OPPOSITION TO EP 2 035 835 B1
(Antibodyshop A/S)
By ADAMS, Harvey Vaughan John

Statement of Facts and Arguments

An opposition to the above-mentioned European patent of Antibodyshop A/S (which is referred to herein as the "Patentee") is filed herewith by ADAMS, Harvey Vaughan John (referred to herein as the "Opponent"). This is the Opponent's Statement of Facts and Arguments in accordance with the provisions of Article 99 EPC and Rule 76 EPC.

1. REQUESTS

1.1 Opponent hereby requests the revocation of European Patent 2 035 835 B1 in its entirety, and for all designated states.

1.2 Opponent also requests that Oral Proceedings be appointed in the event that the Opposition Division (which is referred to herein as the "OD") forms any intention whatsoever to arrive at any other decision on the basis of the written procedure.

1.3 In addition, Opponent hereby reserves the right to expand on the present observations both in writing and at any subsequent Oral Proceedings.

2. CITED DOCUMENTS

2.1 **Document D1** is WO 2004/088276 A2. This document was published on 14 October 2004, which is before the priority date of the opposed patent of 30 May 2006. Thus, the document is part of the state of the art under Article 54(2) EPC and it is relevant for the assessment of both novelty and inventive step.

3. REASONS FOR INVALIDITY

3.1 In the following observations, the Opponent will demonstrate that the claims of the opposed patent introduce subject matter which extends beyond the content of the application as filed, thereby contravening the provisions of Article 123(2) EPC.

3.2 Opponent will also demonstrate that the subject matter of the alleged invention cannot be put into practice by a person of skill in the art, let alone across the full scope of the claims and without an undue burden. Accordingly, the specification of the opposed patent does not provide a sufficient disclosure of the subject matter of the alleged invention and, as a result, the provisions of Article 83 EPC are also contravened.

3.3 Finally, Opponent will also establish that the subject matter that is defined by the claims of the opposed patent lacks novelty and/or is obvious over the disclosure in the state of the art, contrary to the provisions of Articles 54 and/or 56 EPC.

3.4 In summary, the claims of the opposed patent are manifestly invalid and, moreover, there is nothing within the disclosure of the patent which might form the basis for an allowable claim. Thus, the request that the opposed patent be revoked in its entirety, and for all designated states, is fully justified.

4. ADDED MATTER (Articles 123(2) and 100(c) EPC)

4.1 Having regard to the requirements of Article 123(2) EPC, Opponent observes that the claims of the patent as granted clearly introduce subject matter which extends beyond the content of the application as filed, *i.e.* PCT/DK2007/000254. The requirements of Article 123(2) EPC are therefore contravened.

4.2 ***No basis for "an injury that is due to physical causes [which is] traumatic in origin"***

4.3 The granted Claim 1 refers to a method for assessing the severity of an injury which is both due to physical causes and traumatic in origin. However, there is no basis in the application as filed for this specific combination of technical characteristics.

4.4 In the EPO's Communication dated 6 July 2011, which reported a telephone consultation of the Examiner with the Patentee's representative on 30 June 2011, it was asserted that there was basis for the subject matter of the granted Claim 1 (and therefore for the specific type of injury that is recited in the claim) in Claims 1 and 10 of the application as filed. This assertion is, however, incorrect. Specifically, Claim 1 of the application as filed specified "an injury that is due to physical or chemical causes", whilst Claim 10 of the application as filed, which was dependent on Claim 1, stated that the injury "is traumatic in origin". Now as discussed during the prosecution of the application, with reference to the Merriam-Webster Dictionary, injuries that are "traumatic in origin" are not restricted to those injuries which have been caused by physical agents: they also include injuries which are due to chemical agents. As a result, the reference in Claim 10 of the application as filed to an injury which is "traumatic in origin", is not linked *specifically* to the recitation in Claim 1 of the application as filed of an injury that is due to physical causes. Accordingly, the granted Claim 1, by introducing such a linkage in its reference to "an injury that is due to physical causes [*and which is*] traumatic in origin", contains a specific combination of characteristics which was not clearly and unambiguously disclosed within the application as filed. The provisions of Article 123(2) EPC are therefore contravened.

4.5 ***No basis for the specific combination of a type of injury, subject, and sampling time***

4.6 The granted Claim 1 defines a method for assessing the severity of a particular type of injury (an injury that is due to physical causes [and which is] traumatic in origin) in a specific type of subject (a human), wherein the method involves taking a measurement within a particular time frame (six hours after the injury has occurred). In contrast, Claim 1 of the application as filed more broadly referred to "an injury that is due to physical *or* chemical causes", wherein the injury exists in *any* subject (the subject need not be a human patient, as is evidenced by dependent Claim 9 of the application as filed [which demonstrates that the subject being a human is not an obligatory feature] and by the disclosure at page 5, line 28 to page 6, line 2 of the application as filed [referring to the conduct of the method of the alleged invention on animals, such as cattle]). Also in contrast to the granted Claim 1, Claim 1 of the application as filed is more permissive in relation to the time period within which the measurement must

be taken: in the original Claim 1, the measurement must be taken within twelve hours of the injury.

4.7 Now even if the particular type of injury (an injury that is due to physical causes *and* which is traumatic in origin) has basis in the application as filed (which it does not; see the discussion above) the further combination of this specific type of injury with a particular type of subject and a certain time point of measurement does not. More particularly, the granted Claim 1 can in reality only be arrived at by making a series of selections from the original disclosure, *i.e.:* (i) a first selection of the type of injury as an injury which is due to physical causes, from the two possibilities as set forth in Claim 1 of the application as filed [physical and chemical causes]; (ii) the further requirement that the injury is one which is "traumatic in origin" (Claim 10 of the application as filed); (iii) the identification of a human being as the type of subject for which the injury is being assessed (Claim 9 of the application as filed); and (iv) a further selection of a more restrictive time period (six hours) within which the required measurement must be taken. This particular combination of technical elements has not been directly and unambiguously disclosed within the application as filed which means that the requirements of Article 123(2) EPC are clearly contravened.

4.8 ***A fundamental change in the definition of an injury that is "due to physical causes"***

4.9 As a consequence of amendments to the *description* of the application, the definition of one of the features that is set forth in the granted Claim 1 was changed during prosecution. As a result, the subject matter of the claims as granted, which should be interpreted in the light of the description, is not clearly and unambiguously disclosed in the application as filed, and so the provisions of Article 123(2) EPC are therefore contravened. The language in question is the definition of an injury "that is due to physical causes", and, in particular, the definition of the phrase "physical causes". The amendments in question include the amendment that was made to the first paragraph of the "Detailed Description" (see especially page 3, lines 18-26 of the application as filed) and the amendment that was made to the fourth to last paragraph before the Examples (page 10, lines 3-9 of the application).

4.10 To consider the first of these amendments in further detail, the application as filed originally disclosed that injuries that are due to either "burns" or "irradiation" are injuries that are due to "*physical agents*". Thus, a broad definition of the term "physical agents" was being utilised but that was the definition which the Patentee had chosen. In more detail, the application as filed indicated, at page 3, lines 18-26 of the description, that:

> "*The present invention relates to methods and devices for determining the severity and prognosis of injury due to* ***physical agents such as impact, crush, blast, burns or irradiation****, or any type of exposure to noxious chemical agents, in a subject, preferably a mammal, more preferably a human, by measuring a level of neutrophil-gelatinase associated lipocalin (NGAL) …*" [emphasis added]

4.11 In other words, the application envisaged two types of injury: those due to physical agents - which include injuries resulting from impact, crush, blast, burns or irradiation - and those due to chemical agents. This division of different types of injury into physical and chemical, and the allocation of burns and irradiation as injuries that are due to physical agents, is reflected in the original Claim 1 (wherein the injury is due to either physical or chemical causes), and in the original Claim 12, which is dependent on Claim 1 (wherein the recited injury is due to exposure to radiation). Now in the light of the above passage, and given that the Patentee is his/her own lexicographer, any reference in the application as filed to an injury that is due to

"physical causes" (including any reference in the claims) must be understood to encompass injuries that are due to either burns or irradiation.

4.12 Now during the revision of the description, the above-mentioned passage within the Detailed Description was amended such that the specified possibilities of burns and irradiation were deleted from the options for "physical agents". More particularly, the passage was revised to state that:

> "*The present invention relates to methods for determining the severity of injury due to physical agents such as impact, crush, blast in a human …*"

4.13 Now given that the possibilities of the injuries that are due to physical causes was narrowed by this amendment, the scope of Claim 1 of the *Druckexemplar*, which specifically requires assessing the severity of an injury which is due to physical causes, was also altered by the amendment. Before the amendment the claim encompassed assessing injuries that are due to burns or irradiation; after the amendment it did not.

4.14 As an explicit confirmation of this conclusion, reference may be made to other amendments that were made to the description, including *e.g.* the amendment that was made at page 10, lines 3-9 of the application as filed. The original passage stated that:

> "*Another exemplary embodiment is the assessment of whole body radiation exposure in subjects …*"

4.15 But this was changed to read:

> "Another example ***not forming part of the present invention*** is the assessment of whole body radiation exposure in subjects …" [emphasis added]

4.16 This makes it clear that exposure to radiation is not an injury that is due to "physical causes" as set forth in Claim 1 of the *Druckexemplar*, and hence in the patent as granted.

4.17 Of course, the fact that the amendments to the *description* result in a narrowing of the claim scope is in accordance with the provisions of Article 69(1) EPC, second sentence, pursuant to which "the description and drawings shall be used to interpret the claims".

4.18 In sum, therefore, it is clear from the above that what has happened during prosecution as a result of the amendments to the description is that the meaning of the phrase "an injury that is due to physical causes", as set forth in Claim 1 of the granted patent, has been changed: previously it encompassed injuries that are due to burns or irradiation; at present it does not.

4.19 Having said all this, there is no basis within the application as filed for this new subgroup of "injuries that are due to physical causes", *i.e.* a subgroup which does *not* include injuries that are due to burns or irradiation, but which *does* include injuries due to other types of physical agents (including not only the specific types of physical injury as recited in the description as amended (impact, crush and blast) but also any other type of physical injury. The provisions of Article 123(2) EPC are clearly violated. The patent cannot be maintained.[1]

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[1] As an aside, different ways of classifying injuries have been used during the examination of the application. To prevent any confusion, this will now be discussed. In more detail, in the Communication pursuant to Article 94(3) EPC dated 6 July 2010, it was assumed that there are three types of injury, *i.e.*: (i) chemical; (ii) traumatic; (iii) radiation. This interpretation

4.20 Finally in this regard, reference may be made to the established case law of the Board's of Appeal, which confirm that an amendment to the description which affects the meaning of a term within the claims leads to an introduction of subject matter into the application as filed. In particular, the OD is alerted to Appeal Decision **T 500/01**, the Headnote of which reads:

> "*According to Article 123(2) EPC, a European patent application or a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. A claim, the wording of which is essentially identical to a claim as originally filed, can nevertheless contravene the requirements of Article 123(2) EPC, if it contains a feature whose definition has been amended in the description in a non-allowable way.*"

4.21 Reference may also be made to the Appeal Decision **T 1239/03**, where it had to be decided whether the meaning of an unclear term that was set forth in the claims (the percentage of a particular component) and which could be interpreted in (two) different ways (*i.e.* weight % or mol %) had been changed as a result of an amendment to the description (the deletion of certain examples of polyolefin compositions). The Board held that as a result of the deletion, there had been "a shift in the interpretation of the claims" that introduced subject matter into the application as filed (see paragraph 3 of the Reasons for the Decision). The provisions of Article 123(2) EPC were therefore contravened.

4.22 In light of all of the observations presented above, the provisions of Article 123(2) EPC are clearly contravened by both the amendments to the description and the amendments to the claims. The patent as granted cannot be maintained. It should therefore be revoked.

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was perhaps a result of the existence of the original dependent Claims 10, 11, and 12, which respectively referred to an injury that is "traumatic in origin" (original dependent Claim 10); "due to exposure to a chemical agent" (original dependent Claim 11); or "due to exposure to radiation" (original dependent Claim 12). Following this classification, the Examiner held in the above Communication that the data reported in Example 4 of the patent (which example refers to "trauma patients", *i.e.* to class (ii) above) could not be extrapolated to patients having either chemical injuries (class (i); see page 3, lines 13-20 of the Communication) or radiation injuries (class (iii); see page 3, lines 23-31 of the Communication). In essence, the Examiner would seem to have been interpreting injuries that are "traumatic in origin" to be injuries which result from the impact of objects on the bodies of subjects, *e.g.* injuries sustained in traffic crashes, gunfire, earthquakes, *etc.*

Now as was later recognised by the Examiner during the prosecution, injuries which are "of traumatic origin" are not in fact restricted to injuries that result from collisions of objects with the body. For example, they encompass injuries which result from chemical causes (see the Communication dated 6 July 2011, reporting a telephone conference on 30 June 2011). To support this position, the Examiner referred to the Merriam-Webster dictionary, but reference might also have been made to *e.g.* the original Claim 10 of the application as filed. After all, the original Claim 10 required the injury to be traumatic in origin, but this was dependent upon the original Claim 1, which specified that the injury might result from either physical *or chemical causes*. Now in making this correction in interpretation, the Examiner moved some way towards recognising the original classification of injuries in the application as filed, in which only two types of injury, those due to "physical" causes and those due to "chemical" causes were contemplated. However, the classification scheme that was then adopted by the Examiner *still* did not reflect the original definitions and divisions that were present in the application as filed. Specifically, the classification adopted by the Examiner, after recognising that his three way split of injuries between: (i) chemical; (ii) traumatic; and (iii) radiation, was incorrect (on the basis that traumatic injuries include chemical injuries), instead relied on a different three way split between: (i) chemical; (ii) physical; and (iii) radiation, with at least the first two types of injuries including injuries that were not only chemical or physical but also "traumatic in origin". As discussed herein, however, this classification is certainly not in conformity with the content of the application as filed. Under the Examiner's classification, injuries that arise from radiation are indicated to be outside of the definition of injuries which are "due to physical causes", whereas this was not the case in the application as filed. Moreover, because the description of the *Druckexemplar*, which became the opposed patent, was amended into conformity with the Examiner's newly-adopted classification, it introduces subject matter which extends beyond the content of the application as filed: this is because the claims of the opposed patent, interpreted using the description, likewise relate to a subset of physical injuries that was not originally disclosed (a subset of physical injuries which *excludes* those injuries that arise from radiation exposure [and also burns]).

5. INSUFFICIENT DISCLOSURE (Articles 83 and 100(b) EPC)

5.1 In accordance with the provisions of Article 83 EPC, an alleged invention must be disclosed in the patent in a manner which is sufficiently clear and sufficiently complete for it to be put into effect by the person of skill in the art over the entirety of the claim scope and without an undue burden. As will be clear from the following discussion, however, this provision has not been satisfied by the patent in suit. The patent is invalid and it must therefore be revoked.

5.2 ***The measurement of a "functional activity" of NGAL***

5.3 Dependent Claims 7, 8, 9 and 10 recite the measurement of a "functional activity" of NGAL. There is insufficient information within the opposed patent as to the identity of this functional activity – or how it might be measured. The only relevant disclosure of "functional activity" is in paragraph [0017] of the opposed patent, where it is indicated that:

> "*NGAL in a sample can also be measured indirectly, by determining a functional activity of the NGAL, for example by its capacity to bind a natural or synthetic ligand, the concentration of which can also be measured by means of an antibody.*"

5.4 However, there is no indication within the patent in suit as to what this "natural or synthetic ligand" might be, thereby unfairly leaving a skilled person both to identify a ligand and devise an assay for measuring its binding to NGAL. In light of this lack of any guidance, the level of research that is required by the skilled person clearly amounts to an undue burden, and the requirements of Article 83 EPC are therefore contravened. The opposed patent cannot be maintained in the form in which it was granted. It should therefore be revoked.

6. LACK OF NOVELTY (Articles 54 and 100(a) EPC)

6.1 To satisfy the provisions of Article 54 EPC, the subject matter that is defined by the claims of the opposed patent must be novel over the disclosure in the state of the art, which includes the publication of document D1 (WO 2004/088276 A2).

6.2 ***Document D1 (****WO 2004/088276 A2****)***

6.3 Document D1 discloses a method of identifying the extent of a renal tubular cell injury which comprises obtaining a urine sample from a subject and then measuring the level of NGAL in the urine sample. The renal tubular cell injury is caused by an event, and the event may be a surgical procedure. Reference is made to, *inter alia*, paragraphs [0012], [0014] and [0041] of document D1, and also to its original Claims 24 to 26. As an example, paragraph [0041] of the document states that it:

> "… *provides a method and a kit for assessing the extent of renal injury based on a proportional relationship between the extent of injury, which can range from the very onset of renal tubular cell injury, to clinical ARF, with the quantity of NGAL present in the urine passing from the subject. The invention provides a means for a clinician to estimate the degree of renal injury at an initial assessment, and to monitor the change in status of the injury (worsening, improving, or remaining the same) based on the detected amount of NGAL in the urine.*"

6.4 Likewise, the original Claim 24, this defines:

> "*A method of identifying the extent of a renal tubular cell injury, including an ischemic renal injury and a nephrotoxic injury, caused by an event, comprising the steps of:*
>
> *1) obtaining at least one urine sample from a mammalian subject;*
>
> *2) detecting in the urine sample the presence of a biomarker for a renal tubular cell injury; and*
>
> *3) determining the extent of the renal tubular cell injury based on the time for onset of the presence of the biomarker in the urine sample, relative to the time of the event.*

6.5 Claim 25 requires that the biomarker comprises NGAL, whilst Claim 26 states that the event is a surgical procedure.

6.6 The examples of document D1 provide an illustration of such methods.

6.7 For instance, Example 5 of document D1 describes an experiment in which NGAL levels in the urine of human patients were measured two hours after kidney transplantation (compare the reference to measurement within six hours in Claim 1 of the opposed patent). The data show that there was a significant correlation between urinary NGAL and the time period over which the kidneys were stored on ice prior to transplantation (the "cold ischemia time") and that "*NGAL excretion is proportional to the degree of renal injury*" (see paragraph [0098] of document D1, at lines 6-7). The data further show that "*urinary NGAL measured within two hours of transplantation was predictive of ARF*" (paragraph [0098], lines 9-11). Since kidney transplantation is a "*predictable human model of ischemic renal injury*" (paragraph [0098], at lines 1-2), this example shows that the level of NGAL in the urine, measured two hours after a renal injury, can be used to assess the severity of that ischemic renal injury, including *e.g.* its likelihood to lead to acute renal failure (ARF). Reference is also directed to Figure 15B of document D1, which illustrates the proportionality between the level of NGAL in the urine and the extent of the ischemic insult to which the kidney is exposed.

6.8 Turning to Example 6 of document D1, this describes the measurement of the level of NGAL in the urine of 15 human patients undergoing open heart surgery (paragraph [0099], lines 1-2). As can be seen from Figure 16B of the document, NGAL levels were initially measured every two hours, beginning at two hours after the operation. Furthermore, as is reported in *e.g.* paragraph [0099], at lines 13-15 of document D1: "*There was a correlation between the quantity of urinary NGAL and cardiopulmonary bypass time, indicating that NGAL excretion is proportional to the degree of renal injury*". In addition, the data show that the "*quantitation [of NGAL] is predictive of acute renal failure*" (paragraph [099, last three lines).

6.9 ***Claim 1 lacks novelty over the disclosure in document D1***

6.10 In light of passages such as those identified above, the subject matter defined by Claim 1 of the opposed patent lacks novelty over the disclosure in document D1. Particular reference may be made to *e.g.* Example 6 of document D1, which describes a method in which NGAL levels in the urine of human patients were measured, two hours following cardiopulmonary bypass surgery, as a way of assessing the extent of renal injuries caused by the surgery.

6.11 Now it will be noted that the opposed Claim 1 requires that the injury whose severity is being assessed must be "due to physical causes" and must be "traumatic in origin". In this regard, however, the renal injury that is being assessed in Example 6 of document D1 – *i.e.* a renal ischemic injury that is due to cardiopulmonary bypass – may be considered to be injury that is both "due to physical causes" and "traumatic in origin".

6.12 In this regard, in the examination of the application that resulted in the opposed patent, the Examiner must have concluded that the renal injury disclosed in Example 6 of document D1 is *not* an injury which is "due to physical causes" and which is "traumatic in origin". After all, a family member of the document D1 cited herein, US 2004/219603 A1, was identified in the International Preliminary Report on Patentability (paragraph 2.2.1), whereas the Examiner, based on some unknown reasoning, only referred to Example 4 of the document (describing a renal nephrotoxic injury induced by the chemical, cisplatin) and did not consider Examples 5 and 6. Perhaps the Examiner simply overlooked these two examples, because they clearly prejudice the subject matter of the opposed Claim 1 and should therefore have been cited. The only other possibility is that the Examiner *noted* the examples, but formed the incorrect opinion, as discussed above, that a renal injury which occurs due to the surgical intervention of cardiopulmonary bypass is *not* an injury which is "due to physical causes", nor "traumatic in origin". Any such opinion is, however, unjustified, since a cardiopulmonary bypass entails the use of physical implements, including *e.g.* scalpels, clamps, and a sternal saw, to open up the chest cavity and split the breastbone. It is likewise unjustified in light of the typical use of the term "surgical trauma" to describe the damage to the body that is caused by a surgical intervention.

6.13 In this regard, the specification of the opposed patent also offers no clear guidance as to the meaning of the above-quoted phrases which are apparently being employed to characterise the claimed subject matter over the state of the art. In particular, there is no clear definition of either one of these terms.

6.14 In respect of the phrase "physical causes", a list of examples is all that is provided (which list was changed during the prosecution of the patent such that an exposure to radiation, which originally fell within the scope of "physical causes", was later specifically excluded – see the above discussion). In light of the current list, it is assumed that the phrase "physical causes" includes at least impact, crush, and blast (paragraph [0010] of the patent in suit), but none of these three terms are defined, and the scope of the phrase "physical causes" is in any event open-ended (note the language "such as" in paragraph [0010]), which means that it includes *inter alia* the impact on the body of a surgical instrument. As for the term "trauma", there is, as discussed above, no clear definition within the opposed patent, with the Examiner himself observing (with reference to the Merriam-Webster dictionary) that the term is so broad that it encompasses *any* type of adverse insult on the body. Now given this absence of any clear definition for either phrase, it is legitimate to use the broadest technically sensible meaning (this following Appeal Decision **T 79/96** at paragraph 2.1.3 of the Reasons for the Decision[2]). However, this inevitably results in the reasonable conclusion that the subject matter of Claim 1 of the opposed patent, which refers to an injury that is both "due to physical causes" and is "traumatic in origin", encompasses a method of assessing the severity of a renal injury that arises from the traumatic event of cardiopulmonary bypass surgery. In summary, the subject matter that is defined by Claim 1 of the opposed patent lacks novelty over the disclosure in document D1 and the requirements of Article 54 EPC are therefore contravened.

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[2] T 79/96, paragraph 2.1.3 of the Reasons for the Decision: "*The Board takes the view that when assessing novelty of the claimed subject-matter an expression in a claim should be given its broadest technically sensible meaning.*"

6.15 ***Dependent Claims 2, 5, 8 and 9***

6.16 Dependent Claims 2, 5, 8 and 9 of the opposed patent respectively require that "the sample is from within 2 hours after the injury has occurred" (see Claim 2); "the bodily fluid is blood, plasma, serum or urine" (Claim 5); "the measurement of NGAL …is performed by means of one or more antibodies …capable of binding to NGAL" (Claim 8); and "the measurement of NGAL …gives rise to a quantitative or qualitative signal that can be read by visual inspection or by means of a portable reading device" (Claim 9).

6.17 In the method that is described in Example 6 of document D1, NGAL levels are measured in urine samples of patients taken within 2 hours after the injury has occurred (Claims 2 and 5). The measurements are made using Western Blot (Claim 8), which gives rise to a signal that can be read by visual inspection (Claim 9). Reference is made to *e.g.* paragraph [0099] lines 1-3 and 9-13 and Figure 16A. Thus, the subject matter that is defined by Claims 2, 5, 8 and 9 of the opposed patent lacks novelty over the disclosure in document D1.

7. LACK OF INVENTIVE STEP (Articles 56 and 100(a) EPC)

7.1 To the extent that the OD considers that the subject matter of the granted claims is novel, or Patentee amends its claims to establish novelty over the state of the art, the claimed subject matter is nevertheless unpatentable for a failure to meet the requirements of Article 56 EPC. What is presented as an alleged invention would have been obvious to the person of skill in the art at the priority date of the opposed patent for, *inter alia*, the reasons that are set forth below.

7.2 ***Prima facie obviousness over the teaching in document D1***

7.3 Document D1 contains a general teaching about the use of urinary NGAL for assessing the severity of renal injuries which are traumatic in origin. In this regard, reference may be made to *e.g.* paragraph [0036] of document D1, which teaches the use of a simple point-of-care kit for the rapid detection of urinary NGAL in "*patients who are at risk of developing ARF [acute renal failure] including use in …trauma*". Now as the OD will recognise, to the extent that the subject matter of the granted Claim 1 is formally novel over this disclosure in document D1 as a result of the requirement that the injury of traumatic origin is "due to *physical causes*" *in particular*, it merely represents an arbitrary selection of one specific type of traumatic injury from the general disclosure of trauma that is found in paragraph [0036].

7.4 Further in this regard, even without focussing on paragraph [0036], the OD should recognise that Patentee is effectively seeking to *re-monopolise* a part of the disclosure in document D1 merely by reciting one possible 'upstream' cause of the type of damage to the kidneys which results in the release of NGAL into the urine (*i.e.* by specifying within its claims an injury that is "*due to physical causes* [and] *traumatic in origin*"). In particular, document D1 teaches the use of urinary NGAL to assess the extent of, *inter alia*, an *ischemic injury* to the kidneys (see Claim 24 of document D1) and such injuries can, of course, be caused by traumatic events that are due to physical causes, *e.g.* traffic accidents, explosions and gunshot wounds: such events typically involve the rupturing of the blood vessels and an internal and/or external haemorrhage that disrupts the blood supply to the kidneys and thus produces an ischemic renal injury.

7.5 Now had the Patentee defined a set of injuries *which do not encompass injuries that directly or indirectly reduce the blood flow to the kidneys*, its position might be easier to understand (although the lack of any experimental data in support of the assessment of this specific set of injuries would be detrimental to patentability: nothing can be learned from Example 4 of the opposed patent in relation to the types of injuries that were suffered by the patients that are mentioned in that example). However, to the extent that the granted claims encompass the assessment of injuries that inherently result in, amongst other effects, an ischemia of the kidneys, the claims are unpatentable over the teaching in document D1, and especially over the reference within that document to the use of urinary NGAL to assess the extent of an injury that is traumatic in origin (see paragraph [0036]). In sum, *merely specifying a possible upstream cause of an ischemic renal injury* (*i.e.* a *physical cause* which is *traumatic in origin*) does not provide the claimed subject matter with an inventive step, and the requirements of Article 56 EPC are therefore contravened.

7.6 ***No surprising technical effect in assessing the specific injuries set forth in the claims***

7.7 As a further point to note, Patentee cannot pretend that there is a *surprising technical effect* that is associated with specifying its particular 'upstream' cause for the ischemic injuries to the kidneys whose assessment using NGAL has already been taught in document D1 (*i.e.* specifying that the injury is "*due to physical causes* [and] *traumatic in origin*"). Similarly, it is impossible to argue that there is a surprising technical effect associated with assessing the *particular type of traumatic injury* that is recited in its claims (an injury that is *due to physical causes*), which technical effect might be asserted to support the patentability of the claimed subject matter over the *more specific teaching* in document D1 concerning the use of urinary NGAL for determining the extent of an injury which is *traumatic in origin* (paragraph [0036] of document D1).

7.8 In this connection, of course, to the extent that the granted claims of the opposed patent are rendered novel such that they do *not* encompass the assessment of injuries that arise from the physical trauma of a surgical intervention, Patentee cannot rely on the data in document D1 to show, *at a fundamental level*, that the method which is defined by its claims provides a solution to the technical problem of how to assess the severity of an injury which is "due to physical causes [and] traumatic in origin".

7.9 Furthermore, the only experimental data within the opposed patent is that which is found in Example 4, and as discussed above, there is no indication in Example 4 of the cause of the traumatic injuries that the patients that are referred to within that example had sustained (*i.e.* whether the injuries were due to physical causes, or due to chemical causes).

7.10 In light of the above, to the extent that the claims are novel, Patentee cannot demonstrate that the subject matter that is defined by those claims solves the technical problem of how to assess the severity of *even one* type of injury that is *due to physical causes* and is *traumatic in origin* (let alone assert that this problem has been solved across the scope of the claims).

7.11 The lack of disclosure in Example 4 of the opposed patent, in particular, will be discussed below, with reference being made to the examination procedure of the opposed patent.

7.12 ***No evidence that the alleged technical problem has even been solved***

7.13 In the above-identified Communication pursuant to Article 94(3) EPC dated 6 July 2010, the Examiner indicated that document D1 at least discloses "a method for assessing severity of

an injury that is due to chemical causes … arising from medical or diagnostic treatments and which is not due to natural disease in a human, comprising measuring a level of NGAL in a sample of bodily fluid from the human within 6 hours after the injury has occurred" (see *e.g.* paragraph 4.2 of the Communication). Based on this premise, it was found that the technical problem which was allegedly being solved by the subject matter of the claims then on file, which referred to "an injury that is due to physical or chemical causes *arising from accidents, natural disasters or hostile acts*" was a technical problem of "how to extend the use of NGAL as a marker for the severity of injuries", and that the solution to that problem was, allegedly, the use of NGAL as a marker for the severity of injuries that are due to: (a) chemical causes *that arise from accidents, natural disasters, or hostile acts*; or (b) *physical causes* that arise from accidents, natural disasters, or hostile acts. In addition, an inventive step was correctly *denied* on the basis that the data within the application as filed (Example 4) is "…exclusively dedicated to NGAL as a marker for the severity of injuries that are *traumatic* in origin, but fails to provide convincing evidence that these findings can be transferred to injuries that are due to any kind of chemical agent [or injuries due to exposure to radiation] in view of the fact that injuries of traumatic origin, and injuries of chemical origin [or those due to exposure to radiation] are fundamentally different". In this regard, and as set forth in footnote [1] above, it seems that the Examiner was interpreting injuries that are "traumatic in origin" to be injuries that arise from collisions between objects and the body of the subject, *e.g.* injuries sustained in traffic accidents, gunfire, earthquakes, *etc.*

7.14 Now in response to this objection that the results that are reported in the application as filed could not be extrapolated across the full scope of the pending Claim 1, but merely to injuries that are "of traumatic origin", the Patentee amended Claim 1 in order to replace the previous reference to "… an injury that is due to *physical or chemical* causes *arising from accidents, natural disasters or hostile acts*" with a reference to an injury that is "of traumatic origin" (see the Patentee's letter of response dated 11 November 2010). Moreover, when the Examiner subsequently pointed out in the telephone consultation held on 30 June 2011 that "an injury of traumatic origin" was not restricted to injuries that are caused by physical agents but also encompassed injuries that are due to chemical causes (see *e.g.* the report of the telephone consultation dated 6 July 2011), the Patentee further amended its claims so as to refer to an injury that is not only traumatic in origin but also "due to physical causes".

7.15 This last minute manoeuvring by the Patentee in an attempt to rely on the experimental data within the application as filed has, however, failed to achieve its desired objective, not least because the type of trauma that is referred to in Example 4 of the opposed patent *has not been specified*. To explain this in further detail, the Examiner's preliminary concern was that there were insufficient data in the application as filed to justify a conclusion that the claimed method of measuring the level of NGAL provides a solution to the problem of assessing the severity of an injury that is either: (a) "due to chemical causes arising from accidents, natural disasters or hostile acts"; or (b) "due to exposure to radiation". He therefore averred that the claims should be amended to refer to injuries which are "of traumatic origin" (see paragraph 4.2 and 5.1 of the Communication pursuant to Article 94(3) EPC dated 6 July 2010). This latter suggestion was made on the basis of: (i) the Examiner's understanding that the data in Example 4 relate to the assessment of injuries which are "of traumatic origin" (see the title of Example 4); and, moreover, (ii) the Examiner's *assumption*, *at that point in time*, that injuries "of traumatic origin" are injuries which are due to *physical causes* other than radiation (rather than his subsequent understanding that injuries "of traumatic origin" include injuries that are due to chemical causes).

7.16 Given this background, it is important to appreciate that there is *no indication* in Example 4 of the opposed patent that the trauma patients that were being assessed in accordance with that example had *physical* trauma, rather than chemical trauma (and, as the Examiner later recognised [see above], "trauma" should be interpreted to include injuries which arise from chemical agents). Therefore, it remains impossible to conclude that the data in Example 4 of the patent, which might have in fact been obtained from patients having *chemical* trauma, is evidence that the claimed method of measuring the level of NGAL provides a solution to the technical problem of how to assess the severity of a traumatic injury of the type set forth in the claims, *i.e.* the severity of an injury which is "due to *physical* causes [and is] "traumatic in origin".[3]

7.17 In light of the above observations, Opponent notes that to the extent that Claim 1 as granted does *not* encompass the assessment of injuries (including injuries to the kidney) which arise from the physical trauma of surgical intervention, then the Patentee cannot even rely on the data in document D1 to show that the method that is defined by that claim, which comprises the measurement of NGAL in a bodily fluid, provides a solution to the technical problem of how to assess the severity of an injury which is "due to physical causes [and is] traumatic in origin". As a result, and pursuant to the problem-and-solution approach, the Patentee cannot assert that the subject matter of its claims involves an inventive step, and the requirements of Article 56 EPC are therefore contravened.

7.18 ***No evidence of a solution across the scope of the claims – different physical causes***

7.19 With further regard to the lack of any evidence from Example 4 of the patent that the alleged technical problem has been solved, the OD will also note that even if this example *were* held to relate to injuries which are due to a *physical* trauma, there would still be no information in the example as to which tissues, organs or even body parts were damaged, or indeed of the nature of the physical agent that caused the injuries (*e.g.* whether it was an impact injury, a crush injury, or a blast injury, or whether it involved puncture wounds, blunt force trauma, or hyperbaric pressure waves such as would be found in an explosion). Having said this, Claim 1 as granted purports to solve the technical problem of how to assess the severity of *any* of these different types of injury, to *any* part of the body.

7.20 Now it is of course impossible to make *any* extrapolation from the data in Example 4, across these different types of injuries and across different tissues, not least because Example 4 of the opposed patent provides no information, in respect of the tested patients, as to the types of injuries that were sustained or the organs or tissues which were damaged. Accordingly, it is unreasonable, and in fact unfeasible, simply to assume that the alleged technical problem has been solved across the scope of the granted Claim 1. The provisions of Article 56 EPC are therefore contravened (following Appeal Decision **T 939/92**).

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[3] As an aside, to the extent that the OD is *not* inclined to follow the position presented herein that the claims as granted no longer encompass injuries which are due to exposure to radiation (as a result of the amendments that have been made to the description and the subsequent "shift in the interpretation" of the phrase "physical causes"), *i.e.* the OD believes that an injury which is due to exposure to radiation is *still* encompassed by the reference in the granted claims to "*an injury that is due to physical causes [which] is traumatic in origin*", Opponent refers to the statement that was made by the Examiner in prosecution, that the data in Example 4 of the opposed patent [to the extent that these can even be ascribed to patients having physical trauma] do not "provide convincing evidence that these findings can be transferred to injuries that are due to exposure to radiation". In other words, if the OD does not believe the position presented herein regarding the change in the interpretation of the phrase "physical causes", then, according to the Examiner's own statements, the granted claims will be in contravention of the provisions of Article 56 EPC for failing to provide a solution to the technical problem across their full scope, *i.e.* for failing to provide a solution to the problem of assessing the severity of an injury due to irradiation.

7.21 ***No evidence of a solution across the scope of the claims – different bodily fluids***

7.22 As a further deficiency under the provisions of Article 56 EPC, according to the problem and solution approach, it should also be appreciated that the Patentee has failed to demonstrate that the subject matter of Claim 1 as granted, across the ambit of the many different bodily fluids which might permissibly be tested, provides a solution to the technical problem of how to assess the severity of an injury which is "due to physical causes [and which] is traumatic in origin". In this connection, the granted Claim 1 permits the measurement of NGAL to be made on a sample of *any* bodily fluid from the patient, including a sample of blood, plasma, serum and urine (see Claim 5), bronchoalveolar lavage fluid (Claim 6) and many other types of different bodily fluids that are not even recited in the specification (including bile, saliva, peritoneal fluid, pleural fluid, cerebrospinal fluid, *etc.*). However, the data that are presented in Example 4 of the opposed patent have only been obtained using *plasma* samples. Now because it is entirely unreasonable for the skilled person to expect that the results that were allegedly observed for plasma samples would likewise be observed with a markedly different bodily fluid such as *e.g.* cerebrospinal fluid or saliva, it cannot simply be assumed that the technical problem of assessing the severity of an injury, by measuring the level of NGAL in a bodily fluid, will be solved across the full scope of the claim. Accordingly, the provisions of Article 56 EPC have not been satisfied and the opposed patent cannot be maintained.

7.23 ***Prima facie obviousness of the dependent claims***

7.24 Dependent Claims 3, 6, 7 and 10 of the patent respectively require that "the sample is from within 1 hour after the injury has occurred" (see Claim 3); "the bodily fluid is bronchoalveolar lavage fluid" (Claim 6); "a functional activity of NGAL is measured" (Claim 7); and "NGAL or its functional activity is measured by an automated method" (Claim 10).

7.25 In light of the disclosure in Example 6 and Figure 16A of document D1, Opponent submits that a measurement of NGAL levels in (urine) samples of patients taken within 1 hour after the injury has occurred (Claim 3) would have been obvious to a person of skill in the art: the rapid ascent of NGAL levels within the urine between 0 and 2 hours, as shown in Figure 16A of document D1, should be noted. In relation to Claim 6, the defined method does not solve the alleged technical problem across the full scope of Claim 1 because there is no evidence that NGAL levels in *any* bodily fluid, such as *e.g.* bronchoalveolar lavage fluid, will change in response to a (any) physical injury, and, furthermore, will correlate with the severity of that injury and be detectable within the recited time frame (see the above discussion). However, if the Patentee avers that a person of skill in the art *would* have anticipated that an increase in the level of NGAL in one body fluid (*e.g.* plasma, urine) would be mirrored by an increase in the level of NGAL in another body fluid (*i.e.* bronchoalveolar lavage fluid), then the subject matter of Claim 6 should be held to be obvious over the teaching within document D1, which relates to the testing of urine samples. As for Claims 7 and 10 as granted, Opponent notes that if the Patentee contends that the measurement of NGAL levels by means of an assay of NGAL function is sufficiently disclosed within the opposed patent in spite of its complete lack of any disclosure of a specific NGAL function, then it must have been sufficiently well known as to have been obvious to the skilled person as an alternative to the use of a Western Blot or ELISA assay as described in document D1 (see Claim 7). As for the automation of NGAL measurements as recited in Claim 10, this is clearly an obvious measure to expedite sample processing and reduce human error. In conclusion, therefore, the further technical features that are set forth in the dependent Claims 3, 6, 7 and 10 are considered to be obvious over the disclosure in document D1 and the provisions of Article 56 EPC are clearly contravened.

8. CONCLUSION

8.1 In light of the above analysis, the claims of the opposed patent are clearly invalid. Moreover, the opposed patent contains nothing which could form the basis of an allowable claim.

8.2 The request that the opposed patent should be revoked, in its entirety, and for all designated states, is therefore fully justified.

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