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D E C I S I O N
of 23 March 1995

Case Number: T 0149/93 - 3.3.2

Application Number: 87110303.2

Publication Number: 0253393

IPC: A61K 7/48

Language of the proceedings: EN

Title of invention:
Methods for treatment of sundamaged human skin with retinoids

Applicant:
Kligman, Albert M.

Opponent:
-

Headword:
RETINOIDS/Kligman II

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no) - obvious to try"

Decisions cited:
G 0005/83, T 0002/83, T 0019/90, T 0199/94

Catchword:
-

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Case Number: T 0149/93 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.2.2
of 23 March 1995

Appellant: Kligman, Albert M.
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Representative: Koepsell, Helmut, Dipl.-Ing.
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Decision under appeal: Decision of the Examining Division of the European Patent Office dated 30 June 1992 refusing European +patent application No. 87 110 303.2 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: P. A. M. Lançon
Members: I. A. Holliday
E. M. C. Holtz

Summary of Facts and Submissions

I. European patent application No. 87 110 303.2 (publication No. 0 253 393) was refused by a decision of the Examining Division on the grounds of lack of inventive step.

Novelty having been established over Appellant's EP-A-0 230 498, the Examining Division considered: Saurat, Retinoids, New Trends in Research and Therapy, Retinoid Symposium Geneva 1984, pages 265 to 271 (4) to be the closest state of the art. Document (4) discloses the use of all-trans-retinoic acid in compositions for the treatment of UV-damaged dermis, the amounts used for the treatment corresponding to the ranges claimed in the present application. The experiments reported in (4) were carried out using hairless laboratory mice. Treatment was shown to retard and reverse the loss of collagen fibres and abnormal changes in elastic fibres.

Since it was well known that laboratory animals, especially mice, were the standard models used when carrying out research on products destined for human therapy, the Examining Division considered that the skilled person could reasonably expect that any effect obtained would be equally applicable to the human dermis, the problem and solution being the same.

The Examining Division held that the subject-matter presently claimed, i.e. the use of retinoids other than all-trans retinoic acid, was merely a generalisation of the concept of document (4). It was apparent from other prior art cited that retinoids or retinoid analogues other than all trans-retinoic acid

were effective in skin treatment including acne caused by exposure to sunlight. In the absence of surprising effects, the Examining Division concluded that there was no evidence in favour of inventive step.

II. The Appellant lodged an appeal against the decision of the Examining Division. Oral proceedings took place on 23 March 1995.

III. The arguments of the Appellant both in the written procedure and at the oral proceedings may be summarised as follows:

It was not possible to predict that the effects observed on the skin of mice would be applicable to human skin, especially since the experiments reported in (4) were carried out on albino mice. It was to be noted that the types of collagen in human and mice skin were different; collagen III predominates in mice whereas collagen I predominates in human skin. At least two of the effects observed on applying retinoic acid to the human skin in accordance with the present application were not recorded in (4), namely: retarding and reversing abnormal epithelial growth and retarding and reversing the deterioration of small blood vessels.

The Appellant also filed details of experiments with 29 compounds belonging to the group now claimed. The data indicated that percentage of utriculus reduction on rhino-mice for various doses of the compounds administered. It was known prior to mid 1986 that this activity on rhino-mice could be correlated with activity on photo damaged hairless mice. The Appellant argued, however, that a correlation between activity on hairless mice and on sun-damaged human

skin had not been recognised at the priority date of the present application. This was presented as a surprising effect which demonstrated the presence of an inventive step.

In response to a question by the Board concerning the use of a "mouse model", the Appellant replied that although the Mezick declaration dated 1987 and experiments filed with the grounds of appeal concerning derivatives of retinoic acid used experiments carried out on mice exposed to UV light, such experiments could not have been regarded as a standard model in predicting effects on human skin in 1984 when document (4) was made available to the public.

An essential difference existed between mice and humans. It was recorded on page 265 of (4) that, on cessation of irradiation, normal collagen synthesis was resumed so that the skin of the mice recovered from the effects of UV exposure. On the other hand damage to human skin resulting from excessive exposure to the sun was permanent; exposure in youth led to wrinkles and other damage in middle age. The use with which the present application was concerned related to a program of maintenance therapy, that is an ongoing treatment. An amended Claim 1 was filed at the oral proceedings to relate the treatment to the dermis of human skin.

IV. Claim 1 presented at the oral proceedings reads as follows:

"1. Use of a retinoid selected from the group consisting of all natural and/or synthetic analogues of vitamin A or retinol-like compounds which possess the biological activity of vitamin A in the skin, for

the manufacture of a composition comprising a non-toxic, dermatologically acceptable vehicle for the treatment of the dermis of human skin by topical application to the surface of the skin in a program of maintenance therapy for retarding and reversing the loss of collagen fibers, abnormal changes in elastic fibers, the deterioration of small blood vessels, and the formation of the abnormal epithelial growths in sundamaged human skin, the amounts of retinoid except all-trans retinoic acid being selected so as to provide a sub-irritating dose for application."

V. The Appellant requested that the decision of the Examining Division be set aside and that a patent be granted on the basis of Claim 1 as submitted in the oral proceedings on 23 March 1995 and Claims 2 to 9 submitted on 14 August 1991.

Reasons for the Decision

1. The appeal is admissible.

2. *Amendments*

2.1 Claim 1 filed during the oral proceedings is based on Claim 1 as originally filed together with page 6, lines 1-3 and page 14, lines 23-27 of the originally filed description. It is in the form approved in decision G 5/83 (OJ EPO 1985, 64) for a second medical indication.

2.2 Claims 2-9 are based on Claims 2-9 as originally filed.

2.3 The requirements of Articles 84 and 123(2) EPC are accordingly satisfied.

3. *Problem and solution*

3.1 The closest state of the art is document (4) which relates to repair of UV-induced dermal damage by topical retinoic acid. Experiments were carried out in which hairless albino mice were exposed to specific doses of UV-light, the radiation dose being designed to produce mild damage to the skin. Certain animals were left untreated and to others were applied various concentrations of retinoic acid.

3.1.1 Whilst the untreated mice showed some recovery once the exposure to UV light had ceased, those treated with retinoic acid displayed a considerably enhanced recovery once the exposure to UV-light had ceased, which was manifested in normalisation of fibroblast functions, increased collagen synthesis and decreased collagenase activity coupled with new glycosaminoglycans directing collagen fibrillogenesis (page 270, last paragraph). It was also demonstrated that the above noted recovery appears to be retinoic acid specific; experiments with other substances which were not derivatives of retinoic acid failed to produce repair greater than would have been expected from cessation of UV-exposure alone.

3.2 Starting from document (4), the problem to be solved should be seen as an extension of the treatment not only in relation to other species but also to other compounds. However, the Board accepts that the problem set out on page 4, lines 11 and 12 of the originally filed documents (page 2, lines 26 to 27 of the printed version) remains unaffected by citation (4) and is included within such a generalisation.

Accordingly for the purposes of this decision, the problem is "to moderate and retard the photo-aging changes in the skin". From the opening paragraph of the application, it is clear that the problem is particularly directed to human facial skin. The problem is solved by the claimed use which involves topical application of the compounds set out in Claim 1 beginning in middle age.

3.3 From the data presented in the present application, it is apparent that the treatment with vitamin A analogues especially as a maintenance therapy, results in reversing and retarding the effects of exposure to sun. In other words, the Board is satisfied that the problem has indeed been solved.

4. *Novelty*

Neither document (4) nor any other prior art referred to in the procedure discloses the use of retinoic acid derivates for the manufacture of a composition for the topical treatment of the dermis of human skin in accordance with Claim 1 currently on file. In any event, novelty has not been contested in relation to the claims refused by the Examining Division.

5. *Inventive step*

5.1 The use claimed in the present application differs from that disclosed in (4) insofar as it is applied to human skin rather than the skin of mice. The Appellant has argued that experiments carried out on mice are not necessarily transferable to humans. This may well be the case. However, it seems to the Board that the first if not the sole purpose of experiments

involving the exposure of mice to UV-light and subsequently applying therapy must be to act as a model for possible application to humans.

5.2 Whilst it may well be true that successful experiments with mice do not invariably lead to effective therapy for humans, such successful experiments would nevertheless provide a strong incentive at least to try if the results are transferable. In accordance with the case law of the Boards of Appeal, a course of action can be considered obvious within the meaning of Article 56 EPC, if the skilled person would have carried it out in expectation of some improvement or advantage (see e.g. T 2/83, OJ EPO 1984, 265, Reasons, point 7). In other words, obviousness is not only at hand when the results are clearly predictable but also when there is a reasonable expectation of success.

5.3 The Appellant argued at the oral proceedings that in 1984, the priority date of the present application, a mouse model was not standard when considering effects on human beings. This argument is not, however, borne out by the literature references considered in the present case and in the parallel appeal T 199/94 (application No. 86 101 232.6). The paper: Topical and Systematic Effects of Retinoids on Horn-Filled Utriculus Size in the Rhino Mouse, etc, by Mezick et al., Journal of Investigative Dermatology, 83, 110-113 (1984) quoted by the Appellant refers to "a mouse model" to quantify anti-keratinizing effects of retinoids. Reference (25) at the end of the said paper relates to a publication by the Appellant in 1979; this uses a rhino mouse model for experiments relating to the keratinisation of the skin. It is also to be noted that the "Oncomouse" patent (EP-B-0 169 672) of Harvard University, which has become

well-known to the public, has a priority date in 1984. The essence of this patent is to genetically design a mouse for use as a model to predict possible effects in human beings (see T 19/90, OJ EPO 1990, 476).

5.4 There is no doubt an essential difference between the actual collagen present in human and mouse skin; collagen III predominates in mice and collagen I in human dermis. However, the Appellant admits that human dermis does at least contain 10% of collagen III. This finding does not alter the Board's conclusion that, even in 1984, experiments on mice would have provided a basis for possible future experiments with human beings.

5.5 The Appellant has argued that two of the effects obtained on applying the retinoic acid treatment to human skin were not to be found on the mouse model (see III above). In the absence of a prejudice against the use of vitamin A analogues, this objection cannot modify the conclusion reached in relation to the other effects mentioned in the claim. Furthermore, it was acknowledged in the second paragraph of document (4) that retinoids are known to enhance wound repair; such treatment would involve the renewal of small blood vessels in the skin of the patient. According to the Appellant, the vascular proliferation suggested in line 10 on page 270 of (4) was obtained after **oral** absorption in accordance with reference (14) at the end of the article. Such is not in contradiction with the finding of the Board. The known use of retinoic acid in the treatment of acne (Appellants US-A-3 729-568 (6) and Eckstein et al., Arzneim. Forschung, Nr. 8, pp. 1205-1209 (1974) (5)) must also involve the reversal of the formation of

abnormal epithelial growths (see (5), p. 1205 right hand column and (6), sentence bridging columns 3 and 4). The Board can only conclude that such effects would have been predictable at the priority date.

5.6 In the parallel appeal T 199/94 referred to above, the Board decided that a corresponding use involving vitamin A acid would have been obvious in the light of the prior art. If the Appellant had been able to show that the natural and synthetic analogues of vitamin A currently claimed showed some unexpected effect over and above that obtained when using all-trans retinoic acid (i.e. vitamin A acid), this might have provided a basis for an inventive step. However, the Appellant made no attempt to demonstrate any such effect. In fact, it appears from the Experimental Examples of the present application that 13-cis-retinoic acid, at least, gives inferior results than the all-trans isomer.

5.6.1 Furthermore, it is not possible to find any inventive selection in the claims as each and every natural and/or synthetic analogue of vitamin A or retinol like compound possessing the biological activity of vitamin A in the skin is used according to Claim 1 such that the problem of the extension to other compounds is solved by a mere generalisation of the subject-matter claimed in the parallel application No. 86 101 232.6 (EP-A-0 230 498). It is also to be noted that the clinical and histological effects noted at the end of the present application are identical to those recorded in the parallel application.

5.7 According to document (4), the mice exposed to UV-light recovered once exposure to the radiation had been discontinued (references (2) and (3) mentioned in the opening paragraph of (4)). The Appellant argued that this marked a difference since damage to human skin was permanent; over exposure to the skin in youth led to permanent problems in middle age. The Board is not convinced that this marks a real difference. There is no indication that the laboratory mice were kept for a period sufficient to assess any permanent damage to their skins in later life.

5.8 Claim 1 of the application relates to "maintenance" therapy, that is continuous treatment over an indefinite period. It is not clear that "maintenance therapy" really represents any significant distinction from a treatment since it merely amounts to a simple repetition of the same step for the same therapeutic or prophylactic purpose. In any event, such continuous treatment was already envisaged in the known use of retinoids in the treatment of acne. According to (6), column 4, lines 21 to 24, when treatment is discontinued, the comedones develop again. The summary of document (5) on page 1209, refers to "Langzeitbehandlung" in other words "a maintenance therapy".

5.9 From the foregoing, it must be concluded that the use, which is the subject-matter of Claim 1 of the present application, would have been obvious in the light of the cited prior art. An inventive step must be denied and the appeal must be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

P. Martorana

The Chairman:

P. A. M. Lançon

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