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SENT BY FACSIMILE

European Patent No. 382 526 (Application No. 90301335.7)
BioChem Pharma
Opposition by Emory University
Our Ref: KILZ/M4828

2101

We enclose a notice of opposition and supporting statement.

In the event that the opposition division intends to maintain the above patent, oral proceedings are hereby requested.

Yours faithfully
ERIC POTTER CLARKSON

Richard Bassett

sjeh

M. J. Gilding

Enc: Notice of Opposition
Statement

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European Patent No. 382 526

(Application No. 90301335.7)

Biochem Pharma Inc

Opposition by Emory University

Contents

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1. BRIEF INTRODUCTION

It is fundamental that a patent grant should strictly correspond to the technical contribution to the art made by the disclosure of the invention described therein. This excludes that a patent monopoly be granted on subject matter which, after reading the patent specification, would still not be at the disposal of the noninventive routinely skilled person. The routinely skilled person is not expected to undertake a comprehensive search of the literature to obtain the claimed subject matter, and in fact, is not required to exercise more than the common general knowledge at his immediate disposal.

BioChem Pharma has sought, and been awarded, patent protection on an invention that it clearly did not have in its possession at the time of filing its priority document, did not teach the public how to obtain, and, based on patent filings, did not itself obtain until much later, namely, the isolated enantiomers of a synthetic nucleoside, BCH-189. One of the isolated enantiomers, the (-)-enantiomer, is now being commercialized internationally for the treatment of AIDS and hepatitis. The fact that it is an important compound, however, does not lessen the burden on BioChem Pharma to satisfy Article 83.

Dr. Ernest L. Eliel (D1), the preeminent stereochemist, has summarized the central issue of this Opposition as follows:

> **"..this Opposition presents an issue of fundamental legal concern to chemists worldwide. The issue is this: Is the disclosure of a racemic compound always tantamount to a disclosure of the separated enantiomers of that compound? The answer is no. To consider otherwise would trivialize the work, and perhaps the entire careers, of bright scientists who have spent years in the field of stereochemical resolution, and invalidate many patents already issued. Each situation must be considered on its own facts."**

Professor Stephen G. Davies, a founder of Oxford Asymmetry Ltd.,

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Professor of Chemistry at New College, University of Oxford, and Editor in Chief of Tetrahedron Asymmetry states in connection with this Opposition (D2) that:

> **The fact that many of the methods that could have been attempted to obtain the enantiomers of BCH-189 are not successful, as described in the Notice of Opposition, is quite consistent with my observations that obtaining the enantiomers of a pharmaceutical compound is often not routine and that scientists of average skill level who do not have an expertise in any one separation means can find it a difficult challenge. My conclusion, based on a review of the information given to me in connection with this Opposition, is that this project would have required inventive thought and presented a substantial challenge to the average chemist relying only on his common general knowledge in 1989-1990.**

The issue of whether it is routine to obtain the enantiomers of a racemate turns on a number of issues. Who is the routine noninventive worker? What is known about these compounds? What methods failed? What was the state of the art as of the priority date of the patent application? These issues will be addressed below.

Europe is not the only jurisdiction asked to consider these issues. After extensive consideration, the United States Patent Office has concluded that the priority document for the '526 specification, U.S.S.N. 07/308,101, did not teach one of ordinary skill in the art how to obtain the enantiomers of BCH-189 without undue burden on the reader (D3).

2 REQUESTS

2.1 We request that granted European Patent 0 382 526 B1 (referred to below as EP '526) be revoked to the extent that the claims cover individual optical isomers and associated compositions and uses of these compounds. In particular, we request that claims 1, 2, 4-9, and 11-14 (for contracting states AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE), and claims 1-2 and 4-7 (for contracting states ES and GR) be revoked. In the alternative, we request amendment of the claims such

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that they no longer encompass individual optical isomers, and cover only that which is sufficiently enabled by the specification under Article 83, namely racemic mixtures of the disclosed 1,3-oxathiolane nucleosides, and disclosed compositions and uses thereof.

2.2 We request oral proceedings if EP '526 would otherwise be maintained with claims covering individual optical isomers.

3. GROUNDS OF OPPOSITION

3.1 We oppose EP '526 under Article 100(b) EPC, on the basis that the specification does not disclose the preparation of individual optical isomers of the disclosed 1,3-oxathiolane nucleosides in a manner sufficiently clear and complete for them to be made by a **routinely skilled noninventive worker** in the art at the relevant time, and in fact, the specification provides no specific direction whatsoever on how to obtain these claimed materials.

3.2 Third party observations were filed on 19 January 1995 in connection with the application leading to opposed EP '526. These observations were responded to by the Applicants in a letter dated 19 July 1995. No further written comment was issued by the Examiner, who subsequently confirmed, during a telephone conversation with the Opponent, that he felt the issues concerning sufficiency under Article 83 EPC were complex and therefore effectively addressed only through *inter partes* proceedings. The application was allowed to proceed to grant to allow for a full hearing on these issues. We now incorporate the third party observations in this opposition together with a more extensive analysis of EPO Practice and new technical evidence. We request that the Opposition Division read and fully consider the text of these Observations and attached appendices incorporated into this Opposition as D4.

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4 INSUFFICIENT DISCLOSURE

4.1 Summary of EP 0 382 526 and Opponent's position

4.1.1 Stereochemistry.

Stereochemistry refers to chemistry in three dimensions. Compounds that differ only in how the atoms are oriented in space are called stereoisomers. Pairs of stereoisomers exist that differ so little in structure, and thus properties, that the only physical measurement that can be used to detect the difference (other than perhaps melting point) is how the compound rotates a plane of polarized light. A compound is referred to as "chiral" if it is not superimposable on its mirror image. Stereoisomers that are nonsuperimposable mirror images are called enantiomers or optical isomers. Optical isomers rotate a plane of polarized light in opposite directions. The effect of chirality is that the enantiomers have opposite spatial orientations. The enantiomers of a racemate are thus said to have "handedness" in that they resemble a set of human hands. A racemic compound is a 50:50 mixture of mirror image molecules (enantiomers). Stereoisomers that are not mirror images of each other are called diastereomers.

4.1.2 Nucleosides

Nucleosides are chemical compounds that are composed of a nitrogenous base portion and a carbohydrate portion. Naturally occurring nucleosides in the body, such as cytosine, adenosine, thymine, guanine, and uridine, are the building blocks for nucleic acids. The body makes nucleic acids in a stereospecific manner, i.e., in enantiomeric or optically active form. Naturally occurring nucleosides almost always have a β-D-configuration, which is a *cis*-configuration with both groups "up" relative to the plane of the sugar ring when oriented such that the oxygen atom is pointing away from the reader.

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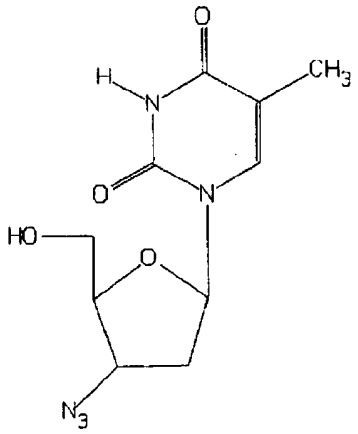
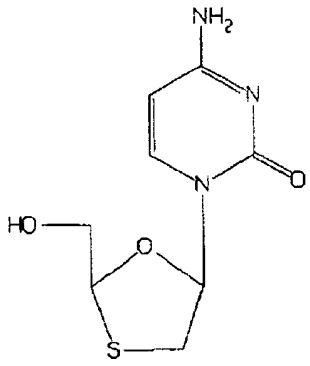
4.1.3 Historical Context

The first synthetic nucleoside that was reported to have activity against HIV was AZT (3'-azido-3'-deoxythymidine):



AZT has a β-D configuration, and is prepared by modification of naturally occurring thymine, which has a β-D configuration. Therefore, stereochemical considerations were not, and have not been, a problem in the manufacture of AZT. The success of AZT against HIV caused a flurry of research activity focused on synthetic nucleosides.

At the 5th Anti-Aids Conference, Montreal, Canada 5th-9th June 1989: Abstracts T.C.O.1 and M.C.P. 63, Dr. Bernard Belleau reported for the first time that he had identified a new synthetic nucleoside, BCH-189, that exhibited activity against HIV and appeared to have low toxicity:



Chung K. Chu was at the June 1989 Montreal meeting. As indicated in his Declaration, the synthesis of and data presented for BCH-189 at this meeting were strictly racemic. There was no discussion whatsoever about the enantiomers of BCH-189.

As discussed in the Declaration of Dr. John A. Montgomery, this new class of nucleosides presented special challenges. Up to that point, synthetic nucleosides were typically made by derivatizing intact, naturally occurring nucleosides that had stereochemistry that had been set by nature. Since the new class of nucleosides had an additional heteroatom in the sugar portion of the ring, the sugar portion had to be made synthetically and then condensed with the base. **This resulted in the formation of a nucleoside that was a racemic compound, not an enantiomer as made by nature.**

4.1.4 Priority Document for EP '526

Dr. Belleau filed a patent application on February 8, 1989 as U.S.S.N. 07/308,101, now U.S. Patent No. 5,047,407 that one can presume included the best information that he had at the time about 1,3-oxathiolane nucleosides, namely a synthetic protocol and biological data on the racemates, as the application was required to disclose the "best mode" for carrying out the invention under United States patent law standards (35 U.S.C. Section 112). This application served as the priority document for European Patent Application No. 0 382 526, which was filed in Europe on February 8, 1990. Certain portions of the EPO '526 patent application did not exist in the priority document. Where relevant to the discussion, this will be noted.

4.1.5 The '526 Patent Application

The EPO '526 patent application originally disclosed a broad group of 1,3-oxathiolane nucleosides to treat HIV. During prosecution, the specification and claims were limited to cover cis-2-hydroxymethyl-5-(cytosin-l'-yl)-1,3-oxathiolane (also known as β-BCH-189, the β-isomer of BCH-189, or

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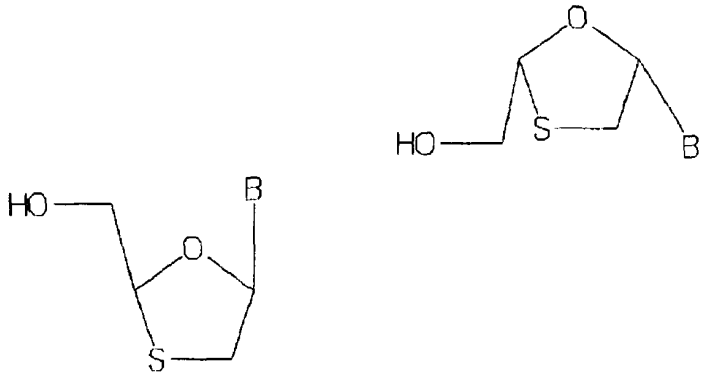
simply BCH-189), and certain derivatives thereof. It is stated, at page 4, lines 33 to 35 of the specification of the Patent, that:

> *"It will be appreciated by those skilled in the art that [BCH 189] contains two chiral centres..... and thus includes two pairs of optical isomers (ie enantiomers) and mixtures thereof including racemic mixtures. Both cis-isomers [ie the enantiomers of BCH 189] and mixtures thereof, including racemic mixtures, are included within the scope of the invention."*

As characterized in T1048/92, this type of boilerplate language is used to place others on notice that patentee believes that the separated optical isomers are considered to be included in the formula. In this Opposition, we challenge the position that isolated optical isomers should be considered to fall within the scope of claims based on a patent application that is sufficient only to obtain racemates under Article 83.

For the OD's convenience, we here take a moment to explain the relevant stereochemistry of 1,3-oxathiolane nucleosides. The substituents on the chiral carbons (the specified purine or pyrimidine base (referred to as the C2 substituent)) and CH_2OH (referred to as the C5 substituent)) of the 1,3-oxathiolane nucleosides can be either *cis* (on the same side) or *trans* (on opposite sides) with respect to the oxathiolane ring system. Both the *cis* and *trans* racemates consist of a pair of optical isomers. Hence, each compound has four individual optical isomers. The four optical isomers are represented by the following configurations (when orienting the oxathiolane moiety in a horizontal plane such that the -S-CH_2- moiety is in front): (1) *cis*, with both groups "up", which is the naturally occurring *β-cis* configuration (2) *cis*, with both groups "down", which is the non-naturally occurring *β-cis* configuration; (3) *trans* with the C2 substituent "up" and the C5 substituent "down"; and (4) *trans* with the C2 substituent "down" and the C5 substituent "up". The two *cis* enantiomers together are referred to as a racemic mixture of β-enantiomers, and the two *trans* enantiomers are referred to as a racemic mixture of α-enantiomers.

The two possible stereoisomers of the claimed cis-1,3-oxathiolane nucleosides such as BCH 189 are illustrated below:



In general, it is fairly standard to be able to separate the pair of *cis* racemic optical isomers from the pair of *trans* racemic optical isomers. It is a significantly more difficult challenge to separate or otherwise obtain the individual enantiomers of the *cis*-configuration.

In the text of the '526 specification (filed on February 8, 1990), but not the priority document (filed on February 8, 1989), page 9 states that:

> "*Where the compound of formula (I) is desired as a single isomer it may be obtained either by resolution of the final product or by stereospecific synthesis from isomerically pure starting material or any convenient intermediate.*
>
> *Resolution of the final product or an intermediate or starting material therefore may be effected by any suitable method known in the art: for example, Stereochemistry of Carbon Compounds, by Ernest L. Eliel (McGraw Hill, 1962) and Tables of Resolving Agents, by S.H. Wilen.*"

In fact, the mere reference to these two textbooks to obtain an applicable protocol to identify a suitable chemical procedure to obtain claimed subject matter in this case is nothing more than an invitation to experiment. It does not assist in any meaningful way to obtain the compound.

As the Opponent establishes herein, the '526 specification merely teaches the reader how to obtain racemic mixtures of BCH-189, but does not provide an enabling disclosure to the noninventive routinely skilled worker on how to obtain single enantiomers of BCH-189. In the case of BCH-189, the separation of the individual enantiomers was not straightforward and could not have been carried out without placing an undue burden on that worker at the priority date of the '526 specification.

Dr. Ernest L. Eliel has provided a Declaration commenting on this excerpt. Dr. Eliel is one of the leading stereochemists in the world, and the 1996 recipient of the Priestley Medal, the highest award bestowed by the American Chemical Society. Other recipients of this award include Linus Pauling, Glenn Seaborg, and Melvin Calvin.

The topic of how to obtain an enantiomer of a racemate is summarized by Dr. Eliel in Chapter 4 (resolution of racemic modifications, section 4-4), Chapter 5 (synthesis of optically active compounds, section 5-5), and and Chapter 15 (stereoselective synthesis, section 15-1). According to Dr. Eliel, these chapters were intended to provide a summary overview of how to obtain enantiomers of organic compounds in purified form, and were never intended to, and did not, provide specific instructions on how to resolve all chiral organic compounds. He goes on to state that

> *"This would be impossible, as each resolution presents its own unique challenges. The book provides the reader with no specific or even general instructions whatsoever on how to obtain the enantiomers of BCH-189, which I understand was reported as one of a new class of compounds over twenty years after this book was published. Therefore, the reference to my book in EPO '526 as authority for how to resolve BCH-189 is inappropriate and meaningless."*

Dr. Eliel further states that:

> *"The majority of Tables of Resolving Agents is a compendium of chiral auxiliaries that had been reported to resolve specific compounds, and conditions for such resolutions. The book did not, and could not have, reported*

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the successful resolution conditions for BCH-189, which had not been made at the time of publication of the book. Based on my close collaboration with Sam Wilen for many years, I am confident that he would disagree with the use of his book as a reference that provides either specific or generally applicable instructions on how to resolve BCH-189. As the Editor of this book, it is my conclusion that the reference to this book as authority for how to resolve BCH-189 is again inappropriate and meaningless."

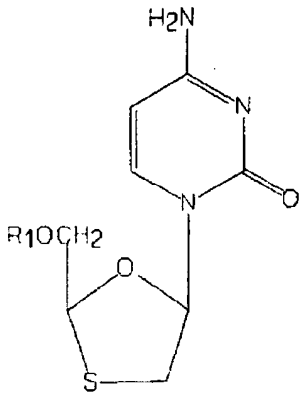
The '526 specification did apparently place racemic BCH-189 into the possession of the public for the first time with an enabling disclosure. However, the '526 specification did not provide any directly applicable instructions for how to obtain the optical isomers of BCH-189. The mere act of drawing the chemical structure of a new enantiomer without more is a paper exercise. In academic and industrial research, one often draws chemical structures on a blackboard or paper for purposes of discussion, however, it is understood that the compound really does not "exist" until it has been successfully prepared or would be clearly routine to prepare. Since these compounds were admittedly novel, there was no directly applicable common general knowledge as of the filing date of this application on how to obtain the individual optical isomers of these compounds.

4.1.6 Allowed Claims of EP '526 B1

For the Opposition Division's convenience, the ***most relevant*** claims for all contracting states are set out below, with the language highlighted that represents the defect under Article 83.

For contracting states AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, and SE

Claim 1. A cis-1,3-oxathiolane of formula:



wherein R_1 represents hydrogen, a C_{1-16} alkanoyl group, a benzoyl group or a benzoyl group substituted by at least one halogen, C_{1-16} alkyl, C_{1-6} alkoxy, nitro, or trifluoromethyl group, or a pharmaceutically acceptable salt thereof in the form of a single optical isomer or a mixture of optical isomers.

Claim 4. A compound according to claim 2 substantially in the form of a single optical isomer.

Claims for a process of manufacture of a compound as claimed in Claim 1 for the other contracting states are included for ES and GR.

4.2 EPO practice and case law

4.2.1 Article 100(b) EPC provides that a patent is to be revoked if it does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

4.2.2 The principles of determination of whether or not an invention is sufficiently disclosed in a granted patent are the same as those laid down for patent applications in connection with Article 83 EPC (see Guidelines for Examination, D-IV, 4,1).

4.2.3 There is a strong public policy in the EPC contracting states against granting to a patent applicant a monopoly interest in subject matter that he does not place in the public's possession. The burden is correctly on

the applicant to teach the public how to carry out the invention, and not on the public to sort through methods to determine how to achieve the invention. If the person is faced with a number of possibilities, and cannot predict which of the methods, if any, would succeed to produce the claimed material as of the priority date, the act of sorting through all of the methods, or devising new methods, in itself is an undue burden.

4.2.4 This is emphasised by the Guidelines for Examination at C-II, 4.1, wherein it is stated that the purpose of the sufficiency provision is to:

> *"(i) ensure that the application (or patent) contains sufficient technical information to enable a skilled person to put the invention into practice, and*
>
> *(ii) enable the reader to understand the contribution to the art which the inventor has made."*

4.2.5 Although mere breadth of claims is no basis for objection under Article 83 EPC as such, the well known case law in this area (eg T226/85) provides that, where there is evidence that the claims cover embodiments which do not belong to the invention (eg because they are unworkable or speculative), there is ground for objection under Article 83.

4.2.6 A position by a patentee that he is entitled to broader protection than that which is disclosed in a specification because the disputed patent would provide an incentive for those skilled in the art to entertain further research activities which might lead to the discovery of how to obtain additional claimed subject matter has no basis in the EPC, and is not supported by the jurisprudence of the Boards of Appeal.

4.2.7 In line with the EPO case law, and in the context of sufficiency, an applicant discharges his burden to teach the public how to carry out the invention only if he provides an enabling disclosure of the invention. That is to say the claimed invention must be disclosed by the applicant

in a manner which will enable its routine reproduction, without an undue burden being placed upon the person of ordinary skill in the art.

4.2.8 This view has, most notably, been supported by EPO Decision T409/91 (Exxon/Fuel Oils; OJEPO 1994, 653). In this case it was held that the test for whether there is a sufficient disclosure under Article 83 to support a claim under EPO practice is whether the whole subject matter that is defined by the claims, and not only part of it, is capable of being carried out by the skilled person without the burden of an undue amount of experimentation or the application of inventive ingenuity. This decision comprehensively addresses the requirement of sufficiency of disclosure in chemical cases.

4.2.9 In T409/91 the patent application claimed a distillate fuel oil that had an average wax crystal particle size less of than 4000 nanometers at 10° below Wax Appearance Temperature (WAT). Claims 2 to 5 defined smaller upper limits of particle size down to 1,000 nanometers. The patent application taught only how to get a fuel oil containing a particle size of 1,200 nm at a temperature of 6.4° C below WAT. There was no information on how to obtain wax particles at a temperature of 10.0° below WAT which were below 1,000 nm. The appellant admitted that no way of obtaining fuel oils with particle sizes smaller than 1,200 nm was disclosed or could be found in the relevant common general knowledge. The means to accomplish the small particle size was the addition of additives to the composition, and the specification did not include any guidance on which additive would be successful in producing particle sizes other than 1,200 nm.

The Technical Board of Appeal held that the subject matter of claim 1 was not sufficiently disclosed under Article 83 EPC, because it included particle sizes less than 1,200 nm. The Board likewise held that claims 2-5 were insufficiently disclosed in the specification because there was no instruction on which additive could produce the subject matter of

these claims.

The Board stated:

"*Although the requirements of Articles 83 and 84 are directed to different parts of the patent application, since Article 83 relates to the disclosure of the invention, while Article 84 deals with the definition of invention by the claims, the underlying purpose of the requirement of support by the description, insofar as its substantive aspect is concerned, and of the requirement of sufficient disclosure is the same, namely to ensure that the patent monopoly should be justified by the actual technical contribution to the art. Thus, a claim may well be supported by the description in the sense that it corresponds to it, but still encompass subject-matter which is not sufficiently disclosed within the meaning of Article 83 EPC as it cannot be performed without undue burden, or vice versa. In the present case, however, the reasons why the invention defined in the claims does not meet the requirement of Article 83 EPC are in effect the same as those that lead to their infringing Article 84 as well, namely, that the invention extends to technical subject-matter not made available to the person skilled in the art by the application as filed.*"

Importantly, the Board said:

"*..the Board does not accept the appellant's submission that sufficiency should be acknowledged simply because one way of performing the invention was disclosed. In the Board's judgement, the disclosure of one way of performing the invention is only sufficient within the meaning of Article 83 EPC if it allows the person skilled in the art to perform the invention in the whole range that is claimed...However, the question whether the disclosure of one way of performing the invention is sufficient to enable a person skilled in the art to carry out the invention in the whole claimed range is a question of fact that must be answered on the basis of the available evidence, and on the balance of probabilities in each individual case. In the present case, the claimed invention concerns a class of fuel oil compositions characterized by a common feature, the presence of wax crystals of a certain size under certain conditions. In the Board's judgement, this case differs from those where a class of chemical compounds is claimed and only one method of preparing them is necessary to enable a skilled person to carry out the invention, in other words, to prepare all of the compounds of the claimed class. Rather, the present case is comparable to cases where a group of chemical compounds is claimed, and not all of the claimed compounds can be prepared by the methods disclosed in the description or being part of the common general knowledge (see for example T206/83, OJ EPO 1987, 5). In the latter case, it was not held sufficient for the purpose of Article 83 to disclose a method of obtaining only some members of the claimed class of chemical compositions. Thus, the Board's finding that the disclosure of the claimed*

invention is only sufficient if it enables the skilled person to obtain substantially all embodiments falling within the ambit of the claims, is consistent with the earlier jurisprudence of the Board of Appeal of the EPO (see also T226/85, OJ EPO 1988, 336)."

4.2.10 In a recent UK decision, the House of Lords cited EPO case law (including T292/85 and T409/91) in arriving at its conclusion that a patent claim will be invalid in so far as it purports to cover subject matter which the skilled person cannot reproduce by means of the technical contribution made to the art by the specification (Biogen v. Medeva (HL), 31 October 1996). In particular it was stated:

> *"[in judging whether or not a claim is invalid due to insuffiency]...It is not whether claimed invention could deliver the goods, but whether the claims cover other ways in which they might be delivered: ways which owe nothing to the teaching of the patent or any principle which it disclosed."*

A claim will thus be insufficient in so far as it covers embodiments which could not be reproduced by the skilled person relying on the technical teaching of the specification and common general knowledge at the relevant time.

4.2.11 The intended addressee of a patent specification is one of no more than average knowledge and competence who is not required to exercise any inventive effort in carrying out the instructions given in the specification. The routinely noninventive skilled person is expected to make use of common general knowledge but he cannot be presumed to have any special knowledge. A specification is insufficient if the skilled addressee cannot carry out its concepts without difficulty and without using ingenuity.

4.2.12 While the skilled addressee may be presumed to have theoretical access to everything in the state of the art, he is not expected to undertake exhaustive

searches. EPO Guideline C-IV, 9.6. states that:

> *"If specific prior art or information is to be relied on to provide the necessary details for working of the invention, reference to this information should be included in the specification."*

4.2.13 That the noninventive routinely skilled person is not expected to exercise any inventive input in reproducing the claimed subject matter, or, in line with T409/91, part of the claimed subject matter, has been in other EPO decisions. In T931/91 it was held that experimental work must be kept within reasonable bounds (see also T475/88 and T418/89) and, moreover, the skilled person is not required to exercise an inventive step in reproducing the invention in accordance with the teaching of the specification. This view is supported by inter alia T32/85, where it was held that, if the skilled person has to solve the problem which the patent itself intends to solve, he/she is making inventive input, which is undue burden; and T721/89, where it was held that, if the skilled person is required to carry out a few undisclosed additional steps to arrive at the claimed subject matter, these steps must be so apparent in the light of common general knowledge that their inclusion is unnecessary. These, and other cases, all clearly state that inventive input must not be required by the skilled in order to reproduce claimed subject matter or the patent specification is insufficient.

4.2.14 This view was supported by Decision T206/83 in which, notably, it was stated that:

> *"Basically any cure of insufficiency lies with the addressee of the document, i.e. the person skilled in the art who has common general knowledge at his immediate disposal. It would be unfair to the public if more were expected of him, ie an awareness of the whole state of the art. It is normally accepted that common general knowledge is represented by basic handbooks and*

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textbooks on the subject in question"
(emphasis added).

Thus, if basic handbooks, for example, those specifically referred to in the text, do not teach the skilled person how to perform a claimed invention, or, (in accordance with T409/91) part of a claimed invention, then the relevant claim, or part thereof, is invalid.

4.2.15 In the context of enantiomers, what does, and what does not, provide an enabling disclosure has been analysed by the Technical Board of Appeal in various cases (T296/87 and T658/91) which are discussed below. Although the cases discussed deal with what constitutes an enabling disclosure in the context of novelty, EPO case law (eg T60/89 and T206/83) has established that the test for whether or not a disclosure is sufficiently enabling, from the point of view of both sufficiency and novelty, is the same.

4.2.16 In T296/87 it was held, at Reason Point 6.2, that the mere publication of a chemical formula containing an asymmetric carbon atom disclosed only the racemate, and did not provide an enabling disclosure of the individual enantiomers.

4.2.17 In T658/91 the prior art disclosed a racemate of an optically active compound along with the following statement.

> *"These compounds comprise an asymmetric carbon atom which may exist in the form of 2 enantiomers. The invention concerns both each of these enantiomers and the mixture thereof"*

It was held, at reason point 2.4, that

> *"In the present case, the invention of enantiomers in the description [of the prior art] is not limited to the conceptual information regarding the existence of such enantiomers, but....expressly....to the fact that these enantiomers are considered to be an integral part of the invention described"*

The Board, **however, importantly**, went on to say:

> "*...[the prior art] therefore unequivocally makes available to the person skilled in the art all the enantiomers of the racemic compounds described individually in the examples, and thus the enantiomer claimed in the present patent application which,* ***as accepted by the appellant,*** *can be prepared by the skilled person using his basic knowledge of methods for resolving racemic compounds....*" (emphasis added).

Therefore, the only reason why the Board concluded in T658/91 that the prior art disclosure was novelty destroying for the enantiomer is that the Board assumed, and the applicant accepted, the fact that the enantiomer in that case could be obtained routinely. In some cases that is certainly true. However, in T296/87, the opposite conclusion was reached because the Board apparently concluded that one would not have obtained the enantiomer of the disclosed racemate by routine means.

4.3 Application of the case law to Opposed EP '526

4.3.1 In the '526 patent, claim 1 for all contracting countries covers a class of compounds that can be broken down into two ***discrete*** subsets:

(i) a racemic 1,3-oxathiolane nucleoside of formula (I) specified in Secion 4.1.6 above; and

(ii) isolated optical isomers of 1,3-oxathiolane nucleosides of that general formula and mixtures thereof other than to racemic (50:50) mixture (i.e. enantiomerically enriched).

Claim 4 covers BCH-189 substantially in the form of one optical isomer.

The language of Claim 1 suggests that a racemate is merely "a mixture of optical isomers". This implies that a racemate also includes enatiomerically-enriched (scalemic) mixtures which it clearly does not. A racemate is a **50:50** mixture (0% enantiomeric excess) of the enantiomers

and in this sense is a discrete and separate **form** of an optically-active compound. Only when some kind of resolution method is provided can one obtain the isolated enantiomers or, indeed, mixtures which are enantiomerically-enriched. Alternatively, once one has the resolved enantiomers in one's possession, enantiomerically enriched mixtures can be made.

We show below that, in the case of BCH-189, resolving methods could only be devised by exercising inventive effort. Thus, out of the infinite range of mixtures covered by Claim 1, only for one (the racemate) is an enabling disclosure provided in EP '526.

4.3.2 The present case is comparable to the situation in which a group of chemical compounds is claimed, and not all of the claimed compounds can be prepared using the same method. According to decision T409/91, it is not sufficient for the purpose of Article 83 to disclose a method of obtaining only some of the classes of the claimed chemicals. There must be an enabling disclosure for each class. According to the decision T409/91, the specification must teach *the noninventive routinely skilled worker* how to obtain each one of the separate classes of compounds in a satisfactory manner under Article 83, or the patentee must establish that the claimed subject matter is capable of being obtained by that ordinary person without the burden of an undue amount of experimentation or the application of inventive ingenuity using common general knowledge. Likewise, under the authority of T296/87 and T658/91, the claimed subject matter directed to isolated enantiomers of 1,3-oxathiolane nucleosides is only valid if it can be obtained by routine noninventive effort. We establish below that, with regard to one of these classes, namely isolated optical isomers of 1,3-oxathiolane derivatives of the general formula (I), this is not true.

4.4 Evidence to show that obtaining the individual enantiomers of BCH-189 was not routine to the noninventive person of average skill in the art in 1989-1990

4.4.1 Introduction

It was admitted by BioChem Pharma, and accepted by the EPO, that 1,3-oxathiolane nucleosides were novel as of the filing date of the priority document, February 8, 1989. Assuming this to be true, then by definition, on that date, there were no articles or other publications available that unambiguously taught the public how to obtain either the racemates or the optical isomers of the claimed 1,3-oxathiolane nucleosides.

Below and in the accompanying documentation, the Opponent addresses in detail nine methods which might have been considered at the priority date of the specification by a noninventive routinely skilled worker as plausible resolution methods. In its Japanese patent application corresponding to the '526 application, Biochem Pharma provided to the Japanese Patent Office a similar list of methods as those that one of ordinary skill would "routinely" use to obtain the enantiomers of BCH-189. Since this list has been presented and approved by Biochem Pharma itself, we adopt the list and expand on it. The methods include those listed on pages 108 and 109 of the chapter titled "Resolving Agents and Resolutions in Organic Chemistry" in Topics in Stereochemistry (vol 6) by Samuel Wilen (Wiley-Interscience, 1971, Eds NL Allinger and EL Eliel) (D5).

The inability of one of ordinary skill in the art to use any of these methods to provide the isolated enantiomers of BCH-189, without significant, and undue, experimentation is established in Declarations of Dr. Ernest L. Eliel (D1), Professor Stephen G. Davies (D2), Dr. Dennis C. Liotta (D6), Professor Manfred P. Schneider (D7), Dr. John A. Secrist, III (D8), Dr. Chung K. Chu (D9), Dr. William Pirkle (D10), Anita T. Shortnacy-Fowler (D11). Dr. Antonin Holy (D12), and Dr. John A. Montgomery (D13). If it were not, or would not have been, routine for these experienced

researchers to obtain the claimed subject matter at the relevant time, it could not have been routine to a noninventive averagely skilled worker, who by definition would have had much less experience than these people.

Dr. Ernest L. Eliel is W.R. Kenan, Jr., Professor Emeritus at the Department of Chemistry, University of North Carolina, Chapel Hill. Dr. Eliel is preeminent in the field of the stereochemistry of organic compounds. He is the author of the book entitled Stereochemistry of Carbon Compounds (McGraw-Hill, New York 1962), and a coauthor of Stereochemistry of Organic Compounds (Wiley-Interscience, New York 1994) with Samuel Wilen and Lewis Mander. These texts are the bibles of stereochemistry referred to by organic chemists worldwide. As stated above, he is also the Editor of the book Table of Resolving Agents by Samuel Wilen and the chapter "Resolving Agents and Resolutions" by Samuel Wilen in Topics in Stereochemistry, referred to in this Notice.

Professor Stephen G. Davies is a founder and the Research Director of Oxford Asymmetry Ltd., Professor of Chemistry at New College, University of Oxford, Oxford England, and Editor in Chief of Tetrahedron Asymmetry. He is generally considered one of the brightest scientists in stereochemistry internationally.

Dr. Dennis C. Liotta was formerly the Head of the Chemistry Department at Emory University and is currently the Vice President for Research at that institution. Dr. Liotta carried out numerous unsuccessful attempts to obtain the isolated enantiomers of BCH-189.

Professor Manfred P. Schneider is a Professor at Bergische Universität, Wuppertal, Germany. Professor Schneider has been conducting research in the area of enzymes as catalysts in organic transformations since 1980.

Dr. Chung K. Chu is a Professor of Medicinal Chemistry at the University of Georgia. He is an expert in the area of stereospecific syntheses of nucleosides, and has a number of granted patents and many scientific

publications in this area.

Dr. William Pirkle is a Professor of Chemistry at the University of Illinois (Urbana). He is one of the leading experts in the world on chiral chromatography.

Dr. Antonin Holy is the Director of the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic and a Member of the Scientific Board of the Academy of Sciences of the Czech Republic. He has been conducting research in the area of synthetic nucleosides since 1963. He was the first scientist to systematically study β-L-nucleosides. He has published over 450 scientific articles, primarily in the area of nucleosides, nucleotides, nucleic acids, acyclic nucleosides, and other antiviral compounds.

Dr. John A. Montgomery is currently an Adjunct Senior Scientist at the Comprehensive Cancer Center, Distinguished Scientist at the Southern Research Institute, Birmingham, Alabama and Executive Vice President and Director of Research/CSO at BioCryst, Birmingham, Alabama. He has been involved in research in the area of nucleosides since 1956. He has authored or coauthored total of four hundred forty-three publications, many of which have been in the area of synthetic nucleosides and nucleotides.

Dr. John A. Secrist, III is the Executive Vice President and Chief Operating Officer of Southern Research Institute, Birmingham, Alabama. He has been conducting research in the area of synthetic nucleosides since 1976. He has published over one-hundred fifty abstracts, journal articles, textbooks, and monographs, many of which are in the area of synthetic nucleosides.

Anita T. Shortnacy-Fowler has a Bachelor of Science degree in Chemistry from the University of Alabama in 1965, when she joined Southern Research Institute. Her research experience has been primarily in the area of synthesis and analysis of nucleosides since joining SRI in 1965.

The issue arises as to who is the "noninventive routinely skilled worker" In a corresponding proceeding in Australia, Biochem Pharma has taken the position that this person has a B.S. or honours degree in organic chemistry with several years of laboratory experience. For the sake of discussion herein, we use BioChem Pharma's opinion on this.

4.4.2 Spontaneous Resolution

The technique of spontaneous crystallization is simple and inexpensive and thus a preferred route of obtaining the enantiomers of a racemate when it works. We have been told that examples of compounds that have been manufactured by this technique include glutamic acid, chloramphenicol and L-menthol.

As discussed by Dr. Eliel, to understand the techniques of spontaneous resolution and mechanical separation of crystals, one must understand the meaning of a conglomerate. A conglomerate is an equimolar mechanical mixture of crystals of two enantiomers that form a eutectic. In other words, it is a macroscopic mixture of crystals of two forms that is found if the (-)- and (+)-enantiomers have a greater affinity for like molecules than molecules of the opposite configuration. The mixture contains: (i) crystals of only the (-)-enantiomer, and; (ii) other crystals of only the (+)-enantiomer. The fact that a wide variety of compounds exist as conglomerates is demonstrated by lengthy discussion in Jacques, Collet and Wilen, *Enantiomers, Racemates and Resolutions*, Chapter 4, John Wiley and Sons, N.Y. 1981; Eliel and Wilen, Stereochemistry of Organic Compounds, pages 298-322.

Spontaneous resolution refers to the resolution by spontaneous separation of individual enantiomers from a solution or melt of the racemate, possible only if the latter is a conglomerate in the solid state. See *Stereochemistry of Carbon Compounds*, 1994, page 1207. It has been estimated that 5-10% of all chiral organic compounds form conglomerates and thus may be separated into the individual enantiomers by spontaneous resolution (*ibid.*,

page 300). Five to ten percent of all chiral organic compounds, however, represents a large absolute number of compounds. See for example, Table 4 of Chapter 2 of *Enantiomers, Racemates and Resolutions.*

To determine if a racemic material is a conglomerate, one may, in the first instance, compare the melting point of the racemic material to that of the separate enantiomers. The melting point of a true racemic mixture (i.e., a conglomerate) is lower than that of either of the enantiomers (like that of any typical chemical mixture). If the melting point of the racemic material is higher than that of either of the enantiomers, the material is not a conglomerate but instead a true racemic compound.

Storer, et al., "The Resolution and Absolute Stereochemistry of the Enantiomers of *cis*-1-[2-(Hydroxymethyl)-1,3-Oxathiolan-5-yl]cytosine (BCH189): Equipotent Anti-HIV Agents." *Nucleosides and Nucleotides*, 12(2), 225-236 (1993) (D15) reports that the melting point of the (-)-enantiomer of BCH-189 is 160-162 degrees centigrade, and that the melting point of the (+)-enantiomer of BCH-189 is 159-161 degrees centigrade. U.S. Patent No. 5,047,407 (D3) reports that the melting point of racemic BCH-189 is 171-173 degrees centigrade.

Dr. Eliel concludes from this information that since racemic BCH-189 has a higher melting point than either its (+)- or (-)-enantiomer, BCH-189 is not a conglomerate, but instead a true racemic compound. Since racemic BCH-189 is not a conglomerate, its enantiomers cannot be separated by spontaneous resolution.

4.4.3 Mechanical separation of crystals

Mechanical separation of crystals refers to the physical process of picking apart macroscopic crystals of separate enantiomers. This technique can only be used if crystals of the separate enantiomers exist (i.e., the material is a conglomerate). As indicated in the attached Declaration of Dr. Ernest

Eliel (D1), BCH-189 cannot be mechanically separated into crystals of separated enantiomers because BCH-189 does not crystallize as a conglomerate; it crystallizes as a racemic compound.

4.4.4 Enzymatic processes

Patent offices around the world, including the European Patent Office and the U.S. Patent Office, have issued patents covering the use of enzymes in organic transformations, showing that the selection of enzymes for this purpose can be inventive. If all enzymatic techniques were routine and noninventive, then all of these patents would be invalid for claiming routine, nonpatentable subject matter.

In fact, one cannot predict whether an enzyme will act on a given substrate, or will preferentially catalyze a reaction in one enantiomer of a racemic mixture, until the reaction is actually carried out. This is because subtle differences in the chemical structure or electronic environment of the substrate can have a very substantial effect on the ability of the enzyme to catalyze the desired reaction.

Professor Schneider indicates in his Declaration that because of his expertise in enzymes, scientists and pharmaceutical companies contact him for advice on the use of enzymes in organic transformations. Although he can suggest possible enzymatic transformations to a client, he can never with confidence assure the client that his suggestions will work, and he advises the client that it is a research project. He screens sometimes up to a hundred enzymes for a given procedure before identifying which enzymes, if any, are appropriate candidates for further research on the project.

As Professor Schneider also indicates in his Declaration, in order for a particular enzyme to be effective as a tool to resolve a racemic mixture of a compound, two requirements must be met: (i) the enzyme must be able to catalyze the desired reaction of the compound (i.e., the compound must be a substrate for the enzyme); and (ii) if the first requirement is met, then

the enzyme must catalyze the reaction in an enantioselective or "chiral" manner (i.e., it must catalyze the reaction of one enantiomer preferentially over the other enantiomer).

Positions taken by BioChem Pharma on Enzymatic Processes

BioChem Pharma is well aware of this phenomenon. It is BioChem Pharma's position that it would have been routine to obtain (*cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane), an 1,3-oxathiolane nucleoside, substantially in the form of a single enantiomer in 1989-1990. During patent prosecution, BioChem Pharma has also, however, taken the position that 1,3-oxathiolane nucleosides are inventive over 1,3-dioxolane nucleosides for the use to treat HIV infections, as a means to establish the patentability of the claimed subject matter in EPO '526 over the cited prior art (EPO 337 713) (see letter to the European Patent Office dated April 23, 1993). As Professor Schneider points out, at least with respect to enzymes, this position is illogical. It is known that synthetic nucleosides exhibit their activity against the human immunodeficiency virus through their interaction with enzymes, and in particular, reverse transcriptase and DNA polymerase, typically after activation (phosphorylation) by kinase enzymes. By taking the position that 1,3-oxathiolane nucleosides are inventive over 1,3-dioxolane nucleosides for the use to treat HIV infections, BioChem Pharma is implying that it is unobvious how a change in one atom in a synthetic nucleoside (oxygen to sulfur in the pseudo-sugar portion of the nucleoside) affects the interaction of the molecule with these enzymes. The corollary to this, however, is as stated above, that one cannot predict whether an enzyme will act on a given substrate based on literature precedent or personal experience with other substrates. It is a matter to be tested.

BioChem Pharma cannot have it both ways. If it argues that the state of the art is such that one of ordinary skill would predict that a selected enzyme would resolve BCH-189, notwithstanding the fact that the reaction has never been carried out on that substrate, then it follows that EP '526

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lacks an inventive step over EPA 337 713.[1]

At least two articles have been published describing the resolution of BCH-189 using enzymes:

(i) Mahmoudian et al., "Enzymatic production of optically pure (2'R-cis)-2'-deoxy-3'-thiacytidine (3TC,Lamivudine): A potent anti-HIV agent," Enzyme Microb. Technol., September 1993, vol 15., 749-755, published by Glaxo Group Research Ltd. (D14); and

(ii) Storer et al., "The Resolution and Absolute Stereochemistry of the Enantiomers of cis-l-[2-(Hydroxymethyl)-1,3-Oxathiolan-5-yl)cytosine (BCH-189): Equipotent Anti-HIV Agents." Nucleosides and Nucleotides, 12(2), 225-236 (1993) (D15).

Neither of these articles formed part of the state of the art on either February 8, 1989, or February 8, 1990. Notwithstanding their publication date, which is later than the priority date of the '526 specification, discussion of certain aspects of these articles is desirable. The Storer article reports that separation of the enantiomers of BCH-189 was first achieved by Glaxo employees using preparative chiral high-pressure liquid chromatography prior to obtaining the compounds enzymatically.

D15 (Storer) reports that chiral HPLC did not allow access to sufficient material for a definitive stereochemical assignment to be made, and thus the enantiospecific hydrolysis of the 5'-monophosphate was investigated using 5'-ribonucleotide phosphohydrolase. Storer cites two prior publications regarding the use of 5'-ribonucleotide phosphohydrolase (Herdewijn et al., J. Med. Chem., 1985, 28, 1385-1386 (D16); Borthwick, J. Chem. Soc. Chem. Commun. 1988, 656-658 (D17)), and admits, at page 226, that:

> *"the scope of this procedure has now been further extended by its successful application in the resolution of the*

[1]It would also follow from this argument that U.S. Patent No. 5,047,407 would be considered invalid over U.S. Patent No. 5,041,449 under 35 U.S.C. Section 103.

enantiomers of [BCH-189]."

Herdewijn describes the resolution of aristomycin enantiomers, which are purine nucleosides, not pyrimidine nucleosides, and Bothwick describes the enzymatic resolution of carbocyclic 2'-ara-fluoroguanosine.

Mahmoudian reports that chiral HPLC was not amenable to scale up and that therefore the use of cytidine deaminase, which had not been used widely for preparative transformations, was investigated as a resolution tool. Mahmoudian indicates that adenosine deaminase had been used on a few isolated occasions to resolve chemically unrelated nucleosides, and that cytidine deaminase had been used in a synthetic scheme to deaminate 1-β-D-arabino-furanosylcytosine. Importantly, Mahmoudian states, at page 754, that:

> "*Our finding that E. coli cytidine deaminase can deaminate racemic [BCH-189] extends the understanding of the specificity of this enzyme*"

In this connection, it is important to note that cytidine deaminase was apparently not even commercially available at the priority date of the '526 application.

Importantly, inventors on behalf of BioChem Pharma clearly perceived that the methods to obtain the enantiomers of BCH-189 with enzymes generally were inventive enough (ie not routine and/or not performed using the basic knowledge of one skilled in the art) to warrant a patent application (see WO 91/17159 (D18) that claimed this method (see Claims 15-18). Of course, the racemate had been part of the state of the art since its February 1989 filing. Presentation of such claims in D18 is totally inconsistent with any argument that the patent application resulting in the opposed '526 Patent did not need to disclose how to separate the enantiomers using these enzymatic techniques because such techniques were such a conventional part of the state of the art in early 1989. The attempt to claim the process

of obtaining the enantiomers of BCH-189 using enzymatic methods in general in D18 shows that BioChem Pharma considered the application of the technique to BCH-189 to be new and inventive in May 1990.

Work of Dr. Secrist

Dr. Secrist (D8), in the mid 1980's spent significant time over several years looking for a way to resolve the racemic mixture of certain carbocyclic nucleosides with no success. A "carbocyclic nucleoside" is a non-naturally occurring nucleoside that does not have a heteroatom in the ring of the sugar portion of the nucleoside.

Dr. Secrist and his coworkers found that that adenosine deaminase recognized the two carbocyclic nucleosides as substrates for the enzyme, although it acted on these compounds at a slower rate than it acted on adenosine itself, indicating that the synthetic substrates did not "fit" into the active site as efficiently as adenosine. It deaminated the D-enantiomer of both carbocyclic nucleosides preferentially. However, if the racemic substrate was exposed to high concentrations of enzyme or to the enzyme for prolonged periods of time, the L-enantiomer was also deaminated. Therefore, the degree of resolution was determined by the length of time that the substrate was exposed to the enzyme and the concentration of the enzyme. At high concentrations or enzyme or long periods of exposure both enantiomers are deaminated and the product is a racemate.

If the resolution of synthetic nucleosides had been routine to an averagely skilled noninventive worker, it would not have taken Dr. Secrist, an expert in nucleosides, as long as it did over several years to identify a successful route to resolve the racemic mixture of these carbocyclic nucleosides.

Experimental work on enzymes by Dr. Liotta

Enzymatic resolution can be used to prepare enantiomerically enriched

BCH-189 only as one step in the total synthesis of the compound. Following extensive laboratory work, it was discovered not only that it matters which enzyme is used with which substrate and under which conditions, but also that it matters at which point in the overall synthetic scheme the enzyme is used. None of this work was trivial; in fact, it was the subject of an article by Hoong printed in J. Org. Chem. (1992) 57, 5563 (D19).

In that article, on page 5563, it is stated that:-

> "*initial attempts to resolve the enantiomers [of β-BCH-189] by either classical techniques or enantioselective synthesis were unsuccessful...Formation of chiral salts between various nucleoside derivatives and camphorsulfonic acid or tartaric acid derivatives was examined, but no detectable enrichment was observed in repeated attempts at crystallization. Efforts directed at enantioselective synthesis were thwarted by racemization during a crucial step involving the formation of the nucleoside via a tin-mediated coupling reaction between acetate 7 and the pyrimidine base*"

As is discussed in detail in D6, Dr. Liotta, with the help of three postdoctoral fellows and one graduate student, spent months investigating a route to obtain enantiomerically enriched BCH-189 that incorporated the use of enzymes as one step in the scheme.

The only enzymatic approach which was successful in this area when tin chloride is used as the condensing agent was the one in which one of the three identified enzymes was used in Route B, after condensation of the oxathiolane with the cytosine base.

It is important to note that it was apparently discovered by workers at BioChem Pharma that if a silicon-based Lewis acid is used to condense the sugar with the base (instead of a tin-based Lewis acid), the 1,3-oxathiolane

enantiomer is not racemized during the condensation step in preparing the nucleoside. This peculiarity in itself is evidence of undue experimentation required to obtain enantiomerically enriched BCH-189, and is the subject of a patent application filed by BioChem Pharma in 1991, which provides a priority date for European Patent Application No. 92304551.2 (D20).

4.4.5 Chiral Auxiliaries

As indicated in D6, when faced with the problems of resolving BCH-189, Dr. Liotta chose this classical method as one of the initial routes for experimentation.

Under Dr. Liotta's supervision, diastereomeric salts of BCH-189 were prepared. None of the attempts to effectively resolve BCH-189 by the separation of these diastereomeric derivatives of BCH-189 was successful.

In this context, the Opposition Division's attention is again drawn to the Hoong paper (D19), in which it is stated that formation of chiral salts between various nucleoside derivatives and camphorsulfonic acid or tartaric acid derivatives was examined, but no detectable enrichment was observed in repeated attempts at crystallization (footnote 2).

In an alternative procedure, chiral derivatives of 2-hydroxymethyl-5-oxo-1,3-oxathiolane were prepared.

None of the attempts to effectively separate these diastereomeric precursors of BCH-189 was successful.

On May 21, 1991, Mansour et al., filed U.S.S.N 07/703,379 directed to a "Process for the diastereoselective synthesis of nucleosides." A counterpart was filed by BioChem Pharma, the assignee, on May 20, 1992 in Europe as European Patent Application No. 92304551.2 (D20). This process is the only publication of which the Opponent is aware that indicates the successful use of a chiral reagent to obtain the enantiomers of BCH-189. The claimed process includes preparing a 1,3-oxathiolane moiety (the sugar

portion of the molecule), preparing diastereomers of the racemic 1,3-oxathiolane (as opposed to the nucleoside) by covalent bonding to a chiral auxiliary, resolving the diastereomers by chromatography, and then condensing the resolved 1,3-oxathiolane with a silicon-based Lewis acid to obtain the desired enantiomer. The fact that BioChem Pharma filed a 1991 patent application on the only published successful process to make enantiomerically enriched BCH-189 using a chiral auxiliary indicates that it considered the process both new and inventive (ie not routine and/or not performed using the basic knowledge of one skilled in the art) in 1991.

4.4.6 Asymmetric Synthesis

Asymmetric synthesis refers to the synthesis of an enantiomer (a chiral substance) from a chiral precursor using a reaction that induces asymmetry (i.e. chirality). The Opponent is not aware of any publication prior to or after the priority date of the present application that reports a successful use of this technique to obtain the enantiomers of BCH-189.

Dr. Liotta has attempted this method to obtain the enantiomers of BCH-189 and failed. Professor Davies, who reviewed Dr. Liotta's protocol, concluded that this experiment, as well as those described below in the sections which discuss equilibration of diastereomers and kinetic resolution, were well designed and adequately performed.

N,N-Dibenzyl-L-alanine is a chiral reagent that has been studied extensively for its ability to influence asymmetric induction when it is fairly remote from the stereogenic carbon of interest. Since this approach appeared to be a generally applicable, well studied, process with a likelihood of success, attempts were made to utilize the stereodirecting effect of this group in the asymmetric synthesis of BCH-189.

Dr. Liotta postulated that if a pre-existing stereocenter containing the N,N-dibenzyl moiety were incorporated into the starting material for the 1,3-oxathiolane component, one could effect a stereoselective ring closure to make an enantiomerically enriched 1,3-oxathiolane which might retain that

stereochemistry on condensation with a base in the presence of $SnCl_4$, thereby giving enantiomerically-enriched BCH-189.

To make the oxathiolane ring, as described in the present application, a glycoaldehyde having the formula OHC-CH_2-OR, wherein R is the protecting group, is added to thioglycolic acid to form a lactone of the formula 2-(R-oxy)-methyl-5-oxo-1,3-oxathiolane. Dr. Liotta attempted to use N,N-dibenzyl-L-alanine as a chiral R protecting group in this reaction. To achieve this, they attempted to react N,N-dibenzylamino-L-alanine with α-hydroxyacetaldehyde to provide OHC-CH_2-OR, wherein R is the residue of N,N-dibenzyl L-alanine. All attempts to achieve success with this reaction failed, and the project was abandoned.

The second approach was to convert the 5'-OH group of an intact 1,3-oxathiolane ring into its corresponding α-N,N-dibenzylamino ester according to synthesis outlined in Scheme II attached to this Declaration, and then react that ester with cytosine in the presence of $SnCl_4$ in the hope that one of the diastereomers of the ester would react preferentially over the other, providing enantiomerically enriched BCH-189. This approach did not work, apparently because the two diastereomers of the α-N,N-dibenzylamino ester of the 1,3-oxathiolane derivative react equally well with cytosine in the presence of $SnCl_4$, and thus there is no equilibration of an intermediate or transition state that favors one enantiomer over the other.

4.4.7 Equilibration of Diastereomers

In this method, components of diastereomeric mixtures, such as those formed in resolutions, are equilibrated. When equilibration is rapid, mixtures are obtained that reflect the relative thermodynamic stability of the diastereomers.

The Opponent is again not aware of any publication prior to or after the priority date of EP '526 that reports a successful use of this technique to obtain the enantiomers of BCH-189.

Dr. Liotta's group has attempted to obtain enantiomerically enriched β-BCH-189 using this method and failed (see D6).

Specifically, in the synthesis of BCH-189, as described in the present application, $SnCl_4$ can be used as a coupling agent to attach the cytosine base to the 1,3-oxathiolane moiety. It has been observed, however, that when $SnCl_4$ is used, the 1,3-oxathiolane goes through a rapid ring opening and closure through an oxonium ion intermediate. Theoretically, the 1,3-oxathiolane can close to form a racemic material, or can close to form an enantiomerically enriched material if the closure mechanism favors one enantiomer over the other. Equilibration of diastereomers of BCH-189 can be attempted under these conditions by placing a chiral group in the 5'-position of the oxathiolane. In the coupling reaction of the now chiral 1,3-oxathiolane with cytosine in the presence of $SnCl_4$, if one diastereomer is preferred over the other, that would be exhibited as an enantiomerically enriched product.

Under Dr. Liotta's direction, this process was attempted using N,N-dibenzylamino-l-alanine as the chiral 5'-oxygen protecting group, and found no enantiomeric enrichment on equilibration of the diastereomers after rapid ring opening and closure using $SnCl_4$. This experiment indicates that these diastereomers of BCH-189 exhibit relatively equal thermodynamic stability, and thus cannot be equilibrated to form enantiomerically enriched BCH-189.

4.4.8 Kinetic Resolution

Kinetic resolution refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, nonracemic agent (reagent, catalyst, or enzyme) under kinetic (as opposed to thermodynamic) conditions.

The only type of kinetic resolution that has been reported to date on nucleosides of the type in issue is enzymatic resolution, which has been

addressed above. Article 83 EPC is not satisfied if a person of ordinary skill in the art is forced to design a totally new method of kinetic resolution of nucleosides using specially selected reagents or catalysts to obtain a claimed compound. The steps in accomplishing this would have to include planning a new reaction, choosing a chiral, non-racemic agent to accomplish the reaction that takes place at different rates among the two enantiomers, determining the appropriate reaction conditions, and testing it to see if the reaction actually works.

Drs. Liotta and Hagar have developed a process for the preparation of 3'-substituted-2',3'-dideoxynucleosides and 2'-deoxynucleosides (not 1,3-oxathiolane nucleosides) from acyclic, achiral precursors which involves an asymmetric epoxidation step which could be considered a type of kinetic resolution of a precursor in the synthesis of a nucleoside. The U.S. Patent and Trademark Office awarded a patent on this invention in July 1995 (U.S. Patent No. 5,432,273, D21).

Dr. Liotta's group also attempted to obtain the enantiomers of BCH-189 using kinetic resolution other than enzymatic resolution using the reaction scheme set out in Schemes II and III described in D6, in which the ratios of reactants were manipulated to see if one enantiomer reacts preferentially over the other under kinetic conditions.

Specifically, they utilized the reaction schemes set out in Schemes II and III and manipulated the ratios of reactants to see if one enantiomer reacts preferentially over the other under kinetic conditions.

Exhaustive benzylation of L-alanine followed by LiOH hydrolysis gave the N,N-dibenzyl amino acid **2**. In a one-pot procedure, the mixed anhydride of the amino acid was generated and then treated with the TBDPS-protected thialactone **3**, followed by TAF, in the presence of a catalytic amount of DMAP, to give the ester **4**. To determine if any kinetic resolution was occurring in the conversion from **2** to **4**, two different reaction conditions were tried. In the first, the ratio of acid **2** to the lactone

3 was 1.5:1 while in the second, the ratio was reversed to 0.5:1. If one enantiomer of 3 reacted faster under kinetic conditions than the other enantiomer, enantiomerically enriched 7 would be produced in the second reaction, and the ratio of enantiomers in the first reaction and the second reaction would be different. In fact, both reaction conditions gave the same 1:1 mixture of diastereomers as products, indicating that one enantiomer does not react preferentially over the other, and no kinetic resolution occurs.

The lactone was then reduced with $LiAl(tBuO)_3H$ and the lactol intermediate was trapped with acetic anhydride *in situ* to give the acetate 5 (Scheme III), which was subsequently coupled with the appropriate silylated cytosine in the presence of $SnCl_4$. Hydrolysis of 6 (Scheme III) with NaOMe in MeOH gave the indicated thiadeoxycytidene 7. The β-isomer crystallized out selectively and HPLC analysis using chiralpak AS with hexanes and isopropanol as eluant showed a racemic mixture, indicating that no kinetic resolution occurred in the course of the reaction.

In summary, using a standard, well accepted technique, the two enantiomers of BCH-189 did not exhibit unequal reaction rates under kinetic conditions.

4.4.9 Stereospecific synthesis from chiral precursors

Stereospecific syntheses from chiral precursors are typically sophisticated, tedious, and involve multiple and lengthy steps.

Dr. David Chu (Chung K. Chu) specialises in the stereospecific synthesis of nucleosides from chiral precursors. His experience confirms that stereospecific synthesis of nucleosides typically takes a long time to accomplish, often includes failure, and requires that a significant number of independent synthetic steps be designed, tested, and often modified (see D9).

Their first synthesis was an asymmetric process for the preparation of enantiomerically pure β-D-(-)-dioxolane-nucleosides. The process involves the initial preparation of (2R,4R)-and (2R,4S)-4-acetoxy-2-(protected-oxymethyl)-dioxolane from 1,6-anhydromannose, a sugar that contains all of the necessary stereochemistry for the final product, including the correct diastereomeric configuration about the 1 position of the sugar (that becomes the 4'-position in the later formed nucleoside). The (2R,4R)- and (2R,4S)-4-acetoxy-2-(protected-oxymethyl)-dioxolane is condensed with a desired heterocyclic base in the presence of trimethylsilyl triflate in an organic solvent to provide the stereochemically pure dioxolane-nucleoside.

The experimental work to complete this synthetic protocol took several person-months and involved approximately twelve steps.

This process was awarded a patent in 1993 (U.S. Patent No. 5,149,104).

They also worked out the synthetic protocol for a stereoselective process for the production of β-L-1,3-oxathiolane-nucleosides. The scheme involved the initial preparation of the key chiral intermediate 2R,5(4,S)-5-(O-protected)-2-(protected-oxymethyl)-1,3-oxathiolane from 1,6-thionanhydro-L-gulose, a sugar that has the required stereochemistry for the production of the β-L-(-)-1,3-oxathiolane nucleoside, including the correct diastereomeric configuration about the 2 position of the sugar (that becomes the 4'-position in the later formed nucleoside). 1,6-Thioanhydro-L-gulose was prepared from L-gulose. The 2R, 5(R,S)-5-(O-protected)-2-(protected-oxymethyl)-1,3-oxathiolane was condensed with a desired heterocyclic base in the presence of $SnCl_4$, other Lewis acid, or trimethylsilyl triflate in an organic solvent to provide the β-L-(-)-1,3-oxathiolane-nucleoside.

The total process involved approximately nine steps to make enantiomerically pure β-L-(-)-1,3-oxathiolane-nucleoside, and took experienced researchers again a number of person-months to complete.

A patent was awarded on this process in 1993 (U.S. Patent No. 5,248,776).

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Dr Chu's experimental work to complete a synthetic protocol in relation to dioxalane and oxathiolane nucleosides took several person-months and involved multiple steps. His processes were awarded US patents in 1993 (U.S. Patent Nos. 5,149,104 (D22) and 5,248,776 (D23) and therefore cannot be regarded as routine and/or performed using the basic knowledge of one skilled in the art.

4.4.10 Chiral (Enantioselective) Chromatography

Chromatography is a technique whereby a mobile phase with a material to be separated is forced past an immobilized phase in a column. The separation of the components of the material is possible if the componentssss equilabrate in different ratios between the mobile phase and the immobilized phase. In classical chromatography, both the mobile phase and the immobilized phase are "achiral," they do not possess handedness. In chiral chromatography, the immobilized phase is chiral, in that it is prepared from one enantiomer of a racemate. The chiral compounds in the immobile phase thus have a directional orientation in space that may bind one enantiomer of a racemate more tightly than the other if there is complementary geometry and polarity.

There were chiral columns available for purchase in the 1980's. However, nucleoside chemists did not **routinely** resort to chiral chromatography in this period because there was no way to predict which column would work. One could end up with a large number of expensive, ineffective chiral columns sitting on the shelf, and no resolution. This was exacerbated by the fact that, as stated in Appendix I to the Observation, on February 8, 1989, or February 1, 1990, Dr Pirkle (and much less one of ordinary skill) could not have known, prior to actually carrying out a procedure, which chiral stationary phase, if any, would suffice to separate a given pair of enantiomers such as that in BCH-189.

Dr. Pirkle evaluated the ability of a series of fifteen HPLC columns containing chiral stationary phases to separate the enantiomers of a

crystalline sample of racemic BCH-189 which was prepared for him under the direction of Dr. Liotta.

The columns employed were from commercial sources and, so far as he was aware, commercially available in 1989.

He approached these attempts at separation in the manner which he believed would be typical of someone who was trying to find a column in 1989 which would resolve BCH-189. He employed conditions suggested by the manufacturers of the various columns.

The columns were:

1) A Daicel Chiracel OD; Lot No. 506-023-40624
2) A Regis Pirkle Covalent D-Phenylglycine; Code No. 733021, Ser. No. 100011
3) A Regis Pirkle Type 1A; Code No. 731020; Serial No. 100100
4) An Astec Cyclobond II; Cat No. 41020; Serial No. 8327
5) An Astec Cyclobond III; Cat. No. 42030; Serial No. 8306
6) A Serva Chiral D-DPG=Si100; Cat. No. Z 42078; Serial No. 02105
7) A Serva Chiral D-DL=Daltosil 100; Cat. No. Sonderanf. Serial No. 16038
8) A Regis Pirkle Covalent D-Naphthylalanine; Code No. 731031; Serial No. 10049
9) A Sumipax OA-2000; No. B-02-03
10) A Sumipax OA-1000; No. B-02-07
11) A Bakerbond DNBLeu Lot No. 43-RD-71-2E
12) A Merck Cellulose Triacetate column; Cat. 50003
13) An Astec Cyclobond I-Beta Cat. No. 41010; Serial No. 8260
14) A Regis Pirkle Covalent L-Leucine; Code No. 731041; Serial No. 100032
15) A Serva Chiral D-DL=Daltosil 100; Cat. No. Sonderanf. Serial No. 24115

Of these, columns 7, 11, 14, and 15 are different manufacturer's variations of the same chiral stationary phase and there are differences in performance. The same may be said for columns 2, 6, and 9.

Chiral columns 1-11 failed to resolve BCH-189 under the standard conditions suggested for each type column. Thus fully 73% of the chiral columns attempted did not work under the conditions employed (typically the manufacturer's suggested conditions or a manipulation of these).

Columns 12-14 were able to resolve BCH-189. Column 15 provided a partial separation of BCH-189.

Specifically, using mobile phases similar to those suggested by the manufacturers, only three types of chiral stationary phases afforded clear separation of the enantiomers of racemic BCH-189. These are the Merck cellulose triacetate column, 12, the covalent 3,5-dinitrobenzoylleucine type (the Regis column, 14, affording the best result of the four columns of this type), and the Cyclobond I-Beta, column 13.

The Cyclobond phases are known to overload readily and while column 13 affords reasonably good performance at the analytical level, its performance drops seriously when 20 μl of an ethanol solution containing ca. 3.3 μg/μl of racemic BCH-189 is injected.

None of the other columns tested gave any indication of enantiomer separation, the criterion being indication of a valley between two equal area peaks. The sample sizes employed were quite small. Typically, one or two μl of ethanol containing approximately 3.3 μg/μl of racemic BCH-189 was injected onto the columns. Small samples avoid column overload and afford one a better opportunity for detecting enantiomer separation.

Some of the columns which ultimately proved to differentiate between the enantiomers of BCH-189 did not do so under the conditions initially employed. For example, the literature which accompanies the Cyclobond columns mentions the use of 1:1 methanol/water and 30:70 acetonitrile/water as mobile phases. These mobile phases fail to afford indication of BCH-189 enantiomer separation as they cause very early elution of BCH-189. Indeed, it required some experimentation to find that reducing the methanol concentration to 10% in water increases retention

and causes column 13 to separate the enantiomers of BCH-189. This was not predictable because these conditions do not lead to success on the other Cyclobond columns. Interestingly, the Bakerbond column, 11, gives no indication of separating the enantiomers of BCH-189 under conditions which suffice, to varying degrees, for counterpart columns prepared by other manufacturers.

Clearly, the manufacturer, as well as the type of chiral selector, and the conditions employed, can make the difference between success and failure in chromatographically separating the enantiomers of BCH-189.

The Opposition Division's attention is directed to the fact that BioChem Pharma actually claimed the method of separating the enantiomers of BCH-189 in D18 using chiral chromatography generally (see claims 13 and 14). Thus Biochem Pharma clearly considered that this process was inventive in 1990, and therefore not routine and/or performed using the basic knowledge of one skilled in the art, in 1989.

4.4.11 Summary of approaches to obtain the enantiomers of BCH-189 in 1989-1990

In summary, as discussed above, a person skilled in the art would have be forced to chose between at least nine techniques which were available to attempt to obtain the enantiomers of BCH-189 in February 1989 or February 1990. Most of these had multiple variable components, reagents, and conditions to select from, each component, reagent or variable of which could easily change the result. Most of the available techniques simply did not work. Others worked but only using specific, unpredictable, pathways, which had to be explored using non-routine effort. All of the methods that have now been identified as eventually successful have been the subject of patents or patent applications, filed by a number of entities, including BioChem Pharma, and therefore considered by the patent office (or by the applicant) to be inventive.

With reference to the established case law of the Technical Board of

Appeal, summarised at Section 3.4 above, the noninventive routinely skilled person should not have been expected to undertake this unreasonable amount of experimentation and/or to make an inventive contribution to obtain the enantiomers of BCH-189.

4.4.12 Conclusion

EP '526 did not place the isolated enantiomers of BCH-189 in the hands of the public. The amount of trial and error that it would have taken the noninventive routinely skilled person with the '526 specification in hand in 1989-1990 to obtain this claimed subject matter demands a conclusion that the '526 specification is not enabling for that subject matter. To conclude otherwise ignores historical facts, and grossly underestimates the hard work required by ordinary scientists in the field to obtain the claimed subject matter. **The amount of work required of the public to obtain the enantiomers of BCH-189 simply does not justify granting a monopoly interest to BioChem Pharma on this subject matter.**

The patent is therefore invalid under Article 100(b) EPC, to the extent that it covers individual optical isomers and enantiomerically-enriched mixtures thereof, because it does not disclose this aspect of the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

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4.5 Response to July 19, 1995 Letter from Biochem Pharma to the European Patent Office regarding Emory's Article 115 Observations

As described in Section 3.2, Observations under Article 115 were filed on 19 January 1995 by Emory University in connection with the application leading to the opposed granted specification. These observations were responded to by the Opponents in a letter dated 19 July 1995. Opponent now comments on BioChem Pharma's response.

4.5.1 General Remarks and Additional Historical Background

In responding to the Observations, BioChem Pharma takes the position that the separation of optical isomers of cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane would have presented no difficulty to a person of skill in the art, who would have readily effected the separation using standard techniques without an undue burden of experimentation (Section I.). This position has been more than adequately addressed above.

4.5.2 Comments on Section I. A(ii)

BioChem Pharma asserted in Section I. A(ii) of the July 1995 letter that:

> "... *separations of enantiomers have been carried out by chemists on a routine basis for decades.*"

Separations have indeed been carried out by chemists in the past, and in fact, have been the subject of numerous patents in Europe and internationally, which is evidence that such techniques are not always routine. As Dr. Eliel has correctly pointed out in his Declaration, the disclosure of a racemic compound is not always tantamount to a disclosure of the separated enantiomers. Each situation must be considered on its own facts.

BioChem Pharma also stated that:

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> *"....it is important to note that nowhere in the [third party] Observations is there any allegation that known methods for separating enantiomers do not work for separating the (+) and (-) enantiomers of cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane. In fact such an allegation could not have been validly made because known methods do work."*

As discussed above, whether or not "known methods do or do not work" is not the test to be applied in establishing whether or not a patent specification provides an enabling disclosure to the noninventive routinely skilled reader. The test to be applied is whether a reader has to exercise more than his "common general knowledge at his immediate disposal" (T206/83) in separating the enantiomers. We have clearly demonstrated above that, to obtain the enantiomers of BCH-189 in 1989-1990, more than common general knowledge was required.

4.5.3 BioChem Pharma's assertion that "In 1989, Chiral HPLC was the separation procedure of choice for separating optical isomers" (Section III).

In the July 1995 letter, BioChem Pharma asserted that "In 1989, Chiral HPLC was the separation procedure of choice for separating optical isomers" (Section III). Biochem Pharma did not present evidence from a single nucleoside chemist in support of the allegation that chiral chromatography would have been the first choice, or indeed any choice.

Biochem Pharma's statement is surprising in view of the fact that chiral chromatography is not specifically referred to in either the text of EP '526 itself or either of the textbooks specifically mentioned therein as disclosing "suitable methods" for obtaining the enantiomers of BCH-189.

As indicated in the Declaration of Dr. Eliel, on the contrary, on page 47 of his book, he states that:

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> *Of the several methods of resolution which will be described in this section, only resolution via conversion to diastereomers (Sec. 4-4b) and resolution by biochemical methods (Sec. 4-4e) are generally useful. The other methods are included mainly because of their considerable theoretical interest.*

Dr. Eliel's book mentions chromatography only in a very brief manner on pages 61-62, as no enantioselective (chiral) columns were commercially available in 1962. Dr. Eliel concludes that:

> "*BioChem Pharma frankly could not have been seeking to use these texts to teach the public that the preferred method of obtaining the enantiomers of BCH-189 would have been by enantioselective chromatography, because they did not. The text of EPO '526 directly preceding the reference to my book (see Paragraph 10) also did not refer to enantioselective (chiral) chromatography. Therefore, I am left with the conclusion that in 1989, enantioselective (chiral) chromatography was not BioChem Pharma's method of choice.*"

Moreover, BioChem Pharma's statement is contrary to the experience of Opponent's Declarants. Dr. Eliel did not have any experience with enantioselective (chiral) chromatography in 1989-1990. The main reason for his reluctance to use such columns was that, at least in the late 1980's their efficiency was unpredictable and largely hit or miss. Therefore it was necessary to have several expensive columns on hand, and try them all, without any guarantee of success. Professor Davies states that in 1989-1990, not only was chiral chromatography not his method of choice for obtaining enantiomers, at that point in time he had not owned or used a chiral stationary phase column. He simply was not convinced that the technique was sufficiently predictable or general in 1989-1990 to warrant the commitment of his time and resources. According to Dr. Chu's recollection, in 1989, he was not aware of any chemists who had reported or discussed the use of chiral column chromatography in connection with the preparation of synthetic nucleosides. He had been involved in the

stereoselective synthesis of nucleosides since the mid-1980s. Dr. Chu states that the technique of chiral column chromatography would not have been his procedure of choice in 1989. In fact, at that time he had never used chiral chromatography to obtain the enantiomer of a nucleoside. It was not Dr. Holy's method of choice. During his thirty-four years of experience in the preparation of synthetic nucleosides, other than one limited observation in 1976, he had never owned, used or even borrowed a chiral column. Other than one limited experience in the 1970's, Professor Schneider did not use chiral chromatography until 1991-1992, when he purchased his first column.

Experience at Southern Research Institute with Chiral Chromatography

Anita Shortnacy-Fowler, working under the direction of Drs. Secrist and Montgomery, both pioneers in nucleoside chemistry, well illustrated the experience of a nucleoside chemist who did actually try to use chiral chromatography to separate the enantiomers of a nucleoside and repeatedly failed.

When they first attempted "chiral" HPLC techniques to separate enantiomers of folic acid derivatives, they used chiral additives in the mobile phase which were passed through a conventional (i.e. achiral) reverse phase HPLC system. They typically used additives such as cupric acetate and a mixture of α-, β- and γ-cyclodextrins. Although the action of the chiral additives was not completely understood at the time, the theory was that they facilitated a preferential interaction between one of the enantiomers and the stationary phase, thus enabling a separation of the enantiomers. However, they were never able to separate enantiomers using these techniques. The high background noise of the chiral additives obscured any separation of enantiomers that may have occurred.

In 1987, they attempted to separate the enantiomers of a racemate of a pteridine derivative (which is not a nucleoside) using chiral stationary phase

chromatography. They had never used a chiral column before. Because these columns were unfamiliar and quite expensive to them, they began to assemble industrial pamphlets and conduct literature searches on available columns to learn more about it. They read the article by Richard Däppin, "Applications and Limitations of Commercially Available Chiral Stationary Phases of High Pressure Liquid Chromatography" in J. Chrom. **373**, 1, (1986) before making their decision about which columns to buy.

In all, they ordered four chiral columns to attempt this resolution; Cyclobond II (γ-cyclodextrin), Chirocel OB (cellulose triacetate), Enantiopac (α-glycoprotein), and Resolvosil (bovine serum albumin).

They found that of the four columns, they were able to separate the enantiomers of the pteridine on the Enantiopac and Resolvosil columns.

The Chiralcel OB column was purchased from J.T. Baker in 1987 after close consultation with the company's technical representative. Prior to making the purchase, they had been assured by the representative that the column was recommended for this separation by the company's outside HPLC consultant, Irving W. Wainer. This column, however, did not separate the enantiomers of the pteridine. In fact, they have never achieved a successful resolution of their compounds using this column.

In April 1992, Ms. Shortnacy-Fowler received a request to attempt to separate the enantiomers of a synthetic nucleoside, D,L-2'-carbocyclic-deoxyguanosine (D,L-2'-CDG) by chiral stationary phase chromatography. This was the first time anyone had asked her to attempt to resolve the enantiomers of a racemic nucleoside using this technique.

They first attempted to use the four columns referred to above to separate the enantiomers of this synthetic nucleoside. Although two of the columns had been able to distinguish between the enantiomers of the pteridine derivative, the columns were not able to achieve a separation of the enantiomers of D,L-2'-CDG on any of these columns. This was the case

after changing such variables as buffer strength, solvent, flow rate and pH, all within the constraints as prescribed by the manufacturer. This process was inevitably long-winded because only one variable could be altered at a time. In fact, the whole process took several months of considerable effort before they decided to give up.

They then reviewed the trade and scientific literature on chiral columns that they had accumulated over the years. They did not obtain any useful information from any of this literature on how to separate the enantiomers of a nucleoside. While the manufacturer's brochures included some suggestions on how to choose a chiral column, none of these suggestions were definite enough to give them any confidence that they could pick the correct column or conditions without experimentation and the purchase of numerous columns until they achieved success. Likewise, the scientific literature that they had already collected did not describe the use of chiral chromatography to separate the enantiomers of a nucleoside, and therefore was not similar enough to what they were asked to do to give us any meaningful assistance. They did not believe that articles on how to separate compounds other than nucleosides would be helpful in directing them to achieve a successful result, because small changes in the chemical structure of a compound could make the difference between success and failure. They did not have any direction on how to proceed.

Moreover, they were cautious in selecting a chiral column because the product information provided by column manufacturers at that time limited the operation of the columns to certain elution systems to prevent destruction of the column. The columns appeared to be to be quite delicate and not versatile. In their opinion, the high cost, delicate nature, and limited operating range of the columns made the choice of a particular column more than a "routine" effort. For these same reasons they would never have loaned a chiral column to others or borrowed a chiral column from anyone else. They would have been concerned that the person who borrowed our column might use a solvent that destroyed the column or

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impaired its effectiveness.

They then went back to the scientific literature in another attempt to obtain guidance. They located an article by Thomas and Surber, (D24), *Preparative separation and analysis of the enantiomers of [^{3}H]Abbott-69992, an HIV-antiinfective nucleoside, by ligand exchange high performance liquid chromatography*, Journal of Chromatography, Vol. 586 (1991) pp. 265-270. The authors, scientists at Abbott Laboratories, a leading pharmaceutical research company, stated that:

"*a thorough search of the literature on chiral chromatography failed to reveal any examples of nucleoside separations.*"

The authors reported that their article appeared to be the first report of the separation of the enantiomers of a nucleoside by chiral high-performance liquid chromatography. This was consistent with the SRI group's inability to identify any specifically relevant articles prior to this time.

The article describes the fact that the Abbott workers tried five types of chiral columns to separate the enantiomers of [^{3}H]Abbott-69992; Nucleosil Chiral-I, Cyclobond I (β-type), Resolvosil, YMC A-KO3, and cellulose triacetate. Of these, only one column out of five, the Nucleosil Chiral-I column was able to separate the enantiomers of this nucleoside. Even then, the authors further noted that attempts to produce "research" and "microgram" amounts of the separated enantiomers resulted in a "poor yield" (Results and Discussion, pages 268-269).

Based on the information in this article, they ordered a Nucleosil Chiral-I column. Of the other four columns mentioned, they had already tried and failed using a Resolvosil column. They would not have ordered a Cyclobond I (β-type), YMC A-KO3, or cellulose triacetate column because the Abbott workers reported that these columns were unable to separate the enantiomers of their nucleoside.

They were unable to achieve any resolution of D,L-2'-CDG using the Nucleosil Chiral-I column, even by altering such variables as buffer strength, solvent, flow rate and pH, all within the constraints as prescribed by the manufacturer. This process was again long-winded because only one variable could be altered at a time.

They then contacted Chiral Technologies, Inc, in Exton Pa., to assist them with this project. Chiral Technologies had just recently begun to offer a service in which, at customer request, it would try to separate the enantiomers of a racemate on a number of its columns.

They sent Chiral Technologies a sample of D,L-2'-CDG. On October 1, 1992, they received a facsimile message from the company informing them that it could not find any columns that could separate their sample. A copy of the letter is attached to Ms. Shortnacy-Fowler's Declaration. Chiral Technologies tried a number of normal and reverse phase chiral columns. The company indicated that a very similar compound, carbovir, was successfully separated on their columns.

Ms. Shortnacy-Fowler concludes in her Declaration that, if a nucleoside chemist of average skill had considered, and then attempted, chiral HPLC at all in 1990, that person would not have considered it to be a "routine" experimental tool for producing separate enantiomers of nucleosides. Despite the fact that she had been working in the area of nucleosides since 1965, as of 1990, because there was lack of direct literature precedent on the use of chiral chromatography, she found the technique difficult and frustrating.

4.5.4 Comments on Section I. A(iii) and A(iv)

Only two pieces of evidence were proferred by BioChem Pharma in its July 1995 letter to support its allegation that one would have selected chiral chromatography to obtain the optical isomers of BCH-189 in 1989-1990. The evidence consists of: (i) an article written by Dr. Pirkle; and (ii) an

"experimental report." These two items are discussed below.

(i) Pirkle Article

Dr. Pirkle published an article in 1987 that summarized a number of chiral stationary phases for use in liquid chromatography: Pirkle, et al., "Chiral Stationary Phases for the Direct LC Separation of Enantiomers," Giddings, J.C., et al., Eds. Marcel Dekker, New York, 1987, Vol. 27, Chapter 3.

BioChem Pharma selectively quoted from this text to support its assertion that in 1989 one would have chosen a cellulose triacetate chiral column to carry out chiral chromatography (because BioChem Pharma determined after it had filed its priority patent application that one could separate the enantiomers of BCH-189 on cellulose triacetate columns). BioChem Pharma apparently ignored the remainder of his paper, which discussed a number of other columns.

In Section IV of the paper, Dr. Pirkle summarized the commercial availability of chiral stationary phases, and in Table 2, did not even mention cellulose triacetate. In fact, according to Dr. Pirkle's Declaration, he had no personal experience with cellulose triacetate columns in 1989-1990. He chose not to use cellulose triacetate columns because, as stated in his paper:

"*Many different types of enantiomers have been separated on TAC, but common denominators between the racemates separable on TAC are not easily found. For that reason, the mechanism(s) of chiral recognition has not yet been established. Hence, prediction of elution order or even the usefulness of TAC in a given case is difficult.*"

page 83-84; and

"*Typically, if a CSP separates the enantiomers of a given compound, it will resolve compounds that are closely related. This generalization does not necessarily extend to CSPs with chiral cavities such as TAC, since a modest change in analyte structure may prevent entry into the cavity.*"

page 118.

Dr. Pirkle also states in his Declaration that it was outside his primary area of interest because:

"his research goal was and is to develop chiral stationary phases

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in a rational manner so that their mode of action might be more easily understood. Cellulose triacetate was developed empirically, its mode of action complex, and even today is not understood."

(ii) Experimental Report.

BioChem Pharma has provided the European Patent Office with a copy of a chromatogram that suggests that BCH-189 was separated on a Combrio-TAC column on July 31, 1989 by "IMM."

a) Dr. Ian M. Mutton

"IMM" refers to Dr. Ian M. Mutton. According to public documents filed with the Australian Patent Office, Mr. Mutton had been employed by Glaxo Wellcome since 1970. In September 1970, he was appointed as a Technical Officer in the Analytical Research Section of Glaxo Laboratories. Between 1970 and 1994, he worked as a Technical Officer, Scientific Officer, and then as a Senior Analyst within the Chromatography Section of the department known as Physical Chemsistry or Structural Chemistry at Glaxo Laboratories. By his own acknowledgement, between 1975 and 1994 his main job at Glaxo was to provide chromatographic analytical data to client chemists.

Mr. Mutton directly assisted in the compilation of a treatise in 1990 entitled *"Chiral Separations"-A Chromatographic Society Literature Survey* I.D. Wilson (ed). A second edition was published in with Mr. Mutton's help in 1992. See Pirkle Declaration, Paragraph 26.

Therefore, far from representing the "noninventive routinely skilled worker," Mr. Mutton had the knowledge of an expert in chiral chromatography at the relevant time.

Dr. Pirkle was invited to tour the separations laboratory and present a talk the Glaxo Laboratories in Greenford, England, where Mr. Mutton was employed, in 1989, after the second International Symposium on Chiral Separations. Dr. Pirkle states in his Declaration that:

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I considered the Chromatography Section at Glaxo Laboratories to be an expert laboratory in chromatographic separations in 1989-1990. The laboratory included scientists who knew more than most analytical or organic chemists about chiral separations. This is evidenced by the fact that scientists in that laboratory contributed to two texts in the area in 1990 and 1992.

During my visit to the Glaxo Labs in 1989, I was shown a number of enantiomeric separations that they were doing by both chiral chromatography and capillary electrophoresis. The group was clearly carrying out these projects at an advanced level, and, in my opinion, a level that few others had yet achieved during this time period. The lab was a reservoir of skill and experience in the separation field. I was quite impressed.

I attach to this Declaration an abstract by R.J. Collicott that indicated that the Chemical Analysis Department at the Glaxo Greenford facility had been performing chiral analyses for at least eight years prior to 1989, and that they had in-house chiral analysis discussion groups during this period.

The separations group of Glaxo Laboratories in 1989 was simply no indication of the routine skill of scientists who did not specialize in chiral chromatography.

b) Analysis of Chromatogram

On review of the Mutton chromatogram provided with the July 1995 letter from BioChem Pharma as well as the specifications of the column size used, Dr. Pirkle concluded that the experiment was carried out on an analytical scale. An analytical separation does not provide any useful information regarding compounds purportedly separated because, by definition, one does not recover the separated compounds in such a procedure. One would not obtain material from an analytical separation, for example, to carry out biological activity or toxicity testing. There was, in fact, no indication iin the July 1995 letter that the enantiomers were collected and characterized in the July 1989 experiment.

At best, an analytical scale separation allows one to determine the relative amounts of the two enantiomers present, but that adds no knew knowledge when one anaylses a racemate (a 1:1 mixture by definition). On review of

the chromatogram, Dr. Pirkle could not establish that the two peaks did not arise from the elution of the enantiomers of BCH-189, nevertheless, he states that the appearance of two peaks on a chromatogram does not rigorously demonstrate that separation of enantiomers has occurred. He goes on to state that:

> **More than one person has been led to report a chromatographic separation of enantiomers when what actually occurred was separation of the nonseparated enantiomers from an impurity.**

4.6 Biochem Pharma cannot rely on hindsight reconstruction to attempt to establish that it was routine to arrive at a certain endpoint.

The truth appears to be that BioChem Pharma never actually separated BCH-189 itself by chiral chromatography in this timeframe or else presumably it would have provided the EPO with evidence **from its own scientists in its own laboratories**, and not evidence from an expert in Glaxo's premier chromatography group.

In considering BioChem Pharma's position, one must ask the following.

(i) If it were so routine to obtain the enantiomers of BCH-189, why wasn't it quickly and easily done and then reported in the February 8, 1989 priority application?

(ii) If it were so routine to obtain the enantiomers of BCH-189, why wasn't it done between February 8, 1989, and the international filing date, February 8, 1990 and then reported in the international application? An assertion that it simply didn't need to be included is quite shallow, given that BioChem Pharma considered BCH-189 to be the most important compound in its portfolio at the time, and the subject of a major licence agreement with Glaxo.

(iii) If "chiral HPLC" were the only obvious choice for the separation of the BCH-189 enantiomers in February 8, 1989 or February 8,

1990, why wasn't the term "chiral HPLC" used in either application?

(iv) Why did the international application refer generally, and inappropriately to two textbooks, instead of easily referring the reader to what BioChem Pharma now refers to the only logical choice? This is especially true in light of the fact that neither textbook referred to by BioChem Pharma in the '526 specification addresses chiral chromatography.

(v) Why did the first disclosure of an enabling method to separate the enantiomers of BCH-189 by BioChem Pharma not occur until fifteen months after the February 8, 1989 filing, and when it did, all of the named inventors were from Glaxo, not BioChem Pharma?

(xi) Why has BioChem Pharma presented claims directed to methods to separate the enantiomers of BCH-189 with chiral chromatography and enzymes generally in patent applications around the world in its May 1990 patent filing?

5 Conclusion

Thus, we have shown that, in the case of BCH-189, resolving methods could only have been devised by the exercising of inventive effort by the routinely skilled worker.

Out of the infinite range of mixtures of the enantiomers of BCH-189 purportedly covered by the claims of EP '526, an enabling disclosure is only provided in respect of one (the racemate).

Based on the evidence and comments provided herein, Opponent requests that European Patent 0 382 526 B1 be revoked to the extent that the claims cover individual optical isomers and enatiomerically-enriched mixtures thereof, as well as associated compositions and uses of these com-

pounds/mixtures. Opponents request that, in the alternative, the claims of EP '526 be limited to racemic mixtures of the disclosed and enabled 1,3-oxathiolane nucleosides and disclosed compositions and uses of these racemates.

6 DOCUMENTS CITED

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D2 Declaration of Prof Davies
D3 US Patent No. 5,047,407
D4 Third Party Observations filed by Emory during prosecution of European Patent Application 90301335.7 which resulted in the opposed Patent
D5 Topics in Stereochemistry (vol 6) by Samuel Wilen (Wiley-Interscience, 1971, Eds NL Allinger and EL Eliel) pages 108 and 109
D6 Declaration of Dr Liotta
D7 Declaration of Dr Schnieder
D8 Declaration of Dr Secrist
D9 Declaration of Dr Chu
D10 Declaration of Dr Pirkle
D11 Declaration of Dr Holy
D12 Declaration of Anita Shortnacy-Fowler
D13 Declaration of Dr Montgomery
D14 "Enzymatic production of optically pure (2'R-*cis*)-2'-deoxy-3'-thiacytidine (3TC, Lamivudine): A potent anti-HIV agent," *Enzyme Microb. Technol.*, September 1993, vol 15., 749-755
D15 "The Resolution and Absolute Stereochemistry of the Enantiomers of *cis*-1-[2-(Hydroxymethyl)-1,3-Oxathiolan-5-yl)cytosine (β-BCH-189): Equipotent Anti-HIV Agents." *Nucleosides and Nucleotides*, 12(2), 225-236 (1993)
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D20 European Patent Application No. 92304551.2
D21 U.S. Patent No. 5,432,273
D22 U.S. Patent No. 5,149,104
D23 U.S. Patent No. 5,248,776
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D22 U.S. Patent No. 5,149,104*

D23 U.S. Patent No. 5,248,776*

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*To follow

†Chromatograms to follow

††CV to follow