediatric Committee's opinion or the Agency's decision regarding candesartan. According to the Agency, the Ombudsman only indicated that an opinion for another medicinal product could have been more transparent for the public.

163. In their observations on the Agency's detailed opinion, the complainants underlined the importance of consistent and complete reasoning in the Agency's decisions. They welcomed the Agency's announcement that it would implement the Ombudsman's draft recommendation by revising its internal operating procedures and documenting fully its assessments of the acceptance or refusal of a request for a PIP, waiver, or deferral.

164. The complainants agreed that the Agency's initiatives will pave the way for greater transparency in its decision-making process and help ensure that decisions adopted by the Agency are properly reasoned and consistent with EU law, as well as with the principles enshrined in the European Code of Good Administrative Behaviour.

165. The complainants underlined, however, that the Agency should provide them with an adequate statement of reasons concerning its adopted decision not to grant a product-specific waiver to candesartan. In their view, a comparative assessment as proposed by the Ombudsman would provide greater clarity on the proper basis for differentiating the decision for candesartan from the prior decisions to grant waivers for losartan and valsartan.

The Ombudsman's assessment after his draft recommendation

166. As a preliminary remark, the Ombudsman notes that the Agency contests the notion of maladministration as it applies to this case. In this regard, the Ombudsman draws the Agency's attention to his analysis in paragraph 15 above, according to which maladministration encompasses failure to respect the law, failure to respect fundamental rights, and failure to respect the principles of good administration. While it is certainly a necessary condition to follow

"all the rules and timelines applicable to the procedure at stake" in order to avoid a finding of maladministration, it is not sufficient, as the Ombudsman's findings of maladministration in this case illustrate.

167. The Ombudsman's draft recommendation consisted of four elements. With regard to the first part of the Ombudsman's draft recommendation that the Agency *"document fully its assessment of all waiver applications"*, the Agency explained that it will publish on its website a lay language summary of the procedure under the Paediatric Regulation and its outcome, as adopted by the Paediatric Committee. According to the Agency, this summary will help stakeholders understand the overall reasoning of the Paediatric Committee. The more detailed scientific grounds underpinning the Paediatric Committee's opinion will continue to form part of the Summary Report, which, the Agency says, is made public after the Commission has decided on the product's marketing authorisation.

168. The Ombudsman recalls that the rationale for including this element in his draft recommendation was driven by his finding of maladministration that, by not documenting a full assessment of valsartan and candesartan in its Summary Report concerning a waiver request for valsartan, the Agency failed to ensure adequate transparency of the process through which it reached its decisions (see paragraph 121 above). The Ombudsman's view is that the aforementioned measures adopted by the Agency, coupled with further measures the Agency has announced to implement the other aspects of the Ombudsman's draft recommendation (see the next paragraph, in particular) should help to ensure that the lack of transparency identified in this case should not occur again.

169. With regard to the second part of the Ombudsman's draft recommendation that the Agency *"should commit to drafting guidelines aimed at assisting its Paediatric Committee to follow a coherent structure of analysis in future cases"*, the Ombudsman notes that the Agency has adopted the necessary measures. Specifically, its guidelines seek to assist the Paediatric Committee in its assessment of applications, and address in detail the issue of proper justification of opinions. The Agency is, moreover, working on improving its guidelines to the Paediatric Committee, with a view to ensuring that the agreement or refusal of PIPs, waivers, and deferrals are better justified.

170. With regard to the fourth part of the Ombudsman's draft recommendation, namely, that the Agency should *"disclose decisions and their annexes resulting from the application of the Paediatric Regulation, including those related to the losartan, valsartan, and candesartan waiver applications"*, the Ombudsman notes the Agency's statement that it has fully accepted it, while adding that it will have to reflect further on how to continue to protect commercially confidential information, in line with Regulation 1049/2201 and the evolving case-law. The Ombudsman notes, in particular, that the Agency's efforts to include more detailed explanations in Paediatric Committee opinions outlining the grounds for granting or refusing a waiver should significantly reduce the risk of the confusion that arose in this case. This would particularly be the case in instances where the waiver request is based on lack of significant therapeutic benefit.

171. The third part of the Ombudsman's draft recommendation asked the Agency (a) to provide the complainants with an adequate statement of reasons concerning the decision not to grant a waiver to candesartan, (b) to ensure that such a statement would confirm to the complainants that the Agency's Paediatric Committee carried out a comparative assessment in the context of its examination of the valsartan waiver application, and (c) to also ensure that the said comparative assessment was consistent with the comparative assessment it carried out in the context of its examination of the candesartan waiver application. The Ombudsman notes that the Agency has put forward two main arguments to contest his position:

(i) the candesartan decision does in fact contain an adequate statement of reasons;

(ii) the Agency does not carry out comparative assessments.

172. The Ombudsman recalls that this part of his draft recommendation stemmed from the confusion that arose in this case as a result of the very general and limited information published in the Agency's decisions concerning waivers for losartan and valsartan. He is reassured that the range of measures outlined by the Agency in response to his draft recommendation should ensure that a similar situation will not arise again. **Specifically, and of great importance to the case at hand, the Ombudsman's understanding is that the measures proposed by the producer of valsartan and agreed to by the Agency constitute the type of information that will form part of the public decision in future. As such, the misconception that arose in this case, that is, that valsartan had been granted an unqualified waiver which required no measures to be taken at all with regard to an examination of the use of valsartan in children, can be avoided in the future.**

173. With regard to (i) above, the Ombudsman notes that the Summary Report on candesartan explains why candesartan was chosen as the **optimal product** on which to carry out tests, why losartan could not be chosen, and why valsartan was **sub-optimal**. Moreover, the Ombudsman notes that, in its detailed opinion on the Ombudsman's draft recommendation, the Agency provides further explanations as to how the Paediatric Committee came to its decision (see paragraph 157 above).

174. With regard to (ii) above, the Ombudsman notes the practical difficulties outlined by the Agency which make it difficult to carry out comparative assessments. A comparative assessment would, says the Agency, require it to have similar information for each product of a class and at

the same time. This position is reasonable, given that pharmaceutical companies follow their own schedules when submitting applications with the result that there are often months, or years, between applications for products of the same class.

175. The Ombudsman finds these arguments convincing and indeed unproblematic. His view is that, in any event, any possible interest in carrying out any type of comparative assessment is unlikely to arise except in the most unusual circumstances[101].

176. This notwithstanding, the Ombudsman notes that, **in the case at hand**, the Paediatric Committee was in possession of information about the three products in the same product class when it was carrying out its analysis. He also notes that, in response to the complainant's request for re-examination, which was based on the argument that there were inconsistencies in how the Agency dealt with the waiver applications for candesartan, losartan, and valsartan (see paragraph 75 above), it at least took appropriate account of this information in its possession. In sum, in its response to this request for reexamination, the Paediatric Committee explained why candesartan was the **optimal product**. Specifically, it said: "*One could also argue that although Val-HeFT and CHARM trials supported the use of both valsartan and candesartan in HF, in light of the results, if a single candidate had to be chosen, it would be candesartan (although it is not clear to what extent the differences seen in those trials were due to the products or chance)*". In the Ombudsman's view, the Agency rightly took account of the relative merits of one product over another, in the case at hand.

177. The Agency also states that it does not have the mandate to initiate a modification of an agreed PIP. The Ombudsman disagrees and already pointed out, in footnote 85 above, that the Agency has a mechanism to review earlier decisions. Acknowledging that knowledge of science and medicine evolves over time, the Paediatric Regulation provides that the Paediatric Committee may, at any time, adopt an opinion advocating the review of a granted waiver. Furthermore, in accordance with the Commission's PIP Guideline, companies are encouraged to inform the Paediatric Committee when new information becomes available which suggests that a class or product specific waiver should be reviewed[102].

178. Finally, the Ombudsman notes that the Agency questions his proposed structure of analysis and contests his view that Article 11 of the Paediatric Regulation is not exhaustive in terms of the grounds for granting a waiver. The Agency goes on to suggest the following structure of analysis: (i) the Paediatric Committee first determines whether there is an unmet paediatric need[103] and (ii) it then determines whether a PIP should be agreed for a medicinal product, which will be the case if the medicinal product brings significant therapeutic benefit in the relevant condition(s). It is then that the Paediatric Committee assesses (iii) whether one of the three grounds for a waiver, as laid down in Article 11 of the Paediatric Regulation, applies to the condition and/or the characteristics of the medicinal product.

179. In the Ombudsman's view, points (i) and (ii) amount to the same result that would come about as a result of applying stage 4 of his structure of analysis. The Ombudsman recalls that stage 4 of his structure of analysis was derived from Article 6(2) of the Paediatric Regulation, according to which, when carrying out its tasks, the Paediatric Committee shall consider whether or not any proposed studies can be expected to be of significant therapeutic benefit to the paediatric population and/or to fulfil a therapeutic need of the paediatric population. The Ombudsman sees no problem in the Agency's suggestion that it carry out these steps before examining the application of the conditions under Article 11 of the Paediatric Regulation. He thus considers that this clarification from the Agency does not alter his view that the Agency has accepted his draft recommendation.

180. The Ombudsman very much welcomes the Agency's positive response to his draft recommendation. In his view, the extensive range of measures adopted by the Agency should help to pre-empt problems such as those which arose in the current case and, more generally, to instill even greater trust in its work for citizens.

D. Conclusion

On the basis of his inquiry into this complaint, the Ombudsman closes it with the following conclusion:

The Agency has accepted the Ombudsman's draft recommendation.

The complainant and the European Medicines Agency will be informed of this decision.

P. Nikiforos Diamandouros

Done in Strasbourg on 22 July 2013

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[1] Candesartan has been marketed in the EU under the trade names Biopress (Amias in the UK) and Atacand and their associated trade names.

[2] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ

2006 L 378, p. 1.

[3] See Recital 4 in the preamble to the Regulation. At the time the Paediatric Regulation was adopted, more than 50% of the medicinal products administered to children in Europe had not been authorised for such use and had not been subjected to appropriate trials (see case T-52/09 Nycomed Danmark ApS v European Medicines Agency (EMA), judgment of 14 December 2011, not yet reported, paragraphs 39-41). Among the problems arising from the absence of suitably adapted medicinal products for the paediatric population are, according to Recital 3 of the Regulation, "*inadequate dosage information, which leads to increased risks of adverse reactions including death, ineffective treatment through under-dosage, non-availability to the paediatric population of therapeutic advances, suitable formulations and routes of administration, as well as use of magistral or officinal formulations to treat the paediatric population which may be of poor quality*".

[4] See Article 2(2) of the Paediatric Regulation.

[5] The Paediatric Regulation creates, in turn, rewards for fully complying with the requirements for studies in children. Specifically, once a marketing authorisation is obtained in all EU Member States and study results are included in the product information, the medicine is eligible for six months' patent extension.

[6] See Article 1 of the Paediatric Regulation, as well as Recital 4 in the preamble to the Regulation.

[7] A Paediatric Committee within the Agency assesses the content of any PIP and formulates an opinion thereon. It also assesses waivers and deferrals.

[8] See Recital 13 in the preamble to the Regulation.

[9] See Article 11 of the Paediatric Regulation. The Regulation also provides for deferrals.

[10] More specifically, the complainants' PIP applications contained the request for a waiver (i) in respect of the condition of heart failure in children of 0-18 years, (ii) for the treatment of diabetic retinopathy in children of 0-18 years, and (iii) for the treatment of hypertension in children of 0-1 years.

[11] An ACEI is a pharmaceutical drug used primarily for the treatment of hypertension (high blood pressure) and heart failure.

[12] The requested limited study included a dose exploratory study in 50 children with heart failure.

[13] The Ombudsman understands the term "off-label" use to refer to the practice of prescribing pharmaceuticals for, inter alia, an unapproved indication, in an unapproved age group, or an unapproved dose.

[14] The complainants therefore apparently dropped their reliance on Article 11(1)(a) of the Paediatric Regulation, according to which a specific medicinal product is likely to be ineffective or unsafe in children, and focused exclusively on Article 11(1)(c) thereof and on the allegation of inconsistency in treatment between the ARBs.

[15] This decision is available at http://www.emea.europa.eu/docs/en_GB/document_library/PIP_decision/WC500005604.pdf

[16] Specifically, the request to inspect documents mentioned:

(i) any documents which identify differences between the properties of candesartan, valsartan, losartan in order to justify the difference in treatment between the products, and which have not been provided to the complainant in the context of the administrative proceeding due to the need to protect confidentiality;

(ii) any documents which have not been provided to the complainant in the context of the administrative proceeding due to the need to protect confidentiality and which identify those properties of ARBs which confer a significant therapeutic advantage over the existing treatment modalities (that is, over ACEIs).

[17] See Diamandouros, P. N., “Legality and good administration: is there a difference?” in J-P. Delevoye and P. N. Diamandouros (eds.), *Rethinking good administration in the European Union*, Luxembourg: Office for Official Publications of the European Communities (2008).

[18] Available at http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500005504.pdf

[19] Available at http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500005311.pdf

[20] Available at http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500005542.pdf

[21] WHO INN stands for World Health Organisation International Non-proprietary Name. The complainants point out that the WHO has assigned the same common stem (-sartan) to these substances.

[22] The World Health Organisation website explains that the Anatomical Therapeutic Chemical ("ATC") classification system divides drugs into different groups according to the organ or system on which they act and their chemical, pharmacological, and therapeutic properties. Drugs are classified into five different levels. According to the complainants, candesartan, losartan, and valsartan have the same ATC code at the third level (C09CA) meaning that they share essentially the same pharmacological properties.

[23] See the Communication from the Commission — Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies, OJ 2008 C 243, p. 1. It should be noted that the PIP Guideline that the complainants annex to their complaint appears to be a draft version from January 2007 and not the definitive version that was published in the Official Journal.

[24] The waiver application in respect of losartan was submitted on 28 June 2007, the waiver application in respect of candesartan was submitted on 12 July 2007, and the waiver application in respect of valsartan was submitted on 1 August 2007.

[25] Article 9 of the Code entitled "Objectivity" reads as follows:

"When taking decisions, the official shall take into consideration the relevant factors and give each of them its proper weight in the decision, whilst excluding any irrelevant element from consideration."

[26] Article 11 of the Code entitled "Fairness" reads as follows:

"The official shall act impartially, fairly and reasonably."

[27] The complainants quote the aforementioned draft version of the PIP Guideline, as follows:

"Significant therapeutic benefit might also be present because existing treatments are not satisfactory and alternative methods with an improved expected benefit risk balance are needed."

The definitive PIP Guideline contains a substantively identical criterion.

[28] The Ombudsman noted that a Summary of Product Characteristics is a document required before any medicinal product is authorized for marketing. This summary is the definitive description of the product both in terms of (i) its chemical, pharmacological, and pharmaceutical properties, and (ii) the clinical use to which the product can be put (the Summary states how the product is to be used for a specific treatment). It thus forms the basis of information for healthcare professionals to know how to use the specific product safely and effectively.

The package leaflet (Patient information leaflet) supplied with a product contains information from the Summary of Product Characteristics (it is thus less extensive than the Summary of Product Characteristics).

[29] The EMEA/PDCO Summary Report contains details of the PIP application, as well as the request for a waiver. It provides an overview of all the stages of the procedure, including the examination and the re-examination carried out by the Paediatric Committee. The Summary Report for candesartan is 126 pages long.

[30] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ 2001 L 121, p. 34.

[31] The complainants provide a weblink to the Swedish national authority responsible for the regulation and surveillance of the development, manufacturing, and marketing of drugs and other medicinal products and a further weblink to a document referring to valsartan (available at: http://www.lakemedelsverket.se/SPC_PIL/Pdf/humspc/Diovan%20oral%20solution.doc)

[32] The complainants refer in this regard to the Commission's *"Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Paediatric Population"* and to the internationally accepted ethical principles set out in the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996). This Declaration is referred to in the second paragraph of Article 3 of Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, OJ 2005 L 91, p. 13.

[33] With respect to losartan, the Ombudsman inspected, in particular, the EMEA/PDCO Summary Report on an application for a PIP including the request for a waiver. With respect to valsartan, the Ombudsman inspected, in particular, the Draft EMEA/PDCO Summary Report on an application for PIP and requests for waiver.

[34] Decision of the European Parliament of 9 March 1994 on the regulations and general conditions governing the performance of the Ombudsman's duties (94/262/ECSC, EC, Euratom), OJ 1994 L 113, p. 15.

[35] Available at http://www.ombudsman.europa.eu/resources/provisions.faces

[36] See Recital 4 in the preamble to the Regulation, as well as Article 1 of the Paediatric Regulation.

[37] See Recital 7 in the preamble to the Regulation.

[38] The Ombudsman notes that, according to the waiver provisions in the Paediatric Regulation, where the Paediatric Committee has not, of its own motion, adopted an opinion to the effect that a class or a product-specific waiver should be granted (Article 12 of the Paediatric Regulation), the applicant may apply to the Agency for a product-specific waiver (Article 13 of the Paediatric Regulation). In this latter case, the burden of proof lies with the applicant, who must provide evidence and arguments to prove that one of the grounds for granting a waiver applies.

[39] Stages 1, 2, and 3 relate to Article 11 of the Paediatric Regulation which states that the requirement to carry out a PIP "shall be waived for specific medicinal products or for classes of medicinal products, if there is evidence showing any of the following:

(a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;

(b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations;

(c) that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients."

Article 11 also states that a waiver may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified therapeutic indications, or to a combination of both.

[40] On the basis of Article 6(2), in combination with Articles 15 and 17 of the Paediatric Regulation.

[41] See footnote 23 above.

[42] See section 2.3.3.B.3 of the PIP Guideline entitled "*Significant therapeutic benefit and/or fulfilment of therapeutic need*".

[43] Also of relevance in this regard are Articles 15 and 17 of the Paediatric Regulation. Article 15 states that a PIP shall specify the timing and the measures proposed to assess the quality, safety, and efficacy of the medicinal product. Article 17(1) provides that the Paediatric Committee shall determine whether the proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits justify the studies proposed. It follows from Article 15 of the Paediatric Regulation, in combination with Article 17 of the Paediatric Regulation, that, if an applicant shows that it is simply not possible (because, for example, the patient population is too small) to design studies which give rise to "therapeutic benefits" in terms of quality, safety, and efficacy of a medicinal product, a waiver should be granted.

[44] It could be argued that if studies meet a "therapeutic need" they will always have a "significant therapeutic benefit". In sum, the category of studies meeting a "therapeutic need" is a subset falling within the broader category of studies giving rise to a "significant therapeutic benefit".

[45] By way of illustration, the Ombudsman notes that the Agency, in its decision of 29 June 2009 concerning a modified PIP for valsartan, grants a waiver as follows: *"The waiver applies to: All paediatric age groups (0 to less than 18 years) for film-coated tablet, hard gelatin capsule for oral use and age appropriate formulation: liquid formulation* ***on the grounds that clinical studies cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the paediatric population****". (emphasis added)*

[46] See Article 17(1) of the Paediatric Regulation.

[47] This may mean that the use of the product remains "off label" even if a PIP is successfully carried out (that is, even if the hoped for data is obtained). It must be underlined that, while in certain cases it may only be possible to carry out a limited PIP, a PIP should always be as extensive as possible in terms of assessing the quality, safety, and efficacy of a medicinal product. What will be deemed appropriate will depend on a number of factors, such as the product's stage of development, results from trials already conducted, and the size and characteristics of the patient population available for testing.

[48] The Ombudsman accepts that the circumstances in which it would prove impossible to do any studies giving rise to significant therapeutic benefits may be rare.

[49] The Ombudsman notes that the complainants in this case acknowledge this fact, despite disputing it elsewhere in their complaint. The complainants state that the Agency mainly reasoned the challenged decision by a reference to Recitals 4 and 7 of the Paediatric Regulation. While, they say, *"(...) this explains the reasons for obliging the testing to be carried out only on one of the ARBs, it does not properly explain the reason why candesartan (rather than another ARB) was selected among the three ARBs for which applications were submitted at the same time"*.

[50] It should be recalled in this regard that one is talking about carrying out trials. If the trials bring forward evidence that the product in question may help meet a therapeutic need, there might be grounds to revoke previous waivers for other products in the same product class, in line with Article 14(2) of the Paediatric Regulation.

[51] Indeed, it would not be unusual to find only minimal differences between the therapeutic benefits of products in the same product class.

[52] Under Articles 15 to 19 of the Paediatric Regulation.

[53] The "agreement procedure" is carried out pursuant to Articles 15 to 19 of the Paediatric Regulation. Article 15 states that where the intention (of a company that has developed a medicinal product) is to apply for a marketing authorisation, a PIP shall be drawn up and submitted to the Agency with a request for agreement. The PIP shall specify the timing and the measures proposed to assess the quality, safety, and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, the PIP shall describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer, or more effective for different subsets of the paediatric population. Article 17 states that, following receipt of a proposed PIP, the Paediatric Committee shall adopt an opinion as to whether or not the proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected "therapeutic benefits" justify the studies proposed. Article 17 of the Paediatric Regulation, read in combination with Article 6(2) of the Paediatric Regulation, however, implies that the reference to "therapeutic benefits" in Article 17 of the Paediatric Regulation must be understood as meaning "significant therapeutic benefits" (such benefits must relate to the quality, safety, and efficacy of the medicinal product for the paediatric population, and must be obtained through the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof). Article 19 states that if, having considered a proposed PIP, the Paediatric Committee concludes that Article 11(1)(a), (b) or (c) applies to the medicinal product concerned, it shall adopt a negative opinion under Article 17(1).

[54] Such benefits – obtained through the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof – must relate to the quality, safety, and efficacy of the medicinal product for the paediatric population.

[55] While the Paediatric Committee could, when deciding upon this issue under a waiver procedure, identify specific characteristics of a PIP giving rise to “significant therapeutic benefits” (in the candesartan decision they identified that a PIP could consist of a dose exploratory study in 50 children), it could be sufficient, in the context of a waiver procedure, for the Paediatric Committee to limit itself to providing a reasoned explanation as regards why a PIP giving rise to “significant therapeutic benefits” would be feasible. It would be for the applicant, who would, subsequent to a rejection of its waiver application, have to undertake the “agreement procedure" under Articles 15 to 19 of the Paediatric Regulation, to set out in detail in the context of that “agreement procedure”, the details of the PIP giving rise to “significant therapeutic benefits”.

[56] In other words, if the complainants in the present case had decided never to seek a waiver, but rather proposed to the Agency, under the “agreement procedure” set out in Articles 15 to 19 of the Paediatric Regulation, a PIP concerning the use of candesartan in heart failure in children which was limited to a dose exploratory study in 50 children, the Agency should have agreed to that PIP (by applying the same benchmarks that apply under the “waiver procedure").

[57] This principle can also be described as the principle of non-discrimination.

[58] See Case C-292/97 Karlsson and Others [2000] ECR I-2737, paragraph 39, and Joined Cases T-228/99 and T-233/99 Westdeutsche Landesbank Girozentale and Land Nordrhein-Westfalen v Commission [2003] ECR II-435, paragraph 272.

[59] Article 21 of the Charter is entitled "Non-discrimination".

[60] The publicly available versions of the losartan and valsartan decisions are much shorter than the versions sent to the waiver applicants. The full decisions include the EMEA/PDCO Summary Report, which contains details of the PIP application, as well as the request for a waiver. The Report provides an overview of all the stages of the procedure, including the examination and the re-examination carried out by the Paediatric Committee.

[61] See footnote 18 above for the weblink to this decision.

[62] See footnote 19 above for the weblink to this decision. A subsequent decision of the Agency in respect of valsartan was adopted on 26 June 2009. See footnote 20 above for the weblink to this latter decision.

[63] The publicly available version of the valsartan decision is certainly misleading as regards heart failure, since heart failure, although rare, does occur in children.

[64] It is, in this context, understandable why the complainants, who only had access to the publicly available versions of the decisions on losartan and valsartan, were surprised when their request for a waiver for candesartan was refused on the basis of an analysis based on Stage 5. As will be seen in Section B (see in particular paragraph 128 below), the Agency informed the

complainants that they should not base their claim of an unjustified different approach on the limited information published on the relevant webpage. That, however, is the only information that was made available to the complainants and, indeed, to the general public. As the Ombudsman notes in paragraph 73 above, the limited information available in the Agency's decisions makes it impossible to decipher exactly on what grounds a waiver is granted for a particular indication.

[65] The complainants did not argue that heart failure only occurs in adult populations (Stage 1 of the analysis). Further, they only argued, under Article 11(1)(a) of the Paediatric Regulation, that candesartan is likely to be ineffective or unsafe in the paediatric population (Stage 2) during the initial part of the waiver procedure. They did not rely on Article 11(1)(a) of the Paediatric Regulation in the re-examination stage of the procedure.

[66] See point (h) of section 2.3.3 B.3 of the Commission's PIP Guideline.

[67] The reason for this difference in the extent of the burden of proof is obvious. It would not be appropriate (or indeed ethical) to impose a requirement to carry out testing if there was a *likelihood* that the product was unsafe or ineffective. However, it would not be appropriate (or indeed ethical) not to carry out testing unless it was shown that the product did not have a *significant* therapeutic benefit over existing treatments.

[68] The Ombudsman has consistently stated that, whenever an institution exercises its margin of discretion in administrative procedures, he will only find maladministration if it is shown that there was a manifest error of appreciation in relation to the exercise of that margin of discretion. The Ombudsman will not, it must be underlined, substitute his own assessment for the administration's assessment, but may rather request that the matter be re-examined in order to address the issues identified. The Ombudsman notes that this approach is in line with the standard applied by the Union courts. See Case T-13/99 Pfizer Animal Heath SA v Council [1999] ECR-II-1961, paragraph 169.

[69] In contrast, a waiver could be granted if it were successfully argued that it was not technically possible to create a suitable paediatric dosage form and a formulation suitable for use in children.

[70] The Ombudsman finds that this constitutes the most basic and minimal information and that the Agency could indeed provide better and more comprehensive information to the complainant, such as that which is included in the Summary Report on losartan.

[71] The Ombudsman notes, in this regard, that in their re-examination request, the complainants relied solely on Article 11(1)(c) of the Paediatric Regulation as grounds for a waiver, without referring any longer to Article 11(1)(a), which provides for the situation where a medicinal product is likely to be ineffective or unsafe for the paediatric population. Even the complainants, therefore, do not appear to be convinced that these considerations justify a waiver.

[72] The Ombudsman points to the guidance of the General Court in this regard. See Case T-52/09 Nycomed Danmark ApS v European Medicines Agency (EMA), order of the President of the General Court of 24 April 2009, nyr, paragraphs 88-91. The Ombudsman notes that the Agency, as the competent public body in the field, denied a waiver. It necessarily follows that that body does not consider that it would be unethical for the complainants to conduct paediatric clinical trials. It should also be borne in mind that any such trials will be conducted in line with *"the specific requirements for the protection of the paediatric population who take part in clinical trials in the Community"*. See Recital 7 in the preamble to the Regulation.

[73] Such evidence would have to be presented in a sufficiently clear manner in order to allow a non-scientific reviewer to determine the manifest nature of the error in the assessment.

[74] Even though, as outlined in paragraph 77 above, the Agency discounted the possibility of studies being carried out on losartan for the indication of heart failure, it included losartan in the comparative analysis.

[75] The Ombudsman recalls the finding by the General Court in Case T-52/09 to the effect that rejection of an application for waiver will be based on objective, scientific evidence. Case T-52/09 Nycomed Danmark ApS v European Medicines Agency (EMA), judgment of 14 December 2011, nyr, paragraph 99.

[76] The complainants contest the Agency's argument pertaining to the *"better taste"* of candesartan. However, the Agency points out that the Summary Report for candesartan is unambiguous as to the fact that the argument of better taste was not the main justification used to designate candesartan as the only agent required to undergo evaluation in the condition of heart failure.

[77] According to the complainants, a suitable paediatric formulation of losartan was approved in 2009, while a paediatric formulation of valsartan was approved in 2010.

[78] The Summary Report on candesartan mentions that *"(...) Val-HeFT and CHARM trials supported the use of both valsartan and candesartan (...)"*.

[79] The Agency appears to agree that taste effects are not determinative.

[80] The Ombudsman notes that, if the standard of proof applied to this choice were based on

certainty, situations would arise where no choice could be made between alternative products, thus implying that no effective PIP could be carried out. Such a standard of proof would thus run counter to the purpose of the Paediatric Regulation.

[81] In doing so, the Ombudsman will not reveal documents which the Agency identified as confidential in the context of his inspection of the Agency's file. Nor will he reveal any information contained in such documents. However, the Ombudsman's analysis will clearly take account of, and draw the appropriate conclusions from, the information contained in these documents.

[82] As this statement is not specific to valsartan, the Ombudsman considers that it is not confidential.

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[84] Article 3.5 of the Ombudsman's Statute states that, as far as possible, the Ombudsman shall seek a solution with the institution or body concerned to eliminate the instance of maladministration and satisfy the complainant.

[85] The Ombudsman notes that the elements taken into account in the valsartan procedure in order to carry out the comparison with candesartan do not need to be strictly identical to the elements taken into account in the candesartan procedure in order for the two decisions to be *consistent* with each other. Indeed, given the fact that the Agency examines waiver applications at slightly different points in time, it is at least possible that the applicant submitting the later waiver application might provide additional information to that which the Agency already holds. However, if this were to occur, it would be necessary to explain expressly why that new information does not call into question the previous comparative assessment. If, however, new information were to emerge in a subsequent waiver procedure which called into question a comparative assessment in an earlier waiver procedure, the Agency has a mechanism to resolve that problem. Acknowledging that knowledge of science and medicine evolves over time, the Paediatric Regulation provides that the Paediatric Committee may, at any time, adopt an opinion advocating the review of a granted waiver. Furthermore, in accordance with the Commission's PIP Guideline, companies are encouraged to inform the Paediatric Committee when new information becomes available which suggests that a class or product specific waiver should be reviewed. See Recital 13 in the preamble to the Regulation, as well as Article 14(2) of the Paediatric Regulation.

[86] See previous footnote.

[87] Article 18 of the Code entitled "Duty to state the grounds of decisions" reads as follows:

"1. Every decision of the Institution which may adversely affect the rights or interests of a private person shall state the grounds on which it is based by indicating clearly the relevant facts and the legal basis of the decision.

2. The official shall avoid making decisions which are based on brief or vague grounds or which do not contain individual reasoning.

(...)."

[88] EMEA/45422/2006, available at:
http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/20

[89] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents, OJ 2001 L 145 p.43.

[90] See footnote 7 of the European Ombudsman's decision closing his inquiry in complaint 3072/2009/MHZ against the European Commission.

[91] Article 25(3) of the Paediatric Regulation.

[92] Article 25(5) of the Paediatric Regulation.

[93] See the Ombudsman's decision in case 2493/2008/(BB)(TS)FOR concerning the Agency's application of Regulation 1049/2001 on public access to documents, paragraphs 39 to 48.

[94] It should also be borne in mind that Article 25(7) of the Paediatric Regulation, which provides that the Agency's decisions shall be made public after deletion of any information of a commercially confidential nature, should be understood in a manner which is consistent with the principles of Regulation 1049/2001. The Ombudsman recalls that Article 73(1) of the Regulation governing the Agency's work (Regulation 726/2004) provides that: *"Regulation (EC) 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents shall apply to documents held by the Agency"*. The importance of ensuring that the Agency conducts its work as openly as possible has already been highlighted in Section A above and is evident from the present case. The Ombudsman has reproduced, in paragraphs 71 and 72 above, the very limited information that was made available to the complainants, and indeed to the general public, as far as the Agency's decisions concerning losartan and valsartan were concerned.

[95] The Ombudsman finds it helpful, in this regard, to refer to his exchanges with the Agency in

the framework of case 2560/2007/BEH. The Agency, referring to recent case-law of the General Court as regards the applicability of the commercial interests exception in Regulation 1049/2001, granted access to the requested documents. In that case, the Agency submitted that, in future cases, it would apply the same principles as far as the deletion of commercial information is concerned. Moreover, it underlined the need to take relevant implementing action in the course of the revision of its policy on public access to documents held by it. Necessary implementing action included taking a decision on the extent of redaction required in order to ensure, inter alia, the protection of commercially confidential information. The Agency also submitted, in that case, that a decision on the applicability of the commercial interests exception in Regulation 1049/2001 requires (i) a concrete examination on a case-by-case basis of a given document, following consultation with the third-party document authors, and (ii) taking into account the possible need to redact that document in line with Regulation 1049/2001.

[96] See Article 4(4) of Regulation 1049/2001.

[97] Readers should note that the structure of Ombudsman decisions following draft recommendations is normally different to the structure of the present decision. Normally, the Ombudsman will deal separately with each allegation in his conclusions following a draft recommendation. However, given the complexity of the present case and the fact that the Agency and the complainant provided comments by dealing with both allegations together, the Ombudsman considers it appropriate, in the interest of clarity, to structure the present decision differently. As such, he will set out the responses to the draft recommendation and deal with them together.

[98] In response to a follow-up question from the Ombudsman's services, the Agency provided the following clarification in this regard: the Agency's policy on access to documents states that the PDCO Summary Report can be made available to requesters after the marketing authorisation covered by the Decision.

This is done on request — the Summary Report is not made systematically available on the Internet. With regard to the case at hand, the products in question are nationally-approved. As far as valsartan and candesartan are concerned, both bear an indication concerning heart failure in adults, but not in children. As a result, the Summary Reports on these products cannot be released because they relate to an indication that the products do not yet bear.

[99] http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/09/WC500003740

[100] The Agency refers, in this regard, to case T-74/00 Artegodan GmbH and Others v Commission, where the General Court stated that *"In the Community system of prior authorisation of medicinal products, the competent authority, when considering an application for authorisation of a medicinal product, in principle exercises its discretion in weighing up the benefits and risks **of that medicinal product** — reserving the right subsequently to revise its assessment of that benefit/risk balance in the light of new scientific data"*. (emphasis added by the Agency), see paragraph 187.

[101] The Ombudsman finds it useful to recall that the structure of analysis suggested in his draft recommendation includes the following under the heading "Stage 5".:

"Stage 5: If there are two or more products in the product class that are suitable for a PIP, and if the relevant patient population is too small to allow for the PIP to be carried out on all the relevant products in the product class, a waiver should be granted to the applicant that has demonstrated that its product is sub-optimal, as far as the PIP is concerned, when compared with the alternative candidate product(s)".

[102] See Recital 13 in the preamble to the Regulation, as well as Article 14(2) of the Paediatric Regulation.

[103] In paragraph 80 above, the Ombudsman expressed his disagreement with the complainants' argument that therapeutic need is not, *per se*, decisive. As the Ombudsman stated, the very purpose of the Paediatric Regulation, according to Article 1 thereof, is to lay down rules concerning the development of medicinal products *"(...) in order **to meet the specific therapeutic needs of the paediatric population** (...)"*. (emphasis added)

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