EU: Falsified Medicines Directive 'Delegated Act' accepted by European Parliament

Richard Price

A 'Delegated Act' of the European Commission setting out requirements hospital pharmacies must fulfil in respect to 'check out' verification of all medicines they receive, has been accepted by the European Parliament. The Act is now formal European Union law and must be implemented by a deadline of 9 February 2019.

The main elements of the Delegated Act for hospital pharmacists to be aware of include:

1. The unique identifier that will be contained on the outer packaging of all medicines, and its components;
2. The end-to-end verification principle, requiring all hospital pharmacies to conduct 'check out' scans of the medicines packages they receive;
3. The governance model of the system;
4. The flexibility provided to hospitals in respect of 'when' they choose to conduct the scan;
5. The 10 day limit on returns.

Hospital pharmacists should give particular attention to Articles 25 and 26 of the Delegated Act.

Following this, EAHP is now advising all its member associations to engage as fully as they are able in national discussions on implementation issues, taking place via the current construction of 'national medicines verification organisations' (NMVOs). These national organisations will, for example, be in charge of defining the national user requirements under which verification systems will operate in the country in question.

EAHP RESPONDS TO EUROPEAN COMMISSION ORPHAN DRUG CONSULTATION

The European Association of Hospital Pharmacists (EAHP) has responded to a European Commission consultation on the EU's orphan drug regulatory framework.

The response:

- Supports the suggestion that hospital produced medicines be included in the comparisons made to establish whether a candidate for orphan designation offers the potential of 'significant benefit' over existing treatments;
- Further suggests that the significant benefit comparison also includes off label use;
- Suggests 'clinically relevant advantage' be also widely understood as meaning improvements in the ease of administration, safety of the patient, and/or quality of life/options of the patient. This would, as an example, be represented in a switch from intravenous administration to oral administration;
- Supports the suggested reforms to the regulatory framework designed to encourage orphan drug designation for treatments targeted at low to zero prevalence but infectious diseases in the EU such as Ebola or the Zika virus;
- Calls for the Commission to undertake further review of the orphan medicine regulatory framework especially in respect to pricing and surveillance and monitoring of the outcomes of treatment by medicines given orphan drug authorisation with unsettled benefit-risk profiles at the time of approval.

DUTCH PRESIDENCY OF THE EU PUTS THE FOCUS ON ANTIMICROBIAL RESISTANCE

The Dutch Presidency of the European Union (EU) has placed a strong emphasis

on international action against antimicrobial resistance (AMR) by holding a special high-level intergovernmental ministerial conference on the subject on 9–10 February 2016.

The event was attended by representatives of the EU's 28 member state countries, as well as Margaret Chan, director general of the World Health Organization (WHO) and Vytenis Andriukaitis, the EU's Commissioner for Health and Food.

The conference, which was for a large part a closed meeting, is the prelude for the separate informal and formal European Council meetings for the Ministers of Health and the Ministers of Agriculture later this spring. The intention is to reach "Council conclusions" (agreed resolutions for action by all EU Member States) during these meetings. The meeting, and the Dutch Government's push for new EU level recommendations on AMR, comes at a time when the existing EU Action Plan on AMR 2011–16 is coming to the end of its lifespan and discussion is commencing on its replacement.

EAHP, on behalf of hospital pharmacy, is engaging in the debate, promoting in particular that greater ambition be reflected in international resolutions, especially in relation to improving stewardship of existing antimicrobials and antibiotics via the hospital pharmacist skillset (eg, prescribing advice, monitoring of use, advice to patients).

EAHP Vice-President Tajda Miharija Gala, who leads EAHP representations on the topic, said:

"The decision of the Dutch presidency of EU to put the combating of antimicrobial resistance at the heart of its 6 month chairing of EU Government meetings is most welcome. AMR is a cross border societal challenge as serious as climate change, economic threats or other topics routinely at the top of intergovernmental dialogue. Its right that AMR finally gets this kind of attention. Reviewing EU level actions on AMR over the past five years, one can only conclude that more ambition must be shown. By ensuring the hospital pharmacist skillset is fully leveraged to improve stewardship of existing

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antibiotics and antimicrobials, Europe can make itself a best practice region that the rest of the internationally community can learn from."

WORLD HEALTH ORGANIZATION OFFERS NEW PLAN ON MEDICINE SHORTAGES

The secretariat of WHO has recently published a paper contributing its thoughts on potential mechanisms to address the globally experienced problem of medicines shortages.

Amongst the key points in the paper are:

- ▶ The suggestion that the 'common denominator' for global medicines shortages *"are products that are mostly old, off-patent or difficult to formulate and that have a tightly-defined shelf life and few or a sole manufacturer."*
- ▶ Factors that the WHO believe worsen the shortages situation include: *"poor availability and quality of data on actual demand; inadequate management practices in procurement and the supply chain, combined with large tender contracts that do not sufficiently define quality standards but whose sole emphasis is on obtaining the lowest prices; and too small profit margins for manufacturers."*
- ▶ Negative impacts of shortages include: inability to fulfill prescriptions as well as poor quality prescribing and poor use of medicines. *"The results are poor health outcomes, which have been documented, for example, in relation to mortality in children owing to lack of cancer treatment and to inappropriate use of antibiotics when first-line regimens are not available"*.

The report goes on to suggest the need for *"mechanisms for combining and sharing notifications for global scrutiny of the status of the supply of individual medicines"*.

Explaining the rationale, WHO state: *"As the supply of pharmaceuticals is a multinational business, having a system for comprehensive evaluation and a future global monitoring mechanism for that supply in place, would anticipate and detect early shortages and assist the development of a joint rapid response mechanism to encourage countries, the international community and other relevant stakeholders to cooperate in developing a joint rapid response."*

Commenting on the report, EAHP Board Member Aida Batista, policy lead on shortages, remarked:

"This latest intervention from the World Health Organization (WHO) is very welcome, particularly the section dealing

with the patient impact of shortages. As EAHP surveys have shown, medicines shortages are a global problem, and so require global solutions. Improving international regulatory cooperation, as well as available information systems about shortages, as suggested in this paper, could not be more strongly supported by the EAHP. We hope the message is beginning to filter through to those in the regulatory community with the capacity to act."

LATEST EVIDENCE PRESENTED OF RISING ANTIMICROBIAL RESISTANCE IN EUROPE

A recent joint report by the European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority has confirmed increasing problems of antimicrobial resistance across EU countries.

The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2014 is an analysis of data submitted by the EU's 28 member countries.

Headline aspects of the report include evidence of growing resistance to antimicrobials used to treat campylobacteriosis and salmonellosis, the two most common reported foodborne diseases in Europe.

For campylobacteriosis, resistance to widely used antimicrobials, such as ciprofloxacin, was commonly detected in bacteria from humans and poultry. High to extremely high resistance to ciprofloxacin was observed in broilers (69.8%), as well as in bacteria from humans (60.2%). High to extremely high resistance to nalidixic acid and to tetracyclines was reported in broilers.

Resistance to widely used antimicrobials was commonly detected in salmonella from humans (tetracyclines 30%, sulphonamides 28.2%, ampicillin 28.2%) and poultry.

The report authors also detected resistance to 'last resort' drug colistin in EU poultry.

"This last resort drug may soon no longer be effective for treating severe human interactions with salmonella", said ECDC chief scientist Mike Catchpole.

EAHP Vice-President Tajda Miharija Gala, who leads EAHP representations on the topic of antimicrobial resistance, said: *"This report marks yet another wake up call, as if needed, that the European Commission's next Action Plan on antimicrobial resistance must exhibit more ambition and rigour than its previous version. That should include better*

defining the role of healthcare professionals in meeting the challenge. EAHP advocate placing hospital pharmacists at the forefront of all national plans for achieving more prudent use and better antibiotic stewardship in the hospital sector."

MEPS SIGNAL SUPPORT FOR SIGNIFICANT REGULATORY CLAMPDOWN ON ANTIMICROBIAL USE IN THE VETERINARY SECTOR

Members of the European Parliament's Environment and Public Health Committee (ENVI) have advocated banning collective and preventive antibiotic treatment of animals, and supported measures to stimulate research into new antibiotics, including longer data protection.

The important signaling vote came as part of the European Parliament's scrutiny of European Commission proposals to modernise the existing EU regulatory framework for veterinary medicine.

French centre-right MEP Françoise Grossetête has the lead 'rapporteur' responsibility for delivering the opinion of the ENVI committee, and her report was overwhelmingly endorsed by political groupings within the Committee, approved with a majority of 60 to 2.

Highlights of the ENVI Committee opinion include amendments intended to:

- ▶ Limit the prophylactic use of antimicrobials (i.e. as a preventive measure, in the absence of clinical signs of infection) to single animals and only when fully justified by a vet;
- ▶ Prevent overuse of collective treatment (ie, treating a group of animals when one shows signs of infection), with treatment restricted to single animals that are identified as being at a high risk of contamination; and,
- ▶ Prevent veterinary medicines being used to improve performance or compensate for poor animal husbandry.

The ENVI Committee report will be put to a full vote of the European Parliament during the March or April plenary sessions in Strasbourg. Following this, the Parliament commences a negotiation with national governments to secure its proposed amendments in the final legislation.

EAHP Vice-President Tajda Gala, who leads the Association's representation on the topic of antimicrobial resistance, commented:

"I would like to add my congratulations to Françoise Grossetête and the ENVI Committee for this well-reasoned report."

It reveals yet again the benefits of subjecting Commission proposals to the proper scrutiny of the Parliament. To combat antimicrobial resistance, and its threat to human health, strong action is needed in all sectors, including the veterinary sector. These sensible amendments from the European Parliament will help to achieve that."

EUROPEAN MEDICINES AGENCY SEEKING TO DEVELOP A HARMONISED DEFINITION OF MEDICINES SHORTAGE

The European Medicines Agency (EMA) has called for the establishment of a harmonised definition of a medicine shortage after hosting a meeting of national regulatory authorities, the pharmaceutical industry, and other stakeholders such as EAHP, to discuss the development of proactive approaches to preventing shortages in supply.

The formal report of the October 2015 meeting has now been published and provides insights to current intended direction of medicines agencies in Europe towards the shortages issue.

Problems with defining shortage

As preparation for the meeting a survey was conducted which revealed that most member states do not have a definition for a shortage (18 out of 28 responses). The lack of a common definition was highlighted several times during the workshop as an obstacle for a common approach in dealing with shortages. The report of the meeting notes: *"This lack of clarity about what a shortage is means that the conditions for reporting shortages differ from one country to another which makes benchmarking and comparisons very difficult."*

The continuing problems faced by patients and healthcare professionals

At the meeting, EAHP presented headline results from its 2014 survey of medicines shortages across Europe. The report of the survey revealed 86% of hospital pharmacists report that medicines shortages are a current problem in the hospital they work in, with 66% stating that shortages are affecting their hospital on a daily or weekly basis. Reported impacts for patients included delayed or interrupted chemotherapy treatment, additional side effects, heightened clostridium difficile risk and deterioration in their condition. EAHP emphasised the need for greater international coordination of efforts to combat what is clearly a global problem. This should include a step change improvement in the information made available to healthcare professionals about shortages, with available national best

practices shared and taken up. Regulatory activity in the United States was pointed to as an example.

Recommendations from the workshop

The recorded recommendations from the workshop are:

- ▶ The need for a harmonized definition of a medicines shortage;
- ▶ The requirement to identify at what point a manufacturing or quality issue becomes likely to lead to a meaningful disruption as well as when it should trigger a report to authorities;
- ▶ National regulators should agree on common trigger points for notification as well as harmonised data requirements across the EU;
- ▶ A European shortages communication network, similar to a rapid alert network, should be constructed; and,
- ▶ The pharmaceutical industry should consider the value of stress tests to evaluate effectiveness of measures in place to prevent shortages.

The European Medicines Agency will update its implementation plan on this topic accordingly and further developments are awaited.

Commenting on the published report of the meeting, EAHP Board Member Aida Batista, who is the Board lead on medicines shortages, said:

"The headline recommendation of this meeting on the need for a harmonized definition on medicines shortages is absolutely right. However it is imperative that that definition is not of a highly restrictive nature. For example, some at the meeting advocated only defining a medicines shortage if it could be categorized as providing a 'high risk'. This will not do. Every medicines shortage causes problems for patients and healthcare professionals, with risks of error contained from substitution to alternatives. This problem must be dealt with holistically and in totality."

"We also emphasised at the meeting the need for transparency in medicines shortage information. As the example of the USA and some countries in Europe show that when you make information on shortages public terrible events do not occur. However public debate and solution-finding are certainly better-informed by such transparency."

EUROPEAN COMMISSION PUBLISH STUDY INVESTIGATING DIFFERING NATIONAL APPROACHES TO THE MEDICINES PRICING CHALLENGE

The European Commission has published a new study examining differing approaches by national governments in

the EU to the challenge of managing medicines expenditure. The report pays particular attention to the phenomena of external reference pricing, and the prospects for a European approach of 'differential pricing' according to country GDP (gross domestic product).

External reference pricing

EPR, also known as external reference pricing or international price comparison/benchmarking, is defined in the report *"as the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of a medicine in a given country."*

EPR is used in 29 countries in the EU, as well as in Iceland, Norway, Switzerland and Turkey, though different approaches are applied in Germany, Sweden and the UK, which employ various forms of EPR, value-based pricing (VBP) and other pricing regulation schemes.

According to a survey from last year, the Commission found that 20 of the 29 countries that apply EPR use this policy as their sole or main pricing policy. Countries most frequently referenced to are France, Belgium, Denmark and Spain, followed by Italy, the UK and to a lesser extent, Austria, Germany and Slovakia.

But the details of how an EPR scheme is designed differs between countries, the report notes, as 21 countries compare medicine prices at the level of ex-factory prices, while eight countries at the pharmacy purchasing price (wholesale price) level.

The study identifies ways in which EU countries could improve the operation of external reference pricing, including improving:

- ▶ The account taken of currently confidential discounts;
- ▶ The operation of the 'Eurepid database' for sharing information between EU countries on pricing;
- ▶ Coordination between EU countries to have more harmonised method of comparison.

Differential pricing

Meanwhile, the report also examines the feasibility of achieving a system of 'differential pricing', the strategy of selling the same product to different customers at different prices, in the case of medicines, dependent on country income (or ability to pay). Such approaches have been used in respect to delivering access to vaccines and other vital medicines in low-income countries outside Europe. The study is sceptical to both the possibility of achieving European agreement for such a

scheme, as well as the proposed benefits that would be achieved.

The study states: *“The introduction of a fully-fledged differential pricing scheme in Europe, as a government policy or EC supported policy in full respect of the subsidiarity principle, though not completely impossible, would however require addressing major obstacles in legal, technical, organisational and political terms and might not be the most preferred policy to address challenges in equitable access to medicines.”*

The study was written by Gesundheit Österreich Forschung-und Planungs

GmbH and funded by the Health Programme of the European Union.

EAHP Board Member Frank Jorgenson, who leads the Association’s activities in relation to medicines access, commented:

“What comes through in this report is to an extent what we know already; that the landscape of medicines pricing in Europe is confused by poor levels of transparency. We, the public, often simply do not really know the true costs of medicines to our Governments. This gets in the way of both scrutiny and informed public debate. Transparency could be improved by some of the sug-

gestions in this report, but calls for greater disclosure on issues such as research and development costs will remain valid and reasonable.”

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