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HPRA MEDICINAL PRODUCTS NEWSLETTER

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Vet Information Day - 2 December

Given that the European Commission has now published its long-awaited proposal on the new draft European legislation governing the authorisation, use, supply and monitoring of veterinary medicinal products, the HPRA plans to host an information day on 2 December 2014. The venue for the event is the Crowne Plaza Hotel, Northwood Park, Santry, Dublin 9. The hotel operates a courtesy coach to and from Dublin Airport (www.cpireland.crowneplaza.com/crowne-plaza-dublin-northwood/location/dublin-airport-shuttle-bus/). Confirmation of the meeting, as well as logistical information and a draft programme will be available on the HPRA website from 30 September. Queries on the Info Day should be sent to **vetinfo@hpra.ie**.

Pharmacovigilance Information Day - 21 November

Human Medicines: Find out more about the impact of the implementation of the revised EU pharmacovigilance legislation for stakeholders by attending the HPRA Pharmacovigilance Information Day on Friday, 21st November 2014 at the Crowne Plaza Hotel, Santry, Dublin 9 (close to Dublin Airport and the M50 motorway). For details and booking, visit our website at: **HPRA Pharmacovigilance Information Day - 21 November 2014.**

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Wholesale Distribution Conference 2014 - 11 November

The HPRA will hold a conference for wholesale distributors of medicinal products on Tuesday 11 November 2014 at the Crowne Plaza Hotel in Santry. Full details of the programme, including details on how to register, have been announced on the HPRA website. Accordingly, those interested in attending this information day should check the 'News & Events Section' for details and updates (www.hpra.ie).

Those interested in attending this information day should register their places as large numbers of attendees are expected and places will be limited. It is planned to have topics which should be of general interest, potentially followed by a one-to-one 'Questions & Answers' sessions with inspectors. The one-to-one inspector 'Q&A' will be made via appointment at registration.

The general topics covered on the day will include a regulatory update encompassing:-

- GDP Updates (Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use)
- Protecting the Supply Chain

The HPRA is requesting suggestions for topics which the industry would like to see covered during the day (e.g. transport of medicinal products, controlled drugs, precursor chemicals, cold chain medicinal products, exempt medicinal products etc.).

Questions may also be submitted in advance of the information day to compliance.infoday@hpra.ie and these may be addressed through the presentations or separately in a panel discussion.

The HPRA will hold a conference for wholesale distributors of medicinal products on Tuesday 11 November 2014 at the Crowne Plaza Hotel in Santry.

GMP Conference 2014 - 12 November

The HPRA will hold a conference, primarily for manufacturers of active substances and medicinal products, on Wednesday 12 November 2014 at the Crowne Plaza Hotel in Santry. Full details of the programme, including how to register, have been announced on the HPRA website. Accordingly, those interested in attending this conference should 'Register for Alerts' on the HPRA website or periodically check the 'News & Events Section' for updates.

Once details are announced, those interested in attending this conference should reserve places at an early stage as a large number of attendees is expected and places will be booked quickly.

Milk Thistle (Silybum Marianum)

Milk thistle fruits (known as "seeds") contain the complex substance silymarin as the active principle, which is itself a mixture of several components. Traditionally it has been widely used for disorders of liver, spleen and gall bladder and for other gastro-intestinal conditions. Current interest is focussed on the hepatoprotective, antioxidant and choleretic properties. Consequently, milk thistle products have been widely supplied in Ireland in health stores as a food supplements. The HPRA has not been convinced that Milk Thistle has a valid place as food supplement since it is aware of the potential pharmacological effects of this plant and in particular its active principle silymarin on liver function.

Over the last year or two we have been looking into this matter in the context of widespread usage of this plant substance to see whether a dose threshold could be established below which pharmacological activity might be held not to be likely. We eventually came to the conclusion that the data which are available in the public domain are not sufficiently powerful and robust to demonstrate a clear pharmacological activity at doses below 200mgs of silymarin daily. However, the HPRA remains convinced that there are a wealth of data at daily doses of 200mgs silymarin or more to be convinced of pharmacological activity at this level. Consequently, the HPRA has decided to make a public statement about this position to allow greater clarity of the situation regarding unregulated products containing Milk Thistle which may be present on the Irish market and which should be regulated therefore as foods or medicinal products depending on the dose.

HPRA has not been convinced that Milk Thistle has a valid place as food supplement since it is aware of the potential pharmacological effects of this plant and in particular its active principle silymarin on liver function.

This new determination allows a much simpler approach such that products with a maximum daily dosage of less than 200mgs silymarin equivalent may continue to be marketed in Ireland as food supplements provided no medicinal claims are made for these products and that the products are notified to the Food Safety Authority of Ireland and labelled under food labelling legislation in the usual way. Products at doses or daily doses of 200mg or more are considered to be medicines and cannot legally be marketed in Ireland without the prior approval of the HPRA in the form of a marketing authorisation or traditional herbal medicines registration.

If there is any uncertainty about whether specific products are regarded as medicinal products enquiries can be made via **classification@hpra.ie**

Re-submission of ICSRs to HPRA

Please note that there is no requirement for MAHs to resubmit cases to the HPRA that have been processed by the company on the basis of ICSRs provided to them by the HPRA only. This creates a reporting and processing burden for both the MAH and the HPRA, with the potential to also lead to the generation of duplicate cases. As such, please note that it is not necessary to resubmit such cases to the HPRA, unless the MAH has become aware of additional case information from another source.

Guide to Clinical Trial Applications update

Please note that an updated version (8.0) of the **Guide to Clinical Trial Applications** was recently published on our website (**www.hpra.ie**). Updated information included a minor change to further clarify SUSAR reporting arrangements (Section 7.1).

Regulation of Clinical Trials on Veterinary Medicines in Ireland

As of 11 August 2014, the HPRA was designated as the competent authority for the granting of 'research licences' for studies on veterinary medicines used for clinical field trials that were previously regulated by the Department of Agriculture, Food and the Marine (DAFM) under SI No. 786 of 2007. Such studies, carried out to support the authorisation of a veterinary medicine in accordance with Directive 2001/82/EC, must now be licensed by the HPRA, in accordance with SI No. 361 of 2014.

The HPRA is obliged to consult with the DAFM before reaching a decision to grant a licence. The HPRA is discussing the precise arrangements for the procedure with the DAFM so as to minimise the time needed for approval. Pending the elaboration of HPRA application specific forms over the coming weeks, the application forms previously required by the DAFM can be used by stakeholders to support applications for such trials being made to the HPRA. The fees for such applications remain unchanged. Updated information will be available on the HPRA website. Queries in relation to this matter should be sent to **vetinfo@hpra.ie.**

The net effect of this change is that the HPRA is now the competent authority in respect of all studies carried out in animals in this country

The net effect of this change is that the HPRA is now the competent authority in respect of all studies carried out in animals in this country, whether pre-clinical studies (being regulated under Directive 2010/63/EU), or clinical field trials (regulated under Directive 2001/82/EC, as amended).

Marketing Status / Sunset Clause

The HPRA would like to remind Marketing Authorisation Holder's (MAH's) that under the European Communities (Animal Remedies) (No. 2) Regulations 2007, you are required to notify the HPRA of changes in the marketing status of authorised veterinary medicinal products. Under the Regulations, the marketing authorisation ceases to be valid if a product is either not marketed at all for a period of three consecutive years or has been marketed but marketing ceases for a period of three consecutive years. This provision is termed the 'sunset clause'. In exceptional circumstances and for public health or animal health reasons, non-marketed products may qualify for an exemption from the sunset clause.

MAH's are required to advise the HPRA of any product that has not been marketed for a period of three consecutive years and for those products not marketed, what if any exemptions apply. The Regulations do not specify the situations in which an exemption may apply. It is up to the MAH to justify why the sunset clause should not apply. For those products where an exemption is applicable, the MAH is obliged to reconfirm the exemption status every 3 years following first notification, unless the product's marketing status changes during the 3 years, in which case the HPRA should be notified at that time. For those products not marketed and not subject to exemption, the authorisation will cease to be valid.

As there are a number of products where the HPRA has not received an update to its marketing status, we are reminding MAH's of their obligation to provide us with this information in a timely manner.

For more information on this topic, please refer to our Guide to Notification of Marketing Status of Veterinary Medicines, which can be found on our website at **www.hpra.ie**.

Veterinary Medicines

Publication of Public Assessment Reports for Veterinary Medicines on the HPRA website

To coincide with the launch of the new HPRA website in July, the Veterinary Sciences Department is undertaking a project to enable automatic publication of Public Assessment Reports onto the HPRA website. This involves a change in our workflow system and minor revisions to the format of the reports. Whilst the project is on-going, not all Public Assessment Reports will be available on the website, but they may be requested at **vetinfo@hpra.ie**.

Over the coming months, all Public Assessment Reports will be migrated to the workflow system and uploaded to the website in the new format. In some cases, this will require the creation of a new case on the workflow system with the result that, when published, the case reference number (CRN) on the SPC and Public Assessment Report will not correspond with the last CRN that resulted from a regulatory activity (renewal, variation etc).

Personnel Changes

Dr. Rhodri Evans resigned from the Advisory Committee for Veterinary Medicines in July, consequent to his taking up an appointment in the UK.

Ms. Louise Flanagan, Administrative Officer, left the Veterinary Sciences Department on 6 August and has moved to the human medicines Pharmacovigilance Section. Louise has been replaced by Ms. Valerie Halpin.

We wish everyone well in their new roles.

Compliance

Biofilm and other Contamination Control Strategies in the Manufacture of Sterile Medicinal Products

Over recent years we have, during inspections of manufacturers of sterile medicinal products, highlighted concerns related to risks associated with biofilms and contamination from environmental sources, including both microbiological, pyrogen and particulate sources.

Contd.

In relation to minimising the risk of microbiological contamination, relevant GMP guidance includes:

- The principle of Annex 1 ('Manufacture of Sterile Medicinal Products') to the EU GMP Guide states *'The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination.'*
- Paragraph 125 of Annex 1 specifies that *'The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured.'*
- The principle of Annex 2 ('Manufacture of Biological Active Substances and Medicinal Products for Human Use') states *'…quality risk management (QRM) principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination.'*

Until relatively recent times the perception of microbiological contamination has been as individual planktonic (free floating) organisms. Evidence suggests that biofilms are actually the preferred mode of microbial growth, with sessile (fixed / immobile) cells outnumbering planktonic organisms by several orders of magnitude. The planktonic model has been the basis for many control strategies that have been in existence for many years and most systems used for detection of microbial contamination focus on planktonic cell detection. This approach tends to be too narrow in order to adequately detect and control biofilms. Therefore, contamination control strategies should include the risk posed by biofilm formation.

In relation to visual inspection of finished parenteral products for the presence of particulate contamination and other defects, the HPRA has encountered a number of significant issues.

Annex 1 states *'Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals.'*

It is expected that a system for 100% inspection of all filled parenteral products is employed by the manufacturer. Such a system, whether manual or automated, should be appropriately evaluated and qualified to ensure that it is sufficiently sensitive to permit identification and rejection of defects. The effectiveness of these systems should be assessed routinely.

In order to minimise the risk of microbiological and particulate contamination, the HPRA is taking a proactive approach and, if not already in place, is seeking the development of appropriate process risk assessments and control strategies by manufacturers of sterile medicinal products.

Contamination control and steps taken to minimise the risk of contamination from microbial and particulate sources are a series of successive linked events / measures. However, we have found that these are typically assessed, controlled and monitored in isolation. In order to be maximally effective a contamination control strategy should integrate all of these measures to ensure a more comprehensive approach is taken with respect to prevention and control of microbiological contamination and of particulate and pyrogen contamination.

The development of such strategies requires thorough process knowledge. Sources of contamination not only include microbiological sources and cellular debris (e.g. pyrogens / endotoxins) but also particulates sources (glass and other visible and sub-visible particles).

Elements to be considered within such a control strategy should include:

(Note: this is not an exhaustive list)

- Personnel
- Design – plant, process
- Equipment and facilities
- Utilities
- Preventative maintenance – Maintaining equipment and premises to a standard that will not add significant risk from a contamination viewpoint
- Cleaning / sanitisation
- Raw Materials Control – including in-process controls
- Process qualification
- Monitoring systems - include an assessment of the feasibility of the introduction of more modern and sensitive methods of detection
- Prevention – Investigations / CAPA / Root cause determination and the need for more robust investigational tools

The strategy should take into consideration all aspects of contamination control and its life cycle.

Guide for Retail Sale of Traditional Herbal Medicinal Products: Public Consultation

The HPRA wishes to inform stakeholders that a 'Guide for Retail Sale of Traditional Herbal Medicinal Products' will be made available for public consultation during October 2014. This guide can be used by retailers in order to identify the Traditional Herbal Medicinal products that they can sell. In addition, the guide will assist retailers in determining which herbal products may be medicinal and, as such, require prior authorisation or registration with the HPRA before being sold. This guide may also be of use to other stakeholders.

The guide comprises

- a decision tree in the form of a flowchart and explanatory text that are to be used in conjunction with three lists which together provide a stepwise approach that assist in determining whether a herbal product can be sold. These lists are;
- **List A** which identifies those Traditional Herbal Medicinal Products (THMPs) that can be sold by retailers,
- **List B** which identifies those herbal substances restricted to prescription control when used in products for oral consumption and
- **List C** which identifies those herbal substances, when presented for oral consumption or topical use, may render that product a medicinal product.

The consultation process will be focused on obtaining feedback from stakeholders on the ease of use of the guide. It is expected that the consultation process will commence during the week of Monday 06 October 2014 for a defined period. Accordingly, stakeholders are advised to monitor the HPRA website **www.hpra.ie** or alerts received from the HPRA so that you can provide comment.

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