STATEMENT OF GROUNDS OF OPPOSITION

European Patent No 1 318 835
In the name of Glaxo Group Limited
Opposition Thereto by 3M Innovative Properties Company
Our File GFOP09455

The above patent is hereby opposed in its entirety by the above-named Opponent ("the Opponent").

1. Introduction

1.1 Basic Details of the Patent

1.1.1 The patent was granted on July 16, 2008 (Bulletin 2008/29) on European Patent Application No 01 967535.4.

1.1.2 The Application was filed on September 20, 2001 as PCT Application No PCT/GB2001/004207.

1.1.3 Priority is claimed from UK Patent Application No 00 23008 dated September 20, 2000.

1.1.4 The application on which the Patent is based was pending on December 13, 2007, the date on which EPC 2000 entered into force, and no decision on the grant of the patent had then taken effect (a grant decision was issued on June 19, 2008); accordingly, the Patent is subject to EPC 2000.

1.2 The Claims of the Patent

1.2.1 As granted, the specification includes 18 claims.

1.2.2 Claim 1 is directed to a vaccine comprising (i) an immunogen component comprising a nucleotide sequence encoding an antigenic peptide or protein associated with a disease state and (ii) an adjuvant component for enhancing an immune response to the antigenic peptide or protein encoded by the nucleotide sequence, wherein the adjuvant component comprises a 1 H-imidazo[4,5-c]quinolin-4-amine derivative, and wherein the adjuvant component is administered between about 1 day prior to and about 3 days post administration of the immunogen component.

1.2.3 It is noted that since Claim 1 is directed to a vaccine, it is therefore not limited to the adjuvant component being administered between about 1 day to and about 3 days post administration of the immunogen component.

1.2.4 In this respect, it is noted that the applicants argued in prosecution [1] that Claim 1 was directed to a "use". The Opponent can see the merit of this in terms of ensuring that the claim is judged under "softer" novelty rules. However, the whole proposition seems to be based entirely on the language *"for enhancing an immune response"* which forms part of, and qualifies only, Integer (ii) of the claim. We take it the applicant intended in its January 2008 submission to suggest that the claim was a claim to a substance **for use** in an excluded method of treatment and that it was making this

[1] See the "Submissions" attached to the applicant's letter of January 21, 2008 (page 1, third paragraph, last four lines)

proposition under EPC 2000[2]. For the claim to qualify as a "use" claim in this sense, it surely needed to have a different form which linked the use to the substance claimed, namely the vaccine, and not to one component of it. Claim 1 as it stands does not recite a use for the substance (vaccine) claimed at all (and specifically not the use the applicant suggested in its January 2008 submissions) but merely adds a commonplace functional definition to the reference to the adjuvant. For these reasons, the Opponent's position is that Claim 1 is to be seen as a *per se* vaccine claim which falls to be considered under general novelty law and practice and not under the special law and practice applicable under Article 54(5) EPC 2000. It is noted in any event that there is some doubt that a dosage regimen can be regarded as contributing novelty of use under Article 54(5) EPC 2000 having regard to recent case law[3].

1.2.5 Claim 2 is directed to a "formulation", which appears to mean "composition". Dependency on Claim 1 leads to various issues more particularly addressed later in this Statement.

Claim 3 limits the adjuvant to particular adjuvant compounds by reference to chemical formulae and is, frankly, an import from D4.

Claims 4 to 7 recite further and progressively narrower adjuvant compound definitions including within their scope imiquimod and S28463/R848 (see Paragraph 1.2.10 below for formulae).

Claims 8 to 10 recite preferred administration features which appear to be routine features which would ordinarily be contemplated by skilled persons at the priority date.

[2] Article 54(5) [of EPC 2000] states "Paragraphs 2 and 3 shall also not exclude the patentability of any substance or composition referred to in paragraph 4 for any specific use in a method referred to in Article 53(c), provided that such use is not comprised in the state of the art"
[3] See T 1319/04

1.2.6 Claim 11 is a second-medical-use type claim and is directed to the use of 1H-imidazo[4,5-c]quinolin-4-amine derivative in the manufacture of a medicament for enhancing immune responses initiated by an antigenic peptide in the treatment of a mammal in a disease state selected from viral, bacterial or parasitic infection, cancer, allergy or autoimmune disorder, said peptide being expressed as a result of administration to a mammal of a nucleotide sequence encoding for said peptide, and wherein the 1H-imidazo[4,5-c]quinolin-4-amine derivative is administered between about 1 day prior to and about 3 days post administration of the nucleotide sequence encoding said peptide.

1.2.7 Claims 12 and 13 are models of Claims 3 and 4 but in "use format".

Claim 14 recites a broad dose limitation to which the Patent appears to attach little technical importance.

Claim 15 recites topical administration for the adjuvant at the same site as particle-mediated gene transfer of the immunogen.

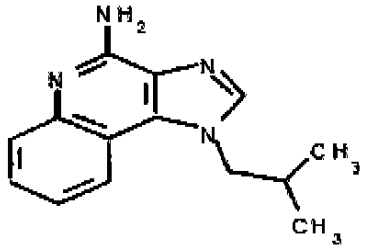
1.2.8 Claim 16 is directed to the use of 1H-imidazo[4,5-c]quinolin-4-amine derivative for use as an adjuvant to enhance an immune response initiated by the antigenic peptide, said peptide being express as a result of administration to a mammal of a nucleotide sequence encoding for said peptide, wherein the 1H-imidazo[4,5-c]quinolin-4-amine derivative is administered between about 1 day prior to and about 3 days post administration of the nucleotide sequence encoding for said people.

1.2.9 Claims 17 and 18 are models of Claims 3 and 4 but in "for use" format.

1.2.10 Relevant to the claims, and referred to in various prior art documents herein are two adjuvant compounds (1H-imidazo[4,5-c]quinolin-4-amine derivatives) which we detail below for convenience (the second has several designations whose equivalence can be seen at the following link: http://www.alexis-biochemicals.com/Search-Results.8+M505abfa3346.0.html):-

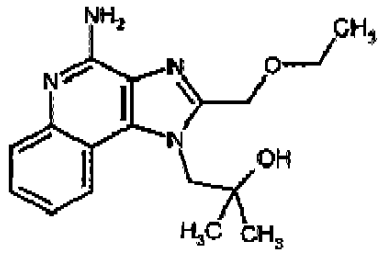
- **Imiquimod:**

1-(2-methylpropyl)1H-imidazo[4-5-c]quinoline-4-amine



- **S28463 (also known as R848 and Resiquimod)**

1-(2-hydroxy-2-methylpropyl)-2-ethoxymethyl-1H-imidazo [4,5-c] quinoline-4-amine **OR** 4-amino-2-ethoxymethyl-alpha, alpha-dimethyl-1 H imidazo[4,5-c]quinoline-1-ethanol



1.3 Prosecution of the Patent Application

1.3.1 Article 96(2) EPC Communications were issued on December 21, 2004 and April 19, 2006 with corresponding responses being filed by the Applicant on April 15, 2005 and July 3, 2006.

1.3.2 A Summons to attend oral proceedings pursuant to Rule 71(1) EPC was issued on September 24, 2007. In response to the Summons, written submissions and amended claims (Main request. First and second Auxiliary requests) were filed on 21 January 2008. The oral proceedings were cancelled by the Examining Division as evidenced by EPO Form 2008A dated February 18, 2008. The Applicant withdrew the Main request and the patent application was granted in the basis of the first auxiliary claim request.

1.4 Documents relied upon in the Opposition

1.4.1 The following documents are relied upon at present by the Opponent:-

D Doc	Document Identity
D1	Harrison et al., Abstract H121, ICAAC, 1996
D2	Tomai et al., Antiviral Research, 28 (1995), pp. 253-264
D3	Vasilakos J P et al., "Adjuvant activities of immune response modifier R – 848 comparison with CpG ODN." Cellular Immunology, (2000 Aug 25) 204 (1), p 64-74., XP001037913
D4	WO 93/20847A (Minnesota Mining & MFG) 28 Oct 1993 (1993-10-28)
D5	Sasaki et al., Infection and Immunity, vol. 65, no. 9, Sept. 1997, p. 3520-3528
D6	Oxford Dictionary of Biochemistry and Molecular Biology, page 18
D7A	DNA Vaccines Methods and Protocols, Lowrie D.B. and Whalen R.G. Published by Humana Press, 1999, Chapter 5, pp 37-39
D7B	DNA Vaccines Methods and Protocols, Lowrie D.B. and

	Whalen R.G. Published by Humana Press, 1999, Chapter 21, pp 241-249
D8	Wagner et al, Cellular Immunology, 191, 1991, pp 10-19
D9	Davis et al, Microbes and Infection, 1, 1999, pp 7-21
D10	Sasaki et al, Infect. Immunol. 66, 1998, pp 823-826
D11	Newman et al, Induction of antigen-specific killer T lymphocyte responses using subunit SIVmac251 gag and env vaccines containing QS-21 saponin adjuvant. AIDS Res. Hum. Retroviruses 1994, 10, pp 853-861
D12	Massoud Daheshia, Nelly Kuklin, Elanchezhiyan Manickan, Sangjun Chun and Barry T. Rouse, Immune induction and modulation by topical ocular administration of plasmid DNA encoding antigens and cytokines, Vaccine, Vol. 16, No. 11112, pp. 1103-1110, 1996

1.4.2 It will be appreciated that each and every document listed above was published prior to the priority date of the Patent and, as such, are all relevant to the state of the art at the priority date of the Patent.

2. Grounds of Opposition in Summary

2.1. Article 100(a) EPC

2.1.1 Article 54(1) and (2) (EPC)

The subject matter of the Patent is not patentable within the terms of Article 54(1) and (2) EPC in that the invention is not new and forms part of the state of the art.

2.1.2 Article 56 EPC

The Invention does not involve an inventive step having regard to the documents forming part of the state of the art .

2.2 Article 100(b) EPC

The Patent 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.

2.3 Article 100(c) EPC

The subject-matter of the Patent extends beyond the content of the Application as filed.

3 Opposition pursuant to Article 100(a) EPC

3.1 Claim 1

Novelty

3.1.1 Claim 1 defines a "*vaccine comprising (i) an immunogen component comprising a nucleotide sequence encoding an antigenic peptide or protein associated with a disease state, and (ii) an adjuvant component for enhancing an immune response to the antigenic peptide or protein encoded by the nucleotide sequence comprising [sic], wherein the adjuvant component comprises a 1H-imidazo[4,5-c]quinolin-4-amine derivative, and wherein the adjuvant component is administered between about 1 day prior to and about 3 days post administration of the immunogen component.*"

3.1.2 As submitted above, the administration schedule of the adjuvant component is not a limiting feature of Claim 1 for novelty assessment purposes in that in the opinion of the Opponent the claim is not an Article 54(5) EPC 2000 claim. However, the schedule's presence in the claim requires that the immunogen and the adjuvant exist separately – in order to facilitate separate administration as required by Claim 1 of the Patent. This is consistent with the fact that in prosecution the applicant removed the word "composition" from the

claim[4]; importantly, this action was stated by the applicant[5] to render as "moot" the objection raised in Paragraph 1[6] of the Annex to the Summons dated September 24, 2007. Additionally, and perhaps most importantly, the reality of separate immunogen and adjuvant components within the vaccine is reinforced for Claim 1 by the existence of Claim 2 which specifies a "single" formulation which contains both components together.

3.1.3 Exactly how the components co-exist in the "vaccine" to give it an identity as a two-component entity as such is not known as the claim does not specify. It seems to the Opponent, however, that the requirement that the entity be so must be fulfilled simply by the components existing (in one embodiment) as no combination at all until *in situ* in the physiology of a patient - in principle, a situation that is no different to the situation in D1 where the "entity" is distributed as two distinct components until they come together within the physiology of the immunized guinea pigs after administration to them of the adjuvant. On that basis, D1 seems to the Opponent to anticipate Claim 1, and the applicant must be regarded as having abandoned the position taken in its letter of July 3, 2006 that D1 does not disclose "Integer A" recited in that letter[7]. Of course, the Patentee may argue that the limitation of the claim to a vaccine has the effect of requiring a *juxtaposition* of some kind between the components in order that they "unify" sufficiently to qualify for that designation. However, this seems fanciful because the immunogen alone is enough to satisfy this requirement: with just that component present, the entity is a "vaccine" already, the needs

[4] See the applicant's letter of January 21, 2008
[5] See the "Submissions" attached to the applicant's letter of January 21, 2008 (page 1, second paragraph)
[6] Article 84EPC objection: "*.....a composition is a single formulation and does not comprise the possibility of two components which can be administered separately*"
[7] See page 3 of that letter arguing that D1 does not disclose the two components as a combined compositional entity

of that designation are then exhausted and the locality of the remaining component (the adjuvant) is immaterial.[8]

3.1.4 D1 was introduced during the prosecution proceedings by the Applicant and is an abstract of the 36th ICAAC meeting, presumably published in 1996. The authors of D1 were well known in this particular field of immunology at the priority date of the Patent and, as evidence of this, are authors of two other documents cited during prosecution of the Application and in this opposition (D2, D4).

3.1.5 The title of D1 directly teaches the skilled person that S28463 acts as an adjuvant to the protein immunogen in an HSV-2 DNA vaccine. The title of D1 is *"Effect of S28463 as an adjuvant for an immunotherapeutic HSV glycoprotein D (gD) DNA vaccine: Reduction of recurrent genital HSV disease in guinea pigs".*

3.1.6 Throughout D1, the term *"adjuvant"* is used to describe S28463, and the term appears to be used in its conventional sense. It is worth reciting the last two sentences of D1 separately as they are a clear teaching that the S28463 imidazoquinoline acted as an adjuvant in the vaccine setting of D1 and may also be used as an adjuvant in other vaccine settings:

> *"S28463 effectively enhanced the protective effect of the dD_2 DNA HSV vaccine"*
>
> *"Adjuvants, such as S28463, may play a role in enhancing responses to DNA Vaccines"*

[8] The fact that the applicant could have written claims to, first, a composition (admixture) and, secondly, a kit, but chose instead to proceed as he has, suggests that Claim 1 is intended to cover something more, for example the immunogen and adjuvant in some less juxtaposed relation in terms of time and/or location such as occurs when the two components are administered at different times - as takes place in both D1 and the preferred embodiments of the invention claimed in the Patent

3.1.7 Of course, as mentioned above, the authors were well-known experts in this field of immunology – apart from the facts set out above, a skilled person reading D1 as a whole would **expect** the term "adjuvant" to have been used by the authors in it's immunological sense, i.e. an adjuvant is a substance that increases or diversifies the immune response to an antigen (for a definition of "adjuvant", see D6).

3.1.8 In prosecution of the Application, the applicant submitted comments on the experimental data reported in D1 which it asserted showed that there was no adjuvant effect for S28463 in the setting of D1. The applicant presented this as an argument that S28463 did not behave as an adjuvant and that D1 was therefore as a matter of definition excluded functionally from the scope of Claim 1 in the form of that claim then before the ED; in all respects material to this particular issue, the form of the claim as granted is unchanged.

3.1.9 However, to treat the matter as one of definition seems to the Opponent to be a wholly synthetic approach which hides reality – at least a reality the applicant believed in prosecution, has admitted and has opted to rely on. This is because S28463 complies with the definitional requirements of Claim 1 – it ***is*** a substance suitable for use as an adjuvant in the particular setting of the experiment reported in D1. This conclusion is supported by the Patent itself as it is, of course, the case that the Patent discloses inter alia that S28463 is "*an adjuvant component [suitable] for enhancing an immune response to the antigenic peptide or protein encoded by the nucleotide sequence [eg the particular HIV-2 protein deployed as an antigen in D1].*[9] It is indeed notable that the Patent does so without any limitation to the effect that the adjuvant must be used in any

[9] This appears to be exactly as the Examiner (correctly) argued in the fourth and fifth complete paragraphs of the Article 96EPC Communication dated April 19,2006

special way (eg administered at some special time in relation to the administration of the immunogen). In fact, the temporal guidance in the Patent is very broadly presented, with lines 9 and 10 of page 14 of the Patent stating that "*.....administration may takes place between about 14 days prior to and about 14 days post administration of the nucleotide sequence, preferably.....*" (ie much more flexible than the 7 days post nucleotide administration specified in D1).

3.1.10 It thus seems to the Opponent that in fact the applicant's argument, notwithstanding the guise in which it was presented, was that D1 was not enabled (in that it failed to show how adjuvanticity was to be achieved in practical reality) and therefore was not to be taken as an anticipation of the claim before the ED for that reason. The Opponent in any event takes the view that the applicant's argument should be interpreted in this way.

3.1.11 Two possible conclusions flow from this set of circumstances:-

- One is that the applicant is wrong in its assertion that D1 is non-enabled, in which case D1 is an anticipation of Claim 1 of the Patent (on the basis set out in Paragraph 3.1.2 above) and the Patent as granted is invalid;
- The second is that applicant is right in its assertion that D1 is non-enabled. In that case, D1 is not an anticipation of Claim 1 of the Patent; however, if D1 does not enable a vaccine comprising S28463 and the gene for the HSV-2 protein antigen referred to in Claim 1, it seems to the Opponent that (i) nor does the Patent and (ii) the fact that the claim embraces that non-enabled subject-matter renders the Patent invalid under Article 83EPC through non-enablement.

3.1.12 The applicant's argument in prosecution[10] that the results in D1 for "AD" (vaccine + S28463) show nothing more than the additive effect of "A" alone plus "D" alone, is in fact incorrect and the ED, if they accepted the argument at all, were misled.

3.1.13 "A" alone and "D" alone did not show any statistically significant reductions: the "A" and "D" results overlapped with and were not statistically any better than the control. The data in D1 actually reports that only guinea pigs given the vaccine **and** S28463 had a statistically significant [p=0.04] reduction in lesions when compared to the vehicle control.

3.1.14 Although the patentee may well argue that the data in D1 does not go far enough conclusively to prove that AD was synergistic over A and D separately, the fact is that, taken at face value, that is what D1 states ". . . but only the AD group was significantly different, p=0.04." - D1 appears to be enabled. The Opponent will if necessary adduce expert evidence to this effect.

3.1.15 For the purposes of the Opponent's novelty challenge under Article 100 (a) EPC, the Opponent takes the present position that D1 discloses a vaccine comprising (i) an immunogen component comprising a nucleotide sequence encoding an antigenic peptide or protein associated with a disease state (plasmid containing the gD gene of HSV-2), and (ii) an adjuvant component for enhancing an immune response to the antigenic peptide or protein encoded by the nucleotide sequence, wherein the adjuvant component comprises a 1-H-imidazo[4,5-c]quinoline-4-amine derivative (S28463). This being so, Claim 1 is not considered by the Opponent to be novel and is consequently invalid under Article 54 EPC.

[10] See pages 4/5 of the applicant's letter of April 15,2005 and pages 3 - 5 of the "Submissions" attached to the applicant's letter of January 21, 2008

3.1.16 The Opponent would in this connection like to refer to the submissions made by the applicant in prosecution based on T158/96[11]. Importantly, T158/96 states that for a citation of prior art to be defeated, it must be the case that what it says about a therapeutic application is "plausibly contradicted by the circumstances" **and** at the same time the content of the citation did not allow any conclusion to be drawn with regard to the existence of an underlying effect. The unsuccessful argument in T158/96 was that a drug in Phase II trials would have passed through Phase I trials which had shown therapeutic effect, an assumption that was shown to be "plausibly contradicted" by the real facts applicable generally and specifically in the case of OCD drugs. In the case of D1, the situation is different. D1 says what it says: that the imidazoquinoline has an adjuvant effect. The statement is made on the back of experiments reported in the abstract and interpreted by the researchers. There is a statistically significant result in observed disease regression from using a combination of the HSV immunogen and the imidazoquinoline which cannot be explained as the additive immune response of the two components (see Paragraphs 3.1.12 to 3.1.14). The disclosure in D1 cannot be "plausibly contradicted by the circumstances".

Inventive Step

3.1.17 DNA vaccines had been known for over ten years of the date of the Patent[12]. How to make them and how to use them had been documented in a variety of publications forming part of scientific literature and, whilst information on detailed mechanisms of action

[11] See the "Submissions" attached to the applicant's letter of January 21, 2008 (pages 2 to 3)
[12] The first research on DNA vaccines appears to date from observations made in 1998 by Wolff et al, which were described in a 1989 patent and published in 1990 – see DNA Vaccines Methods and Protocols, Lowrie D.B. and Whalen R.G. Published by Humana Press, 1999, Page V (Preface)

reflected the fact that this was an area still being investigated at the priority date, certain key mechanistic information was well known to those expert in the art. DNA vaccines were in clinical development and trial by 1998[13]. The principle practical advantages of DNA vaccines over vaccines containing antigenic peptides and proteins were also well known to experts in the field and were well-documented.

3.1.18 Section 1.4 of D9[14] (page 8) lists advantages of DNA vaccines. According to Section 4.2 on page 11 (Column 1) of D9, one of the most desirable features of DNA vaccines is the *in vivo* synthesis of antigen resulting in induction of CD8+ cells. In almost all cases, according to D9, this is greatly superior to CTL induced by a protein vaccine. Strong CTL induction by DNA-based immunisation indicates that Th1-response is an important aspect in the mode of immunological action of DNA vaccines; Th1 response is typified by secretion of IL-2, gamma interferon and IL-12.

3.1.19 Turning to the Patent, the invention relates to improvements in DNA vaccines and accordingly the objective problem in the art would appear from the Patent to be the problem of how to provide DNA vaccines which have been improved (through inclusion or use of an adjuvant). It does not seem to the opponent at present that any prior art at the disposal of the opponent suggests that the objective problem is other than as just set forth.

3.1.20 It seems to the Opponent in light of the problem disclosed by the Patent that the closest prior art should be a document which discloses DNA vaccines.

[13] See D12, page 1103, Column 1
[14] Importantly, D9 is a review article,

3.1.21 In the Opponent's current view the closest prior art is D9. D9 discloses DNA vaccines generally, setting forth a large number of disease models in Table I on Page 10. As mentioned previously, this publication is a review article; it was published in 1999, just before the priority date of the Patent. The document contains a detailed disclosure of design and delivery of vaccines at Section 2, and Section 3 commencing on Page 9 deals with the mechanism of DNA vaccines. Alternatively, the Opponent asserts that either D1 or D7 (D7A, D7B) is the closest prior art as these references also disclose DNA vaccines.

3.1.22 Treating D9 as the closest prior art, the final paragraph of Section 6.1 in the second column on Page 13 of D9 refers to the use of adjuvants both in the form of CpG immunostimulatory motifs[15] plus the use of non-DNA adjuvants. In respect of non-DNA adjuvants there is a cross-reference to documents D10 and D5 both of which disclose DNA vaccines used in conjunction with an MPL adjuvant (monophosphoryl lipid A). D5 itself cross-refers to D11 which deploys a QS-21 saponin adjuvant. Although in D11 this adjuvant is used with a subunit protein vaccine, column 2 on Page 3520 of D5 states that use, for example, of this adjuvant with DNA vaccines should be effective for enhancing an induced immune response and in particular CTL induction.

3.1.23 The Opponent's contention is that a skilled man faced with the disclosures of D9 would be motivated to combine with a DNA vaccine a non-DNA adjuvant because both D9 and common belief in the art promote the idea that this will lead to advantage. In selecting particular non-DNA adjuvants to use in combination with a DNA vaccine, a skilled man would not restrict himself to adjuvants

[15] Note from D9 that since plasmids contain many CpG motifs DNA vaccines can be self-adjuvantitious (D9, Section 3.3, Column 1, Page 11)

disclosed in documents concerning DNA vaccines but would also refer to documents which refer to vaccines more generally. This seems to the opponent to be self-evident and, importantly, the paragraph in Section 6.1 in D9 just referred to (see Paragraph 3.1.22) is signally formulated without any particular restriction on types of adjuvant which might be used. However, in addition there is express support for the contention to be found in:-

- the fact that Section 6.1 of D9 cross refers to specific non-DNA adjuvants disclosed in other prior art documents[16]

- D7B is a chapter from a text book dealing with DNA vaccine compositions using conventional[17] adjuvants; the title of the relevant chapter is "The Use of Conventional Immunologic Adjuvants in DNA Vaccine Preparations".

3.1.24 Accordingly, it seems to the Opponent that a person of average skill in the DNA vaccine art faced with the disclosures of D9 would look to the overall state of the art on vaccine adjuvants in pursuit of a solution to the problem disclosed in the Patent. This would in particular include the following documents which give guidance on how imidazoquinoline compounds interact with the immune responses of antigens:

- D4 (which is a PCT application published in late 1993),
- D8 (which was published in 1999) and
- D3 (which was published in August 2000[18])

[16] D5, D10 and D11

[17] Defined as "adjuvants that are derived from microorganisms and plants or are synthesized chemically" (last sentence on page 241)

[18] According to the ED – see the Communication accompanying the Summons to Oral Proceedings dated 24th September 2008).

3.1.25 D4 discloses a vaccine composition comprising an immunogen together with a 1H-imidazo[4,5-c]quinolin-4-amine, the latter used as an adjuvant to effect an increase in the immune response to the immunogen. D4 clearly teaches that although the antibody response was only slightly increased by using an adjuvant within the foregoing class in combination with HSV-2 glycoprotein, the presence of the adjuvant significantly reduced viral shedding and recurrence, pointing to a cellular immune response. In this respect, attention is drawn to page 30, lines 14-26, page 31 lines 17-37, the passage bridging pages 32 and 33, page 33, lines 18-33 and page 33 lines 30-35.

3.1.26 D8 is concerned with the modulation of Th1 and Th2 cytokine production by inter alia imiquimod or R848 (both of which are referred to as "immune response modifiers" and described as members of the imidazoquinoline family of compounds – see D3). As stated in the abstract of D8, the data reported in that paper suggests that both these immune response modifiers have clinical utility in diseases with cell-mediated immune responses and in disease associated with over-expression of the Th2 cytokines IL-4 and IL-5 (e.g. atopic disease).

3.1.27 D3 is also concerned with the adjuvant activities of R-848 (S28463). The sentence beginning at the third line of the first column on page 65 reports that the adjuvant effect of imiquimod has been linked to enhancement of a cell-mediated immune response. The same column goes on to say that the studies overall suggest the potential of the imidazoquinolines to act as adjuvants for enhancing cell-mediated immune responses whilst antagonising Th2 responses in humans.

3.1.28 As noted in Paragraph 3.1.18, cellular immune response is a significant aspect of the mode of action of DNA vaccines. Not only

would it be an objective of any skilled man in the art to seek to improve DNA vaccine efficacy by addressing the issue of adjuvanticity but this naturally would be approached having due regard to desirability for alignment between how the vaccine works and how the adjuvant works. In short, there is considerable motivation to deploy an adjuvant which enhances the most desirable properties of the DNA vaccine. Specifically, given that a DNA vaccine acts through a Th1 response and is favoured for that reason, an attractive adjuvant for use therewith is one which the art shows operates by enhancing that response.

3.1.29 Accordingly, the Opponent submits that a person of average skill in the art, faced with the problem posed by D9, would see choosing an adjuvant as disclosed in D3, D4 or D8 as having a reasonable likelihood of producing an improved DNA vaccine when combined with DNA encoding a protein/peptide antigen.

3.1.30 The Opponent therefore submits that Claim 1 is obvious over the disclosure of D9 having regard to the disclosures of D3, D4 and D8.

3.1.31 Alternatively, as Claim 1 is anticipated by D1 in its embodiments containing the components for separate administration, it is axiomatic that Claim 1 of the Patent also lacks an inventive step over D1 to this extent. Claim 1 of the Patent so far as it includes the embodiment of Claim 2 lacks inventive step for the reasons stated in Paragraph 3.2.5 below in relation to Claim 2.

3.2 Claim 2

Novelty

3.2.1 Claim 2 recites an embodiment of Claim 1 in which the two essential components (DNA immunogen and adjuvant) are *"within a single pharmaceutically acceptable formulation"*. Such embodiment is not disclosed expressly in D1 and is distinct therefrom in that the components are in admixture - as opposed to being separate so as to be administrable separately. A noted below, the Opponent takes the view that such embodiment lacks inventive step.

Inventive Step

3.2.2 The problem to be solved in the context of Claim 2 is the problem of providing an improved DNA vaccine by combining the DNA immunogen with an adjuvant in single composition form. The closest art remains D9. The distinction of Claim 2 over D1 (single composition form) is not a further distinction over D9 as D9 comprehends single composition form and indeed cross refers to art which uses single composition forms, for example D5 (see Materials and Methods/Immunization and Vaccine Formulations[19]). Even if this were not the case, restriction to such a form is incapable of supporting inventive step as simultaneous administration of adjuvant and immunogen is conventional in the art for immunogen/adjuvant combinations, the administration of both at the same time in the form of a composition comprising the two components being ubiquitous in the literature forming part of the state of the art at the priority date - D7B, in particular, makes reference on pages 244 *et seq* to compositions of antigen and e.g. MPL adjuvants.

3.2.3 The Opponent submits that the manner of mention of single compositions in the Patent is in itself an admission by the patentee that such is not inventive over separate administration/separate

[19] Intramuscular injection of immunogen diluted in 100ml of sterile PBS containing various volumes of MPL-based adjuvant; see D5, page 3521, Column 1.

presentation of components as disclosed in D1. In sympathy with Paragraph 3.2.2, it will be noted that Paragraph 64 of the Patent refers to co-administration of the adjuvant and immunogen (i.e. simultaneous) as preferred; co-administration ordinarily is by administration of a single composition in which the components have been brought together. The latter is indeed suggested as preferred at Paragraphs 71 and 72 of the Patent and inferred at Paragraph 75, the portrayal not being that this is unusually applicable to the invention of the Patent but a reflection of the customs in the art.

3.2.4 The Opponent in short submits that Claim 2 lacks inventive step over D9 having regard to D3, D4, and D8.

3.2.5 Alternatively, Claim 2 lacks inventive step over D1. D1 discloses all the features of Claim 2 save for the requirement for the DNA immunogen and the adjuvant to be in single formulation form. That limitation is, however, incapable of supporting inventive step for the reasons set forth in Paragraphs 3.2.2 and 3.2.3, it being obvious to solve the problem of providing the D1 "system" as an improved DNA vaccine in more convenient form by combining the components.

3.3 Claim 3

Novelty

3.3.1 Claim 3, which is dependent on Claim 1 or Claim 2, requires that the 1-H-imidazo [4,5-c]quinolin-4-amine derivative is a compound defined by one of formulae I to VI.

3.3.2 As mentioned above, D1 discloses the imidazoquinoline S28463. The structure of S28463 falls within the group of compounds defined by formula VI of claim 3, when R_t is hydrogen, R_u is 2-hydroxy-2-

methylpropyl and R_v is alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about four carbon atoms.

3.3.3 Accordingly, D1 anticipates Claim 3 of the Patent.

Inventive Step

3.3.4 1-H-imidazo [4,5-c]quinolin-4-amine derivatives according to formulae I to VI of Claim 3 of the Patent are not mentioned in D9.

3.3.5 However, D4 discloses compounds that fall within the definition of formula VI of Claim 3 – see, for example, the passage in D4 from page 12, line 28 to page 13, line 2 which lists the following preferred compounds:-

- 1-(2-methylpropyl)- 1H-imidazo[4,5-c]quinolin-4-amine;
- 1-(2-hydroxy-2-methylpropyl)- 1H-imidazo[4,5-c]quinolin-4-amine;
- 1-(2-hydroxy-2-methylpropyl)-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine; and
- 1-(2-hydroxy-2-methylpropyl)-2-ethoxymethyl-1H-imidazo[4,5-c]quinolin-4-amine.

3.3.6 D8 also discloses compounds that fall within the scope of Claim 3, for example Imiquimod[20] which falls within the definition of formula VI. As noted earlier, D1 also discloses the use of S28463[21] which falls within the definition of formula VI.

[20] Recall: 1-(2-methylpropyl)1H-imidazo[4-5-c]quinoline-4-amine
[21] Recall: 1-(2-hydroxy-2-methylpropyl)-2-ethoxymethyl-1H-imidazo [4,5-c] quinoline-4-amine

3.3.7 Since D1, D4 and D8 disclose compounds which fall within the scope of Claim 3, Claim 3 fails to involve an inventive step over D9 as the aforementioned art teaches the skilled man to deploy a compound as specified in Claim 3 of the Patent in seeking an adjuvant to use in the context of D9.

3.3.8 Alternatively, as Claim 3 is anticipated by D1, it is axiomatic that Claim 3 of the Patent also lacks an inventive step over D1. The Opponent's submissions in Paragraph 3.2.5 apply *mutatis mutandis* to Claim 3 so far as the claim incorporates the limitations of Claim 2.

3.4 Claim 4

Novelty

3.4.1 Claim 4, which is dependent on Claim 3, requires that the 1H-imidazo[4,5-c]quinolin-4-amine derivative is a compound of formula VI, compounds of that formula being disclosed in D1, D4 and D8.

3.4.2 Accordingly, D1 anticipates Claim 4 of the Patent.

Inventive Step

3.4.3 In that compounds of formula VI are disclosed in D1, D4 and D8, Paragraph 3.3.7 applies to Claim 4 *mutatis mutandis;* Claim 4 lacks an inventive step over D9 having regard to D1, D4 and D8.

3.4.4 Alternatively or additionally, as Claim 4 is anticipated by D1, it is axiomatic that Claim 4 of the Patent also lacks an inventive step over D1. The Opponent's submissions in Paragraph 3.2.5 apply *mutatis mutandis* to Claim 4 so far as the claim incorporates the limitations of Claim 2.

3.5 Claim 5

Novelty

3.5.1 Claim 5, which is dependent on Claim 4, recites compounds of formula VI in which R_t is hydrogen, compounds so defined being disclosed in D1, D4 and D8.

3.5.2 Accordingly, D1 anticipates Claim 5 of the Patent.

Inventive Step

3.5.3 In that compounds of formula VI in which R_t is hydrogen are disclosed in D1, D4 and D8, Paragraph 3.3.7 applies to Claim 4 *mutatis mutandis;* Claim 5 lacks an inventive step over D9 having regard to D1, D4 and D8.

3.5.4 Alternatively or additionally, as Claim 5 is anticipated by D1, it is axiomatic that Claim 5 of the Patent also lacks an inventive step over D1. The Opponent's submissions in Paragraph 3.2.5 apply *mutatis mutandis* to Claim 5 so far as the claim incorporates the limitations of Claim 2.

3.6 Claim 6

Novelty

3.6.1 Claim 6, which is dependent on Claim 5, recites compounds of formula VI in which R_u is 2-methylpropyl or 2-hydroxy-2-methylpropyl, and R_v is hydrogen, methyl or ethoxymethyl, compounds so defined being disclosed in various of D1, D4 and D8.

3.6.2 More specifically, and referring to formula VI, D1 discloses compounds where R_u is 2-hydroxy-2-methylpropyl and R_v is hydrogen. D4 discloses compounds where R_u is 2-methylpropyl or 2-hydroxy-2-methylpropyl and R_v is hydrogen, methyl or ethoxymethyl. D8 discloses compounds where R_u is 2-methylpropyl and R_v is hydrogen.

3.6.3 Accordingly, D1 anticipates Claim 6 of the Patent.

Inventive Step

3.6.4 In that D1 discloses compounds of formula VI where R_u is 2-hydroxy-2-methylpropyl and R_v is hydrogen, D4 discloses compounds of formula VI where R_u is 2-methylpropyl or 2-hydroxy-2-methylpropyl and R_v is hydrogen, methyl or ethoxymethyl and D8 discloses compounds of formula VI where R_u is 2-methylpropyl and R_v is hydrogen, Paragraph 3.3.7 applies to Claim 6 *mutatis mutandis;* Claim 6 lacks an inventive step over D9 having regard to D1, D4 and D8.

3.6.5 Alternatively or additionally, as Claim 6 is anticipated by D1, it is axiomatic that Claim 6 of the Patent also lacks an inventive step over D1. The Opponent's submissions in Paragraph 3.2.5 apply *mutatis mutandis* to Claim 6 so far as the claim incorporates the limitations of Claim 2.

3.7 Claim 7

Novelty

3.7.1 Claim 7, which is dependent on Claim 6 recites the following compounds of formula VI:-

- 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine
- 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine
- 1-(2-hydroxy-2-methylpropyl)-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine
- 1-(2-hydroxy-2-methylpropyl)-2-ethoxymethyl-1H-imidazo[4,5-c]quinolin-4-amine.

3.7.2 D1 specifically discloses S28463, which is the last compound in the list in Claim 7.

3.7.3 D4 discloses all the compounds listed in Claim 7 on page 12 line 28 to page 13 line 2.

3.7.4 D8 discloses 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine.

3.7.5 Accordingly, D1 anticipates Claim 7 of the Patent.

Inventive Step

3.7.6 Insofar as the specifically recited compounds listed in Claim 7 of are disclosed in D1, D4 and D8, Paragraph 3.3.7 applies to Claim 7 *mutatis mutandis;* Claim 7 lacks an Inventive step over D9 having regard to D1, D4 and D8.

3.7.7 Alternatively or additionally, as Claim 7 is anticipated by D1, it is axiomatic that Claim 7 of the Patent also lacks an Inventive step over D1. The Opponent's submissions in Paragraph 3.2.5 apply *mutatis mutandis* to Claim 7 so far as the claim incorporates the limitations of Claim 2.

3.8 Claim 8

Novelty

3.8.1 Claim 8, which is dependent on any preceding claim, requires that each component is in a form suitable for administration via any of the oral, nasal, topical, pulmonary, intramuscular, subcutaneous or intradermal routes. Such suitability is not expressly disclosed in D1.

Inventive Step

3.8.2 Since the claimed routes of administration are conventional and well known to those skilled in the art, a limitation to such routes is not capable of conferring inventive step on Claim 8.

3.8.3 For example, D4 lists a number of conventional routes of administration (oral, subcutaneous, nasal, topical) on Page 15, lines 17-21.

3.8.4 It appears to the Opponent that Claim 8 lacks inventive step, for the reasons set forth in paragraph 3.8.2, over D9, and also over D1, it being obvious to design the D1 vaccine (whether in single composition form or not) for the administration routes recited in Claim 8.

3.9 Claim 9

Novelty

3.9.1 Claim 9, which is dependent on Claim 8, requires that the immunogen component is in a form suitable for administration using a particle-mediated gene transfer technique.

3.9.2 Particle-mediated delivery of plasmid DNA was known at the priority date of the Patent - see for example, D9, Section 2.2.2, second paragraph and Section 2.2.2 (I), both on Page 9 of D9. However, it is not disclosed in D1.

Inventive Step

3.9.3 Since D9 clearly discloses that the immunogen compound may be administered using a particle-mediated gene transfer technique, no inventive step can be conferred by limitation to this mode of administration in Claim 9. Claim 9 thus fails to involve an inventive step over D9 and does not comply with Article 56EPC.

3.9.4 It appears to the Opponent that Claim 9 also lacks inventive step over D1, it being obvious to design the vaccine (whether in single composition form or not) for the administration routes recited in Claim 8.

3.10 Claim 10

Novelty

3.10.1 Claim 10, which is dependent on Claim 9, requires that the adjuvant component is in a form suitable for administration using a particle mediated gene transfer technique. We reiterate Paragraph 3.9.2 above.

Inventive Step

3.10.2 We reiterate Paragraph 3.9.3 and 3.9.4 above *mutatis mutandis*.

3.11 Claim 11 and Claim 16

Novelty

3.11.1 Neither the subject-matter of Claim 11 nor that of Claim 16 appears to be anticipated by D1.

Inventive Step

3.11.2 Claim 11 is a standard second medical indication claim whose elements are as follows:-

- Use of a 1H-imidazo[4,5-c]quinolin-4-amine derivative to manufacture a medicament
- the medicament is for enhancing immune response initiated by an antigenic peptide
- the enhancement is in the treatment of a mammal in a viral, bacterial, cancerous, allergic or autoimmune disease state
- the peptide is express through administration to the mammal of a nucleotide coding sequence for the peptide
- the imidazoquinoline derivative is administered between about 1 day prior to and 3 days post administration of the nucleotide sequence.

3.11.3 Setting the claim form to one side for a moment, the essential difference between Claim 11 and Claim 1 is the fact that the former is effectively limited to a treatment regime. The treatment regime includes simultaneous administration of immunogen and adjuvant.

3.11.4 Simultaneous administration is conventional in the art for immunogen/adjuvant combinations, the administration of both at the same time in the form of a composition comprising the two

components being ubiquitous in the art, for example in D4 and in D5 (see Materials and Methods/Immunization and Vaccine Formulations[22]. In D7B in particular, reference is made on pages 244 *et seq* to compositions of antigen and e.g. MPL adjuvants whilst Table 1 (page 243) refers to instances of administering adjuvant separately prior to vaccination. Comparing this with the Patent, it will be noted that Paragraph 64 of the Patent in very relaxed fashion refers to co-administration as preferred (i.e. simultaneous), whilst administration of the adjuvant can be anywhere between 14 days prior to immunization and 14 days after immunization. The protocol can indeed be "varied as necessary" according to line 16 on page 14 of the Patent.

3.11.5 In conclusion, there is no evidence that the administration protocol is especially sensitive and every indication that it can vary widely, with roughly simultaneous administration most convenient. The Opponent submits that the administration protocol limitation in Claim 11 is incapable of supporting any notion that it confers inventive step on the claim over D9.

3.11.6 Turning to the problem and solution approach the OD will no doubt wish to apply:

- The problem in the art in the context of D9 is that of providing an improved adjuvanting of a DNA immunogen

- The solution to the problem, by providing the defined administration schedule and a specific class of antigen, lacks inventive step over D9 in that the adjuvant would be an obvious choice for the man of average skill in the art for the

[22] Intramuscular injection of immunogen diluted in 100ml of sterile PBS containing various volumes of MPL-based adjuvant; see D5, page 3521, Column 1).

reasons given in Paragraph 3.1.29 above and the administration schedule is a routine option which would ordinarily be considered by a man of average skill in the art

☞ Claim 11 does not comply with Article 56 EPC

3.11.17 The forgoing comments on inventive step in regard to Claim 11 apply mutatis mutandis to Claim 16.

3.12 Claim 12

Novelty

3.12.1 The Opponent makes no submissions on novelty.

Inventive Step

3.12 2 Claim 12 recites the 1H-imidazo[4,5-c]quinolin-4-amine derivative defined in Claim 3.

3.12.3 Claim 11 fails to demonstrate an inventive step over D9 as the administration schedule of Claim 11 is a routine variant which would ordinarily be considered by a man of average skill in the art. Limitation of Claim 11 to the adjuvant of Claim 3 to produce present Claim 12 does not confer inventive step as D1, D4 and D8 teach the skilled man to deploy a compound as specified in Claim 3 of the Patent in seeking an adjuvant to use in the context of D9. In the result, Claim 12 also falls to demonstrate an inventive step over D9.

3.13 Claim 13

Novelty

3.13.1 The Opponent makes no submissions on novelty.

Inventive Step

3.13.2 Claim 13 recites the 1H-imidazo[4,5-c]quinolin-4-amine derivative defined in Claim 4.

3.13.3 As noted above, Claim 11 of the Patent fails to demonstrate an inventive step over D9 as the administration schedule of Claim 11 is a routine option which would ordinarily be considered by a man of average skill in the art. Limitation of Claim 11 to the adjuvant of Claim 4 to produce present Claim 13 does not confer inventive step as D1, D4 and D8 teach the skilled man to deploy a compound as specified in Claim 4 of the Patent in seeking an adjuvant to use in the context of D9. In the result, Claim 13 also fails to demonstrate an inventive step over D9.

3.14 Claim 14

Novelty

3.14.1 The Opponent makes no submissions on novelty.

Inventive Step

3.14.2 Claim 14, which is dependent on any one of claims 11 to 13, requires that the 1H-imidazo[4,5-c]quinolin-4-amine derivative is administered at a dose of between about 1mg/kg to 50 mg/kg.

3.14.2 D4 discloses that the adjuvant is generally administered in an amount of about 0.0003 to about 5mg/kg, when the adjuvant derivative is administered independently from the immunogen (D4, page 13, lines 7-11). The dosages disclosed in D4 fall partially within the scope of the broad range recited in Claim 14 of the Patent.

3.14.3 The Opponent's contention is that this limitation fails to confer inventive step on Claim 14.

3.15 Claim 15

Novelty

3.15.1 The Opponent makes no submissions on novelty.

Inventive Step

3.15.2 Claim 15, which is dependent on any one of claims 11 to 14, requires that the nucleotide sequence encoding for said peptide is administered by a particle-mediated gene transfer technique and the 1H-imidazo[4,5-c]quinolin-4-amine derivative is administered topically at the site of administration of the nucleotide sequence.

3.15.3 The Opponent will rely on the comments made in Paragraphs 3.9 and 3.10.

3.16 Claim 16

3.16.1 See the comments in Paragraph 3.11 above

3.17 Claim 17

Novelty

3.17.1 The Opponent makes no submissions on novelty.

Inventive Step

3.17.2 The Opponent will rely on the comments made in Paragraphs 3.9 and 3.10.

3.18 Claim 18

Novelty

3.18.1 The Opponent makes no submissions on novelty.

Inventive Step

3.18.2 The Opponent will rely on the comments made in Paragraphs 3.9 and 3.10.

3.19 All Claims

Novelty and Inventive Step

3.19.1 All the claims rely on a recited dosage regimen (administration of the adjuvant between 1 day prior to and 3 days post administration of the immunogen). It is noted that there is some doubt that a dosage regimen can be regarded as contributing novelty (or inventive step) of use under Article 54(5) EPC 2000 having regard to recent case

law[23]. On the basis that the dosage regimen cannot be regarded as contributing novelty or inventive step, none of the claims demonstrates an inventive step.

3.19.2 The problem said to be solved by the invention is that of providing improved DNA immunization. It seems doubtful that this solution is delivered across the scope of the Patent (which is a pre-requisite for inventive step) at least insofar as Claim 1 appears to include within its scope compositions (admixtures) whose components must be separately administrable over a time interval.

3.19.3 The Opponent has indicated a current view that D9 is the closest art for inventive step assessment purposes. The Opponent believes that lack of inventive step over D4 can also be argued. D4 discloses vaccines using an imidazoquinolinamine adjuvant in combination with immunogens generally. D4 gives a wide range of examples of immunogens, mentioning T-dependent immunogens as a particular class (Claim 10 and lines 25-29 of page 14). Page 13, lines 27 *et seq* of D4 state that because the adjuvant enhances both humoral and cell-mediated immune responses, the immunogen can be any material that raises either type of immune response. There is no suggestion in D4 that there is any limitation on the immunogens which may be use with the adjuvant and indeed lines 14 *et seq* on page 14 of D4 suggest that experimental immunogens may be useful in the invention of D4. D7A and D7B in turn present DNA vaccines as new advanced technology with a number of advantages, as does D9; D4 and D7 point out the benefits of combining DNA immunogens with adjuvants.

[23] See T 1319/04

3.19.4 Taking D4 as the closest prior art, the problem in the art is the problem of how to deploy the adjuvants of D4 with immunogens offering the advantages of new technology. In the Opponent's view, a solution to the problem as just formulated which would present itself to skilled persons would be the use of DNA immunogens as disclosed in D7A/D7B; the Opponent reiterates that D7A/D7B themselves encourage combination of the nucleic acid immunogens disclosed with adjuvants. As such, the solution would be obvious to the skilled man as one which it would be reasonable to try with a reasonable expectation of success.

4. Opposition pursuant to Article 100(b) EPC

4.1 The Patent discloses more than 50 very broad disorders or disease states which can be protected against or treated by using the methods or compositions according to the invention. Furthermore, paragraphs [0032] to [0052] provide a long list of antigens which, according to the opposed patent, can be used in a vaccine of the invention. The claims insofar as they are open-ended permit the presence of plural DNA immunogens, which will, of course produce plural *in vivo* antigen syntheses, together with plural adjuvantitious chemical entities. Over and above this the Patent specifies a range for administration times for the adjuvant without making it possible for the skilled man to discern how all the physical formats embraced by Claim 1 will facilitate reduction to practice.

4.2 It has been established by the Enlarged Board of Appeal that an invention is sufficiently disclosed only if the disclosures of the patent allow the invention to be performed across the whole range claimed so that the skilled person is able to obtain substantially all the embodiments falling within the ambit of the claims. Furthermore,

these embodiments must be obtainable without undue burden on the part of the skilled person.

4.3 Specifically, it is not disclosed in the Patent how the invention of Claim 1 insofar as it claims the embodiment of Claim 2 can be reduced to practice by the specified mode of administering the two components at separate times even though they are mixed together according to the claim.

4.4 It is submitted that the Patent does not satisfy the requirements of Article 83 EPC.

5. Opposition pursuant to Article 100(c) EPC

5.1 Claim 1 as granted adds matter over the Application as originally filed.

5.2 During prosecution Claim 1 was amended to specify that the adjuvant component is administered between about 1 day prior to and about 3 days post administration of the immunogen component.

5.3 A range of possible administration schedules of the immunogen and the adjuvant is provided in the Application as filed starting at line 26 on page 26 and finishing at line 17, page 27. Page 27, lines 7-8 of the Application specifically mentions that the adjuvant component may be administered between about 1 day prior to and about 3 days post administration of the immunogen component. However, these disclosures appear in the limited context of administration of the adjuvant component via the oral, pulmonary, intramuscular, subcutaneous, intradermal or topical routes. The fact that the dosage timing has been taken from the above context and exported to Claims 1, 11 and 16 as such adds subject-matter as the result is the definition of a new domain in the claims which is larger than the

domain from which the subject-matter was taken from the description.

5.4 Claim 1 now covers compositions which are deconstructed to administer the components separately. This possibility was absent from the application as filed and thus constitutes new subject-matter.

5.5 Whilst original Claim 1 was directed to a composition and Claim 2 to a kit, Claim 1 appears now to claim something else (see Paragraph 3.1.3 above). There is no basis in the original filed application for this additional scope and the subject-matter which occupies it.

6. Requests

The Opponent makes the following Requests:-

6.1 Revocation of the Patent in its entirety.

6.2 Appointment of oral proceedings in the event that the Opposition Division is not minded to grant the above Request upon the written submissions of the Opponent. Oral proceedings are requested to be in English with simultaneous translation between English and any other language used orally by another party with the Opposition Division's permission.

6.3 An award of costs to the Opponent.

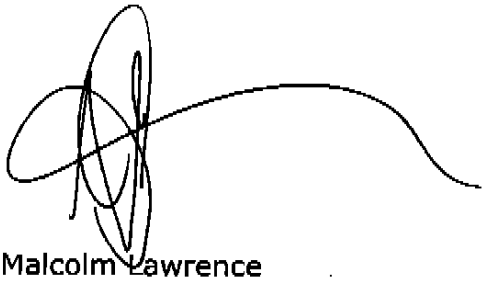
7. Fees

7.1 The opposition fee is being paid by EPO Form 1010 which is enclosed with the Notice of Opposition (Form 2300). In the event that no fee

is debited on that authority, this Paragraph 7 of this Statement of Opposition constitutes alternative debit authority.

8. Experiments and Expert Evidence

8.1 The Opponents reserve the right to present experimental evidence and give formal notice to this effect.



Malcolm Lawrence
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April 15, 2009