European Patent No 1 512 429

Our File: GFAP09483

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1. Introduction

1.1 Overview

1.1.1 The opposed patent ("the Patent") is opposed by two opponents and is based on a divisional divided from European Patent Application No 01 962862.7. The parent application ("the Parent Application") has been granted as European Patent No 1 308 238 ("the Parent Patent"). The Parent Patent is currently under opposition by Opponent II ("OII") and that opposition ("the Parent Opposition") is before the Board of Appeal.

1.1.2 The Parent Patent has been limited (in its Main Request) to skin patches which are comprised of "*microneedles or microblades*" (as opposed to "*skin-piercing protrusions*"), those members are specified to be present as an "*array*" (as opposed to as "*a plurality*"), and the pharmaceutical agent is stated specifically to be a vaccine (as opposed to being without limitation). The monopoly sought is thus much more ambitious in these proceedings before the OD in the above senses. However, conversely, the Patentee appears resistant in the case of the Parent Patent to change the expression "*forms a glass*" to "*is in the form of a glass*", as he has done in these proceedings by means of the new Main Request.

1.1.3 The Patentee filed observations on the opposition by its submissions dated June 29, 2009. Those submissions included the filing of a new Main Request. Notably, whilst the claims being pursued in the Parent Opposition are already significantly more limited than the Main Request now before the OD, the

Patentee has recognised the need to have Auxiliary Claim Requests on file in those parallel proceedings – there are in fact a total of ten Claim Requests before the Board of Appeal in the Parent Opposition.

1.1.4 OI filed on November 19, 2009, a response to the Patentee's June 2009 submissions.

1.1.5 OII would like to place before the OD the observations contained in this submission. OII's primary purpose is to focus on a set of primary topics in order to narrow the issues. Of course, whilst narrowing the issues, OII is also concerned to provide its views on the new Main Request filed by the Patentee, and here there are significant concerns.

1.1.6 In this respect, the Patentee has taken positions on plural crucial issues and in doing so has made many assertions without the support of facts and evidence. To assist the OD, OII responds here in proper detail to each and every assertion. OII does so in all cases with the support of documents; to do respond otherwise would, unacceptably, rely on hearsay only.

1.2 Summary of Principle Issues on which the OD may wish to focus

1.2.1 The following appear to be the crucial issues. Documents in square brackets in each paragraph below are those new documents relied on by OII herein in relation to the issues mentioned in the respective paragraphs.

1.2.2 Echoing the Parent Opposition, there is considerable debate on the meaning of "*patch*" and the argument has plural dimensions. The Patentee is prosecuting a definition which is misconceived and which evokes meanings associated with classical patches, such as the "*nicotine patch*", which the invention is not. On the basis of the definitional assertions it

makes, the Patentee questions the relevance of art before the OD. However, the Patentee's position on patch definition is at odds with the Patent and this entirely undermines his assertions. OII has in this submission placed comment before the OD to deal with this; OII has done so partly by necessarily outlining the overall prior art setting and supporting this, equally necessarily, with new documents. In short, OII's view is that the Patentee's position is fantasy. **[D44, D47, D50, D55]**

1.2.3 As in the Parent Opposition, there are also other disputes between the parties since OII does not share the misconceived views of the Patentee on the meaning of "*vaccine*" and "*array*". OII would like to comment also on the issues surrounding the term "*forms a glass*", which appear to OII to be much more complex than the Patentee has disclosed in its submissions to date, and the serious consequences of its amendment in the new Main Request to read "is in the form of a glass". **[D46, D48, D49, D51, D54]**

1.2.4 As in the case of the Parent Patent, the invention claimed in the Patent has not in reality been made. It had not been made at the claimed priority date, and the text added at the time of filing the Parent Application (under the PCT) changes nothing and is, indeed, largely cosmetic. To elaborate, the information content of the Patent is second hand and does not make it plausible that the problems in the art have been solved; there can thus be no inventive step (T1329/04) even before applying the problem-and-solution approach. For example, (i) the Patent covers polyol glasses which would not be expected to deliver a stability solution for pharmaceutical agents (whether vaccines or otherwise), (ii) it provides no insight into how the practical problems set out in Paragraph [0025][1,2] can be overcome

[1] Counter-intuitively, the corresponding paragraph in the Parent Patent (Paragraph [0026]) was deleted before the OD in the Parent Opposition

bearing in mind common general knowledge that glasses are fragile/brittle, and (iii) it contains no adequate guidance on patch/microneedle/microblade[3] geometry nor on polyol selection. **[D46, D51, D53, D54, D56]**

1.2.5 The Patentee takes the view that the average skilled man sees no point or advantage in using polyol glasses. However, this departs from the reality that, led by WHO, the vaccine community sees embodiments of sugar glass technology as potentially avoiding need for the so-called "cold chain" used for storing/transporting vaccine. **[D43, D52]**

1.2.6 Most claims are ***disentitled*** to the claimed priority date although it is clear that there is disagreement between the parties here. One consequence of this non-entitlement of claims to the priority date is that the claims are open to inventive step challenge on the basis of D1. In many cases, the claims are also anticipated by more specific subject-matter which ***is entitled*** to the priority date and which is contained in the published Parent Application. The latter ***is*** citable under Article 54(3) EPC. **[D45, D57].**

1.2.7 There is also debate on the relevance of prior art relating to "*active*" patches. The Patentee's position is at odds with the Patent as well as materials (eg D17) it has filed to support its position on other issues[4]. OII has provided comment to ensure understanding of the relevant technology so that this issue can properly be considered and decided. **[D42].**

1.2.8 Inevitably, in a case such as this, considerable problems arise under Articles 84 and 123 EPC eg so far as amendment before

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[2] As the OD will recall, Paragraph [0026] states "*....the reservoir must be capable of adhering to the microprotrusion to a sufficient extent that the reservoir remains physically stable and attached during prolonged storage, and also remains substantially intact during administration procedure when the coated microprotrusion pierce the stratum corneum*"

[3] Of course, the Main Request recites the general language "*skin-piercing members*"

[4] The Patentee's position that the invention is limited to passive patch devices for the purposes of prior art evaluation - without the claims actually being so limited - is in OII's view entirely fanciful

the OD is concerned. OII will, of course, provide detailed reaction to the Article 84 and 123 EPC issues[5] raised by the new Main Request. In this respect, the Patentee has generated some confusion by referring throughout its submission to basis in the "*application as filed*"[6] but in doing so has given page/line references which are in fact points in the **PCT pamphlet**. For example, the basis for recitation in the Main Request, Claim 1 of "*patch*" is stated to be (*inter alia*) page 8, lines 4 to 7 of "*the application as filed*" – in fact this disclosure appears at:-

Lines 4 to 7 of page 8 of the PCT pamphlet
Lines 30 to 33 of page 7 of the specification filed originally

1.2.9 OII will emulate the Patentee as this now seems sensible in the circumstances. However, OII also provides for the assistance of the OD a concordance table showing, for all referenced text herein, the page/line references in the originally filed (divisional) application registered against the corresponding page/line references in the PCT pamphlet and the Paragraphs which correspond in EP-A-1512429. The concordance is contained in Part D of the Annex attached.

1.3 Documents

1.3.1.1 As noted in the Consolidated Document List (see Part D of the Annex attached), the Patentee has filed four further documents, namely D38, D39, D40 and D41.

1.3.1.2 The draft submissions referred to in the fax to the EPO on behalf of OII dated May 21, 2010 set down a document numbering sequence as a continuum from that adopted by the Patentee in the Patentee's further submissions dated 29th June

[5] See Paragraph 6 below and Part A of the Annex filed with this Submission, respectively
[6] As OI has pointed out, the Patentee must show compliance (eg with Article 123(2) EPC) by reference to both the divisional application as filed originally and the original PCT pamphlet

2009. The OD will note that the Patentee took numbering up to "D41"; accordingly, OII adopts document numbering as far as new documents are concerned starting at "D42". Third Party Observations have now been received but were not to hand at the time the document numbering was fixed. **In any event**, the Third Party document numbering appears to be in error in using the numbers "D41" and "D42" for new documents - this fails to recognise all of the new documents D38-D41 referred to in the Patentee's June 2009 submissions. It appears to OII therefore to make sense for the document numbering fixed by OII to prevail over the Third Party document numbering. Accordingly, Third Party documents D41 and D42 are numbered in the attached Consolidated Document List as D58 and D59, respectively.

1.3.2 As mentioned in Paragraph 1.1.6 above, OII would like to introduce new documents, as also noted in the Consolidated Document List. In the case of the documents other than D45 and D50, the documents are submitted in order to support OII's responsive observations on the Patentee's response. D45 and D50 are new documents cited, respectively, as anticipatory under Article 54(3) EPC and as potential closest art for Article 56 EPC purposes[7].

1.3.3 In the panel below, OII provides more detailed explanations for introduction of the additional documents filed by OII referred to in Paragraphs 1.1.6 and 1.3.2 above (and the Paragraphs hereafter where they are mentioned):

Doc	Narrative	Paras
D42	Responds to Patentee's allegations that some prior art is irrelevant for disclosing approaches involving electroporative/iontophoretic interventions; D42 provides an understanding of the role of such	2.3.3 (i)(ii) 2.4.1 9.1.3 9.3.4

[7] It is noted that copies of Documents D45 and D50 were provided to the OD and OI on 14 April 2010 with copies being provided to the Patentee in late March 2010 in the Parent Opposition appeal

	approaches which is material to OII's ability to deal with the Patentee's allegations	
D43	Potentially important document on the issue of inventive step as it sets out in some detail from an internationally recognised and respected source (WHO) practical scientific facts about sugar glasses which make it absolutely clear that a skilled man would be motivated to try using appropriate embodiments in microneedle/microblade skin patches instead of the other (sugar-containing) antigen formulations mentioned in the prior art	2.6.3 9.10.2.6 9.10.4.4
D44	Responds to the Patentee's allegation that when a device has a handle (eg as in D10) it is definitionally not a skin patch. D44 shows a modern patch with a member stated to be a handle and is thus important as evidence in dealing with the Patentee's allegation	3.1.2 3.1.8.4
D45	PCT pamphlet of the Parent Patent. OII contends this is "whole contents" prior art against any claim of the Patent which is not entitled to the claimed date of UK 00 1799.4 dated July 21, 2000 (D57); the relationship between a parent and a divisional does not mean that a parent cannot be cited against a divisional thereof	7.2.4-7.2.7 9.3.8
D46	Post-priority date evidence of (a) the general importance of microneedle geometry and (b) what is meant by the term *"array"* (as contrasted with *"plurality"*)	3.3.1 9.8.2(a)(i) 9.8.2(a)(iii) 9.8.2(b)(iv)
D47	Addresses allegations made by Patentee that certain prior art is not relevant as it discloses devices which are structurally distinct from patches and do not use the expression *"patch"*. The Patentee's assertions treat the invention and the prior art in question as if they relate to classical patches (which, of course, seek to achieve slow-release of pharmaceutical agent over a patch dwell time). D47 shows that the term *"patch"* was also used at about the priority date in a non-classical sense where the devices in question are about vaccine administration and thus concerned with rapid administration - bolus administration or what might at least be called *"quasi-bolus"* administration[8] - and, as a result of this different functionality, are subject to different structural considerations	2.3.4(ii)(v) 3.1.2 3.1.5.8 3.1.8.4
D48	Responds to the Patentee's submission in its June 29, 2009 submission (see (c) on page 6 of the that submission) that D9 is not *"a product for vaccination"*	7.1.4
D49	D49 is in response to the same Patentee contention as D48	7.1.4

[8] For convenience, OII will refer herein to this form of administration, intended as a substitute for hypodermic administration with rapid delivery, as *bolus* or *quasi-bolus* administration

D50	Responds to the Patentee's assertions that a patch must have a means of fixing it to the patient so that it is "worn" (in the Patentee's view, the article is otherwise not a patch at all). Discloses an adhesive patch, and is a candidate for closest prior art	3.1.2 9.3.11 9.9.1 9.10.4
D51	Responds to the Patentee's assertions concerning "array" and "plurality" and also shows that little information on microneedle array geometry was available even after the priority date	9.8.2(a)(i)
D52	Shows the state of expert opinion on sugar glass technology for the vaccine art at around the priority date; underlines its potential importance	9.10.2.6(ii)
D53	Shows the state of expert opinion on microneedle technology immediately before the priority date[9]	9.8.2(d)(ii) 9.8.2(d)(iii)
D54	Explains serious threats to the ability of eg sucrose glasses to confer stability on biologicals	9.5.5 9.6.1 9.10.4.3(ii)
D55	Parent Opposition OD Minutes (mainly page 4, sixth paragraph)	3.1.5.6 3.1.6.2 3.1.8.3
D56	"Annex I" to submissions filed in the appeal stage of the Parent Opposition by a third party ("Third Party")	9.6.1
D57	Copy of priority document for Opposed Patent (UK 00 1799.4 dated July 21, 2000)	6.1-6.12 7.2.1 7.2.4-7.2.7 9.3.7(iv)
D61	Discloses matter relevant to the issue of use of eg trehalose to stabilize vaccines	2.6.2
D62	Discloses matter relevant to the issue of use of eg trehalose to stabilize vaccines	2.6.2 9.10.2.6

NOTE:

Documents D58 to 60 are documents filed with the Third Party submissions filed in the EPO on May 17, 2010, rather than being new documents now relied on by OII

[9] This paper is acknowledged by Patentee in Paragraph [0019] of Patent

2. **Overall Prior Art Setting**

2.1 Overview

2.1.1 Before addressing the issues before the OD in detail, OII would, as already noted, like to portray the prior art setting in which the invention sits. OII believes this will establish in the OD's mind two important contextual points:-

(i) the administration speed issue the invention seeks to address is an issue which sits in the overall context of the challenges presented to the art by exchange of conventional hypodermic needle administration for non-hypodermic administration approaches[10]; and

(ii) the agent stability issue the invention seeks to address is an issue which sits in the overall context of an art permanently tasked with improved stability because pharmaceutical agents (especially biologicals such as vaccines) are susceptible to thermal degradation.[11]

2.2 The Hypodermic Syringe Issue

2.2.1 As Paragraph [0005] of the Patent states, a hypodermic needle and syringe were, at the priority date, the primary conventional mode for administration of pharmaceutical agents into or across the skin. This mode involves several disadvantages, which Paragraph [0005] of the Patent acknowledges at lines 35 et seq of page 2 (see also Paragraph [0007], second sentence). In terms of what the Patent explicitly recognises, these are disadvantages associated with the presence of a sharp

[10] In a vaccine context where the challenges are more specific and extreme than in some drug contexts, there is a particular need to ensure that *bolus* or *quasi-bolus* administration is achieved

[11] As is well-known, pharmaceutical agents are commonly stored under refrigeration and transited within a cold chain in to ensure adequate stability of the active agent. This applies particularly to biologicals. However, small molecule drugs are also prone to eg thermal degradation – anti-biotic eye drops as sold OTC, for example, have a product insert directing refrigerated storage

implement, namely the hypodermic needle. For example, needle insertion into the patient involves pain and produces an expectation of pain leading to so-called "*needle fear*".

2.2.2 Hypodermic needles and syringes are designed for bolus administration and are not designed for so-called slow-release administration through the skin.

2.2.3 The art at the priority date evidences a trend in development effort leading away from hypodermic needle administration towards other approaches. This trend has been driven by:-

- the desire for patient comfort/safety/well-being and/or
- the need to enable transdermal administration in non-bolus fashion (ie slow or gradual release).

2.2.4 In a small number of cases, the trend has been driven by unsuitability of the agent for hypodermic administration and unsatisfactory attributes of substitutes. For example, smallpox vaccine has commonly been administered by means of a deposit of formulation on the skin and then puncturing the skin by use of a needle and BCG is most commonly not administered to neonates hypodermically. However, the primary drivers are those stated in Paragraph 2.2.3.

2.3 <u>Patch Types</u>

2.3.1 Skin patches, as one approach to solving these problems, are referred to in Paragraph [0006] of the Patent. As seen in one dimension, patches deliver pharmaceutical agent through the skin without penetration whilst others are penetrative.

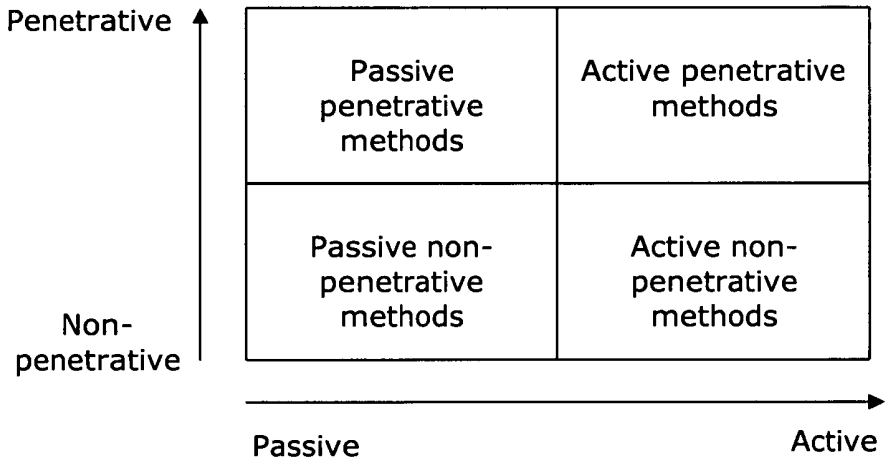
Referring to Figure 2.3.1 below, looked at in another dimension[12], such patches may be[13]:-

(a) "*active*" - agent is delivered with assistance of:-

- iontophoresis or electroporation (these being termed "*iontophoretic patches*" and "*electroporative patches*", respectively) or
- mechanical activation such as agitation

(b) "passive" - agent is delivered without such intervention.

Figure 2.3.1



2.3.2 Penetrative approaches using patches normally employ microneedles or microblades[14]. D1 and D10 are examples of patch devices where a pharmaceutical agent, in both cases a biological, is coated onto the microneedles/microblades rather than, for example, supplied to the microneedles/microblades from an integral reservoir of the agent. At the priority date, knowledge of the role of microneedle/microblade geometry on patch performance was limited and there is no real evidence of

[12] It appears the Patentee, like OII, sees two dimensions, with penetrative patches a different dimension to patches which are active (for example, in the sense of those in whose operation electro-assisted transport or mechanical activity intervenes) – see quadrant diagram in 2.3.1 below

[13] These are three main examples of "*active*" approaches – OII will only focus on these herein when referring to "*active*" approaches

[14] Sometimes called ""*tines*", "*points*" or "*prongs*"

such knowledge in the more complex context of microneedles/microblades carrying solid coatings.

2.3.3 Referring to "*active*" patches:-

(i) Electroporation acts primarily on the skin, rather than at a molecular level on the pharmaceutical agent, to increase its permeability to pharmaceutical agents in a reversible manner. Electroporation is mentioned in the Patent in a prior art context of the invention. However, importantly, the claims of the Patent do not exclude patches constructed so that the microneedles serve as electroporation electrodes. Additionally, the Patentee applied it, in trying to demonstrate how embodiments of the invention might perform, as recorded in D17 and D40. In addition, D1 mentions electroporation in the second complete paragraph of page 2 and D42 mentions it in Paragraph 9.3.3 (second and third sub-paragraphs).

(ii) Iontophoresis acts primarily on the pharmaceutical agent to assist transdermal passage. Iontophoresis overcomes the physical barrier represented by the skin and in tests conducted against an inactive control patch, delivery of insulin was reported in D42[15] to be elevated as evidenced by serum insulin levels exceeding that of the control. Iontophoresis is mentioned in Paragraph [0006] of the Patent. The claims of the Patent do not exclude patches constructed so that the microneedles serve as iontophoretic electrodes.

(iii) Mechanical agitation may also serve to assist pharmaceutical agent delivery. D10 discloses this type of

[15] See D42, Paragraph 9.3.2

intervention as a preferred feature[16]. The claims of the Patent do not exclude patches constructed so that this can take place and Paragraph [0073] exemplifies how the same may be achieved in practise.

2.3.4 Where there is intervention by electro-assisted transport eg iontophoresis, the overall system commonly comprises a patch component and a separable, distinct applicator component, the former being applied using the latter. The same is true of what OII will simply call *"mechanically-assisted"* administration although here there is less financial value in the applicator component, making it discardable with the patch component:

(i) In the case of D1, the patch component is shown by electrode array 12 and the applicator by electrode holder 13 ("handle"), the array or patch component normally being disposed of after use and a fresh one provided from a sterile package such as shown in Figure 8 of D1. The array (patch) remains attached to the applicator in delivery of the antigen, rather like a finger pressing on the patch.

(ii) In the case of D47, the patch component is stated in the paragraph beneath Figure 1 on page 64 to be applied using an impact applicator - perhaps analogous to a finger quickly pressed on the patch - and then left on the skin for the short period required for delivery of antigen (5 seconds – see legend to Figure 4 on page 67).

(iii) In the case of D10, the patch component is shown at 16 in Figure 5 and, as shown in Figure 8, plate 16 is provided with coated *"needle-like projections"* 16b. Plate 16 is mounted to platform 12a and members 13, 14 form a handle which serves to assist and locate finger pressure to

[16] See the top of Column 6 of D10

achieve needle penetration as well as for facilitating the manipulation described at the top of Column 6.

(iv) In the case of the invention, it is to be noted that Figures 1 and 2 show what is there stated to be a *"patch member"*, suggesting it is a component of an entity including other components, and it appears that the Patentee expects this patch *"member"* to be applied using the pressure of a figure[17].

(v) Operationally:-

- D1 uses the applicator to keep the patch on the skin and sources electrical power through the applicator
- D47 relies on the alternative use of an adhesive member integral with the patch itself to keep the patch on the skin, this being facilitated as the patch per se contains its own integral source of electrical power[18]
- In the Patent, the Examples are set in an artificial non-patient context and, as far as the specification as a whole is concerned, no means of application to skin is disclosed[19]
- The Examples are also set in an artificial non-clinical context using individual sewing needles stuck on a rubber stopper and applied by embedding them in a gel body at penetration depths of 2cm – neither microneedles nor microblades nor any other form of *"skin-piercing members"* were used.

2.3.5 D40 newly filed by the Patentee records Patentee experiments and makes clear that *"active"* penetrative methods are applicable to the invention; it would be astonishing if this were

[17] See the Patentee's minuted representations in D55, page 4, sixth paragraph

[18] Where electrical power is supplied from an extrinsic source, connection thereto makes adhesive attachment of a patch to the patient somewhat difficult

[19] But see D55

not the case as the objective is ordinarily the achievement of bolus or quasi-bolus delivery, in the context of vaccine administration in particular[20]. The OD is referred in particular to Experiments 3 and 4 of D40, where electroporative approaches are adopted by the Patentee in trying to exercise somewhat contrived embodiments of the invention in optimal fashion. It will be noted that the Patentee uses in Experiment 3 two "*needle-array electrodes*" spaced apart and each coated with plasmid DNA/sucrose formulations; electrical pulses are directed to these electrodes from a proprietary square wave electroporation device to which they are connected.

2.4 Transdermal delivery problems using non-penetrative patches

2.4.1 With or without the assistance of iontophoresis or electroporation, non-penetrative modes of administration demonstrate inadequacies in the context of the administration of pharmaceutical agents, particularly but not exclusively biological molecules, such as found in vaccines[21]. Large molecules are especially impeded by the stratum corneum.

2.4.2 The Patent states in the final sentence of Paragraph [0007] that there is inter alia "*very poor*" uptake of "*antigen across the intact stratum corneum*" in the case of "*active*" non-penetrative devices. Intuitively, of course, "*passive*" devices which are non-penetrative will be expected to perform even more poorly.

2.4.3 In short, the issue of pain associated with hypodermic needles gave rise to a move away[22] from such technology in terms of research and development effort but at the expense of severe losses in administration efficiency as far as all non-penetrative approaches to administration of large molecules is concerned.

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[20] See also the statements of the Patentee in this regard in the seventh of the tabbed paragraphs on page 10 of the Patentee's February 13, 2008 submissions on the Parent Patent (see Annex C)

[21] D42, Paragraph 9.3.3, third sub-paragraph, refers to the inadequacies of "passive" devices

[22] See Paragraph 2.1.1 (i) above

2.5 Transdermal delivery problems using penetrative patches

2.5.1 According to Paragraph [0008] of the Patent at lines 53/54 of page 1, rates of pharmaceutical agent uptake achieved by use of penetrative methods (other than conventional hypodermic needles) are *"generally poor"*.

2.5.2 In short, just as non-penetrative methods *trade off* efficiency for patient comfort/well-being, so do alternative penetrative modes of administration proposed as a substitute for conventional hypodermic needles - but to a lesser extent.[23] This inefficiency is particularly but not exclusively noticed in the context of vaccines, which are normally intended to be administered as a bolus injection.

2.5.3 In discussing the short-comings of penetrative methods used as a substitute for hypodermic syringe administration:-

(i) The prior art references mentioned in this context in Paragraph [0008] of the Patent as background to the invention mention electroporation and/or iontophoresis as attempts to overcome delivery speed problems rather than solutions to those problems, citing *"poor rates of uptake"* experienced in using *"these types of devices"* (line 53 of page 2 of the Patent) :

- those mentioned in Paragraph [0008] at line 51 of page 2 of the Patent disclose electroporative devices
- the first two references mentioned in line 52 on page 2 of the Patent disclose electroporative devices
- US Patent 5279544 (lines 53/54 of page 2 of the Patent) discloses both electroporative and iontophoretic devices

[23] Again, see Paragraph 2.1.1 (i) above

(ii) In discussing art which precedes it in date, D1 (see the first complete paragraph on page 3) discloses that electroporation can be applied to assist pharmaceutical agent delivery via penetrative approaches. However, D1 makes clear that such electroporative approaches are nevertheless subject to problems, many arising in trying to reach a balance between overcoming the problems of hypodermic needles and avoiding delivery inefficiency[24].

2.5.4 It can also be the case that efforts to maintain efficiency of transdermal delivery in the *"trade off"* result incidentally in a different type of patient discomfort – ie one which is electrically mediated. D1 goes so far as to address just that kind of situation (see page 1, lines 15/16 and the paragraph commencing at line 19 of page 5). D1 tackles this by providing a specially designed electrical wave-form input to the patch member 12 via the separable applicator portion 13 to which it is attached in use.

2.5.5 It is worth mentioning at this relatively early point that the Patentee has gone to some considerable lengths to deny that the invention addresses the problems of *"active"* patches. Thus, the Patentee has set out substantive comments in the central paragraph on page 11 of its June 29, 2009 submission in which it contrasts what the Patent *"describes"* with the disclosures of D10 (and, impliedly, D1)[25]. This is no doubt motivated by the desire ultimately to address inventive step through the problem-and-solution approach in a manner which favours the invention, but it is nevertheless a fanciful denial which is at odds with the Patent itself. As already noted in Paragraph 2.3.3 above, the claims do not exclude microneedles/microblades

[24] The paragraph starting at line 11 of page 3 refers to an electroporative method which seeks patient comfort at the expense of delivery efficiency, which latter is prejudiced for the reasons given at lines 17-21 and lines 27-30 of that page

[25] See the reference to *"electrical means as described in other documents"* in the last line of the central paragraph on page 11 of the Patentee's June 29, 2009 submission

being provided which serve as electrophoretic electrodes – one would hardly expect a patentee to accept anything less as a commercial ambition – and D40 appears to be a concession by the Patentee that this is indeed the case.

2.5.6 The Patentee further tries to distance the context of the Patent from D10 by submitting in the above passage on page 9 of its June 29, 2009 submission that the invention excludes (a) devices which apply mechanical activation such as disclosed in D10 ("*stab, rotate, wipe*" as the Patentee has referred to it at line 12 of page 9 of the above submissions) and (b) the agent delivery performance (which the Patentee calls "*extremely rapid administration*") achieved by D10. However, the Patentee is contradicting the Patent itself. In common with D10, the Patent recognises that agitation of a microneedle during administration further increases speed of delivery (see the last sentence of Paragraph [0073] of the Patent on page 10) and presents this as desirable in the context of the invention; significantly, the above teaching is set in the context of a passage in the Patent which appears to be concerned especially (and, indeed, exclusively) with optimising pharmaceutical delivery rate. OII finds this surprisingly blatant contradiction to be unhelpful.

2.6 Vaccine Stability

2.6.1 The Patent mentions in its prior art summary (see Paragraph [0007], line 1 of page 3) the issue of pharmaceutical (eg vaccine) stability. This is very well-documented in the art elsewhere and the economic and logistical disadvantages of the so-called "*cold chain*" necessary to preserve substance stability have been thoroughly discussed. OII does not see it as necessary at this point to detail prior art disclosures to this effect; stability of drugs and vaccines is self-evidently on the "*shopping list*" of all art-skilled persons. Pharmaceutical agent stability on the skin-piercing members of the patches of the

invention is indeed, in the context of rapid delivery also achieved, an objective of the invention - see the Patent at page 2, line 8 – Paragraph [0001], page 3, line 6 - Paragraph [0010], and page 4, lines 40 to 42 – Paragraph [0026]. The OD will note that the disclosures in Paragraph [0026] are directed to physical stability (of coatings on microprotrusions) as opposed to chemical stability of chemical entities.

2.6.2 Sugars such as trehalose are known to stabilise eg antigens. Use of trehalose-based drying of biological molecules is disclosed, for example, on page 1010 of D61 (first complete paragraph). D1 discloses at lines 1 to 4 of page 28 that a sugar may be used as a protectant in the context of DNA vaccines applied to microneedles/microblades; the tenor of that disclosure suggests it is well-known, and indeed axiomatic, that sugars are in practice used as protectants to stabilise antigens. The Patentee states that *"Sugars have been known to stabilize proteins"* for a great length of time in the fifth complete paragraph on page 2 of its June 29, 2009 submission.

2.6.3 Whilst eg trehalose is *per se* known for its stabilizing properties (as opposed to being known as such only in sugar glass form), there is no doubt that some sugar glasses were known at the priority date to have notable stabilizing powers by virtue specifically of their glass form. D43 addresses vaccine stability as a broad subject on pages 18 – 25 and discloses there the use of sugar glasses specifically as a technology for achieving vaccine stability and avoiding the need for a cold chain. The disclosure includes specific reference to a range of advantages of sugar glasses on page 20, and in the second headed section on page 23, reference is made to *"sugar needles"*. In a broader context, D12 states that it was, at the date of that document (1999), well-accepted that immobilization of a protein within a

glass matrix is essential for achieving good stability during storage (see D12, page 236, 2nd full paragraph)[26].

2.7 Summary of Prior Art Setting

2.7.1 A reasonable summary of this prior art setting is as follows:-

- hypodermic needles involve pain (and hazards) which is (are) to be avoided
- they are designed for bolus administration, not slow-release
- many drugs require bolus administration or a compromise which is as close to bolus administration as possible[27]
- non-penetrative patches avoid pain but offer only very poor take-up of eg vaccine
- intervention by means of eg iontophoretic or electroporative methods assists take-up in non-penetrative patches but it is still poor for vaccines at least
- penetrative patches offer improved take-up of pharmaceutical agents but there is obvious room for further improvement as they remain somewhat inefficient in the context of the need for such agents (eg vaccines) to be administered as a bolus or quasi-bolus dose
- some such further improvement can be provided by eg iontophoretic or electroporative methods applied to penetrative administration approaches
- there is scope for further improvement in delivery (eg *vaccine* delivery) in the case of penetrative skin patches, even if they are iontophoretically or electroporatively assisted
- many approaches to pharmaceutical agent delivery devices require cold-chain treatment to preserve stability, and this is self-evidently a disadvantage and very well-known

[26] In this respect, D12 (which, of course, is a handbook) confirms statements in D13, D19, D20 and D21

[27] ie "quasi-bolus" administration

- sugars are known to provide stability (as so-called "protectants")
- some sugar *glasses* have been proven to provide substance stability for pharmaceutical agents, eg as sugar needles, and this has, importantly, been documented by WHO

3. Terminology

3.1 The term "*skin patch*"

3.1.1 The invention is stated by the Patentee to be a "*skin **patch***". The Patentee has submitted as a Main Request a schedule of claims, all of which direct the invention to a "*skin patch*" or its preparation. This contrasts in terms of terminology with the application as filed (and with the Patent as granted) which (both of which) used the general term "*delivery device*" and "*skin patch*" interchangeably. On that subject, OII notes that Paragraph [0008] of the Patent states that each patent in a list of twelve prior patent documents concerns patches whereas a reading of seven of these (ie WO9748440A1, WO9748442A1, WO9828037A1, WO9929298A2, US5279544A and US3964482A) reveals that none actually uses the term "*patch*". The Patentee has asserted that the limitation to "p*atches*" is based on lines 20 et seq on page 5 and lines 4 to 7 of page 8 of the application as filed originally[28][29] and despite the interchangeable use of the above two expressions in the original PCT application (ie the Parent Application) and the divisional application as filed, the Patentee now seeks to assert that they have different meanings which indeed (in the view of the Patentee) involve significant differences.

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[28] See Paragraph 1.2.8 above

[29] More accurately, the basis is actually the these two disclosures subject to the overall context - of the paragraph commencing at line 9 of page 4 in particular - into which OII considers they fit (ie all the limitations of the context defined by that paragraph are attached to the asserted basis, including the limitation to coatings which are "*external*"). In this respect, the OD may wish to refer to Paragraphs 1.1.4 and 1.1.5 in Part A of the Annex

3.1.2 In the view of OII, it must first be recognised that the meaning of technology terms changes over time to accommodate developments in the technology, thus subsuming new and different entities. What was understood at the priority date as a "*patch*" was not the same as evoked by say "*nicotine patches*" at the outset of patch technology. A patch at the priority date is in OII's view a device which comprises a member which presents a skin-contacting administration surface which in use covers a skin administration area to administer pharmaceutical agent into the contacted skin, the device being optionally constructed and arranged for fitting to an applicator or source of active intervention such as iontophoresis[30]. Patches according to this definition include those of the invention, those mentioned in Paragraph [0008] of the Patent, those of D1, D10 and D9/D24 and those referred to in D44[31], D47[32] and D50. A comparison between, say, D1 and the patch "*definition*" in Paragraph [0016] is instructive. D1 includes coated microneedles 16 – the invention includes coated microneedles or microblades (and, more generally, "*skin-piercing members*"). D1 includes a plate-like mounting member which mounts the skin-piercing members, this and the skin-piercing members forming part of overall assembly 12, 14, 16 (see Abstract) – the invention includes a backing plate from which the "*protrusions*" depend.

3.1.3 The Patentee has been very exercised, however, to assert that, whilst the invention is a *patch*, the devices of eg D10 and D9/D24 do not disclose *patches*. This assertion is based on a highly self-serving approach to patch definition adopted by the Patentee in order to tailor the definitional result to the objective of establishing a distinction over the prior art. As will appear from later submissions in this regard, this does, however, result

[30] This definition appears broadly aligned with that presented by the Third Party in the penultimate paragraph of its recently received submissions
[31] See Paragraph 3.1.8.4 below
[32] See Paragraph 3.1.5.5 below

in double standards, with some aspects of the Patentee's position being inconsistent with what the Patent appears to say. The Patentee's arguments appear to be as follows:

(i) At sub-paragraph (a) near the base of page 3 of its June 29, 2009 submission, the Patentee states that a "..... *skin patch, as any skilled person would know, is an article < attached to and worn by a host (see D38....".* The Patentee has cited D38 as support for his assertion and the Patentee continues on page 4 of its June 29, 2009 submission by stating that a patch is something that is placed on the skin for a specified and generally prolonged length of time[33].

(ii) The Patentee adds in the second complete paragraph on page 4 of its June 29, 2009 submission (ie the next paragraph) that the "..... *intracutaneous injector of D24 is not a skin patch".* The Patentee goes on in the two subsequent paragraphs to say this is so because (a) the prongs of D24 are too long[34] and (b) skin patches do not have handles as does D24.

(iii) In the third paragraph on page 10 of its June 2009 submission, the Patentee states (in asserting inventive step) that "*D10 discloses neither a skin patch, nor .....*".

(iv) Whilst there is no cogent reason given by the Patentee, the Patentee's statement towards the end of the second complete paragraph on page 11 of its June 29, 2009 submission invites the OD to accept that a patch in the sense of the invention must be *inactive* as opposed to *active* (ie it must not be assisted by, or constructed to be

[33] The Patentee states at the same point that, according to the invention, a skin patch has skin-piercing members which are between 1um and 1000um (ie 1mm), the Patentee citing Paragraph [0017] of the Patent in this regard. However, this makes no sense to OII as none of the independent claims in the new MR is limited in any way to any particular member length; in addition, in Examples 1 and 3 of the Patent, needle penetration depths of 2cm were used

[34] See preceding footnote

assisted by, mechanical agitation, iontophoresis or by electroporation) if it is to be regarded as a patch at all[35].

3.1.4 The Patentee accordingly seems to be submitting that a patch according to the invention as claimed must meet all the following criteria (i) to (v) and that prior art must meet these same criteria if it is to be seen by the OD as relevant. OII considers the Patentee's position to part from reality for the reasons given in Paragraphs 3.1.5 to 3.1.9 below in dealing in order with the Patentee's suggested criteria:-

(i) Criterion 1: The device is "worn" by the patient
(ii) Criterion 2: The device has an adhesive backing (or other means of attachment to the patient)[36]
(iii) Criterion 3: The skin-piercing protrusions are not too long (eg more than 1mm)
(iv) Criterion 4: The device has no handle
(v) Criterion 5: The device is "*passive*" as opposed to "*active*" (ie the device is not *constructed* to be suitable for application of iontophoresis or electroporation).

3.1.5 Criterion 1 *[The device is "worn" by the patient]*

3.1.5.1 For an item to be worn, real duration is implied. The Patentee has invited the OD to accept that the invention involves wear in this sense and that this contrasts with eg D10. There is no basis in the Patent for taking this position.

3.1.5.2 By way of background, when a patient is injected using a hypodermic syringe, the needle of the syringe is first inserted and then it and the patient remain "*joined*" for the duration of

[35] See Paragraph 2.5.5 and 2.5.6 above

[36] This seems implied by the Patentee although it is surprising as (a) the Patent itself does not disclose the use of adhesive attachment nor indeed any means of patient attachment and (b) the Patentee has stated in D55, page 4, sixth paragraph that a finger is used to press the patch onto the skin (and, presumably, the skin-piercing members into the skin through the stratum corneum)

the flow of the injectable. The latter (ie post-insertion duration) is a very short time and cannot be described as "wearing". In contrast, an earring of the piercing type is carried by an ear for a real duration and is "worn".

3.1.5.3 Remembering that the invention aims to be a substitute for hypodermic needle administration, in the case of the invention, "dwell times" of over 15 minutes are to be avoided as undesirable - according to Paragraph [0008] of the Patent at line 56 on page 2. Further objective reading of the Patent shows that dwell times of this order are much more than undesirable in reality. One leg of the objective problem in the art which the invention claims to solve is, according to the Patentee, the provision of rapid drug delivery (and thus much depleted dwell times). This is admirably clear from the Patentee's emphasis of this objective in the formulation of the problem in the art, and its solution, at the centre of page 9 of its June 2009 submission[37]; it is even clearer where the problem and solution are differently formulated in Paragraph 2 of the Patentee's January 2007 submission to the ED (which latter should be viewed in the setting of the paragraph at lines 16-17 of page 22 of the specification as originally filed[38] - to which the Patentee refers in Paragraph 2 of its January 2007 submission to the ED).

3.1.5.4 Indeed, the preferred (and apparently achievable) dwell time according to Paragraph [0033] of the Patent (see line 20 of page 5) is 30 seconds maximum and it is presumed that less is desirable, with immediacy of dosage being in fact the essence of what the invention is about. In this latter respect, the OD is referred, for example, to the references to means such as use of agitation of inserted microneedles disclosed in Paragraph

[37] See also page 10 of the Patentee's June 29, 2009 submission, second line of the second complete paragraph of the section headed "*The invention is not obvious over D10*"
[38] This corresponds to Paragraph [0074] of the Patent

[00074] of the Patent for ensuring that rapidity and yield of administration are "*....even further enhanced.....*" and the reference to thermally enhanced speed of delivery at lines 23 to 25 of page 5 of the Patent.

3.1.5.5 The OD will note also in this connection that Paragraph [0023] of the Patent refers to separation – impliedly right after insertion - of the piercing protrusions (when they actually constitute the reservoir) from the back plate of the patch after skin penetration "*thus allowing the patch to be removed from the skin*"[39]. This suggests anything but "*wearing*" of the patch. If this is what "*patch*" meant prior to the Patentee's limitation to glass coated microprotrusions (which was made to exclude eg solid glass microprotrusions), it is difficult to understand the basis for now changing the meaning.

3.1.5.6 In this respect, it is to be noted that the Patentee chose to delete, from the corresponding disclosure of the Parent Patent, the description referring to separation of the protrusions from the patch back plate (see the adapted Parent Patent description which forms part of D55 and which is mentioned in the parts of D55 bridging pages 4 and 5 thereof). The OD will appreciate that this description amendment in fact seeks to leverage a different interpretation of the term "*patch*".

3.1.5.7 Accordingly, the patches of the invention are not necessarily of the type that are "*worn*" at all; the Patent does not mention the word "*wear*" or any derivative of that word. Being "worn" is the 'defining feature' of typical conventional patches as understood in the art (ie classical patches, such as nicotine patches and those described in D38[40], used for sustained release) but it is clear that, in the invention according to the Patent, the claimed patch does not necessarily accord with this conventional

[39] See lines 27/28 on page 4 of the Patent
[40] See paragraph 3.1.6.2 below

typicity. This is because the invention does not relate to classical patches in the sense evoked by say "*nicotine patches*" (which are worn). These classical patches address partly the problem of patient comfort (ie they avoid "*hypodermic pain*") but mostly they deal with the need for some drugs to be administered incrementally over time as opposed to administering pharmaceutical agent as a bolus dose. In sharp and complete contrast, the invention is concerned with patches which are of "*non-classical*" type and which, to the contrary, are concerned with bolus administration (or, at least, administration which is rapid so as to be "*quasi-bolus*"). Nobody "*wears*" a patch whose job is over in an instant. In this respect, in Paragraph 4.1 (a) of its June 2009 submission, the Patentee states that the term "*patch*" refers to an item placed on the skin "*for a specified and generally prolonged length of time*". This is incorrect because the dwell time is not prolonged in the case of the invention – which aims to provide "*rapid*" delivery.

3.1.5.8 MACROFLUX is a trade mark of Alza Corporation for a modern product described in D47 as a microprojection array patch for delivery of protein antigens (see title and first paragraph) in just this manner. The paper was written at approximately the claimed priority date of the Patent (see title panel on page 63). The MACROFLUX patches are stated to achieve "*rapid and reproducible intracutaneous administration of dry-coated antigen*" (page 63, fourth paragraph of Column 1). Delivery took place over a 5 second application period to provide dosages of 1, 5, 20 or 80mg OVA to HGP models (see the third complete paragraph of the second column of page 66 and especially the Figure 4 and Figure 5 legends). The final paragraph immediately prior to "ACKNOWLEDGENTS" in the second column on page 69 states that the patches are a technology which "*allows bolus or short-duration administration of dry-coated antigen*". Equally, D10 and D1 are, like the

invention, non-classical types of patch products intended to deliver a bolus or quasi-bolus dosage of a vaccine.

3.1.6 Criterion 2 *["The device has an adhesive backing (or other means of attachment to the patient")]*

3.1.6.1 One would expect a "*worn*" device to have a means of attachment to the patient. Typically, a classical "*patch*" employs an adhesive layer to achieve this. However, this does not mean the presence of an adhesive layer is essential to all patches – a defining component. There are two reasons for this:-

(i) In cases of *de minimis* dwell times, there will be other methods of attachment (or, rather, methods of maintaining patch:skin contact) which are available as an alternative.

(ii) In some cases (eg D1), designing a patch for connection to a source of electrical enhancement is an obstacle in the context of adhesive attachment[41].

3.1.6.2 Both D1 and D10 disclose alternative approaches, the first in an "*active*" context and the second sometimes in a "*passive*" context. In both cases, the approach is to apply the patch and maintain skin contact by manual means (component 13 in Figure 1 of D1 and component 13, 14 in Figure 5 of D10). The remark of the Patentee at first instance oral proceedings on the Parent Patent about finger pressure, as recorded in the sixth paragraph on page 4 of D55, concedes this is also the means by which the patch of the invention is applied to the skin. OII cannot reconcile this with the Patentee's assertion in the first line of paragraph (a) of page 3 of its June 2009 submission that "*any skilled person would know*" that a patch is "*attached to and worn by a host*". In this respect, the Patentee refers to D38

[41] Of course, as product design has advanced, patches became available with integral power sources (see D42, Paragraph 9.3.3, third sub-paragraph, lines 19-21) in order to overcome this obstacle

which it states supports its contention that patches are worn. This does not explain the conundrum that apparently the patches of the invention are not worn, and the Patentee should recall that, as it is the Patent which is under opposition, it is what "*patch*" means in the Patent that matters.

3.1.6.3 Turning to D38, however, the Patentee has again forgotten the cruciality of context. The context of the invention and that of D38 are entirely different. As a consequence, the fact that the patch of D38 is worn is of no relevance to D1, D10 or indeed the invention, and it certainly does not mean that a patch in the latter three cases is also to be worn; in fact, this is absurd, as OII explains below, keeping in mind Paragraph 3.1.5.4 above:

- in the context of the invention, D1 and D10:
    - administration is rapid (*quasi-bolus),*
    - administration proceeds from a microneedle deposit of vaccine composition, and
    - wearing is neither necessary nor sensible (it would be inconsistent with administration which takes place so quickly)

- in the context of D38:
    - administration is by "*sustained release*" (see page 25, line 2) over a period,
    - the patch includes a repository layer 14 (see lines 12 et seq on page 14) which contains therapeutic agent in substantial quantities intended to maintain an "*effective blood level of the drug*" over an "*extended period of time*" (page 25, lines 3-4), and
    - wearing (over the *sustained release period*) is absolutely essential
    - the patch is useful for delivery of "*smoking cessation agents such as nicotine, bupropion and ibogaine*" (page 20, line 23)

3.1.7 Criterion 3 *["The microblades/microneedles are not too long (e.g. more than 1mm)"]*

3.1.7.1 If needle size was to be seen by readers of the Patent as a defining feature of the invention, one would expect the Patent to say so in appropriate terms and indeed to say so in the broadest claims. In contrast, needle length has never been mentioned in the claims at all at any time – not in the application as filed, nor the claims as granted, nor in any Claim Request before the OD.

3.1.7.2 OII refers to Paragraph (a) commencing near to the base of page 3 of the Patentee's June 29, 2009 submission (see the paragraph on page 4 immediately following the quotation). It will be seen here that the Patentee, in essence, asserts that the invention is concerned with short needle lengths and the Patentee refers the OD in this respect to Paragraph [0017] of the Patent. This is, however, completely misconceived. The paragraph is concerned with typical and preferred needle lengths in the range 1 to 1000 μm but, over-riding this, is the overall functional purpose of providing an approach to administration which includes dermal delivery of pharmaceutical agent to the dermis at depths ranging up to (and exceeding) 3000μm (ie 3mm)[42]. OII draws the OD's attention in the above respects to several important disclosures in the Patent itself which illustrate the fact that the Patentee's submissions in the respect, as is the case more generally, are misconceived:-

[42] OII does not follow the Patentee's reference, in the paragraph on page 4 of its June 29, 2009 submission following the quotations, to epidermal delivery Claim 7 as granted and Paragraph [0017] of the Patent express the preferred targeting of the dermis. The Patentee's comments in the above-noted paragraph refer to lengths of up to 1000μm, and protrusions of this length will also target skin strata deeper than the 120 μm maximum thickness of the entire epithelium

- lines 22/23 of page 2 of the Patent state that the dermis is located within a depth range of 0.3 to 3mm below the stratum corneum;
- lines 28/29 of page 2 state that the stratum corneum has a thickness of 30 to 70 μm;
- lines 11 to 13 of page 1 and lines 53 to 55 of page 3 of the Patent state that preferred devices are constructed to deliver pharmaceutical agent to the dermis (ie at a depth potentially as deep as 3070μm);
- Example 1 (Paragraph [0082]) and Example 3 (Paragraph [0086]) of the Patent state that dry coated needles of each formulation are inserted 2cm deep (into gel).

3.1.7.3 The Patentee's motivation is, at least in part, to draw a definitional distinction between D24 and a limitation which does not even exist in the claims used to define the invention. Even if the claims were to support the Patentee in terms of any mention of a needle length limitation, it does not seem to OII that the Patent as a whole supports a distinction between D24 and the invention which is real, as D24 discloses needle lengths as short as 2mm as compared with the Patent mentioning 1mm expressly and 3mm+ impliedly. Notably, D10 discloses at lines 56/57 of Column 3 needle-like projections which may be 1mm in length.

3.1.8 Criterion 4 *["The device has no handle"]*

3.1.8.1 The Patentee's proposition appears to be that if one takes a device that the Patentee would regard as a "patch", it ceases to be a patch if it is provided with a handle. The Patentee even goes so far as to say - by way perhaps of emphasis - in the fourth line of the paragraph which bridges pages 20 and 21 of its June 2009 paper, that a device (which would otherwise be a patch) with a handle would need its handle to be removed in order to become a patch.

3.1.8.2 A handle provided as part a patch is in essence an applicator, and so providing it is merely an alternative to providing it as a separate adjunct (or an alternative to a finger). OII's view is that making that choice is not something that occasions a radical change in either device nature or nomenclature.

3.1.8.3 One may expect the invention itself to be applied using an integral handle or a non-integral applicator bearing in mind that use of an adhesive layer makes only limited practical sense in the context (see above[43]) and is not mentioned by the Patent. A handle, certainly in the sense of electrode holder 13 in D1, would replace the *"finger"* the Patentee stated was used to provide finger pressure recorded on page 4 of D55 (sixth paragraph of OD Minutes on the Parent Patent opposition).

3.1.8.4 It is noted that D44 discloses a patch with a graspable portion which the document states is to be used *"as a handle"* (see fifth bullet point on the first page) (as does D10) and that D47 discloses use of an applicator[44] (as does D1).

3.1.9 Criterion 5 *["The device is "passive" as opposed to "active" (ie the device is not constructed to be suitable for application of iontophoresis or electroporation)"]*

3.1.9.1 As intimated earlier (see Paragraph 2.5.5 in particular), the central paragraph on page 11 of the Patentee's June 2009 submission are an exhibition in inconsistency. For the purposes of assessing patentability, the Patentee seeks to persuade the OD that prior art directed to *"active"* devices should be disregarded. Thus, the Patentee contrasts the invention with D10 on the basis that D10 in the view of the Patentee is not concerned with *"passive"* diffusion or dissolution (see line 6 of the central paragraph on page 11 of the Patentee's June 2009

[43] See Paragraph 3.1.6.1 above
[44] See Paragraph 2.3.4(ii) above

submission[45]). In short, the Patentee's proposition appears to be that the invention solves problems with "*passive*" delivery devices rather than those associated with "*active*" devices and that "*active*" devices are excluded from the invention. However, for the purposes of protecting its claimed monopoly against third parties, the Patentee seeks claims which do not exclude patches which OII submits <u>are</u> "*active*" devices. Specifically, the claims requested are all open-ended and thus include (a) patches constructed for coupling to extrinsic sources of eg electroporative enhancement and (b) integrated devices which include an integral source of eg iontophoretic pulses.

3.1.9.2 OII makes the following submissions in this regard:-

(i) No reasonable skilled person reading the Patent would regard such "*active*" patches as OII has identified above as *not* patches included within the Patent's scope - there is no reason to suppose the Patentee has basis to say otherwise.

(ii) In support of this is the fact that the overall impression to be grasped from the statements of the Patentee in the first complete paragraph on page 10 of its June 29, 2009 submission[46] is that the Patentee sees as included within the scope of the Patent:-

(a) patches which are assemblies including means to execute electro-assisted transport (eg electroporation) and

(b) patches which are configured to unite to separate such means.

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[45] This disclosure echoes that in the final sentence of the immediately preceding paragraph of the Patentee's June 2009 submission

[46] These statements assert that D40 is evidence that "*the problem has demonstrably been solved by the present invention*" (see the last sub-heading on page 9 of the June 2009 Patentee submission) and expressly assert in "*(e)*" at the centre of page 10 that electroporatively assisted patches according to the invention result in "*good levels of gene expression*"

(iii) The idea that the invention excludes "*active*" devices is contradicted by eg Paragraphs [0008] and [0074] of the Patent itself[47].

(iv) One would reasonably expect the Patentee to have stated definitely in argument and in the requested claims that the invention only concerns passive patches if that was a genuine belief the Patentee wished the OD to take into account. The Patentee skirts around the issue and demonstrates a clear reluctance properly to limit the claims in line with the arguments on inventive step on which he wishes to rely.

3.1.9.3 Alternatively, focussing on construction as the claims are not method claims, it is noted from the description of the Patent that (i) the invention comprises a "*patch member*" (see drawings) in the form of a backing plate from which depend a plurality of eg microneedles (see Paragraph [0016]) (undisclosed separate means optionally being used for applying the patch member), (ii) the device of D10 comprises a patch member in the form of a metal plate 16 with punched projections 16a (backing member 11 mounting the patch member and having wings 14 serving as handles) and (iii) the device of D1 comprises a patch member in the form of electrode assembly 12 (electrode assembly holder 13 mounting the assembly 12 and serving as an applicator handle).

3.1.10 It is also tempting to suspect that the Patentee also considers – or at least wishes the OD to believe - that a patch in a prior art document is only a patch if it is actually called a "*patch*" in the

[47] Paragraph [0008] cites various patent publications disclosing the use of eg electroporative approaches to enhance antigen delivery (see Paragraph 2.5.3 above), forming a backdrop to the express teaching in Paragraph [0074] to deploy "*.....a number of means, comprising.....*" to achieve such enhancement and the use of electroporosis in Example 3 of the Patent (Paragraph [0086])

document concerned. However, the contrary appears to be the case from the Patent itself:

(i) As mentioned in Paragraph 3.1.1 above, Paragraph [0008] of the Patent is specifically directed to devices disclosed in some twelve patent publications.

(ii) As also stated in Paragraph 3.1.1 above, the Patentee plainly regards these devices as "*patches*" – because the Patent states clearly that Paragraph [0008] of the Patent is concerned with "*Other patches*" (see the opening words at line 48 on page 2 of the Patent) and goes on to say that the body of twelve patent publications are examples of "*metal microblade patches*".

(iii) However, OII considers the body of twelve prior art documents as a whole fails to support the assertion the Patentee has in mind; OII's study shows that of the twelve documents, none of WO9748440A1, WO9748442A1, WO9828037A1, WO9929298A2, US5279544A and US3964482A uses the term "*patch*".

(iv) OII notes that the Patentee fails consistently to refer in the Patent to the invention as a patch but sometimes just calls it a "*device*".

3.2. The term "*forms a glass*"

3.2.1 It is stated in the granted claims that the reservoir material "*forms a glass*". OII has expressed its view that this is unclear terminology which is completely unacceptable[48] under Article 84 EPC; in response to this challenge, the Patentee has sought an amendment of this language to "*is in the form of a* glass", whilst

[48] The terminology, as the OD will recall, embraces at least two interpretations, namely that the material *is in the form of a glass* or that the material is one which *will form a glass*

stating at the top of page 3 of its June 2009 submission that it does not agree with OII's challenge.

3.2.2 Not only does OII object to the term "*forms a glass*" under Article 84 EPC but OII also objects to the amended terminology; as explained in Paragraph 6 below, OII considers the Patent does not make it clear how a skilled addressee of the Patent can achieve a reservoir which is (wholly) in the form of a glass.

3.2.3 The OD is referred to Paragraphs 5 and 7 of OII's current submission (Articles 84 and 54 EPC) as regards the consequences which OII considers flow from the above remarks.

3.3 <u>The term "*an array*" (of microneedles or microblades)</u>

3.3.1 The above term is not used in the claims of the new Main Request (the Patentee has instead resorted to use of the term "*plurality*") but the term remains relevant as there are, for example, claims which OII considers ought to use it if those claims are to be acceptable, all other things being equal, on formal grounds[49]. The reasons for this belief are based on the distinct meaning which the term "away", in the view of OII, clearly has in the art:-

- OII submits that the Patentee in reality agrees that "*array*" and "*plurality*" are <u>not</u> the same - notwithstanding the somewhat casual assertion that they <u>are</u> which OII reports in Paragraph 3.3.3 below. The term "*array*" was added at the time of the original PCT filing - it was not present in the priority document - and was plainly a deliberate change intended to convey information not conveyed by

[49] See, for example, Paragraph 1.1.11 in Part A of the Annex attached

the originally filed UK patent application from which priority is claimed[50].

- The term conveys a sense that the microblades/microneedles in the "*array*" have been made to conform to a *geometric order* or pattern, as distinct from having adopted random form.

- Subjection to an act of "*arrangement*" is implied by the term; D46 refers at line 3 of the first complete paragraph in Column 2 on page 1197 to microneedles being "*arranged*" into an array.

3.3.2 OII would like to draw attention to the following dictionary definition of the expression "*array*" taken from the New Shorter Oxford English Dictionary:

- *Arrangement in line or ranks, esp. martial order; orderly disposition.*
- *An imposing or well-ordered series of persons or things; an assemblage, an arrangement.*
- *A matrix or other ordered arrangement of quantities.*
- *A set of memory locations or data items of which each member is identified by a common identifier together with one or more subscripts.*

3.3.3 OII will not here support it with a copy of the document mentioned below from the Parent Opposition. However, OII nevertheless notes the Patentee's statement in the fifth paragraph of page 12 of its March 31, 2009 submission to the Board in the Parent Opposition. Here, the Patentee states that a "*plurality*" of protrusions actually implies an array. OII

[50] It could be said that the priority document is simply not alive to the essentiality of having the microneedles in array form so as to deliver the stated solution to the problem in the art. OII expands on this issue later in this submission

submits that this is fanciful and self-serving and, quite simply, wrong.

4. Article 123 EPC, Article 76 EPC

4.1 Article 123(2) EPC

4.1.1 The Patent bears all the hallmarks of an invention that has never actually been made in concrete terms but that is, rather, a collection of speculative ideas on paper. As already noted, much complexity flows from this and from the consequently challenging milieu for amendment which it produces. The issue of Article 123 EPC non-compliance is therefore a detailed issue. OII deals with this in Paragraph 1.1 of Part A of the Annex, hopefully without the same forming an interruption to the OD's review of the substantive issues (and the Article 84 EPC issues which in this case are very materially linked to those substantive issues).

4.2 Article 123(3) EPC

4.2.1 Article 123(2) EPC issues arising herein are also dealt with by OII in Part A of the Annex (see Paragraph 1.2 thereof).

4.3 Article 76(1) EPC

4.3.1 In view of the infringements of Article 123 EPC referred to in Part A of the Annex, OII requests that the divisional application on which the Patent was granted be assigned the date the divisional application was actually lodged in the EPO, namely September 16, 2004. As antedated, the Patent is not entitled to the make the claim to priority which it currently contains and that claim should be struck out. All claims of the Main Request, and all claims of any possible further Request, are then completely anticipated by the contents of D45 (namely, the

original parent PCT pamphlet), with the ultimate result that the Patent fails to comply with EPC and should be revoked in its entirety.

5. Article 84 EPC

5.1 As noted in Paragraph 3.2.1, the Patentee has sought to amend the claims to recite that the polyol-based reservoir material "*is in the form of a glass*". The Patentee has made minimal submissions to justify the amendment or support its candidature as language which is acceptable under Article 84 EPC. OII's position is that the amendment cannot be acceptable as it is not clear. It lacks clarity because:-

(a) it creates a new domain which is unclear when considered in the light of the fact that , as supported by the broader technical reality (see below), exercise of the processes of the Patent (again, see below) shows that the coating will at least normally be a mixed phase and not the single phase defined by the suggested amendment language "*.....the solid biodegradable reservoir medium is [in the form of] a glass.....*" and

(b) the amendment is unclear as it appears to recite a situation which cannot easily, and perhaps not at all, be delivered in practice and is not enabled by the Patent[51].

5.2 Just as it is not easy to produce a perfect crystal, so it is also difficult to produce a perfect amorph; in this connection, the OD should refer to D58, page 91 (D58 corresponds incidentally to E53 in the Parent Patent appeal proceedings). On the face of

[51] As noted in the Statement of Opposition in the first complete paragraph on page 5, the Patent is generally unhelpful in teaching the skilled man how to ascertain whether a particular reservoir material "*forms a glass*" in the sense of the Patent and this remains a handicap with the new Main Request. Of course, as noted in the immediately following paragraph on page 5 of the Statement of Opposition, the Examples are in particular unhelpful as they fail to distinguish reservoir form at all

it, D39 shows that making a monophasic glass is not easy at best (D39 incidentally appears to be a *re-execution* of the declaration of the same expert witness who deposed to the same facts in E51 in the Parent Patent appeal) . The Patentee's own Experiment 5[52] in D17 also shows this and states in its third paragraph (see page 6 of D17):-

"In the sample lyophilized for 1 hour (indicated by "1ST^T") an amorphous glass was formed with no evidence for the formation of crystalline particles. In the sample lyophilized for 24 hours (indicated by "1AM") the bulk of the sample consists of sheets of amorphous glassy material. There are [few] crystalline particles present."

This statement can accurately be summarized as follows:-

- In the case of the 1ST sample, an amorphous glass forms <u>in</u> the sample - the language suggests that the sample is amorphous glass in a matrix of non-glassy material

- The lyophilized 1ST sample is thus not *"in the form of a glass"* - it merely contains a glass

- The bulk of sample 1AM is glass but not all of it

- The sample whose bulk is glass also contains a crystalline component[53] - and it is unclear whether this is the whole balance of the sample or whether in fact there is another non-glass component such as a rubbery matrix.

5.3 In addition, D56 shows that a process for making a monophasic glass using information contained in the Patent leads to

[52] It is noted that this Example is presented not as a *"Comparative Example"* but as an Example in accordance with the invention

[53] Consistent with the second paragraph on page 91 of D58

multiphasic forms. D56 shows multiphasic forms where the amorphic phase is rubbery rather than a glass but equally OII contends that the multiphasic form may be a mixture of crystalline and glass phases. The OD will also wish to note in these respects the conclusion expressed by the Third Party on the basis of its "Annex 2" (which OII has numbered as "D60" – see Consolidated Document List) at the top of page 10 of the Third Party submissions just received.[54]

5.4 In summary, the material used to start with, namely a sugar (eg trehalose) reservoir material, is capable of forming a glass and thus satisfies the original claim language (*"forms a glass"*). However, a mixed phase result could not be regarded as similarly satisfying a claim requirement for a reservoir material which is defined as being **in the form of a glass** as the form is not a glass *per se* but a multiphasic form in which one phase only is a glass.

5.5 Of course, even if one produced a perfect amorph, amorphs have a capacity to revert to crystalline form, especially as moisture is absorbed into the amorph during eg storage, leading to a form which, again, is not a glass *per se* but a multiphasic form in which one phase only is a glass.

5.6 On a more formalistic note – but entirely in support of the contentions of OII set out above – the OD will note that Paragraph [0029][55] of the Patent states that the coating may be multiphasic, and specifically that it may comprise amorphous and crystalline mixed phases, with the result that there is inconsistency between the Main Request and the description. In that Paragraph [0029] of the Patent appears to be a statement

[54] OII notes, however, that it has not had an opportunity of considering these submissions, preferring to place its own submissions before the parties and the OD as soon as possible
[55] See final sentence – page 5, lines 2 and 3

of fact rather one of design, OII contends that it cannot be deleted to remedy the Article 84 EPC problem.

5.7 It is worth recalling in this regard that the Patentee had planned to monopolise the broad idea of using the capacity of sugars (regardless of form) both to stabilize biologicals and to release them at a dosage site. The Patentee has, it will be recalled, said a great deal about the fact that sugars, whether or not dried to a glass, are known per se for stabilizing pharmaceutical agents. In terms of the original claim scope context, the expression "*forms a glass*" was one on which little turned; in the present claim scope context[56], this is far from the case.

5.8 OII requests that the Patentee now not be permitted to restore the original language "*forms a glass*". In OII's view, the OD has clear discretion in such matters and is entitled to exercise it as it sees fit having regard to the equities of the situation. There are two interlinked considerations which OII respectfully submits should weigh on the OD's mind in considering the exercise of this discretion. One is the general undesirability of major and fundamental "*U-turns*" with Claim Requests, both in terms of public certainty and procedural economy. The second arises directly from the fact that the original language is per se unacceptable - it is OII's position that the *prima facie* unlikelihood that an amendment would comply with the EPC must influence an OD in considering whether an amendment request even be admitted (even one which reverts to "*as granted*" language). In this latter respect, OII makes the following submissions as set out in Paragraphs 5.9 to 5.12.

5.9 On the issue of reversion to the originally granted language, OII would first refer to the issue of jurisdiction. Traditionally, clarity

[56] Notably, the Patentee has transformed the scope of the Patent, through amendments made in the opposition, to limit it to what might be called "*glass embodiments*", whilst the specific teachings in the specification remain unchanged

objections have in the past only been allowed in opposition proceedings where amendments introduce new language. T0472/88 stated that challenges could be made under Article 84 EPC in cases where lack of clarity could be shown to "*arise out of*" amendments made even if they were to use language already assessed in prosecution. However, it has frequently been difficult for opponents to avail themselves of this decision in practical reality. However, T0656/07 has clarified the law and made it clear that whenever amendments are requested by a patentee in the course of opposition proceedings, EPC confers upon *inter alia* opposition divisions a jurisdiction to apply the whole of the EPC including, specifically, Article 84 EPC. Reason 2.2 of T0656/07 states as follows:

"This lack of clarity can be objected to in opposition proceedings because it is generated by the amendments made during this procedure, even if the contested feature as such was already present in the claims as granted but in another combination ..... This means that a lack of clarity also arises out of an amendment when this amendment brings into notice an ambiguity that has existed all along."

5.10 Turning to the facts in this case the original expression "*forms a glass*", if reverted to, would result in lack of clarity in Claims 1 to 7 for reasons given elsewhere in this submission[57] and as elaborated in more detail hereinafter.

5.11 The lack of clarity is more poignant in the circumstances as the Patentee at least hints that the limitation "*forms a glass*" is a feature which distinguishes the invention from the prior art. Such a lack of clarity in patents can make it impossible to

[57] See the discussion of terminology in Paragraph 3.2 above

compare subject-matter claimed to the state of the art and to proceed with any opposition proceedings.[58]

5.12 The Patent fails to explain what tests a skilled man is to use to verify whether a material falls under the claim language (indeed, this is so regardless of which of the two alternative phraseologies is used) and under what conditions a material must form a glass in order to fall within the claim scope. The problem is exacerbated by the use in the Patent of terms such as *"amorphous/glassy"* and *"glassy sugar"* (respectively in Paragraphs [0036] and [0035]) and the fact that, as noted in the second paragraph of Section VI of the Statement of Opposition, *"glassy"* and *"amorphous glass"* apparently have different meanings.

5.13 Claim 3 is unclear as the language "skin....." has no meaning whatsoever.

5.14 Claim 6 is unclear because it refers to a non-existent claim (namely, Claim "10").

5.15 Claims 4 and 5 are unclear because the term "antigen" is sufficiently broad in the meaning ascribed to it in Paragraph [0058] of the Patent to embrace nucleic acids. In consequence, it is unclear what the difference is between Claims 4 and 5.

5.16 Claim 7 is unclear on several counts:

(i) It is not evident from the claim and in any event how lyophilisation will produce a coating which is porous. There is no disclosure in the body of the Patent to assist a skilled addressee of the Patent in this respect. It is not the case that

[58] Paraphrasing part of Reason 2.1 of T0656/07

porosity is an automatic consequence of any lyophilisation protocol.

(ii) The claim recites a protocol made up of two steps, namely (a) dip coating (dipping one or more times) followed by (b) lyophilisation, but it appears to be essential from a reading of the paragraph bridging pages 10 and 11 of the PCT pamphlet that one or both of steps (a) and (b) of the above protocol **must** be repeated to achieve a depth of coating which line 4 of page 11, using *imperative* language, specifically and expressly states is "required".[59]

5.17 Claim 8 is unclear as it is not limited to the presence of "*skin-piercing members*"[60], which appear from the description to be an essential feature of the invention in all embodiments. In the alternative, if this feature is not essential, it is unclear how the invention is intended to function as a non-penetrative approach to eg bolus or *quasi-bolus* administration of vaccines.

6. Priority

6.1 Claim 1 of the Main Request is not entitled to the claimed priority date because there is no basis in the priority document (D57) for reciting that the solid biodegradable reservoir material is in the form of a glass in the context of the rest of the claim.

6.2 The description from page 10 onwards of D57 fails to mention glasses at all and there are no links in that part of the description which import any earlier reference to glasses. There are no claims. It is thus only necessary to consider pages 1 to 9 of D57 in assessing the priority entitlement of Claim 1.

[59] See also Paragraph 1.1.13 (iii) of Part A of the Annex
[60] See Paragraph 1.2.3 of Part A of the Annex

6.3 The biodegradable reservoir medium is not exemplified in the part of the above description (pages 1 to 9) until line 23 of page 6 of D57. OII therefore proposes to ignore pages 1 to 5 and lines 1 to 22 of page 6 of D57.

6.4 Line 23 of page 6 of D57 states that the reservoir medium can be any material "*that fulfils the function required for the present invention*". There is no granularity of detail anywhere in the whole paragraph and certainly no basis for what OII will, for the moment, simply call the "*glass feature*".

6.5 The paragraph starting at line 1 of page 7 of D57 does not change any of this. The reference to "*(crystalline or amorphous)*" again provides no granularity – the expression covers the solid substance universe.

6.6 The paragraph starting at line 16 of page 7 of D57 gives a range of specific substances as examples and at lines 21 et seq states that "*microblade*" coatings may again be amorphous or crystalline (and partially amorphous and partially crystalline).

6.7 The description at lines 24 et seq of the page refers to pharmaceutical agent (a) dissolved in polyol glass, (b) dispersed in polyol glass or (c) dried in polyol (of unspecified, but presumably non-glass, form) which are stable over prolonged periods, but this disclosure is not of subject-matter concerning the invention but a statement of subject-matter known in the art, reference being made to support this statement to various prior art patent publications identified in parentheses in lines 26 and 27 of page 7 of D57. The latter is followed by a statement of preference according to the invention which reads onto the disclosure of polyols in the prior art patent publications[61]. The foregoing disclosures of D57 are priority support for reciting

[61] The OD may wish to reflect here on Paragraph 1.1.8 of Part A of the Annex

particular polyols in Claim 1 and not for reciting polyol glasses as a class.

6.8 Lines 7 to 9 on page 8 of D57 state that the reservoir medium may be in any of a list of forms. For example, the medium may be solid, and crystalline forms are mentioned as well as amorphous forms. The solid substance universe is thus mentioned. The expression "*amorphous/glassy*" is not clear and not clearly anything other than a reference to glass and other amorphous forms together.

6.9 The paragraph commencing at line 11 of page 8 of D57 does not mention glasses and nor does the next paragraph. Both refer to methods of forming reservoir coatings in different contexts.

6.10 The paragraph starting at line 29 of page 8 of D57 describes detailed procedures for producing reservoir coatings by means other than dipping. The context is very specific whilst impliedly refering to glass coatings.

6.11 The disclosures of page 9 of D57 are directed to alternative coating techniques. No mention of glass is made.

6.12 D57 does disclose pluralities of coated eg microblades in very specific contexts such as the arrays shown in the drawings (eg Figures 1 and 2) and those referred to in the paragraph of D57 which bridges pages 8 and 9. However, OII submits that these disclosures are far too specific to support a priority claim for Claim 1 of the Main Request.

7. Anticipation

7.1 Novelty - Article 54(2) EPC

7.1.1 OII maintains its objections already articulated under this head in previous submissions, including in particular its challenges based on D1 and D9. The maintained challenge based on D1 is based on a contingency as explained below:-

- It is agreed arguendo that D1 does not disclose expressis verbis a vaccine-containing polyol glass coating of the electrodes 16 (microneedles)
- However, the claims prior to the new Main Request were not limited to glass coatings by the language "forms a glass"
- The language used instead in the new Main Request is not allowable
- Notwithstanding the Main Request has been submitted, that the original "forms a glass" language is not acceptable under Article 84 EPC and that OII has requested, with reasons, in Paragraph 5.8 above that the Patentee not be permitted to restore the original language, OII wishes to recognise that this request has not been considered by the OD and to make the comments below in this Paragraph 7.1.

7.1.2 The Patentee has made various comments on D1 in his June 2009 submissions which OII believes are, for present purposes dealt with adequately elsewhere herein.

7.1.3 The Patentee submits in its June 29, 2009 submissions at (c) on page 6 of the document that D9 is concerned with a "*diagnostic skin test*" product and that "*a skilled person knows that a product for diagnosis is not a pharmaceutical agent*". The heading to this paragraph is "*D9 does not disclose a pharmaceutical agent*". The Patentee makes a variety of further submissions but, as will become apparent from what follows, nothing turns on these additional remarks.

7.1.4 Supplementing remarks already made in the Statement of Opposition, OT and PPD contain, according to D48, Antigen A60

as the main thermostable immunogen - see Summary (page 262), lines 1 and 2. At lines 12 et seq of the same paragraph of D48, it is concluded that Antigen A60 is a major immunogenic component of mycobacterial cytoplasm (tuberculosis bacterium cytoplasm). D49 states in the Summary on page 129 that administering Antigen A60 to mice previously having received a first dose of the antigen confers protective immunity in the mice as evidenced by enhanced resistance to virulent aerogenic challenge with M. tuberculosis two weeks later. Accordingly, it is clear from D48 and D49 that OT and PPD contain antigenic elements which produce protective immunity in mice when administered following what might be called a "*primer*" dose of the same antigen, and thus that OT and PPD function as vaccines even if their intended purpose in D9 is diagnostic.

7.1.5 Presumably, the Patent is intended to include within its scope patches which deliver a dose of Antigen A60 to a patient who is no longer immunologically naïve (ie a patient who has already received one dose of that antigen) – and, in any event, it is hard to see how it can be argued that the Patent excludes such patches. It is noted at the first complete paragraph on page 21 of the Statement of Opposition that Paragraph [0044] (see line 21 of that page) of the Patent expressly mentions antigens of M. tuberculosis.

7.1.6 Paragraph [0013] of the Patent makes clear that the invention is not limited to prophylactic or therapeutic vaccinations but that it also subsumes administration of vaccines for "*priming and/or boosting the immune response*"[62].

7.1.7 The Patentee submits at (c) on page 6 of its June 2009 submission that the Patent is not intended to present any special meaning for the expression "pharmaceutical agent"

[62] See line 28 of Paragraph [0013]

which, the Patentee asserts, simply means something which has a prophylactic or therapeutic effect.[63] OII submits that it is clear from the foregoing comments in this Paragraph 7.1 that the OT/PPD of D9 **is** such a substance. In this respect, it does not matter whether the "*prophylactic or therapeutic effect*" is subsidiary to another effect or whether the converse is true; equally, it is immaterial whether or not the "*prophylactic or therapeutic effect*" is subsidiary to a diagnostic purpose.

7.1.8 Despite what the Patentee is asserting to the exact contrary, it seems to OII that the Patentee is, in respect of this matter, arguing a position **which requires that a special meaning is ascribed to terminology** which_the Patentee says does not have a special meaning. Exactly what that meaning is, however, has not been made clear by the Patentee; it is certainly not contained in the Patent.

7.1.9 In short, it seems to OII that (i) D9 discloses transdermal delivery of a formulation which serves as a vaccine in that it contains a vaccine antigen that confers protective immunity, (ii) this immunity is cell-mediated and (iii) the Patent encompasses patches which contain the vaccine mentioned at (i) above as disclosed by D9.

7.2 Novelty - Article 54(3) EPC

7.2.1 In view of its failure to have entitlement to the date of D57, Claim 1 of the Main Request is susceptible to challenge under Article 54(3) EPC based on the state of the art immediately prior to July 18, 2001. 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* (= priority date, for

[63] See the third sentence of (c) on page 6 of the Patentee's June 29, 2009 submission

this purpose) prior to the July 18, 2001 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*.

7.2.3 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 of July 21, 2000) and if that other European application has been published since then under Article 93 EPC.

7.2.4 One such citable other European patent application is EP-A-1308238 (D45) filed herewith. This application is the Parent Application of the divisional application on which the Patent was granted. Its relationship per se with the Patent pursuant to Article 76 EPC is not material to its citability. D45 was published on April 15, 1998 and discloses subject-matter relevant to the novelty of Claim 1 of the Main Request. OII asserts that it successfully claims for such relevant subject-matter the priority date of July 21, 2000. That priority date is claimed in D45 from UK Patent Application No 00 17999.4, namely the same application as that from which the Patent claims priority (D57).

7.2.5 Anticipatory subject-matter of this priority date is contained in D45 in a number of places as noted below:

(i) Figures 1 and 2 of the drawings of D45 disclose a patch member comprising plural microblades/microneedles presented as an array and each coated with a reservoir medium. Lines 13 et seq on page 9 of D45 state that "*particularly preferred*" reservoir media are represented by reservoir media which stabilise the pharmaceutical agent over the storage period, and preferred materials in this regard include, for example, the sucrose/epichlorohydrin glass-forming copolymer disclosed in Example 1 of US

Patent 5098893, which is referred to at line 15 on page 9 of the D45. These disclosures of D45 thus collectively enunciate all the features of Claim 1 of the Main Request. D57 contains equivalent disclosures on the first sheet of drawings and at lines 24 et seq on page 7, with the result that the above-mentioned disclosures in D45 are entitled to the claimed priority date of D57, namely July 21, 2000, and thus anticipate Claim 1 of the Main Request.

(ii) As elaborated in Paragraphs 7.2.6 to 7.2.8 below, subject matter of this priority date is also contained in D45 at the points noted in Table 7.2.5 attached, which tabulates the integers which appear from Claim 1 of the Main Request in concordance with the locations where specific disclosures within the scope of each integer appear first in D57 and secondly in D45; note that, to assist the OD, Table 7.2.5 also shows the corresponding disclosures in the parent PCT pamphlet. In the case of certain integers, OII takes the view that the feature concerned is inherent to the overall context of the invention in terms of the document concerned and that it would be trite to list specific relevant disclosures; in such cases, the relevant box in the matrix of Table 7.2.5 simply states "Context".

7.2.6 Referring to Table 7.2.5, lines 11 to 21 on page 8 of D57 disclose that a vaccine antigen is mixed with trehalose or other polyol as reservoir medium in aqueous solution and the latter coated onto microblades by dipping. A vaccine "*antigen*" includes within its definition nucleic acids as present to make a DNA vaccine)[64]. The solution coated onto the microblades is dried. A depth of coating is achieved and in this connection reference is made to coating of the patch array shown in Figure 2. The preceding paragraph states that the reservoir medium may, preferably, be "*amorphous/glassy*". Line 11 of page 8 of

[64] See line 21 of page 18 of the PCT pamphlet

D57 states that the reservoir medium is biodegradable. This overall disclosure is repeated in the two paragraphs commencing at line 24 of page 10 of the PCT pamphlet/D45, page 5, line 33, the latter thus being entitled to the date of D57. The latter D45 disclosure anticipates Claims 1 and 11 of the Main Request.

7.2.7 Alternative approaches to achieving the coating are disclosed in the paragraph commencing at line 29 of page 8 of D57. These include individualised coating of "*blades*" (= microblades) using bubble jet technology, which the OD appreciates will jet material to individual pixel locations which, in the context of that part of D57, are occupied by microneedles; microneedles located at pixel addresses are necessarily arranged in a geometric order constituting an array. These alternative approaches additionally result in a patch falling within the scope of Claims 1 and 11 of the Main Request. Priority-supported disclosures corresponding to the above-summarized disclosures of D57 appear in the paragraph commencing at page 5, line 49 of D45 (line 16 on page 11 of the PCT pamphlet)

8. Enablement (Article 83 EPC)

8.1 OII refers the OD to Paragraphs 9.5 to 9.8 below.

9. Inventive Step

9.1 Relevant Technical Field

9.1.1 The originally filed specification was stated to be directed to transdermal delivery devices. It thus used the term "delivery device" in referring to the subject of the invention but this was used interchangeably with the term "patch". The Patent is now stated to be "*limited*" to skin patches (although some references

to delivery devices remain as a vestige following the amendment process which took place in prosecution).

9.1.2 Transdermal delivery devices all have a skin-contacting component. The latter may be penetrative or non-penetrative. A component which provides an *emf* [65] to drive delivery of pharmaceutical agent to a dosage site in a patient may be provided, and is commonly essential in the case of non-penetrative delivery devices. OII's position is that the skin-contacting component is a patch.

9.1.3 However, in terms of the technical field relevant to the application of the problem-and-solution approach, OII's position is also that it does not matter how the definitional dispute as to what "*patch*" means is resolved as the relevant field for patches and transdermal delivery devices is the same field. This is clear from the Patent itself (eg Paragraph [0008]) and eg from D42.

9.1.4 Paragraph [0008] of the Patent, for example, refers to twelve patent publications describing "*delivery devices*" which the Patent states are documents relevant to prior art "*patches*" [66] even though at least those mentioned in Paragraph 3.1.1 do not use the term "*patch*" at all.

9.1.5 In the alternative, patches are a specific field within the general field of transdermal delivery devices. OII's position in this alternative scenario is that the functional aims of a skilled man in the skin patch field and the problems which challenge those aims are moreover at least allied to those in the rest of the delivery device field – efficient pharmaceutical agent delivery, pharmaceutical agent stability and patient welfare concern those working in the delivery device field generally and those working in the skin patch field specifically. There are crucial

[65] "emf" means electromotive force

[66] See the use of that expression in line 48 and in line 49 of page 2 of the Patent

structural commonalities shared by patches and other delivery devices, as would be expected to be the case bearing in mind their shared functionality.

9.2 The Skilled Man

9.2.1 There are two aspects to definition of the skilled man which OII would like to cover in the following paragraphs.

9.2.2 First, in the light of Paragraph 9.1 above, a skilled man in the field of microneedle/microblade skin patches is, in the view of OII, a person who is well aware of relevant science in the field of delivery devices[67] , even if the OD's view is that the patch field is to be seen as distinct form (but included within) the transdermal delivery device field and "borrows" from that reservoir of knowledge to practise in the field of microneedle/microblade skin patches[68].

9.2.3 Secondly, the man skilled in the art of pharmaceutical delivery devices recognises that technologies related to vaccines to be delivered using pharmaceutical delivery devices involve a different and specific expertise. The skilled man in the pharmaceutical delivery device field would thus second persons expert in the area of vaccine formulation in order to address such issues as vaccine stability on the microneedles and efficiency of vaccine release from microneedle coatings.

9.3 The Closest Prior Art - General

9.3.1 OII considers the approach taken to identification of the closest prior art by the Patentee (as well as that taken by the OD) to be deficient and unsafe. OII submits based on the documents in

[67] See eg T195/84, T176/84, T891/91

[68] The converse is also true in that the man skilled in the broader field is well aware of relevant science in the narrow field of patches and "*borrows*" from that reservoir of knowledge to practise in his broader field

the proceedings that the closest prior art document should be one having the following attributes:

(i) Functionally, as between art concerned with administration of large molecules such as antigens and art concerned with small molecule drug administration, the closest art will, all other things being equal, be the former (eg "*vaccine*" administration devices) as vaccines are emphasised in the Patent.

(ii) Functionally, it must be concerned with bolus (or "*quasi-bolus*") administration of pharmaceutical agent as distinct from slow release (which would almost always be the case for vaccine administration and most other pharmaceutical agents in any event).

(iii) Structurally, it must be arranged to administer the pharmaceutical agent from a body of the latter provided as a coating on microneedles/microblades or other skin-piercing members.

(iv) It should recognise pre-administration pharmaceutical agent stability as an issue, as it is believed is impliedly the case for all prior art in the technical field.

9.3.2 Prior art having these four attributes will satisfy the standard test adopted in the case law of the Boards of Appeal for prior art to qualify as closest art:-

(i) The art has the same overall purpose and effect as the invention.

(ii) The art and invention are meaningfully linked by the objective problem in the art.

(iii) The art is the most promising springboard to obtaining the results of the invention.

9.3.3 D1, as the Patentee has stated, is concerned with the delivery of macromolecules to the skin, in particular delivery of vaccines such as polynucleotide vaccines (DNA vaccine and/or RNA vaccine) and protein-based vaccines, into selected cells, such as Langerhans cells, in the epidermis of the patient (see Abstract and Technical Field sections of D1). From the description of D1, it is clear that the invention of D1 is concerned with a range of problems. In short, however, D1 recognises the disadvantage of hypodermic needles from a patient comfort viewpoint (ie they cause pain in varying degrees), and finding effective substitutes for this approach which nevertheless achieve bolus or quasi bolus delivery forms the basis of what the D1 inventors set out to achieve. The D1 inventors provide microneedle methods of administration, depositing the macromolecular agent as a coating 18 on the microneedles. The first complete paragraph on page 21 refers to the coating of electrodes 16 with a solid phase vaccine. The microneedles are shown at 16 in the figure depicted in the Abstract and form part of overall assembly 12, 14, 16. The microneedles do, of course, function also as electrodes, and are referred to as such in D1, and the D1 device is configured so that it can be combined with a means for applying electroporation in order to achieve speed of delivery of the macromolecules. The assembly 12, 14, 16 is a separate element of the overall D1 apparatus (which also includes the electroporative pulse-generating elements shown in Figure 1) intended to be disposable; it is intended to be stored, with coating in place, as the sterile package shown in Figure 8.

9.3.4 As noted above, D1 is concerned with optimising speed of biological molecule delivery and OII would like to explain this. Referring to Paragraph 2.3.3 above as background, it will be noted that the D1 system employs an electroporative approach

to increase delivery speed. D1 applies a small number of DC pulses to the skin in order to open the pores to agent penetration, these being generated by a waveform generator 15 via the electrode assembly holder 13 (see Figure 1). Paragraph 9.3.3 of D42 explains that such pulses are in the art applied for a total time of "*a few milliseconds*". Similarly, Example 3 of D17 states that the Patentee applied three pulses of 100 microseconds of one polarity and then three pulses of the same magnitude and duration but opposite polarity. It is thus self-evident that D1 is concerned with rapid delivery of agent.

9.3.5 As also noted above, D1 is also concerned to ensure that agent delivery speed is achieved whilst at the same time being concerned with ensuring stability of the agent – as is always the case automatically in the vaccine art. Lines 1 to 3 of page 28 of D1 disclose the use of protectants and it is understood by the skilled man that the purpose of this is to protect the macromolecules on the electrodes 16 from decay pre-administration and in particular whilst the patch is in storage as the sterile package shown in Figure 8 of the drawings of D1 (see Sheet 5 of D1's drawings). In the case of the embodiment described on page 28, the macromolecules are DNA molecules. Sugars are mentioned in line 3 of page 28 as an example of a protectant. A solid phase vaccine composition (as noted above, the first complete paragraph of page 21 refers to solid phase vaccines) also containing sugar serves as a reservoir medium on the electrode microneedles supplying the macromolecules. The reservoir coating is biodegradable. The OD will note in this regard that the term "biodegradable" is defined in Paragraph [0027] of the Patent as a change from a non-release state to a release state such as achieved *inter alia* through dissolution whereby agent is transported into the skin at a molecular level, just as in D1 macromolecules are driven off the electrodes 16 in electroporosis by the pulse waveform as described at lines 10 to 12 on page 22 of D1.

9.3.6 The device of D1 has all the structural features of the invention save that in D1 no sugar glass is mentioned specifically as the form taken by the sugar protectant. Fundamentally, D1 shadows the invention in that it adopts the same principle of avoiding the pain and hazard potential of hypodermic needles, administering agent instead by direct deposit as a reservoir on microneedles which, on application of the patch member to the skin, form an administration channel for the macromolecules of D1 through the skin.

9.3.7 OII submits in the light of the comments in Paragraph 9.3.1 to 9.3.6 above that:-

(i) D1 is clearly aimed at the same overall purpose and effect as the invention of the Patent, namely efficient delivery of macromolecules (in particular vaccines) into the skin (without the disadvantages of hypodermic administration), combined with stabilization of the macromolecules on the microneedles/microblades.

(ii) Equally, D1 and the invention of the Patent are, of course, linked meaningfully by the technical problem which the Patent identifies.

(iii) The most promising springboard towards obtaining the results achieved by an invention is the one which forms a so-called "bridgehead" which would realistically be selected as such by a skilled person. It seems to OII that D1 also satisfies this qualification.

(iv) Accordingly, D1 is in the view of OII an excellent candidate for selection as the closest prior art document for the purposes of assessing inventive step of claims not entitled to the priority date of D57.

9.3.8 As noted earlier, the Patentee considers the invention excludes "*active*" skin patches whilst suggesting that D1 is concerned with "*active*" skin patches. As also noted, OII disagrees with this assessment. In OII's view, the fact that D1 provides a pulse system which reduces pain sensation associated with electroporation does not have any bearing on whether D1 is relevant as closest prior art – it is still an excellent starting point for modification of the electrode assembly 12 to provide the sugar-protected DNA coating in sugar glass form with the motivations mentioned later in this submission. The Patentee also takes the view that D1 is irrelevant as it asserts that all claims of the Patent enjoy the priority date of D45. Again, OII disagrees – see Paragraph 6 above.

9.3.9 OII asserts that D10 is equally a promising springboard (for the invention according to claims having any priority date claimed). Like D1, D10 is clearly aimed at the same overall purpose and effect as the invention of the Patent, namely efficient delivery of macromolecules through the skin without the disadvantages of hypodermic administration. D10 relates to a "*transcutaneous injection*" device specifically for vaccine delivery. A principle object of the device is, from Column 1, lines 55 -59, to enable ready storage in large numbers without special precautions; storage under refrigerated conditions and use of a cold chain would, of course, be the first special conditions which would come to the mind of an average skilled man at the priority date in order to preserve the antigen formulation freeze-dried on the skin-piercing members. Lines 38/39 of Column 5 refer to the capacity for "*normal channels of trade*" to be used in terms of the supply line, and for the devices to be stored (apparently in *mass storage*) for "*substantial periods*" at locations within this *normal* supply line. Moreover, stabilization is always a "*silent agenda*" item. Another objective of the invention is to enable speed of use and D10 refers at Column 6, lines 3 – 5 to achievement of delivery to the dosage site in a "*few moments*"

and this has support from the description at lines 33 – 39 of Column 2 of D10.

9.3.11 OII would as an alternative like to refer the OD to D50. D50 discloses in the first column of page 119 a variety of approaches to stabilizing/preserving vaccines specifically. In the second complete paragraph of the first column on page 220, vaccination is described of sixty three unvaccinated infants with a then new type of scarifier which consists of an adhesive bandage with a stainless steel metal plate inserted and taped in place on the adhesive surface of the bandage. The surface of the metal plate had nine metal points (ie skin-piercing members) each 0.15cm long, arranged in rows of three. The width of the scarifying surface measured 0.35cm and the points were mounted on a metal platform, which was 0.07cm thick. The platform rested on a metal base 0.06cm thick and 0.9cm wide. Figure 1 on page 220 of D50 depicts the above arrangement, which appears to be a patch even though D50 does not refer to it by that term. In use, the scarifier, which had been autoclaved for 20 minutes, was unwrapped from its sterile cover, and one end of the adhesive bandage was taped adjacent to the vaccination site on the arm of the subject. The points of the scarifier were brought directly over a drop of vaccine previously deposited on the skin of the patient, and pressed firmly into the epidermis by applying pressure with the thumb (as shown in Figure 3 on page 220 of D50). The adhesive bandage with the scarifier were then immediately removed. Importantly, in an alternative procedure (see the second column of page 220 bridging onto the first column of page 221), the vaccine is instead applied to the points themselves (thus forming a coating on the points).

9.4 <u>The Objective Problem in the Art</u>

9.4.1 The problem in the art appears to be as follows so far as the Main Request is concerned:

How to provide a skin patch pharmaceutical agent delivery device which employs skin-piercing members coated with a pharmaceutical agent, in which stabilization of the pharmaceutical agent on the skin-piercing members is improved while still delivering pharmaceutical agent to the dosage site rapidly with short dwell times of the patch

9.4.2 As explained in more detail later herein, OII submits and maintains that the claimed invention is invalid for lack of inventive step because the question of whether or not the invention is *"a solution to the problem to be solved"* cannot be answered positively.

9.5 Plausibility of the Alleged Solution – Case Law and Overview

9.5.1 This submission already makes the point that the invention makes no contribution to the art. In this present submission, OII would like to develop this submission in alignment with the case law of the Boards of Appeal. The case law of the Boards of Appeal stipulates that (i) the problem the invention claims to solve must be solved by the invention over its entire scope (ie it must be fully solved) and (ii) the content of the application as filed must make it at least plausible that the problem has been fully solved. At the discretion of the OD a Patentee may file information in an attempt to satisfy the first of the above requirements. However, if that information is the first evidence that the problem has plausibly been fully solved, then the claimed solution to the problem cannot be taken into account for the purposes of establishing inventive step.

9.5.2 OII refers the OD to Decisions T1329/04, T1336/04 and T1396/06. In Reasons 10 and 11 of Decision T1329/04, the Board stated (emphasis added):

Reason 10:

"...in a first-to-file system the (earlier) filing date of the application, not the date at which the invention was made determines to whom of several persons having made an invention independently of each other, the right to a European patent belongs (cf. Article 60(2) EPC). Hence, it is particularly important in such a system that the application allows to conclude that the invention had been made, i.e. that a problem had indeed been solved, not merely put forward at the filing date of the application. Therefore, the issue here is rather how much weight can be given to speculations in the application in the framework of assessing inventive step, which assessment requires that facts be established before starting the relevant reasoning.

Reason 12:

".....it is concluded that .....there is not enough evidence in the application to make it at least plausible that a solution was found to the problem which was purportedly solved."

9.5.3 The Patent bears all the hallmarks of an invention that has never actually been made in concrete terms but that is, rather, a collection of speculative ideas on paper. It is to be noted that at least one of the inventors is a patent attorney rather than a scientist.

9.5.4 Rather than provide original information, the specification generally incorporates *"second hand"* information by referring to extrinsic documents (this is no doubt because there is in fact no original information to provide). The Patent relies on the prior

art to teach the skilled man but does not provide a compilation which is more than the sum of the parts.

9.5.5 For example, the very first paragraph of the Patent which starts to describe the invention in any detail (Paragraph [0016]), does so almost exclusively by referring to eleven (11) prior extrinsic documents. The very next paragraph relies on no less than fifteen (15) prior extrinsic documents, whilst the next relies on two (2) such documents but is a paragraph of only three lines. The specification proceeds throughout its length in much the same way, interspersing passages which rely on extrinsic documents with passages in general terms and passages which seem to have been "*made up*". The Examples are almost trite in their attempt to demonstrate the practical workings of an invention in the medical field by the use of sewing needles which are plunged into masses of a gel to a depth of 2cm (which, of course, is 20,000μm), which latter is presented bizarrely as a skin tissue model, after dip coating the sewing needles and lyophilisation, both using largely undisclosed methods which may - or may not - produce a glass. According to Paragraph [0030] of the Patent, polyol reservoir media that are or are not glasses work equally well – at least, the Patent refers in this statement of prior art experience to both options with apparently equal status. In addition no stability data is provided in the Examples of the Patent, nor in the Experiments of D17. Furthermore, the invention is concerned with rapid drug delivery but does not indicate what this means, reference merely being made to a range of delivery times in Paragraph [0033] but there is nothing to say how, or even if, this can be measured/achieved[69] and the central paragraph of page 11 of the Patentee's submission of June 2009 suggests that even the Patentee doubts that the aspirations of Paragraph [0033] can be achieved. Perhaps one of the most obvious indications that the

[69] See the Statement of Opposition at page 8, first complete paragraph

Patent is constructed of "*made up*" information rather than information deriving from having actually having solved the problem it claims to have solved comes from Paragraph [0031] of the Patent and the Patentee's changing position on what it states. Paragraph [0031] of the Patent states that **mannitol is a preferred polyol** for use in the invention. The Patentee **asserted the paragraph strongly** on page 7 of its submissions dated July 3, 2007 in connection with the Parent Application (see Part C of Annex hereto) despite its implausibility when compared with D12 and D54 but has astonishingly taken the **equally strong converse position** in its submissions dated June 29, 2009.

9.5.6 OII's proposition to the OD is that a patent for an invention which has not in reality been made in any concrete sense is inherently unlikely to allow a skilled man to conclude that the invention has been made in the sense of the Patent disclosing how to provide the solution it is claimed to provide. OII's further proposition is that, in this case, the onus is on the Patentee to prove otherwise[70] in circumstances where *prima facie* the invention has not been made in the concrete sense.

9.5.7 For the assistance of the OD, OII provides in Paragraphs 9.6 to 9.8 below additional comments on this issue.

9.5.8 Nevertheless, on the basis of the above, it is OII's position that, in accordance with Decision T1329/04, none of the claim requests complies with Article 56 EPC and that all requests should thus be rejected.

9.6 Plausibility of the Alleged Solution – Stability

[70] The Patentee has filed experimental results in D19 but (i) these suffer from substantially the flaws suffered by the Examples in the Patent as, for example, they use sewing needles and (ii) it must be possible for the skilled man to see the Patent, and not later filed information, as disclosing how to provide the solution the invention is claimed to provide

9.6.1 The Patentee claims the use of polyols in general and states they form glasses. In producing patches, an initial coating of polyol/antigen is applied to the microneedles and formed into a glass, lyophilisation being the preferred glass-forming technique applied. OII notes:

- It appears from the second complete paragraph in the second column on page 972 of D21 that high molecular weight polyols fail to stabilise antigenic protein unfolding during lyophilisation, presumably resulting in a loss of protein tertiary structure (they are also stated in the same location typically to fail to provide substance stabilization of antigenic proteins during storage). Such polyols are thus not capable of providing the stability solution promised by the invention – apart from anything else, there is an instability during the lyophilisation step which is at least partially nugatory of further stabilization steps.

- In D56, the Third Party reports the results of experiments it carried out to determine the state of sucrose in coatings prepared using coating and drying conditions which reproduced those in the Patent *"as closely as possible"* (page 1, third paragraph of D56). The Third Party reports that the sucrose products produced were a multiphasic rubbery material and not a monophasic sugar glass.

- Experiment 5 in D17 – an experiment whose results the Patentee has submitted to the EPO as establishing part of its case - shows that in the plasmid DNA/sucrose *"... sample lyophilised for 24 hours (indicated by "1AM" ... there are few crystalline particles present"* (Figure 6 and page 6, bottom)[71].

[71] See also the Statement of Opposition at the end of the paragraph bridging pages 4 and 5

- Section 7.2.2.1 commencing on page 236 of D12 is concerned with stabilization within a glass matrix and states on page 237 that human growth hormone (hGH) is not stabilized in the amorphous solid formed by lyophilising hGH with dextran; in the first complete paragraph on page 6 of the Patentee's June 2009 submission, the Patentee appears to concede this.

- The first complete paragraph on page 24 of D13 states that not all sugar glasses are suitable for preservation purposes.

- The third complete paragraph of the second column on page 972 of D21 adds that reducing sugars[72] such as lactose may have the propensity to degrade proteins via a Maillard (browning) reaction.

- In D54, serious threats to the ability of sucrose to confer stability on a biological are mentioned in the second paragraph of Section 1.8 on page 14:

  "Thus, if a sucrose based product is subjected to even 1 h at a temperature 5°C above the glass transition, there is a high risk that crystallisation will take place. As a result, the protective effect of the amorphous matrix that the sucrose glass provides will be permanently lost, even if the product is subsequently returned to lower temperatures."

- The same paper mentions that a sucrose-based product could be formulated to have a T_g much in excess of the temperatures it will experience during storage. However, this relies either on formulation with additional excipients with higher T_g's or very thorough drying. The paper notes later in the same paragraph:

[72] All common monosaccharides (eg glucose) are reducing sugars; the disaccharides maltose and lactose are reducing sugars

"It should be noted that a water content of 2 to 3% is typical of many products after 1-2 months storage, as moisture ingress from the stopper into the product takes place. Moisture content of this magnitude reduces the T_g of sucrose to between 28 and 40°C - temperatures that are commonly experienced during storage."

- Referring to the last bullet point above and to D56, it is noted that in the final paragraph on page 5 of D56, the Third Party reports that, in its experimental experience, it was difficult to dehydrate the 40% sucrose formulation of Example 3 of the Patent to a water content below 5%.

- The Patent in summary (a) fails to recognise that some polyols embraced by the scope of the claims are incapable in practice of delivering the stability promise which is the claimed objective of the invention and (b) gives no meaningful guidance to the skilled man as to how the above part of the Patent's scope can be performed in a manner which delivers on the stability promise the invention makes.

9.6.2 Example 1[73] does not address stability in the same context as that in which the invention claims stability as a solution to the problem in the art. The context for the claimed stability of the patches of the invention is obviously crucial; in relation to the claimed solution to the problem in the art, the context is (or includes) **stability during storage.** Indeed, the Patent makes this context clear - see, for example, the first sentence of Paragraph [0030] of the Patent. However, the test conducted in Example 1 does not involve storage at all and this is clearly

[73] In Example 1, HepB/sugar solutions are described and the Patentee gives a description of the needles to which these are applied as a coating - the needles are sewing needles. The Patentee outlines a lyophilisation step and then carries out SDS-PAGE upon needles with non-lyophilised and lyophilised coatings showing the presence of protein on each. This test is claimed by the Patentee to show the presence of protein on each needle, "similar pictures" for non-lyophilised and lyophilised coatings and "no difference" (in performance) between the various sugars

wholly inadequate to establish that the biologicals in the coatings are storage-stable.

9.6.3 The test in Example 1 is only claimed to show protein presence and is not sensitive enough to show that any protein remaining after lyophilisation is active and capable of eliciting equivalent or adequate immunological response as compared to the "raw" HepB Purified Bulk used as starting material.

9.6.4 Of course, many antigenic materials are far more unstable than HB_sAg so that the tests performed by the Patentee in Example 1 of the Patent in any event have no credibility as regards antigens generally.

9.6.5 In Example 3[74], the Patentee outlines a procedure somewhat allied to that of Example 1 but using 40% sucrose in the coating formulation and single and quintuple dippings are used alternatively for the coating. In OII's view, this test suffers from the same failings as those set out above for Example 1, and thus it does not support the idea that the specification makes it credible that the invention delivers the claimed stability across its scope.

9.6.6 In short, the Examples just do not contain any information which makes it credible that the invention solves the stability problem it purports to solve.

9.7 Plausibility of the Alleged Solution – Rapid Release

9.7.1 A problem the invention is supposed to have solved is also the problem of achieving rapid agent delivery whilst at the same time solving the above stability problem. In some of the claims of the requests, rapid release is quantified. In these respects,

[74] In the previous Example, namely Example 2, the Patentee outlines a release kinetic test. This is. of course, not relevant to the issue of vaccine storage-stability

the Examples are again of no relevance in practice, and thus do not support the idea that the specification makes it credible that the invention delivers the claimed rapid release across its scope.

9.7.2 In Example 2 of the Patent [75], a release kinetic test is outlined, again as noted hereinabove. However, this is wholly artificial in terms of the "device" used and in terms of the "skin model" used. In addition, the test is not performed on a device which has suffered storage.

9.7.3 Referring first to the "device" used:

- it is to be noted that all the Examples use Sewing Needle Number 8 from Prym (Product Code 121 29**2** [0079]). It is not clear from Example 2 what the length of the needle is that is coated but it is noted that a 2.5cm plunge depth is adopted in Examples 1 and 3 when plunging the sewing needles into the coating formulation; microneedles according to the invention are in practice far shorter than this with correspondingly smaller capacity to carry, and delver, pharmaceutical agent;

- Prym's catalogue has changed since the Patent was published and it appears that Prym no longer sells this specific needle. However, it does sell Needles Numbers 7 and 9, with Product Codes 121 29**1** and 121 29**3**, respectively. These needles are hand sewing needles and the Number 8 Needle used in the Examples would have had a diameter of between 0.7 and 0.6mm. By comparison, the smallest gauge hypodermic needle used for insulin injection, a 30 gauge needle, would have an outside diameter of 0.3mm. A microneedle would typically taper from a diameter of 0.06mm to 0.03mm at the tip – ie an order of magnitude smaller than the smallest

[75] In Example 1, as noted already, materials and methods are outlined and SDS-PAGE is conducted. The Example has no relevance to the issue of agent delivery

gauge hypodermic needle and even smaller still than the sewing needles used in Example 2 of the Patent;

- release from a single large needle of the trehalose-based and other sugar-based formulations of the Examples (as tested in Example 2) cannot be expected to translate to the context of an array of one or more microneedles with vastly different geometries. The test in Example 2 is, on this count, thus meaningless, and simply not adequate in any sense to assist a skilled man reading the specification to the view that its content makes it plausible[76] that the invention solves across the claim scope the particular release efficiency problem it claims to solve.

9.7.4 Referring to the "skin model" used:

- Example 2 uses a gel (Novex Gel[77]) into which the sewing needles are inserted and withdrawn;

- it is assumed that the insertion depth is of the order of the 2.0 - 2.5cm length of needle coating (see first bullet point of Paragraph 9.7.3 above and note that in Example 1, the plunge depth is 2cm);

- it is self-evident that this is an unrealistic skin and tissue model - the test is of no value to the skilled man; thus, in asking himself whether the Patent contains subject-matter which indicates plausibly that the claimed stability is achieved in a context in which rapid agent delivery to a site in a

[76] Incidentally in this regard, it is noted that in the second paragraph on page 11 of its June 29, 2009 submissions, the Patentee concedes that "passive" approaches to patch design included within the scope of the invention fail to achieve agent delivery with the rapidity of the device of D10. However, patches with this level of performance are included within the scope of the Patentee's claims according to all claim Requests put before the OD so far in these proceedings

[77] See lines 50/51 on page 10 of the Patent

patient is also achieved, the use of this unrealistic "*skin model*" [78] would lead him to a negative conclusion.

9.7.5 In some cases, coated microneedle/microblade embodiments of the invention seem intrinsically unworkable. Figure 5 of the Patent shows a microneedle having a lumen (or central bore). The reservoir is disposed within the lumen. It is not plausible that this construction[79] is workable. Notably, hollow microneedles were, at the priority date, a form of protrusion which had not enjoyed successful implementation[80].

9.8 Plausibility of the Alleged Solution – Claimed Solutions Generally

9.8.1 It also appears that not all polyols (and, moreover, not all sugars[81]) satisfy the requirement that they "*form a glass*" (and it appears that some of those that do call for exercise of considerable effort), but how the skilled man is to select those that do from those that do not is not a task on which the Patent provides any assistance. Accordingly, the Patent fails on this count also to make it plausible the invention has solved, for all included embodiments, the problem in the art it claims to solve.

9.8.2 The situation in the Patent with respect to guidance on microneedle/microblade and array geometry is far short of satisfactory; a skilled man at the priority date could not

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[78] Release of the antigen from the sewing needle into an essentially aqueous gel, as used in Example 2, will differ significantly to that following insertion into the skin. Skin penetration will be significantly harder to achieve in view of the physical barrier properties of the skin. Additionally, the skin is a complex membrane with proteins, cells, enzymes, tissue fluids, lipids and salts and so the rate of dissolution of the antigen-containing coating in Example 2 of the Patent will not be the same as in the aqueous gel which that Example uses. Thus the residence time for coated microneedles to release antigen may be significantly longer than in Example 2 and thus the "data" provided by that Example is meaningless.

[79] Even if enough capillarity is assumed for body fluids to rise into the lumen in use, it is not plausible that (i) this will present enough body fluid to the reservoir medium to dissolve more than a de minimis amount or (ii) resulting solution can escape the lumen to a dosage site against the same capillarity. That Figure 5B shows reservoir only in the lumen is puzzling from manufacture **and** use viewpoints

[80] D53 does not disclose hollow microneedles at all. D46 and D51 focus on solid microneedles and mention hollow microneedles in the Introduction only, pointing out that they have received less attention as they have weaker structures and engender problems with clogging of the bore hole (D46, page 1197, right hand column, 2nd and 3rd paragraph; D51, page 846, left hand column)

[81] The first sentence of the first complete paragraph on page 25 of D13 states that it is only "most" sugars that can form a glass.

conceivably be convinced that the Patent contains enough information in terms of microneedle/microblade and array geometry to make it plausible the invention solves the problems in the art it claims to have solved. There are a number of crucial issues here:

a) Expectation that geometry is a crucial factor

i. A skilled man would intuitively expect microneedle/microblade and array geometry to be a major influence on the ability of the solid sugar glass coated microneedle/microblade patches of the invention to perform. The importance of optimising microneedle and array geometry (as opposed to the geometry of *sewing* needles) for transdermal delivery with insulin coated microneedles was highlighted in D46 as a major obstacle to their clinical use but there is a dearth of study, and published information, on such issues prior to that time (as noted in D51).

ii. The skilled man understands that penetration of "blades" requires care and effort to achieve. It will be appreciated that when a skin-piercing projection engages the skin, the skin is first dented inwards prior to skin perforation and that accordingly short blades may not perforate the skin at all. However, the Patent covers microblades and microneedles of various lengths including those which are very short, exacerbated by the fact that the patches claimed in the Patent may also contain such a large number of microblades/microneedles (Paragraph [0019] states *"up to 1000"* is preferred) that individual point pressures are too small to achieve skin penetration[82].

iii. As reported in D46, on page 1202, Section 3.2, lines 13 et seq of the first paragraph, the experience of a skilled man attempting to use the invention would be that

[82] It appears that the Patentee concedes the points made in this paragraph of these Submissions of OII – see the final paragraph on page 11 of the Patentee's June 2009 submissions

"microneedles tend to buckle for a given diameter and length by increasing microneedles length but of the same diameter at pressure less than that needed to penetrate the stratum corneum", thus compounding the problem outlined above.

b) Coating changes the geometric context completely

i. Adding an external surface coating adds to complexity and uncertainty as a coating radically changes geometry; this is not a minor step.

ii. For example, the insertion force necessary to pierce human skin with microneedles depends on their original geometry **and** on the coating (which would provide a bigger cross-section to resist effective piercing).

iii. In addition, such coating will materially affect the leading tip of a microneedle and the cutting edge of a microblade.

iv. Importantly, page 1201 of D46 reports (first complete paragraph of Section 3.1) that comparison of penetration depth of coated with uncoated microneedles found a significant reduction in penetration depth for coated microneedles. This appears intuitive and, moreover, would be the experience of a skilled man attempting to perform the invention; the impression given to him by the Patent, however, is that microneedles etc can be treated in the same way whether coated or uncoated.

c) Coating jeopardises overall microblade/microneedle integrity

i. The invention must achieve a physical stability of the coating; this is intuitive and it is stated in Paragraph [0026] of the Patent. Although this much makes common sense[83], the Patentee has proposed to delete Paragraph [0026] (see D55 - first instance Minutes and attached

[83] A skilled man would intuitively believe that, in the absence of special measures, sugar glass could be too brittle to survive, in coating form, the handling suffered in manufacture of the needles/patch, the handling suffered in use and the stresses of skin piercing

copy of Parent Patent page 4 attached thereto) from the Parent Patent and in any event it is unclear what special measures are to be implemented to ensure that such physical stability (during manufacture, storage, clinical handling and skin insertion) is achieved for all embodiments the claims embrace.

ii. The OD will appreciate that in administration (in the sense of skin piercing) in particular, a coating is subject to significant load. The insertion force of a microneedle into human skin, and the effect on the coating, would intuitively be expected to threaten coating integrity and stability because of the brittleness of the sugar glass coating material[84]. Paragraph [0022] of the Patent refers to surface treatment of the microneedles/microblades but this does not deal with the risk of coating fracture due to brittleness.

iii. Importantly, the same paragraph mentions that friable coatings are recognised as a risk and suggests that the forms of microneedle/microblade which are necessary to address such risks and restrict breakage are much more limited than the claims reflect at present - in any claim Request.

iv. D13 states in the first complete paragraph on page 24 that most sugars will convert to syrup if exposed to moisture. This radical change in form would essentially "unravel" the invention, and it is unclear from the Patent what steps the inventors recommend for preventing/alleviating this problem.

v. This whole matter of coating physical stability would need to be explored by a skilled man in order to determine what is required of the coating and then a coating process and materials selection would need to be designed around

[84] Paragraph [0023] appears to suggest (it is believed conjecturally) practical embodiments where a sugar glass microneedle is in fact so brittle that it actually shears from the base plate - intentionally - to remain in the skin at the insertion site.

these needs to the extent possible. Importantly, as the Patent stands, there is nothing to provide the skilled man with evidence or suggestion that this stability could plausibly be achieved (indeed, the converse seems to be the case); and, of course, loss of coating on administration would seriously impair, and probably prevent in most scenarios, rapid or dose-accurate (or perhaps any) delivery of vaccine to the desired dosage site. The Examples state that the sewing needles used are inserted into a gel; however, the composition and mechanical properties of the gel will differ significantly to that of human skin and a sewing needle bears no similarity to a microneedle and even less to a microblade.

d) How the Patent ineffectively tries to provide information

i. The issue of microneedle/microblade selection is addressed only in general terms in the Patent, reference being made essentially just to various primarily patent publications in Paragraph [0017]. Most of these are also mentioned in previously mentioned Paragraph [0008] as associated with poor agent uptake rates; the Patentee's proposition is therefore apparently that applying a coating to these prior art devices cures their problems.

ii. The Patent specifies sewing needles in the Examples, and two preferred forms of "microblade devices" are specified in Paragraph [0018]. The first relates to stents comprising a helical mesh coil and is irrelevant. The second is a paper by an author named Henry. This paper was published a month before the priority date and can best be described as an experimental approach to microfabrication. The paper has the title: *"Microfabricated microneedles: A novel approach to transdermal drug delivery"* (the Patent does not mention the title) and its Abstract (D53) states that it describes "*the first published*

study on the use of microfabricated microneedles to enhance drug delivery across skin" [emphasis added].

iii. OII suggests that the Patentee had no idea at all at the priority date how it could add a coating of a polyol glass to the microfabricated microneedle arrays of D53 and achieve a solution to the problems the invention is claimed to provide; in any event, that information is not materially contained in the Patent.

9.8.3 The Patentee has filed details of experiments carried out to reproduce the Examples. However, these add nothing relevant to the Examples as they do not deal with the issues OII has raised above. In any event, as set down *inter alia* in Decision T1329/04, this later filed information could not be relied on as the sole basis for establishing that the claimed problem has been solved (see Reason 12 of T1329/04, last sentence), as evidence at least plausibly indicating the problem addressed has been solved must be shown at the filing date.

9.9 Prior Art and Invention Compared

9.9.1 Table 9.9.1 attached in its three parts compares the Main Request with D1, D10 and D50.

9.10 Motivation for Skilled Man to Modify Closest Art

9.10.1 Theoretically Limited Claims

9.10.1.1 It seems to OII that the Patentee may well wish to file additional claim requests in which the claims are limited to particular sugars (eg one or more of lactose, sucrose, raffinose, trehalose) which it then argues plausibly achieve the stability goal the invention purports to deliver and for which in particular it argues that there is plausible evidence in the state of the art that a glass can be formed without undue effort. This plausibility

state would need, it is emphasised, to be based on the information the average skilled man could reasonably be said to have placed in his possession from the state of the art – the Patent itself contains no such information – as a result of due (rather than undue) effort. For example, it does appear that it is a reasonable proposition for a skilled man to prepare a glass from trehalose and there is sufficient indication in the art to indicate that trehalose glass will act as a stabilizer to achieve stabilisation of a vaccine antigen eg in a microneedle coating.

9.10.1.2 OII's view remains that the invention, even if restricted to such subject-matter, is unsupported by information establishing that it plausibly (even in this more limited embodiment) solves the problem of achieving vaccine stability and, at the same time, rapid vaccine delivery. Reference is made in this regard to Paragraphs 9.7 and 9.8.2 to 9.8.5, which refer inter alia to such pre-conditions for good delivery performance as the need to ensure that the reservoir coating remains intact on a microneedle dimensioned to be capable of acceptable dermal penetration.

9.10.1.3 If OII is correct in this maintained position, then the invention (even in this limited form) seems to be invalid for lack of inventive step because the question of whether or not the invention is *"a solution to the problem to be solved"* has to be *"positively answered before any other criteria are taken into consideration"* (see T1329/04, Reason 13).

9.10.1.4 However, if OII is not correct in this position, it seems to OII the invention then fails to establish itself as having an inventive step when the rest of the criteria of the problem-and-solution approach are applied – as to this, the OD is referred to Paragraphs 9.10.2.6 below (and see T1396/04, Reason 7).

9.10.2 Inventive Step with D1 as Closest Prior Art

9.10.2.1 Looking at the Main Request, there is only one difference between D1 on the one hand and the invention according to the Main Request on the other hand, namely that D1, whilst disclosing a sugar as a protectant for the antigen (DNA), does not state that the coating is a reservoir in which the sugar "*is in* the *form of a glass*".

9.10.2.2 Claims limited to particular sugars, as postulated in Paragraph 9.10.1.1 above (remembering that such embodiment may fall within all the "*patch*" claims of all the claim requests), would obviously demonstrate an additional difference. Nevertheless, it seems clear to OII that a skilled man would be motivated to adopt this difference as well as that identified in Paragraph 9.10.2.1.

9.10.2.3 Such motivation takes two forms. The first is that it was known at the priority date that trehalose sugar glasses provide an acceptable stabilizing environment for biological molecules in particular. The second is that it was known that trehalose sugar glasses rapidly dissolve in patient tissue to release a pharmaceutical agent contained in the sugar glass.

9.10.2.4 This first motivation needs to be seen against a background in which vaccine stability is a well-recognised issue. Vaccines and many drugs are in general sensitive to thermal degradation and, as mentioned previously, vaccines and many drugs are customarily stored under refrigeration and transited via a cold chain. The Patent makes this point in Paragraph [0008][85] and references to this issue are ubiquitous in the art. D1 mentions the use of a protectant for the antigen (DNA) on the electrodes 16 at line 3 of page 28 and thus D1 plainly acknowledges the issue of vaccine stabilization. It would in any event be expected

[85] See the sentence bridging pages 2 and 3 of the Patent

that the inventors of D1 had stabilization in mind as an issue as this is an area which is of general topicality in the vaccine field.

9.10.2.5 The second motivation needs to be looked at against a background in which, as a substitute for use of hypodermic administration of vaccines (bolus administration), efficiency of antigen delivery through use of patches (which are inherently at a relative disadvantage) is a clear candidate for development of alternative approaches and thus a clear "target" for the skilled man. D1 already addresses the problem by using electroporative intervention and seeking to avoid the disadvantages which accompany that approach. The problem, in the sense of *the problem-and-solution approach*, which the invention addresses, is that of providing an alternative approach to rapid delivery, which might be a combination with the electroporative intervention of D1.

9.10.2.6 OII will be pleased to outline in detail in the documents on file where evidence can be found of the above motivations. However, the OD will note the following. D61 and D62 generally and D12 at page 236, Section 7.2.2.1, lines 10 et seq of the second paragraph refer to benefits of using trehalose glass to stabilise biologicals. A skilled man would have a reasonable expectation based on this common general knowledge in the art that eg trehalose glass would achieve stabilization of vaccine antigen contained therein. It is generally known eg from page 20 of D43 that such glasses are soluble in tissue fluids so that it would be expected to release antigen to tissue rapidly[86]. The question to be answered is whether a skilled man, based on these factors, would be motivated to formulate vaccine in the sugar and apply the formulation in glass coating form to microneedles/microblades

[86] In this respect, it is noted that the Third Party has drawn a similar conclusion based on the disclosures on pages 91 to 94 and the Summary section of D59 (numbered *out-of-sequence* by the Third Party as D41)

in a patch. There are four points in this respect which OII considers should be weighed in the OD's mind in addressing and deciding the question:-

(i) According to T1396/04, Reason 7, the skilled man does not require certainty of success in order to be motivated but rather, in the case before then the OD, *"...either some expectations of success or, at worst, no particular expectations of any sort, but only a 'try and see' attitude....*

(ii) Referring to D52 (see page 11 - first headed section, second paragraph and first bullet point in the final paragraph of the page), the skilled man (a) on the one hand is aware that glass technology in a vaccine context may still require additional validation at the priority date (and the same skilled man sees no proof in the Patent which convinces him that the invention plausibly solves the problem(s) in the art) but (b) on the other hand, recognises in a positive manner and with a sense that it is achievable, a need for embodiments of glass technology to be applied and reduced to effective practise in the vaccine delivery field.

(iii) The potential value of trehalose glass coatings, especially the promise that stabilization could avoid the need for a cold chain, would be seen as unusually highly appealing motivation for the skilled man to try to make these modifications to the skin patch element 12, 14, 16 of D1. This motivation is so high that it overcomes the lack of information in the art to indicate certainty of success.

(iv) The <u>fundamental</u> question in testing an invention against the problem-and-solution approach is not whether the skilled man would associate an alleged inventive step with a reasonable expectation of success but <u>whether he would,</u>

in all the circumstances applicable in the case concerned, be motivated to formulate the invention. In this respect, the value of the "*prize*" which success would achieve is as capable as forming motivation as the likelihood of achieving the success.

9.10.2.8 The Patentee can be expected to assert that, by limiting the claims to reservoirs having a glass transition temperature of more than 30°C, both novelty and inventive step are achieved. OII disagrees. The above T_g limitation does not involve a technical feature causing a proven additional technical effect which can be considered for the purposes of the assessment of inventive step (moreover, a glass transition temperature approximating mammalian physiological temperature is an obvious and routine choice for the skilled man). The same applies to all the features of the sub-claims (ie dependent claims) in the Main Request.

9.10.3 Inventive Step with D10 as closest prior art

9.10.3.1 Looking at the Main Request, there is only one difference between D10 on the one hand and the invention according to the Main Request on the other hand, namely that D10, whilst disclosing an antigen composition freeze-dried on the "*projections*", does not state that the coating is a reservoir in which a polyol is present and "*is in the form of a glass*".

9.10.3.2 Claims limited to particular sugars, as postulated in Paragraph 9.10.1.1 above (remembering that such embodiment may fall within all the "*patch*" claims of all the claim requests), would obviously demonstrate an additional difference. Nevertheless, it seems clear to OII that a skilled man would be motivated to adopt this difference as well as that identified in Paragraph 9.10.3.1.

9.10.3.3 Such motivation takes two forms. The first is that it was known at the priority date that eg trehalose sugar glasses provide a pharmaceutically-acceptable stabilizing environment for biological molecules in particular. The second is that it was known that eg trehalose sugar glasses rapidly dissolve in patient tissue to release a pharmaceutical agent contained in the sugar glass. In short, given the indications in the art of the role sugars can importantly play in the stabilization of antigens, it would be obvious to freeze-dry the compositions mentioned at lines 61-65 of Column 4 of D10 in the form a coating containing a glass-forming sugar such as trehalose.

9.10.3.4 As noted in Paragraph 9.10.2.4 above, the first motivation needs to be seen against a background in which vaccine stability is a well-recognised issue and OII refers the OD to that paragraph.

9.10.3.5 As shown in D55 (see D55, Paragraph 6.1, fifth sub-paragraph), the OD in the Parent Opposition took the view that the problem of stabilization is not mentioned in D10 (the present OD should note that D10 herein corresponds to E1b in the Parent Opposition). OII submits that the OD in the Parent Opposition was incorrect in taking this view. The OD is respectfully referred to the comments of OII in the paragraph which bridges pages 31 and 32 of the Statement of Opposition of OII. Additionally, as noted in Paragraph 9.3.10 above, stabilization is always a "*silent agenda*" item in the pharmaceutical field (especially the vaccine field of D10) but, in the case of D10 specifically, the principle object of the device[87] is to enable ready storage in large numbers without special precautions and reference is made[88] to the capacity for "*normal channels of trade*" to be used in terms of the supply line and for the devices

[87] See D10, Column 1, lines 55 -59
[88] See D10, lines 38/39 of Column 5

to be stored for *"substantial periods"* at locations within this *normal* supply line.

9.10.3.6 Similarly, as noted in Paragraph 9.10.2.5 above, the second motivation needs to be looked at against a background in which, as a substitute for use of hypodermic administration of vaccines (bolus administration), efficiency of antigen delivery through use of patches (which are inherently at a relative disadvantage) is a clear candidate for development of alternative approaches and thus a clear "target" for the skilled man. Even though D10 claims very rapid delivery, the skilled man has always been depicted in EPO case law as a person who is deemed to be someone who is constantly seeking improvement. In this light, the skilled man is not to be seen as a person who is so satisfied with the rate of take up of antigens offered by D10 that he will not seek additional improvements. In this respect, he has patient comfort also in his mind and he would, for example, seek improvements which permit an increase in patient comfort whilst at the same time compensating for the slowing of administration speed which is sometimes accompanied by improved patient comfort. A problem in the case of D10 emerges from lines 1 to 16 of Column 6 where it is clear that ensuring complete antigen delivery is accomplished by a rotary motion of the patch. This will no doubt threaten patient comfort and instil an analogue of needle fear as well as risking bleeding and scarring. It is additionally clear that an extra level of care in administration is needed to ensure that patient welfare is not compromised (line 9 of Column 6 states that a *"gentle"* rotary motion is required in practice). By using a rapidly dissolving antigen coating, the antigen can nevertheless be delivered rapidly - the rotating step can be omitted as redundant. The use of a rapidly dissolving coating may be seen as likely to match the delivery speed of D10 or as simply setting a new balance of speed and comfort.

9.10.3.7 The OD is referred to Paragraphs 9.10.2.6 to 9.10.2.8 above.

9.10.4 Inventive Step with D50 as closest prior art

9.10.4.1 Looking at the Main Request, D50 differs from the invention in that it does not disclose a solid reservoir material in which there is sugar which forms a glass (but the coating of liquid is biodegradable in the sense meant by the Patent).

9.10.4.2 OII's view is that at the priority date the skilled man would be motivated to modify the D50 disclosure to conform to what the Patent claims.

9.10.4.3 D50 is dated 1961. In the period up to the priority date, there is a clear trend to do what seems intuitively perfectly natural – namely to use the device of D50 with other vaccine compositions and to do so using solid compositions. In D50, the studies were basic and intended to "*prove*" the value of the "*new type of scarifier*" (page 220, second paragraph). The studies were limited by the vaccine used – smallpox liquid vaccine. In short, they were experimental and the method approach in the study referred to in D50 as the Group III study was to use the liquid vaccine available. It is noted that:-

(i) By 1963, D10 (for example) – primarily proposed initially for smallpox vaccination – had developed to the point where a fundamentally very similar device used solid compositions pre-provided on the "points" (lines 59 et seq of Column 4 of D10 describe eg freeze drying a solution on the points), and was applicable more broadly to "*biological substances*" (line 12, Column 6) and "*a great variety of transcutaneous injections....*" (lines 20-40 of Column 4).

(ii) The background to the trend for dry (ie solid) coatings is, of course, described in Paragraph 1.1 on page 11 of D54.

The continuation of the trend past the earliest claimed priority date is evidenced in D1 (see page 28, lines 1 to 4).

(iii) Notwithstanding that D50 is experimental, the experiment was a success, making the D50 device a ripe candidate for skilled persons to develop on the line of applying it to different disease models and on the line of improving the mode of use to include the antigens in a solid coating bound to the surface of the "*points*" (ie microneedles).

9.10.4.4 There can be no doubt that a skilled man would be motivated to take the further step of modification to use the vaccine in the form of a composition in which (a) the antigens are stabilized by a sugar and (b) the composition forms a glass coating. The pre-provision of a vaccine coating exposes it to forces of decay which the skilled man would want to address. Secondly, art such as D43 (and the "*mood*" of the vaccine community shown in other documents mentioned herein) suggest to the skilled man glass preservation in the coatings.

9.10.4.5 Claims limited to particular sugars, as postulated in Paragraph 9.10.1.1 above (remembering that such embodiment may fall within all the "*patch*" claims of all the claim requests), would, of course, demonstrate an additional difference. Nevertheless, it seems clear to OII that a skilled man would be motivated to adopt this additional difference.

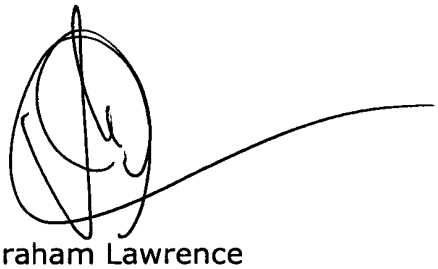
9.10.4.6 The OD is referred to Paragraphs 9.10.2.6 to 9.10.2.8 above.

10. Requests

10.1 OII requests revocation of the Patent in its entirety.

10.2 OII requests appointment of oral proceedings in the event that the OD is not minded to grant the above Request upon the written submissions of OII. Oral proceedings are requested to be in English with simultaneous translation between English and any other language used as a spoken or listening language by another party with the OD's permission.

10.4 OII requests an award of costs to OII.



Malcolm Graham Lawrence

Dated: June 4, 2010