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# Datasheet for the decision of 5 February 2009

**Case Number:** T 0696/05 - 3.3.02

**Application Number:** 99961890.3

**Publication Number:** 1049467

**IPC:** A61K 9/20

**Language of the proceedings:** EN

**Title of invention:**
Celecoxib compositions

**Patentee:**
G.D.Searle & Co.

**Opponent:**
Teva Pharmaceutical Industries Ltd.
Fako Ilaçlari a.s.
PLIVA d.d.

**Headword:**
Celecoxib compositions/SEARLE

**Relevant legal provisions:**
EPC Art. 123(2), 83, 54

**Relevant legal provisions (EPC 1973):**
-

**Keyword:**
"Main request lacks novelty; auxiliary requests are not allowable"

**Decisions cited:**
-

**Catchword:**
-

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**Case Number:** T 0696/05 **-** 3.3.02

# D E C I S I O N
## of the Technical Board of Appeal 3.3.02
## of 5 February 2009

**Appellant:** (Patent Proprietor)
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**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 30 March 2005 revoking European patent No. 1049467 pursuant to Article 102(1) EPC 1973.**

**Composition of the Board:**

**Chairman:** U. Oswald
**Members:** M. C. Ortega Plaza
C.-P. Brandt

## Summary of Facts and Submissions

I. European patent No. 1 049 467, which was filed as application number 99 961 890.3, based on international application WO 00/032189, was granted on the basis of nine claims.

Claim 1 as granted read as follows:

"1. A pharmaceutical composition comprising one or more discrete solid orally deliverable dose units, each comprising particulate celecoxib in an amount of 10 mg to 1000 mg in intimate mixture with one or more pharmaceutical acceptable excipients, and having a distribution of celecoxib particle sizes such that $D_{90}$ of the particles is less than 200 µm, preferably less than 100 µm, more preferably less than 40 µm, and most preferably less than 25 µm, in the longest dimension of said particles."

II. The following documents and exhibits cited during the proceedings are relevant for the present decision:

(1) WO 95/15316
(2) Prescription Pharmacy: Dosage Formulation and Pharmaceutical Adjuncts, ed., Joseph B. Sprowls, Jr., J.B. Lippincott Company, 1963, page 56
(5) Pharmaceutics: The Science of Dosage Form Design, ed. M.E. Aulton, Churchill Livingstone, 1988, page 156
(23) L. Lachman, H.A. Liberman, J.L. Kanig, The Theory and Practice of Industrial Pharmacy, third edition, Lee and Febiger, Philadelphia, 1986, pages 21-45; 321; 325-328

(24) Physical Pharmacy 1993, A. Martin, P. Bustamante, A.H.C. Chun, Physical Pharmacy, Physical Chemical Principles in the Pharmaceutical Sciences; 4th ed. Lee & Febiger, London 1993. pages 331, 423-436

(26) A. W. Basit et al., Pharmaceutical Research, vol. 18 (8), pages 1146 to 1150 (2001)

(32) Pierges A. et al. (1997), Abstract of paper contributed to the 1997 AAPS Annual Meeting, November 2-6, Boston, MA (US); Pharm. Res. 14 (Suppl. 11), 1997, S 617, abstract No 3469

(44) D. Barber et al., Pharmaceutical Development and Technology, 3(2), pages 153-161, 1998

(47) Pfizer's Test report dated 26 July 2007 about "Particle Size Analysis of Celecoxib in Arti X 200 mg tablets manufactured by Farmaindustria S.A."

(50) B.R. Jennings and K. Parslow, Proc.R. Soc. Lond. A 419, 137-149, 1988

(E1) "Test report" relating to the experiments concerning the repetition of example 2 of document (1), filed by opponent II with its notice of opposition dated 8 July 2003

(E2) "Experimental Protocol-Crystallization Experiments" filed by opponent II with letter dated 19 November 2004

(E3) Declaration of Prof. Ian G. Tucker dated 4 July 2003 filed by opponent III with its notice of opposition dated 8 July 2003

III. Oppositions were filed and revocation of the patent in its entirety was requested pursuant to Articles 100(c) (added matter), 100(b) (insufficiency of disclosure) and 100(a) EPC (lack of novelty and inventive step).

IV. The appeal lies from a decision of the opposition division revoking the patent (Article 102(1),(3) EPC 1973).

Claim 1 of the first auxiliary request was identical to claim 1 of the main request (claim 1 as granted).

Claim 1 of the second auxiliary request read as follows:

"1. A pharmaceutical composition comprising one or more discrete solid orally deliverable dose units, each comprising particulate celecoxib in an amount of 10 mg to 1000 mg in intimate mixture with one or more pharmaceutical acceptable excipients, having a distribution of celecoxib particle sizes such that $D_{90}$ of the particles is less than 200 µm, preferably less than 100 µm, more preferably less than 40 µm, and most preferably less than 25 µm, in the longest dimension of said particles, and having a relative bioavailability of celecoxib not less than 50%, preferably not less than 70% by comparison with an orally delivered solution containing the same dose of celecoxib."

Claim 1 of the third auxiliary request differed from claim 1 of the second auxiliary request in that the following definition was added after the expression "solution of celecoxib" and before the expression "containing the same dose of celecoxib":

"in a mixture of polyethylene glycol having an average molecular weight of 400 and water in a ratio of 2:1 by volume".

Claim 1 of the fourth auxiliary request differed from claim 1 as granted in that the following was added at the end of the claim's wording:

", wherein the composition comprises
(a) one or more pharmaceutically acceptable diluents in a total amount of 10% to 85% by weight of the composition:
(b) one or more pharmaceutically acceptable disintegrants in a total amount of 0.2% to 10% by weight of the composition;
(c) one or more pharmaceutically acceptable binding agents in an amount of 0.75% to 15% by weight of the composition;
(d) optionally one or more pharmaceutically acceptable wetting agents in a total amount of 0.4% to 10% by weight of the composition; and
(e) optionally one or more pharmaceutically acceptable lubricants in a total amount of 0.2% to 8% by weight of the composition."

V. The opposition division considered that contested claim 5 of the main request (set of claims as granted) did not extend beyond the content of the application as filed since the specified range for binding agents was disclosed as a preferred range in the specification of the application as filed.

Furthermore, the opposition division considered that the main request (set of claims as granted) met the requirements of sufficiency of disclosure (Article 83 EPC). In particular, the opposition division was satisfied, in the light of the examples, of the reproducibility of the claimed "invention". Moreover,

in the opposition division's view, the parameter $D_{90}$ which was used in claim 1 to characterise the compositions was a well known parameter to the skilled person. The opposition division cited in this context document (23). Additionally, the opposition division stated that said parameter was also defined "in the application as filed" as meaning "the particle size value for which 90% of the particles in a sample had a particle size smaller than the stated size". The opposition division considered that a meaningful reading of said term implied samples with "normal" (meaning homogeneous) distribution of particles.

As regards novelty of the subject-matter claimed in claim 1 of the main request, the opposition division considered that the celecoxib capsules identified in the abstract document (32) by means of pharmacokinetic parameters were novelty-destroying. Moreover, in the opposition division's view, document (32) concerned an enabling disclosure since the skilled person would be able to produce said capsules, making use of his common general knowledge. In particular, the opposition division considered that the skilled person would inevitably consider fine or ultra-fine particle sizes of celecoxib in view of its poor water-solubility.

However, the opposition division considered that document (1) did not anticipate the subject-matter of the main request. In particular, the opposition division considered that document (1) did not explicitly disclose a solid dosage unit form containing celecoxib in an amount of 10 mg to 1000 mg.

In relation to auxiliary request 1 the opposition division considered that claim 1 was identical to claim 1 of the main request and hence, the same reasons also applied.

The opposition division rejected auxiliary request 2 for lack of clarity (Article 84 EPC) of amended claim 1.

Furthermore, the opposition division considered that claim 1 of auxiliary request 3 extended beyond the content of the application as filed, since it related to an unallowable generalisation from the content of an example.

The opposition division admitted the late-filed auxiliary request 4 into the proceedings, since it merely related to "a simple combination of the claims as granted". Furthermore, in the opposition division's view the requirements of Articles 123(2), 84 and 83 EPC were met. Moreover, according to the opposition division's findings the subject-matter claimed was novel.

However, the opposition division considered that the subject-matter claimed in auxiliary request 4 lacked an inventive step (Article 56 EPC). Basically, the opposition division defined document (32) as the closest prior art. Although the opposition division did not define the problem to be solved, it mentioned that the only difference was the presence of "disintegrants". Thus, according to the opposition division's findings, the formulation of dosage form by adding disintegrants was a conventional technical measure, which did not involve an inventive step.

VI. The patent proprietor filed an appeal against said decision.

The appellant (patent proprietor) maintained with the grounds of appeal its main request and four auxiliary requests filed during the opposition proceedings.

VII. The respondents I to III (opponents I to III) filed counterarguments thereto.

Opponent II filed an "Expert declaration" by Mr Taskin dated 8 February 2006.

VIII. A communication expressing the preliminary opinion of the board was sent to the parties on 11 April 2008. In this communication example 2 of document (1) was explicitly mentioned as disclosing celecoxib.

IX. The appellant filed with letter dated 13 October 2008 a response to the board's communication and filed additional documents as annex thereto (*inter alia* document (47)).

X. The respondents also filed replies to the board's communication.

Respondent I filed with its letter of 16 January 2009 further counterarguments, as well as additional documents (*inter alia* document (50)).

XI. Oral proceedings took place on 5 February 2009.

XII. At the oral proceedings the appellant filed new auxiliary requests 1 to 4 which were not admitted into the proceedings.

Claim 1 of the new auxiliary request 1 basically differed from claim 1 as granted in that the value of $D_{90}$ was defined as "less than 100 µm", i.e. the definition of $D_{90}$ as less than 200 µm was deleted.

Claim 1 of the new auxiliary request 2 read as follows:

"1. A pharmaceutical composition comprising one or more discrete solid orally deliverable dose units, each comprising particulate celecoxib in an amount of 10 mg to 1000 mg in intimate mixture with one or more pharmaceutical acceptable excipients, and having a distribution of celecoxib particle sizes such that $D_{90}$ of the particles is less than 100 µm, preferably less than 40 µm, and most preferably less than 25 µm, in the longest dimension of said particles, wherein the composition is in the form of unit dosage capsules or tablets, comprising

(a) one or more pharmaceutically acceptable diluents in a total amount of 10% to 85% by weight of the composition;
(b) one or more pharmaceutically acceptable disintegrants in a total amount of 0.2% to 10% by weight of the composition;
(c) one or more pharmaceutically acceptable binding agents in an amount of 0.5% to 10% by weight of the composition;

(d) optionally one or more pharmaceutically acceptable wetting agents in a total amount of 0.4% to 10% by weight of the composition; and
(e) optionally one or more pharmaceutically acceptable lubricants in a total amount of 0.2% to 8% by weight of the composition."

Claim 1 of the new auxiliary request 3 read as follows:

"1. A pharmaceutical composition comprising one or more discrete solid orally deliverable dose units, each comprising particulate celecoxib in an amount of 10 mg to 1000 mg in intimate mixture with one or more pharmaceutical acceptable excipients, and having a distribution of celecoxib particle sizes such that $D_{90}$ of the particles is less than 100 µm, more preferably less than 40 µm, and most preferably less than 25 µm, in the longest dimension of said particles, and

having a relative bioavailability of celecoxib not less than about 50%, preferably not less than about 70%, by comparison with an orally delivered solution in a mixture of polyethylene glycol having an average molecular weight of 400 and water in a ratio of 2:1 by volume containing the same dose of celecoxib."

Claim 1 of the new auxiliary request 4 read as follows:

"1. A pharmaceutical composition comprising one or more discrete solid orally deliverable dose units, each comprising particulate celecoxib in an amount of 10 mg to 1000 mg in intimate mixture with one or more pharmaceutical acceptable excipients, and having a distribution of celecoxib particle sizes such that $D_{90}$

of the particles is less than 100 µm, preferably less than 40 µm, and most preferably less than 25 µm, in the longest dimension of said particles, wherein the composition is in the form of unit dosage capsules or tablets, comprising

(a) one or more pharmaceutically acceptable diluents in a total amount of 10% to 85% by weight of the composition;
(b) one or more pharmaceutically acceptable disintegrants in a total amount of 0.2% to 10% by weight of the composition;
(c) one or more pharmaceutically acceptable binding agents in an amount of 0.5% to 10% by weight of the composition;
(d) optionally one or more pharmaceutically acceptable wetting agents in a total amount of 0.4% to 10% by weight of the composition; and
(e) optionally one or more pharmaceutically acceptable lubricants in a total amount of 0.2% to 8% by weight of the composition,
and said composition having a relative bioavailability of celecoxib not less than about 50%, preferably not less than about 70%, by comparison with an orally delivered solution in a mixture of polyethylene glycol having an average molecular weight of 400 and water in a ratio of 2:1 by volume containing the same dose of celecoxib."

XIII. The appellant's arguments, as far as relevant for the present decision, can be summarised as follows:

As regards the admissibility of the requests filed at the oral proceedings the appellant submitted that the

amendment relating to the restriction of celecoxib particle size (expressed as $D_{90}$ less than 100 µm) was a response to the discussion of lack of novelty of claim 1 of the main request which took place earlier at the oral proceedings. Moreover, nobody could be surprised since this value was already present as preferred in granted claim 1. It was the patentee's last chance to defend the patent and hence it would be unfair not to allow the auxiliary requests. Apart from that the requests were similar to those previously on file but addressed the raised objections of added matter.

The appellant submitted that the definition in the claims of the celecoxib particle sizes made it clear that the values of the parameter $D_{90}$ referred to the longest dimension of the particles. The reason was that the particles were not spherical. In fact, as explained in the patent in suit, celecoxib tended to form long needle-shaped crystals.

The fact that reference was made to the longest dimension meant that the only way to measure the particle size was by actually looking into the individual particles, in order to be able to measure each particle in its longest dimension. Therefore, it followed logically and unambiguously that the method of choice for determining the particle size was by microscopy.

The appellant referred to document (47) which concerned an experimental investigation produced for proceedings in Peru. This experimental exhibit showed in great detail how the formulation used (originating from a

celecoxib tablet which was dispersed in mineral oil) was analysed. The celecoxib particles could be looked at on the microscope, taking a yardstick (i.e. a scale-bar) to measure the particle sizes on their longest dimension. Moreover, the appellant stated that the skilled person knows how to deal with statistical parameters and to assess mean values, either manually or using computer software.

The appellant acknowledged that there were different methods such as light scattering or sieving for measuring particle sizes expressed as $D_{90}$, but these other methods were indirect methods which measured properties influenced by particle size. These other methods dealt with average values and hypothetical spherical parameters. The appellant acknowledged, however, that the "indirect methods" may also be able to give valid results if the measures were standardised.

The appellant also submitted that the parameter $D_{90}$ appearing in claim 1 referred to the celecoxib particles and not to all particles in the mixture. Thus laser diffraction or light scattering techniques would not function for a mixture. The same problem applied to the case of sedimentation techniques. The microscopic techniques made it possible to look at the particles and distinguish celecoxib from excipient. Moreover, it could be accepted that microscopy showed the particles in two dimensions but, since the particles were not spherical, one of the two dimensions would be the longest.

The appellant also mentioned that $D_{90}$ in the patent in suit had to be by number, and not in terms of weight, since one had to look for individual particles.

In the appellant's view, $D_{90}$ was a clear-cut value in the claim because the skilled person would contemplate the direct measurement using a yardstick and this could only be done with microscopy.

The appellant submitted that document (1) did not disclose the pharmaceutical composition claimed in claim 1 as granted. Example 2 described the synthesis of celecoxib as a solid product which was then recrystallized from methylene chloride and hexane to get an analytically pure sample.

The sparse information in document (1) about the crystallization (apart from the choice of methylene chloride and hexane) did not allow the conclusion that the experiments submitted by respondent II (solution of the solid celecoxib in methylene chloride and addition of hexane as anti-solvent) were a "reproduction" of example 2, since other ways were also possible for recrystallizing celecoxib. Moreover, the way in which recrystallization was performed had an influence on particle size. Therefore, following the teaching of document (1) would not inevitably lead to celecoxib crystals having a $D_{90}$ less than 200 µm in the longest dimension.

Additionally, the appellant stressed that methylene chloride was toxic and hence it was not a solvent to choose in case of pharmaceutical compositions.

The appellant did not dispute, however, that the recrystallization methods used in the experiments submitted by respondent II were conventional. Moreover, the appellant did not dispute the validity of measuring the $D_{90}$ in relation to the primary particle sizes before the formulation.

The appellant also submitted that, even assuming example 2 disclosed celecoxib particles of the appropriate size, document (1) would still not be novelty-destroying since the disclosure in example 2 had to be combined with the disclosure about the pharmaceutical composition on pages 182 and 183 of document (1). In particular, several selections had to be performed (solid form, administration route) in order to arrive at the pharmaceutical composition of claim 1 as granted.

As regards the first auxiliary request and Rule 80 EPC, the appellant mentioned that granted claim 2 had been modified in order to overcome an objection of insufficiency of disclosure made against it by the opponents.

In relation to the second auxiliary request the appellant referred to its written submissions filed with the grounds of appeal. In particular, it contended that the nature of the solvent was not relevant for the absorption of the active ingredient into the body of the subject under examination. Additionally, as expressed in the grounds of appeal, the content of document (26) did not "support the assumption that the solvent in the comparative celecoxib solution would have a significant effect on the absorption of

celecoxib from the gastrointestinal tract into the bloodstream which is the essential step determining bioavailability". The appellant further submitted that "the absorption of the preparation into the bloodstream of the subject was not investigated" in document (26). Moreover, the number of pharmaceutically acceptable solvents in which a poorly water-soluble drug could be dissolved for oral administration to humans was rather limited.

As regards the arguments of respondent II about $AUC_{0-\infty}$, the appellant stated that it had to be calculated as stated in paragraph [0053] of the patent in suit. This was standard pharmaceutical science.

As regards the third auxiliary request the appellant submitted that document (1) did not disclose "relative bioavailability" and did not disclose the composition in respect to the particle size. Thus, document (1) did not specifically disclose pharmaceutical compositions for achieving the bioavailability defined in the claim. Moreover, it was not inevitable that each and every one of the pharmaceutical compositions generically disclosed in document (1) had a bioavailability as defined in claim 1 of the third auxiliary request.

In relation to sufficiency of disclosure the appellant argued that only one way of reproducing the invention was required. The appellant stated that he knew the decisions cited by respondent I; however, a straight line should be drawn to separate Articles 83 and 84 EPC in opposition proceedings, since Article 83 EPC should not be misused to bring Article 84 EPC through the back door (and contrary to Article 100 EPC) into opposition

proceedings. The EPO should make itself clear on the question of adopting such an artificial and unrealistic approach and think of the skilled person's reaction (the skilled practitioner working in the laboratories) when told that $D_{90}$ was not clear.

The appellant further argued that the parameter $D_{90}$ is commonly used through the whole literature and is a common parameter in real life. The fact that it was possible to express it by number or by weight had nothing to do with insufficiency of disclosure. Moreover, such an artificial objection would apply to many other parameters which were commonly accepted, such as average molecular weight for polymers. Furthermore, the claims had to be construed in a technically meaningful manner and should be read with a will to understand them. The skilled person would read $D_{90}$ as by number in view of the fact that it referred to the longest dimension of the particles. This was confirmed by the passage on page 4, lines 20-21 of the application as filed: "90% of a sample of particles is smaller than the $D_{90}$ value". This passage had unfortunately been deleted in the specification of the patent document.

The appellant argued that the "indirect" measurement methods did not allow $D_{90}$ to be established in relation to the longest dimension of the particles. The natural method was the yardstick since length was defined as the international measurement in relation to yardstick. The only method using yardstick and allowing the measurement of celecoxib particles in the mixture was microscopy; anything else would have to be validated.

The appellant submitted that document (50) referred to a size scale (even below 1 µm) much smaller than those claimed. Values in the range of 100 nm (0.1 µm) were below visible light and could not be inspected under the microscope. For the samples depicted in document (50) the direct measurement method could not be used.

The appellant explained that an extremely inhomogeneous sample with an adequate $D_{90}$ by number, but without fulfilling bioavailability criteria, was theoretically thinkable, but one was dealing, within the context of the patent, with samples of particulate material distributed as a normal distribution bell-shaped curve.

Example 11 showed that a composition falling within claim 1 could be made. The only composition in Table 11-2C not fulfilling the criteria of 50% relative bioavailability was composition B.

The appellant acknowledged that one might have a composition with celecoxib particles of appropriate $D_{90}$ value but in the "wrong" capsule and, thus, such dosage form would not have the required bioavailability.

A reasonable formulation of tablets or capsules was required not to destroy the favourable effects of small-size celecoxib particles.

As regards the fourth auxiliary request, the appellant submitted that amended claim 1 met the requirements of Article 123(2) EPC since there was a basis in the application as filed for all the definitions of components and ranges appearing in the claim. In particular, it argued that the general description

applied to each pharmaceutical composition of the application and mentioned the following basis in the application as originally filed: for diluents in the preferred amounts of 10% to 85% page 20, lines 17-18; for disintegrants in the preferred amounts of 0.2% to 10% page 21, lines 12-13; for binding agents in the preferred amounts of 0.75% to 15% page 22, lines 2-3; for wetting agents in the preferred amounts of 0.4% to 10% page 22, lines 27-29; and for lubricants in the preferred amounts of 0.2% to 8% page 23, lines 11-13. Additionally, the claim met the requirements of Article 123(3) EPC since the scope had been restricted.

As regards the request for remittal, the appellant stated that the analysis of document (32) by the opposition division was "so bad" that it justified a remittal, since there must be both a first and a second instance for dealing appropriately with the state of the art on a technically sound basis, in particular for the discussion of inventive step.

XIV. The arguments of respondent I can be summarised as follows:

The requests filed by the appellant at the oral proceedings should not be admitted since their late-filing could not be justified. The objections were raised and known to the appellant years ago. No new objections were raised during the oral proceedings.

Respondent I stressed that the appellant had accepted that there were several methods for measuring particle sizes expressed as $D_{90}$ and that it was self-evident that different methods gave different results.

Respondent I contested, however, that microscopy was the only method of choice in view of the needle-shaped form of celecoxib crystals, as alleged by the appellant at the oral proceedings. The respondent recalled that the appellant had filed shortly before the oral proceedings several scientific articles showing light scattering as a valid method for measuring particle size. Moreover, if the particles were milled when formulated, then the needle-shaped structure of celecoxib particles was destroyed and, hence, the appellant's argument was no longer valid. The respondent cited in this context paragraph [0027] of the patent in suit.

Additionally, respondent I argued that, apart from the different methods available, $D_{90}$ could be expressed in number or in weight and referred to its written submissions in this respect.

Furthermore, respondent I quoted the following passage of the book about physical pharmacy (document (24)): "Although the microscope allows the observer to view the actual particles, the results obtained are probably no more "direct" than those resulting from other methods since only two of the three particle dimensions are ordinarily seen". Thus, microscopy had also its limitations: depending on the orientation of the non-spherical particles in a two-dimensional system, one would get different values, so mathematical calculations or correlation were also necessary. Moreover, if one assumed a solid block with several particles together it was not immediately clear which size of which particles to measure.

The patent in suit was silent about the technique to be used and about the $D_{90}$ to be chosen (by number or by weight). Hence, the skilled person faced several arbitrary choices when he was trying to establish the $D_{90}$ value.

Respondent I submitted that the appellant's arguments in favour of microscopy as the technique of choice in view of the presence of excipients might be true for infringement proceedings but, in the context of the patent and when carrying out the "invention", the particle size was measured prior to formulation. In this context it cited paragraph [0180] of the patent in suit. Respondent I also mentioned that it could not be ignored that the particle size was referred to as a mean value in the patent in suit (it cited paragraph [0026]) and that there was no other hint in the patent regarding a measurement technique, apart from the indication in the examples that particle sizes were measured before formulation. Thus, the $D_{90}$ mentioned in the patent could be measured by any of the available methods.

Respondent I submitted that, although several recrystallization techniques were possible, it was part of the disclosure in example 2 of document (1) to use a polar (methylene chloride) and a non-polar solvent. Hence, it was inherent and self-evident to use the non-polar solvent as anti-solvent in the recrystallization. Thus, in the respondent's view, document (1) contained a complete disclosure.

In the view of respondent I, the first auxiliary request was not admissible since the amendments were not in accordance with 80 EPC. Moreover, claim 1 was identical to claim 1 as granted and hence not novel vis-à-vis document (1).

As regards the second auxiliary request respondent I submitted that the claimed composition inevitably lacked novelty, since bioavailability and particle size were intrinsically linked. It cited in this context document (5), left-hand column, second paragraph under the heading "Particle size and surface area". It also objected to this auxiliary request under Article 83 EPC.

As regards the third auxiliary request, respondent I objected to the deletion of the term "about".

Respondent I cited document (2) and quoted page 56, the paragraph under the heading "Dissolution Rate". When dissolution was rate-limiting in the absorption process, the Noyes-Whitney law applied, and there was a correlation between particle size reduction and improved bioavailability.

Respondent I further submitted that the definition of the relative bioavailability was either not novelty-bringing or caused serious problems of insufficiency of disclosure, since claim 1 included a functional limitation for which the necessary technical measures were not disclosed in the patent in suit. Respondent I put as an example the following question: Was a specific coating responsible?

Respondent I pointed to the results shown in Table 11-2C and stated that tested composition A fulfilled the criteria now in the claim but the other compositions tested apparently did not. Compositions B and C certainly did not, since E was the reference solution. Thus, it was not disclosed in the patent in suit which features were needed to achieve that goal.

Respondent I submitted that claim 1 of the third auxiliary request relied upon two features: the parameter $D_{90}$ and the functional feature regarding the relative bioavailability. The patentee had chosen two parameters to define its "invention" for which it should have included in the specification a sufficient disclosure; however, this was lacking.

According to respondent I, for sufficiency of disclosure, the skilled person had to understand from the specification of the patent whether or not you do something which is covered by the claim. In this respect it cited decision T 201/83, EPO OJ 1984, 481, and the non-published decisions of board 3.2.6: T 252/02 dated 7 December 2004; T 611/02 dated November 2004; T 387/01 dated 13 January 2004 and T 815/07 dated 15 July 2008. Respondent I argued that the findings in these decisions applied to the present case because there was no method for measuring the parameter $D_{90}$ disclosed in the patent in suit. It was true that several methods were known but all of them were equally valid. There was an absence of sufficiency of disclosure except in so far as it was obvious what method was to be used, or in case that all methods gave the same results.

There was no link between the geometry of the crystals and the choice of microscopy as alleged by the appellant, since the particles were milled and therefore modified in their shape, and it was the mean particle size that was measured. Moreover, the appellant had contended that laser diffraction technique was a valid method until shortly before the oral proceedings. In this context, respondent I cited document (50) in order to show that the results obtained varied depending on the physical principles underlying the measurement methods since the equivalent spherical diameters obtained varied. It pointed to the three curves represented on page 148.

Therefore, respondent I argued that the skilled person could know whether he was working within the claim since, depending on the method chosen, one would be in the claim or outside the claim.

Respondent I also submitted that even if one knew the equivalent spherical diameter in relation to the longest dimension, $D_{90}$ could be expressed by number (90% of particles as counted), by weight or by volume. For particles of the same material, by weight and by volume gave analogous results, but not by number. In this context, respondent I cited document (44), page 156, second full paragraph of right-hand column, in order to show that when calculating $D_{50}$ using laser diffraction particle size distribution, the relevant value was the median volume diameter.

Respondent I submitted that the $D_{90}$ by number was different to the $D_{90}$ by weight and that one would get

different dissolution profiles. It referred to Prof. Tucker's declaration (E3), paragraph [16].

Respondent I accepted that particle sizes as a number distribution were collected by a counting technique such as microscopy, but they could be converted into a weight distribution. It cited document (24), page 428 and Fig. 16-2 and 16-3, in order to show that there were significant differences in the values of the two distributions. The respondent argued that the patent in suit remained silent about how the $D_{90}$ values were expressed. Moreover, microscopy was not a "direct yardstick technique" since it depended on the angle of observation of the three-dimensional particles. Furthermore, $D_{90}$ was not a minor term in the claim, but a fundamental issue.

As regards the functional feature expressed as bioavailability requirement it was insufficiently disclosed in the patent in suit how to attain it since the only example dedicated to bioavailability left open which technical means were to be undertaken. The functional limitation should have been linked in the description, for instance, to specific celecoxib particle sizes and specific excipients. The patent in suit mentioned in paragraph [0132] particle size reduction as being able to increase bioavailability but the whole description did not sufficiently disclose $D_{90}$.

If the only thing to do, as stated by the appellant, was to take small particles and formulate them in a way which was not detrimental to bioavailability, then this teaching was lacking in the patent since example 11

therein showed that reasonable formulations did not work.

The representative present at the oral proceedings for respondent I also represented respondent III and in this function he stated that respondent III endorsed all the submissions of respondent I.

XV. Respondent II endorsed the submissions of respondent I and added the following:

The requests filed by the appellant at the oral proceedings should be found inadmissible in order to provide for a fair procedure. The first experimental reports relevant for the novelty analysis vis-à-vis document (1) had been filed six years before. The microscopic photography showed particle sizes of less than 100 µm. The amendments introduced in the requests filed at the oral proceedings did not clearly overcome the discussed objections. Hence, the amended sets of claims were not ***prima facie*** allowable.

The lack of disclosure in the patent in suit concerning the method for measuring particle sizes expressed as $D_{90}$ was irreparable. Several methods existed, not only one.

Document (1) disclosed novelty-destroying pharmaceutical compositions since the specific compounds were disclosed in the normal context of a patent application in the pharmaceutical field which disclosed the medical application of the active ingredients prepared.

Respondent II argued that it had made real efforts in submitting early in the opposition proceedings the experimental reports in order to show why document (1) was novelty-destroying. If the appellant contended that bigger crystals were obtained following example 2, then it should have proved it with experimental data. Thus, in the opinion of respondent II, the burden of proof lay now with the appellant and this was a question of procedural fairness.

Moreover, the primary target in example 2 was to obtain a pure product, which was fit for microanalysis (example 2 showed the results of microanalysis), and for attaining big crystals or crystal growth techniques were not required.

Therefore, the experiments submitted related to fair reproductions of example 2.

Moreover, the primary particle sizes of celecoxib, expressed as $D_{90}$, were less than 200 µm, so the prerequisite of claim 1 as granted was fulfilled.

As regards the second auxiliary request, respondent II submitted that the function appearing in claim 1 was the "relative bioavailability" as defined in paragraph [0050] of the patent in suit. However, none of the examples illustrated how to calculate it, since in example 11 the $AUC_{0-24}$ was measured and not $AUC_{0-\infty}$.

Moreover, there was no standard solvent known in the art for such calculations. Additionally, respondent II had submitted in writing (cf. response to the grounds of appeal dated 21 February 2006) that the appellant's

arguments about the absorption of the preparation into the bloodstream of the subject and the gastro-intestinal transit of the preparation were artificial since the dissolution of the drug was the rate-limiting step for bioavailability of poorly-soluble materials like celecoxib. Moreover, document (26) stated that there was a correlation between the gastrointestinal transit and the bioavailability of the drug, on which the solvent had an influence.

Respondent II further argued that insufficiency of disclosure also affected the third auxiliary request. There were different measurement methods available which led to different results for particle sizes. One could try all methods but it would be a gratuitous exercise, since $D_{90}$ could still be expressed by number or by weight. Moreover, if $D_{90}$ was expressed by number then it would be meaningless (no direct correlation with bioavailability) without sufficient homogeneity in the sample.

Respondent II asked the appellant to state which example in the patent in suit fulfilled the bioavailability criteria appearing in claim 1 of the third auxiliary request since the technical teaching in the patent in suit did not allow the skilled person to produce a final oral dosage form having the bioavailability appearing in claim 1.

Respondent II argued that the patent in suit taught for celecoxib that particle size reduction increased bioavailability but the particle size in the claim was that of the product known from document (1). There was no teaching in the patent in suit in relation to the

constitution of the dosage form which ensured that it did not negatively influence the effect due to particle size reduction.

As regards the fourth auxiliary request, respondent II submitted that it did not meet the requirements of Article 123(2) EPC in view of the arbitrary combinations and selections which were not disclosed in the application as filed.

XVI. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained as granted, or alternatively, the patent be maintained in amended form on the basis of one of the auxiliary requests 1 to 4 submitted during the first instance proceedings and serving as basis for the opposition division's decision. Furthermore, the appellant requested that the case be remitted to the first instance for assessment of inventive step on the basis of the main request, or in the alternative, on the basis of the auxiliary request 1 to 4, serving as basis for the decision under appeal.

The respondents (opponents I to III) requested that the appeal be dismissed.

## Reasons for the Decision

1. *Admissibility*

1.1 The appeal is admissible.

1.2 *Admissibility of the auxiliary requests filed at the oral proceedings before the board*

Although the patent proprietor (appellant) may submit amended claims during the proceedings, in case of ***inter partes*** appeal proceedings the principles of fairness and equity in relation to all parties must apply.

Furthermore, it is a generally applicable principle that amendments made after oral proceedings have been arranged shall not be admitted if they raise issues which the board or the other party or parties cannot reasonably be expected to deal with without adjournment of the oral proceedings (Article 13(3) RPBA, 2007).

Moreover, the admissibility of late-filed requests is at the board's discretion and depends upon the overall circumstances of the case under consideration, a general principle being that the later the requests are filed, the less likely they are to be held admissible. Additionally, account has to be taken, ***inter alia***, of whether they could have been filed earlier and if so the reason why they were not, and of whether they immediately appear to fulfil the formal criterion for allowability.

The appellant submitted that the amendment relating to the specification of the $D_{90}$ value as less than 100 µm was made as a direct response to the discussion of lack of novelty vis-à-vis document (1) which took place during the oral proceedings before the board.

However, the objection of lack of novelty of claim 1 as granted vis-à-vis document (1) (numbered as document

(13) in the grounds of opposition filed by opponent II) had already been raised by opponent II in its grounds of opposition dated 8 July 2003 (i.e. almost six years before). Furthermore, opponent II filed the test report (E1), in which it reproduced example 2 of document (1), as an annex to its opposition grounds. Opponent II filed supplementary experimental tests on 19 November 2004 (i.e. more than four years before), in order to respond to the patentee's arguments in this respect.

It is a fact that the opposition division found that claim 1 as granted lacked novelty on the basis on another document, and that the opposition division expressed in its decision that the claimed subject-matter was novel vis-à-vis document (1) owing to the definition of the amount of 10 mg to 1000 mg for celecoxib in the claim.

However, the decision underlying the appeal has to be investigated in the appeal proceedings in order to assess whether or not it holds. Thus, it is within the board's duties to examine the novelty of the claimed subject-matter vis-à-vis both documents cited. Accordingly, in the board's communication dated 11 April 2008 the parties' attention was explicitly drawn to example 2 in document (1), which discloses celecoxib.

Therefore, in view of the circumstances depicted above, the board considers that the appellant had ample opportunities to file such an amendment before the date of the oral proceedings. Consequently, the new first auxiliary request is not admissible.

The amendment mentioned above for the first auxiliary request is also present in each claim 1 of the new auxiliary requests 2 to 4. Hence, the above analysis applies *mutatis mutandis* to the new auxiliary requests 2 to 4.

Moreover, as regards new auxiliary requests 2 and 4, they are not "clearly allowable" since they relate to combinations of features for which there is no direct counterpart in the application as filed, and for which it is necessary to combine several claims as originally filed with several passages of the description without having a clear and direct pointer thereto. In fact, the claims of the application as filed cited by the appellant as a basis for the amended requests are simultaneously dependent on several independent claims in which the pharmaceutical compositions are defined in a different way than in claim 1 as granted.

2. *Main request*

2.1 *Novelty*

Claim 1 as granted relates to a pharmaceutical composition *comprising*
**. one or more** discrete solid orally deliverable **dose units,** each *comprising*
.. **particulate celecoxib** in an amount of 10 mg to 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and *having*

... **a distribution of celecoxib particle sizes** such that **$D_{90}$** of the particles **is less than 200 µm in the longest dimension of said particles**.

Paragraph [0046] of the patent in suit explains that the "term "dose unit" herein means **a portion of a pharmaceutical composition** that contains a single unit dose of the active ingredient".

Paragraph [0016] of the patent in suit states that the "dose units comprising the composition can be in the form of discrete solid articles such as tablets, pills, hard or soft capsules, lozenges, sachets or pastilles".

Paragraph [0025] of the patent in suit states: "Compositions of the present invention contain celecoxib in particulate form. Primary celecoxib particles, generated for example by milling or grinding, or **by precipitation from solution**, can agglomerate to form secondary aggregate particles. The term "particle size" as used herein refers **to size**, in the longest dimension, **of the primary particles**, unless the context demands otherwise" (***emphasis added***).

Hence, it has to be investigated whether the celecoxib compositions disclosed in document (1) are encompassed by claim 1 as granted.

Document (1) discloses substituted pyrazolyl benzenesulfonamides, compositions containing them, and their use for treating inflammation and inflammation-associated disorders, such as arthritis (page 1, first paragraph).

Example 2 of document (1) specifically discloses 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl] benzenesulfonamide, i.e. celecoxib.

Example 2 discloses particulate celecoxib, in particular primary particles obtainable by precipitation from solution in the form of crystals ("the solid was recrystallized from methylene chloride/hexane") (end of page 73).

Claim 1 as granted does not exclude that the primary particles in relation to which the parameter $D_{90}$ is defined are crystals. This is also confirmed by the appellant's argumentation in relation to the experiments about the size of the celecoxib crystals contained in the tablets analysed in document (47).

Although document (1) does not explicitly state the size of the primary particles of celecoxib obtained in example 2, the experimental data submitted by respondent II (see exhibits (E1) and (E2)) show that the size of the primary particles obtainable when reproducing example 2 fulfil the requirement stated in claim 1 concerning the $D_{90}$ value. In fact, the size of the particles of celecoxib in the sample shown by electron microscopy in exhibit (E1) is less than 100 µm in the longest dimension. Moreover, the size of the particles in the experiments in exhibit (E2) has a $D_{99}$, measured by laser diffraction technique, of less than 200 µm (this directly implies that $D_{90}$ is less than 200 µm).

Hence, the experiments submitted by respondent II, which concern conventional crystallization techniques, have made it plausible that the crystal particles obtainable when following example 2, using the usual and conventional laboratory techniques, have a particle

size, expressed as $D_{90}$ in their longest dimension, of less than 200 µm.

Additionally, document (1) also discloses pharmaceutical compositions containing each of the specific substituted pyrazolyl benzenesulfonamides in the examples as active ingredient. Thus, document (1) states: "**For oral administration, the composition may be in the form of, for example, a tablet, a capsule, suspension or liquid**. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. **Examples of such dosage units are tablets and capsules**" (page 182, lines 4 to 10) (emphasis added).

Apart from the fact that tablets and capsules are the preferred dosage unit forms according to document (1), the active drug celecoxib is, before being in the form of a suspension or a liquid (solution), necessarily in the form of a solid pharmaceutical composition in admixture with at least one (nature undetermined in claim 1 as granted) excipient. Accordingly, document (1) discloses pharmaceutical compositions of celecoxib encompassed by claim 1 as granted.

Moreover, as regards the amount of celecoxib appearing in the claim, i.e. 10 mg to 1000 mg celecoxib per dose unit, the claim encompasses pharmaceutical compositions comprising "one **or more** dose units". Moreover, the specified amounts cannot be considered as a novel selection from the content of document (1), since the claim specifies a range of amounts for the dose unit which is broader than the preferred ranges for the amount of active drug disclosed in document (1).

In fact, document (1) states: "The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, **preferably in the range of about 0.5 to 500 mg** and **most preferably between about 1 and 100 mg**" (page 182, lines 23 to 26) (emphasis added).

Consequently, the pharmaceutical composition claimed in claim 1 as granted lacks novelty vis-à-vis document (1).

2.2 The appellant's arguments in favour of the novelty of the claimed compositions do not hold for the following reasons.

Example 2 in document (1) does not give every detail about the recrystallization technique apart from the fact that it is made from methylene chloride and hexane. However, the experimental data provided by respondent II show that the skilled person can complete the information in document (1) with his common general knowledge using conventional recrystallization techniques (see reproduction of example 2 in exhibits (E1) and (E2)). In fact the techniques used in these experiments are generally applicable to the case of recrystallization from a mixture of a solvent (methylene chloride) and an anti-solvent (hexane).

It has been alleged by the appellant that in the absence of the specific details about the recrystallization the skilled person would not have been able to reproduce example 2, and that the skilled person would have considered other ways of proceeding during the recrystallization than those chosen by respondent II in its experimental reports. However, the

first allegation amounts to an objection of non-enabling disclosure vis-à-vis document (1) for which no evidence has been provided. Moreover, none of these allegations has been made plausible either by the appellant's technical arguments or by means of any technical or documental evidence. Thus, the appellant has not discharged its burden of proof for the facts it has invoked. In other words, in order to make its position plausible the appellant should have supplied its own experimental data showing the alleged divergences with respect to the experimental data of respondent II.

As regards the argument that methylene chloride is a toxic substance, the appellant has not shown that methylene chloride inevitably remains (after the usual drying and/or washing steps of any recrystallization technique) in the celecoxib particles obtained following example 2.

Additionally, the appellant has not disputed the measurements of particle sizes made in the experimental reports of exhibits (E1) and (E2).

As regards the argument that the pharmaceutical composition claimed is a novel selection from the content of document (1), it has to be said that the skilled person does not need to choose celecoxib as active ingredient among the compound class generically disclosed in document (1) because example 2 singularises celecoxib as the active ingredient. The generic disclosure concerning the form and amounts of the pharmaceutical composition applies directly to each

of the active ingredients specified (and singularised) in the examples.

Moreover, apart from the fact that oral administration is commonly the first-choice route, even in case of considering an intravascular, subcutaneous, intramuscular or topical administration, it is inevitable that there must be first a pharmaceutical composition containing solid particulate celecoxib comprising the primary particles obtained in example 2 in admixture with at least one (undetermined in the claim's wording) excipient.

The granted claim's wording encompasses also the basic pharmaceutical composition (of particulate celecoxib as primary particles and an excipient) on the condition that it is suitable for being put in a solid dosage form for oral administration. Hence, a capsule for oral administration may be filled with the same basic pharmaceutical composition as one which is to be put in suspension or solution for e.g. intravenous infusion (see example 11-1 in the patent in suit).

2.3 Consequently, the main request fails for lack of novelty of claim 1 vis-à-vis document (1) (Article 54(1) EPC).

2.4 *First auxiliary request*

Claim 1 of the first auxiliary request is identical to claim 1 of the main request. Hence, the conclusion reached in point 2.3 above directly applies to the first auxiliary request.

2.5 *Second auxiliary request*

2.5.1 Claim 1 of the second auxiliary request basically differs from claim 1 as granted in that the pharmaceutical composition has to further fulfil the following requirement:

"having a relative bioavailability of celecoxib not less than 50%, preferably not less than 70%, by comparison with an orally delivered solution containing the same dose of celecoxib".

The composition claimed in claim 1 of the second auxiliary request is exactly that claimed in claim 2 as granted (claim 2 as granted was drafted as clearly dependent on claim 1 as granted), with the only distinction that the word "about" has been deleted before the values "50%" and "70%" (the appellant asked for an opportunity at the oral proceedings to re-instate this word in the claim if its deletion was the reason for rejecting the request; however, the present decision is not based upon the deletion, or reinstatement, of the term "about" in claim 1 of the second auxiliary request).

2.5.2 Even if one considers in the appellant's favour, that Article 84 EPC should not be introduced artificially in opposition proceedings for examining claims as granted (claim 1 of the second auxiliary request **is** indeed claim 2 as granted) since this would amount to the introduction (contrary to Article 100 EPC) of Article 84 EPC as an opposition ground, it has to be investigated whether the feature which distinguishes granted claim 2 from granted claim 1 suffices and

serves as a clearly delimiting feature vis-à-vis the prior art.

As already mentioned above, the feature which distinguishes claim 1 of the second auxiliary request from claim 1 as granted is in the form of a prerequisite or result-to-be-achieved (concerning the "relative bioavailability"). The bioavailability and correspondingly the "relative bioavailability" depends on the size of the celecoxib particles (primary particles) in the basic pharmaceutical composition (as particulate celecoxib) owing to the generally favourable influence of particle size reduction on surface area increase, and, hence, on the improvement of dissolution rate and absorption.

It is in fact generally known, as expressed in the technical book numbered as document (5), that "poorly soluble drugs showing a dissolution rate-limiting step in the absorption process will be more readily available when administered in a finely subdivided form with larger surface than as a coarse material" (page 156, left-hand column, second paragraph under the heading "Particle size and surface area").

However, bioavailability also depends on the actual constitution of the final dosage form which controls the release profile of the drug from the dosage form and influences the actual form in which the active ingredient is released. The final dosage form (undefined in the claim) may even oppose the effect attainable by particle size reduction.

Moreover, the "relative bioavailability" is not directly measured but is relative to "an **orally delivered solution** containing the same dose of celecoxib", wherein the solvent is undetermined in the claim.

The solvent or excipient admixed with the poorly soluble drug celecoxib may enhance the dissolution rate (and this influences the absorption) of the active drug, and hence the choice of the solvent modifies the reference values in relation to which the "relative bioavailability" has to be calculated.

Accordingly, the board considers that the introduction of the definition relating to the "relative bioavailability" from claim 2 into claim 1 as granted does not provide for a clear distinction vis-à-vis the known products (found to have celecoxib particle sizes as defined in the claim), since determining whether or not the condition expressed as result-to-be-achieved applies is open to the arbitrary selection of too many undefined parameters concerning the constitution of both formulations to be tested and compared with each other. Hence, said feature cannot be acknowledged as a delimiting feature on which novelty vis-à-vis the known pharmaceutical compositions could be based.

2.5.3 The appellant referred to its written submissions in support of its defence of the second auxiliary request. However, the fact that the dissolution rate of the particulate active agent in a medium (and correspondingly its absorption into the body) correlates with the particle sizes of said active agent present in an unformulated preparation is one thing;

the actual absorption into the body (from which the blood serum concentration originates) when the active agent is administered as ingredient in an orally final dosage form is another. When administered orally as ingredient in a final dosage form the active agent has to be released from it, and the specific excipients constituting said final dosage form may enhance or modulate its dissolution rate.

According to paragraphs [0050] to [0053], for determining the "relative bioavailability" one requires several measurements (and corresponding calculations) of AUC (area under the curve) relating to **blood serum concentrations at a certain time after administration.**

However, such values would depend on the availability of the active ingredient to be effectively released from the pharmaceutical composition (or final dosage form) in a (particulate) form allowing good absorption. Moreover, adequate residence times of the dosage form in the gastrointestinal tract are also needed.

Thus, claim 1 of the second auxiliary request sets an unclear delimitation to the pharmaceutical composition claimed vis-à-vis the known compositions since the particle sizes of celecoxib particles remain unchanged.

Furthermore, the "relative bioavailability" has to be calculated in relation to that of a solution of the active agent in which the undefined solvent may enhance or influence the dissolution rate.

Consequently, in the absence of a definition of the constituents of the pharmaceutical composition (or of

the final dosage form), and at the same time of the solution, too many factors remain unknown to allow the conclusion that the "relative bioavailability" is a delimiting feature on which novelty can be based.

Finally, although it is a post-published publication, document (D26), which is a scientific publication about "The effect of Polyethylene Glycol 400 on gastrointestinal transit" confirms that the solvent has an influence on the residence time within the intestinal tract of poorly soluble drugs (see page 1149, last two paragraphs right-hand column) and that the residence time in the gastrointestinal tract also has a bearing on the bioavailability of the drug.

2.5.4 Consequently, claim 1 of the second auxiliary request does not meet the requirements of novelty vis-à-vis document (1).

2.6 *Third auxiliary request*

2.6.1 *Added matter*

According to the opposition division's findings, claim 1 of the third auxiliary request contained added matter since the specification:

"in a mixture of polyethylene glycol having an average molecular weight of 400 and water in a ratio of 2:1 by volume"

was taken from the examples, and this caused a generalisation which was unallowable under Article 123(2) EPC.

It is a fact that the contested information appeared in example 11-1 and in the footnote to Table 11-2A of the application as filed, and that the mentioned example relates to "Bioavailability in a dog model". The vehicle of the solution of celecoxib to be given orally, and employed as reference, is in fact "a mixture of polyethylene glycol having an average molecular weight of 400 and water in a ratio of 2:1 by volume".

The vehicle is adequate for keeping celecoxib in solution and it is also the adequate vehicle for the solution used for reference purposes when measuring the several pharmacokinetic parameters as presented in example 11-1 and Tables 11-2B to 2D (pages 45 to 49 of the application as filed). Hence, the nature of the vehicle for the celecoxib solution to be used as a reference has been defined in said examples and can be taken over into the claim without contravention of Article 123(2) EPC.

The respondents' arguments of lack of support are not convincing since, as confirmed by the description (see paragraph [0053] of the patent in suit and page 14 of the application as filed), the value $AUC_{(0-\infty)}$ has to be calculated from AUC values at the time when the concentration was last quantifiable, and is not directly measured.

No further objections were raised in respect of added matter for claim 1 of the third auxiliary request and the board sees no reason to differ.

2.6.2 *Sufficiency of disclosure*

The product claimed in claim 1 of the third auxiliary request, which encompasses the pharmaceutical basic composition and the final oral dosage form, is defined by means of a parameter ($D_{90}$ for celecoxib primary particles) and a functional definition ("relative bioavailability" of the pharmaceutical composition or of the final oral dosage form).

$D_{90}$ is a parameter commonly used in particle science in relation to particle size. There are several standard methods commonly available for measuring particle size (e.g. light scattering, sieving, microscopy).

However, the size of the particle is "in the longest dimension" and $D_{90}$ is expressed in relation to particles of celecoxib in admixture with at least one excipient.

Microscopic examination of the raw drug is an important step in pre-formulation work. It gives immediately an indication of particle size and size range along with crystal structure. Microscopy examination was carried out within the context of the patent, which mentions crystal morphology (long needles) as possible cause for agglomeration (paragraph [0027] of the patent in suit). Although the patent in suit does not go into any detail in relation to the measurement technique for particle size, there is an indirect indication that microscopy is the technique used when looking at particle sizes. In particular, footnote (2) below Table 11-2A clearly states "until particles were approximately 1 µm in diameter as estimated by **microscopy**" (emphasis added).

In fact photomicrography was the technique chosen by respondent II for establishing particle size and shape in its first reproduction of example 2 of document (1), submitted with the grounds of appeal (see (E1)).

Moreover, Prof. Tucker's declaration (E3) which was filed by respondent III clearly states in paragraph [16]: "Since the patent specification under claim 1 states the "*longest dimension of said particles*", it can be deduced that sieve analysis was not used".

Additionally, as shown by document (47) microscopy is the technique of choice for successfully determining celecoxib particle size within a mixture with excipients.

Correspondingly, it is plausible that microscopy is the technique of choice for measuring the parameter $D_{90}$ appearing in claim 1.

Therefore, the board cannot agree that the lack of detail in the patent in suit about the measurement and calculation of $D_{90}$ causes a major problem of insufficiency of disclosure in the present case.

However, even if microscopy is the technique of choice, the values are "mean values" and "calculated values" and, hence, both options -"by number" and "by weight"- are in principle possible.

Additionally, neither the claim nor the description disqualifies light scattering (in particular laser diffraction) as a valid technique, especially when particle size is measured before formulating the

composition, i.e. when trying to reproduce the "invention".

However, the existence of two variations for the parameter values (number *versus* weight) and more than one valid measurement technique only demonstrates that it may be laborious to determine whether the particles have a size falling within the claim. The consequence of having diverse options for the $D_{90}$ parameter is that the claim defines a palette of values, and not a singular value, as the upper limit for the range of particle size. To this effect the relativity of the definition is underlined, but this alone does not hinder the skilled person from dealing with the claim in a technically meaningful manner.

As regards the "relative bioavailability", it is a functional definition which attempts to delimit the claim. It is a fact that functional definitions are broad and relative in their nature, with boundaries which are not sharp or specific. However, in the present case the "invention" is intended to be defined by two relative definitions which have a certain interaction.

In order to provide a complete disclosure, a patent does not have to give every single detail and to repeat what was commonly known to the skilled person at the filing date. However, if the "invention" is defined by means of functional definitions expressed as result-to-be-achieved, the patent should contain sufficient technical information to allow the skilled person to identify which technical measures are to be undertaken

in order to attain the intended technical effect or result.

If the alleged technical effect underlying the "invention" reflected by claim 1 is the increase of bioavailability by size reduction of the celecoxib particles, then the question arises as to which constitution and form the oral dosage form should have in order that the technical effect is maintained in the claimed product. In other words, what has to be done by the skilled person in order to provide a pharmaceutical composition (or a final dosage form of particulate celecoxib) which conforms to the functional limitation in the claim.

An inspection of the specification of the patent in suit shows no guidance in respect of the technical measures to be undertaken in order to achieve the "relative bioavailability of celecoxib not less than about 50% by comparison with an orally delivered solution in a mixture of polyethylene glycol having an average molecular weight of 400 and water in a ratio of 2:1 by volume containing the same dose of celecoxib".

Furthermore, an inspection of the examples shows the following. Example 11-1 (bioavailability in a dog model) investigates several pharmacokinetic parameters for an intravenous infusion of celecoxib, an oral solution of celecoxib (in both cases polyethylene glycol having an average molecular weight of 400 and water in a ratio of 2:1 by volume is the vehicle) and a capsule containing unformulated celecoxib (particle size unknown). Bioavailability (%) is calculated for the oral solution

and the capsule. The capsule shows a poor bioavailability.

Example 11-2 (relative bioavailability of formulations in a dog model) states that "the effect of such formulation parameters as celecoxib particle size, increased concentration of wetting agent, pH, and dispersion as a suspension were evaluated relative to an oral solution on bioavailability in a dog model".

Example 11-2 further states: "The effect of micronizing the celecoxib (mean particle size 10-20 µm) prior to formulating was tested in composition A. The combined effect of micronization (***size of particles is not stated***), added wetting agent (sodium lauryl sulfate), and increased micro-environmental pH ($Na_3PO_4$. $12H_2O$) was tested in composition B. The effect of bringing wetting agent (Tween 80) into intimate contact with celecoxib (co-precipitating vs. simple dry mixing) (***size of resulting coated particles unknown***) was tested in composition C. The effect of further particle size reduction (1 µm) and dispersing the particles in a suspension was tested in composition D. A solution of celecoxib similar to that used in Example 11-1 (composition E) was included as a reference. In addition, data from Example 11-1 for unmilled, unformulated celecoxib in a capsule (composition F) is also included as a reference" (page 24 of patent in suit).

Further in example 11-2 it is stated: "The results indicated that decreasing the particle size (composition A) or co-precipitating the celecoxib with a wetting agent (composition C) increased the

bioavailability (as measured by $AUC_{(0-24)}$) of celecoxib **compared to the earlier study of unformulated celecoxib** shown in Example 1-11" (*emphasis added*).

These conclusions are reached after comparison with the unformulated celecoxib (solid particulate of undefined particle size) filled into a capsule and, hence, do not help to identify the functional definition "relative bioavailability" (in relation to a specific solution of celecoxib) appearing in the claim.

Moreover, from the bioavailability (%) values depicted in Table 11-2C, only the composition A appears to fulfil the criteria of claim 1. The composition A comprises 25% celecoxib (particle size 10-20 µm), 2% sodium lauryl sulfate (wetting agent), 73% microcrystalline cellulose (diluent) and is a capsule formulation.

Therefore, even considering that composition A illustrates the claimed "invention", the extra fine particle size (10-20 µm) of celecoxib in the composition does not allow any conclusion applicable to the case of particle sizes of about 200 µm, as encompassed by claim 1.

Correspondingly, there is no disclosure in the patent in suit enabling the reproduction of the functional definition of relative bioavailability appearing in claim 1 for all the celecoxib particle sizes encompassed by the claim. Additionally, there is a lack of information in the patent in suit concerning the technical measures required for attaining the "relative bioavailability" defined in the claim, since

example 11-2 tests conventional compositions ("reasonable formulations", as expressed by the appellant) which have extra fine particle sizes and do not fulfil the relevant condition.

Therefore, the subject-matter claimed in claim 1 of the third auxiliary request is insufficiently disclosed (Article 83 EPC).

The appellant argued that the only thing required was to find an adequate particle size and then choose the formulation so as not to influence too negatively the effect attained by diminishing particle size. However, as shown in the analysis above, this is not a simple question, especially since too many variations are possible for whose influence upon bioavailability no indication whatsoever has been given in the patent.

Therefore, in view of the lack of information in the patent in suit in relation to the condition set out in the claim, claim 1 amounts to an invitation to perform a research programme to find out the conditions essential for an adequate oral dosage form.

2.7 *Fourth auxiliary request*

2.7.1 The basis for the amendments introduced in claim 1 as granted has to be looked for in the description of the application as filed, since the originally filed claims do not contain the combination of all the excipients in the defined amount ranges.

However, in order to arrive at amended claim 1 one has to perform several selections of amount ranges (among

different preferred ranges) and combine them in relation to all the ingredients.

Therefore, amended claim 1 singularises a subgroup of definitions of ingredients having specified particular ranges which was not directly and unambiguously derivable from the application as filed.

Accordingly, the fourth auxiliary request fails since it does not meet the requirements of Article 123(2) EPC.

2.8 *Remittal (Article 111(1) EPC)*

The decision under appeal revoked the patent, although for different reasons from those expressed in the present decision. However, there is no absolute right to have the same issues dealt with by two different instances. Moreover, the opposition division has already examined the same requests as those underlying the present decision in respect of the EPC articles concerning which the board has come to a conclusion.

Additionally, the appellant requested remittal for assessment of inventive step but none of the requests filed fulfils§ the requirements of novelty, sufficiency of disclosure and non-added matter. Hence, remittal cannot take place.

## Order

## For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald