Further to Lucy Ticomb’s Article (Are quality standards being reduced as eye drops are classified as devices? (PJ, 26 June 2010, p633)), Bausch & Lomb would like to endorse the opinion that it is time for the Royal Pharmaceutical Society to update the guidelines on the safe use of unit-dose eye drops. Specifically, we would like to see the same stringent standards of safety applied to unit-dose eye preparations classified as devices through the CE marking scheme as those for unit-dose eye preparations licensed as pharmaceuticals.

The CE marking system is a well recognised and respected system for certifying the quality and safety of medical devices. Bausch & Lomb plans to expand its presence in the CE-marked eye drops sector and does not wish to see the high standards compromised in any way, but would like to see harmonisation with regard to single use recommendations.

Medicines licensed for single use are just that. This means that, after they have been used once, they must be discarded and not be stored for any length of time for reuse. Recent studies on the Minims range of single-use preservative-free ophthalmic drops have clearly documented the potential for unit-dose preparations to act as a vehicle for cross-contamination if reused. Of course, some preparations are more likely to support spontaneous contamination than others but, ethically, the only guidance that can be given for all unpreserved unit-dose eye drops is, surely, not to reuse at all.

For units that are reused by the same patient, the only justification for a less stringent application of this guideline would need to be supported by instructions based on an established guideline on the timeframe during which the product can be reused, and a statement that the unit must not be shared between individuals. This data requirement is mandatory for preparations licensed as pharmaceuticals, and should be applicable to those single-use preparations sold through the CE marking scheme as part of their technical document requirements.

In the case of single-dose eye drops classified as devices, the absence of clear usage guidelines apparently leaves the safety instructions open to interpretation by each manufacturer. Perhaps the Society should approach notified bodies that grant CE mark status to highlight the potential safety issue with single-dose ophthalmics and ask that they review their guidance to manufacturers of such products to harmonise packaging information.

There appears to be a loophole under which manufacturers of CE marked ophthalmics are not required to state that the device is for single use, even though it is unpreserved. This has led to the emergence of alternative timescales during which each manufacturer claims its unit-dose product to be safe to reuse, with consequential public safety concerns. We urge the Society to review the current guidance as a matter of urgency.

Anne Davies
Pharmaceuticals Division, UK, Ireland & Nordics
Bausch & Lomb UK Ltd

REFERENCES

Quality is being consistently assured
From M. T. E. H. Merikangas

Lucy Ticomb’s Article (Are quality standards being reduced as eye drops are classified as devices? (PJ, 26 June 2010, p33)) gives a comprehensive picture of medical device eye drops. As the manufacturer of Optive, one of the products referenced in the article, we would like to address some of the points that have been raised.

With regards to Optive, the “in-use” shelf-life of six months is questioned, as well as the overall efficacy of its relatively novel preservative oxicloro complex (Pelite). The article implies that, although there are acknowledged benefits of the low toxicity of Optive, these could be outweighed by the potential risk of contamination due to failure of the preservative.

In order to fulfil the regulatory requirements for approval of Optive, stability testing was conducted to demonstrate the preservative efficacy of Optive. This testing was carried out using product samples of Optive, which contain 0.01 per cent Purite rather than the lower concentration of 0.005 per cent used in the study by Charnock (2006) and cited in the article.1

In our study, testing was performed according to ISO 14730:2000, the standard discussed by Mrs Ticomb, aimed at determining discard dates for ophthalmic products. However, unlike the 28-day assessment protocol described in the article, Annex E of the standard describes further inoculation times up to 24 weeks and even at further six-week intervals if required. Our company inoculated product samples with test organisms at regular intervals over 180 days and samples were assayed for viable micro-organisms at nine time-points. The final assay was at day 194 (14 days past the 180 day discard date), with final inoculation at day 180.

Analysis of the data showed that the numbers of bacteria and fungi were reduced by the required three logs by day 14 and did not increase in numbers thereafter. Therefore all test criteria outlined in ISO 14730:2000 were met and Purite consistently satisfied the requirements of this standard, thus supporting a six-month shelf-life for the product.

To support further the validity of the approved in-use shelf-life, it is appropriate to look to our safety database. In addition to the pre-marketing studies carried out, there is also now a substantial experience of post-marketing vigilance for Optive. Optive preserved with Purite was first launched as an over-the-counter product in the US in September 2006. The patient exposure from first launch to 30 June 2010 is approximately 4.8 million patient-years. During this time, the profile of adverse events seen has been in line with that observed in clinical studies.

Although we accept that there is always considerable under-reporting of adverse events for any product, it is also known that serious and significant events, for example, infections, are more likely to be reported by both patients and healthcare professionals. It is of note that the adverse events received by Allergan from all sources are not indicative of an ocular infection signal associated with Optive use. Furthermore, the events reported are, in essence, those already known to occur with this product.

It is also worth noting that Optive is manufactured at a facility that also manufactures medicinal products and, therefore, the same controls are used during its manufacture. The facility and manufacturing process is regularly audited by authorities from all over the world and, in Europe, it is accredited to the ISO 13485:2003 standard and pharmaceutical Good Manufacturing Practice standards. Optive is CE marked by the appropriate authorities, demonstrating that all European requirements for medical devices are completely fulfilled.

We trust that this information contributes to the topic being discussed and provides arguments that the quality of Optive is being consistently assured to allow patients to benefit from this product.

Nick Hill
Quality/Regulatory, European Region
Allergan Ltd

REFERENCE
Incomplete information

From Ms D. Gross

Regarding the Article by Lucy Titcomb “Are quality standards being reduced as eye drops are classed as devices?” (PJ, 26 June 2010, p633), I would like to comment on Panel 2: “Eye drops available in the COMOD and ABAK system”.

The panel says that Timo-COMOD is no longer available or discontinued in Malaysia. We would like to clarify that Timo-COMOD is available and marketed in Malaysia. The information given in this panel is unfortunately incomplete concerning other products and countries as well. Therefore, we are happy to provide further information about the availability of eye drops in the COMOD system if requested.

Doretha Gross
Head of Medical Science Department
URSAPHARM Arzenmittel GmbH
Saarbrücken, Germany

PRODUCTS AND DEVICES

A change in definition is required

From Mr J. C. Deavin, MPHarmS

The Broad spectrum by Laurence Goldberg (PJ, 24/31 July 2010, p113) on the borderline between medicinal products and medical devices raises a number of issues that regulators and regulatory people within the healthcare industries have been aware of for some time.

The root cause of the difficulties in classifying certain products is that the definitions of medicinal product and medical device respectively in Directive 2001/83/EC (Medicinal Products Directive [MPD]) and Directive 93/42/EEC (Medical Devices Directive [MDD]) as amended by Directive 2007/47/EC, are inconsistent.

A strict application of the MDD results in neither the MPD nor the MDD applying to certain products. Changes in the advised regulatory route for certain groups of products as listed in the Broad spectrum came about because of amendments to European Commission (EC) guidance documents and not the underlying legislation. Although changing master lists of borderline products, as reflected in the EC guideline document MEDDEV 2.1/3 rev3 and supplemented by the EC Manual on the Borderline, is helpful, it does not address the underlying inconsistency in the legal framework and does not assist courts in classifying novel products.

Concerning the example of TauroLock given in the article, without entering into a debate as to how such a product can be classified as a medical device, all medicinal substances that are used in an auxiliary manner to the primary action of the medical device must comply with the requirements of 2001/83/EC.

It should be noted that the revised MDD includes software as a medical device in its own right in the definition. Furthermore, the crucial terms for making the determination that a product is not a medical device (pharmacological, metabolic, immunological) are defined in the non-legislative binding minor guidance documents but not in the legislation. The term “physical means” , although mentioned in the guidelines, does not appear in either the MPD or the MDD and, indeed, there are established medicinal products whose primary action is physical. The same comment applies to the term “chemical action”.

The essential problem with the differentiation of medicinal products and medical device is the focus by the EC on the principal intended action rather than the consistent application of Article 2.2 of the MPD.

In my view, a change is required in the definition of a medical device and medicinal product in further revisions of the directives.

John Deavin
Deavin Associates
Peterfield, Hampshire

The GPhC will provide no option for non-practising pharmacists to join automatically on 27 September (first day of operation) simply by paying the first full 12-month fee. Instead, they will have to submit documentation associated with a new application and, assuming the application is successful, pay an initial entry fee of £262 and an application fee of £100 (assuming that the proposed fees levels currently being consulted on are agreed). How can such treatment be viewed as fair or just?

Surely, new application and entry fees should not be charged to non-practising members who choose to join on the first day of operation (or even within the first three months of the GPhC). If separation were delayed to 1 January 2011, this situation would not arise.

A. Matalia
Croydon

MARGARET MORGAN, interim communications manager, General Pharmaceutical Council, responds: Although I appreciate Mr Matalia’s concern, the GPhC has to put in place what it considers to be appropriate requirements to satisfy its primary objective of public protection. After the GPhC goes live, those who were formerly on the Society’s non-practising register (and thus are under no obligation to keep their skills up to date via continuing professional development, for example) and who have chosen not to move onto the Society’s practising register before the switch will have to prove to the new organisation that they are fit to practise if they want to join its register. This is in keeping with the GPhC’s primary objective. It will be for each individual non-practising registrant to decide whether it is important for him or her to be on the GPhC register as soon as the GPhC goes live. If the answer is “yes”, they should transfer to the Society’s practising Register in good time before regulation transfers, so that their registration will transfer automatically to the GPhC. If the answer is “no”, but they do wish to join the GPhC register at a later date, they will be able to apply for registration with the GPhC as a new applicant, subject to meeting the registration requirements.
Letters

We would encourage the use of peer review to ensure quality
From Miss S. V. Sonecha, MPharmS, and others

We write regarding the need for The Pharmaceutical Journal to introduce a peer review process for its recently introduced case studies.

The purpose of a clinical case study is not to learn about an individual patient, but to use him or her as an example to highlight and discuss available guidelines and evidence, and the practical implementation of these. Furthermore, case studies featuring unusual presentations or rare diseases where there is a lack of available data may themselves be used by other clinicians as a basis for informing decisions on patient care.

Although we commend the PJ for its decision to use case studies as an educational tool, we would argue that this should not happen without a peer review process to ensure the quality of educational material and to confirm that it has been appropriately referenced and researched.

We would encourage the use of peer review for all published material intended for education to ensure the quality and integrity of future clinical articles.

Sonali Sonecha
Lead Directorate Pharmacist — HIV/GUM
Laura Baber
Highly Specialist Pharmacist — HIV/GUM
Barry Jubraj
Lead Pharmacist — Academic Studies
Chelsea and Westminster Hospital Foundation Trust

Sharon Byrne
Principal Pharmacist — HIV/GUM
Kingston Hospital NHS Trust

OLIVIA TIMBS, editor, The Pharmaceutical Journal, responds: I thank Miss Sonecha and colleagues for their letter. Unlike the BMJ or The Lancet, the PJ does not focus predominantly on research and educational material. It is a hybrid publication that carries some peer-reviewed material, but plenty of political articles and comment pieces of a non-clinical nature.

Nevertheless, the PJ is keen to revisit its peer review processes and make it clear what sort of review our clinical articles have undergone, and we will be revising those processes this month with a view to publishing new guidance in due course.

We are also keen to attract more case reports and, in the early stages of this new series, we would not wish to deter would-be contributors by appearing to be heavy-handed in our approach. In future, we will publish any case report as it is presented to us, and invite a specialist in the field to provide a commentary, which will be published simultaneously, putting it into the context of available guidance. Any other person who wishes to comment thereafter will be invited to join the debate on PJ Online.

We believe that this is the best way to ensure that real-life practices are reflected (for healthcare is more grey than black and white) while accommodating the need for peer review.

NOTICE-BOARD

There is no such chemical as dexamethasone base
From Mr M. J. Busse, MPharmS

I refer to the summary of product characteristics change of Hospira dexamethasone solution for injection on Notice-board (PJ, 24/31 July 2010, p111) Dexamethasone sodium equivalence is expressed in terms of dexamethasone alcohol, which is the active moiety. There is no such chemical as dexamethasone base.

Michael J. Busse
Widnes Garden City, Hertfordshire

Hospira has declined our invitation to respond. — EDITOR.

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