Questionnaire for Further Clarification

Exemption Request 11 "Lead as an activator in the fluorescent powder of discharge lamps when used as photophoresis lamps containing phosphors such as BSP (BaSi2O5:Pb)"

Background

The Öko-Institut together with Fraunhofer IZM has been appointed within a framework contract for the evaluation of applications for granting, renewing or revoking an exemption to be included in or deleted from Annexes III and IV of the new RoHS Directive 2011/65/EU (RoHS 2) by the European Commission.

You have submitted the above mentioned request for exemption which has been subject to a first completeness and understandability check. As a result we have identified that there is some information missing and a few questions to clarify before we can proceed with the online stakeholder consultation on your request. Therefore we kindly ask you to reformulate your request taking the following points into consideration.

Questions

1. Please clarify the scope of the exemption request.
   a) Please clarify, why the mentioned exemption request is more general than the subsequent description taken. Are photophoresis lamps containing BSP phosphors currently in use for any other applications besides extracorporeal photophoresis (hereinafter ECP) treatment?

      While it is very likely that a non-extracorporeal type of photopheresis called "PUVA therapy[1]" relies on BSP phosphors, our concern is focused solely on extracorporeal photopheresis. We had omitted the term "extracorporeal" from the exemption title only because it isn't one commonly used. Its addition to the exemption title would be acceptable to us.
      It should be noted that we inadvertently misspelled "photopheresis" in some sections of our original application. The correct spelling is "photopheresis" not "photophoresis".
      With both these changes, the edited exemption title would now read:

[1] PUVA is a type of ultraviolet radiation treatment (phototherapy) used for severe skin diseases. It is a combination treatment which consists of Psoralens (P) and then exposing the skin to UVA (long wave ultraviolet radiation). It has been available in its present form since 1976.

"Lead as an activator in the fluorescent powder of discharge lamps when used as extracorporeal photopheresis lamps containing phosphors such as BSP ($BaSi_2O_5$:Pb)"

b) Are these lamps in use for applications that are beyond the scope of the 8th category of the RoHS Directive?

No, the Therakos photopheresis lamps are not used beyond the scope of RoHS Category 8 medical devices. They are used solely as medical devices. The lamps are of course used for sun tanning applications as well (Exemption #18b).

2. In your proposal you state that research has shown that the wavelength of the UV light is critical to photo activate the drug and that longer and shorter wavelengths result in less favorable affects. For this reason you conclude that a replacement is not achievable, further explaining that the referenced phosphorus 2091, 2093 and 2095 would not be suitable substitutes. Please provide test results/protocols to verify the stated affects attributed to exposure of the drug (8-methoxypsoralen) treated cells to shorter and longer wavelengths such as those common to the above referenced phosphorus's.

As early as 1984, studies have been conducted to evaluate the effectiveness of various UVA lamps for phototherapy. One such study was documented by Cole, Forbes, and Davies in the Journal of the American Academy of Dermatology (11 (4 Pt 1):599-606, 1984 Oct): "Different biologic effectiveness of blacklight fluorescent lamps available for therapy with psoralens plus UVA". That paper is included with this response. It shows that that the efficacy of the treatment may be dramatically impacted depending on spectral characteristics of the lamps used.

The study summarized in this paper looked at the commercially available blacklight fluorescent lamps used in phototherapy booths conducting PUVA therapy at that time. The concern was that the proliferation of PUVA light booths and hence lamp suppliers was resulting in lamps with significantly different spectral distributions. The study included both spectral irradiance measurement along with in vivo studies using mice. Effectiveness in the treatment of psoriasis was determined by finding the lowest UVA dose required to cause a phototoxic response in each animal.

The study demonstrated that the available lamps differed in spectral distribution and most importantly in biologic effectiveness without being easily distinguished. The authors called on the need for lamp manufacturers to employ a distinguishing code to denote the spectral output of the blacklight lamps.

In 1984 during the early development of our ECP technology, and based on the results of the study quoted above, we performed *in vitro* cell studies with no light, white light, UVB light, and UVA light. The only spectral output that caused the specified cell death and phytohaemagglutinin (PHA) response[2] was UVA light. Furthermore, using the extensive available published literature and knowledge base that existed on PUVA therapy (see below), all research and development focused on lamps with spectral output centered at 350 nm with a narrow bell shaped curve that includes 320-400 nm as the optimal distribution to photoactivate psoralen.

One of the primary experts in the field of photobiology and the use of psoralens for treatment of psoriasis and other conditions is photobiochemist Francis P. Gasparro, Ph.D. In research documented as early as 1989[3], Gasparro showed that irradiation with wavelengths in the 320-370 nm range leads to efficient formation of the essential crosslinks of the psoralen drug with DNA in the diseased blood cells. (That paper is included with this response.)

[2] PHAs are plant-derived compounds that induce changes in lymphocytes normally associated with antigen challenge. These changes are used to test for competence of cell-mediated immunity and to demonstrate the efficacy of treatments.

[3] Gasparro, Dall'Amico, Goldminz, Simmons, and Weingold. "Molecular Aspects of Extracorporeal Photochemotherapy". The Yale Journal of Biology and Medicine 62 (1989), 579-593.

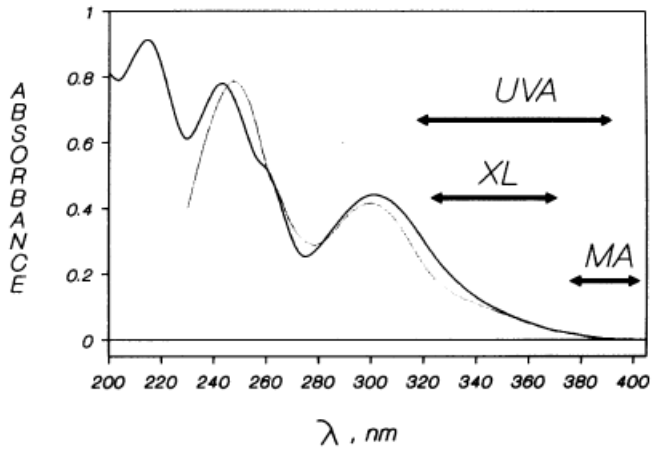

FIG. 2. UV spectrum of 8-MOP. *Solid line:* 10 μg/ml 8-MOP in ethanol recorded by the author, using a Pharmacia-LKB spectrophotometer interfaced with an IBM PC; *dashed line:* 8 μg/ml in ethanol recorded by Aaron Lerner in 1958, using a Beckmann DU spectrophotometer. **UVA** indicates the spectral output of the UVA lamps used to activate psoralens. **MA** indicates the wavelength region in which monoadducts are the sole photoproduct, and **XL** indicates wavelengths capable of inducing cross-link formation.

The above curve from the Gasparro reference shows that the drug 8-MOP does not absorb UV light at wavelengths greater than ~390nm and so longer wavelengths will not be effective. This paper shows the complexity of the photochemical reactions. It states that irradiation with wavelengths in the range 320-370 nm (but not significantly longer), leads to the efficient formation of cross-links (XL in the above figure) which is desirable for photopheresis. Wavelengths in this range are a major component of BPA lamps and strongly overlap with the absorption spectrum of 8-MOP (as shown in the above figure). Gasparro also showed that wavelengths less than 320 nm cause photoreversal of previously formed adducts and degradation of molecules, which is undesirable and so lamps with UV wavelengths less than 320nm are unsuitable.

We have not conducted studies on the safety and efficacy of other phoshors in ECP treatment as we have not identified any replacement phoshors with the same spectral output as the BSP lamp we currently use. Given the conclusions from the studies summarized above, coupled with the photochemistry principles summarized in our application, we know that the use of a phosphor without an almost identical emission spectrum will result in a less safe and less effective ECP treatment. As such, medical device directive licenses are unlikely to be granted for such a system.

3. In 2011 an exemption for lamps containing SMS phosphorus ($(Sr,Ba)_2MgSi_2O_7$:Pb), expired. This phosphorus is said to generate a broad emission peak centered at 360 nm. Could SMS phosphorus serve as a feasible substitute for BSP and if so would such lamps than have a lower content of lead, subsequently reducing the total amount of lead required for the practice of ECP treatment in the EU?

   No, the SMS phosphor could not serve as a feasible substitute for the current BSP phosphor. The emission spectrum for the BSP phosphor that we are currently using peaks at 350 nm and is fairly narrow (peak width of 40 nm). The SMS phosphor activated with lead ($(Sr,Ba)_2MgSi_2O_7$:Pb) peaks at 365 nm and is much broader (peak width of 68 nm). [4]

   A spectral distribution curve for SMS[5] shows a very broad curve extending well beyond 400 nm. (It should be noted that this reference indicates “SMS” as a (Sr,Zn) phosphor, not a (Sr,Ba) phosphor as listed in the question above. We have found references to several “SMS” phosphors, including the Wikipedia reference, but believe the spectral curve shapes should be similar.)

   The longer maximum wavelength and broader spectrum dictate that the phosphor is NOT optimized for photoactivation of the psoralen drug, as described in the answer to question #2 above.

   Additionally, it should be noted that the spectral range for the lamp is specified in the approval of the ECP device and the drug as well. Specifically, the label insert for oral 8-MOP (methoxsalen) used in PUVA therapy (the same active ingredient used in the drug UVADEX used with ECP), clearly dictates the spectral output distribution for the lamp as shown below:

[4] http://en.wikipedia.org/wiki/Phosphor. The reference to SMS here is $Sr_2MgSi_2O_7$:Pb. Not $(Sr,Ba)_2MgSi_2O_7$:Pb.

[5] T. Justel, H. Nikol, and C. Ronhda. „New Developments in the Field of Luminescent Materials for Lighting and Displays”. Angew. Chem. Int. Ed.1998,37,3084±3103

D. UVA SPECTRAL OUTPUT DISTRIBUTION

The spectral distributions of the lamps should meet the following specifications:

Wavelength Band (Nanometers)	Output*
<310	<1
310 to 320	1 to 3
320 to 330	4 to 8
330 to 340	11 to 17
340 to 350	18 to 25
350 to 360	19 to 28
360 to 370	15 to 23
370 to 380	8 to 12
380 to 390	3 to 7
390 to 400	1 to 3

This required emission spectrum data is shown pictorially in Figure 1 below.

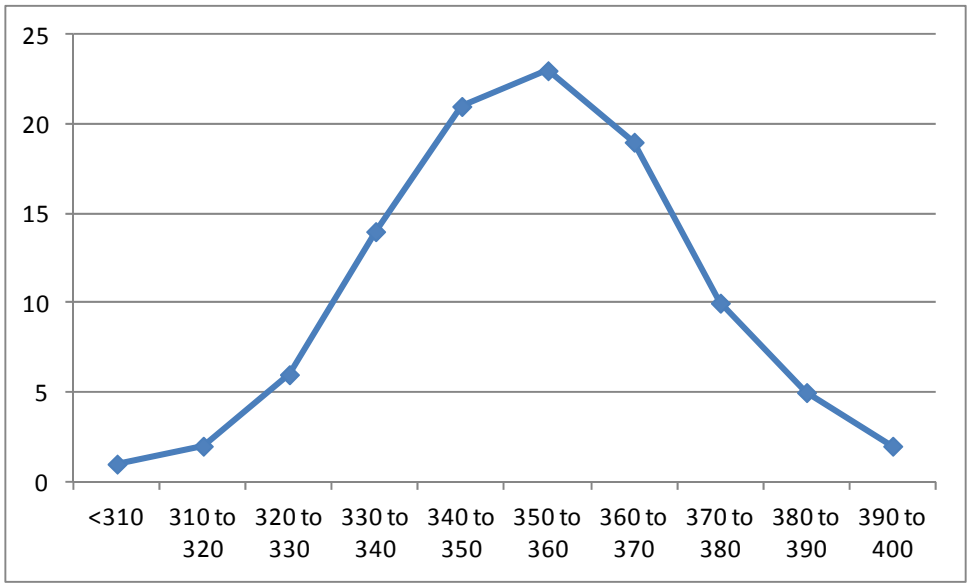

Figure 1. Required Spectral Distribution of Lamps used for Photoactivation of Methoxsalen

Therefore, SMS would not meet these requirements and therefore we could not legally use it. It extends beyond 400 nm and does not meet the relative output requirements within the 320 – 370 nm range in particular.

It should also be noted that another version of the SMS phosphor is doped with Europium, not lead. However this phosphor peaks at 460 and so it totally unsuitable for the ECP application.

4. In your proposal you explain and provide possible timetables for the development of substitutes for BSP Phosphors. However are any such development efforts underway? Could you please elaborate on the efforts which have been made to develop substitutes during the last three years?

   We were not aware of the presence of lead in the ECP system until we determined where RoHS substances are used in our product portfolio and subsequently conducted an investigation into whether any RoHS exemptions for medical devices would be required. This was just prior to the recast of the RoHS Directive in mid 2011. While the presence of mercury in the lamp was known and confirmed to be covered by an existing exemption, it was not until our custom lamp supplier described the phosphor in detail that we realized that an exemption would be required as no lead-free lamp with an identical spectrum is available. It was at this point that a cross functional team was assembled to begin the investigation process and as a result a timetable for replacement was defined. It was agreed that the replacement of the phosphor would require one with a spectral distribution that is almost identical to that of the current phosphor. Such a phosphor has not yet been identified. Until one is located it is not possible to conduct any evaluations as this would need to include clinical trials with very sick patients (life threatening) with Orphan diseases. It is unacceptable to test lamps that may not be safe and/or effective. The available substitute lamps would result only in a less safe and effective treatment or ineffective treatment which would not receive the required approvals/ licenses.

5. In your proposal you state that the use of substitute lamps, emitting less UV light in the useful wavelength range, would require longer treatment times and thus enhance energy consumption. Could you please quantify the increase in electricity consumption caused by the possible substitutes per application?

   We cannot quantify the increased energy consumption associated with substitute lamps with actual data as we are not permitted to evalute less efficient phosphors with sick patients as noted above. However, we know that more energy would be required to activate the psoralen drug if using less efficient phosphors. Based on the Cole paper (referenced in Question 2), where commercially available lamps were compared, we can estimate the impact. In those studies, a longer wavelength lamp (peaking at ~ 370 nm) required treatments about three times as long as those using a shorter wavelength lamp (peaking at ~ 350 nm). The increased time will of course require a proportionate increase in energy.

During a typical 3-4 hour treatment time with BSP lamps, the lamp is activated for one hour on average. The energy consumed is 440 watt-hours. If the lamp were to run 3 times as long, it would consume an additional 880 watt-hours. That would equate to roughly 6 x 150 watt flood lamps running for 1 hour each. Equivalently, the increased energy consumption would be that used by a typical household microwave running for 30 minutes.

In 2011 in the EU there were 36,201 ECP treatments administered. Therefore the increased energy consumed in the EU in one year using a less efficient higher wavelength lamp would have been 32,000 kwatt-hours.This would be the energy required to power eight UK households for one full year.

This is however only a theoretical exercise as the longer treatment times (even if the drug was activated) pose significant health risks to the patient, especially an enhanced risk of infection. Additionally, such increased treatment times are unacceptable as blood bank requirements dictate that the blood not be out of the body for extended periods of time. These requirements vary by region but are generally not greater than 2 hours.

6. What is the risk of emission of lead from the lamps during use and during improper waste treatment? Are there any lead related safety hazard risks to patients or to employees exposed to the ECP units during use or exclusively during maintenance (changing of lamps)?

Use phase: The phosphor is located inside the sealed lamps and so no exposure to patients or hospital staff occurs in use. Additionally, the lamps are housed within the ECP device.

Improper waste treatment: 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. The BSP phosphor is bonded to the inside of the lamp glass so when broken there is very little dust. The amount of lead in this glass will 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 weigh 64 grams (90% glass) so 0.2% of this is 115 mg (115,000 µg) of lead, far more than in the lamp phosphor.

Maintenance: 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.

We have done extensive simulated transportation testing of the packaged lamps based on ASTM method D4169 as required by our 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.

If a lamp is broken after unpacking, most of the phosphor will adhere to the inner surface of the glass. It is quite strongly bonded and so will create very little dust. The phosphor is also not water soluble and lead adsorption through skin contact will not occur to a significant extent. Finally, each lamp contains only 7µg of lead and so even in the extremely unlikely event that all of this from one lamp were to be ingested, this lead would have no long term ill-effects, Research has shown that the lowest NOAEL (no observable adverse effect limit) for children is 5µg/dL, in adults, the NOAEL is higher and WHO estimates[6] that the tolerable weekly intake of lead in children is 25µg/kg (body weight). Therefore the breakage of a few lamps with the consequent adsorption or ingestion of a small proportion of the phosphor will have no effect. In comparison, the RoHS directive permits a minimum of 3.5 mg of mercury in fluorescent lamps, 500 times the amount of lead in one BSP lamps and mercury has a lower tolerable daily intake than lead (Hg = 2µg/kg/day, Pb = 3.6µg/kg/day) but SCHER has concluded that children exposed to the mercury in one broken fluorescent lamp does not pose a risk[7].

7. In your proposal, it can be understood that at present ECP is a last therapeutic option for patients with acute symptoms of immune modulated diseases[8] that have failed treatment with other therapies. It can thus be understood that ECP is also the only treatment that can be given to patients at this stage.

   a) Are there at present any alternative treatment procedures in various development stages and if so, can any preliminary conclusions be drawn concerning the possible substitutes for this treatment and respective timeframes?

   Many pharmaceutical companies including Johnson and Johnson are working on alternative treatments for several of the conditions for which ECP is utilized. Even if one or several of these are successful, ECP will still remain a viable and valuable

[6] http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/lead-plomb/iii-eng.php

[7] http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_159.pdf

[8] As stated in the application: 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; Lung transplant rejection

treatment option for these patients which would continue to be used if there are no superior treatments for individual patients.

Therakos continues to conduct research on how to enhance its instrument and therapy and identify other disease states for which ECP could provide benefit. We are not carrying out research into alternative methods of delivering the treatment (as there are no alternative approaches known) and we are unaware of any other companies which are developing any similar competing technologies.

b) In close relation to b), as the spectrum of the lamps used for exposure is prescribed by the drug used to treat the cells (8-methoxypsoralen), is there any research in progress concerning alternative agents for this drug that may in turn require a different spectrum of UV light for activation?

There is currently no research being conducted by Therakos on alternatives to 8-methoxysporalen. This has been due to the complexity, time and expense of such a project but is also because of the effectiveness of this drug. An alternative substitute would have to meet all the pharmaceutical drug requirements including animal toxicology testing, pharmacokinetics testing and clinical studies to demonstrate safety and effectiveness. Such requirements make alternative clinical drug development prohibitive.

8-methoxysporalen is derived from a natural plant source and is unique in its effectiveness. There are no known alternatives and as the mechanism of the ECP treatment is not fully understood, it is not possible to design a different molecular structure that would be equally or more effective.