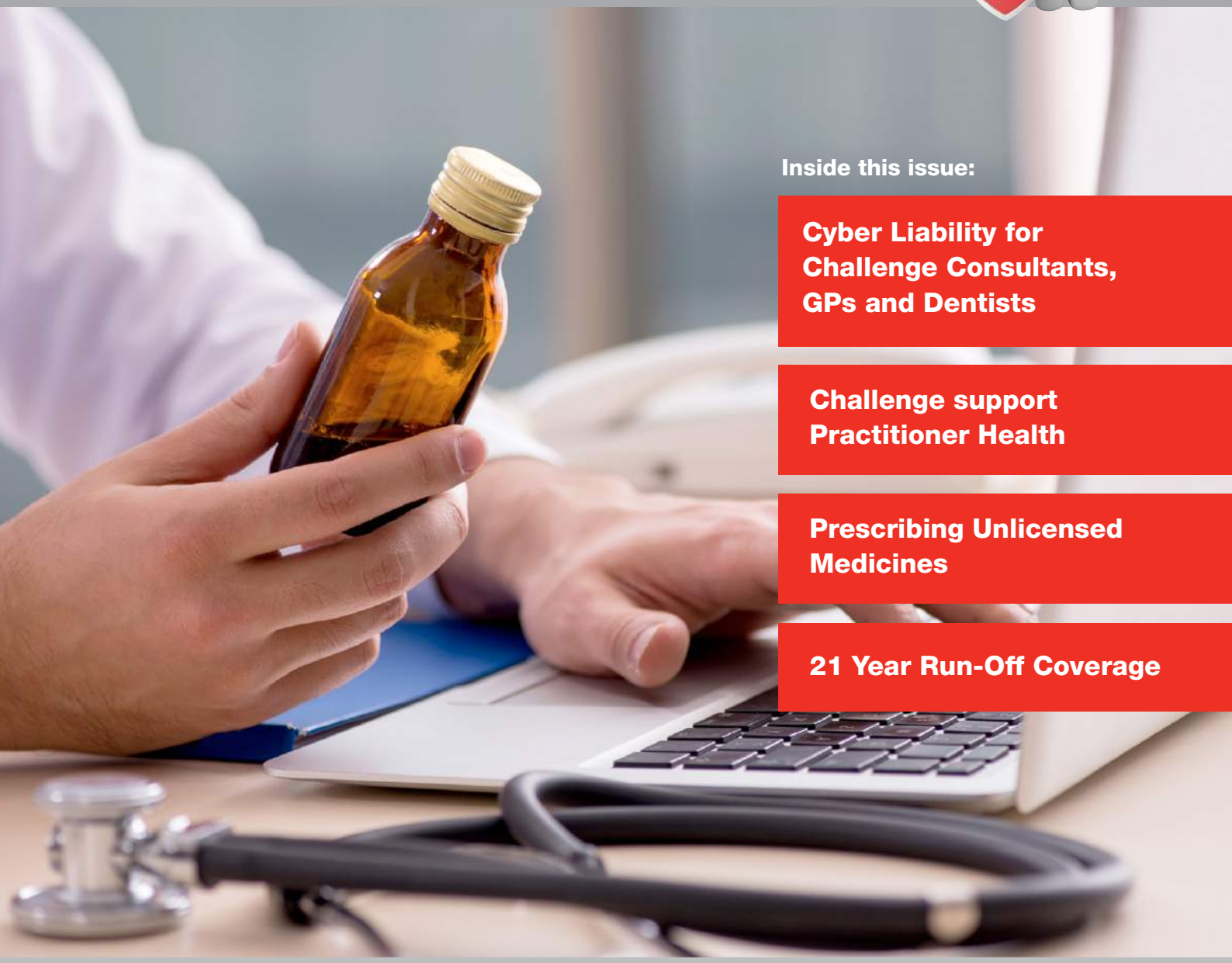
Issue 12 • July 2021

Challenge Medical Indemnity



Inside this issue:

24 Hour 7 Day Medico-Legal Helpline

The number of the Helpline is
01-8395942

Client Online Portal

All Challenge clients also have 24 hour, 7 day communication channel and access to their insurance documents via our online client portal at **www.challenge.ie**

To all our valued clients and partners,

I hope all is well with you and your family at this time.

We are pleased to bring you issue 12 in our newsletter series.

It has been a busy period for us at Challenge HQ as we complete another round of successful annual negotiations with your insurers. The broking teams have been busy securing significant additional coverages whilst maintaining competitive premiums across the range of Challenge indemnity products. In the main we are happy to report that rates have remained largely consistent again this year which is in keeping with our commitment to delivering you comprehensive and competitive indemnity solutions.

Prior to the recent HSE cyber attack we had been looking at the ever increasing exposure to our healthcare professionals in this area. We are delighted to confirm that Cyber Liability coverage has been included as standard on our individual Consultant, GP and Dental Indemnity wordings. You will see this on your next renewal quotation so don't hesitate to contact us with any queries in relation to the significant coverage which we have secured for you here.

I would also like to take this opportunity to remind our clients and new applicants of the technical nature of your indemnity coverage. There are legal and regulatory requirements which the terms of your coverage must meet. With that in mind I would urge you to seek all indemnity related advices directly from the Challenge broking team who are both qualified and experienced to ensure you are receiving the most up to date and most accurate information which is best for you and your practice.

In this edition we are pleased to bring you an article on prescribing unlicensed medicines which is an area generating a number of queries recently. We were delighted when Dr Patrick Salmon agreed to share his comprehensive knowledge and thoughts on this matter with us.

We are also pleased to announce that Challenge are a supporting partner of Practitioner Health which is a confidential telephone line and email contact point for an expert clinical advice service. Please do not suffer in silence, this is an independent service with an experienced team there waiting to take your call in the strictest of confidence.

Wishing you a sun filled and enjoyable summer.

David Walsh
Managing Director
Challenge.ie

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Cyber Liability	Security and privacy liability	Network interruption expenses
Event support expenses	Privacy regulatory defence and penalties	Network extortion

PractitionerHealth

LOOKING AFTER YOUR WELLBEING IN CONFIDENCE

challenge

Challenge are pleased to become a supporting partner of Practitioner Health.

This is a service which we have wanted to bring to our clients and were delighted to learn that an established programme was already up and running. Practitioner Health provides appropriate care and support for health professionals in Ireland who may have mental health issues such as stress, anxiety or burnout or who may have a substance misuse problem. It is fully independent and separate from insurers, regulatory bodies and employers. It has been endorsed by Memorandum of Understanding by the relevant professional councils and is supported by representative organisations and training bodies.

The Practitioner Health Matters Programme operates on a not-for-profit basis and Challenge are proud to be a supporting partner. It has been an unprecedented year and we would encourage our medical and dental practitioners to avail of this professional service if they feel the need to do so.

Please do not suffer in silence

– email us on **confidential@practitionerhealth.ie**

or call us on **(01) 278 9369**

Support, in Confidence

Prescribing Unlicensed Medicines

Patrick Salmon

Much pharmaceutical legislation in the EU relates to prescription of licensed medicines.

Prescribers can prescribe authorised products according to the conditions 'on-label' or outside those conditions ('off-label'). They can also prescribe unauthorised products, even if they are unlicensed.

Prescription of unlicensed medicines does arise in particular clinical situations and requires a careful consideration of the benefit/risk of use of the medicine in a particular patient in a particular situation. It is also sometimes necessary to prescribe a medicine off label i.e., prescribing is not in compliance with the Summary of Product Characteristics ("SmPC").

In order to examine these issues, we first need to address a number of questions.

What is product information?

Product information is the information (relating to a specific product) that has been agreed between the assessing regulatory authority and the company seeking marketing authorisation. In the EU, product information usually means the SmPC addressed to health care professionals, and the Patient Information Leaflet (PIL) based on the SmPC and addressed to the patient.

The structure of the Summary of Product Characteristics is laid down in Directive 2001/83/EC, as amended, and the content is determined by the data on the product which are contained in the application dossier. A comprehensive guideline known as the **European Commission Guideline on the Summary of Product Characteristics** provides advice on how to draw up an SmPC and is available on the EC website[1]. The SmPC contains a mixture of administrative and scientific/clinical information. Clinicians are mainly interested in Section 4 (Clinical Particulars) of the SmPC, especially Sections 4.1 (Therapeutic Indications) and 4.2 (Posology and Method of Administration).

Marketing Authorisation Holder (Section 7 of the SmPC)

The marketing authorisation holder is the name of the pharmaceutical company who owns the licence to sell the medicine.

What is a Marketing Authorisation?

A marketing authorisation (MA), also known as a product authorisation, provides assurance that a medicine conforms to agreed standards and that a product has been manufactured, stored and distributed in compliance with the required standards. A licensed medicine is identified by the presence of a licence number, and this is included in the authorisation which in Ireland is issued by the Health Products Regulatory Authority or by the European Commission.

The existence of an MA guarantees the quality, safety and efficacy of medicinal products and helps to protect the prescriber from liability if adverse effects arise from the use of the drug.

[1] https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

Prescribing Unlicensed Medicines (Continued)

What are Licensed Medicines?

A licensed medicine is one that has a marketing authorisation and so is considered to meet acceptable standards of efficacy, safety, and quality. A licensed medicine has been assessed for efficacy, safety, and quality; has been manufactured to appropriate demonstrated quality standards, and when placed on the market is accompanied by appropriate product information and labelling.

What are Unlicensed Medicines?

Unlicensed medicines are products that do not have a marketing authorisation. This means that such a product may not have been assessed for quality, safety or efficacy.

There may be many reasons why a product does not have an authorisation. A company may not have sought a product authorisation because the cost of an authorisation could be considered excessive and uneconomical, or because they consider that the level of evidence available in support of licensing is insufficient to satisfy regulatory requirements.

Who can prescribe?

A prescription is an instruction that authorises a patient to be issued with a medicine or treatment. It is issued by those legally entitled to prescribe such as a registered medical practitioner, or registered dentist or by a practitioner of equivalent status practising in another Member State. In Ireland, doctors, dentists and nurses may prescribe.

What is off-label prescribing?

Off-label prescribing refers to any intentional use of licensed products not covered by the terms of its marketing authorisation and therefore not in accordance with the SmPC. This includes prescribing for unlicensed indications, use of a different dosage, dosing frequency or duration of use, by routes and to patient groups not included in the licence (e.g., children instead of adults). It can also refer to use in situations where use is usually contraindicated.

Prescribing Unlicensed Medicines

There are clinical situations where the use of unlicensed medicines or use of medicines outside the terms of the licence (i.e., 'off-label') may be judged by the prescriber to be in the best interest of the patient on the basis of available evidence.

Off-label drug use can be influenced by several factors. A medication may not have been studied or approved for use in a specific population (e.g., paediatric, geriatric, or pregnant patients). The cost of performing adequate or appropriate clinical trials may mean that licensing would be uneconomical. This would apply especially in the case of medicines that no longer have patent protection.

A life-threatening or terminal medical condition may motivate a health care professional to give any treatment that is logical and available, whether approved or not. If one medication from a pharmacological class of drugs has approval, physicians may use other medications in the same class without specific regulatory approval for that use for the same indication. The branded formulation might not be approved for a specific indication, but other branded formulation may be approved.

In addition, if the pathologic or physiologic features of 2 conditions are similar, a physician may use a medication approved for 1 of these conditions for both (e.g., diabetes and metabolic syndrome; psychiatric diseases such as anxiety and post-traumatic stress disorder).

Clinical treatment regimens reflect clinical experience and may not necessarily consider regulatory/ licensed status of a medicine. In a 2017 paper, **'Off -label drug use in oncology: a systematic review of the literature',**[2] it was stated that "Off-label drug use in in-patients ranged from 18% to 41%. Among adult patients with cancer, 13%-71% received a minimum of one off-label chemotherapy. The main reasons for off-label drug use were 'drug unapproved for specific tumour' and 'modified drug applications'. Among adults, metastatic cancers and palliative care patients received the most off-label drugs. The off-label drug use unsupported by standard treatment guidelines or drug compendia was in the range of 7%-31%.

However, all healthcare professionals who prescribe off-label or unlicensed medicines must do so within their individual clinical competence and the professional codes and ethics of their statutory bodies. **The responsibility that falls on healthcare professionals when prescribing an unlicensed medicine or a medicine off-label is greater than when prescribing a licensed medicine within the terms of its licence.**

Prescribers should also consider the risks associated with using unlicensed medicines or using a licensed medicine off-label. These risks may include new adverse reactions; issues with product quality; or problems with product information or labelling (e.g., absence of information for some unlicensed medicines and potential confusion for patients or carers when the patient information leaflet is inconsistent with a medicine's off-label use).

[2] Saiyed et al, J Clin Pharm Ther 2017 Jun;42(3):251-258.

Prescribing Unlicensed Medicines (Continued)

The guidance from the Royal College of Ophthalmologists in **'Prescribing Unlicensed Medicines – A Brief Guide' (2018)** includes advice such as:

- Prescribe unlicensed medicines knowingly and after careful consideration
- Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy
- Document the reasons for choosing the unlicensed medicine in the patient's records.
- Ensure the patient is aware that the medicine is unlicensed and document in the patient records informed consent for the use of unlicensed medicines and also for off-label use when this is not routine, accepted practice
- Explain to the GP and/or other colleagues the recommendation for the use of an unlicensed product together with any requested supporting evidence, and to ensure that they have all necessary prescribing information. The full agreement of the patient's GP must be obtained before prescribing is transferred to ensure continuity of therapy. A GP is not obliged to prescribe in such circumstances.
- Review treatment if appropriate licensed medication becomes available.

NICE (UK)

In the UK, the National Institute for Health and Care Excellence (NICE) has produced evidence summaries for off-label or unlicensed medicines which summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They can be used to support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

General Medical Council (UK)

If considering prescribing unlicensed medicines, the UK GMC guidelines, **'Prescribing Unlicensed Medicines' (April 2021)**, provides a useful guide.

Implications of Use of Unlicensed or Off-Label Medicinal Products

- Doctors are free to prescribe approved medicines as they deem appropriate.
- However, prescribers have a duty in common law to take reasonable care and to act in a way consistent with the practice of a responsible body of their peers of similar professional standing and have evidence to support the use of medicines in an unlicensed or off-label manner. This may include using the medication for purposes not investigated or in patient groups not studied as part of the licence application. However, since all healthcare professionals have a duty of care to act in the best interests of their patients, the prescriber then accepts the liability normally assumed by the product licence holder.
- **The ultimate responsibility for prescribing any drug rests with the prescriber who signs the prescription, who is professionally accountable for her/his judgment.** Consequently, when prescribing an unlicensed or off-label product the prescriber is professionally accountable and personally responsible for any adverse consequences arising from its use. The manufacturer is only likely to be found liable if harm results from a defect in the product, thus putting a greater responsibility on individual prescribers and where applicable their organisation.
- The prescriber must have sufficient knowledge, information, or experience to be able to show they are acting reasonably and in the best interests of the patient.
- Since unlicensed products have not usually been subjected to the rigorous independent assessment of efficacy and safety applied to licensed products, their use may carry a higher level of risk for patients.
- Liability arising out of the use of the unlicensed or off-label medicinal product can include fault (or negligent liability) and strict liability. Strict liability is where the manufacturer is liable for a defective product under the **Consumer Protection Act or Product Liability Directive (EEC/85/374).** Fault liability is where a prescriber gives an unlicensed or off-label drug and prescribes or administers it negligently, fails to inform the patient of side effects or fails to obtain informed consent.
- In using an unlicensed or off-label medicine, the prescriber must act with reasonable care and skill. If they fail to do so, they may be exposed to claims in negligence.

Prescribing Unlicensed Medicines (Continued)

The EU and STAMP (Safe and Timely Access to Medicines for Patients)

The EU (see STAMP below) has examined this issue and confirms that off label use and use of unlicensed medicines are common. Member States do not deal consistently with this issue. They state that the European Court of Justice has confirmed that *"off-label prescribing is not prohibited, or even regulated, by EU law"* and that "There is no provision which prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted."

Pharmacotherapy in children and orphan diseases, and treatment of patients in the areas of oncology/haematology, psychiatry and rheumatology are often situations where off label use can occur.

STAMP and EU Legislation

European Commission examination of Off-Label use of Medicines

The STAMP expert group (Safe and Timely Access to Medicines for Patients) was set up to provide advice and expertise to the Commission services in relation to the implementation of the EU Pharmaceutical legislation. The STAMP exchanges views and information about the experience of Member States, examines national initiatives, and identifies ways to use existing EU regulatory tools more effectively with the aim to further improve safe and timely access and availability of medicines for patients.

STAMP has recently investigated the balance between the benefits and risks that off-label use has for patients, and the regulatory framework for the off-label use of medicines http://ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf

EU Legislation

Legislation on medicinal products in the European Union (EU) regulates the market access of these products by setting standards of safety, quality and efficacy. With this legislation, the EU aims to safeguard public health and to protect the free movement of medicinal products. The terms under which a medicinal product can be used safely and efficaciously are established during the marketing authorisation procedure. These are described in the product information and are the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. In daily practice, however, medicinal products may be used off-label.

EU legislation does not regulate the way medicinal products are ultimately used in medical practice. The prescribing of a medicinal product, on-label or off-label, is a decision taken within the relationship between a patient and his or her treating healthcare professional (HCP). The way Member States organise their healthcare system and the way HCPs conduct their practice is not a topic that falls within the remit of the EU. The EU has limited competence in the field of public health; the ultimate responsibility for the definition of health policy and the delivery of health services and medical care lies with the Member States (Article 168 (7) TFEU).

The European Court of Justice has confirmed that *"off-label prescribing is not prohibited, or even regulated, by EU law"* and that "There is no provision which prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted.**" (T-452/14 Laboratoires CTRS v Commission, paragraph 79).** Off-label use is, however, recognised as a concept by EU pharmaceutical law **(recital 2 of Paediatric Regulation and pharmacovigilance provisions in Directive 2010/84/EU).**

Prescribing Unlicensed Medicines (Continued)

Main Findings of STAMP Investigation

Data from scientific literature reveal that the prevalence of off-label use in the EU within the paediatric population is generally high, covers a broad range of therapeutic areas and is common practice for many prescribers in both the hospital and the outpatient settings.

Thirty-two studies which took place in various paediatric populations within a hospital setting (covering data from 16 EU Member States) showed that a range of 13-69% of the prescriptions investigated was off-label. In forty studies in the outpatient setting (covering data from 12 Member States) there was a range of 2-100%. A similar pattern was observed for the adult population. Twenty-three studies in various adult populations in an inpatient setting (covering data from six Member States) showed that a range of 7- 95% of the prescriptions investigated being off-label. In 13 studies in the outpatient setting (covering data from six Member States) a range of 6-72% was found.

Literature data reveal that *pharmacotherapy in children and orphan diseases* remain areas of particular interest, since off-label use within these areas is still widespread. Elderly patients and pregnant women may also deserve special attention although less information on the extent of off-label use in these two groups is available.

According to literature, clinical areas of interest regarding off-label use are *oncology/haematology, psychiatry and rheumatology*. These all represent unmet medical needs. These clinical areas were also mentioned by all stakeholder groups.

There are limited incentives for pharmaceutical industry to extend the labelling of existing medicinal products; legislation allows for a one year extra market protection if a new indication is registered in the first eight years after a marketing authorisation has been granted and if this new indication brings significant clinical benefit over existing therapies; however, off-label sales will continue without investment in such a new indication anyway; and specifically for off-patent products, generic competition and/or low medicinal product price have a negative impact on return for investments in new indications.

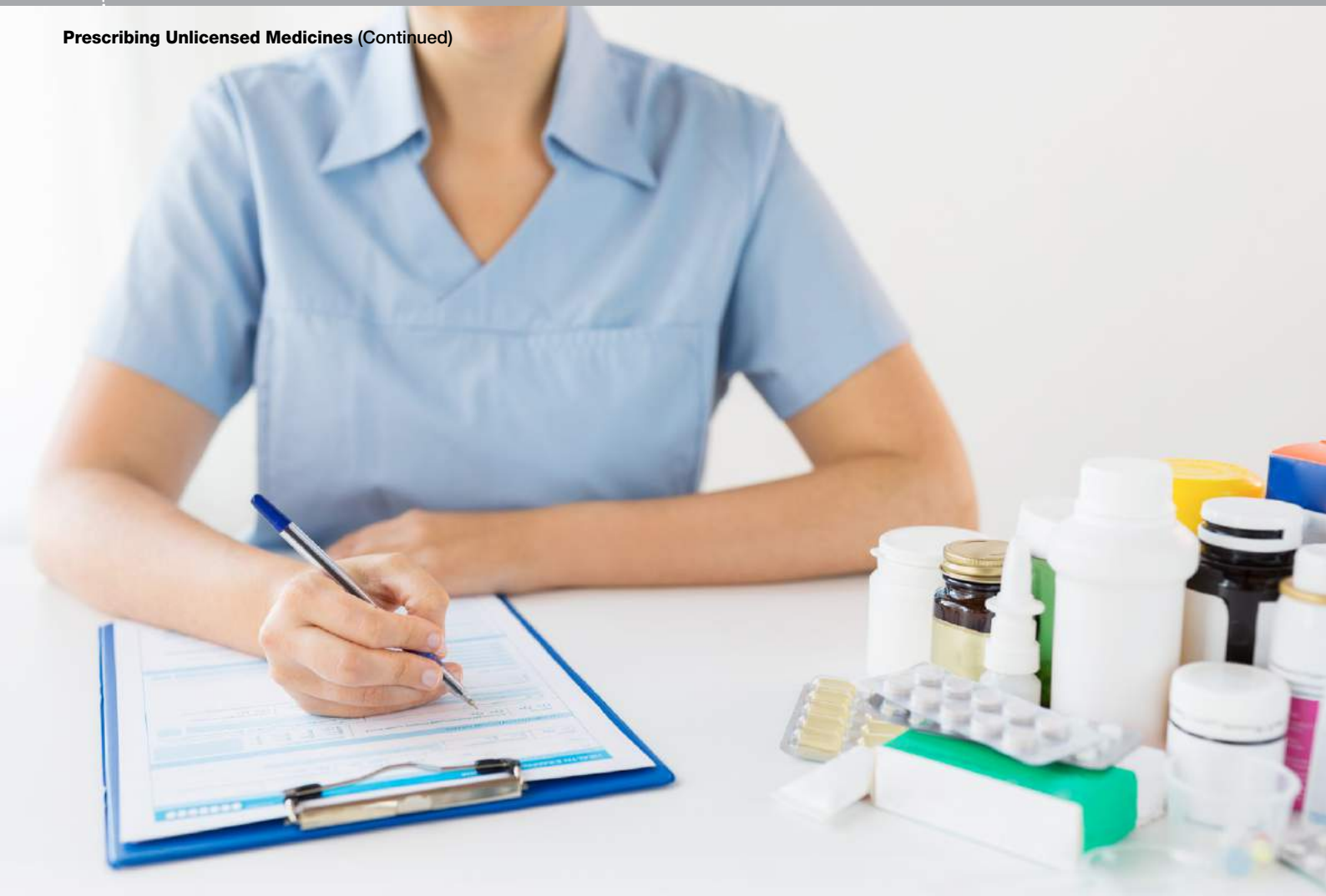
Various drivers may provoke off-label use of medicinal products. These drivers relate to the marketing authorisation process, post marketing authorisation events (e.g., withdrawal from the market/product not available), pricing and reimbursement, aspects connected with the work of HCPs, and patient related factors.

There are limited incentives for the pharmaceutical industry to extend the labelling of existing medicinal products, especially for off-patent products. In addition, there are increasing costs and requirements for marketing authorisation over the years as well as the, sometimes, long development times and high costs to investigate a new indication. An important driver on a patient and HCP level is the fact that there is sometimes no other choice than prescribing off-label.

The way Member States deal with off-label use is not harmonised with 10 out of the 21 countries that participated in the study having specific policy tools in place for off-label use. For example: Policy tools providing guidance for prescribers such as the General Medical Council Guidance (Good practice in prescribing and managing medicines and devices, 2013) in the UK.

In EU Member States without specific policy tools on off-label use, the dominant view is that off-label use is an issue to be dealt with at the level of the prescriber rather than at the regulatory or healthcare system level. Prescribers are trusted to know what is best for the well-being of the patient, with the medical need of the patient leading their decisions.

Prescribing Unlicensed Medicines (Continued)



In summary, prescription of unlicensed medicines or prescription off-label are both possible and within the law.

Recommendations for best practice when prescribing an unlicensed medicine, or prescribing outside the terms of the licence:

- A prescriber of an unlicensed medicine should be satisfied that an alternative, licensed medicine would not meet the patient's needs. If prescribing a medicine off-label, the prescriber should be satisfied that such use would better serve the patient's needs than an appropriately licensed alternative. In either case, there should be a **sufficient evidence** base and/or experience of using the medicine to document its safety and efficacy.
- A prescriber takes **responsibility** for prescribing the medicine and for overseeing the patient's care, including monitoring and follow-up.
- A prescriber should ensure that there are **appropriate records:** Record the medicine prescribed and, where common practice is not being followed, the reasons for prescribing this medicine; if it has been done, record that the issue has been discussed with the patient. Sufficient information about the proposed treatment, including known serious or common adverse reactions, should be provided to the patient to enable them to make an informed decision. The reasons for prescribing a medicine off-license or prescribing an unlicensed medicine where there is little evidence to support its use, or where the use of a medicine is innovative, should be provided.
- If appropriate, a prescriber should explain to the GP and/or other colleagues the recommendation for the use of an unlicensed product and, if necessary, provide any requested supporting evidence, as well as ensuring that they have all necessary prescribing information.

Prescribing Unlicensed Medicines (Continued)

HPRA Exempt Medical Products

Guidance from the Health Products Regulatory Authority on the notification system for exempt drugs "applies principally to wholesalers and manufacturers that receive or import exempt medicinal products. It may also be of interest to healthcare professionals wishing to understand the requirements around obtaining such exempt medicines.[3]"

An exempt medicinal product (EMP) is a medicinal product that is not authorised or registered in Ireland either by the HPRA or in the case of a centrally authorised medicinal product, by the European Commission (via the European Medicines Agency), but which can be legally supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of a registered medical practitioner or registered dentist for use by their individual patients on her/his direct personal responsibility, in order to fulfil the special needs of those patients **(Ref. Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended.)** This legislation provides statutory authority for a medical practitioner to treat a patient under her/his care, using exempt medicinal products.

The term "exempt" refers to the fact that such *products are exempt from the legal requirement to hold a MA,* on condition that their supply is in line with the above requirements. **An EMP may not be prescribed or supplied in situations where an authorised or registered equivalent (i.e., same active substance(s), strength and dosage form) is available in Ireland.**

It is essential that all healthcare professionals in the supply chain are aware that EMPs have not been assessed by the HPRA against the criteria of safety, quality and efficacy, and that the responsibility for the clinical use of such products lies with the prescriber. Under the relevant legislation, Irish manufacturers and wholesalers of medicinal products are required to notify the HPRA of their sourcing or receipt of EMPs. These EMPs are then distributed in response to orders from pharmacies, hospitals and registered practitioners who confirm that the EMP has been ordered in response to a bona fide unsolicited order from a registered medical practitioner or registered dentist or RN/MP.

Currently, there is no requirement in Irish law for healthcare professionals to notify the HPRA where they have directly imported an unauthorised medicine from a wholesaler or manufacturer outside of Ireland (but within the EEA) for the treatment of a patient.

When a pharmacist receives a prescription for an 'exempt' medicinal product, the pharmacist should ensure that the prescribing practitioner is aware of the unauthorised status of the product. The pharmacist should, where possible, inform the practitioner why the medicinal product is unauthorised, for example, if the medicinal product was recently withdrawn from the Irish market. A record, outlining that this information has been imparted, should be inserted in the patient's file.

Pharmacists should be aware, and should inform prescribers, that 'exempt' medicinal products should not be sourced and supplied if a suitable authorised alternative is available in Ireland.[4]

The HPRA therefore maintains a database for the notification, by wholesalers and manufacturers, of EMPs sourced for supply to the Irish market from outside the state.

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[3] https://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/aut-g0090-guide-to-the-notification-system-for-exempt-medicinal-products-v5.pdf?sfvrsn=37

[4] https://www.thepsi.ie/Libraries/Folder_Pharmacy_Practice_Guidance/01_4_Guidelines_on_the_Sourcing_of_Medicinal_Products_for_Sale_or_Supply_within_a_Retail_Pharmacy_Business.sflb.ashx

Professional Profile

Patrick Salmon graduated from TCD as a physician, worked in clinical medicine before joining a Pharmaceutical Company and finally moved to the Irish Medicines Regulatory Authority. He became a Specialist in Pharmaceutical Medicine.

He was one of the Irish representatives at the EMA Committee for Human Medicinal Products (CHMP) for 17 years and has a particular interest in product information and the SmPC.

Automatic 21 years coverage when you retire from practice

At Challenge individual practitioners, underwritten on our Consultant, GP and Dental practitioners' scheme policy wordings benefit from 21 year run-off cover at no additional cost in the event of permanent retirement, death or disability.

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