Assistance to the Commission on Technological Socio-Economic and Cost-Benefit Assessment Related to Exemptions from the Substance Restrictions in Electrical and Electronic Equipment (RoHS Directive)

Final Report

Report for the European Commission DG Environment under Framework Contract No ENV.C.2/FRA/2011/0020

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14.0 Exemption Request No. 11: "Lead as an Activator in the Fluorescent Powder of Discharge Lamps when used as Photopheresis Lamps Containing Phosphors such as BSP (BaSi2O5:Pb)"

Abbreviations

BSP	Barium Silicate Phosphor
ECP	ExtraCorporeal Photopheresis
UVA	Ultraviolet A (light)

According to the applicant, Therakos Photopheresis [394], Certain medical conditions (see below) are characterized by states of immunologically induced inflammation. Patients with these conditions are, for the most part, extremely acutely ill. Extracorporeal photopheresis (ECP) is frequently the last therapeutic option offered to patients. ECP is used to treat several medical conditions including:

- Cutaneous T-cell Lymphoma (CTCL), which is a type of Non-Hodgkin's lymphoma cancer that manifests itself primarily in the skin;
- Graft versus Host disease which is a serious complication of bone marrow transplants;
- Cardiac transplant rejection; and
- Lung transplant rejection.

The applicant further elaborates that the treatment involves exposure of leukocytes, temporarily removed from the patient's blood, to light from lamps with lead doped barium silicate phosphor (BSP). The light activates a drug which has been introduced into the leukocyte fraction of the blood. This type of phosphor emits a unique spectrum that is optimal for this medical treatment. All other UVA phosphors contain less light of the effective wavelengths, or have shorter wavelengths that cause further damage to cells. There is currently no substitute lamp type that may be used for treatment of this disease with extracorporeal photopheresis.

[394] Therakos Photopheresis (2012a) Original request for exemption no 11, submitted 20 April 2012, http://rohs.exemptions.oeko.info/fileadmin/user_upload/RoHS_VI/Request_11/Therakos_ROHS_Exemption_Request_20_Apr_2012.pdf

Therakos Photopheresis has therefore applied for an exemption for

"*Lead as an activator in the fluorescent powder of discharge lamps when used as photepheresis lamps containing phosphors such as BSP (BaSi2O5:Pb)*"

14.1 Description of Requested Exemption

The applicant[395] explains that an ECP treatment is comprised of the *ex vivo* exposure of autologous leukocytes (a type of white blood cell transferred from the patient's own body) to a liquid formulation of 8-methoxypsoralen and ultraviolet A (UVA) light, followed by the subsequent reinfusion of the white blood cells to the patient. During an ECP treatment, blood is drawn from the patient into the Therakos Photopheresis system instrument and is centrifuged in order to separate it into its components. The red blood cells and plasma components are returned back to the patient. The white blood cells are collected, concentrated and prepared for treatment with 8-methoxypsoralen and UVA light. The treated white blood cells are then returned back to the patient. The 8-methoxypsoralen is inert until exposed to UVA light and its activation is dependent on exposure to UVA light frequencies. The activation of the 8-methoxypsoralen is critical to the entire process. This drug (brand name UVADEX™ 20 mcg/mL Solution) is exposed to a computer controlled, specific dose of intense ultraviolet light from a BSP lamp of 1–2 joules per cell. The UV light causes a photochemical reaction to occur between the drug and DNA of the white blood cells which forms cross links between the drug molecules and the DNA. The exposure to psoralen, and subsequent photo-activation of the white blood cells, induces apoptosis (normal programmed cell death) of the treated white cells. Administration of cells which have been induced to undergo apoptosis has the effect of creating a state of immunologic tolerance. The overall effect of this therapy can be thought of in terms of having an anti-inflammatory effect.

The exact mechanism by which this treatment works is not understood, but it is clear that the induced process alleviates the patients' devastating symptoms. These symptoms include extensive itching, fissuring, scaling and oedema. The skin of many patients resembles burn victims. In these cases, and without photopheresis treatment, 50% of these patients die from infection. ECP is administered only in medical centres which have undergone specific training for the administration of this unique therapy. The above conditions are also considered as "orphan conditions"[396] since the numbers of patients who have these conditions is very small. The cumulative number of patients (< 20,000), with the above 4 conditions, who would be candidates for this therapy, meets the criteria for orphan status (less than 200,000 cases in EU annually).

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[395] Ibid.

[396] "Orphan" diseases are defined in the EU as ones which affect less than 5 per 10,000 of the population (<1 in 200,000 in the USA) http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf

14.2 Applicant's Justification for Exemption

Therakos Photopheresis[397] states that research has shown that the wavelength of the UV light used is critical to photo activate the drug and that the BSP lamps are ideally suited, having a relatively narrow UVA emission spectrum. The wavelength peaks at 350nm. The spectral range and most appropriate light dose (1-2 joules per cell) of this lamp are specified in the US FDA PMA and NDA approval and the EU Medical Device Directive (CE Mark) approvals for this equipment. Although the 350nm peak is important, the entire curve of the UVA spectrum generated by the custom BSP lamp has been proven to be safe and effective in delivering the 1-2 joules of energy to each collected cell. The aim is for complete binding of DNA so that cancerous cells cannot reproduce. If cancerous cells die, then the body will clear them out. If this step is not carried out correctly, incomplete damage to the DNA may occur which can cause further mutations to the leukocytes and consequently more cancer. The shape of the emission spectrum is required to elicit the desired response and to avoid negative consequences as discussed below:

- The energy attributed to light of longer wavelengths is too low[398], thus it will not promote the photochemical reaction
- The energy attributed to light of shorter wavelengths is higher and may thus result in damage to DNA, possibly promoting undesirable side-reactions between the drug and DNA, such as incomplete cross linking of the DNA and sister chromatid exchanges of the DNA
- Broader spectra have less energy at the critical 350nm wavelength so that longer treatment times are needed for the same effect which increases the risk of infection. The risk of infection is proportional to the time that the patient is connected to the treatment system.

Any changes to the UV light wavelength will alter the proportions of desired light spectrum to adequately photo-activate the drug combined with the DNA of the collected cells and disturb the desirable balance that is created to benefit the patient. In addition, shorter wavelengths could cause patient safety issues, undesirable damage to DNA, side-effects and certain lack of efficacy.

To treat a patient, the UV exposure unit contains 18 special BSP lamps that are designed solely for this treatment. In this treatment the current passed to the BSP lamps is much greater than is normally used for other applications for BSP lamps. This is to produce as much UV light as possible from the lamp, to achieve the shortest possible treatment time. This type of use greatly shortens the lamp's life to 150 hours. As the lamps decay the photoactivation time set by the computer increases. Once the lamps have been used for 150 hours the computer controlled photopheresis instrument instructs the operator to change the lamps.

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[397] Op. cit. Therakos Photopheresis (2012a)

[398] UV radiation energy is inversely proportion to its wavelength so that long wavelengths (e.g. visible light) have less energy than short wavelengths (e.g. UV): $E = hv = hc/\lambda$
Where E = energy, h = planks constant, v = frequency, c = speed of light and λ = wavelength.

Each lamp contains ~1 gram of phosphor material and this material contains ~0.7% lead as the dopant. Therefore each lamp will contain 7µg of lead. The estimated number of BSP lamps placed on the EU market in 2012 for photopheresis treatment is 4600.Therefore it is estimated that EU consumption of lead for this application is ~ 32g. Market usage is expected to grow to an equivalent of 74 grams of lead by 2020.

14.2.1 UV Lamps

The applicant explains[399] that ultraviolet light is generated by the interaction between the emission spectrum from excited mercury vapour with specially designed phosphors which adsorb the mercury emission wavelengths and emit their own characteristic spectrum. UV lamps therefore consist of a glass tube with electrodes at each end, containing a partial vacuum with a small amount of mercury. When a voltage is passed between the two electrodes, a plasma is created in the low pressure gas inside the tube which vaporises the mercury, subsequently emitting a light of high energy and relatively short wavelengths, with most falling between 200 – 360nm. The short wavelengths are very harmful so these must be completely converted into longer wavelength light, which is achieved by the coating of phosphor material on the inside of the glass tube. The chemical composition of the phosphor controls the emission spectrum.

Phosphors are available for a very wide variety of spectral emissions. Phosphors used in fluorescent lamps, used for ambient lighting, convert all of the mercury emission into visible light with no dangerous UV. Several phosphors have been developed that emit UV light with wavelengths that are longer than the mercury emission. One composition, barium silicate doped with lead, gives the optimum narrow spectrum with a maximum emission at 350nm. This is the BSP lamp.

14.2.2 Risk of Substance Emissions from the Application

Concerning possible emissions of lead from the application, the applicant[400] elaborates that the phosphor is located inside the sealed lamps and so no exposure to patients or hospital staff occurs during proper use.

Additionally, the lamps are housed within the ECP device so breakage during proper usage is not likely. If a lamp should break during maintenance, the BSP phosphor is bonded to the inside of the lamp glass, so very little dust (if any) should be emitted in such a case due to the phosphor. In general the amount of lead in this glass will

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[399] Op. cit. Therakos Photopheresis (2012a)

[400] Therakos Photopheresis (2012b) Answers to clarification questions for exemption no 11, submitted 21 June 2012, http://rohs.exemptions.oeko.info/fileadmin/user_upload/RoHS_VI/Request_11/Request_11_1st_Clarification_Questions_final_Therakos_response__21_June.pdf

greatly exceed the lead in the phosphor. RoHS exemption 5(b) allows up to 0.2% lead in the glass of fluorescent tubes so the presence of an additional 7µg lead per BSP lamp will have a negligible impact. 1 BSP lamp weighs 64 grams (90% glass) so 0.2% of this is 115 mg (115,000 µg) of lead, far more than in the lamp phosphor.

The 18 lamps are removed and replaced by new lamps. These lamps are relatively short tubes (14 inches in length) and so are not easily broken, so damage to more than one or two is unlikely to occur.

The applicant mentions having performed extensive simulated transportation testing of the packaged lamps based on ASTM method D4169 as required by the medical device licenses. There were no failures. This demonstrates that the likelihood of exposure to lead during unpacking for routine lamp changes is extremely slight.

The applicant further elaborates on the risk of emission and health effects in cases where a lamp is broken. To summarize, in these cases, the emitted amount of lead would not be substantial enough to result in significant health effects.

As for the recycling and reuse at end of use, relatively small numbers of BSP lamps will normally be recycled with large numbers of other fluorescent lamps. The glass used to make fluorescent lamps will contain a small amount of lead as an impurity, partly from recycled lamp glass. As detailed above, the additional amount of lead attributed to the phosphor is negligible, in comparison with the lead present within the lamp glass itself.

14.2.3 Possible Substitute Alternatives

According to Therakos Photopheresis[401] the light emission spectrum is governed by the crystal structure dimensions of the phosphor. Each crystalline chemical compound has different crystal lattice dimensions and so, is capable of emitting different ranges of light output wavelength. To emit light, the crystal lattice needs to be distorted by a dopant atom and the size and valence of the dopant affect the amount of distortion and as a result the output wavelengths. Several compounds are used for UV phosphors apart from barium silicate including several borates, phosphates and silicates, although these emit UV light only with the correct dopant atoms.

BSP lamp phosphors use lead as the dopant in barium silicate. Both lead and barium are divalent so lead can easily bond inside the barium silicate lattice but as lead is larger than barium, the lattice is distorted. There are no other large divalent ions that can be used in the barium silicate lattice. In the periodic table, the other large atoms are stable only in different valence states and so will not be able to bond in the same way to the barium silicate. The largest divalent ion apart from lead is Europium but this is significantly smaller and so gives a completely different spectrum. If even smaller ions such as manganese are used as the dopant, only visible light emission occurs.

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[401] Op. cit. Therakos Photopheresis (2012a)

Therakos Photopheresis[402] put forward that there are about 17 phosphors that emit in the ultraviolet spectrum and provide a comparison of these phosphors that may be seen in Table 14-1 below.

Table 14-1: UV Lamp Phosphors

Reference	Chemical composition	Peak wavelength (nm)	Band width (nm)
2011	BaSi2O5:Pb	**350**	41
2030	YMgB5O10:Gd,Ce,Pr	312	2
2040	YPO4:Ce	335 & 357	35
2052	SrB4O7:Eu	371	18
2080	LaPO4:Ce	318 & 335	41
2090	(Sr,Mg)Al11O19:Ce	338	53
2091	(Ba,Mg)Al11O19:Ce	**347**	53
2093	(Ba,Mg)Al11O19:Ce	**347**	54
2094	CaAl11O19:Ce	333	39
2095	(Y,Mg)Al11O19:Ce	344	51
2096	(Sr,Mg)Al11O19:Ce	309	38
	(Ca,Na)P2O7:Ce	330	40
	(Mg,Sr)P2O7:Eu	395	40
	CaSO4:Eu	388	16
U738	(La,Gd)B3O6:Bi	312	2
NP-804	Ca3(PO4)2:Ti	326	57
NP-803	(Ca,Zn)3(PO4)2:Ti	306	39

Source: Op. cit. Therakos Photopheresis (2012a)

The applicant explains that the currently used BSP phosphor is 2011 which has a symmetrical spectrum with a peak wavelength of 350nm and a bandwidth of 41 nm. This has a symmetrical spectrum which is the basis for the entire safety and effectiveness profile of this lamp. The entire procedure is based on this requirement given the unique photo-activation properties of Methoxsalen. There is very little radiation emitted below 310nm and also very little above 390 nm. Of the phosphors in the above table, only types 2091 and 2093 have similar peak wavelengths but they have broader spectra and 2093 also has a secondary peak at ~380nm. So with both 2091 and 2093, there is less energy available at the important 350nm wavelength. 2095 will also be less suitable as its peak wavelength is at a higher energy of 344nm and

[402] Ibid.

has a broader spectrum than 2011. In the original request for exemption, further details are given to complete the comparison, including, comparison of the emission spectra for similar phosphors.

14.2.4 Possible Design Alternatives

Therakos Photopheresis[403] states that suitable alternative fluorescent lamps that have a lead-free phosphor emitting ultraviolet light with a spectrum that is identical to the spectrum from the BSP lamp are not available. There would be a risk to human health from using alternative UV lamps that emit shorter, more energetic wavelengths as these could cause harmful side-effects, whereas UVA lamps that emit longer wavelengths will have no medical effect. Additionally, alternative lamps lack authorisation and thus could not be used as an immediate substitute as these are not approved by the medical devices Directive and approval will require many years of clinical trials as described in Section 14.2.6 below.

Therakos Photopheresis[404] also contends that alternatives to the ECP treatment are, at present, unavailable. The same holds true concerning alternatives to the drug in use with this treatment, which could, in theory, be substituted with a photo-activated drug, sensitive to a different spectrum.

14.2.5 Environmental Arguments

Even though no technically viable substitute has been identified at present, Therakos Photopheresis[405] has submitted further information concerning life cycle assessment aspects, to further enhance their argumentation. Information includes reference to extraction and production of materials, resources required in lamp production, and information concerning the re-use and recycling of waste.

Concerning the use phase, the applicant emphasises that if the substitute lamps emit less UV light in the useful wavelength range, treatment times would need to be longer, and so energy consumption would increase in proportion to the treatment time. This is also likely to increase the risk of infection for patients.

14.2.6 Road Map for Substitution

According to the applicant[406] there are several medical treatments for cutaneous T-cell lymphoma (and the other disease states mentioned above) but the procedure

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[403] Ibid.

[404] Op. cit. Therakos Photopheresis (2012b)

[405] Op. cit. Therakos Photopheresis (2012a)

[406] Ibid.

using BSP lamps is the only option, once other approaches have been exhausted. As explained above, the only option for a substitute would be an alternative UV lamp phosphor that does not contain lead. Use of one of the currently available UV emitting phosphors such as one from Table 14-1 could be evaluated for the medical treatment but as the spectra of all of the lamps are different, they cannot replace BSP without first carrying out extensive clinical trials and gaining approval under the medical devices and drug Directives. For these trials, only the lamps with similar wavelengths to BSP could be used as lamps with much shorter wavelengths are likely to be harmful. It is noteworthy that this procedure requires both a device and drug approval to be able to market it. As all lamps are different, therefore posing a risk to patients who are already ill, trials will need to be carried out in several stages:

- Before clinical trials could begin there would need to be extensive in-vitro (adduct formation, cell viability and PHA mitogen stimulation studies) and animal non-clinical toxicology work to demonstrate the new lamp photo-activates the cells according to company specifications;
- The instrument would require new software to control the photo-activation time if a lamp with the correct spectral output could be found;
- The instrument would need to be reengineered and electrically safety tested;
- The redesigned instrument would then need to pass EMC emissions and susceptibility requirements to comply with EU legislation and to ensure that it does not interfere with other medical equipment;
- Given the orphan rare nature of the disease, finding suitable patients with this rare disease for trials will take much longer than would be needed for common illness. The first trial would be with a small group of patients over at least 4 years (time needed for finding suitable patients, treatment and follow up) to ensure that the alternative lamps are effective and do not cause undesirable side-effects;
- If these trials show that the alternative lamp is equally effective, that there are no serious side-effects and that treatment times do not need to be extended, then a larger trial will be carried out. This would be to confirm that the small-scale results are correct and to look for less common undesirable side-effects. This trial would establish whether any alternative lamps afford the patient with the same medical benefits attributed to the BSP lamps. Inferior treatments would not be acceptable. These trials would last at least 5 years given the specific patient population that would be required to be enrolled; and
- Assuming an alternative lamp is found to give the same benefits to patients with no increase rate of harmful side-effects, then approval under the medical device and drug Directives can be sought. This procedure will take a minimum of 1 year and the treatment cannot be used until approval is granted from both the device and drug regulatory authorities in the EU and other global markets.

Development of new phosphors – The development of lamp phosphors is very mature and it is very unlikely that a new phosphor with an emission spectrum identical to BSP will be found. The chances of success are extremely low as so many combinations of materials have already been prepared and evaluated. Research could be carried out

but it is likely to be at least three years, the length of a PhD research project, before any alternatives are available for clinical trials.

Possible timetable

Basic science and non-clinical studies	2 years
Preliminary clinical trial	4 years
Evaluation of results	6 months
Larger clinical trial	5 years
Evaluation of results	6 months
Medical Device Directive approval	1 year
Drug approval /can be concurrent with device approval	(1 year)
Total without development of a new type of phosphor	**13 years**

Once approval is granted, patients are monitored for a further 5 years (post treatment follow up) to ensure that the change to the treatment is safe and effective. If any evidence is found that it is not safe, the approval can be withdrawn.

14.3 Critical Review

14.3.1 REACH Compliance – Relation to the REACH Regulation

Chapter 5.0 of this report lists entry 30 restricting the use of lead and its compounds in Annex XVII and the related authorization and restriction processes in the REACH Regulation.

In the consultants' understanding, entry 30 of Annex XVII does not apply to the use of lead in extracorporeal photopheresis lamps since lead is not made available to the public as a substance, as a constituent of another substance or in a mixture, but rather within an application. In other words, the use of Lead in question is not subject to any restrictions by REACH.

The consultants conclude that the use of lead in extracorporeal photopheresis lamps does not weaken the environmental and health protection afforded by the REACH Regulation.

An exemption could therefore be granted if other criteria of Art. 5(1)(a) apply.

14.3.2 Scientific and Technical Practicability of Lead Substitution

The applicant[407] provides sufficient evidence to demonstrate that at present, neither substitution of lead in the phosphor used for ECP treatment lamps, nor the elimination of the use of these lamps or the ECP application, is possible. The applicant further enhances its case by providing evidence concerning the possible health risks associated to using the available phosphors that possess a similar output spectrum. This is also enhanced through the likelihood of the additional energy consumption that would result from the longer wavelengths comprising alternative phosphor spectrums. The technical information provided, as well as the timeframe outlined in the provided substitution roadmap, plausibly justify that the current use of lead in this application cannot be eliminated, and nor does a feasible substitute appear to be available.

14.3.3 Environmental Arguments

Therakos Photopheresis[408] present environmental data and statements concerning the life cycle aspects of lead. As none of the substitutes can actually be used at present, these arguments were not reviewed.

The consultants would like to point out, however, that this neither indicates agreement nor disagreement with the applicant's environmental arguments

14.3.4 Conclusion

The applicant's scientific and technical arguments are plausible. Based on the information submitted, it appears that a scientifically and technically practicable possibility for substitution or elimination of lead in this application is currently not available.

In this regard, and in the absence of substitution and elimination possibilities, as well as knowledge concerning the development of such possibilities, there seems to be no clear reason to recommend an expiry date prior to the seven years maximum validity of exemptions adopted to Annex IV.

An exemption for a similar application exists and is still valid. Exemption 18(b)[409] regards "Lead as activator in the fluorescent powder (1% lead by weight or less) of discharge lamps when used as sun tanning lamps containing phosphors such as BSP ($BaSi_2O_5$:Pb)".

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[407] Ibid.

[408] Ibid.

[409] RoHS Directive (2011) Directive 2011/65/EU of the European Parliament and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and electronic equipment (recast), http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32011L0065:EN:NOT

As no information was provided during the stakeholder consultation, it is assumed that the validity of the current exemption granted for lead in BSP lamps used for sun tanning applications is sufficient for this application, and that BSP lamps are not in use for any other application in which lead substitutes are not sufficiently available.

It appears, therefore, that the requested exemption is required only for a specific application falling under category 8 (medical devices) and as a result, it seems the exemption should be granted only for this application.

14.4 Recommendation

After consulting the applicant, the wording has been altered to address the specific application and it is recommend that an exemption is granted for:

> *"Lead as an activator in the fluorescent powder of discharge lamps when used for extracorporeal photopheresis lamps containing BSP (BaSi2O5:Pb) phosphors"*

The exemption is to be added to Annex IV, as it shall be applicable only for category 8 applications.

As for the validity period, under the foreseeable circumstances concerning possible substitutes, there appears to be no reason not to grant the exemption for the maximum period of 7 years. The consultants therefore recommend setting the expiration date at 22 July 2021.

14.5 References Exemption Request 11

Therakos Photopheresis (2012a) Original request for exemption no 11, submitted 20 April 2012, http://rohs.exemptions.oeko.info/fileadmin/user_upload/RoHS_VI/Request_11/Therakos_ROHS_Exemption_Request_20_Apr_2012.pdf

Therakos Photopheresis (2012b) Answers to clarification questions for exemption no 11, submitted 21 June 2012, http://rohs.exemptions.oeko.info/fileadmin/user_upload/RoHS_VI/Request_11/Request_11_1st_Clarification_Questions_final_Therakos_response__21_June.pdf

RoHS Directive (2011) Directive 2011/65/EU of the European Parliament and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and electronic equipment (recast), http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32011L0065:EN:NOT