EU Pharmaceutical Law Forum 2021

VAN BAEL & BELLIS

"Expanding possibilities for unauthorised / off-label use of medicines before and after marketing authorisation?"

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Agenda

I. Background – Reminder of Regulatory Principles

II. Growing Tolerance for Unauthorised / Off-label Use of Medicines

III. Covid-19

IV. Questions and Issues

Background – Reminder of Regulatory Principles

Background – Reminder of Regulatory Principles

Co-existence of/tension between EU competence and Member State competence

EU Competence : Article 114 TFEU: harmonisation of laws to ensure functioning of internal market => placing of pharmaceutical products on the internal market

- placing on the market;
- manufacture / importation
- labelling
- classification

of medicinal products

Background – Reminder of Regulatory Principles

Co-existence of/tension between EU competence and Member State competence

Member State Competence : Article 168 TFEU: Member States responsible for the organisation and delivery of health services and medical care

- Unauthorised use of medicines regulated by EU law, but only in part;
- Off-label prescribing is not regulated by EU law

Background – Reminder of Regulatory Principles

EU v. Member States

Directive 2001/83/EC

Article 6 – MARKETING AUTHORISATION

1) *No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 726/2004 [...].*

Article 5 - INDIVIDUAL SPECIAL NEEDS

5 (1) A Member State may, in accordance with legislation in force and to fulfill special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.

Background – Reminder of Regulatory Principles

EU v. Member States

Directive 2001/83/EC

Article 5 – UNAUTHORISED MEDICINAL PRODUCT IN CASE OF EMERGENCY

5 (2) Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

Article 3 – MAGISTRAL FORMULA

This Directive shall not apply to:

1) *Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).*
2) *Any medicinal product prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).*

Background – Reminder of Regulatory Principles

Broad EU competence to harmonise laws to put products on the market (Art. 114 TFEU)

Directive 2001/83/EC

Article 40 – MANUFACTURING PACKAGING PRESENTATION

1) *Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorisation […]*

2) *The authorisation referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.*

   However, such authorisation shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes.

Background – Reminder of Regulatory Principles

General rule:

Medicinal products require a marketing authorisation (***MA***), except if prepared in a pharmacy for an individual patient (and under certain other exceptional conditions)

Off-label use:

Any intentional use of an **authorised** product not covered by the terms of its MA and therefore not in accordance with the SmPC, e.g.

- use for a different indication
- use of a different dosage
- dosing frequency or duration of use
- use of a different method of administration
- use for a different patient group (e.g. children instead of adults)

Liability issues:

Off label use is under the responsibility of the prescribing physician

Growing Tolerance for Unauthorised / Off-label Use of Medicines

Growing Tolerance for Unauthorised/Off label use of medicines

2017 EU Study on Off-Label Use

- Shows very high prevalence of off-label use in EU across a **wide range of settings**

- Incentives for off-label use are varied and involve:
  - —MA process (e.g. MA process long and costly; MA process lags behind scientific evidence; little incentive and no power to enforce extending label)
  - —Post-MA events (e.g. shortages due to supply interruptions, medicine withdrawals; products not authorised/available in EU market)

Growing Tolerance for Unauthorised/Off label use of medicines

2017 EU Study on Off-Label Use

Professional factors e.g. more treatment options – compare recent US study: "off-label prescription of psychotropic medications may be more the rule than the exception", Syed et al., JAAPL.200049-20 (2021)

KCE estimated figures Belgium (2015):

- Oncology: at least 50%
- Pediatrics: 80%

HCP guidance includes off-label and not aligned with MA process

Growing Tolerance for Unauthorised/Off label use of medicines

2017 EU Study on Off-Label Use

- Patient factors (e.g. no available alternatives; last resort; side-effects/patient preferences)
- Pricing and reimbursement (e.g. high costs of on-label – CJEU declared off-label use for budgetary reasons compatible with EU law (case c-29/17, *Novartis v. AIFA,* 21 November 2018); no reimbursement of existing on-label indication)

- **Covid-19 gave further impetus**

Growing Tolerance for Unauthorised/Off label use of medicines

Does this trend give rise to contradiction between tolerance for (even encouragement of) off-label use and zero tolerance for off-label promotion?

Government bodies can promote / **HCP's** can recommend off label use <-> **MA holders** are prohibited from promoting off-label use (and *Avastin – Lucentis* shows that they should refrain from discouraging such use as well – see e.g., CJEU, case C-179/16; most recently *Autorité de la concurrence* – 9 September 2020)

Covid-19

Covid-19

Covid-19 has resulted in increased:

- Compassionate Use – both Cohort and Named Patient
- "Temporary Exemptions" from MA requirements
- Off-label Use

Covid-19 - CU

- **Compassionate Use**:

- Article 83 of Regulation No. 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency:

  - making a **medicinal product available for compassionate** reasons

  - to a **group of patients**

  - with **a chronically or seriously debilitating disease** or **whose disease is considered to be life-threatening**

Covid-19 - CU

- **Compassionate Use**:
  - and who **cannot be treated satisfactorily by an authorised medicinal product**
- Medicinal product is either the subject of application for centralised MA or is undergoing clinical trials for the indication concerned in EU and/or elsewhere

- CU implementation remains competence of MS

Covid-19 - CU

- Patients taking part in CUP should have access to new medicinal product during period between authorisation and placing on market

- Facilitative opinion of Committee for Medicinal Products for Human Use (CHMP) on conditions for use and distribution and patients targeted – example: remdesivir for specific Covid-19 indication

- CHMP Guideline on CU of medicinal products pursuant to (EC) 726/ 2004 Article 83 (adopted 19 July 2007): patients should always be considered for inclusion in clinical trials before being offered CU programs

- CU data will be included within an MA application and may support safety conclusions – may in *exceptional* cases (rare conditions) even allow for efficacy inferences

Covid-19 - CU

- Obvious benefits: patient access to new treatments in cases that matter (debilitating or life-threatening disorders)

- Drawback: patchwork of national rules

Covid-19 - CU

- **Named Patient Supply** is possible in the EU in accordance with Member State law (Art. 5(1) of Directive 2001/83/EC)
  - Requirements and implementation differ per country
  - Unapproved products (although Member State laws vary)

Covid-19 - CU

- **Cohort compassionate use**: Article 83, Regulation (EC) No 726/2004: Member State can request CHMP to adopt opinions on the conditions for use, conditions for distribution and the patients targeted for CU for a group of patients

- Member States are required to notify EMA when making use of CU for group of patients

- Of Member States that notified EMA of CUP, only 6 have so far made use of option to request CHMP Opinion

- Member State 'cohort' frameworks vary and some do not have clear rules – but more manageable than individual requests, especially in times of pandemic

Covid-19 – Temporary Exemptions

- **“Temporary exemptions” from MA requirements**

Article 5(2) of Directive 2001/83/EC:

> “Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm”

Covid-19 – Temporary Exemptions

▪**"Temporary exemptions" from MA requirements**:

- Articles 5(3) & (4) govern liability:

  Member States must ensure that MAH, manufacturers and health professionals are **not** subject to civil or administrative liability for any consequences resulting from the use of a medicinal product (exception authorised indications) when such use is recommended or required by a competent authority in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

- Liability for defective products remains

Covid-19 – Temporary Exemptions

- **“Temporary exemptions” from MA requirements**
- Decision of national competent authority
- Dependent on member state national law
  - Law is high-level, there is little to no guidance regarding e.g. supporting evidence requirements, labelling, prescribing information etc.
  - Differing requirements can include e.g. contractual arrangements
  - Appropriate instructions for HCPs?
  - Specific liability regime (different from, e.g., conditional marketing authorisation)

Covid-19 – Temporary Exemptions

- **“Temporary exemptions” from MA requirements – Example: Belgium**
- Royal Decree initially enabled use of unauthorised medicines to treat Covid-19 patients
- Health Crisis Law will create more permanent solution : bill 55K1929 – to be adopted shortly
- Bill makes it possible to have the government import, distribute and supply unauthorised medicines to tackle the Covid-19 pandemic during a limited period of time (Bill, Article 8)
- Bill goes beyond Covid-19 pandemic and creates possibility, subject to strict conditions, to make an unauthorised alternative for an authorised medicine available, regardless of medical condition at issue (Bill, Articles 10 and following).

Covid-19 – Temporary Exemptions

- **"Temporary exemptions" from MA requirements – contrast with Conditional Marketing Authorisation**

EU CONDITIONAL MARKETING AUTHORISATION (e.g. for Covid-19 vaccines)	EMERGENCY USE AUTHORISATION ISSUED BY SOME MEMBER STATES (Art. 5.2 of Community Code)
Is a marketing authorisation, albeit on a conditional basis, for the whole EU	Not a marketing authorisation, but authorisation of temporary use of UNAUTHORISED vaccine in a Member State under its responsibility as long as emergency circumstances apply
Follows controlled and robust framework providing safeguards (pharmacovigilance, batch controls, risk management plan, investigation plan for future use of medicine in children, etc.)	Framework may be less robust (decided at national level)
Liability rests with holder of MA (but see deviating liability clauses in Advance Purchase Agreements between EU and vaccine manufacturers)	Member State must remove administrative and civil liability from manufacturer and MAH when emergency use required or recommended by Member State
Thorough assessment of safety and efficacy data by EMA (benefit/risk analysis) and imposing of requirements on risk management and monitoring post-authorisation	Member State decides which data is required so possible that less detailed data is required. Idem as regards requirements for use and supervision.

Covid-19 – Off-label use

- **Off-label use**

Off-label use for Covid-19 : medicines used for influenza, HIV and other viruses, and also anthelmintics (ivermectin, nitazoxanide, niclosamide), and antimalarials

FAMHP (Belgium) strongly discouraged off-label use of hydroxycholoroquine outside clinical trials

Covid-19 – Off-label use

- **Off-label use**

remdesivir:

- Off label use
- CU (and Article 83 opinion by EMA's CHMP)
- complemented by European Commission's Conditional Marketing Authorisation for a Covid-19 indication (3 July 2020)(treatment of coronavirus disease 2019 (Covid-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)
- CU and CMA co-exist in different Covid-19 indications

Questions and Issues

Questions and Issues

- **Consistency – Off label use**

- Off-label use forms part of relevant product market for competition purposes (CJEU, case C-179/16, *Hoffmann-La Roche et al. v. Autorità Garante*, judgment of 23 January 2018)

- "a national competition authority may include in the relevant market, in addition to the medicinal products authorised for the treatment of the diseases concerned, another medicinal product whose MA does not cover that treatment but which is used for that purpose and is thus actually substitutable with the former" (§ 67)

Questions and Issues

- **Consistency – Off label use**

- By contrast, off label use cannot play a role in determining the existence of a "satisfactory method" of diagnosis, prevention or treatment in the EU as an alternative for the candidate orphan medicine (General Court, case T-549/19, Medac v. European Commission, judgment of 23 September 2020)

- *"the off-label use of a medicinal product cannot be regarded (…) as being 'authorised' (…) consequently, a medicinal product used off-label cannot constitute a 'satisfactory method… that has been authorised in the [European Union]' within the meaning of Article 3(1)(b)of Regulation No 141/2000*."

Questions and Issues

- **Consistency – Off label use**

- A medicinal product used off-label cannot constitute a “satisfactory method” against which the candidate product had to be compared under Regulation 141/2000 since the SmPC showed different intended treatment conditions and patient populations

- melphalan- and cyclophosphamide-based medicinal products are not an alternative satisfactory method for treosulfan, indicated for conditioning treatment prior to haematopoietic progenitor cell transplantation

Questions and Issues

- **Off label use**

- How far can pharmaceutical companies go in participating knowingly in sale of medication intended for off-label use, such as considering the number of patients treated off label in pricing and reimbursement negotiations?
- How far can companies go in promoting on-label use?
- Is the best course of action to stay out of the off-label debate entirely?

Questions and Issues

- **Off label use**

- Physicians can prescribe any product for off-label use consistent with national laws as off-label use is not regulated at EU level

- However, off-label supply must remain individual to the patient (*i.e.*, must be supplied in response to a prescription) leaving the off-label determination under the doctor's care; off-label products must not be "marketed"

- Hospital pharmacies can repackage products for off-label use without the need to obtain either a new MA or a manufacturing authorisation, provided this is in response to individual prescriptions, does not alter the product and is for retail supply

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