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Human Medicines

Genotoxic medicinal products and duration of contraceptive use for male and female patients

Implementation of Safety Working Party (SWP) recommendations – action required

Following on from [Safety Working Party \(SWP\) recommendations](#) on the duration of contraceptive use in male and female patients after cessation of treatment with a medicinal product which is genotoxic (updated March 2022), marketing authorisation holders (MAHs) are reminded of the need to review and update the product information of their medicinal products where necessary. This advice applies to medicines used in the context of clinical trial applications, as well as authorised medicinal products.

It has been clarified that the scope of the SWP recommendations (regarding genotoxic medicinal products and contraception duration period) apply to any genotoxic active substance, regardless of its therapeutic indication. However, the recommendations do not apply to active substances whose mechanism of genotoxicity is known to have a threshold that is not expected to be reached in patients.

It is part of the MAH's responsibility to determine the genotoxic potential of their medicinal product(s) and MAHs should take account of the recommendations, along with the totality of clinical experience to date, when reviewing the need to update their product information. The most current data should be used to determine the genotoxic potential of a medicinal product.

Any update to the product information arising from these recommendations should be consistent with information provided in section 5.3 of the authorised SmPC (which should inform on whether the active substance does or does not have genotoxic potential). As previously outlined by CMDh, MAHs are reminded of the relevance of [ICH Guideline S2 \(R1\) Genotoxicity testing and data interpretation for pharmaceuticals intended for human use](#) to assess the genotoxic potential of an active substance.

The MAH can also consider other sources, such as published literature and any other relevant data from non-clinical studies.

Further guidance on updating the contraception duration period, taking into account the half-life of a medicinal product, is provided in the SWP recommendations.

In this context, where a calculation of the duration of contraception is submitted as part of this update, an assessment will be required. These cases should be submitted as type II variations under classification C.I.4, using worksharing

procedures where possible. If the calculation is taken over from another product and no new calculation of the duration of contraception is required, a type IB C.1.z variation is sufficient.

The following general wording can be used as a basis for the implementation of the SWP recommendations in section 4.6 of the SmPC, although some product-specific adjustments may be necessary based on the MAH's analysis.

Wording for SmPC section 4.6: Fertility, pregnancy and lactation

Women of childbearing potential/contraception in men and women

Due to the genotoxic potential of active substance name (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with product name and for X months following completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving product name and for Y months following completion of treatment.

The package leaflet should be updated accordingly.

References

1. [SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug](#)
2. [Report from the CMDh meeting 22-23 February 2022](#)
3. [CMDh press release July 2021](#)

Contamination of (traditional) herbal medicinal products with pyrrolizidine alkaloids – update

Pyrrolizidine alkaloids (PAs) are naturally occurring, hepatotoxic constituents present in many plants. A number of reports have shown the presence of these alkaloids in herbal products, although they do not contain plants that produce PAs. It is reasonable to assume that this is caused by contamination with weeds during harvesting. In principle, contamination of herbal substances with PA-containing weeds

should not occur at all due to existing requirements on pharmaceutical product quality and compliance with GACP/GMP. The fact that it occurs is a serious issue and highlights the necessity of further measures to reduce contamination levels to as low as reasonably achievable (ALARA).

A public statement on the contamination of herbal medicinal products with pyrrolizidine alkaloids was published by the EMA's Committee on Herbal Medicinal Products (HMPC) in May 2016. Since then, based on the review of available data, HMPC published a revised public statement [EMA/HMPC/893108/2011 Rev. 1](#) in July 2021. Some of the main points in this statement include:

- An acceptable oral intake equivalent to 1.0 µg/day for an adult can be used as the limit for PAs. The amount must be adjusted for children based on bodyweight.
- Confirmation that regulatory specifications for herbal medicinal products (HMPs) should include controls for PAs, referencing the posology of the HMP. The most appropriate stage for testing to take place should be considered; i.e. at the level of the herbal substance, the herbal preparation or the herbal product.
- Recommendations on measures to avoid or reduce PA contamination in HMPs.

Having considered the updated statement and reviewed available data, the HPRA is concerned about the risk of contamination with PAs in HMPs. The HPRA requests that all herbal product authorisation and registration holders introduce appropriate measures and specifications for their products at an appropriate control point to ensure that HMPs will comply with the above limit (note: for a combination product containing more than one herbal substance, the sum of PAs should not exceed 1.0 µg/day, relative to the maximum daily dose of the product). The herbal preparation and/or herbal product specifications should be updated accordingly by means of a variation. Any alternative proposals must be robustly justified.

Furthermore, the HPRA wishes to highlight the following herbal substances that are of particular concern: St. John's wort, chamomile, dandelion leaf and root, horsetail, lady's mantle, lemon balm, liquorice root, nettle, passion flower, peppermint,

sage and thyme. For these substances, it is expected that if PA specifications are not already in place, that they be included by variation as soon as possible. Please note that this list of herbal substances has been updated since previous newsletter articles on PAs and may be updated in future as more data are gathered. Furthermore, all herbal preparations of plants with biosynthesised PAs must be tested for PA content.

Brexit – products availing of a derogation under Directive 2022/642/EC

On 20 April 2022, Directive 2022/642/EC of the European Parliament entered into force. This Directive amends Directives 2001/20/EC and 2001/83/EC regarding derogations from certain obligations concerning certain medicinal products for human use made available in the United Kingdom in respect of Northern Ireland, and in Cyprus, Ireland and Malta. The objectives of amending Directive 2022/642/EC are to facilitate continued supply of medicinal products and to maintain a high level of public health protection. In order to ensure uniform application of Union law in all Member States, the derogations applicable in Cyprus, Ireland and Malta will apply until 31 December 2024.

To ensure transparency, the Directive stipulates that the competent authorities of Cyprus, Ireland and Malta and the United Kingdom in respect of Northern Ireland publish on their website a list of the medicinal products marketed to which these derogations have been granted.

The HPRA has compiled the [list of products](#) availing of the derogations as permitted in Directive 2022/642/EC. Products are identified by product name, PA number and MAH. This list is required to be updated on at least a six-monthly basis.

MAHs to whom derogations have been granted, are required to check the details of this list below and to contact the HPRA at brexit@hpra.ie when a particular derogation is no longer required, specifying which derogation is no longer needed. When full regulatory

compliance has been achieved, please contact the HPRA and the product can be removed from the list. Please note that products on the list must not be onward supplied outside of IE.

Applicants who in exceptional cases, wish to newly apply the derogations outlined in the Directive must engage with HPRA in advance as follows, to avoid invalidation of their new application, variation or renewal submissions to MS.

Applicants must fill in a justification template outlining their [request for a justifiable case](#), in order to proceed with a variation/new application /renewal which includes a UK (GB) site on a licence. Where the HPRA agrees to such a justification, the HPRA will revert with the completed template which must then be included by the applicant in their submission to the RMS (in Module 1). After approval of the relevant new application/variation/renewal procedure and at the time of marketing of the new product in IE or for existing products, a second step is required to formally [request a derogation](#) from the HPRA and to include this product on the published list held by the HPRA.

Clinical Trials Regulation – reminder of EMA and HPRA supports and key timelines

On 31 January 2022, the [Clinical Trials Regulation](#) came into effect in the EU. Among the primary aims of the Regulation is to increase the harmonisation and transparency of clinical trials submitted in the European Union.

Clinical Trials Information System (CTIS)

To facilitate the submission and assessment of clinical trials in the EU, the Clinical Trials Information System (CTIS) was created. To support understanding of the new system, the EMA has created an extensive catalogue of [training material](#) for users to access. In addition to this material, sponsors can avail of a more thorough understanding of the system by attending EMA bitesized talks (where aspects of the

system are demonstrated live) or EMA-run CTIS walk-in-clinics (where questions can be raised regarding the functionality of the system). Information regarding these sessions can be located [on the EMA webpage for events](#).

To support the increased transparency for clinical trial applications in the EU that is the cornerstone of the Regulation, the CTIS public website was also established. The public website reflects information on clinical trials that have been submitted under the Regulation, with some exceptions. Stakeholders wishing to review the information that is now publically available can do so by accessing the [CTIS public website](#). Included on the website is information relating to the first trial authorised in Ireland under the CTR on 5 May 2022. Stakeholders wishing to obtain more information in relation to clinical trials submitted in the EU can also review the recently published [EMA key performance indicators](#), which were released to coincide with the International Clinical Trials Day on 20 May 2022.

Application information

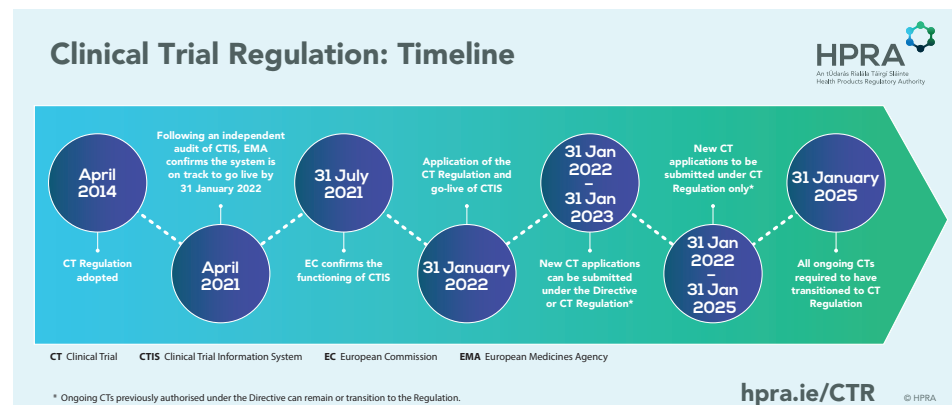
To further support sponsors who currently wish to submit under, or transition to, the Regulation in Ireland the HPRA has created a dedicated [Clinical Trials Regulation page](#) on their website. Among the resources available on the webpage is a link to the Clinical Trials Regulation webinar, which was run in conjunction with the National Office for Research Ethics Committees from the 22 to 25 November 2021, as well as the HPRA [Guide to Clinical Trials Conducted under the Clinical Trials Regulation \(CTR\) in Ireland](#). The HPRA has also established a dedicated HPRA Clinical Trials Regulation mailbox to assist in addressing questions relating to the submission of trials in Ireland under

the Regulation. Stakeholders can email questions to ctreg@hpra.ie. Additionally, sponsors are directed to the dedicated Clinical Trials Regulation webpages of both the [European Medicines Agency](#) and the [European Commission](#).

Key timelines

The new Regulation will replace the current European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, SI No 190 of 2004 which transposed into law the provision of Council Directive 2001/20/EC). A three-year transition period is now underway to allow sponsors of clinical trials time to adapt. During this transition period, sponsors can continue to submit initial applications under either the Directive or the new Regulation. Sponsors are reminded that this transition period finishes on **31 January 2023**. **From 31 January 2023, all new clinical trial applications will be required to be submitted under the Regulation** while clinical trials authorised under the Directive are entitled to remain under the Directive until the end of the transition period (31 January 2025).

Although the three-year transition period has been established, sponsors are strongly encouraged to consider engaging with the Regulation as soon as possible and to consider when they propose to both submit and/or transition clinical trials. Sponsors should give careful thought to submitting, and transitioning, clinical trials under the CTR at their earliest convenience and should, where possible, avoid waiting until the end of the respective transition stages. Sponsors who have any concerns, or questions, relating to submitting under the Regulation in Ireland are welcome to engage on these points with the HPRA.



Please click on the image above to view a larger version.

Veterinary Medicines

Update on implementation of requirements of Regulation 2019/6

The HPRA has provided detailed updates on progress of the [implementation of Regulation 2019/6 on our website](#). We have held a number of webinars to address specific concerns of stakeholders and [webinar materials](#) are available to view on our website.

Article 34 of Regulation 2019/6

Article 34 relates to the classification of a veterinary medicinal product either under veterinary prescription or not under veterinary prescription. The Committee for Veterinary Medicinal Products (CVMP) adopted a concept paper on the elaboration of guidance for the application of Article 34 of Regulation (EU) 2019/6 (EMA/CVMP/65618/2022) for a one-month period of [public consultation](#) and expects to develop a guideline on this matter before the end of 2022. This guideline is expected to set out the principles for deciding whether a medicine should be subject to prescription or not.

Separately, discussions at the level of national competent authorities have started in relation to whether the requirement for prescription will apply to existing products in the Community. Depending on the outcome of the discussions, the matter may have significant implications for stakeholders dispensing or marketing the products concerned.

New national legislation on veterinary medicines

The HPRA meets with the Department of Agriculture, Food and the Marine (DAFM) on a periodic basis. From our last meeting, the DAFM advised that a number of separate legal acts are currently being developed:

1. An SI, which corrects some errors in SI No 36 of 2022, especially regarding certain functions of the national competent authority.
2. A new SI which temporarily restores the national methods of supply (CAM, LM, PS, POM(e)), which had been abolished in January when SI No 786 of 2007 was revoked. This new legislation is expected imminently.
3. A new bill, which sets out a framework for the Minister to develop further specific national legislation for the regulation of veterinary medicinal products. This bill will now include veterinary medicinal products, medicated feeds and fertilisers. Both Houses of the Oireachtas will consider the bill over the next period.

Update on antiparasitic veterinary medicinal products for food-producing animals

The HPRA notes the announcement on 9 May 2022 by the Minister for Agriculture, Food and the Marine of an extension of the transition period for the requirement of a veterinary prescription to dispense antiparasitic medicines until 1 December 2022. This development does not have a material impact on the labelling requirements for the products involved, which now bear the prescription-only medicine designation, in compliance with the HPRA report on this matter.

HPRA Veterinary Department – changes in responsibility and personnel

Having completed two terms as CVMP Chairman, Dr David Murphy returned to HPRA duties on 6 June 2022. Together with Dr Paul McNeill, he will take up the role of Veterinary Assessment Manager, with responsibility for the safety and efficacy assessment of veterinary medicines as well as for their pharmacovigilance compliance. Dr McNeill will take up the role as national CVMP member in July.

A number of colleagues have left the HPRA in recent months, including Dr Aideen Brownen, Dr Andres Garcia-Campos and Dr Aoife Lordan. We wish the colleagues well in their new roles.

European Commission call for data on salicylic esters used in cosmetic products

The European Commission has issued a call for data in order to **identify the various salicylic esters used in cosmetic products that are metabolised to salicylic acid** in the framework of Regulation (EC) 1223/2009.

In 2021, the Scientific Committee on Consumer Safety (SCCS) adopted their final Opinion on homosalate and methyl salicylate whereby the SCCS raised concerns over the potential overexposure of consumers to salicylic acid from various salicylates used in cosmetic products.

The European Commission intends to request the SCCS to perform a safety assessment, specifically on the aggregate exposure to salicylic acid from salicylic esters used in cosmetic products. In order to prepare a mandate to the SCCS, interested parties have been invited to submit any relevant information and data in order to identify the various salicylic esters used in cosmetic products that are metabolised to salicylic acid.

More information in relation to the requirements for the submission of data and the background to this topic is available on the [European Commission website](#).

The last date for submission of relevant information to the European Commission is 06 January 2023.

Keeping up to date with legal changes to ingredients in cosmetic products

Cosmetic products on the Irish market must comply with European Regulation (EC) No. 1223/2009. This regulation contains Annexes that include lists of substances either prohibited or restricted in cosmetic products:

- Annex II: substances prohibited from cosmetic products;
- Annex III: substances only permitted in cosmetic products if they meet the restrictions and conditions stated;
- Annex IV: substances permitted as colourants in cosmetic products;
- Annex V: substances permitted as preservatives in cosmetic products;
- Annex VI: substances permitted as UV filters in cosmetic products.

The annexes are updated regularly by the publication of amendments to Regulation (EC) No. 1223/2009. Manufacturers, responsible persons (RPs), importers and distributors should refer to the amendments to find out if a change to the list affects a cosmetic product on the EEA market.

These amendments are published on the [European Commission website](#).

Receiving notifications about legal changes to ingredients

If you wish to receive notifications when such amendments are published, you can sign up to the HPRA alert system. There are [instructions on the HPRA website](#) on how to do this. If you have previously signed up to receive HPRA alerts, please check our website instructions to ensure your subscription preferences cover these alerts.

Please see the [Cosmetics section of the HPRA website](#) for further information regarding cosmetic products.

Presentations from GDP and GMP conferences

The HPRA held Good Distribution Practice (GDP) and Good Manufacturing Practice (GMP) conferences during May 2022. The conferences took place as in-person events at the Radisson Blu Royal Hotel, Golden Lane, Dublin 8. We would like to thank everyone who attended the conferences.

The GDP conference covered key current topics of interest and provided an insight into GDP inspection trends with a detailed focus on the most commonly identified deficiencies. The GMP conference provided insight into key topics, quality defects and deficiency trends observed by the GMP inspection and market compliance teams.

For conference attendees and those who missed out, the [presentation slides](#) from both conferences are available on our website. The presentation slides with voiceovers will also be available shortly.

Stakeholder consultation – Registration of processes exempted under Article 61(5) and applicable requirements under Article 61(6) of the Clinical Trials Regulation

Article 61(5) of the Clinical Trials Regulation (CTR) (EU Regulation 536/2014) provides an exemption from the requirement to hold a manufacturer's authorisation for the following processes, where they are carried out in a hospital, health centre or a clinic participating in the clinical trial:

- a) Re-labelling or re-packaging of an investigational medicinal product (IMP);
- b) Preparation of radiopharmaceuticals used as diagnostic IMPs;
- c) Preparation of an IMP in accordance with a doctor's prescription or in accordance with a pharmacopoeial monograph.

Register of exemptions

The European Union (Clinical Trials on Medicinal Products for Human Use) (Principal) Regulations 2022 (S.I. No. 99 of 2022) defines, at national level, where the above processes can be performed and by whom. These national regulations also describe the requirement for these processes to be included on a 'Register of Exemptions' which is maintained by the HPRA.

A HPRA set of 'Questions and Answers on Article 61(5) Processes' has been drafted and includes a number of questions and answers to assist in identifying which processes would be required to be included on the Register of Exemptions.

The HPRA will publish an application form and associated guidance to be used for the purpose of registering processes which fall within scope of Article 61(5).

Appropriate and proportionate requirements that should apply to exempted processes

Under Article 61(6) of the CTR, the processes may also be inspected against appropriate and proportionate requirements. The Minister may publish these requirements as provided for in Regulation 30(1)b of SI 99 of 2022.

The HPRA is proposing that the [PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments](#) would be the appropriate core guidance for these processes and there are also questions and answers dealing with its application to the inspection process.

Stakeholder consultation

Through a [public consultation](#), we are seeking feedback from stakeholders on the draft 'Questions and Answers' document on Article 61(5) processes. We are also seeking feedback on our proposal to refer to the 'PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments' as the core guidance for the appropriate and proportionate requirements for the exempted processes.

Documents for stakeholder consultation

Comments are invited from stakeholders on the following:

1. The use of the PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments as the basis for the appropriate and proportionate requirements for exempted processes carried out under Article 61(5) of the CTR;
2. Questions and Answers on Article 61(5) Processes.

The [consultation document](#) is on the HPRA website. Any comments should be submitted as per the instructions in the consultation document to Article61.5@hpra.ie by the deadline of **22 August 2022**.