PROTECTING EUROPEAN CITIZENS BY USING THE MOST SUITABLE SKIN DISINFECTANTS BEFORE MEDICAL TREATMENT (WIP)

Call for Action

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Surgical Site Infections (SSIs), Catheter-Related Infections (CRBSIs) and Blood Culture Contamination (BCC) have become an increasing challenge for European hospitals and healthcare systems for which they pose a significant human and financial burden

SSIs, i.e., a type of healthcare-associated infection in which a wound infection occurs after an invasive (surgical) procedure[1], are among the most common healthcare-associated infections, accounting for between 15%[23]and 20%[45]of all healthcare-associated infections. As these serious infections significantly affect the quality of life for the patient[67], the World Health Organization (WHO) has prioritised minimising the risk of SSIs as one of their ten essential objectives for safe surgery.[8]

CRBSIs can be a critical complication with catheter devices. Like SSIs, CRBSIs are consistently associated with prolonged hospitalisation, increased mortality, and elevated costs. Extended length of stay in hospital is reported to represent the primary cost burden, with additional costs arising from the diagnosis and treatment of infected patients.

BCC, which plays an important role in the diagnosis of serious infections, is also a common problem within the hospital setting. Contamination of blood samples and the consequent false positives often cause patients to be treated with inappropriate and unnecessary antibiotics that can extend hospital length of stay, which in turn increases the risk of hospital-acquired infections or conditions.[910111213] Target rates for blood contamination have been set at 2 to 3%[1415], however actual rates vary widely between institutions, from as little as 0.6% to over 6%[16171819202122232425] or more[26].[27] There is also some evidence to suggest that in recent decades, these rates have been on the increase[28].

The threat posed by the unnecessary use of antibiotics must not be disregarded either. Their misuse not only places patients at risk of serious adverse events with no clinical benefit but has also contributed to the growing problem of antibiotic resistance, currently one of the most serious and growing threats to public health.[29]

SSIs, CRBSIs and BCC are preventable. Skin antisepsis has a proven and demonstrable role in preventing these adverse events. It helps avert the contamination of wounds or blood samples by pathogens present in the patient's skin

A disharmonised approach to the classification of preoperative disinfectant products

Depending on the intended application, **skin disinfectants used to prevent SSIs, CRBSIs and BCC may fall under different legal frameworks** and as such are currently classified as 'borderline products'.

Within the European Union, the classification of disinfectants is not uniform. The Commission recognised that a clear distinction between the Biocidal Products Directive 98/8/EC and the Human Medicinal Products Directive 2001/83/EC is a crucial issue and that, for borderline products, there is a need to give practical guidance and examples.[30]

In accordance with Article 2(2) of the Medicinal Products Directive, when, considering all its characteristics, a product may fall both within the definition of a 'medicinal product' and within the definition of a product covered by other Community legislation, such as the Biocidal Products Regulation, the Medicinal Products Directive shall apply.

However, while there are guidelines on the distinction between Biocidal products and other types of products (e.g., cosmetics[313233], medical devices[34]) the distinction between biocidal

products and medicinal products for the classification of disinfectants for use in 'preoperative skin disinfection' seems to remain unclear. Some international authorities have provided guidance for manufacturers to help them determine how a specific Member State will treat their products.

To clarify this situation, the **European Chemical Agency (ECHA),** in a guidance approved in February 2017, stated that: "*Products for disinfection of damaged skin (e.g. wound disinfection) or disinfection of undamaged skin before a medical treatment of a patient (e.g. pre-operative skin disinfection before surgery and disinfection before injection) and products with a claim of medicinal use, **are always medicinal products** (covered by the Directive 2001/83/EC on medicinal products for human use)*".[35]

Despite this, the Commission, in response to a parliamentary question tabled in May 2017 on the disharmonised classification of skin disinfectants for certain medical interventions[36], stated that "*disinfectants used for human hygiene purposes, and applied on or in contact with human skin, are biocidal products*" and that "*a biocidal product for skin disinfection can be authorised provided it is safe for patients*".[37]

The legal definitions of biocidal and medicinal products are not interpreted uniformly by the Member States. Whereas a majority of EU Member States' (e.g., Germany, Belgium, United Kingdom) health authorities consider these preoperative disinfectant medicinal products, in line with the ECHA's[38]position, some other countries (**France, Italy, Spain**) regard all products used on intact skin as biocidal products, including antiseptics used on patients.

While this may be perceived as a mere classification issue that only affects the individual assessment of the specific products, it raises a significant and highly relevant medical concern: that some Member States allow and accept the use of biocidal products as medicinal products. They do this in the knowledge that many biocidal products do not have a marketing authorisation under the legislation regulating medicinal products (and hence are subject to different controls and standards which can lead in certain situations to inadequate antisepsis/decontamination of the preoperative intact skin area as well as patient harm) nor the appropriate pharmacovigilance that comes with medicinal use. Whilst there is demonstrable patient harm from biocides these are not routinely captured nor acted upon as would be the case for a medicine.

Biocides are not medicines

It is undoubtedly true that the EU's strict rules and procedures on biocidal products ensure a high, if not the highest, level of protection for human health, animal health and the environment. However, **key differences exist between medicinal and biocidal products** that explain why biocides should not be used as medicines.

These differences refer to aspects such as **registration, manufacturing, quality control, medical indications, pharmacovigilance, and sterility**. A key difference also relates to the clinical trials that medicinal products need to undergo to obtain a marketing authorisation. Such trials generate robust scientific data on safety and efficacy of medicines, which are not required under the regulations that govern the licensing of biocide products.

Similarly, while legislation[39] requires that all medicinal products for human use are manufactured and monitored in accordance with the principles and guidelines of good manufacturing practice (GMP), which ensures that the product meets all the batch

manufacturing specifications (levels of active ingredients and excipients, etc.), biocides do not have such specific requirements for the manufacturing process.

As a result of these differences, medicines are subject to more controlled dispensing (delivery of the product for a specific patient by professionals), special storage conditions (greater safety and hygiene controls of the stores) and increased control of supplies (assurance of product availability through the pharmaceutical distribution chain).

Protecting patients, healthcare workers and the environment by using an appropriately authorised product

The use of biocides for a medicinal purpose not only contradicts the purpose of the biocidal products' and medicinal products' provisions, but it also raises concerns from the patient and occupational safety standpoints as well as from the environment and antimicrobial resistance perspectives.

Patient safety

We have established that biocides and medicines are subject to very different regulatory regimes which confer different standards in term of safety efficacy and quality. It therefore follows that using biocidal products as medicines, while biocides do not have a marketing authorisation under the legislation regulating medicinal products, may jeopardise patient's safety.

As highlighted by the MHRA, there are health risks associated with that practice and "using the appropriately authorised product for its specific intended use, in accordance with the manufacturer's instructions for use, is the best way of minimising harm"[40].

Antimicrobial resistance

The former European Commission Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) stressed[41] that, in order to preserve the role of biocides in infection control and hygiene, it is paramount to prevent the emergence of bacterial resistance and cross-resistance through their appropriate and prudent use."*The need for proper use of disinfectant and antiseptics should be stressed and health care workers should be trained to comply with clear and agreed policies and practices, avoiding unnecessary and incorrect use of biocides*", they added.[42]

In other words: in the specific case of skin disinfection prior to medical treatments, the use of biocides must be limited to those cases where it is strictly required and no other similar or more suitable alternative to the biocide, such as a medicine, could be used instead.

Furthermore, as explained in the introductory section of this paper, the misuse of antibiotics following false positive blood cultures not only places patients at risk for serious adverse events with no clinical benefit but contributes to an increased antimicrobial resistance.

Occupational safety

Healthcare workers can be exposed to biocides either directly (primary exposure, i.e., the worker/operator actively uses the biocidal product) or indirectly (secondary exposure, i.e., after the actual use or application of biocidal products). As mentioned above, biocides may have toxic, carcinogen, and endocrine disrupting properties, which, especially in the case of workers, may be undetectable.

Under the Carcinogens and Mutagens Directive 2004/37/EC the employer must ensure that the risk to workers' health and safety from dangerous substances is eliminated or reduced to a minimum (first level in the hierarchy of risk control). In order to fulfil this obligation, the first priority for the employer is to substitute or eliminate the risk of biocides, which can be done by using alternative disinfectants or replacing them with less harmful procedures, substances, preparations or products.

While various European and national guidelines exist providing instructions for working safely with disinfections in the healthcare sector, the EU is lacking harmonised specific guidelines on the safe use of biocides in the healthcare sector. The European Commission DG Employment guideline provided a general description of good practice on safe working in disinfection activities[43]which did not dwell on biocides and the use of these in the healthcare sector.

Environmental impact

The use of biocides can also have significant adverse effects on the natural environment. In the healthcare sector, disposal of used or unwanted biocides must be undertaken carefully to avoid serious and potentially long-lasting damage to the environment.

Recommended actions

The European Union (EU) has a responsibility to seize every opportunity to increase patient and occupational safety, to decrease antimicrobial resistance and to protect the environment. In this regard, we call upon the European Commission to ensure a uniform interpretation and consistent implementation of the biocidal and medicinal products legislation and hence protect European patients from avoidable harm. **The signatories of this call for action call on the European Commission to:**

Issue guidelines on the differences between biocidal products and medicinal products regarding the classification of disinfectants to be used for the safest skin antisepsis before surgery and injection.

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