

**Internal distribution code:**

- (A)  Publication in OJ  
(B)  To Chairmen and Members  
(C)  To Chairmen  
(D)  No distribution

**D E C I S I O N**  
**of 11 May 2006**

**Case Number:** T 0630/03 - 3.3.02

**Application Number:** 94901568.9

**Publication Number:** 0690719

**IPC:** A61K 31/66

**Language of the proceedings:** EN

**Title of invention:**

Dry mix formulation for bisphosphonic acids

**Patentee:**

Merck & Co., Inc.

**Opponent:**

TECNIMEDE

**Headword:**

Direct compression tablet/MERCK & CO.

**Relevant legal provisions:**

EPC Art. 56

**Keyword:**

"Inventive step (no): The subject-matter claimed in claim 1 is obvious in the light of the common general knowledge"

**Decisions cited:**

-

**Catchword:**

-



Case Number: T 0630/03 - 3.3.02

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.02  
of 11 May 2006

**Appellant:** TECNIMEDE  
(Opponent) Sociedade Técnico-Medicinal S.A.  
Rua Prof. Henrique de Barros, Edifício Sagres 3  
PT-2685-338 PRIOR VELHO (PT)

**Representative:** Savic, Bojan  
Viering, Jentschura & Partner  
Patent- und Rechtsanwälte  
Centroallee 263  
D-46047 Oberhausen (DE)

**Respondent:** Merck & Co., Inc.  
(Patent Proprietor) 126, East Lincoln Avenue  
P.O. Box 2000  
Rahway  
New Jersey 07065-0900 (US)

**Representative:** Rollins, Anthony  
Merck & Co., Inc.  
European Patent Department  
Terlings Park  
Eastwick Road  
Harlow, Essex CM20 2QR (GB)

**Decision under appeal:** Interlocutory decision of the Opposition  
Division of the European Patent Office posted  
25 March 2003 concerning maintenance of  
European patent No. 0690719 in amended form.

**Composition of the Board:**

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

## Summary of Facts and Submissions

- I. European patent No 0 690 719, based on European application No 94 901 568.9, which was filed as international application WO 94/12200, was granted on the basis of 15 claims.

Claim 1 as granted read as follows:

"1. A pharmaceutical composition comprising from 0.5 to 40% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof and from 60 to 99.5% by weight of excipients, said excipients comprising a diluent selected from anhydrous lactose or hydrous fast flow lactose, a dry binder, a disintegrant, and a lubricant."

Independent claim 2 as granted read as follows:

"2. A pharmaceutical composition comprising 0.5 to 40% by weight 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof and from 60 to 99.5% by weight of excipients consisting of: anhydrous lactose or hydrous fast flow lactose; microcrystalline cellulose, croscarmallose sodium; and magnesium stearate."

Independent claim 3 as granted read as follows:

"3. A pharmaceutical composition comprising: 0.5 to 40% by weight of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof; 10 to 80% by weight of anhydrous lactose

or hydrous fast flow lactose; 5 to 50% by weight of microcrystalline cellulose; 0.5 to 10% by weight of croscarmallose sodium; and 0.1 to 5% by weight of magnesium stearate."

Independent claim 8 as granted read as follows:

"8. A tablet prepared from the pharmaceutical composition of any one of Claims 1 to 7."

Independent claim 9 as granted read as follows:

"9. A process for the preparation of a tablet containing 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or a pharmaceutically acceptable salt thereof; which process comprises:

forming a mixture by mixing the active ingredient with:  
a diluent, selected from anhydrous lactose and hydrous fast flow lactose,  
a dry binder,  
a disintegrant,  
and optionally one or more additional ingredients selected from the group consisting of: compression aids, flavours, flavours enhancers, sweeteners and preservatives; lubricating the mixture with a lubricant; and compressing the resulting lubricated mixture into a desired tablet form."

II. The following documents inter alia were cited during the proceedings:

(3) Handbook of Pharmaceutical Excipients, The Pharmaceutical Society of Great Britain, London 1986, pages 161-162

- (4) Pharmaceutical dosage forms-tablets, second edition, Eds. Lieberman, Lachman and Schwartz, Marcel Dekker Inc., New York 1989, pages 97-98, 125, 195-246
- (5) The Theory and Practice of Industrial Pharmacy, third edition, Eds. Lieberman, Lachman and Schwartz, Marcel Dekker Inc., New York 1986, pages 297, 313, 318, 325, 326, Appendices
- (7) US-A-4 621 077
- (11) GB-A- 1435 885
- (13) Encyclopedia of Pharmaceutical Technology, Eds. Swarbrick & Boylan, Marcel Dekker Inc., New York 1991, vol. 4, pages 85-106 (different pages submitted by different opponents in opposition proceedings with different document numbers)
- (16) N. L. Henderson and A. J. Bruno, Journal of Pharmaceutical Sciences, vol. 59(9), pages 1336-1340 (1970)
- (17) Encyclopedia of Pharmaceutical Technology, Eds. Swarbrick & Boylan, Marcel Dekker Inc., New York 1988, vol. 1, pages 451-464
- (20) The Merck Index, twelfth edition, 1996, entry 233, page ONR-56
- (22) Römpp Chemie Lexikon, ninth edition, 1995, page 2605
- (23) Food Colourants, three pages, from internet [www.agsci.ubc.ca/courses](http://www.agsci.ubc.ca/courses), filed by patent proprietor with letter of 16 April 2004
- (24) M. Whiteman and R. J. Yarwood, Wyeth Research (U.K.), Drug Development and Industrial Pharmacy, 14(8), 1023-1040 (1988)
- (25) N. H. Batuyios, J. Pharmaceutical Sciences vol. 55(7), pages 727-730 (1966)

III. Opposition was filed and revocation of the patent in its entirety was requested pursuant to Article 100(a) EPC on the grounds of lack of novelty and lack of inventive step.

IV. The appeal lies from the interlocutory decision of the opposition division maintaining the patent in amended form (Articles 102(3) and 106(3) EPC) on the basis of the set of claims filed during the oral proceedings before the opposition division.

Claims 1, 2 and 3 of the main request filed during the oral proceedings before the opposition division differ from claims 1, 2 and 3 as granted owing to the introduction of the following expression "**in the form of a direct compression tablet**" after the words "Pharmaceutical composition". Claim 8 as granted was deleted in the set of claims of the main request and independent process claim 8 corresponded to a renumbered claim 9 as granted.

V. The opposition division considered that the main request met the requirements of Articles 123 and 84 EPC. In particular, the expression "direct compression tablet" was found to be clear in the light of the description and several documents submitted.

According to the opposition division's findings, the novelty of the subject-matter claimed had not been disputed. In particular, the subject-matter claimed in claims 1 to 7 was novel over the content of document (7) in view *inter alia* of the different galenic form and the different diluent. As regards the subject-matter of claims 8 to 14, the opposition division considered that

none of the prior art documents disclosed a direct compression process involving 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid as active ingredient.

As regards the requirements of Article 56 EPC, the opposition division considered that the subject-matter claimed in claims 1 to 14 involved an inventive step.

Document (7) was considered to be the closest prior art. In the opposition division's view the problem to be solved concerned the provision of alternative pharmaceutical compositions comprising 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid as active ingredient. The solution, in the opposition division's opinion, related to a tablet obtainable by a direct compression process. Although the opposition division considered that neither the choice of a tablet as galenic form, nor the choice of the type of lactose used implied the presence of an inventive step, the choice of the manufacturing process (as "direct-compression tableting") involved an inventive step. In the opposition division's opinion, this process was claimed in claim 8 and was "an essential feature in the composition claims 1-3".

- VI. The opponent 1 (appellant) lodged an appeal against said decision and filed grounds of appeal.
- VII. The respondent (patent proprietor) filed counter-arguments to the grounds of appeal.
- VIII. A board's communication dated 14 June 2005 conveyed the board's preliminary opinion in respect of the fact that

the product claims 1 to 3 were of different scope and that the products obtained by the process of claim 8 were not necessarily the products of claims 1 to 3. Furthermore, the suitability of anhydrous lactose and fast flow lactose as excipients for direct compression was discussed in the light of the further document (24).

IX. The respondent filed further arguments with its letter of 14 October 2005 and announced, as an auxiliary request, a set of claims identical to the main request, where the option concerning fast flow lactose was to be deleted.

X. The appellant filed a response in a letter dated 17 October 2005 sent by fax the 19 October 2005.

XI. Oral proceedings took place on 11 May 2006.

During the oral proceedings the respondent filed four sets of claims (auxiliary requests 1 to 4).

Auxiliary request 3 differed from the main request in that all process claims were deleted.

XII. The respondent's arguments in favour of the admissibility of the auxiliary requests filed during the oral proceedings may be summarised as follows:

The only amendment introduced in auxiliary request 1 was in the introductory part of claim 8 which read: "A process for the preparation of a **direct compression** tablet **according to any one of claims 1 to 7**" followed by the words beginning "containing". (*emphasis added*)



This amendment related to a clear limitation which was made in response to the previous discussion in the oral proceedings about the patentability of the process claim 8.

The amendments introduced in auxiliary request 2 corresponded to those introduced in auxiliary request 1 and, additionally, this set of claims incorporated the amendment announced in the letter of 14 October 2005 which basically concerned the incorporation of claim 6 into claim 1 and amounted to the deletion of hydrous fast flow lactose.

Auxiliary request 3 corresponded to the main request without process claims (i.e. claims 8 to 14 were deleted). Hence the amendment related to a clear and simple restriction in response to the objections made against the process claim at the beginning of the oral proceedings.

Auxiliary request 4 incorporated the amendments of auxiliary request 3 and, additionally, the amendment announced in the letter of 14 October 2005.

XIII. The appellant contested the admissibility of all auxiliary requests filed during the oral proceedings since, in its opinion, all arguments were already present in the written proceedings and the respondent had had ample opportunity to file auxiliary requests at an earlier stage. Moreover, the amendments introduced in the auxiliary requests 1, 2 and 4 were not easy to handle since they required an extra assessment in respect of Articles 84 and 123(2) EPC.

- XIV. For convenience, the board will use the expression "alendronic acid" in this decision to mean the active ingredient 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.
- XV. The appellant did not raise any formal objection to the main request and auxiliary request 3. Moreover, it did not dispute the novelty of the products of claims 1 to 3 of both requests.

The appellant's arguments in respect of the inventive step of the product claims 1 to 3 of the main request and the auxiliary request 3 may be summarised as follows:

Claim 1 related to a pharmaceutical form of alendronic acid for oral administration comprising alendronic acid and excipients. Among these, anhydrous lactose or hydrous fast flow lactose were listed together with a dry binder, a disintegrant and a lubricant. Claims 1 to 3 varied from the point of view of the different ratios of the components. All of the ingredients of the tablets were well known in the prior art. The claimed tablets were conventional galenic forms of alendronic acid. The patent proprietor wanted to make its case on the basis that there had been a prejudice in combining lactose with alendronic acid. However, anhydrous lactose was commonly used in the prior art for preparing tablets by direct compression and there was no prejudice in using alendronic acid with anhydrous lactose. Therefore, there was a lack of inventive step when providing a tablet by direct compression, especially given that some problems with alendronic acid were known. Additionally, the experimental data

provided by the patent proprietor in relation to the stability of the tablets, concerned the presence of microcrystalline cellulose, which was not specified in claim 1 as excipient. Furthermore, there was no data available in relation to stability of tablets at concurrent high humidity and high temperature. Hence, the improvement in stability alleged by the respondent could not be incorporated into the definition of the technical problem. Document (7), which represented the closest prior art, disclosed alendronic acid as a pharmaceutically active ingredient and taught that pharmaceutical compositions containing the active ingredient could be formulated in tablet form (end of column 12). To use the well-known direct compression did not involve an inventive step, since this manufacturing process had been proposed on many occasions in the prior art as an advantageous alternative to wet granulation for avoiding humidity and heat.

The appellant stated that most of the disadvantages put forward by the respondent in relation to the use of lactose concerned old references (1970 or older) and/or related to the use of spray dried lactose, which was not encompassed by the claims.

The appellant further submitted that document (5) clearly stated that anhydrous lactose did not undergo the Maillard reaction. Therefore, there was no prejudice in using it with alendronic acid.

It was not denied by the appellant that the fillers to be used when producing a tablet had to be checked for their compatibility with the other ingredients, but

lactose was the most common filler and hence constituted a first-choice option.

Additionally, the appellant stated that, contrary to the respondent's submissions, document (16) recommended anhydrous lactose as a preferred excipient for direct compression owing to its ability to withstand the effects of high temperature, moisture and exposure to light (sentence bridging pages 1337-1338).

In respect of the problems caused by the presence of magnesium stearate, the appellant stated that document (4) suggested how to overcome them in the direct compression process, namely by not including the lubricant throughout most of the blending period.

As regards the respondent's high-dose argument, the appellant stated that most of the tablets prepared in the examples were low dose and that only two examples could have been meant by the respondent as high dose. However, none of them contained more than 50 mg of the active ingredient alendronic acid. Moreover, in the appellant's view, if compressibility of the active ingredient had been a problem for the skilled person when formulating the tablets, the commonly known solution would have been to use the known fillers. Moreover, the appellant stressed that, owing to the three product claims' wording, the fillers and binders could be present in an amount of more than 90% and this would overcome any possible disadvantages in the compressibility of the active ingredient. Moreover, microcrystalline cellulose was known to have very good compressibility.

Furthermore, the appellant contested that the example tested according to Table I of the patent in suit was representative of the subject-matter claimed, in particular for claim 1.

The appellant disagreed with the respondent's assertion that the examples of pharmaceutical formulations given in document (7) were prophetic.

Finally, the respondent stated that the wet granulation process would obviously lead to a tablet with higher moisture content and hence more degradable than the direct compression tablet.

XVI. The respondent's main arguments in respect of inventive step of the product claims 1 to 3 of the main request and the auxiliary request 3 were as follows:

Direct compression tablets of alendronic acid were not obvious since the choice of direct compression as manufacturing process was not obvious. Additionally, even if the direct compression process was considered to be an obvious choice, it was not obvious to use lactose as excipient. Moreover, there was a prejudice in using lactose and an active ingredient bearing a primary amino group, such as alendronic acid.

The respondent's first line of argumentation for the product claims related to the alleged non-obviousness in the choice of their manufacturing process. According to the respondent's view, direct compression was one of several alternatives, namely wet granulation, dry granulation, direct compression, and pre-granulation followed by direct compression.

In this respect, the respondent quoted the passage bridging pages 3 and 4 of the opposition division's decision. In particular, it stressed that, although the simplicity of the direct-compression process over the wet granulation was undeniable, to use direct compression would have not been the skilled person's first choice when preparing tablets. The reason was that wet granulation was the most prevalent method and tableting by direct compression had not been universally adopted at the time of the invention.

Additionally, the respondent cited document (5) (pages 318 and 325), which taught that, in some instances, the direct compression diluent may interact with the drug. This occurred, especially, between amino compounds and spray-dried lactose. Moreover, document (5) also taught that the diluents and the other excipients must meet certain criteria in the formulation, inter alia, they must be physically and chemically stable by themselves and in combination with the drug and the other tablet components; and they must produce no off-colour appearance. The respondent submission was that in view of these prior art teachings the skilled person would not have used lactose and alendronic acid together in a tablet.

The respondent further stated that it was known from the prior art (document (13)) that for direct compression tableting, flow properties and compactibility both play a major role, especially in high-dose (more than 50 mg) pharmaceutical forms. The respondent acknowledged that the alendronic salt employed in the examples of the patent in suit was

known in the prior art to have good flow properties but it denied that the skilled person would know about its compactibility behaviour. The respondent pointed out that some of the examples in the patent in suit showed the unexpected suitability of the claimed pharmaceutical form for high doses.

In respect of its second line of argumentation, the respondent focused on the suitability of the required excipients and cited document (16), in particular the paragraph bridging the two columns on page 1336. Moreover, the respondent contended that document (13) showed a whole range of excipients for direct compression, most of them binders. In the respondent's view, lactose was not a first-choice excipient, especially for a drug bearing a primary amine. In this context, it cited page 125 of document (4). The main reason not to choose lactose was because lactose was reactive with primary amines owing to the Maillard reaction (documents (20), (22) and (23)).

The respondent stated that the issue, contrary to the appellant's submissions, was not merely to avoid water during the manufacturing, but to attain tablets which were stable during storage. The skilled person knew how to produce tablets, but the obtained tablets would get brown on storage. In this context, the respondent cited document (3), which taught that lactose gets some brown coloration on storage and that this reaction was accelerated by warm, damp conditions. It also cited table III of document (16) about colour stability of direct compression sugar tablets. The respondent also stated that document (16) referred to document (25)

which, in its opinion, confirmed the off-white colour development for tablets containing anhydrous lactose.

The respondent pointed to the experimental data shown in table I of the patent in suit. Table I showed tests within the temperature range 40°C to 60° C and also tests at 90% RH. The claimed tablets gave good stability results at high temperatures and high relative humidity.

The respondent further submitted that anhydrous lactose would have been disregarded by the skilled person as a suitable excipient, since it "picked up" water at high relative humidity as shown in document (4) (page 206). This was also shown in document (4) (page 98) together with a recommendation to test blister packages at elevated temperatures and humidity in order to establish their "acceptability" with lactose-based formulations. It also cited document (5), page 326.

Moreover, the respondent submitted that the skilled person would have been discouraged from using magnesium stearate since it was known that alkaline lubricants accelerated the darkening (document (4) pages 98 and 200-201). Furthermore, it was known that the Maillard reaction was base-catalysed and hence accelerated by the presence of alkaline lubricants (document (3), page 161).

The respondent also stated that the crucial question was to determine the common general knowledge available to the skilled person at the effective date of the patent in suit. From all the cited references representing common general knowledge only one



suggested that anhydrous lactose did not undergo the Maillard reaction. This was in clear contradistinction with the many passages previously quoted, referring to the degradation of primary amines in the presence of lactose. Therefore, there was a prejudice in the prior art in using lactose and a primary amine and this also applied to anhydrous lactose.

The respondent qualified the examples shown in table 6 of document (7) as prophetic and contended that the skilled person when starting from document (7) would not have considered oral tablet formulations of the active ingredient disclosed therein, especially of alendronic acid.

XVII. The appellant (opponent 1) requested that the decision under appeal be set aside and that the patent be revoked.

The respondent (patentee) requested that the appeal be dismissed (main request) or that the patent be maintained in amended form on the basis of one of the auxiliary requests 1 to 4 filed in the oral proceedings.

### **Reasons for the decision**

1. The appeal is admissible.
2. *Admissibility of the late-filed requests*
  - 2.1 Auxiliary request 3 filed during the oral proceedings is admissible since it merely relates to the deletion from the set of claims of the main request of the

process claims. This is a clear and simple amendment, concerning a restriction, and it does not require further substantial discussion.

2.2 Auxiliary requests 1, 2 and 4 are not admissible for the following reasons:

Having regard to the fact that the products of claims 1 to 3 are different from the products obtainable by the process of claim 8 of the auxiliary request 1 and of claim 7 of auxiliary request 2 (both claims correspond identically to the wording of claim 9 as granted), owing to the differences in the specification of the characterising features, and given that the said process claims were drafted without any reference to any of the products of claims 1 to 3 in any of the previous claim versions (either granted version or main request), the amendment introduced in the process claim 8 of auxiliary request 1 (and claim 7 of the auxiliary requests 2 respectively) concerning the introduction of the expression "(a) compression tablet according to any one of the claims 1 to 3" is not one which immediately appears allowable. On the contrary, such an amendment extends and expands in an unjustified manner at such a late stage in the proceedings the scope of the discussion. In this respect the board wishes to point out that the respondent did not satisfactorily justify such a late filing, since its argumentation disregarded the fact that the board's communication dated 14 June 2005 already conveyed to the parties that the different scope of the independent claims with respect to the nature of the tablets (claimed in the product claims or directly obtained by the process claimed) would result in separate analysis

when assessing their patentability. This and nothing else took place at the beginning of the oral proceedings.

As regards the set of claims of auxiliary request 4, claim 6 was deleted and claim 7 (initially dependent on claim 6) was redrafted as an independent product claim. This new claim's wording resulted *de facto* in the inadmissible introduction of a new independent product claim, without abandoning the other independent product claims, which could be hardly taken as a response to any of the matters discussed previously during the oral proceedings.

3. *Main request and auxiliary request 3*

3.1 The sets of claims of both requests contain the same independent product claims 1 to 3, since the only difference between both sets of claims is that in auxiliary request 3 all process claims have been deleted.

Therefore, the subsequent reasoning, insofar as it concerns the subject-matter of the product claims shared by both sets of claims, applies simultaneously to both requests.

3.2 No formal objections were raised against the sets of claims of the main request and auxiliary request 3 and the board sees no reasons to diverge therefrom.

Moreover, the board is satisfied that the feature "in the form of a direct compression tablet", introduced in claims 1 to 3, amounts to a restriction of the

pharmaceutical product claims to **tablets obtainable by direct compression** (i.e. a tablet with a "product-by-process" definition).

- 3.3 The novelty of the subject-matter of the product claims 1 to 3 was not disputed by the appellant and the board has no reason to differ.
- 3.4 As regards the assessment of inventive step, the board agrees with the opposition division in that document (7) represents the closest prior art. This was not disputed by the parties.
- 3.5 Document (7) discloses pharmacologically active bisphosphonic acid derivatives, a process for their preparation and pharmaceutical compositions and formulations thereof. In particular, document (7) discloses alendronic acid or alendronate, which is identified as AHBuBP, 4-amino-1-hydroxybutan-1,1-biphosphonic acid (non-systematic name) or 4-amino-1-hydroxybutylidene-1,1-bisphosphonate (column 6, lines 49-50, table 6 in column 13, column 14, lines 25-26 and 30-31, and table 7, table 8 in columns 14/15).

Document (7) states: "The pharmaceutical compositions according to the present invention may be prepared for use in the form of capsules or **tablets** or in solution for oral administration or for systemic use. The compositions are advantageously prepared together with inert carriers such as sugars (saccharose, glucose, lactose), starch and derivatives, cellulose and derivatives, gums, fatty acids and their salts, polyalcohols, talc, aromatic esters." (paragraph bridging columns 12 and 13) (*emphasis added*)

Table 6 exemplifies, inter alia, opercolated capsules containing alendronic acid and lactose.

- 3.6 In the light of the closest prior art the problem to be solved lies in the provision of a further galenic form, containing alendronic acid, for oral administration.

The solution according to claim 1 of both requests relates to tablets obtainable by direct compression, comprising anhydrous lactose or fast flow lactose.

The board is satisfied that the problem has been plausibly solved in the light of the description, in particular the examples.

- 3.7 It has now to be assessed whether the proposed solution is obvious in the light of the prior art.

- 3.8 It was not disputed by the parties that tablets are normally the preferred solid galenic form for oral administration. Additionally, document (7) discloses, generically, tablets of, inter alia, the active ingredient alendronic acid.

It was also undisputed that direct compression was known at the effective date of the patent in suit as one manufacturing process for preparing tablets and that lactose is a commonly used, generally desirable inert diluent for oral solid forms (cf. the last sentence of paragraph [0003] in the patent in suit).

However, when looking to solve the technical problem, the skilled person faces a rational choice concerning

the manufacturing process and the excipients for producing the tablets, which has to be taken in the light of his general knowledge in the field of pharmaceutical technology.

Therefore, it has to be investigated what the common general knowledge of the skilled person was at the effective date of the patent in suit.

- 3.9 There was common ground between the parties that most of the documents cited represent common general knowledge of the skilled person in the field of pharmaceutical technology. In particular, documents (3), (4), (5), (13), (17) relate to handbooks, manuals and encyclopaedia in the field of pharmaceutical technology. In relation to documents (16) and (24) they represent general knowledge concerning excipients for direct compression.

As regards the post-published handbooks and/or technical dictionaries (20) and (22), it was accepted by the parties that they reflect common general knowledge already available at the effective date of the patent in suit. Moreover, the board has checked that the relevant passages under the heading "Maillard-Reaktion" on page 2605 of the post-published version of the Römpp Chemie Lexikon, document (22), correspond identically to the earlier version published 1991.

- 3.9.1 It is generally known that compounds bearing primary amino groups such as amino acids or peptides undergo degradation in the presence of reductive sugars (lactose is a reductive sugar) via the Maillard reaction. Apart from the fact that it is known that the

chemical structure of the substrate influences the reaction kinetics, water content, high temperatures and basic pH conditions are also known to play an essential role.

The active ingredient alendronic acid, although not encompassed by the compound classes of amino acids and peptide derivatives, generally cited in connection with the Maillard reaction, bears a reactive primary amino group.

3.9.2 However, as clearly stated in the manual about pharmaceutical forms-tablets, document (4) (page 97), **"Lactose USP is the most widely used diluent in tablet formulation.** It displays good stability in combination with most drugs whether used in the hydrous or anhydrous form."

Moreover, "(I)t is most important not to assume that one form of lactose will perform in a similar manner as another form." (further on page 97 of document (4))

Indeed, **"Lactose USP, anhydrous** offers most of the advantages of lactose *USP*, hydrous, **without the reactivity of the Maillard reaction**, which leads to browning. Tablets generally show fast disintegration, good friability, and low weight variation, with the absence of sticking, binding and capping. The applications of the anhydrous form have recently been evaluated by a number of investigators... Mendell ... has reported on the relative sensitivity of lactose to moisture pickup at elevated temperatures and humidity. Blister packages should be tested at elevated temperatures and humidity to establish their

acceptability with lactose-based formulas." (page 98 of document (4)) (emphasis added)

Further on page 98 of document (4) another type of lactose is analysed, namely spray-dried lactose: "Brownley and Lachman ... reported that, as with lactose *USP*, care must be taken in using **spray-dried lactose** since it **tends to become brown** due to the presence of 5-(hydroxymethyl)-2-furaldehyde, **when combined with** moisture, **amines**, phosphates, lactates and acetates. Similar findings were reported by Duvall et al. ... even in systems not containing amines. The employment of neutral or acid lubricants such as stearic acid appears to retard discoloration, **while alkaline lubricants (e.g. magnesium stearate) accelerate the darkening**. Bases as well as drugs which release radicals (e.g. amino salts) can bring about this browning, known as the Maillard reaction." (emphasis added)

- 3.9.3 The handbook (document (5)) confirms and complements the teaching of the previously cited general books, since it states:

"A classic case of a chemical incompatibility that went unrecognized for several years was the interaction of **certain amine drugs** with the commonly used diluent **lactose**, in the presence of **a metal stearate lubricant** (such as magnesium stearate); **the resulting tablets were gradually discolored with time**. Tablet formulators should remember that physical and chemical interactions between formulation components may be promoted by the intimate contact between potential reactants that are tightly compressed together in a tablet compact."



(page 326, first paragraph, left-hand column) (emphasis added)

"**Lactose** is the first diluent listed in Table 11-4 because it **is still the most widely used diluent in tablet formulation**. Lactose is an excipient that has no reaction with most drugs, whether it is used in the hydrous or anhydrous form. **Anhydrous lactose** has the **advantage over lactose** in that it **does not undergo the Maillard reaction**, which can lead to browning and discoloration with certain drugs, as noted previously. The anhydrous form, however picks up moisture when exposed to elevated humidity. Such tablets may have to be carefully packaged to prevent moisture exposure. **When a wet granulation process is employed, the hydrous form of lactose should generally be used.**" (page 326, last paragraph, left-hand column) (emphasis added)

As regards the other type of lactose, namely spray-dried lactose, document (5) states: "Spray-dried lactose is one of several diluents now available for direct compression ..." "**Spray-dried lactose is especially prone to darkening in the presence of excess moisture, amines, and other compounds, owing to the presence of furaldehyde.**" (page 326, second paragraph, right-hand column) (emphasis added)

3.9.4 The handbook (document (3)) also refers to the problem of the Maillard reaction.

In particular, document (3) states: "**Lactose may develop a brown coloration on storage** (see also section 1.3). This reaction is accelerated by warm,

damp conditions." (page 161, last paragraph, left-hand column)

The above cited paragraph 1.3, with the heading "Incompatibilities", reads as follows: "A **Maillard-type condensation** is likely to occur between **lactose** and **compounds with a primary amino group** (e.g. amphetamines and amino acids) to form brown-colored products. This reaction occurs **more readily with amorphous than crystalline lactose**, and the **spray-dried material** (which contains about 10% amorphous lactose) is **more prone to discoloration**. The browning reaction is **base-catalyzed** and, may, therefore, be accelerated if alkaline lubricants are used." (page 161, paragraph 1.3, right-hand column)

Although document (3) does not specify the behaviour of anhydrous lactose, it clearly states that the Maillard reaction occurs more readily with amorphous than crystalline lactose. Anhydrous lactose is a free-flowing **crystalline** substance (cf. document 13, page 94, last paragraph but one) and hence less prone to react with amines.

- 3.10 In view of the above, the common general knowledge is consistent in that lactose is the most widely used diluent for tablet formulations and that when dealing with ingredients having a primary amino group one should use anhydrous lactose in order to avoid or reduce the Maillard reaction.

Moreover, the skilled person is openly discouraged, when amines are ingredients of the pharmaceutical composition, from employing spray-dried lactose.

Additionally, it is also apparent that the presence of magnesium stearate may accelerate the Maillard reaction, in particular if intimate contact with the reactive components is not avoided in the solid form or during the manufacturing process.

- 3.11 Even the older document (16) (published 1970) does not contradict with this commonly accepted teaching. Although document (16) refers to different degrees of discoloration in tablets prepared by direct compression when lactose and amines are present, it mainly recommends the use of anhydrous lactose.

"A study was undertaken to determine the degree of discoloration produced in the five sugars (for agents for direct compression plus a lactose USP control) when stored in open containers under four testing conditions -heat, moisture, heat/moisture, and light- in the presence of lubricants and selected amines." (page 1337, right-hand column)

"It was found that the incorporation of amines such as *d*-amphetamine sulfate USP or phenylephrine hydrochloride USP, in the formulations both accentuated and accelerated the degree of darkening produced under all test conditions. In the presence of amines, magnesium stearate USP showed a greater tendency than stearic acid USP toward producing discolored sugar tablets.

Of the four materials tested for direct compression, **only anhydrous lactose USP was able to withstand**

**adequately the effects of high temperature, humidity and exposure to light."** (pages 1337-1338)

Moreover, table III on page 1338 clearly shows no discoloration (Degree of discoloration: "None") for anhydrous lactose.

- 3.12 As regards the information concerning the tendency of anhydrous lactose to pick up moisture at elevated temperatures and humidity, this cannot be seen as a generally accepted prejudice deterring the skilled person from using anhydrous lactose as diluent in tablet formulations, since the said information belongs to an analysis of pros and cons concerning the choice of different diluents and excipients, and this information is accompanied by clear indications how to overcome the difficulties just by choosing the appropriate package type.

Additionally, table II on page 1338 of document (16) shows that at very high humidity values not only anhydrous lactose picks up moisture but also other types of lactose. However, this has not hindered lactose in becoming the most widely used diluent in tablet formulations.

- 3.13 As regards the choice of manufacturing process for preparing the tablets with anhydrous lactose as diluent, wet granulation does not represent a first-choice option in the light of document (5) (page 326, last paragraph, left-hand column).

- 3.13.1 Moreover, both the Encyclopaedia of Pharmaceutical Technology (document (13)) and the manual on

Pharmaceutical dosage forms-tablets (document (4)) agree that a successful general acceptance for the direct compression tableting had been dependent in earlier years on the availability of suitable diluents and excipients (with the appropriate flowability and compressibility) and on economically accessible equipment (document (13) pages 85, 86, document (4) page 196). As regards the first prerequisite, suitable diluents and excipients for direct compression were available at the effective time of the patent in suit, as shown by the analysis made in documents (4) and (13) about fillers and binders and by the examples for direct compression formulations given (see, inter alia, pages 203-214, 229-245 of document (4) and pages 92-99 of document (13)). With respect to the second prerequisite, this is an irrelevant argument for the assessment of the obviousness of the manufacturing process.

3.13.2 Furthermore, anhydrous lactose, NF, which qualified as "the best" lactose material as excipient for direct compression by the study published in document (24), was commercially available at the effective time of the patent in suit (see document (13), table 1 on page 93, first excipient listed and document (24), under the heading "Experimental", end of page 1025).

3.13.3 Moreover, both general books mentioned above, documents (4) and (13), also agree that the most significant advantages of direct compression **in terms of tablet quality** are that of processing without the need for moisture and heat, which is inherent in most wet granulation procedures (document (13), page 87, document (4), page 198). Among the problems of wet

- granulation listed in document (13) are "the effects of temperature, time and rate of drying on drug stability and distribution during the drying process". (page 87, end of first paragraph)
- 3.14 Therefore, the skilled person aware of the effect of elevated temperature and moisture in the increase in degradation of the active ingredient would tend to avoid them and use the direct compression tableting which would be his first-choice option in view of the known suitability of commercially available anhydrous lactose NF as a diluent for direct compression.
- 3.15 In view of the above analysis, the solution proposed in claim 1 of both requests is obvious in the light of the prior art document (7), taking into account the common general knowledge of the skilled person.
- 3.16 The respondent's arguments in favour of the presence of an inventive step on the basis of the existence of a general prejudice which would have deterred the skilled person from using lactose does not hold when looking at the prior art representing the common general knowledge of the skilled person in the field of pharmaceutical technology, which does not show such a prejudice in connection with **anhydrous lactose**. The use of the general word "lactose" in table 9 on page 125 of document (4) as not being a filler of first priority for primary amines only reflects a recommendation which embraces inter alia the very common and for that purpose highly unsuitable spray dried lactose. Moreover, as mentioned in points 3.9.2, 3.9.3 and 3.10 above, anhydrous lactose is explicitly recommended in the same

- book for avoiding the Maillard reaction (i.e. when ingredients having primary amino groups are present).
- 3.17 In relation to the respondent's argument of lack of incentive for using direct compression as the first-choice option, it becomes apparent from paragraphs 3.13 to 3.14 above that such a process would be the first choice for obtaining quality tablets without heat or moisture damage.
- 3.18 With respect to the argument that the claimed subject-matter overcomes an existing prejudice concerning the use of magnesium stearate as lubricant in tablets where an active ingredient and a diluent sensitive to the Maillard reaction were present, the following has to be said. Firstly, claim 1 does not specify the nature of the lubricant to be used and hence includes other options apart from magnesium stearate, for instance non-basic lubricants. Secondly, the prior art general books, documents (4) and (13), already teach how to overcome problems with magnesium stearate by substantially limiting the time of lubricant blending and by including the lubricant at the very end of the blending process, just before compression (document (4), top of page 201, document (13), page 91). Nothing else has been done in example 1 of the patent in suit.
- 3.19 As regards the argument concerning a lack of suitability of direct compression for high-dose drugs, it has to be said that claim 1 also encompasses low-dose drugs and hence such argument even if valid does not apply to the claimed subject-matter in full.

3.20 It is a fact that flowability and compressibility play a major role in direct compression tableting but, as acknowledged by the respondent, the alendronic acid salt used in the examples of the patent in suit was known in the prior art to have good flow properties. Additionally, the board agrees with the appellant in that the problems of compressibility are to be solved by the selection of the appropriate excipients, which are present in the tablet in amounts up to 99.5%. Anhydrous lactose is not used alone but together with an appropriate binder which can be chosen from among those with the best compressibility properties, such as microcrystalline cellulose.

3.21 The respondent also submitted that the actual problem lay in the provision of tablets that were stable during storage, especially at elevated temperatures and humidity.

In respect of this definition of the problem to be solved it has to be said that the comparative examples shown on table I on page 7 of the patent in suit do not prove that such a problem has been actually solved by the claimed subject-matter.

On the one hand it cannot be accepted that they represent a fair comparison since the anhydrous lactose will lose its structure (document (4), page 206, last paragraph), responsible for its inertia to the Maillard reaction, during the heat and water treatment underlying the wet granulation process. Hence, the basic catalysis by magnesium stearate will be more evident in such a tablet, already more prone to degradation, especially when submitted to elevated



temperatures and humidity during storage under open-dish conditions.

On the other hand, the tested tablets according to example 1 cannot be considered to be representative of the whole subject-matter of claim 1, since they are specific low-dose tablets (5 mgs of active ingredient) produced with a high amount of microcrystalline cellulose (80.0 mg to be blended with 110.45 mg of anhydrous lactose). These features are relevant for the stability of the tablet and are not reflected by the wording of claim 1 which also includes high-dose options (up to 40% of the active ingredient), does not specify microcrystalline cellulose as excipient, and does not provide for a ratio of diluent to dry binder.

3.22 Consequently, both requests fail for lack of inventive step (Article 56 EPC) of the subject-matter claimed in claim 1.

**Order**

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

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:

A. Townend

U. Oswald