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**D E C I S I O N**  
**of 14 June 2005**

**Case Number:** T 0635/01 - 3.3.2

**Application Number:** 94928221.4

**Publication Number:** 0720480

**IPC:** A61K 31/66

**Language of the proceedings:** EN

**Title of invention:**

Enteric coated oral compositions containing bisphosphonic acid derivatives

**Applicant:**

Merck Frosst Canada & Co.

**Opponent:**

-

**Headword:**

Enteric-coated dosage form/MERCK FROSST CANADA

**Relevant legal provisions:**

EPC Art. 52, 54, 56, 106, 107, 108, 113(1)

EPC R. 64

RPBA Art. 11(3)

**Keyword:**

"Inventive step (no): claimed enteric-coated oral dosage form results from a simple combination of the teaching of citation (2) with that of citation (1) or vice versa"

**Decisions cited:**

-

**Catchword:**

-



Case Number: T 0635/01 - 3.3.2

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.2  
of 14 June 2005

**Appellant:**

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**Decision under appeal:**

Decision of the Examining Division of the  
European Patent Office posted 26 January 2001  
refusing European application No. 94928221.4  
pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairman:** J. Riolo  
**Members:** G. F. E. Rampold  
J. H. P. Willems

## Summary of Facts and Submissions

I. The appellant is the applicant of European patent application No. 94 928 221.4 ("the application"). The application was filed on 21 September 1994 (International application No. PCT/CA 94/00518), claiming priority from an earlier US application on 21 September 1993, and is entitled "Enteric coated oral compositions containing bisphosphonic acid derivatives".

The appeal was filed on 26 March 2001 and lies against a decision of the examining division of the EPO pronounced at the close of the oral proceedings on 24 October 2000, with written reasons notified on 26 January 2001, by which the application was refused pursuant to Article 97(1) EPC. The appellant paid the appeal fee and submitted the statement setting out the grounds of appeal within the prescribed time limits.

II. The decision under appeal was based on an amended set of six claims which were filed on 25 September 1995 and formed also the basis of the IPER. The sole independent claim reads as follows:

- "1. An enteric-coated oral dosage form comprising:
- (i) a core tablet containing a therapeutically effective amount of a bisphosphonic acid active ingredient selected from the group consisting of: alendronic acid, risedronic acid, tiludronic acid and a pharmaceutically acceptable salt of any of the foregoing;
  - (ii) an enteric coating comprising a polymer selected from the group consisting of:

- cellulose acetate phthalate, methyl acrylate-methacrylic acid co-polymers, cellulose acetate succinate, hydroxy propyl methyl cellulose phthalate, polyvinyl acetate phthalate and methyl methacrylate-methacrylic acid copolymers; and
- (iii) a subcoat comprising a pH independent polymeric film selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxypropyl ethyl cellulose, polyvinyl pyrrolidone and a 50:50 mixture of hydroxypropyl methyl cellulose and hydroxy propyl cellulose, wherein the polymeric film is applied to said core tablet wherein said polymeric film prevents the migration of the bisphosphonic acid or pharmaceutically acceptable salt to the outer enteric coating."

Dependent claims 2 to 6 are directed to specific embodiments of the enteric-coated oral dosage form according to claim 1.

III. The following documents, all already cited in the first-instance proceedings, are also referred to in the present decision:

- (1) EP-A-421 921
- (2) WO-A-93/0985
- (4) N. Kaniwa et al, J. Pharmacobio-Dyn., 11, 571-575, 1988
- (5) K. Sugito et al, Chem. Pharm. Bull., (40)(12), 3343-3345, 1992

IV. The essence of the reasoning in the decision under appeal was as follows:

(A) The examining division acknowledged the novelty of the subject-matter of the claims as amended over the cited state of the art.

(B) As regards inventive step, the examining division in its introductory remarks noted that the closest state of the art, viz. citation (1), was entitled "Double-coated granules" and described a novel oral administration form for 3-amino-1-hydroxypropane-1,1-diphosphonate ("disodium pamidronate") for use in the treatment of diseases involving bone resorption and formulated in an enteric-coated form.

(C) Since salts of pamidronic acid ("pamidronates") used in (1) as the active ingredients still fell within the group of the active bisphosphonic acid compounds represented by formula (I) on page 4 of the application, the examining division concluded that the acknowledgment of an inventive step could not be based on the limitation of the claimed subject-matter to the three particular bisphosphonic acid derivatives ("alendronate", "risedronate" and "tiludronate") which are used as the active ingredients of the claimed enteric-coated oral dosage form in claim 1 as amended (see I above).

(D) The examining division also noted that the coating materials used for the inner subcoat and the outer enteric coat, respectively, of the double-coated pellets or granules disclosed in (1) were exactly the

same as those used for the inner subcoat and the outer enteric coat of the claimed double-coated tablets in claim 1 of the application. It thus found that the essential difference between disclosure of citation (1) and the claimed oral dosage form was the nature of the core which was coated. In contrast to the prior art of (1), where a granule or pellet core was used, a core in the form of a tablet was used in the claimed invention.

**(E)** The examining division then referred to page 2, lines 21-26, of citation (1) where it was stated that there were admittedly two aspects of the advantageous oral administration forms in (1). Not only was a double-coated formulation adopted, but also the size of the granules containing disodium pamidronate was important - in particular, due to their accelerated gastric passage. In this context, the examining division also noted that citation (4) confirmed that there was a significant correlation between the gastric emptying rates and the sizes of oral dosage forms.

**(F)** However, in the context of the above-mentioned disclosure in citation (1), the examining division first quoted the description of the claimed invention on page 6, lines 22-23, of the application where it was stated that "the term "tablet" is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes". From this it concluded that no minimum size for the claimed dosage form (tablets) was stipulated in the application.

**(G)** Further, in the paragraph bridging pages 3 and 4 of the contested decision, the examining division referred to page 3, lines 5-8, of citation (1) where it

specified that the granules were solid preparations which contained the active ingredient, disodium pamidronate and carriers, and that the granules could be used to make tablets.

(H) Finally, in the first paragraph on page 4 of the decision under appeal, the examining division referred to Examples 1 to 3 of citation (1) and compared them to the specific example in the application. It concluded therefrom that the weight of the core tablet of the application was lighter than the weight of the core pellet of citation (1).

(J) From these observations the examining division concluded that the size as such of the tablet used in the application could not serve as a basis for the acknowledgment of an inventive step. In this context, the examining division also noted that no experimental evidence was available showing some advantageous technical effects for the claimed double-coated oral dosage form (tablet) in the application compared with the double-coated granules or pellets disclosed in (1), and refused the application for lack of inventive step.

V. In a communication dated 26 January 2005, the appellant was duly summoned to oral proceedings pursuant to Rule 71(1) EPC. In a fax dated 24 May 2005, the appellant announced that it would not be attending the hearing scheduled to take place on 14 June 2005. Since the appellant was not represented, the oral proceedings were continued without it, as provided for in Rule 71(2) EPC and Article 11(3) RPBA.

VI. The appellant's submissions in the statement of grounds of appeal could be summarised as follows:

[01] In the technical field of enteric-coated pharmaceutical preparations, and particularly relating to the formulation of bisphosphonates, the closest prior art had been identified by the examining division as citation (1). This citation was entitled "Double-coated granules" and described a particularly advantageous oral administration form for disodium 3-amino-1-hydroxypropane-1,1-diphosphonate ("pamidronate"). As stated in (1), the disodium pamidronate compositions were not limited to those containing granules, but included as a particularly preferred embodiment the use of spherical pellets having a particle size of less than 1.5 mm (see page 2, lines 46-47).

[02] The differences between citation (1) and the presently claimed invention were, in the appellant's opinion, as follows:

- citation (1) disclosed oral dosage forms in the form of capsules/sachets comprising a granule or pellet core and disodium pamidronate as the active ingredient;
- the claimed invention disclosed oral dosage forms in the form of tablets comprising a tablet core and "alendronate", "risedronate" or "tiludronate" as the active ingredients.

[03] The appellant, however, indicated that, for the purpose of these appeal proceedings, it did not intend



to present any argument concerning the difference between the choice of active ingredient in (1) and in the application (see [2] above). The key difference to be discussed was thus the nature of the core which was coated, ie either a granule or pellet as disclosed in (1) or a tablet as claimed in the present claims.

**[04]** The appellant defined the technical problem in respect of the prior art of citation (1) as the provision of further oral dosage forms containing a bisphosphonic acid or a salt thereof wherein said dosage form is adapted for administration to a patient exhibiting upper gastrointestinal tract sensitivity to bisphosphonic acids.

**[05]** As regards inventive step, the appellant argued essentially as follows:

The oral administration forms of citation (1) comprised granules having a small diameter. In particular, (1) related to pellets having a diameter of less than about 1.5 mm. In (1) the skilled person read that "for orally administered granules having a small diameter, in particular pellets having a diameter of less than about 1.5 mm, their accelerated gastric passage is characteristic <.....>. If the granules, in particular the pellets, are further coated with a gastric juice-resistant, intestinal juice-soluble coating, release of the active ingredient in the stomach, which is still possible despite relatively rapid further transport, can be essentially eliminated." (see page 2, lines 21-26).

[06] The skilled person reading this passage would appreciate that there were two aspects of the advantageous oral administration form described in (1). Not only was a double-coated formulation adopted, but also the size of the granules containing disodium pamidronate was important - in particular, due to their "accelerated gastric passage". The importance of granule size was also emphasized in claims 3 and 4 in (1) where the granules are said to be spherical pellets having a diameter of about 0.3 to 1.5 mm (claim 3) or of about 0.5 to 1.25 mm (claim 4). The skilled person would not be surprised to see a reference in (1) to the importance of accelerated gastric passage since the relationship between gastric emptying rates and particle size was well documented. Two publications relating to this aspect of pharmaceutical formulation technology were referred to in the contested decision as citations (4) and (5).

[07] Citation (4) confirmed that there was a significant correlation between the gastric emptying rates and sizes of dosage forms. Thus, in view of the disclosure in (1) concerning the importance of accelerated gastric passage, it would not have been obvious to a person of ordinary skill in the art, faced with the actual problem, to prepare tablets (rather than sachets or capsules) containing alendronic acid, risedronic acid or tiludronic acid or a salt thereof, consisting of a double-coated tablet (rather than granule or pellet) core in order to provide a further oral dosage form adapted for administration to a patient exhibiting upper gastrointestinal tract sensitivity to bisphosphonic acids. If the skilled person chose to use a double-coating technique, he

would not have obviously chosen a double-coated tablet core. Of course, the skilled person could have chosen to coat a tablet core, but this was not the appropriate measure to be applied to the question of inventive step. In view of the clear preference in the closest prior art for small (granular or preferably pellet) particles, as confirmed by (4), the skilled person would not, in the light of the state of the art, have adapted the closest prior art of citation (1), to arrive at something falling within the claims of the present application.

[08] In the appellant's view, the examining division had also erred in relying on the teaching that the granules disclosed in (1) could be used to make tablets (see IV(G) above). In particular, a tablet prepared by compressing double-coated granules would be very different to a tablet comprising a double-coated tablet core as claimed in the application. A tablet comprising double-coated granules can break up in the stomach, thereby releasing the double-coated granules. The dosage form claimed in the present application could not break up in the stomach and must pass through the stomach and into the proximal portion of the lower gastrointestinal tract intact. Therefore, the fact that (1) taught that double-coated granules may be processed to give tablets did not render obvious the claimed dosage form of the application.

[09] The appellant also drew attention to the fact that the examining division's conclusion that the weight of the core "tablet" of the present application was lighter than that of the pellet of (1) (see IV(H) above) was based on an inaccurate reading of the

disclosure of the examples in (1). Examples 1 to 3 referred to pellet compositions prepared from 197.3 mg of disodium pamidronate. The examining division concluded that the total weight of the core pellet was 390 mg (in the case of Example 1). It had, however, misunderstood the teaching of the examples of (1). The 197.3 mg of disodium pamidronate was mixed with Avicel® PH 105, moistened with water and kneaded, extruded and formed into spheres (see (1), page 6, lines 35-36). This did not teach that the disodium pamidronate and the Avicel® were formed into one big sphere but, rather, it was stated that the mixture was extruded and formed into spheres. Quite clearly, (1) did not teach that each individual pellet should contain a single dosage of disodium pamidronate, but rather this was further subdivided into a number of individual pellets. In particular, the examples in (1) simply taught that 197.3 mg of disodium pamidronate and 52.7 mg of Avicel® PH 105 provided the correct proportions of active to filler for consistent and accurate formation of the pellet cores. The examining division's conclusion that the weight of the core "tablet" of the present application is lighter than those of the pellet of (1) was thus based on an inaccurate reading of the disclosure of the examples in citation (1).

[10] In view of the foregoing, the appellant concluded that the examining division erred in finding that the claimed subject-matter in the application lacked inventive step.

VII. The appellant requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the description, pages 1 to 8 as

published, and the claims 1 to 6 as submitted on 25 September 1995.

### **Reasons for the decision**

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.
2. *Procedural matters*

The Rules of Procedure of the Boards of Appeal of the EPA (below RPBA), approved by decision of the Administrative Council of 12 December 2002 (OJ EPO 2003, 60), apply to the present case.

Article 11(3) RPBA states: "The Board shall not be obliged to delay any step in the proceedings, including its decision, by reasons only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying on its written case."

- 2.1 As is apparent from V above, the appellant did not appear as summoned at the oral proceedings. Accordingly, oral proceedings were held in the appellant's absence, as provided for in Rule 71(2) EPC and Article 11(3) RPBA.
- 2.2 Under Article 113(1) EPC a decision of the EPO may only be based on grounds or evidence on which the parties concerned have had an opportunity to present their comments. This procedural right is intended to ensure that no party is caught unawares by a decision turning

- down its request on the basis of grounds or evidence on which it has not had the opportunity to comment.
- 2.3 The decision to dismiss this appeal is based entirely on grounds, facts and evidence which were already known to the appellant from the proceedings before the examining division. In particular, the examining division cited the prior art of citations (1) and (2) against inventive step already in its communication pursuant to Article 96(2) and Rule 51(2) EPC of 12 December 1997 and again in the contested decision to refuse the application. In its reply to that communication of the examining division and in its statement setting out the grounds of appeal as well, the appellant had sufficient opportunity to present its comments on the facts and evidence on which both the decision under appeal and the present decision are based.
- 2.4 As substantiated in more detail below, on the basis of the state of the art according to citations (1) and (2), the board will arrive at the same final conclusion as the examining division, namely that the claims, which are incidentally identical with those before the examining division, lack inventive step.
- 2.5 On the basis of the above considerations, the board comes to the conclusion that, in the circumstances of the present case, considering and deciding in substance on the refusal of this application does not contravene the appellant's procedural rights as laid down in Article 113(1) EPC. Consequently, in order to avoid any unnecessary delay in the proceedings, the board makes use of its discretion under Rule 71(2) EPC and

Article 11(3) RPBA to give a final decision on this appeal, in spite of the appellant's absence during oral proceedings.

3. *The closest state of the art*

3.1 The board considers citation (2) to represent the closest state of the art. As has already been acknowledged in the introductory portion of the description of the application as originally filed (see International application published under the PCT, page 2, lines 15-18), citation (2) discloses enterically-coated dosage forms of the drug "risedronate" (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid), one embodiment of which is a compressed tablet of active ingredient coated with a single layer of enteric polymer.

It is stated in (2) that the enterically-coated dosage forms prohibit the exposure of the "risedronate" active ingredient to the patient's epithelial and mucosal tissues of the buccal cavity, pharynx, oesophagus, and stomach and thereby protect said tissues from erosion, ulceration or other like irritation. Accordingly, the said dosage forms effect the delivery to the lower intestinal tract of said patient of a safe and effective amount of the "risedronate" active ingredient, and substantially alleviate the oesophagitis or oesophageal irritation which sometimes accompanies the oral administration of "risedronate" active ingredients (see (2), especially page 1, lines 5-15).

3.2 In order to achieve the stated aims, the oral dosage form of citation (2) utilises a pH dependent enteric coating material, preferably made from a partly methyl esterified methacrylic acid polymer. The most preferred coating material is a methacrylic acid copolymer selected from the Eudragit L<sup>®</sup> series in combination with a plasticiser and possibly other coating excipients such as colouring agents, talc and/or magnesium stearate, dibutyl phtalate, polyethylene glycol, triethyl citrate and triacetin (see page 15, line 32, to page 18, line 10).

In particular, the preferred coating material used in (2) is exactly the same as that preferably used for "enterically-coating" the claimed oral dosage form in the application containing a bisphosphonic acid active ingredient selected from the group consisting of alendronic acid, risedronic acid, tiludronic acid and a pharmaceutically acceptable salt thereof (see citation (2), page 7, line 31, to page 9, line 6).

3.3 Further, citation (2) also teaches that for enteric-coated tablets utilising methacrylate copolymers as the coating material, when the desired site of delivery is the small intestine, a coating thickness of between 20 and 100 microns is usually required. Preferably, the coating thickness is between 30 and 50 microns, and most preferably between 30 and 50 microns. Moreover, Examples I and III of citation (2) describe methods suitable for use in coating a compressed tablet core containing the risedronate active ingredient which will effect the delivery of the active ingredient to the small intestine (see especially page 19, lines 19-28, and pages 24-25 and 28 for the examples).



4. *Novelty*

4.1 If the enteric-coated dosage form disclosed in (2) is compared with the claimed subject-matter in the application, it will be seen that the dosage form according to (2) does not differ from that claimed in the application with regard to the bisphosphonic active ingredient ("risedronate") and the nature of the core (tablet) which is coated. There is also agreement in respect of the nature of the outer enteric coating. The sole difference between the two dosage forms consists in the use of a core tablet which is subcoated with a stability enhancing inner coating.

4.2 After examination of the citations uncovered by the search report and those introduced by the appellant during the proceedings, the board is satisfied that none of them discloses an enteric-coated oral dosage form including all the features stated in claim 1. Since novelty of the present claims has already been acknowledged by the examining division in the decision under appeal and the board agrees, it is not necessary to give detailed reasons for that finding.

5. *The problem and its solution*

5.1 In the description of the application it is stated that enteric coated compositions of the type disclosed in (2), containing a bisphosphonic active ingredient, can suffer from a stability problem as a result of interactions between the active drug and the acidic enteric coating. It is also stated that in particular bisphosphonate compounds which have a basic nitrogen

containing moiety are susceptible to interaction with acidic carboxyl groups present in the enteric-coating polymer (see application, especially the paragraph bridging pages 2 and 3).

Bisphosphonate compounds having a basic nitrogen containing moiety are, for example, those recited in present claim 1, namely "alendronate" (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid), and "risedronate" (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid).

5.2 Starting from citation (2) as the closest state of the art, the problem to be solved was the provision of an improved oral dosage form of a bisphosphonic active ingredient. This improved dosage form should ensure the delivery to the lower intestinal tract of said bisphosphonic active ingredient, thereby protecting the tissues of the upper gastrointestinal tract from erosion, ulceration or other like irritation, but should at the same time overcome the known difficulties and disadvantages associated with the poor stability of oral dosage forms of the type disclosed in citation (2) (see 5.1 above).

5.3 The solution of the problem was the provision of an enteric-coated dosage form which consists of a core tablet containing as the active ingredient a therapeutically effective amount of alendronic acid, risedronic acid, tiludronic acid or a pharmaceutically acceptable salt of any of the foregoing. This core tablet is subcoated with a stability-enhancing polymeric film having the effect of preventing or at

least minimising migration of the active ingredient from the core tablet to the outer enteric coating.

5.4 In view of the examples in the application, and in the absence of any evidence to the contrary, the board is satisfied that the problem posed has been plausibly solved.

6. *Inventive step*

6.1 The allowability of claim 1 depends, therefore, on the answer to the question whether or not an inventive step was necessary in order to arrive at the claimed subject-matter when starting from the disclosure of citation (2).

6.2 The skilled person seeking in the state of the art a solution to the problem posed would have carefully studied the disclosure of citation (1). In doing so, he would certainly have learned with great interest that the problem posed has already been solved in (1) in a case where the core of the oral dosage form is a granule or pellet.

6.3 Thus, citation (1) already teaches that the incompatibility or interaction between the outer enteric-coating material and the bisphosphonic active ingredient (disodium pamidronate), leading to instability of the dosage form, can successfully be avoided when

- (i) in a first step the core granules or pellets containing the bisphosphonic active ingredient are

subcoated with a hydrophilic elastic inner coating material; and

- (ii) in a second step the protected granulates or pellets from the first step are further coated with an outer "enteric-coating" material which prevents the release of the active ingredient in the mouth, oesophagus or stomach, but which rapidly and completely releases the drug when the dosage form passes into the proximal portion (small intestine) of the lower gastrointestinal tract (see citation (1), especially page 2, lines 38-45, and lines 52-56).

6.4 It should also be noted that both

- (i) the preferred subcoating ("inner-coating") material used in (1), eg hydroxypropyl methylcellulose or polyvinylpyrrolidone (see the paragraph bridging pages 3 and 4), and also
- (ii) the preferred outer, "enteric-coating" material used in (1), eg a methacrylic acid copolymer selected from the Eudragit L<sup>®</sup> series in combination with a plasticiser and possibly other coating excipients such as colouring agents, talc and/or magnesium stearate, dibutyl phthalate, polyethylene glycol (see (1), page 4, lines 48-57),

are the same materials as those preferably used for the claimed double-coated oral dosage forms in the application.

- 6.5 In particular, citation (1) relates to double-coated pellets having a diameter between about 0.3 and 1.5 mm, preferably between 0.5 and 1.25 mm (see especially page 3, lines 12-13). The application states in lines 21-23 on page 4 that "*the term "tablet" as used herein is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes*" (emphasis added and highlighted by the board). Thus, even the application itself sets no minimum requirements or standards for the shape and the size of the "core tablet" to be coated.
- 6.6 In sum, those skilled in the art, starting from the prior art of (2) and faced with the problem posed, would directly and immediately arrive at the claimed solution in the application from the simple combination of the teaching of citation (2) with that of citation (1). The proposed solution consisting of a core tablet, which is subcoated with a stability enhancing polymeric film having the effect of preventing migration of the active ingredient from the core tablet to the outer enteric coating was straightforwardly obvious to a person skilled in the art, knowing the cited state of the art according to citations (1) and (2).
- 6.7 Reverting, for the sake of completeness, to the examining division's arguments referred to in IV(G) and IV(H) above, the board concurs with the appellant's opinion that these arguments cannot stand for the reasons presented by the appellant in its statement of the grounds of appeal and summarised in VI[08] and VI[09] above. However, this cannot alter the board's finding that the claimed subject-matter in the

application lacks an inventive step for the reasons explained in detail above.

7. The result arrived at if citation (1) is taken as the closest state of the art instead of (2), and if the technical problem addressed by the present application is taken as that of providing a further double-coated oral dosage form of a bisphosphonic active ingredient to effect the delivery to the lower intestinal tract of said active ingredient and to prevent interactions between the active drug and the enteric coating, does not lead to a more favourable outcome for the appellant.
- 7.1 The solution to the problem defined in 7 above must of course be the same as the solution mentioned in 5.3 to the problem defined in 5.2 above.
- 7.2 As shown above, citation (2) discloses oral dosage forms of risedronate active ingredient, which are preferred enteric-coated compressed tablets. Tablets are made combining, mixing, or otherwise adding the risedronate active ingredient to suitable pharmaceutical excipients including eg sucrose, maltodextrin, lactose, magnesium stearate microcrystalline cellulose, talc, starch-glycolate. That mixture is then compressed into a core tablet utilising various tableting techniques available to those skilled in the art. The compressed core tablet is then coated with an enteric-coating material which consists of suitable pharmaceutical excipients, preferably a methacrylic acid copolymer selected from the Eudragit L<sup>®</sup> series (see (2), page 18, especially lines 19-30).

- 7.3 Moreover, those skilled in the art are given precise directions - should they need them - as to the thickness required for the outer enteric coating utilising methyl acrylate copolymers, when the desired site of delivery is the small intestine (see (2), especially page 19, lines 19-27, and Examples I and III).
- 7.4 Accordingly, one skilled in the art faced with the problem posed and knowing from citation (1) that a stability-enhancing subcoat prevents or at least minimises migration of the active ingredient from the pellet core to the surface of the enteric coating would have reasonably expected that the same effect is achieved when the core which is coated is a tablet in place of a pellet or a granule and would thus have been directly led to the claimed solution in the application by a simple combination of the teaching of citation (1) with that of citation (2).
- 7.5 In view of the clear teaching of citation (2) relating to the successful use of enteric-coated tablets for the oral administration of bisphosphonic acid derivatives, the alleged prejudice against using double-coated tablets in place of double-coated granules or pellets did not of course exist. As already indicated above, from citation (2) it was known that enteric-coated tablets prohibit the exposure of risedronate active ingredient to the patient's epithelial and mucosal tissues of the buccal cavity, pharynx, oesophagus, and stomach and thereby protect said tissues from erosion, ulceration or other like irritation.

8. From the foregoing, it is clear that the claimed subject-matter in the application lacks inventive step and that the appeal cannot, therefore, succeed.

## **Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman:

U. Bultmann

J. Riolo