THERAKOS EUROPE • C/O JOHNSON & JOHNSON MEDICAL LIMITED • PINEWOOD CAMPUS
NINE MILE RIDE • WOKINGHAM, BERKSHIRE, RG40 3EW • WWW.THERAKOS.CO.UK

Application for Exemption under EU ROHS (Directive 2011/65/EU)

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

Applicant Details:

Heather Hendrix
Environmental Product Compliance Manager
Ortho Clinical Diagnostics,
Part of the Johnson & Johnson Family of Companies
100 Indigo Creek Drive
Rochester, New York 14626 United States
Email: hhendrix@its.jnj.com
Phone: +1-585-453-3025

Summary

This exemption is required to allow the use of lead in a UVA lamp phosphor used for extracorporeal photophoresis (ECP) treatment of cutaneous T-cell Lymphoma (and other T-cell related diseases). The treatment involves exposure of leukocytes that are temporarily removed from patient's blood to light from lamps with lead doped barium silicate phosphor. 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 optimum 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. Therefore there is currently no substitute lamp type for treatment of this disease by extracorporeal photophoresis as described in this application.

Description of materials and equipment required for exemption

An ECP treatment is comprised of the *ex vivo* exposure of autologous leukocytes (a type of white blood cells transferred from the patients 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, whole blood is drawn from the patient into the Therakos photopheresis system instrument and is subjected to centrifugation in order to separate the whole blood into its components. The red blood cells and plasma components are returned

back to the patient. The white blood cells are collected (the collected cells are known as buffy coat), concentrated and prepared for treatment with 8-methoxypsoralen and ultraviolet A 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 photoactivation of the white blood cells in the buffy coat 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.

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
- Lung transplant rejection

The above medical conditions are characterized by states of immunologically induced inflammation. Patients with these conditions are for the most part extremely acutely ill. ECP is frequently the last therapeutic option offered to patients and therefore frequently represents salvage treatment status. ECP is administered only in medical centers which have undergone specific training for the administration of this unique therapy. The above conditions are also considered as "orphan conditions"[1] since the numbers of patients who have these conditions is very small. In fact, the cumulative number of patients (< 20,000) with the above 4 conditions who would be candidates for this therapy still meets the criteria for orphan status (less than 200,000 cases in EU annually).

In the EU, Therakos' Photopheresis systems are indicated for the administration of a photopheresis treatment.

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 light dose (1-2 joules per cell) of this lamp is 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

[1] "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

in delivering the 1-2 joules of energy to each collected cell. 1-2 joules has been deemed (by cell viability testing post photopheresis) to be the appropriate dose of UVA energy to elicit the photochemical reaction described above between the drug and the leukocytes' DNA. 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 hence MORE cancer. The shape of the emission spectrum is required to elicit the desired response and avoid the negative consequences as discussed below:

- Light of longer wavelengths have too low energy to promote the photochemical reaction
- Light of shorter wavelengths have higher energy which can cause damage to DNA and could promote 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 will be proportional to the time that the patient is connected to the treatment system.

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. Once the lamps have been used for 150 hours the computer controlled photopheresis instrument instruct the operator to change the lamps. As the lamps decay the photoactivation time set by the computer increases. To treat a patient, the UV exposure unit contains 18 special BSP lamps that are designed solely for this treatment.

As discussed above, the exact mechanism by which this treatment works is not understood, but it is clear that many complex processes are induced that alleviate the patients' devastating symptoms. These symptoms include extensive itching, fissuring, scaling and edema. The skin of many patients resembles burn victims. In these cases, and without photopheresis treatment, 50% of these patient's die from infection. Therefore, any changes to the UV light wavelength will alter the proportions of desired light spectrum to adequately photoactivate 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 certainly lack of efficacy.

Photochemistry

To understand why these specific UV light wavelengths are important, the photochemical reactions that can occur between organic molecules and ultraviolet light are described here. When organic substances are exposed to UV light, bonding and paired electrons are excited from their ground states to excited σ^* and π^* states. 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):

$$E = h\nu = hc/\lambda$$

Where E = energy, h = planks constant, ν = frequency, c= speed of light and λ = wavelength.
The energy required to excite an electron depends on the type of bond. For example, a C-C single bond has σ electrons which are excited only by short UV wavelengths of <140nm to σ* states whereas C=C double bonds require lower energy radiation of ~180nm to excite π electrons to excited π*. Single bonds have only σ electrons which require the most energy to excite whereas double bonds have π electrons which require lower energy from longer wavelengths than is needed for σ electrons. Double bonded oxygen and nitrogen atoms also have unbonded electrons which can be excited into excited π energy bands with lower energy that is needed to excite double bond π electrons. The structure of organic molecules governs the minimum energy required to excite electrons so that adjacent bonds affect the minimum excitation energy of a bond. For example, two double bonds separated by a single bond are referred to as being conjugated and the minimum energy required to excite a conjugated π electron is less than a non-conjugated π electron and is excited by longer wavelengths, typically ~220nm.
The electrons in each bond of a complex molecule are excited by different minimum energy levels and so, the UV light spectrum will affect which electrons are affected. As the UV wavelength decreases, its energy increases and can excite more of the bonds in a molecule potentially causing additional chemical interactions.
The drug used for this treatment is 9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one. This complex molecule has several conjugated C=C double bonds and these are also conjugated to a C=O ketone bond and so the peak adsorption wavelength is ~300nm.
When an electron is excited by UV light, three things can occur.

- The electron falls back to its unexcited state with the emission of radiation
- The electron falls back to its unexcited state with the heat radiation
- A chemical reaction occurs

Of these, the first two are harmless although are in effect a waste of UV energy whereas the desired chemical reaction between the drug and DNA gives the beneficial treatment to the patient. It is important however to avoid undesirable photochemical reactions. With light of 350nm, the desired reaction between the drug and DNA occurs to give covalently bonded methoxsalen to single DNA strands or bridging pairs of DNA strands. If shorter wavelengths are used, additional photochemical reactions would occur as the higher energy level would excite different electrons in the methoxysalen molecule and also in the white blood cell molecules causes different chemical reactions to occur some of which will be harmful and could also destroy the desired reaction product.

UV lamps

Ultraviolet light is generated by the interaction between the emission spectrum from excited mercury vapour with specially designed phoshors which adsorb the mercury emission wavelengths and emit their own characteristic spectrum. UV lamps therefore consist of a glass tube containing a partial vacuum with a small amount of mercury and there are electrodes at each end. 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 which emits light of high energy and relatively short wavelengths with most 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 that are 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.
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 valency 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 valency 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. Alternative UV phosphors are discussed below.

Justification for this exemption

This exemption request is based on there being no suitable alternative fluorescent lamp that has a lead-free phosphor that emits ultraviolet light with a spectrum that is identical to the spectrum from the BSP lamp. 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. Alternative lamps would not be permitted as these are not approved by the medical devices directive and approval will require many years of clinical trials as described below. The spectra from alternative phosphors would also not provide effective treatment when these emit less desirable wavelengths. UVA lamps that emit longer wavelengths will have no medical effect and shorter wavelengths could be harmful to human health.

Analysis of possible alternatives

There are about 17 phosphors that emit in the ultraviolet spectrum. The characteristics of the UV phosphors are compared in the table below.

Table 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

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 photactivation 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. 2095 will also be less suitable as its peak wavelength is at a higher energy of 344nm and has a broader spectrum than 2011.

Spectra of UV phosphors which are similar to the BSP phosphor (reference number 2011) are compared below with the spectrum of the BSP phosphor for comparison. Note that these spectra are of light from the phosphor only as mercury emission lines have been omitted.

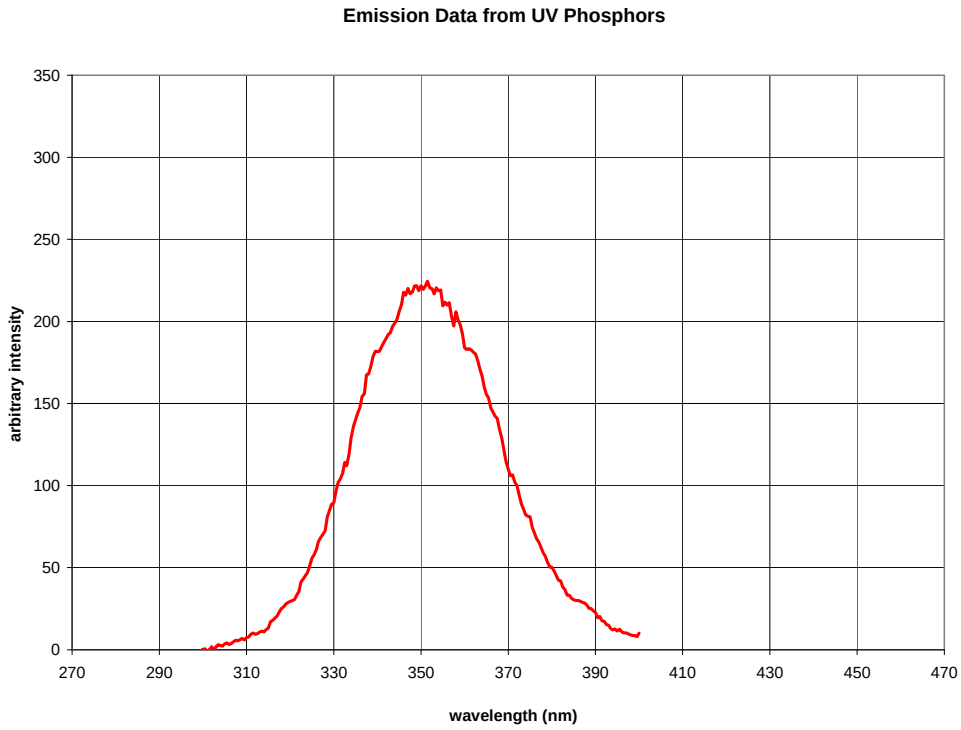


Figure 1. Spectrum of light emission from BSP lead-doped barium silicate phosphor (2011)

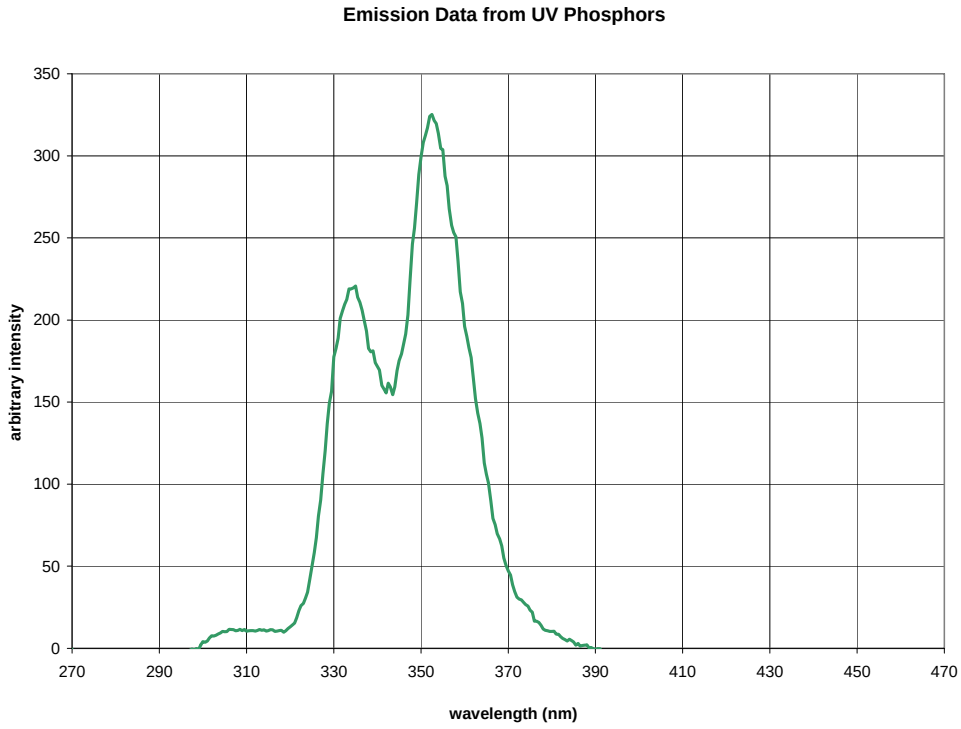


Figure 2. Spectrum of light emission from cerium-doped-yttrium phosphate phosphor (2040)

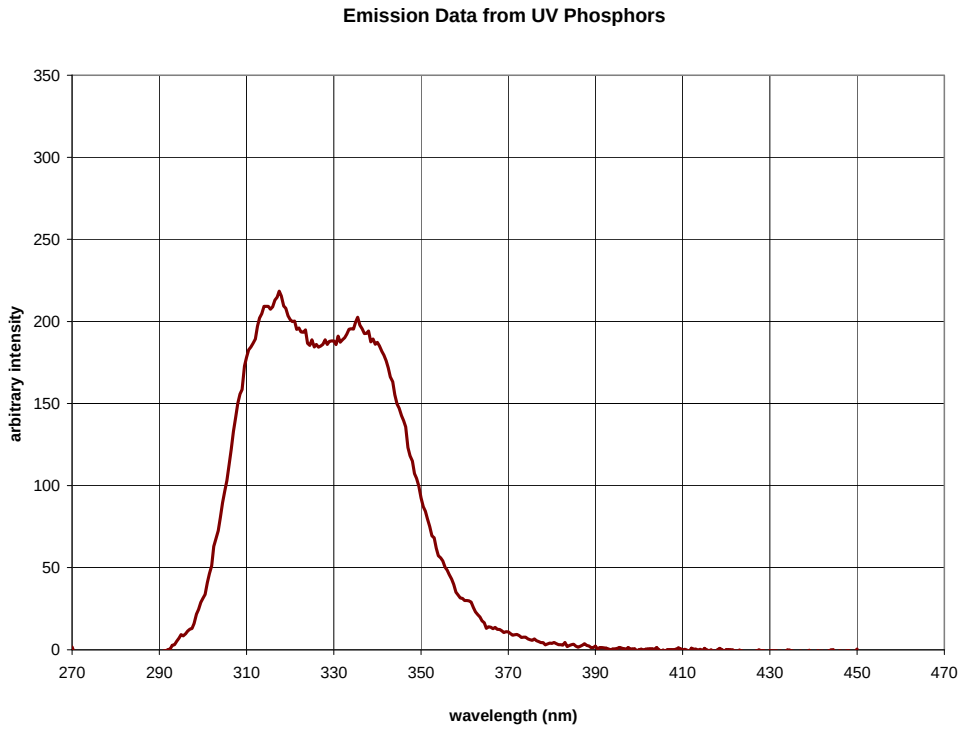


Figure 3. Spectrum of light emission from cerium doped lanthanum phosphate phosphor (2080)

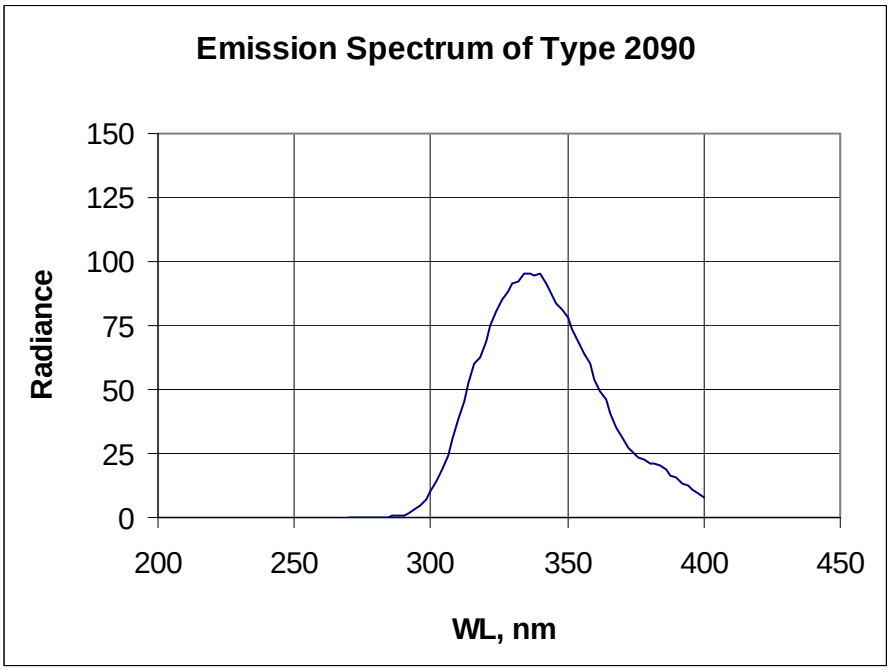


Figure 4. Spectrum of light emission from cerium doped strontium, magnesium aluminate phosphor (2090)

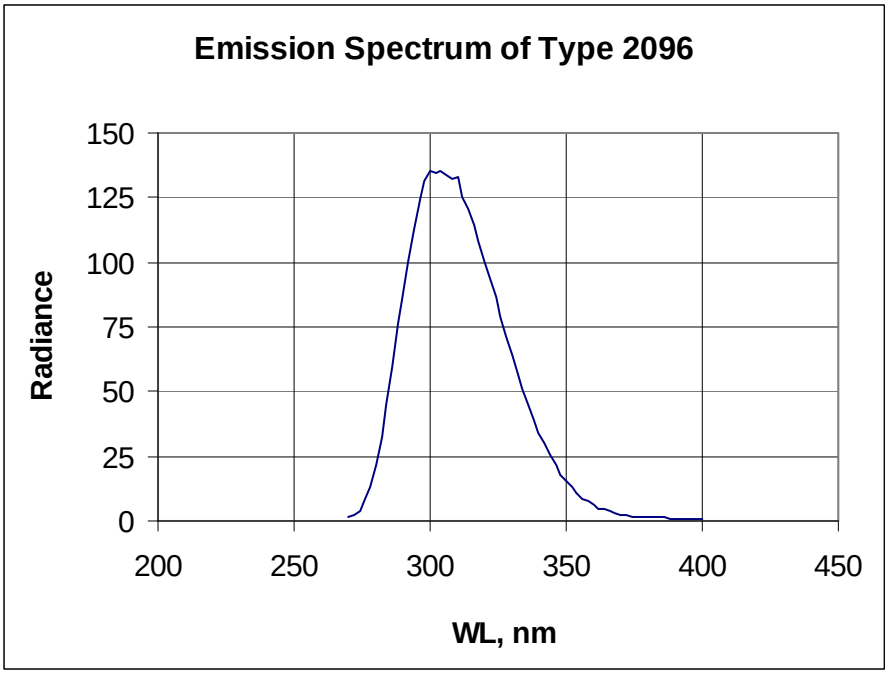


Figure 5. Spectrum of a different composition of cerium doped strontium, magnesium aluminate phosphor (2096)

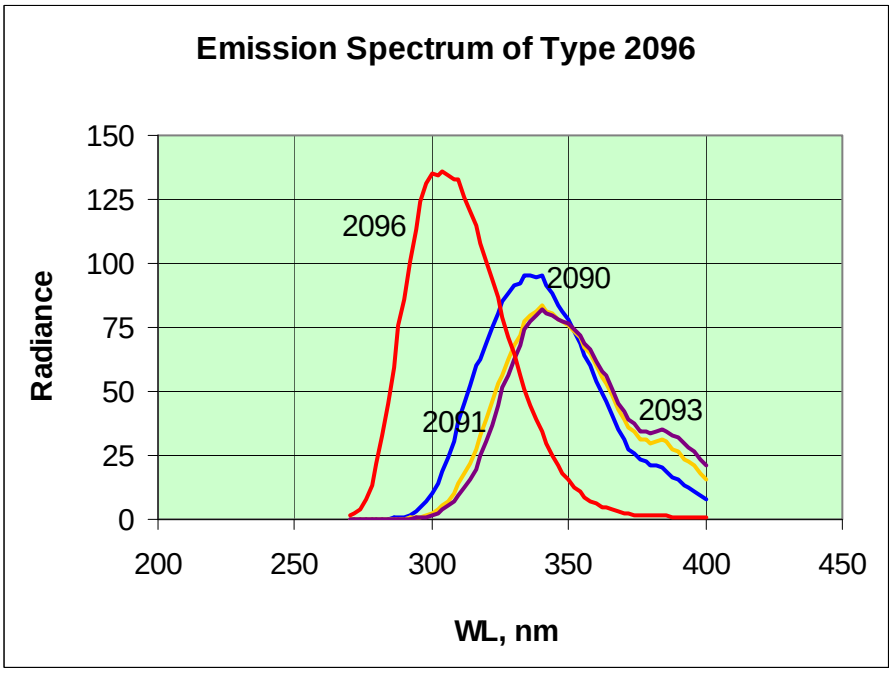


Figure 6. Comparison of doped Ba,Mg and Sr,Mg aluminosilicate phosphors

Other information

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 photophoresis 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.

However, given the lamp lifetime and treatment time, the number of lamps required to support market growth is minimal compared to the number of treatments delivered.

Life cycle assessment

Extraction and refining: BSP lamp phosphors contain abundant and readily available elements, barium, silicon and lead. The phosphor types with spectra closest to BSP are $(Ba,Mg)Al_{11}O_{19}$:Ce which also contains mostly abundant elements. Cerium is a rare earth element which is not rare although currently its supply is restricted. Most rare earths are produced in China which restricts exports so that the supply of some is lower than demand although cerium is one of the most abundant and supplies are not too small.

Phophor and lamp production: The production process used to make all types of lamp phosphors include similar process steps such as precipitation, milling and heating and so changing from one type of phosphor to another may not significantly change the manufacturing step. Lamp manufacture is the same irrespective of phosphor composition as only the internal coating material is changed.

Use phase: 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.

Re-use and recycling of materials from waste EEE

At end of life, fluorescent lamps should be collected and recycled as separate waste streams because of the need to recover and dispose of safely the mercury content. BSP lamp packaging is marked to indicate that mercury is present and that it should be discarded in accordance with local regulation. EU WEEE Directive "Compliance Schemes" have been set up in all EU Member States to collect and safely dispose of all types of end of life electrical equipment and this includes fluorescent lamps and so suitable disposal procedures have been established and are available. It is probable that some consumers do not dispose of their household fluorescent lamps in an environmentally acceptable manner but businesses including hospitals and medical clinics that provide photophoresis treatments will generate a moderate number of used lamps and so are more likely to use waste disposal operators who are able to recover mercury safely.

The standard recycling process is to crush the lamps in a sealed vessel. This separates the metal end caps, the glass and the phosphor powder that also contains the majority of the mercury. Metal and glass can be reused and mercury is recovered from the phosphor by distillation. The remaining phosphor will be a mixture of phosphor types from all of the types of fluorescent lamp that were treated plus some glass powder. It is feasible to reuse phosphor powder to make new lamps but where mixtures of lamp types are recycled, the mixed phosphor cannot easily be used in this way[2]. Room lighting phosphors from the most common type of fluorescent lamp are based on rare earth phosphates, typically doped with europium, terbium and cerium and so contain scarce elements although rare earth recycling is very uncommon in the EU and elsewhere. The lead content of recovered phosphors will be extremely low as the lead

[2] Example processes http://www.hse.gov.uk/foi/internalops/sectors/manuf/03-11-01/appendix-3.htm http://www.recolight.co.uk/downloads/pdf/GUIDE%20FINAL.pdf

content of BSP is <1% and BSP lamps will be an extremely small proportion of all fluorescent lamps that are recycled and so lead recovery would be impractical.

Proposed plan to develop substitutes and timetable

There are several medical treatments for cutaneous T-cell lymphoma (and the other disease states mentioned above) but the procedure using BSP lamps is the only option once other approaches have been used and failed to be effective. Therefore the only option for a substitute would be an alternative UV lamp phosphor that does not contain lead. Use of a currently available UV phosphor such as one from table 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. It is noteworthy that this procedure requires both a device and drug approval to be able to market it. As all lamps are different and so pose a risk to patients who are already ill, trials will need to be carried out in several stages. 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.

- 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 photoactivated the cells according to company specification.
- The instrument would require new software to control the photactivation time if a lamp with the correct spectral output could be found
- The instrument would need to be re engineered 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 the first trial would be with a small group of patients over at least four 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. Finding suitable patients with this rare disease for these trials will take much longer than would be needed for common illness.
- If these trials show that the alternative lamp is equally effective, there are no serious side-effects and that treatment times do not need to be extended, then a larger trial can 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 give the same medical benefit to the patient as BSP. Inferior treatments would not be acceptable and a medical device directive approval would be refused. These trials would last at least 5 years given the specific patient population that would be required to be enrolled i.e new cases of CTCL.
- Once trials are complete and if an alternative lamp has been shown 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 can take a minimum one year and the treatment cannot be used until

regulatory 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 could 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.

Proposed wording for exemption

This exemption is required only for category 8 medical devices.
Lead as an activator in the fluorescent powder discharge lamps when used as photophoresis lamps containing phosphors such as BSP (BaSi2O5:Pb)

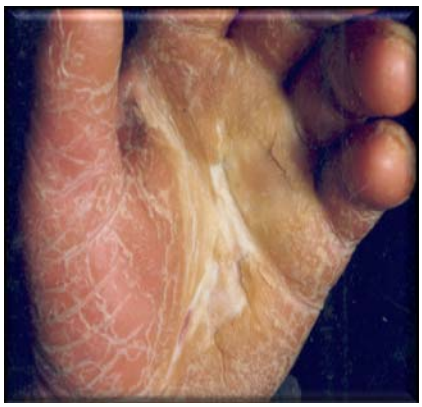
APPENDIX

Therakos Photopheresis systems, which rely on BSP lamps, are used to treat individuals with immune-modulated diseases including those that have failed other therapies (Indications vary by region). This well-tolerated option offers an alternative to topical and pill-based solutions that may have serious side-effects including immune-suppression/secondary infections (a leading cause of death for immune-compromised patients), secondary malignancies or lipid or endocrine abnormalities.

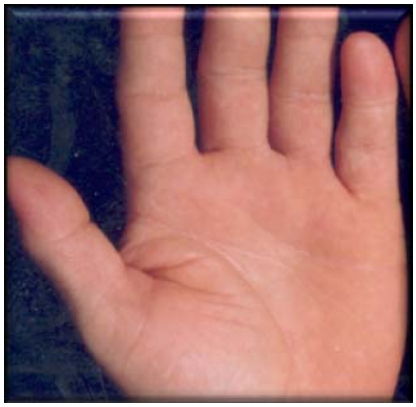
Therakos Photopheresis is a reliable and proven therapy used in over 700,000 treatments conducted across the world with a rare (<0.01%) incidence of serious adverse events in 25 years. The Therakos systems are the only regulatory approved integrated systems for ECP.

In the U.S., Therakos instruments are indicated for the palliative treatment of Cutaneous T-Cell Lymphoma (CTCL), to help patients manage the symptoms of this sometimes deadly disease. Patients with the disease suffer from patches and plaques covering large percentages of their bodies, and tumors may also develop. These debilitating skin symptoms frequently cause itching that cannot be relieved by topical or oral medications.

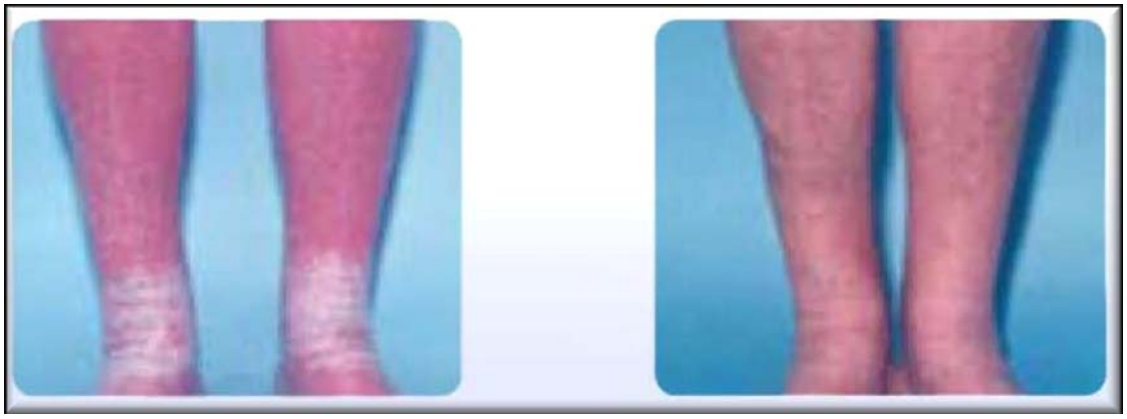
The photos below are of a patient with advanced-stage CTCL who was treated with the Therakos extracorporeal photopheresis (ECP) system. This patient developed severe cracks (fissures) in the skin which can be extremely painful and more importantly serve as a source of bacterial infection. After six months of treatment, normally twice a month, the photo on the right shows a significant reduction in skin fissures and a return of a functioning hand and reduced leg cracks.



Before



After



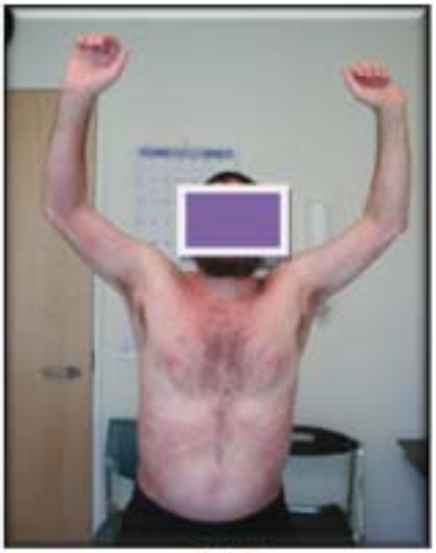
Before After

In Europe, Therakos instruments are indicated for photopheresis. One of the disease states ECP is commonly used for is Graft-versus-host disease (GVHD) a serious and frequent complication of bone marrow transplantation that occurs partly due to the reaction of the donor cells. Both chronic and acute forms of the disease can occur.

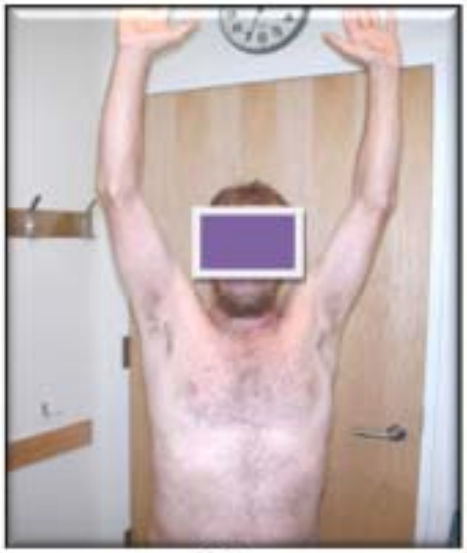
Symptoms of acute GVHD (aGVHD) can range from mild to severe. The first sign of aGVHD is typically a skin rash that appears on the palms of the hands and soles of the feet. Patients may complain of severe itching or tenderness in affected areas, and rash onset frequently correlates with engraftment of donor cells. The other two areas that are typically affected by aGVHD are the gastrointestinal (GI) tract and the liver. The severity of aGVHD is determined by the extent of involvement of the skin, GI tract and liver; and the disease can be graded (from I to IV) depending on severity. Steroids are the first-line treatment for aGVHD, but photopheresis has also been shown to be useful as an adjunctive therapy when a patient stops responding to a previously-effective treatment. .

A chronic form of GVHD also can occur. Symptoms can range from mild to severe and commonly affect the skin, mouth, eyes and vaginal mucosa. Chronic GVHD can also affect the gut, nails, hair, liver, lungs, kidneys and heart, and may persist even when skin changes have resolved.

The photo below is a patient who has chronic GvHD following a bone marrow transplant. He has severe scleradermatous skin disease which has caused his skin to become so taut that he cannot lift his arms above his head. After not responding to other therapies he received approximately six months of photophoresis treatments and was able to recover almost complete range of motion.

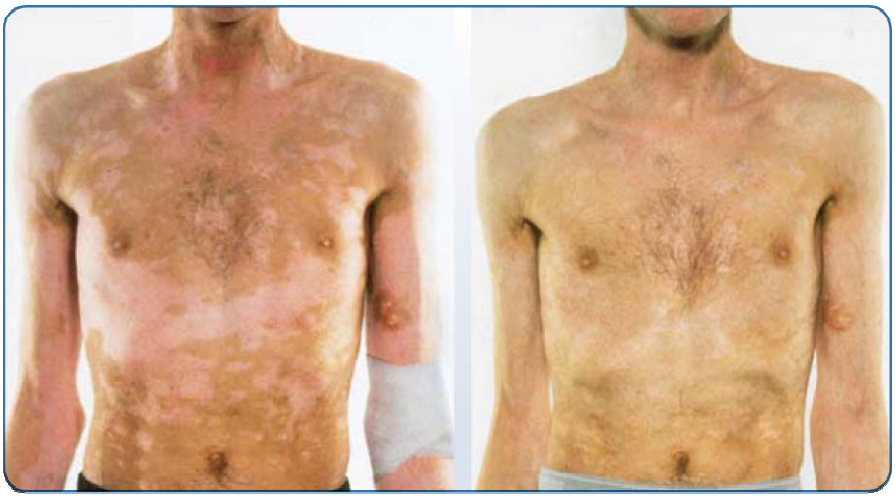


Before



After

The patient in these before-and-after photographs experienced skin lesions after a bone marrow transplant. After photopheresis the patient experienced skin lesion closure.



Before After