Last Written Submissions

European Patent No 0 642 355

In the name of GlaxoSmithKline Beecham Biologicals SA

Opposed by Chiron Corporation (OI) and Aventis Pasteur Ltd (OII)

Appeal No: T1193/03-334

Our File: GFAP99463

In preparation for oral proceedings scheduled before the OD for January 31, 2006 to February 2, 2006, we request on behalf of Respondent to (referred to herein as Opponent II) that the Further Observations herein should be considered by the OD, together with the following documents which are being filed separately today by telefax:-

D108	EP-A-0 835 663
D109	Letter from Merck regarding HEXAVAC
D110	Shirodkar, et al., Pharmaceutical Research, 7:1282-1288 (1990)
D111	Press Release issued by the European Medicines Agency, London, 20 September 2005
D112	Hem, S. and White, J.L., Characterization of aluminum-containing adjuvants, Developmental Biology 217-228, 2000
D113	Rinella, J.V.; White, J.L. and Hem, S.L., Effect of anions on model aluminum-adjuvant-containing vaccines, Journal of Colloid and Interface Science 169: 121-130, 1995.
D114	Seeber et. al. Predicting the adsorption of proteins by aluminum-containing adjuvants, Vaccine, Vol. 9, p 201-203, March 1991
D115	EP-A-0 278 940
D116	WHO Technical Report Series, No. 800, 1990 – Annex 2 Requirements for Diphtheria, Tetanus, Pertussis and Combined Vaccines

1. **Article 123(2) EPC**

1.1 In addition to the Article 123(2) EPC challenges already made, OII would draw the following also to the Board's attention.

1.2 The application as filed is limited to vaccine compositions which do not contain AH-adjuvanted HBsAg. Claim 1 of the application as filed states this *expressis verbis*. The same restriction is stated in the consistory clause commencing at line 14 of originally filed page 2 (see line 18). The original claim language must be construed in the light of the originally filed description. On original page 2, there is, importantly, a statement introducing the invention in its prior art setting, which statement extends from line 3 to line 6 of the page and is directed to the avoidance of use of AH for HBsAg; this passage refers to "the need to avoid aluminium hydroxide as an adjuvant". Similarly, lines 24 to 25 of the page refer to the avoidance of "the use of AH to adsorb the HBsAg". Original Claim 1 thus appears to exclude even the *possibility* of there being any HBsAg in the composition which is adsorbed to AH.

1.3 The granted claims and all the Claim Requests on file express the adjuvanting of the HBsAg in different language, namely "the adjuvant used to adsorb the HBsAg is AP". The effect may be intended by the Patentee to be the same, namely that the vaccine contains AP-adjuvanted/adsorbed HBsAg but not AH-adjuvanted/adsorbed HBsAg but this is unclear. The granted version of Claim 1, and most of the broad claims in the various Claim Requests, are open-ended (e.g. Claim 1 of Claim Set A) - as such, the claims concerned may permit the presence of AH-adjuvanted HBsAg (whether deliberate or in the "inadvertent" sense explained in Paragraph 1.4 below).

1.4 Although the claim might thus possibly be complied with if the HBsAg is adsorbed to AP (AP having been used to adsorb it in the first place) but a small amount of HBsAg in fact has become AH-adsorbed, the latter

interpretation could not apply with the original "negative" language of originally filed Claim 1 (use no AH) construed in the light of the patent specification; it is a possibility only with the "positive" language of the granted version and later versions of Claim 1.

1.5 If those versions of Claim 1 have the broader meaning, the amendments made to achieve it contravene Article 123(2) EPC. The problem is more complex if these versions of Claim 1 retain the narrower meaning. It is now known that the mechanism by which e.g. HBsAg binds to "aluminium" adjuvants is primarily so-called "ligand exchange" (see D93). Ligand exchange is, importantly, much more significant as an attractive force between the adjuvant and the antigen than e.g. electrostatic attraction. Because AH has a greater concentration of surface hydroxyl groups available for participation in ligand exchange, AH has a greater propensity for HBsAg adsorption. It will be appreciated that in many circumstances where the vaccine also contains, for example, DTP (AH), the additional propensity for HBsAg to adsorb to AH (as compared to AP) is likely to mean competitive redistribution of antigen from an AP adsorption site to an AH adsorption site. The patent does not say how this is to be avoided so that compliance with a requirement for no AH-adsorbed HBsAg can be ensured. A similar situation in practice may arise because HB absorption to AP will never be absolutely complete, some antigen being non-absorbed to the AP and therefore available for adsorption by AH in an overall formulation comprising AP, AH and a portfolio of antigens[1].

1.6 The above gives rise, of course, to an Article 83 EPC issue and that is referred to later[2]. However, on the subject of Article 123(2) EPC, claims in which the "other" antigen (e.g. D, P or T) is AH-adjuvanted appear to fall outside the scope of the claims as they infer compositions in which competitive redistribution of HBsAg from AP to AH has taken place. Such a composition is excluded by the original patent

[1] See Paragraph 11 of D46 and Paragraph 10 of D73 in this respect
[2] See Paragraph 4.5.2 below

application with the result that the relevant claims of the relevant Claim Requests contravene Article 123(2) EPC.

2. Novelty - Article 54(3) EPC

2.1 The Failure of Claim A1 to Enjoy the Priority Date of UK 92 11081.6

2.1.1 Claim 1 of Claim Set A requires the presence of two or more antigens other than hepatitis B surface antigen (i.e. n is 2 or more). It further requires that those "other" antigens be selected from a list of antigens implied by the list of pathogens appearing in the claim. The claim does not require the "other" antigens (or any of them) to be adsorbed.

2.1.2 The first priority document (P1), namely UK Patent Application No 92 11081.6 (dated May 23, 1992), contains no basis for the recitation in Claim 1 of Claim Set A of the presence of two or more "other" antigens as a general feature; it provides basis for the presence of two or more "other" antigens in the context of certain specific vaccines, such as those exemplified in the Examples, but that does not support the claim to that priority date for the claim concerned.

2.1.3.1 Additionally, P1 also does not disclose in the required general setting the list of antigens implied by the list of pathogens recited in Claim 1 of Claim Set A. Claim 3 of P1 recites that "the antigen" may be selected from a similar list but is limited to circumstances where the antigen concerned is adsorbed to AH whereas Claim 1 of Claim Set A is not. The "other" antigens of the claim are, of course, mentioned (at least most of them) in the panel at lines 7-11 of page 3 of P1, but this disclosure is in narrow contexts which do not support the priority claim. Similarly, the paragraph commencing at line 13 of page 5 of P1

constitutes a limited context which does not support the claim that the priority date of P1 is enjoyed by Claim 1 of Claim Set A.

2.1.3.2 It is to be noted additionally that P1 discloses, in the part of the specification directed to the subject-matter of the invention, only IPV; IPV is more specific than Claim 1 of Claim Set A (which covers inter alia OPV); of course, the reference to "polio" as such on page 1 (see line 24) of P1 is not relevant for priority date assessment purposes as it forms part of the P1 disclosure concerned with the prior art background to the invention and not part of the P1 disclosure relating to the invention.

2.1.4 P1, unlike Claim 1 of Claim Set A, requires not only that "one or more other antigens" be "adsorbed" but also expressly requires adsorption to AH or AP. In this further respect therefore, P1 fails to support the claim that its date should be accorded to Claim 1 of Claim Set A.

2.1.5 In short, Claim 1 or Claim Set A (i) fails on three counts to satisfy the accepted legal tests for priority dated entitlement and accordingly (ii) is not entitled to the date of P1.

2.2 Lack of Novelty of Claim 1A

2.2.1 In view of its failure to have entitlement to the date of P1, Claim 1 of Claim Set A is susceptible to challenge under Article 54 EPC based on the state of the art immediately prior to the later date to which it is entitled.

2.2.2 Under Article 54(3) EPC specifically, the claim is not valid if any of its subject-matter forms part of the state of the art represented by the content of any European patent application having *a date of*

filing prior to the priority date of the claimed subject-matter provided that such European patent application was published under Article 93 EPC on or after that *date of filing*.

2.2.3 As noted above (see Paragraph 1.2.1), the priority date of the claimed subject-matter of Claim 1 of Claim Set A is later than May 23, 1992; another published European application is therefore citable under Article 54(3) EPC if its relevant subject-matter has an earlier priority date (e.g. a priority date actually of May 23, 1992) and if that other European application has been published since then under Article 93 EPC.

2.2.4.1 One such citable other European patent application is EP-A-0 835 663 A2 (D108) filed herewith. This application was divided from the application on which the opposed patent was granted. Its relationship per se with the opposed patent pursuant to Article 76 EPC is not material to its citability.

2.2.4.2 D108 was published on April 15, 1998 and OII asserts that it successfully claims for some of its subject-matter the priority date of May 23, 1992. That priority date is claimed in D108 from UK Patent Application No 92 11081.6. This has been referred to in Paragraph 2.1.2 above as P1. A copy is on file in these proceedings.

2.2.4.3 Such subject-matter of this date appears e.g. in the paragraph from line 35 of page 8 to line 3 of page 9 of D108 and in the description from line 15 of page 9 to the end of page 17 of D108.

2.2.4.4 The above passages derive their entitlement to priority from the paragraph commencing at line 13 of page 5 of P1

and from the description in the passages from line 34 of page 5 to the end of page 15 of P1.

2.2.5 Accordingly, Claim 1 of Claim Set A is anticipated under Article 54(3) EPC by D108 and the claim request concerned is thus disallowable.

2.2.6 OII will be pleased to explain to the Board and to the other parties at the oral proceedings the position with regard to the other claims in Claim Set A. However, it seems to OII that economy of procedure is best served by not attempting to do so at the present time.

2.3 Claim Sets B, C, D, E and G

2.3.1 For similar reasons to those set out for Claim Set A, Claim Sets B, C, D, E and G are disallowable.

2.3.2 OII will make appropriate oral submissions in this respect at the oral proceedings.

2.4 Claim Set F

2.4.1 Claim Set F is also disallowable but the reasons are slightly different.

2.4.2 Claim 1 of Claim Set F recites a DT-HB vaccine wherein the D and T antigens are adsorbed to AH or AP and the HBsAg is adsorbed to AP. The word "stable" has the meaning assigned to it at lines 33 to 35 on page 4 of the application (lines 36 to 37 on page 3 of the opposed patent).

2.4.3 The paragraph commencing at line 13 on page 5 of P1 discloses as an essential feature that the combined vaccines there referred

to are a combination of components which have enjoyed "complete and stable adsorption" prior to combination to form the combined vaccine. The word "stable" is not defined in P1 at all and P1, in using that word in the above paragraph of page 5, is not limited to the narrow terms in which the word is defined in the opposed patent. Additionally, Claim 1 of Claim Set F requires "stability" in relation to the final products whereas page 5 of P1 is referring to precursor vaccine components. It follows from the above that neither page 5 of P1, nor any other part of its disclosure, supports the proposition that Claim 1 of Claim Set F should be assigned the priority date of P1. Claim 1 of Claim Set F therefore does not enjoy a priority date of May 23, 1992.

2.4.4 "Stable" DT-HB vaccine compositions falling within the scope of Claim 1 of Claim Set F are disclosed in the body of description from line 15 of page 9 to the end of page 17 of D108.

2.4.5 The above passages derive their entitlement to priority from the disclosure of DT-HB vaccines in the body of the description from line 34 of page 5 to the end of page 15 of P1.

2.4.6 D108 therefore stands as an anticipation of Claim 1 of Claim Set F under Article 54(3) EPC.

2.4.7 Claim 2 of Claim Set F recites a "stable" DTP-HB vaccine in terms which, other than for the additional P valence and abbreviations for e.g. aluminium hydroxide, are identical to those of Claim 1 of Claim Set F.

2.4.8 For the reasons given in Paragraph 2.4.3, Claim 2 of Claim Set F does not enjoy the priority date of May 23, 1992 claimed in the opposed patent and the claim is thus anticipated under Article 54(3) EPC by the "stable" DTP-HB vaccine formulations disclosed in the description of D108 from line 15 of page 9 to the end of page

18. The latter passages are entitled to the earlier date of P1, deriving that entitlement from the disclosures of DTP-HB vaccines in P1 from line 34 of page 5 to the end of page 15.

2.5 Claim Set H

2.5.1 Claim Set H is unallowable, but again for slightly different reasons, because at least Claim 1 is unallowable.

2.5.2 Claim 1 of Claim Set H is to a process which is defined in open-ended language. However, the passage from line 13 to line 18 of page 5 of P1 does not support open-ended language (and no other part of P1 provides any basis for the claim whatsoever). The process there disclosed is portrayed as a process for assembling a vaccine having the valences (i) DT, DTPw, DTPa or HA together with (ii) HB. It is not disclosed as a process which can be adopted in the preparation of a vaccine having additional valences (in contrast, the published application discloses "DT, DTPw, DTPa, HA or other components").

2.5.3 For the above reasons, Claim 1 of Claim Set H does not enjoy the priority date of P1 and is anticipated under Article 54(3) EPC by (i) the disclosures of the paragraph commencing at line 35 on page 8 of D7 (which derive priority from the paragraph commencing at line 13 on page 5 of P1) and (ii) the disclosures from line 15 of page 9 of D7 to the end of page 17 (which derive priority from the passages in P1 from line 33 of page 5 to the end of page 13).

2.6 Claim Set I

2.6.1 Claim 1 is anticipated under Article 54(3) EPC by the disclosures of D108. The claim corresponds to Claim 1 of Claim Set F. We refer to Paragraph 2.4.2 to 2.4.6 above.

2.6.2 Claim 2 is anticipated under Article 54(3) EPC by the disclosures of D108. The claim corresponds to Claim 1 of Claim Set F. We refer to Paragraphs 2.4.7 and 2.4.8 above.

2.7 Claim Set J

2.7.1 P1 contains no disclosure of "DTP-HBsAg containing" vaccines with the result that Claim 1 of Claim Set J cannot validly claim the priority date of P1.

2.7.2 However, P1 does disclose particular DTP-HBsAg vaccines in the body of description from line 33 of page 5 to the end of page 13. That disclosure supports assignment of the date of P1 to the corresponding disclosure occupying the part of D2 from line 15 of page 9 to the end of page 17. The latter thus anticipates Claim 1 of Claim Set J.

2.7.3 Claim 16 of Claim Set J is mutatis mutandis anticipated by D108. The requirement that the vaccine to which the claim refers be "stable and effective" adds to the failure of the claim to enjoy the priority date of P1 whilst, however, the DTP-HB vaccines disclosed on pages 9 to 17 satisfy this requirement. Similarly, the stated requirement for superior stability and/or immunogenicity of the vaccines as compared to the HB (AH) analogs underlines the lack of entitlement to the date of P1 whilst not distinguishing the claim from D108, pages 9 to 17.

2.8 Claim Set K

2.8.1 This is the Patentee's 11th auxiliary claim request – if one ignores the fact that Claim Sets E and J were originally filed in erroneous form and have had to be replaced. OII is, however, grateful that, at least so far, the Patentee's claim requests do not demonstrate

the mesmerizing quality of those submitted in the period up to the close of the first instance debate.

2.8.2 Claim 1 of Claim Set K takes Claim 1 of Claim Set A and adds to it a requirement for the HB antigen to be in particle form and it appears that the particle must be in a form expressed in yeast.

2.8.3 In the passage which bridges pages 3 and 4 of P1, it is stated that HBsAg for the purposes of the invention includes HBsAg containing all or part of a pre – S sequence as described in EP-A 0 278 940 (D115) in addition to the 226 AA sequence of the HBsAg S antigen. The description at lines 39 et seq on page 36 of D115 discloses insertion into yeast of a yeast expression vector incorporating a Pre S2-s protein coding region resulting in synthesis of particles (which resemble authentic 22mm HBsAg particles). The passage bridging pages 3 and 4 of P1 thus exemplifies HBsAg for the purposes of the invention as these particular particles expressed in yeast. The relevant parts of the passage also appears in D108, duly supported as to priority date by the above passage of P1.

2.8.4 Example 1 in D108 mentions an HBsAg concentrate in general terms containing HBsAg which may, by virtue of the sentence at lines 9 to 1 of page 6, be a yeast-expressed pre-S2-5-containing HBsAg particle as mentioned above. In this regard, Example 1 defines by reference to materials and methods a range of AP-adsorbed HBsAg preparations and it is clear that the nature of the antigen is no less open to variation than defining parameters such as the amount of adjuvant.

2.8.5 Example 1 of D108 with the HBsAg concentrate exemplified as noted above appears to OII to enjoy the priority date of P1. However, Claim 1 of Claim Set K relies on the paragraph from line 24 to line 27 of page 6 of the application and this appears not to

enjoy such an early priority date – compare this with line 6 of page 4 of P1. D108 thus anticipates Claim 1 of Claim Set K under Article 54(3) EPC.

3. **Novelty - Article 54(2) EPC**

3.1 D85c discloses in Section II.8 thereof (pages 5 *et seq* of D85c) the preparation of HBsAg-DTPw in which AP used as adjuvant. According to Paragraph 2) of this Section (page 6 of D85c), HBsAg, diphtheria toxoid, tetanus toxoid and pertussis bacteria:-

> "*.....are mixed to be 1 ml and stirred for 12 hours with 100 rpm (Gyrotary shaker, G-2, NBS Co, USA) to be adsorbed.*"

3.2 D85c repeats the above preparative procedure in Paragraphs 3) and 4) of page 6 using, first, JE vaccine instead of the DTP of Paragraph 2) and, then, MMR vaccine instead of the DTP of Paragraph 2). The same language "*....to be adsorbed*" is used in Paragraphs 3) and 4) on page 6 as in Paragraph 2).

3.3 It seems clear from the above that the HBsAg was adsorbed to the AP. It is thus unsurprising that this was confirmed in the experiments reported in the declaration of Dr Contorni (D86).

3.4 Preparation of AP in gel form is described in Section 6 of D85c on page 5. It is to be noted that the separate phosphate and aluminium sources are mixed and stirred "*...to be pH 4.2*" (page 5, Section 7, line 2). However, importantly, it is also be noted that the AP was not used to adjuvant the HBsAg at pH 4.2 but that the mixture was allowed to stand for 2 days to separate a solid from a supernatant, the supernatant and residue separated, and the residue "washed" and then re-suspended in normal saline. Following this, the gel obtained was sterilized according to the thermal sterilization protocol set out in the final sentence of Section 7 on page 5 of D85c. According to the second line of page 6 of

D85c, 1.2 mg of this AP was then used to adsorb the HBsAg and other antigens in preparation of HBsAg-DTPw (AP) in Section 8 of D85c.

3.5 In short, preparation of HBsAg-DTPw (AP) in Section 8 of D85c is NOT carried out at pH=4.2 but at the pH of normal saline.

3.6 D85c also reports on immunogenicity tests (Section 9 of D85c) and, as these are self-evident, OII will make no specific comment on them in this submission.

3.7 The Patent as sought to be amended by, for example, Claims Set A of the Patentee's Claim Requests very clearly lacks novelty over D85 which clearly discloses and enables e.g. HBsAg-DTPw combination vaccine in which AP used as adjuvant and in which the HBsAg is adsorbed to the AP.

3.8 The Patentee has attempted to discredit D85c by challenging its enablement. That the reproducibility of its experimental work is challenged is an understandable recognition that D85c, a document having an obvious novelty-destroying nature, cannot be challenged in any other way – the Patentee has no other choice. However, the Patentee's challenge has no merit for two reasons, although it should be stated immediately that nothing in the Patentee's challenge or its flaws supports the assertion of complexity set out in Paragraph 10.3 of the Patentee's February 2005 Submission.

3.9 The first is that D107, the document which the Patentee puts forward as establishing that the procedures of D85c do not produce the results D85c asserts, is fatally flawed, as set forth in Paragraphs 3.11 and 3.12 below. The second reason (see Paragraphs 3.13 to 3.15 below) is that, in any event, a person of average skill in the art at the priority date claimed would have had no difficulty, based on the knowledge he would be expected to possess, in adapting the procedures of D85c to

more successful effect were it necessary to do so (which, it is submitted, it was not).

3.10 D107 is a declaration in which the declarant, Dr Garcon, reports on experiments she declares she has had carried out under her "direction" (see *inter alia* Paragraph 5 on page 2 of D107). The declarant states that work carried out repeated the experiments of Dr Contorni reported in D86 (Paragraph 5 of D107) and that in so doing "*efforts have been made to repeat the conditions described in the Choi thesis as closely as possible*".

3.11 Notwithstanding the D107 declarant's plain inference that Choi was followed, it is clear from even superficial scrutiny of her report of experimental conditions that this is not so in reality. Specifically, although it is well recognized in the art that pH is a material condition which may well effect outcome[3], the declarant reports in Paragraph 30 of D107 that the plasma derived HBsAg formulation prepared in Experiment 1 was "*prepared at pH 4.2*". As noted above in Paragraph 3.5 above, preparation of the HBsAg-DTPw (AP) in Section 8 of D85c is not carried out at pH=4.2 but at the pH of normal saline. Formulating the HBsAg-DTPw (AP) in D107 at pH 4.2 seems a most odd choice of experimental condition as the pH is too acid to be considered reasonable for human administration; it is specifically contrary to WHO guidelines[4]. The experiments, and the declaration as to their conduct in D107, appear to be perversions of what the scientist reporting in D85c actually teaches rather than reasonable attempts to follow the teaching of D85c.

3.12 The experiments reported in D107 are in any event generally scientifically weak in a number of respects. For example, having found

[3] For example, D84 filed by the Patentee mentions pH as a mediator of *"possible adverse consequences"* on Sheet 11

[4] See, for example, D116 which states in the first paragraph of page 146 that the pH of DT and DTP vaccines shall be 6.0-7.0

conflicting results to what is described in D85c, the declarant did not try to tease out why the finding of poor results occurred. In particular, the declarant has not performed an experiment where she tries to make the adjuvant without adding HBsAg to see if it aggregates by itself. Further, one would have expected an experiment in which HBsAg alone is adsorbed to the AP – if that did not aggregate the declarant's conclusion would have been very different. One wonders what degree of adsorption might have been achieved at, say, pH=5.7; it is noted that at pH 6.5 there was 20% adsorption (in contrast to the assertion of the Patentee in Paragraph 10.9.2.2 of his February 2005 Submission).

3.13 OII can thus be forgiven for feeling that the experiments set forth in D107 seem results-oriented, rather than oriented to follow the work reported in D85c, and to represent a conscious decision to avoid the pH range that an average scientist knows would result in adsorption of the HBsAg component to the aluminum phosphate. The conclusion the Patentee draws from the D107 experiments are no less flawed than D107 itself and do not displace the prima facie case that D85c discloses exactly what it purports to disclose – namely a DTP-w-HB (AP) vaccine.

3.14 In this respect, it is informative to note that the selection of adjuvants, antigens and adsorption conditions were considered sufficiently well understood at the date of D85c (1988) that a project of this type was considered at this time to be Masters Degree level research at a Korean Food Institute. At the priority date claimed by the opposed patent, a few years later in 1992, how a person of average skill in the art should go about preparing a quadrivalent vaccine composition such as DTP-HB was well-known throughout the art. Specifically, the factors that must be considered in selecting the conditions for adsorbing various antigens to various aluminum salts had been known for some years (see, for example, D114).

3.15 As OI has noted in Paragraph 5.10 of its May 2004 submission (first and second bullet points), the Patentee has always taken the position that the invention resides in the inventive act of *selecting* AP to adjuvant the HBsAg, the number of antigens not per se being a procedural problem either in the context of DTP-HB quadrivalent vaccines or indeed in the context of vaccines having larger numbers of antigens. In short, there is no *process difficulty* involved once the idea is realized.

3.16 In the setting of DTP-HB quadrivalent vaccines, of course, the Patentee's position on how to prepare inter alia DTP-HB quadrivalent vaccines, is actually set down in the patent specification itself in a way which is entirely consistent with this; the first two lines of page 4 of the opposed patent state:-

> *"The preparation of the antigens and adsorption procedure with the adjuvants are well known in the art, see for example as given below."*

3.17 Rather importantly, D22 recognized this in the first half of 1992 in predicting, *inter alia* at the base of page 8 (Section 5 of the document), that *".....the commercial development of DTP-HB should be entirely possible."*

3.18 No doubt the Patentee will challenge this. He has already challenged the very clear atmosphere of optimism which runs through D22 (so far as OII puts that forward at First Instance). Thus in Paragraph 5.4.2.1 on page 16 of his Statement of Grounds of Appeal he takes two passages of D22 and attempts to dilute them with arguments which are simply unrealistic, repeating the same in Paragraphs 11.3.4 and 11.3.5 of his February 2005 Submission.

3.19 In relation to Section 6 on page 9 and the connected content of the third paragraph on page 10 of D22, the Patentee's position seems to

be that D22 is pointing to a major DTP-HB combination vaccine preparation problem and that D22 concedes that the problem is also **so insoluble** that those skilled in the art should just give up and accept a rather poor compromise. However, this is not what D22 is saying at all. Rather D22 is saying in the first of the quoted paragraphs that a degree of loss of HB performance was lost in small scale trials carried out thus far – but this is far outweighed by the optimistic statement everywhere else in D22 that a successful DTP-HB vaccine *can and will be produced*. The document has a high note overall and not in reality a low note even in the paragraph the Patentee quotes if this is taken in context and given perspective.

3.20 In the second of the quoted paragraphs, it should be noted that the authors of D22 refer to a good compromise not a poor one. A seroconversion rate of 95% is quoted as acceptable; this seems to be much in accord with what has been achieved by HB monovalent vaccines. In this respect, the Board should note D56, a March 1992 publication quoting broadly similar seroconversion rates for two commercial HB monovalent vaccines.

3.21 In short, the Patentee has exhibited a talent for telling good news as if it were bad news. The WHO recommendations for including HBsAg in combination vaccines (D22) and the clear teachings in Genentech (D19) of the 2.36X superiority of AP for adjuvanting HBsAg in HB vaccines inevitably led to what D85c discloses and what the Patentee claims to be inventive. The fact that Mr Choi in D85c did the obvious does not detract from the overall high quality of the thesis that memorializes his work, but it does clearly demonstrate the unpatentable nature of the subject-matter of the opposed patent.

4. **Article 83 EPC Sufficiency**

4.1 General

4.1.1 OII has elucidated in Section 4.1 below, a number of reasons why the patent fails to provide the skilled man with the information necessary to put the invention claimed into practice, without undue effort or the exercise of inventive ingenuity, across the scope of the claims. OII submits that the patent fails to explain how the invention can be put into practice with a complement of antigens other than those constituting the core invention.

4.1.2 In short, everyone knew within a comparatively short space of time after the priority date that making a safe, effective, stable combination vaccine beyond the DTP-HB core invention involved considerable problems. The patent specification, however, was apparently constructed without that knowledge and simply does not contain any guidance on how these problems might be tackled to reduce the penumbra of inventions to practice.

4.2 The comparison between HEXAVAC and INFANRIX-HEXA vaccines

4.2.1 Opponent II brought the dispute between the Patentee and Opponent I as to the adjuvant used for the Hepatitis B component of HEXAVAC, the vaccine sold by Sanofi Pasteur MSD, formerly Aventis Pasteur MSD to the attention of Merck and Company. Opponent II, Sanofi Pasteur, formerly Aventis Pasteur, and Merck and Company operate as a 50:50 partnership in Europe, Sanofi Pasteur MSD. Merck and Company supply the joint venture with the HepB bulk vaccine for combination with the other vaccine components to produce HEXAVAC. The response Opponent II received from Merck is attached as D109.

4.2.2 The bulk vaccine that has always been used for Merck's and the joint venture's monovalent HepB products is identical to the ones provided to Sanofi Pasteur for formulating HEXAVAC. The chemical composition of the aluminum salt in all the bulk HepB lots is aluminum hydroxyphosphate sulfate.

4.2.3 It is important to understand that the aluminum salt used in all of Merck's HepB vaccines was reasonably believed to be aluminum hydroxide for many years. The categorical approach to calling all the aluminum salts either aluminum phosphate or aluminum hydroxide only began to change in the late 1980s and early 1990s when the actual chemical compositions of the various aluminum salts began to emerge (See D110).

4.2.4.1 The specific aluminum salt used to adjuvant the HepB component of HEXAVAC, aluminum hydroxyphosphate sulfate, is defined in the opposed patent as an aluminum phosphate adjuvant.

4.2.4.2 As shown in a Press Release issued by the European Medicines Agency, London, 20 September 2005 (D111) the Agency recommended as a precautionary measure the suspension of the marketing authorization for HEXAVAC due to concerns about its capacity to provide long-term protection against Hepatitis B. The vaccine is not licensed for US marketing.

4.2.4.3 The Patentee argues that its hexavalent vaccine is superior to HEXAVAC because the Patentee uses aluminum phosphate to adjuvant the HepB component while Sanofi Pasteur MSD uses aluminum hydroxide to adjuvant the HepB component of HEXVAC. It is abundantly clear that both products use an aluminum phosphate as that term is defined in the opposed patent.

4.2.4.4 Accordingly, the Patentee's arguments that HEXAVAC's Hepatitis B antigen component is inferior because it is adjuvanted with aluminum hydroxide (the "wrong adjuvant") instead of with aluminum phosphate (which Patentee invites the Board to regard as the "magic adjuvant" that eliminates all immunogenicity and stability issues for combination vaccines) completely undermines the patentability of the patent under appeal.

4.2.4.5 When the fact that HEXAVAC is adjuvanted with aluminum hydroxyphosphate sulfate, which is aluminum phosphate according to the patent, is combined with the Patentee's own arguments that HEXAVAC does not work in the same manner as the combination vaccines claimed by the opposed patent, the invalidity of the patent is abundantly clear. In particular, the Patentee is actually arguing that the problem of reduced immunogenicity is not solved simply by using an AP-adsorbed HBsAg (which appears to amount to an admission that the scope of the invention claimed is not enabled).

4.3 The Nature of the Aluminum Adjuvants

4.3.1 Opponent II does not wish to further inundate the Board with facts and evidence, but a brief discourse on aluminum salts is provided below to help resolve the confusion over which aluminum salts are used as vaccines and how much of the history of aluminum adjuvants has been based on mistaken assumptions as to what was believed to be "aluminum hydroxide" and what was believed to be "aluminum phosphate".

4.3.2 Historically, vaccines containing aluminum adjuvants have been prepared by two distinct methods. First, commercially prepared adjuvant, labelled aluminum hydroxide or aluminum phosphate is

mixed with the antigen resulting in aluminum hydroxide or aluminum phosphate adsorbed vaccine. Second, an aluminum-containing adjuvant can be prepared by in situ precipitation. Generally, a solution of $KAl(SO_4)_2 - 12H_2O$, is mixed with the antigen in a buffered solution and mixed with NH_4OH to pH 6.5 to form a precipitate which has been called protein aluminate.

4.3.3 Commercial aluminum hydroxide adjuvants are generally labeled aluminum hydroxide, but have been characterized as crystalline aluminum oxyhydroxide, AlOOH (see D110). The hydroxylated surfaces of aluminum hydroxide may become charged, either through amphoteric dissociation of the surface OH groups, or by adsorption of H^+ or OH^- or other potential-determining ions. Crystalline aluminum oxyhydroxide has a small particle size and a large surface area. Aluminum hydroxide has an isoelectric point (pI) of about 11, and at a physiological pH range of around 7.4 the adjuvant surface is positively charged and will adsorb negatively charged antigens by electrostatic attraction (see D112).

4.3.4 Commercial aluminum phosphate adjuvants do not exhibit a crystalline phase and are characterized as being amorphous. IR spectroscopy reveals the presence of structural hydroxyls which has resulted in these adjuvants being designated amorphous aluminum hydroxyphosphate (see D110). Commercial amorphous aluminum hydroxyphosphate adjuvants, such as Adju-phos, have an isoelectric point around 5[5]. In physiological solutions at pH 7.4, these antigens have a negative charge and exhibit an electrostatic attraction for antigens that are positively charged at pH 7.4.

4.3.5 Alum precipitated adjuvants are generally prepared by mixing an antigen in a buffered solution with $KAl(SO_4)_2 - 12H_2O$ and NH_4OH. The resulting adjuvant not only contains aluminum hydroxide but

[5] Aluminum phosphate adjuvants have a PO_4/Al molar ratio of 0.8 – 0.9.

also contains sulfate ions and anions from the buffer solution. Depending on the buffer the ions could be acetate, carbonate, citrate, phosphate or others. The precipitate exhibits an amorphous structure and the IR spectra contains bands associated with sulfate and the buffer ion. The chemical and structural analysis suggests that alum precipitated adjuvants are amorphous aluminum hydroxy (buffer anion) sulfates. The composition and properties are dependent upon the precipitation conditions and the buffer. Many adjuvants are prepared using alum and an antigen in phosphate buffer and are best described as amorphous aluminum hydroxyphosphate sulfate (D112)[6]. The level of substitution of phosphate for hydroxyl depends on the concentration of the phosphate buffer and the precipitation conditions.

4.3.6 In light of the preceding, aluminum phosphate is not a term clearly defined in the patent. At page 3, lines 6-12, the specification states:-

"For example, aluminum phosphate can be a precipitate of insoluble aluminum phosphate (amorphous, semi-crystalline or crystalline), which can be optionally but not exclusively prepared by mixing soluble aluminum salts, and phosphoric acids salts. "Aluminum hydroxide" can be a precipitate of insoluble (amorphous, semi-crystalline, or crystalline) aluminum hydroxide, which can be optionally but not exclusively prepared by neutralizing a solution of aluminum salts. Particularly suitable are the various forms of aluminum hydroxide and aluminum phosphate gels available from commercial sources, for example, Alhydrogel (aluminum hydroxide, 3% suspension in water) and Adju-phos (aluminum phosphate, 2% suspension in saline) supplied by Superfos (Vedbaek, 2950 Denmark)."

[6] Alum-precipitated adjuvants have a PO_4/Al molar ratio in the range of 0.3-0.6

4.3.7 Based on this description, aluminum phosphate might mean crystalline or semi-crystalline aluminum phosphate with no hydroxyl groups present at all. It might mean aluminum hydroxyphosphate preformed gels and all the possible combinations of phosphate and hydroxide that this range of compositions encompasses. It might mean alum-precipitated adjuvant including aluminum hydroxyphosphate sulfate and all the possible combinations of phosphate and hydroxide and sulfate that this range of compositions encompasses. It could also mean aluminum hydroxide adjuvants dissolved in phosphate buffer as free phosphate anions adsorb onto the surface of aluminum hydroxide through ligand exchange (see D113).

4.3.8 Furthermore, the definition of aluminum hydroxide is also unclear. The opposed patent states that "aluminum hydroxide" can be a precipitate of insoluble (amorphous, semi-crystalline, or crystalline) aluminum hydroxide, which can be optionally but not exclusively prepared by neutralizing a solution of aluminum salts." This definition permits the use of phosphoric acid to neutralize the solution of aluminum salts which would give rise to an adjuvant containing both hydoxyl groups and phosphate groups.

4.3.9 The only Example (Example 1) in the opposed patent describing the aluminum phosphate adjuvant used in all the experiments conducted in the rest of the Examples does not make clear to one of skill in the art how the aluminum adjuvant was made. Example 1 states:-

"A suspension of aluminum phosphate containing 0.03 to 0.3 g aluminum (as aluminum phosphate) in isotonic saline is mixed with HBsAg concentrate, containing 10 mg HBsAg protein, in a final volume of 10 to 100 ml. After adjusting the pH to 5 – 6.5 the mixture is left 10-24 hrs at room temperature with stirring."

4.3.10 The patent poses too many questions:-

What aluminum phosphate was used, crystalline, semi-crystalline, pre-formed gel?

What solution was used to adjust the pH-sodium hydroxide?

What was the aluminum phosphate adjuvant that the patentee used to perform its Examples?

4.3.11 While the opposed patent specification would lead one to believe that the choice of adjuvant does not matter as long as there is some phosphate present the data would indicate otherwise. It is inconceivable that the use of all the possible compounds covered by the term aluminum phosphate as defined in the patent in suit solves the problem stated by the Patentee.

4.3.12 The relevance of the meaning of aluminum phosphate in the context of these proceedings is highlighted in D73. In D73, the declarant goes to some length to demonstrate that aluminum phosphate-adsorbed HBsAg is superior to aluminum hydroxide-adsorbed HBsAg in a combination vaccine. What he fails to reveal is that the aluminum hydroxide adsorbed HBsAg vaccine, which he indicates has lower HBsAg titers in one case, is in fact alum-precipitated HBsAg which is chemically aluminum hydroxyphosphate sulfate. Thus, according to the declarant's data, the skilled man is faced with a dilemma: either the claimed invention does not cover alum-precipitated HBsAg adsorbed combination vaccines or the invention covers a large number of non-enabled embodiments that the patentee has not defined.

4.3.13 Aluminum adjuvants are influenced by many other factors including pH, age of the solution, preparation, formulation. There

is absolutely no guidance in the patent, nor is there any indication as to what conditions are required to obtain the desired effect.

4.4 The Nature of the Antigens/Pathogens

4.4.1 The "definition" of Hepatitis B antigen in the patent appears at page 4, lines 6-20 of the patent. This definition includes any HBsAg or fragment thereof, the HBsAg and part of a pre-S sequence, the preS1-S2 polypeptide as well as analogs thereof, mutants of HBsAg as well a particles containing HBsAg - apparently anything that remotely resembles Hepatitis B is covered by the patent.

4.4.2.1 The patent provides even less information regarding the other antigens, which in combination with the HBsAg, the Patentee seeks to cover. According to page 4, lines 21 and 22 of the patent:-

"Suitable antigens for use in vaccines according to the invention are already commercially available and details may be obtained from the World Health Organization."

4.4.2.2 The extreme generality of this "guidance" is interesting when considered in isolation and absurd when combined with the Patentee's statements and arguments in its Appeal submissions on the invention extending to subsequently discovered pathogens and subsequently discovered antigens from these new pathogens.

4.4.3.1 The Patentee's submissions of 5 December 2003 state at page 25, final sentence (continuing on page 26):-

"We submit that it would be unfair if the patent claim was found invalid purely because it could not envisage a new virus being identified."

4.4.3.2 The patent attempts to rely on details from the WHO and the availability of commercial vaccines for operating the invention yet attempts to cover vaccines for subsequently discovered diseases.

4.4.4.1 The IPV component for inclusion in the vaccines of the invention is discussed at page 4, lines 22 and 23 of the patent:-

"the IPV component may be the Salk inactivated polio vaccine".

4.4.4.2 Of course it may be something else, but what else is not clear. Typically, inactivated polio vaccines contain a mixture of inactivated poliovirus types 1, 2, and 3. As members of the family Picornaviradae, each of the poliovirus types in the typical trivalent inactivated poliovirus vaccine (SALK vaccines) contains a genome that expresses a polyprotein that is cleaved to yield at least 12 polypeptides (D92).

4.4.5 Thus, the typical trivalent inactivated poliovirus vaccine contains at least 36 distinct proteins. The guidance in the patent as to what is a reasonable number of antigens for the combination vaccines is on page 2, lines 38-42. The preferred number of antigens that can be included with the HBsAg is 2,3,4,5 or 6. Thus, the combination of HBsAg and IPV results in 30 antigens above the preferred number of antigens. Perhaps "antigens" and "pathogens" are among the things that are confused in the patent, but that is what the patent describes.

4.4.6 The guidance provided by the patent as to the selection of pertussis vaccine components is equally enlightening. According to the patent (page 4 lines 23-26), whole cell pertussis, acellular products and recombinant pertussis proteins are acceptable. Obviously, the hundreds or thousands of antigens present in a whole cell pertussis vaccine would surpass the preferred upper limit of antigens (6), but that is what the patent teaches then contradicts. The patentee makes no distinction among the myriad possible pertussis components except to mention PT (pertussis toxins) or sub-fragments thereof, FHA, agglutinogens and other outer membrane proteins including 69 kDa protein.

4.4.7 Despite first hand knowledge of the criticality of proper production methodology and formulation of the pertussis components, this is not even mentioned and thus no guidance is provided. D105, Table 2: Immunogenicity and Efficacy of Several Accelular Pertussis Vaccines from Pertussis Vaccine Trials, Developments in Biological Standardization highlights this point. The obvious inferiority (59% efficacy) of the SKB vaccine containing 25 ug of PT and 25 ug of FHA relative to the "equivalent" PT and FHA vaccines of Connaught (95% efficacy) and Pasteur Merieux (85% efficacy) is striking. The data of Table 2 underscore the comments of Francois Andre in D74 that "the possible deleterious interactions between the antigens, preservatives, adjuvants, stabilizers, excipients, residual contaminants are so numerous and unpredictable that it is highly likely that the immunogenicity and stability of some of the antigens will be adversely affected." Of course, Andre was referring to a hexavalent vaccine, but Table 2 is conclusive proof that the same unpredictability exists at the level of a simple DTP vaccine.

4.4.8 The Examples of the patent that utilize acellular pertussis components indicate that PT (25ug), FHA (25ug) and an optional 8 ug of 69 kDa OMP were used. This combination corresponds to

the pertussis components in the 3 valent pertussis component of the DTP vaccine described in Table 2 of Pertussis Vaccine Trials, Developments in Biological Standardization that was cited above. The combinations of pertussis components in Table 2, i.e., 59 % efficacy for the 2 valent: 25 ug PT, 25 ug of FHA and 84 % efficacy for the 3-valent formed by addition of 8 ug 69 kDa component. The 3-valent combination reported in Table 2 also corresponds to the pertussis component of Pediarix ™, a GSK combination vaccine (see D106 for this product). A comparison of the seroconversion data in the patent and the GSK Prescribing Information at page 8 is interesting. In addition to the differences in seroconversion rates, the suppression of the response to FHA in Pediarix ™, a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B and IPV vaccine is notable.

4.4.9 The patent indicates that Havrix™, a GSK inactivated Hepatitis A vaccine is suitable as the Hepatitis A component of the Patentee's limitless combination vaccines. This seems to be at odds with the Patentee's views in EP 1 107 787 (D91) wherein they report incompatibilities of a Salmonella typhi vaccine and Hepatitis A vaccine. If inactivated Hepatitis A vaccine is used, it is worth noting that Fields Virology, volume 4, at page 806 (D92) indicates that Hepatitis A encodes 4 capsid proteins (1A, 1B, 1C and 1D), 3 non-structural proteins (2A, 2B and 2C) and 4 non-structural and Vg products (3A, 3B, 3C and 3D). At page 4, lines 36-37 of the patent we learn that these proteins can be expressed recombinantly and used in the Patentee's vaccines. In other words, there are many choices, but no guidance. The Patentee's guidance on HepA also adds another potential 11 antigens to the Patentee's vaccine, which the Patentee indicates has a preferred upper limit of 6 antigens in addition to whatever HBsAg is used.

4.5 The Amount of Antigens

4.5.1 The inconsistency and resulting confusion over the patent's preferred number of antigens and the limitless choices of antigens the Patentee offers is unsettling, but the patent's instructions on how much total immunogen should be used is dumbfounding. At page 4, lines 40-43, the skilled artisan is instructed as follows: "generally it is expected that each dose will comprise 1-1000 ug of total immunogen, preferably 2-100 ug, more preferably 1-40 ug, most preferably 1-5 ug." Thus, the patent's indication of the preferred amount of total immunogen per dose, 1-5 ug, is entirely inconsistent with the remainder of the specification and the Examples. The only components of the Patentee's vaccines that are referred to by weight are the acellular pertussis components (25 ug PT, 25 ug FHA and optionally 8 ug of 69 kDa OMP) and HBsAg (5 ug or 10 ug). The diphtheria and tetanus components are described in terms of units. The whole cell pertussis component is defined in Elisa units. Viewed in the best possible light, one component, the HBsAg component fits the preferred range in 1 of 2 cases.

4.5.2. In particular, in light of the issues pointed out in Paragraph 1.5 above, it is not clear how the patent could enable a man of average skill to ensure avoidance of competitive redistribution of HBsAg from AP to AH.

4.5.3. In conclusion, the patent offers an "invitation to experiment". It does not provide a sufficient description of combination vaccines.

5. Inventive Step and Enablement Must be Considered Together

5.1 The sufficiency of a patent specification depends inter alia on the sum of the enablement it contains and the enablement which exists in the

art already at the priority date. The specification must contain what the art does not provide; if it does, Article 83 EPC is complied with, the converse also being true.

5.2 The specification and the state of art contain sufficient information to enable the DTP-HB (AP) vaccines to be made. However, the specification adds little in that regard to the state of the art, if anything; the substance of the enablement for DTP-HB (AP) vaccines appears in the state of the art[7].

5.3 So far as the invention extends beyond DTP-HB (AP) to other multi-valent vaccines, this is even more so. It is thus to the state of the art that one must look to find enablement for this additional scope of protection[8]. If it exists in the state of the art, then there is enablement but not otherwise.

5.4 With information necessary to provide enablement and information which is antithetic to inventive step not just coming from the same source (i.e. the state of the art) but being coincidental in substance, it seems to OII that Articles 56 and 83 EPC are unusually bound together in this instance. They are tests for validity of the patent which must be asked together and not in separate compartments.

5.5 The difficulty practically in these proceedings is in relation to what set of claims these tests are actually to be asked.

5.6 Claim Sets A to G, I and J are not allowable for reasons which include non-compliance with Article 54 EPC.

5.7.1 Claim Set H distinguishes itself from the other claim sets by being a preparative method limited to "complete and stable adsorption of the respective components". Disregarding issues under Article 54

[7] As the opposed patent itself admits at lines 1/2 of page 4 thereof
[8] See Paragraph F3.6 on page 48 of OII's May 2004 Observations

EPC for a moment as well as formal issues under Articles 84 and 123(2) EPC, it might be argued by the Patentee that the above-quoted passage confers inventive step under Article 56 EPC. However, this seems indefensible. The opposed patent states at page 4, lines 1/2 that the adsorption procedures to be used (eg separate adsorption of antigens) are well-known in the art and that those used in the Examples fall into this category. Specifically, no special measures are indicated for achieving "complete and stable adsorption" in any particular context for the invention, the measures to be adopted simply being the adoption of procedures the patent says "well-known in the art". As such, the limitation in Claim 1 relates to routine laboratory techniques incapable of conferring inventive step unless eg "complete" adsorption is practically impossible or an objective requiring special measures in which *either* case the patent lacks enablement under Article 83 EPC[9].

5.7.2 Claim 1 of Claim Set K requires the HBsAg to be particles in the form in which they are expressed in yeast, a form of the antigen the Patentee submits replaced plasma-derived antigen "in the late 1980's". The "new form" of antigen was the favourite at the priority date, appears to be Patentee's submission. The question to be posed in terms of inventive step assessment would thus appear to be whether a skilled man reading D85c at the priority date would be motivated to use the "favourite form" of the antigen instead of plasma-derived antigen. Influenced by the "shift" to which the Patentee refers in Paragraph 11.17.2 of his February 2005 Submission, the answer appears to be in the affirmative. D107 might have been expected to have discussed the differences between the two forms of antigen in its Paragraph 7 had there been a reason to suppose they were differences material to the exercise of choice. However, D107 enters into no such discussion and it is impossible to resist the conclusion that it regards use of

[9] See D46 (Paragraph 11) and D73 (Paragraph 10)

recombinant (and particulate yeast –expressed) HBsAg as conforming to D85c (see D107, e.g. Paragraph 8).

5.8 OII would like to postulate limitation of the claims to DTP-HB (AP) – [IPV and/or Hib] although (i) it is not seen how any such claim could be formulated in allowable form nor (ii) why discretion should be exercised by the Board to admit a yet further claim request at this late stage in the proceedings.

5.9 In the context of this penumbra invention as the Patentee might choose to define it in any purportedly formally allowable further claim request which the Board might admit, the closest art is D85c. As noted in Paragraph 3 above, D85c discloses HBsAg-DTPw (AP) multivalent vaccine. D85c appears on the face of it to be a more well-qualified candidate for closest prior art than D22 (contrary to Paragraph 11.5 of the Patentee's February 2005 Submission). However, D22 (optionally in combination with D61[10] which refers more generally to larger numbers of disease valencies beyond the core invention), remains an important publication in the overall prior art matrix.

5.10 The objective problem might then be formulated (contrary to Paragraph 11.7.1 of the Patentee's February 2005 Submission) as follows:-

> *How to provide polyvalent vaccines with additional disease valencies to DTPw- HB (AP), namely polyvalent vaccines including antigens selected to provide immunity against (i) diphtheria, tetanus, pertussis and Hepatitis B and (ii) polio [using IPV as antigenic component] and/or Hib, such polyvalent vaccines being safe, stable and having at least acceptable immunogenicity in all disease valencies.*

[10] D22 is a WHO publication of joint WHO and Task Force work, and D61 is a Task Force publication, As explained in D63, the Task Force is a WHO sub-organisation specifically assigned to development of the WHO "EPI programme" mentioned throughout D22 and D61 and the fulcrum of the work reported in each document. The Chair of the Task Force (see D63, page 4), Dr Maynard, was primarily responsible for D22 (see D77 and Exhibits). D22 and D61 may therefore be combined according to T176/89 and T487/95.

5.11 It seems to OII that at the priority date the questions to be asked in relation to the assessment of inventive step are the usual ones:-

1. *Would a skilled man consider the addition of the further disease valences to the DTP-HB (AP) with a reasonable expectation that the objective problem could be solved by so doing?*

2. *If the answer to this question is "yes", would the skilled man, in attempting to reduce this addition of disease valences to practice based on the state of the art, then encounter difficulty requiring for its resolution either (i) the exercise of inventive ingenuity or (ii) some other undue burden which caused him to dismiss his initial hypothesis that the further disease valences could be added to the DTP-HB (AP) with a reasonable expectation that this would solve the objective problem?*

5.12 If the answer to Question 2 is "***yes***", then the claims concerned may have inventive step but by the same token, the patent (whose specification contains nothing by way of enablement which is not also in the state of the art), contravenes Article 83EPC[11].

5.13 If the answer to Question 2 is "***no***", then there is a lack of inventive step but by the same token, the specification may be enabling and the patent may comply with Article 83 EPC.

5.14 There is a wealth of evidence to support the idea that there are serious technical problems associated with the provision of additional

[11] See Paragraph F3.7 on pages 48 and 49 of OII's May 2004 Observations

antigens[12] to what OII has referred in its May 2004 Observations as the Patentee's "core invention". OII will wish to make oral submissions on these points at oral proceedings but for the moment wishes just to recall to the minds of the members of the Board the admissions by the Patentee in these respects contained in documents in the authorship of the Patentee's own scientific personnel. D74 is perhaps a prime example worthy of the Board's immediate attention.

5.15 The Patentee's response to these issues is, of course, to dilute what its own scientists have said and in any event to reformulate the objective problem in an attempt to exclude them from serious and proper consideration in assessing inventive step/enablement.

5.16 D74, for example, is plainly bad news for the development of polyvalent vaccines, but the Patentee invites the reader to think otherwise. To this end, he launches (i) on pages 31 an 32 of the Statement of Grounds of Appeal into a linguistic analysis of the document (which it seems to OII back-fires, as will be explained at oral proceedings) and (ii) a submission, in the second paragraph on page 32 of the Statement of Grounds of Appeal, that the author is really just talking about regulatory approval when he mentions the word "insurmountable" near the base of page 1 of D74. In essence, the Patentee invites the reader to see clear bad news as news which is not really too bad at all.

5.17 However, this is misconceived, and it is not difficult to come to an objective balanced view on the basis of D74 as whole (it is a short document) that 7.5 years after the claimed priority date, the Patentee's "*experience accumulated at SmithKline Beecham Biologicals over the last ten years*" indicates that (i) the hexavalent vaccine referred to took "*several years*" to develop (no doubt for the reasons set forth in 1992 by the Patentee's same scientist in D63[13] and by the same scientist

[12] See Paragraphs F3.8 to F3.11 of OII's May 2004 Observations and D85 as discussed on page 31 of those Observations

[13] See the second half of the fourth internal sheet

again in 1994 in D66[14]) and (ii) the Patentee expected, even as late as 1999, that making other polyvalent vaccines would be seriously problematical.

5.18 Of course, the Board must decide this issue. With it currently undecided, OII would like to move on to the issue of adjuvant choice.

5.19 The Patentee's position has always been that AP is a counterintuitive choice which a skilled man would not make. OII's position has always been that it is clear that there are a number of reasons why AP would be seen as a candidate for use in HBsAg adsorption in an HB monovalent or multivalent vaccine; in any event, the directions which are clear in D22 are directions to mix pre-existing vaccines, some of which contain AP-adsorbed HBsAg in the first place. As the Patentee asserts that none of this is true, it seems worth reminding the Board at this point why the Patentee is wrong.

5.20 D19 (Genentech) provides a direct comparison of the immunogenicity of HBsAg adsorbed to AP and AH in Table 1 at page 18. The AP adsorbed HBsAg was 2.36 times more potent than the AH-adsorbed HBsAg. Any objective scientist would have seriously considered selecting, for use in e.g. DTP-HB multivalent vaccine, the best of the 2 possible aluminum salts based on a clear 2.36 X superiority, and he would do so with a reasonable expectation that the result would be to his advantage.

5.21 D19 does not present human data as the experiments which are reported in D19 were conducted using mice. However, it is, of course, normal practice (and was normal practice in 1992) in vaccinology initially to test a candidate vaccine in a mouse model, and it is considered in the art, and was considered in 1992, that acceptable results achieved in such a test indicated a sufficient likelihood of

[14] See the "Conclusion" section on page 320

efficacy in human patients to justify confirmatory tests. Satisfactory mouse tests constituted in 1992 a widely used (see D22, top of page 10) indicator serving as a clear incentive to consider and use an antigen formulation for use in a vaccine.

5.22 The title of Example 7 of the patent states that the Example relates to "*Mouse immunogenicity tests and results of accelerated stability tests for combination vaccines comprising HBsAg with aluminum hydroxide (AH) or aluminum phosphate (AP)*". This suggests the Patentee is confident about the extrapolation of mouse data, and it is to be noted that Example 7 is the only Example in the two priority documents to address performance of DT-HB (AP) and DTPa-HB (AP) vaccines in accordance with the invention.

5.23 In any event, as noted by OI at Paragraph 9.6 on page 16 of its February 28, 2003 submission, D56 set forth results that are complementary to D19 from a human clinical trial that compared AH and AP as adjuvant in two commercial HB monovalent vaccines, namely Heppacine-B (AP-adjuvanted HBsAg) and Hevac-B Pasteur (AH-adjuvanted HBsAg). The paper reports seroconversion rates for the two vaccines which were broadly comparable but with Heppacine superior (e.g. 95.8% at month 9) and with Heppacine having the highest GMT at month 15 (Heppacine GMT = 584mIU/ml; Hevac GMT = 323mIU/ml); importantly, D56 notes in the paragraph bridging pages 19 and 20 that a previously conducted trial reported in 1987 showed Heppacine-B to have achieved a seroconversion rate of 96% (dose schedule: 3micrograms AP-adjuvanted HBsAg at 0, 1 and 6 months).

5.24 Interestingly, consistent with the 2.36 superiority factor reported in D19 for AP over AH, Table 1, page 7 of D106, a later document published after the priority date, reports GMCs of 1661.2 for HBsAg-AP (Pediarix) versus GMC's of 804.9 for HBsAg-AH (Infanrix) - a superiority factor of 2.06 for AP over AH in the context of a pentavalent vaccine.

5.25 The Patentee has suggested that the prior art actually teaches away from the use of AP as an adjuvant for HBsAg (see the Patentee's February 2005 Submission at Paragraph 11.8.2 et seq, and elsewhere). Specifically, the position the Patentee has taken in D45[15] (a declaration by Koen De-Heyder) is that:-

> *"...if one knows the charge of the antigen (from the pI [isoelectric point of or pH at which the antigen has zero charge]), one can predict to which aluminum salt the antigen would most strongly absorb. Taking the specific example of HBsAg, the clear preference is for aluminum hydroxide. The pI of HBsAg is 4-5, so its electrical charge at neutral pH is negative. Aluminum hydroxide is positively charged at neutral pH which makes it a better candidate for HBsAg absorption than aluminum phosphate (which is negatively charged at neutral pH and so would be a very weak adsorbent for HBsAg). This is probably the reason why most of the commercially available HBsAg containing vaccines, like our own Engerix™ use aluminum hydroxide as an adsorbant."*

5.26 Mr. De-Heyder is telling only part of the story. First, he presents his points (a) as if they are current thinking today and (b) as if actual practice at the priority date provides empirical support his theory. On both counts, this is just is not true.

5.27 Dealing with the first of these criticisms, antigens may be adsorbed to aluminum antigens by a variety of mechanisms including electrostatic attraction, hydrophobic interaction and ligand exchange. HBsAg is a phospholipid containing antigen and recent studies indicate electrostatic interaction, as implicated by Mr De-Heyder, plays almost no role in HBsAg adsorption. In fact, ligand exchange is the predominant mechanism by which aluminum containing adjuvants are,

[15] See also the Patentee's February 2005 Submission at Paragraph 11.8.14

in today's understanding of adjuvant behavior, adsorbed to HBsAg (see D93). Therefore, the fact that aluminum hydroxide is positively charged and HBsAg is negatively charged is of no consequence, according to modern thinking, concerning adsorption of the adjuvant to this antigen.

5.28 Dealing now more importantly with the second criticism of Mr De-Heyder's testimony, he states that AP is negatively charged at neutral pH and so would be a very weak adsorbent for HBsAg. On that basis, one would expect that it would *never* be used to adsorb HBsAg, not merely that *"most"* commercially available HBsAg-containing vaccines would use AH. This must follow from the fact that adsorption was, crucially, regarded by those in the art in 1992 as essential for the manifestation of at least the adjuvanting of immunogenicity. Both D46 (the declaration of Dr Petre – see Paragraph 11) and D73 (the declaration of Dr Desmons – see Paragraph 8) state that "*the prevailing view*" in 1992 in the art was that all antigens ***had to be adsorbed*** to be immunogenic.

5.29 The fact of the matter is that there is no evidence at all to support the idea that AP would *never* be used to adsorb HBsAg. In this connection, as noted throughout these proceedings, AP had been used over a period of many years to adjuvant HBsAg in a monovalent vaccine context; it was, for example, commonly used for this purpose in Holland. There is support for the above assertions in, for example, D9, D10, D11, D28, D56, D79 and D101a. D19 and D85, of course, clearly show no prejudice against AP. D38 may (as the Patentee states) expresse the view that continued use of AP is a "puzzling enigma" but it does seem to recognise its use as an empirical fact; a bumble bee does fly although it should not be able to. D38 is dated 1992. Interestingly, Paragraph 11 of D73 (the affidavit of Dr Desmons) points to a specific procedural incentive to use AP rather than AH to adsorb HBsAg.

5.30 There is accordingly no evidence at all that Mr De-Heyder's opinion has been borne out in empirical experience in the vaccine field. OII suggests that there were in fact no cogent reasons at all not to employ AP to adsorb/adjuvant the HBsAg.

5.31 This raises the question of why the Patentee, prior to making the alleged invention, ignored the clear teachings in the prior art and decided to use HBsAg-AH as the HepB component as described at line 19 *et seq* of the opposed patent. The Patentee's well articulated, but scientifically baseless arguments regarding the "bias" against using AP provide interesting reading, but the actual reason is obvious: the Patentee's pre-existing monovalent Hepatitis B vaccine was one which was adjuvanted with AH and it seemed to the Patentee that to use anything else as a HB vaccine to mix with DTP vaccine made no sense. The parallel with D22's suggestion of mixing *ready-prepared* HB *monovalent vaccine* with *ready-prepared* DTP trivalent vaccine is obvious. It is that which D22 urges be done and suggests is successfully achievable to produce an acceptable quadrivalent DTP-HB vaccine, circumventing the issue of whether AP per se would be chosen as adjuvant.

6. Procedural and formal matters

OII does not feel that economy of proceedings will be served by any of the parties filing voluminous submissions on procedural and formal matters, and it does not intend to do so (whilst expressly requesting the opportunity of making oral submissions at the oral proceedings). In short, OII's position is as follows:-

- There were significant procedural abuses in the Statement of Grounds of Appeal, both in terms of the requests made and in the complete failure to support the discretionary requests for multiple alternative sets of claims with explanation or justification.

- In the circumstances, the Board should give serious consideration to refusing any further claim requests (and OII is very concerned at the "seeds" sown throughout the Patentee's submissions but there will be further claim requests of one kind or another – in many cases, the Patentee has in effect already made a further quasi – claim requests.

- It would make little sense in OII's view to divorce enablement and inventive step in this particular case.

- There is no cause for referral of questions to an Enlarged Board of Appeal and it would be against the public interest to do so.

7. **Requests**

OII requests revocation of the opposed patent in its entirety and for the avoidance of all doubt maintains previous requests made in these proceedings.

Malcolm Graham Lawrence
HLBBshaw

Signed: _____

Dated: _____

NS/RESPONSES/GFAP99463LWS