CLINICAL CONSENSUS PANEL REPORT ON THE USE OF FLUORESCEIN IN PRIMARY CARE

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Executive Summary

- Fluorescein is an essential ophthalmic staining agent that is routinely used by optometrists and contact lens opticians in primary care.

- Fluorescein strips licensed as medicines are no longer available in the UK after the withdrawal of the Bausch & Lomb (B&L) product Fluorets – a registered trademark.

- Failure to use fluorescein when clinically indicated in a primary care setting due to non-availability of a suitable pharmaceutical preparation will put patients at risk through a failure or delay to recognise sight threatening ocular conditions.

- Best clinical practice is to instill the lowest dose of fluorescein to achieve the required effect.

- Fluorescein strips provide better control of the volume of fluorescein instilled into the eye and provide a significantly lower fluorescein concentration than the currently available 0.5ml unit dose preservative free fluorescein eye drops (for example 1% or 2% Minims – a registered trademark) referred to below as 'unit dose eye drops'.

- Any potential risk posed by the use of CE marked fluorescein strips is considered to be more than offset by the benefits of using such strips for contact lens fitting or to analyse the external eye and tear film or the failure to use fluorescein at all when clinically appropriate.

- An infection risk has been identified with the re-use of unit dose eye drop fluorescein.

CLINICAL CONSENSUS PANEL STATEMENT ON USE OF FLUORESCEIN

It is the view of the Clinical Consensus Panel based on the evidence available and practice and clinical opinion, that optometrists and contact lens opticians in the UK may within their scope of practice use a CE marked medical device fluorescein strip permitted to be supplied in the UK by MHRA as an alternative to a fluorescein sodium unit dose eye drop formulation for clinical investigations in primary care until further notice.

This Statement will be reviewed should new information come to light on the classification, clinical use or safety of fluorescein.

Context

Fluorescein is widely used in primary care by Eye Care Professionals (ECPs)[1] for contact lens fitting and the assessment of the tear film and ocular surface. The preferred modality of use in the UK has for many years been by impregnated strips produced by Bausch and Lomb (B&L) under the brand name Fluorets.

In March 2013, ECPs received notice of the intent to withdraw B&L's Fluorets from the market globally for business reasons. There were no concerns about product safety. At the time of writing – August 2013 – Fluorets are no longer available from B&L or distributors and stocks of Fluorets in primary care settings are running out. In addition there has been confusion regarding the classification of Fluorescein strips in Europe and a lack of legal certainty regarding the use of alternative products such as CE marked medical device fluorescein strips which have been authorized for sale in the UK. This has left ECPs facing uncertainty about the optimal clinical substitute for Fluorets.

Fluorescein strips have for some time been considered by EU advisers to be 'borderline' products which meant that there was scope for them to be classified as either a medical device or medicine and as such were classified differently in different European countries – the UK classified Fluorets as a medicinal product (a 'P' medicine – see Annex IV). Despite Meddev guidance since 2001 suggesting that fluorescein strips should be classified as medicines, a majority of EU Member States' competent authorities continued to classify them as medical devices (which meant that CE marked strips were in use elsewhere in Europe). This difference in approach has been brought to the attention of the European Commission which is expected to advise further on their classification in October 2013. The withdrawal of Fluorets means that there is no longer a fluorescein strip available as a licensed medicine in the UK or globally. In anticipation of a further ruling in October, MHRA in the UK, recognizing the potential consequences of the withdrawal of Fluorets, has decided not to take enforcement action against suppliers of CE marked medical device fluorescein strips to the UK market until the position in the EU has been clarified, therefore permitting their sale in the UK.

In view of the uncertain position over fluorescein (in advance of October and potentially beyond that date), the Optical Confederation, supported by the British Contact Lens Association (BCLA), College of Optometrists (COptom) and General Optical Council (GOC) convened a Clinical Consensus Panel (Panel) consisting of:

- Clinical academics with a special interest in the anterior eye and scope of practice in primary eye care
- Eye care clinicians experienced in the fitting of contact lenses and the use of therapeutics
- Professional advisors to the UK optical bodies to provide opinion from the perspective of insurance and
- An observer from the GOC.

A list of invitees and attendees is available at Annex I.

[1] In the context of this document ECPs refers to optometrists and contact lens opticians (CLOs).

Consensus Panel Meeting

The Panel meeting took place on 30 July 2013 in London. An Agenda and a range of peer-reviewed scientific publications and other background papers were circulated in advance to all those invited to attend. Invited individuals who could not attend on the day were encouraged to submit views and feedback supported by appropriate references in writing in advance of the meeting. A list of those who submitted views in advance is included in Annex I.

The circulated documents included a literature review by Professor Steve Taylor, advice leaflets from various marketed fluorescein sodium products, correspondence from the MHRA, copies of issued advice and a range of relevant peer-reviewed publications. A copy of the Agenda is available at Annex II, the list of background papers is at Annex III and the literature review from Professor Taylor is at Annex IV.

Consensus Panel Discussions

Given the complexities of the underlying issues, the Panel agreed to set parameters for their discussions. The agreed parameters were:

- the use of fluorescein. (It was acknowledged that there might be pertinent information relating to other CE marked strips - e.g. Lissamine Green - but the meeting should not be drawn into prolonged discussion on these areas).
- UK primary care (not in other countries or in UK secondary care)
- use by optometrists and contact lens opticians.

The Panel briefly discussed whether the range of uses of fluorescein in primary eye care would be considered 'diagnosis'. They considered that 'diagnosis' is an undefined term in the relevant EU legislation that created confusion since it appeared in both the definitions of a medicine product and a medical device (see MHRA Bulletin 17 detailed in Annex IV). Additionally as guidance on 'diagnosis' with respect to fluorescein and other preparations to visualise body tissues was being prepared by the European Commission's Working Group it was inappropriate to pursue this at this stage, and the Panel should instead focus on what is the optimal clinical substitute.

The Panel agreed however that should new information come to light with respect to the classification and uses of fluorescein ophthalmic strips, their findings and conclusions would be reviewed.

The Panel's discussions centred on the most clinically effective ways to use fluorescein in primary care, the scope of use of fluorescein in primary eye care and the most suitable preparation for a range of clinical investigations.

A list of the common uses of fluorescein in a primary care setting were discussed and the most suitable preparation of Fluorescein for each. The outcomes are shown in Table 1.

Use of Fluorescein by Optometrists and CLOs in Primary Care

The Panel was of the opinion that in general terms instilling the lowest dose of a preparation to achieve the desired outcome produced the most timely and optimal clinical results. This therefore should be the preferred option for ECPs when providing care in the best interests of their patients. The Panel agreed that use of a strip would ensure that a significantly lower dose of fluorescein could be instilled into the eye

In terms of visualising the anterior eye, the Panel considered that there was a risk of 'quenching' (loss of fluorescence) occurring, particularly with the use of unit dose eye drops where the volume being instilled could not be well controlled and the resultant fluorescein concentration was higher. This could lead to masking of the clinical signs that were being assessed. Results from the literature and the clinical experiences around the Panel were that fluorescein strips provide a more flexible and effective preparation than unit dose eye drops for most primary care functions.

A recurring theme throughout the discussions was that the current confusion regarding the use of an appropriate substitute might result in some ECPs not using a staining agent even when its use was clinically appropriate. The risk of not using fluorescein to investigate ocular signs and symptoms could lead to delayed detection of sight threatening eye disease, for example microbial keratitis. The Panel unanimously agreed that this situation posed a risk to patient safety and that it was therefore important to ensure fluorescein in suitable preparations remains available to primary care ECPs.

The issues of contamination and the potential re-use of a preparation were explored. Although intended for single-use, the greater likelihood of re-use with a unit dose eye drop formulation increases the risk of cross-infection compared to using a paper strip. There was no evidence that strips were being re-used in practice. It was noted however that re-use of either unit dose eye drop or strip is inappropriate in all circumstances and should not occur.

Availability of Fluorescein Strips

The most suitable preparation for primary care clinical practice was considered to be a fluorescein strip, however there is no alternative strip to Fluorets licensed as a medicine in the UK. The Panel therefore considered the current options regarding availability. The Panel recognised that there is currently no fluorescein strip available as a medicinal product globally. The substitute products available in the UK at present are

- unit dose eye drops (for example 1% or 2% Minims) which are classified as medicines and
- CE marked medical device strips (which are not licensed as medicines however MHRA has permitted their sale in the UK).

It had been hoped that the results of a GOC commissioned pharmaco-analysis comparing several fluorescein strips (including Fluorets and two CE marked alternative strips) would be available for the meeting, however the analysis had not been completed. In discussion it was felt that fluorescein strips are more convenient, effective and pose a lower infection risk than

unit dose eye drops. It was also considered that the information currently available on the various preparations themselves and from previously recorded adverse incidents indicated that the strips posed minimal patient risk. Moreover, the Panel noted that the alternative fluorescein strips have been in use in other parts of Europe and North America for several years and are not aware of any adverse reports.

Conclusions

The risk posed to patients by not using staining agents when clinically indicated is significant and ECPs should continue to use fluorescein for relevant clinical investigations in primary care. It is unacceptable to avoid using fluorescein and delay detection of clinical problems that may result in sight loss.

Based on the current available evidence, the Panel concludes that it would be appropriate, and in certain clinical situations more suitable, to use CE marked fluorescein strips as an alternative to currently available unit dose eye drops.

The Panel has agreed this statement based on the perceived advantages of using fluorescein impregnated strips rather than unit dose eye drops. The Panel strongly agreed that given the existing circumstances, optometrists and contact lens opticians should only use CE marked medical device fluorescein strips that MHRA has permitted for supply to the UK.

The Panel agreed that this Report would be published and could be made available to third parties as appropriate. The Optical Confederation and BCLA would communicate this advice to their respective membership.

CLINICAL CONSENSUS PANEL STATEMENT ON USE OF FLUORESCEIN

It is the view of the Clinical Consensus Panel based on the evidence available and practice and clinical opinion, that optometrists and contact lens opticians in the UK may within their scope of practice use a CE marked medical device fluorescein strip permitted to be supplied in the UK by MHRA as an alternative to a fluorescein sodium unit dose eye drop formulation for clinical investigations in primary care until further notice.

This Statement will be reviewed should new information come to light on the classification, clinical use or safety of fluorescein.

Table 1: Summary of Panel's Comparison of Strips and Unit Dose Eye Drops by Type of Clinical Assessment

Clinical Assessment	Panel Comments
Contact Lens Fitting	When reviewing the fit of RGP contact lenses, an excess of fluorescein on the front surface of the lens can make it difficult to assess accurately an optimal lens fit. The most effective way to reduce volume and concentration is to use a fluorescein strip (where any excess solution can be shaken off prior to instillation).
Contact Lens Aftercare	The Panel agreed that strips are better than unit dose eye drops at controlling instillation and producing timely staining patterns.
Dry Eye Examination	For similar reasons relating to the volume instilled and resultant tear staining and break up patterns, the Panel considered strips clinically more appropriate than unit dose eye drops.
The Assessment of an Eye post Trauma (including surgery) and Certain Inflammatory Conditions	The Panel felt that in certain investigations of inflammatory conditions and trauma to the anterior eye, particularly involving potential penetrating injuries or post surgery, the use of the higher concentration of fluorescein from unit dose eye drops may be appropriate.
Contact Tonometry	The use of fluorescein and anaesthetic combination was not considered to be the optimum. Rather, the use of a separate anaesthetic drop and fluorescein from a strip provided less error from quenching and more accurate IOP measurement when performing contact applanation tonometry.
Reuse and Other Risks of Infection	Although intended for single-use, the greater likelihood of re-use with a unit dose eye drop increases the risk of cross-infection compared to a paper strip. The panel noted that the re-use of either a unit dose eye drop formulation or a paper strip is inappropriate in all circumstances.

ANNEX I

Attendees at Clinical Consensus Panel on Fluorescein on Tuesday 30th July 2013

Name	Other Details
Professor Roger Buckley (ophthalmologist)	http://www.anglia.ac.uk/ruskin/en/home/microsites/veru/contact/professor_roger_buckley.html
Dr Catharine Chisholm (Representing the BCLA)	http://www.brad.ac.uk/optometry/our-staff/academic-staff/Dr.-Catharine-Chisholm/
Professor John Lawrenson (Representing the College of Optometrists)	http://www.city.ac.uk/health/staff-directory/professor-john-lawrenson
Angela McNamee (Representing ABDO)	Member of ABDO's Advice and Guidelines Working Group. Chair of ABDO's Contact Lens Committee. Practical examiner in contact lenses for ABDO. Principal theory examiner in contact lenses for ABDO's dispensing diploma.
Mark Nevin (Panel Chair and Representing FODO)	Director of Policy and Strategy at ACLM, FMO, and FODO (optometrist, economist and leads on a wide policy portfolio including European Union, regulatory affairs and external relations)
Professor Steve Parrish	Visiting Professor Anglia Ruskin University, Cambridge Practicing Optometrists and Principle examiner in contact lenses for ADBO, and Editor of Optometry in Practice
Geoff Roberson (Representing the AOP)	Professional Adviser to the AOP and community optometrist
Nick Rumney	Optometrist with experience in primary care, contact lenses and evaluation of clinical equipment. Former GOC Council Member. Registered Independent Prescriber, Additional Supply Specialty and Supplementary Prescribing Specialty.
Professor Steve Taylor	Honorary Professor University of Plymouth. Practicing optometrist, with a special interest in primary care, professional law and vision and driving. Professional Adviser to FODO, General Optical Council FTP Panel Member Optometry adviser to Wessex Area Team and Dorset CCGs
Professor James Wolffsohn	http://www1.aston.ac.uk/lhs/staff/az-index/wolffjsw/
Observers:	
Kiran Gill	Head of Legal Compliance at the GOC
Jo Mullin	Director of Policy and Strategy at the College of Optometrists
Meeting Support:	
Harjit Sandhu	Optometrist and facilitator

Unable to Attend – invited to submit views in writing

Dr Julie-Anne Little	http://biomed.science.ulster.ac.uk/vision/Dr-Julie-Anne-Little.html#page=background
Professor Chris Purslow*	http://www.plymouth.ac.uk/staff/cpurslow
Linda Ford	Director of Education and Standards at the GOC
Trevor Warburton*	Practicing optometrist and clinical advisor to AOP legal services
Lyndon Taylor*	Practicing optometrist in community practice and Chairman of the AOP
Professor Phil Morgan	http://www.manchester.ac.uk/research/philip.morgan/
Mike George	Chairman of Optometry Wales, practicing Optometrist in South Wales and an Associate Tutor at the School of Optometry in Cardiff. He is also Optometry Adviser at Aneurin Bevan Health Board,
Andrena McElvanney	Consultant ophthalmic surgeon with special interest in ocular surface disease, cornea, eyelids, medical contact lens, and cataract.
Brian Tompkins	Practicing optometrist with a special interest in contact lens practice – AOP contact lens practitioner of the year 2012.
Dr Michel Guillion	http://www.michelguillon.com/about-us/dr-michel-guillon/
John Parker*	Represents the ACLM on the Euromcontact Regulatory Affairs Working Group and BSI, CEN and ISO Standards Committees on Contact Lens Standards; 'Biological testing of medical and dental materials and devices'; 'Quality systems for the manufacture of medical devices'; and 'Quality Systems' (ISO9000). Currently Convenor (chairman) of ISO TC172/SC7/WG9 Contact Lens Standards Committee and Chairman of BSI CH172/9 Contact Lens Standards Committee.

**Submitted views in writing*

ANNEX II

Protocol for Roundtable Meeting and Attendees

Objectives

Focusing on patient safety, best care and outcomes, and considering all the factors which influence these issues in contemporary community practice, the Roundtable meeting will seek to

1. Clarify the risks and benefits associated with products that might replace Fluorets®, in particular.
2. Ascertain whether an updated statement of clinical consensus should be issued which advised community eye care practitioners on the use of such products.
3. Discuss and agree what the content of such a public statement of consensus might be.

Planned Agenda for Roundtable Meeting

1) Introductions and Plans for the Meeting
2) A review of the legislation
3) A systematic review of the scientific literature and
4) Summary of GOC's pharmaco-analysis comparing alternative fluorescein strips (if available)
5) A review of alternative fluorescein products on UK market – dose, pharmacology, effectiveness, their respective risks and benefits
6) A roundtable discussion to analyse and review 2 – 5
7) To ascertain findings and consensus amongst the panel - based on clinical expertise, available evidence and legislation
8) Subject to the degree of consensus, agree a written statement of clinical consensus to publish in due course.

Actions

1) Summary of applicable legislation to be provided to all attendees (to follow)
2) Each individual attending should declare any conflicts of interest via email to harjit@fodo.com
3) All attendees to submit evidence or any supporting documents to harjit@fodo.com by 29 July. The evidence will be compiled along with the current legal position and provided to those attending the roundtable discussion
4) All attendees to submit specific questions that they feel should be answered in order for a clinical consensus to be reached – for example "are minims 1% less effective than Fluorets® for all clinical tasks?"
5) Submit comments on the objectives and agenda for the Roundtable by Monday 29th July.

Outputs

Those attending should be able to offer their clinical/professional opinion without influence or favour and this must be maintained at all times.

Regardless of the final conclusion the group reaches, findings will be published [method of communicating and final content subject to agreement].

There is no defined outcome because this will depend on consideration given to the weight of evidence or clinical opinion or both. However, the group should aim to produce a statement of consensus which will provide guidance to practitioners on what they should do, in the best interests of patients, when the supply of Fluorets® is exhausted.

NOTE: Where travel expenses (to the meeting) are not covered by the organisation you represent, these should be submitted to harjit@fodo.com

ANNEX III

List of Papers Provided to Attendees Prior to Meeting

Title	Details
Fluorescein and the Optical Professions	Provided in Annex IV
Agenda for roundtable meeting and list of Attendees	Provided in Annex I and II
Comments submitted by those that could not attend	Four people that could not attend submitted feedback via email.
The Science Behind the "Stain" (2011), Bausch and Lomb	*Available at* www.bausch.com/~/.../C628B362A03F4247B9E2FC984BB88D32.pdf
Anaphylactic response to topical fluorescein 2% eye drops: a case report (2010), Journal of Medical Case Reports. 4:27	*Available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2837668/
Anaphylactic shock after fluorescein staining corneal abrasion (2011), Bull Soc Belge Optalmol. (317): 29-31	Available at http://www.ncbi.nlm.nih.gov/pubmed/21560853
The use of Minims fluorescein compared with the use of BioGlo fluorescein ocular strips. College of Optometrists	Available on request: please email harjit@fodo.com
Fluorets and Minims fluorescein: frequently asked questions. College of Optometrists.	Available at http://www.college-optometrists.org/en/utilities/document-summary.cfm/docid/CDF0FC76-D7A2-428F-B75D9BFB1DE99914
Information leaflets on - Fluorets - Minims Fluorescein Sodium 1% - Minims Fluorescein Sodium 2%	Available at http://www.medicines.ie/medicine/12384/XPIL/Minims+Fluorescein+sodium+1++%26+2++w+v
Irish Medicines Board. Letter to AOI, Ireland. "Availability of fluorescein strips used for ophthalmic diagnosis"	Available on request: please email harjit@fodo.com
MHRA letter to Jesse Normal MP. "Licensing of Lissamine Green and Fluorescein for Use in Ophthalmology"	Available on request: please email harjit@fodo.com
Comments on the Fluorescein availability survey (EGS September 2012). European Glaucoma Society	Available at http://www.eugs.org/pdf/Fluorescein%20survey%20EGS%202012.pdf
Mid-Optic Announces Exclusive UK Distributorship of BioGlo, Lisssamine Green and Teat Flo. Press Release by Mid.Optic	

Optimization of Anterior Eye Fluorescein Viewing (2006). Rachael Peterson, James Wolffsohn and Colin Fowler	Available for purchase at http://www.journals.elsevierhealth.com/periodicals/ajopht/article/S0002-9394(06)00573-3/abstract
The reuse of ophthalmic minims® an unacceptable cross-infection risk? (2010). Rautenbach et al. Nature. (24), 50-52	Available at http://www.ncbi.nlm.nih.gov/pubmed/19247391
The precautionary principle: what is the risk of reusing disposable drops in routine ophthalmology consultations and what are the costs of reducing this risk to zero? (2010). Somner et al. Eye (24) 261-363	Available at http://www.ncbi.nlm.nih.gov/pubmed/19521427

ANNEX IV

Fluorescein and the Optical Professions

This paper was prepared by Professor Steve Taylor for a Clinical Consensus Panel discussion on Fluorescein strips on 30 July 2013.

Objective

The purpose of this briefing note is to provide a background on the current issues relating to fluorescein. A clinical panel will be invited to use the information in addition to their own information and expertise to provide a consensus view on the clinical efficacy of fluorescein sodium minims and fluorescein strips in community optometric practice and to provide a view on whether it is safe and in patients' best interests for optometrists and contact lens opticians to use CE marked but unlicensed fluorescein strips in optical practice.

Legal Context in the UK

Sodium fluorescein minims and strips have been classified as a pharmacy medicine (P Med) for several years in the UK under the legislation noted below. Other parts of the legislative framework have recently been updated under the Human Medicines Regulations 2012 but these do not relate to fluorescein strips. Optometrists have a specific legal exemption permitting them to use these classified medicines in the community.

The legislation governing medical devices and medicinal products (medicines) has been implemented in the UK in line with a series of EU Directives. The extract below from MRHA guidance outlines the overarching legislation.

Medical Devices

"There are 3 main Directives covering medical devices:

- *Medical Devices Directive 93/42/EEC*
- *In Vitro Diagnostic Medical Device Directive 98/79/EC*
- *Active Implantable Medical device Directive 90/385/EC'*

Directive 93/42/EEC has been supplemented by Directives 2000/70/EC and 2001/104/EC covering devices that incorporate as an integral part stable blood derivatives.

These directives were transposed into UK law by Statutory Instrument 2002 No 618, the Medical Devices Regulations 2002 and SI 1697 the Medical Devices (amendment) regulations 2003 (referred to as MDR from now on) (p.2 MHRA 2011).

Medicines

Medicinal products are regulated under the Medicines Act 1968 and the Medicines for Human Use (*Marketing Authorisations Etc) Regulations 1994 (SI 1994 No 3144) and amending regulations (SI 2005 No. 2759). These are the principal provisions, which transposed into UK law European legislation on medicinal products (Directive 2001/83/EC, amending Directive 2004/27/EC and Regulation (EC) 726/2004)"* (p.2 MHRA 2011).

MHRA has responsibility in the UK for determining the classification of medicinal products (medicines) and medical devices. The extract below provides the definitions as described by MHRA.

"Products making medical claims, as a general rule, will be regulated either by the Medical Devices Regulations or by medicines legislation'.

The revised definition of a **medicine** is:
I. Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
II. Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis

Article 2(2) of Directive 2001/83/EC also provides that, in cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a "medicinal product" and within the definition of a product covered by other Community legislation the provisions of the Directive shall apply.

The definition of a **medical device** is:
any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:
- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,

- control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means". (p.3 MHRA 2011)

There is a series of borderline products that might fit either classification depending on their specific use. Further information about these is available on the MHRA website: http://www.mhra.gov.uk/Howweregulate/Medicines/Doesmyproductneedalicence/Borderlineproducts/.

Legal Context Europe

Other countries have taken a different interpretation of medicines and medical devices regulations and classify fluorescein strips as medical devices. In the past, these had been available for import to the UK, however this ceased following the production of guidance by Meddev (originally from 2001) which looked at borderline classifications of medicines and medical devices, and gave fluorescein strips as an example of a medicine (see pages 9-10), provided that relevant criteria were met (Meddev 2009). As this was guidance, it was not adopted uniformly across Europe.

During 2012, some countries decided to align with the recommendation in the Meddev Guidance to classify fluorescein strips as a medicine which led to withdrawal of CE marked fluorescein ophthalmic strips from a number of EU Member States (e.g. Switzerland and Germany). The problems created by the change were taken by ECOO and UEMS to the EU Commission's '**Borderline and Classification Medical Devices Expert Group'** which agreed to consider the matter further and issue clarification in October 2013.

UK Current Position

The only supplier of licensed medicinal product fluorescein strips to the UK (B&L supplying as Fluorets) decided to withdraw from the market for business reasons which were unrelated to their classification. This was announced on 21 March 2013 and has interrupted the supply of fluorescein strips. It has not been possible to purchase Fluorets since the start of July 2013.

The discontinuation of B&L's Fluorets means that there are no longer any sodium fluorescein ophthalmic strips licenced as a medicine in the UK.

The CEO of MHRA has issued a statement making clear that in the UK fluorescein strips to be used solely for the purpose of assessing a contact lens fit will be treated as medical devices and regulated under the Medical Devices Directive until further notification. MHRA has been approached by a supplier of CE marked fluorescein strips, and MHRA has

authorised their sale and supply to the UK market pending a classification decision being taken at EU level in October 2013. These CE marked fluorescein strips are being openly marketed in the UK which has led to confusion over the legal use of alternative fluorescein strips by optometrists and contact lens opticians. These strips have CE approval as medical devices in other European countries, but are not licensed as medicines. Although MHRA has authorised the supply of CE marked fluorescein strips to the UK market, it has remained silent on who can use them.

MHRA has indicated that it continues to believe that the use of sodium fluorescein for diagnostic purposes (and the assessment of corneal integrity is likely to fall within this category) whether by minims or fluorescein strips would take the product into the medicines category. This creates a circular problem as there are now no fluorescein strips available that are licensed as a medicine. The MHRA has stated that once clarification has been received from the EU the position of fluorescein strips for diagnostic purposes would be reviewed.

It would seem to be therefore that the issue over the use of fluorescein strips does not solely relate to safety as they may be used as a means of instilling dye into the tear layer to ascertain the fit of a contact lens which is not considered a diagnostic act. The issue seems to be more one of what additional observations may be made once fluorescein from a strip has been instilled.

In the UK optometrists and contact lens opticians have been advised that they should use fluorescein sodium in minim form to enable observation of corneal integrity and identification of abnormalities, pending further advice (Optical Confederation 2013). Several clinicians have voiced concerns about whether it is an effective substitute product, which will be explored in more detail by the Clinical Consensus Panel.

European situation

Across Europe, the majority of countries do not allow optometrists or opticians to use diagnostic drugs (which would include Fluorescein sodium minims), which is a restriction on the scope of practice of the professions in those countries. The exceptions to this are the UK, Netherlands, Austria, Norway and Ireland (ECOO 2013). ECOO has put forward a scientific paper to the European Commission Working Group seeking a review and asking for Fluorescein strips to be granted dual classification as both medical devices and medicines depending on their usage (ECOO 2013).

The following is taken from an ECOO document submitted to the European Commission:

'Fluorescein as a Medical device: For contact lens fitting and assessment of tear break up time the use of fluorescein is in conjunction with the Slit lamp device. In both these cases fluorescein is clearly acting as a medical device. It has no diagnostic capacity and is acting as a visualiser to observe the fit of a contact lens or the coverage of the tears.

According to Council directive 93/42/EEC, the definition of a medical device is
"any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- *diagnosis, prevention, monitoring, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,*
- *investigation, replacement or modification of the anatomy or of a physiological process,*
- *control of conception,*

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means"

By this definition, for contact lens fitting and assessment of tear break-up time, fluorescein ophthalmic strips should be regarded as a medical device, as they help investigate the anatomy of the anterior eye and assess eye health and do not achieve their principal intended action by pharmacological, immunological or metabolic means.

The Meddev Guidance states: "in-vivo diagnostic agents; e.g. fluorescent ophthalmic strips for diagnostic purposes" in its example of a medicinal product. The guidance does not address non-diagnostic usages. Therefore, the guideline should be expanded to include fluorescent ophthalmic strips for non-diagnostic purposes. Furthermore, for non-diagnostic purposes, we believe that fluorescent ophthalmic strips should be considered a medical device.'

<u>Properties of Fluorescein</u>

Fluorescein is a synthetic organic compound which is a weak dibasic acid of the xanthene group with a molecular weight of 330, first synthesized by Baeyer in 1871.. It is poorly soluble and is generally employed as its sodium salt which is soluble in alcohol and water. It is deeply coloured, and the conversion of the absorbed light to fluorescent light is almost 100 per cent. The absorption (or excitation) spectrum has a peak in the blue at 490 microns, falls in the violet, and rises again in the ultraviolet. The emission spectrum peaks in the green, at 520 microns, and declines gradually to the red.

Contamination

There have been reports on the potential contamination of fluorescein and particularly with reference to pseudomonas contamination. A paper by Norn and Thomsen (1967) quotes three sources (Theodore, Vaughan, Ridley) where extensive contamination had been demonstrated. The paper by Vaughan (1955) is frequently cited in relation to fluorescein contamination. These papers however appear to be related to multi-use dropper bottles of fluorescein solution rather than the modern minim or strip form of fluorescein which are intended as single use devices.

In the 1950s efforts were made by Kimura (1951) to develop a contamination free alternative to the fluorescein solution available at that time. The result was a fluorescein impregnated paper that was developed commercially into the current fluorescein strips.

The early contamination reports conflict with a later publication by Claoue in 1986 assessing the likelihood of contamination of minims of Fluorescein Sodium. This paper suggests that under normal clinical usage conditions it is extremely difficult to promote pseudomonas contamination in minims. There does not appear to be any reports on contamination of individually sealed fluorescein strips which supports the origin of the strip's design as a way of minimising contamination.

Serious Adverse Reactions to Fluorescein

A literature review shows that adverse sensitivity issues can occur with topical, oral and intravenous applications of fluorescein. Reaction can vary from mild discomfort to anaphylactic reaction. However most anaphylactic reactions appear to have been noted when the intravenous application is used and therefore unlikely in European optometric situations. The numbers recorded are very small and a literature review by Kwan et al (2006) found that over a six year period in which 11,898 patients were reported as having undergone fluorescein angiography only 132 adverse reactions occurred none of which resulted in death.

A handful of cases are reported in the literature over the last 25 years relating to serious adverse reaction resulting from topical conjunctival/corneal application (El Harrar et al 1996, Anderson 2002, Shahid & Salmon 2010, Kaimbo 2011). In most of these extreme reaction cases it has been linked to patients with additional health issues. These reports on topical reaction also relate to the use of minim application rather than the strip form and in particular the use of a higher concentration (2%) (Shahid et al. 2010).

Use of Fluorescein in Eye care

Reference to the use of fluorescein in ophthalmology can be found from as early as 1882 and its clinical application for the detection of corneal ulcers and abrasions was recognised in the 1880s. A paper by Maurice (1967) reviews the history and potential future use of fluorescein in eye research.

The first reported use of fluorescein in contact lens fitting is thought to have been in 1920 when Muller reported using fluorescein to view the tear space on a haptic lens (Pearson 2006). Their use became more widespread in the 1950s.

Fluorescein strips were first produced by Kimura in the 1950s (Kimura 1951) in an attempt to eliminate potential contamination issues and the use of fluorescein appears to increase once these strips are commercially available.

There are a number of available forms of fluorescein however in optometric eyecare it is generally used in the Sodium form as either 1% or 2% solution in minims or as fluorescein strips incorporating 0.5mg or 1 mg of sodium fluorescein.

Clinical publications into the biology of corneal fluorescein staining did not begin to appear in the peer-reviewed literature until the late-1960s and early 1970s. Throughout the 1970s and 1980s, and up to the present with the growing market uptake of contact lenses the number of descriptive case studies of superficial corneal fluorescein staining has increased significantly in the scientific literature (Ward 2007, Davies and Veys 2009) (See Fig. 1 below).

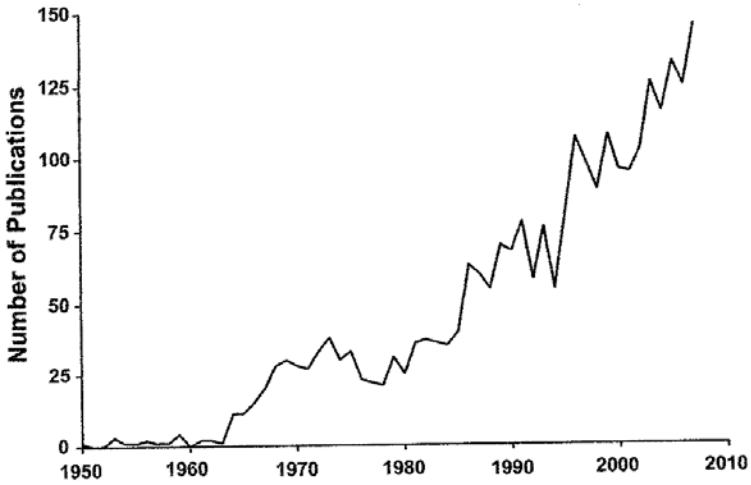

FIGURE 1.

Peer-reviewed scientific articles related to corneal staining. Data in this Figure were derived from a literature search (1950 to present) using the terms "staining and (contact lens or cornea)." 2007 value is estimated based on 61 relevant citations appearing by approximately mid-year.

Taken from Ward 2008

Today, the use of fluorescein by optometrists in the UK is common for a variety of purposes including assessment of contact lens fitting, tear layer assessment, contact tonometry, assessment of corneal integrity and tear duct patency. It is also used extensively in contact lens fitting by contact lens opticians.

Strip v Minim

There is little reported evidence for advantages of using minims versus strips or vice versa, but in the experience of the author, control of the volume of fluorescein instillation is easier with a strip. The benefit of improved control with a strip is that hyperfluorescence can be minimised and in the case of assessing a GP contact lens fit for example less time has to be left before assessment can take place as there is less problem from misinterpretation of the tears on the surface of the lens. A number of reports appear to support the benefits of lower volume from in vitro (Abdul-Fattah et al 2002) and in vivo studies (Johnson, M E, Murphy, P J 2005, Peterson et al 2006). However it is difficult to relate a practical situation to research studies in which calibrated micropipettes are used to instill v small quantities (1 microl) of the fluorescein sodium solution. It has been demonstrated that a drop from a minim in a clinical situation would on average deliver 30 microl (German et al 1997).

Comparing the use of minims to strips for fluorescein instillation it is suggested that there are four potential advantages to the use of strips:

1. Whilst serious reported adverse events are extremely rare after topical application of fluorescein, where they have been recorded, to the best of our knowledge they have only been due the use of minims which instils a higher volume of fluid
2. The potential for contamination (and the likelihood of re-use) is greater with minims than strips creating a risk of infection with potential sight-threating consequences
3. The volume of fluorescein instilled is harder to control with a minim which may affect interpretation of results and delay assessments
4. The storage time for strips is significantly longer than that of minims

Potential Safety Issues

From the available evidence and reporting mechanisms in the UK and USA there does not appear to be a risk of serious adverse events with the use of fluorescein strips, and only a small risk with the use of 2% fluorescein sodium minims. In addition lower concentrations of fluorescein delivered using strips or 1% minims are shown to improve the efficiency of clinical examination (Peterson et al. 2006). Where practitioners substitute for 2% minims, this may increase the risk to patients of anaphylactic shock and can adversely affect contact lens fitting due to errors in interpretation of fluorescein patterns.

The current position of uncertainty over the legal use of fluorescein amongst practitioners is likely to lead to a reduction in the use of the dye overall which in turn may lead to a reduction in the detection of anterior eye problems and therefore impact on patient safety.

Pharmacology of Fluorescein Strips

A review of the manufacturers' data for 3 fluorescein strips shows that Fluorets, BioGlo and fluorescein glostrips contain the same active pharmaceutical ingredient of 1mg fluorescein sodium on each strip. All manufacturers state on their product that no other substance is used. There is no indication that the paper used for the different strips is the same but it is unlikely that any of the papers used in production will contain an active pharmaceutical agent. On this basis the likelihood is that the fluorescein strips are equivalent.

Suggested Questions for Consideration by the Clinical Consensus Panel on 30 July 2013

1. *Is the panel aware of any alternative fluorescein strips that would be considered pharmacologically equivalent to and a safe alternative to B&L Fluorets? As a note the only other CE approved strip available in the UK is BioGlo but this is not licensed as a medicine.*

2. *Is it agreed that minims offer a greater potential risk to patients than strips including the risk of anaphylaxis?*

3. *Is it agreed that the volume of sodium fluorescein introduced to the anterior eye using a strip provides more suitable assessment of tear film and contact lens fit than use of a minim?*

4. *Insurers have stated that they would be happy for fluorescein strips to be used in clinical situations even if the legal position is unclear providing that the clinical panel can reach a consensus that there are no particular risks associated with their use. Can such a consensus be achieved?*

5. *Would the panel support the use of Bioglo as a suitable alternative to fluorets?*

6. *Would the clinical panel support lobbying MHRA to approve the use of fluorescein strips in optical practice as a medical device and a medicine rather than a medicine alone to enable contact lens fitting and tear film assessment by contact lens opticians?*

7. *Would the clinical panel add any other uses of fluorescein strips for exemption from classification as a medicine on the basis that the use is non-diagnostic?*

8. *Would the clinical panel agree to sign up to a letter to MHRA, the GOC and the professional journals based on the introduction to this discussion and the responses to the above questions?*

These questions were prepared by Prof Steve Taylor on behalf of the Optcal Confederation.

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Further Information

The European Commission has also published guidance on the demarcation between medical devices and medicinal products in their MEDDEV 2.1/3. This is available, without charge, from the Commission website at http://ec.europa.eu/comm/enterprise/medical_devices/meddev/index.htm .

Information on specific borderline cases may also be obtained from the 'manual of decisions' a copy of which may be obtained from the European Commission's website at: http://ec.europa.eu/enterprise/medical_devices/borderline_classification_en.htm

Printed copies of the Medical Device Directives:
- Medical Devices Directive 93/42/EEC and supplements 2000/70/EC and 2001/104/EC
- In Vitro Diagnostic Medical Device Directive 98/79/EC
- Active Implantable Medical Device Directive 90/385/EC

and the Medicinal Products Directives 2001/83/EC & 2004/27/EC are available to purchase from:

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Tel 020 7873 8372
Fax 020 7873 8247
Copies of the Medical Device Directives are also available from the European Commission website at:
www.europa.eu.int/comm/enterprise/newapproach/standardization/harmstds/reflist.html

Copies of the UK medical devices regulations are available from
www.legislation.hmso.gov.uk/si/si2002/20020618.htm
and
http://www.opsi.gov.uk/si/si2003/20031697.htm

Copies of Guidance Note 8 'A Guide To What is A Medicinal Product' are available from the MHRA website http://www.mhra.gov.uk
(This document is currently being revised.)