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D E C I S I O N
of 14 February 2006

Case Number: T 0629/03 - 3.3.02

Application Number: 96901349.9

Publication Number: 0773025

IPC: A61K 31/44

Language of the proceedings: EN

Title of invention:
New stable galenic formulations containing an acid-labile benzimidazol compound, and production process

Patentee:
LABORATORIOS DEL DR. ESTEVE, S.A.

Opponent:
ETHYPHARM

Headword:
Stable galenic formulations of omeprazole/LABORATORIOS DR. ESTEVE

Relevant legal provisions:
EPC Art. 100(c), 123(2)

Keyword:
"Main request: claim 1 as granted extends beyond the content of the application as filed"
"First auxiliary request: identical reasons"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0629/03 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 14 February 2006

Appellant: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 15 May 2003 rejecting the opposition filed against European patent No. 0773025 pursuant to Article 102(2) EPC.**

Composition of the Board:

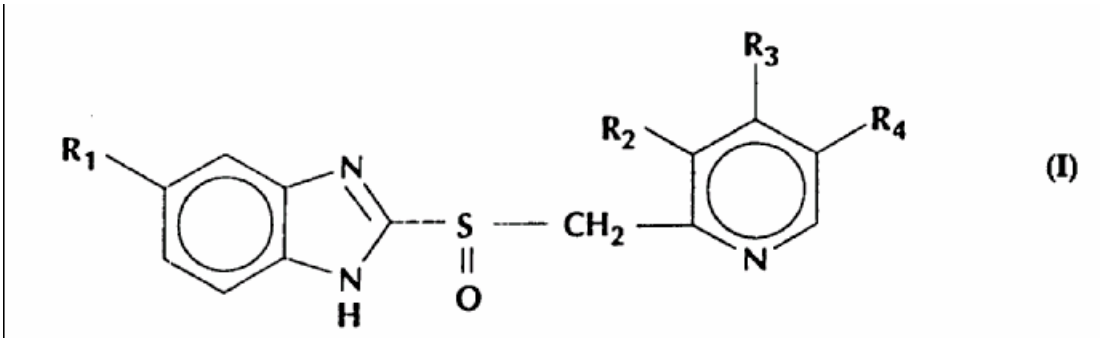
Chairman: U. Oswald
Members: M. C. Ortega Plaza
S. Hoffmann

Summary of Facts and Submissions

I. European patent EP-0 773 025, based on European application No 96 901 349.9, which was filed as international application WO 96/23500, was granted on the basis of 3 claims.

Claim 1 as granted read as follows:

"1. A stable oral pharmaceutical preparation containing an acid labile benzimidazole compound of formula I:



(I)

wherein R_1 is methoxy, R_2 is methyl, R_3 is methoxy, R_4 is methyl which comprises:

(a) a nucleus formed by coating a spherical inert core with the acid labile benzimidazole, hydroxy-propylmethylcellulose and talc;

(b) an inert coating disposed on said nucleus, formed by hydroxypropylmethylcellulose, titanium dioxide and talc;

(c) an outer layer disposed on the previous coating comprising an enteric coating containing co-polymerized methacrylic acid/methacrylic acid methyl ester, triethylcitrate and talc."

Claim 2 as granted read as follows:

"2. A process for the preparation of a stable oral pharmaceutical preparation containing an acid labile benzimidazole compound of formula I as defined in claim 1 as active ingredient, which comprises: preparing a nucleus formed by spraying a layer that contains the acid labile benzimidazole, hydroxypropylmethylcellulose and talc on an inert core in a fluidized bed apparatus, drying, coating said nucleus by spraying an inert layer formed by hydroxypropylmethylcellulose, titanium dioxide and talc, drying, and finally coating by spraying an enteric coating containing co-polymerized methacrylic acid methyl ester, triethyl citrate and talc, and drying."

Claim 3 as granted read as follows:

"3. A galenic preparation in the form of capsules or tablets containing the stable oral pharmaceutical preparation according to claim 1."

II. Opposition was filed and revocation of the patent in its entirety was requested pursuant to Articles 100(a), (b) and (c) EPC.

III. The appeal lies from the decision of the opposition division rejecting the opposition under Article 102(2) EPC, based on the auxiliary request (set of claims as granted) filed during the oral proceedings before the opposition division.

The opposition division considered that the main request (amended set of claims filed with letter of 07 February 2003) did not meet the requirements of Article 84 EPC. In particular, the opposition division considered that the functional expression "alkaline reacting compound" did not clearly define which compounds were excluded from the claimed compositions. Moreover, according to the opposition division's findings, the mentioned term even encompassed talc, since water suspensions of talc showed a basic pH due to the usual impurities present. Furthermore, the opposition division did not agree with the patentee's submissions that the mentioned term referred to substances able to provide an alkaline buffering effect.

In respect of the ground of opposition under Article 100(c) EPC, the opposition division considered that the auxiliary request (set of claims as granted) did not extend beyond the content of the application as originally filed.

Moreover, the opposition division stated that novelty had not been contested by the opponent and that the requirements of novelty were met by the claimed subject-matter (Article 54 EPC).

As regards the requirements of Article 83 EPC, the opposition division considered that the specification taken as a whole contained all the information needed for the skilled person to carry out the invention in its whole scope.

With respect to inventive step, the opposition division considered document (7) (WO 92/22284) to represent the closest prior art.

The problem was defined by the opposition division as to provide an alternative formulation for acid-labile benzimidazole derivatives.

The opposition division considered that the solution involved an inventive step since the presence of an alkaline buffering agent was a necessary prerequisite in the light of the prior art.

IV. Both patentee and opponent (initially opponent 2) lodged an appeal against said decision and filed grounds of appeal.

V. A board's communication dated 21 April 2005, which conveyed rapporteur's preliminary opinion, was sent to the parties.

VI. The appellant-opponent filed further arguments in a response to the board's communication.

VII. The board's preliminary non-binding opinion was expressed in a communication sent as an annex to the invitation to oral proceedings.

VIII. The appellant-patentee filed with its letter of 10 January 2006 a main request and a first auxiliary request. It also stated that the set of claims as granted represented its second auxiliary request.

IX. The appellant-opponent filed with its letter of 12 January 2006 further arguments in relation to Article 100(c) EPC and, inter alia, a copy of Handbook of Pharmaceutical Excipients, 2nd Edition, 1994, pages 362-366 (document (23)).

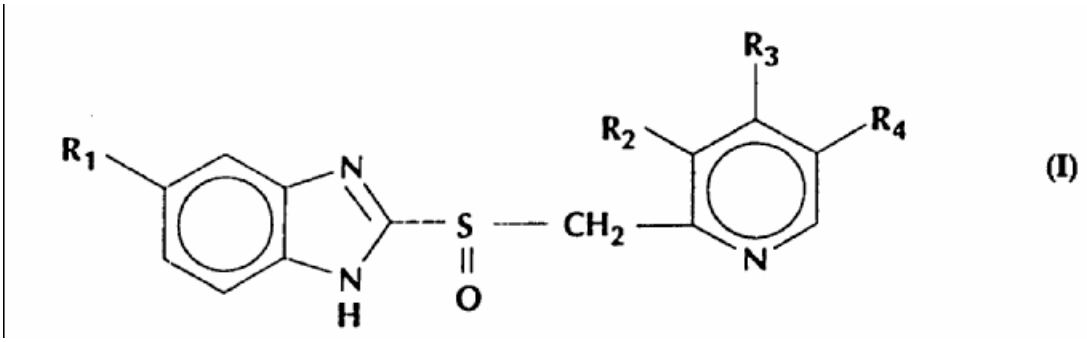
X. During the oral proceedings the appellant-patentee submitted as main request the set of claims as granted (this request equates to request that the appellant-opponent's appeal be dismissed) and three auxiliary requests. The first auxiliary request corresponds to the main request filed with the letter of 7 February 2003, in which the missing formula I is now shown.

Claim 1 of the first auxiliary request differs from claim 1 as granted in that it contains at the end of the claim the following:

"and wherein the pharmaceutical preparation does not contain alkaline reacting compounds."

Claim 1 of the second auxiliary request read as follows:

"1. A stable oral pharmaceutical preparation containing an acid labile benzimidazole compound of formula I:



(I)

wherein R_1 is methoxy, R_2 is methyl, R_3 is methoxy, R_4 is methyl, which comprises:

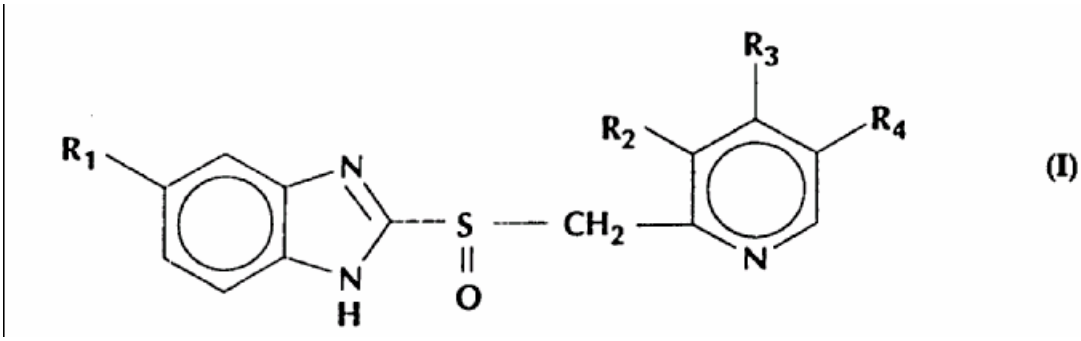
(a) a nucleus of uniform spherical inert cores coated with a first layer consisting of the acid labile benzimidazole, hydroxypropylmethylcellulose and talc;

(b) an inert coating disposed on said nucleus, formed by hydroxypropylmethylcellulose, titanium dioxide and talc;

(c) an outer layer disposed on the previous coating comprising an enteric coating containing co-polymerized methacrylic acid/methacrylic acid methyl ester, triethylcitrate and talc."

Claim 1 of the third auxiliary request read as follows:

"1. A stable oral pharmaceutical preparation containing an acid labile benzimidazole compound of formula I:



(I)

wherein R_1 is methoxy, R_2 is methyl, R_3 is methoxy, R_4 is methyl, which comprises:

(a) a nucleus formed by coating a spherical inert core with only the acid labile benzimidazole, hydroxy-propylmethylcellulose and talc;

(b) an inert coating disposed on said nucleus, formed only by hydroxypropylmethylcellulose, titanium dioxide and talc,

(c) an outer layer disposed on the previous coating comprising only an enteric coating containing co-polymerized methacrylic acid/methacrylic acid methyl ester, triethylcitrate and talc."

XI. The appellant-opponent submitted during the oral proceedings an additional document, namely US-A-5 045 321.

XII. The appellant-opponent contested the admissibility of the second and third auxiliary requests filed during the oral proceedings since they were completely new requests and they addressed speculative issues.

As regards the filing of a late-filed document, the appellant-opponent could not clearly explain the reasons for the late filing.

The appellant-opponent recalled that Article 100(c) EPC was a ground of opposition in the case under appeal. It also referred to its written submissions during the appeal proceedings.

Basically, the following arguments were put forward by the appellant-opponent:

The specification as originally filed required as an essential characterising feature that the pharmaceutical preparation did not contain "alkaline

reacting compounds" (cf. especially the paragraph under the heading "Outline of the invention"), whatever that meant. The claim's wording was open-ended, in the sense that other components were allowed, due to the use of expressions such as "comprises". Therefore the skilled reader would read into the claim the presence of other ingredients.

The claims as originally filed contained a generic formula encompassing a long list of possible active ingredients. Furthermore, the inert water-soluble polymer had to be selected for the nucleus (a) and the intermediate layer (b). Further selections were undertaken in respect to the excipients of the first and intermediate layers and in respect of the composition of the enteric coating.

The disclosure on page 4 was on the one hand of a generic nature in relation to the active ingredient and on the other hand was limited by the expression "consists of" when defining the actual components. In a preparation which has to be suitable as a stable oral pharmaceutical preparation all the ingredients play an essential role. Therefore, claim 1 as granted was not directly and unambiguously derivable from the application as originally filed.

The appellant-opponent made reference to its written submissions as proof that the pharmaceutical preparation of Example 1 could not serve as basis for granted claim 1 since the co-polymerized methacrylic acid derivative forming the enteric coating was different from that specified in claim 1 as granted. Furthermore, example 1 was also not in line with the

generic disclosure on page 4 as originally filed, in view of the different nature of the co-polymer forming the enteric coating (namely methacrylic acid/acrylic acid ethyl ester instead of methacrylic acid/methacrylic acid methyl ester). Such different co-polymers possess different dispersion properties.

Additionally, apart from the fact that the appellant-opponent still contested that talc was not encompassed by the definition "alkaline reacting compound", it stated that originally filed claim 1 required that all the excipients included in the nucleus (a) were "non-alkaline reacting" excipients.

Moreover, the appellant-opponent stated that the subject-matter of claim 1 as granted was not directly and unambiguously derivable from the application as originally filed and that this was evident when using either the "disclosure test" or the "novelty test". As a result, claim 1 as granted related to an unallowable singling out.

Finally, in the appellant-opponent's view the claims had to be interpreted as they stand and not as a result of wishful thinking in the light of "something standing somewhere else".

The appellant-opponent stated that it had no further comments in respect of the first auxiliary request.

XIII. With respect to the requests filed during the oral proceedings the appellant-patentee submitted that the main request (set of claims as granted) and the first auxiliary request were already on file before the

letter of 10 January 2006, although in reverse order. Therefore, the appellant-opponent was not taken by surprise.

As regards the second and third auxiliary requests the appellant-patentee stated that the amendments had been introduced in order to address the appellant-opponent's interpretation of the granted claim's wording in relation to the presence of alkaline reacting compounds, especially in the light of the appellant-opponent's late submissions. The spherical inert core was specified as "uniform" since the definition for (a) appearing in the application as originally filed was taken verbatim, in order not to offend against Article 123(2) EPC.

The late-filed document submitted by the appellant-opponent should not be admitted into the proceedings since it was completely irrelevant.

With respect to the grounds of opposition under Article 100(c) EPC the appellant-patentee's submissions may be summarised as follows:

The basis for claim 1 as granted should be found in claim 1 as originally filed together with claim 2 (with deletion of one possibility among two in relation to the definition of the water-soluble polymer) and claim 3 with respect to the nature of the enteric coating. The specification of the labile benzimidazole as omeprazole was directly derivable from the application as originally filed since omeprazole was the only benzimidazole exemplified (example 1 on page 5) and tested (Table 4, page 10). The specification as

originally filed made it clear that omeprazole was preferred.

The further specifications were made in the light of page 4 of the originally filed description (under the heading "Detailed description of the invention"). The only "non-alkaline reacting" pharmaceutically acceptable excipient mentioned on page 4 as originally filed in connection with the first layer was talc. The only pharmaceutically acceptable excipients mentioned on page 4 in connection with the intermediate layer were titanium dioxide and talc and the only pharmaceutically acceptable excipient mentioned on page 4 in connection with the enteric coating was talc.

In a "novelty test" the subject-matter of the granted claim 1 would not be considered as novel.

The appellant-patentee acknowledged that the co-polymer forming the enteric coating in the preparation of example 1 was different from that defined in claim 1 as granted.

The appellant-patentee also stated that the applicant had chosen to define the subject-matter claimed in positive terms and to specify those components which were mandatory to have a stable preparation. Therefore, it would be an undue restriction to have the claims restricted so as to exclude all possible alkaline reacting compounds.

In the appellant-patentee's view the claims were clear and had to be construed in the light of the specification. It would therefore be bizarre to

interpret the claims so as to include an alkaline reacting compound.

The appellant-patentee stated that the same arguments applied mutatis mutandis to the first auxiliary request.

XIV. The appellant-opponent requested that the decision under appeal be set aside and that the European patent No 0773 025 be revoked.

The appellant-patentee requested that the opponent's appeal be dismissed (main request) or, in the alternative, that the patent be maintained on the basis of the first, second or third auxiliary requests filed during the oral proceedings.

Reasons for the decision

1. Both appeals are admissible.

2. The patent in suit is based on European application No 96 901 349.9, which was filed as international application WO 96/23500 in the Spanish language. Therefore, when referring to the documents of the application as originally filed in the present decision the English translation filed within the meaning of Article 14(2) and Rule 5 EPC will be meant.

3. For the sake of completeness is has to be said that the name of the compound of formula I (this generic formula is shown in claim 1 of all requests), wherein R_1 is methoxy, R_2 is methyl, R_3 is methoxy and R_4 is methyl, is omeprazole.

4. *Admissibility of the late-filed requests and additional document*

4.1 The main request and the first auxiliary request were on file from the beginning of the appeal proceedings, although in inverse order, as they served as the basis for the appealed first-instance decision. Therefore, the appellant-opponent was not taken by surprise. Moreover, a change in the ranking of the sets of claims serving as the basis for the appellant-patentee's requests at the beginning of the oral proceedings is admissible.

Additionally, the appellant-opponent has not contested the admissibility of these requests.

Therefore, the main request and the first auxiliary request filed during the oral proceedings are admissible.

4.2 As regards the admissibility of the second and third auxiliary requests the following considerations apply:

The second and third auxiliary requests were per se late-filed since they were filed by the appellant-patentee during the oral proceedings before the board. Moreover, the discussion in relation to the claim's wording concerning the use of the terms "comprises", "formed by" and "comprising" in connection with the possible exclusion of further components in the pharmaceutical preparation was already addressed in the rapporteur's communication dated 21 April 2005 (especially point 8).

Hence, the appellant-patentee's argument that the new sets of claims should be considered as an attempt to overcome recently raised objections fails.

Additionally, the specification of the spherical inert core forming the coated nucleus (a) as "uniform" does not represent a direct response to the problem of the presence or absence of the so-called "alkaline reacting compound", which was extensively discussed during the written proceedings.

Finally, although it can be agreed that the wording of component (a) has been taken from that appearing on page 4, lines 16-21 of the application as originally filed, the claim's wording does not reproduce verbatim the whole text. In particular, the generic process disclosed on page 4, lines 16-28 of the application as originally filed relates to a pharmaceutical preparation with limited definitions in relation to the components for (b) and (c), owing to the repeated use of the expression "consists of". Hence, the amendment made in claim 1 of the second auxiliary request results in a pharmaceutical preparation which is only partly reflected by page 4 of the original description and prima facie not allowable under Article 123(2) EPC.

The amendments introduced in the third auxiliary request correspond to the introduction of the word "only" in (a), (b) and (c). However, the definition of the outer layer (c) as "comprising" "**only**" an enteric coating "**containing**" ... relates to a combination of an apparently restrictive term ("only" an enteric coating) with an open definition ("containing", which is

independent thereof, as regards the composition of the enteric coating. Hence, there is prima facie a lack of clarity caused by the amendments introduced (Article 84 EPC).

Therefore, the amendments introduced in claim 1 of the third auxiliary request are not clear and easy to deal with.

Consequently, the sets of claims of the second and third auxiliary requests filed during the oral proceedings have to be refused as filed too late.

4.3 The introduction into the proceedings of the document put forward by the appellant-opponent during the oral proceedings is inadmissible since the document was filed too late and prima facie irrelevant to a decision on the case.

Additionally, the appellant-opponent did not provide any convincing arguments in favour of the admissibility of the additional document.

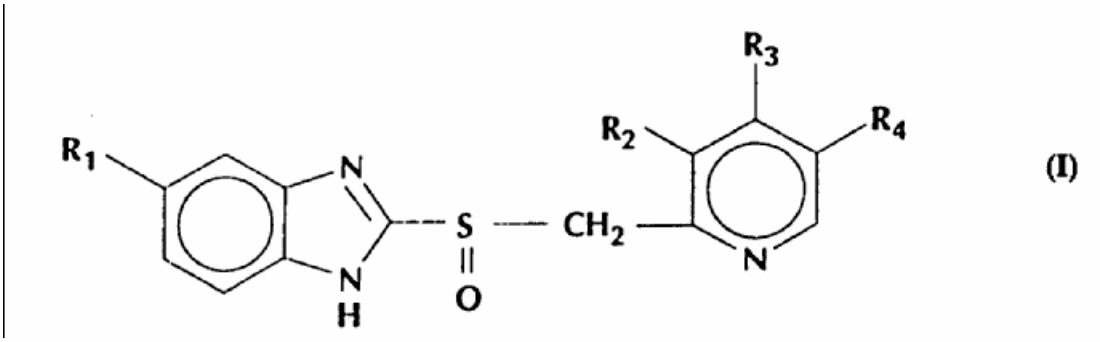
5. *Main request (set of claims as granted)*

5.1 It is an undisputed fact that Article 100(c) EPC was filed as a ground of opposition in the present case.

Therefore it has to be investigated whether the subject-matter of the European patent extends beyond the content of the application as filed.

5.2 Claim 1 as filed read as follows:

"A stable oral pharmaceutical preparation containing an acid labile benzimidazole compound of formula I:



wherein R_1 is hydrogen, methoxy or difluoromethoxy, R_2 is methyl or methoxy, R_3 is methoxy, 2,2,2-trifluoroethoxy or 3-methoxypropoxy, R_4 is hydrogen or methyl which comprises:

(a) a nucleus formed by an inert core, the acid labile benzimidazole, an inert water soluble polymer and non-alkaline reacting pharmaceutical acceptable excipients;

(b) an inert coating disposed on said nucleus, formed by a water soluble polymer and other pharmaceutical acceptable excipients;

(c) an outer layer disposed on the previous coating comprising an enteric coating."

5.3 It is self-evident from a comparison with claim 1 as granted that whereas the originally filed claim related to a generically defined oral pharmaceutical preparation comprising as active ingredient an acid labile benzimidazole also defined generically, the granted claim relates to a much more specific oral

pharmaceutical preparation. Indeed, the pharmaceutically active ingredient has been individualized to a single compound in the multi-layer pharmaceutical form and the constitution of the different layers has been specified in respect of the (essential) components.

5.4 There is one aspect which immediately appears not to be explicitly reflected by the granted claim, namely the fact that whatever pharmaceutically acceptable excipients are used when forming the nucleus, they should be "non-alkaline reacting".

Leaving aside the discussion concerning the clarity of the mentioned expression, this condition has been left out of the granted claim. Instead, the excipient used when forming the nucleus has been specified as talc (cf. paragraph (a) of the granted claim). It is however immaterial for the outcome of the present case whether talc falls within the definition "non-alkaline reacting excipient" since the claim fails for other reasons as given below.

5.5 It is undisputed by the appellant-patentee that the specific oral pharmaceutical preparation of example 1 differs from that of claim 1 as granted in the nature of the co-polymer forming the enteric coating.

Therefore, the specific multi-layer pharmaceutical preparation of example 1 as filed cannot be taken as the basis for a multi-layer preparation with a different constitution in respect of one of the essential features, namely the enteric coating. The nature of the individual layers cannot, without

extending the content of the initial disclosure in an unallowable manner, be specified in respect of the nucleus and intermediate layer on the basis of a specific individual oral pharmaceutical preparation (namely that of example 1) and, simultaneously, be combined with a different specific meaning for the enteric coating taken from another pharmaceutical preparation disclosed separately and independently somewhere else in the description (page 4, lines 16-28) - particularly, since the preparations on page 4 do not encompass that of example 1.

5.6 As regards the combination of originally filed claims 1 and 2, it has to be said that this requires not only the deletion of one of two possible options, but a double selection. A combination of claims 1 and 2 as filed results in four options, since it is not mandatory from the claim's wording that the inert water-soluble polymer of the nucleus (a) and that of the intermediate layer (b) has to be the same. This means that two selections have to take place in order to arrive at the wording of the granted claim 1: first the inert water-soluble polymer for (a) and (b) be the same and, second, it has to be hydroxypropyl-methylcellulose.

5.7 Furthermore, even if such double selection is considered as allowable, it is still required, in order to arrive at the wording of the granted claim 1, to find a basis for the specification of the other components of the nucleus (omeprazole as single active ingredient, talc in the first layer), intermediate layer (talc and titanium dioxide) and enteric coating (talc) not specified in claims 2 and 3 as filed.

Accordingly, the contents of the whole paragraph appearing on page 4, lines 16-28, of the application as originally filed have to be examined.

The said paragraph reads as follows:

"In a fluidized bed apparatus, **uniform** spherical inert cores (composition as per US Pharmacopoeia) are coated with a first layer **consisting of** the **acid labile benzimidazole compound**, an inert water soluble polymer such as hydroxy-propylmethylcellulose or hydroxypropylcellulose, and talc. The second layer **consists of** an inert water soluble polymer such as hydroxypropylmethylcellulose or hydroxpropylcellulose [*sic*], talc and a pigment such as titanium dioxide. The third and enteric coating layer **consists of** an enteric coating polymer such as copolymerized methacrylic acid/ methacrylic acid methyl esters, a plasticizer such as triethylcitrate or similar plasticizers and talc." (emphasis added)

The above passage relates to the disclosure of a generic process which leads to a pharmaceutical preparation in which the active ingredient is defined in generic terms but for which the multi-layer form is restrictively defined in relation to the number of layers and the components of each layer, which are defined in a limited way owing to the repeated use of the term "consists of". In contrast, claim 1 as granted singularizes the active ingredient as omeprazole but at the same time leaves open the option of including further layers or components due to the use of the expressions "comprises", "formed by" and "comprising".

Correspondingly, it cannot be considered to be allowable to select from the restricted disclosure of the multi-layer form on page 4 as filed certain single components and incorporate them into open-ended definitions of the preparation of claim 1 as originally filed.

5.8 As regards the basis for the specification of the active ingredient, there are **two** labile benzimidazole compounds of formula I as originally filed which have been exemplified as active ingredients of specific preparations, namely omeprazole as active ingredient in the pharmaceutical preparation of example 1 and lansoprazole as active ingredient in example 2, these being the only two examples in the original description.

Apart from the fact that it appears difficult to conclude from this exemplification ratio that omeprazole was unambiguously disclosed as the preferred active ingredient, the pharmaceutical preparation of example 1 has to be taken in its whole constitution as a multi-layer form where the active ingredient forms an essential part of the first layer covering the inert spherical core. As mentioned in paragraph 5.5 above, the specific multi-layer form disclosed in example 1 is different from that claimed in granted claim 1.

Additionally, the "omeprazole new formulation" used for the biopharmaceutical studies (cf. results on table 4, page 10 as originally filed) relates to hard gelatin capsules filled with the galenic form of omeprazole prepared according to example 1 (page 8, lines 34-36).

6. Consequently, in the light of the above, the board concludes that claim 1 as granted extends beyond the content of the application as filed since it relates to an unallowable singling out which is achieved by an unallowable combination of specific choices in several directions.

6.1 It is to be noticed that the appellant-patentee had no longer argued during the oral proceedings before the board that the preparation of example 1 should be taken as the basis for granted claim 1. The appellant-patentee's submissions in respect of example 1 merely concern the argument of the choice of omeprazole as the preferred active ingredient.

However, the claimed invention relates to a "stable" pharmaceutical multi-layer form in which the choice of every component plays an essential role in the desired stability, which is directly linked to the labile benzimidazole to be chosen as active ingredient.

Since a combination of only certain aspects of the preparation obtained by the preparation process on page 4 with a broadly defined multi-layer form cannot be considered allowable in view of the reasons given in point 5.7 above, the combination of claims 1, 2 and 3 as originally filed, even if taken into consideration, remains insufficient for the purpose of arriving at claim 1 as granted.

7. *First auxiliary request*

7.1 Claim 1 of the first auxiliary request extends beyond the content of the application as filed for the same reasons as claim 1 of the main request.

7.2 None of the parties has brought forward any further arguments in this respect.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairman:

A. Townend U. Oswald