When Is a Medicine Not a Medicine?

European Alliance for
Access to Safe Medicines

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Foreword

Jim Thomson

When is a medicine not a medicine? It isn't a trick question, but a very real one. It should only have one answer. "When it is prescribed and dispensed with only the best interests of the patient in mind, and with the patient fully informed and involved in the decision-making process." That isn't an ideal, but the very least a patient deserves. This report examines what can happen when other factors enter the equation. For example, when money clouds the issue. Or when regulatory vagaries or loopholes exist. The EAASM has researched and uncovered a number of disturbing incidences of what can happen when healthcare decisions are made as a result of considerations other than the patient's best interests. They make shocking reading.

Of course, it is entirely legitimate and acceptable to decide on or modify a treatment regimen taking into account the financial implications, AFTER discussion with the patient and considering the patient safety implications.

- ★ It is not acceptable when the patient (or indeed doctor) is ignorant of decisions affecting the patient's health.
- ★ It is not acceptable when the mutual bond of trust between patient and healthcare provider is broken through omission to fully inform.
- ★ It is not acceptable when, in essence, that trust becomes a one-way street.
- ★ In any event, it is wholly unacceptable when such action compromises patient safety – with or without consent.

Since its inception in 2007, the EAASM has fought hard to enhance patient safety and indeed this is the Alliance's raison d'etre. Up to this point it has concentrated on raising awareness of counterfeit medicines, and has campaigned tirelessly for improvements to the supply chain. As this report goes to press, Europe stands on the brink of legislation to better protect patients from fake medicines. Simultaneously, the EAASM has returned to another vitally important area that is very damaging to patients and their heatlh, that of the internet. It is again campaigning for effective measures to prevent international criminals from utilising spurious websites to prey, for profit, on unwitting patients.

This report takes the EAASM into a new area of campaigning. It emphasises the importance of the "S" in EAASM and reinforces our mission to campaign for patient safety, whenever and wherever it is under threat.

Jim Thomson, London, April 2011

Executive Summary

The timing and content of this report are influenced by a number of factors, not least media coverage of some of the more unfortunate results of unlicensed medicines usage. The EAASM asked itself the following questions: “How are “off-label” adverse reactions recorded? Who is regulating this? Are there other anomalous issues, such as unlicensed products being used instead of licensed ones, and does this compromise patient safety?” Ultimately, the Alliance resolved to find some answers.

The report is a critical examination of a small number of cases. The common thread running throughout, is money. The suggestion is that therapeutic decisions have been and are being made on the basis of cost, that patients and often healthcare professionals are routinely unaware of these decisions, and that this is morally unacceptable. The report asks whether, in a society that promotes patient choice and patient-centred healthcare, this should also be illegal.

Given the desire quickly to bring the subject matter of this report to the attention of patients and decision-makers alike, it is necessarily brief, and may well form the basis of further study.

The eponymous introductory overview, “When is a Medicine Not a Medicine?” sets the scene, looking at the factors influencing the cases covered in the report. It also summarises other recent cases, indicating that the selected case studies are far from isolated incidents. On the contrary, they were selected because they are typical of three very different types of incident.

The first case study focuses on a number of preparations used in a surgical pre-operative setting and asks how, in this of all environments, cost-cutting can supercede evidence-based quality care-giving.

The second features two leading, pharmaceutical products. Both are used to treat a relatively rare condition, wet AMD (Age-related Macular Degeneration). Only one is licensed by the European Medicines Agency (EMA), and recommended for ocular use, the other is widely used “off-label” (unlicensed), giving rise to horrifying adverse reactions.

The report’s final case study deals with the re-cycling and re-use of medical devices, some for implant in patients. Given that many of these devices are licensed for one patient use only and are being passed on ”second hand” to other patients it shows evidence that the quality and safety of these can be compromised and that, on occasion they can retain blood, body fluid and tissue from previous use.

When is a Medicine Not a Medicine?

Medicines[i] are considered to be among the tightest regulated products in the world. They are licensed, for specific conditions, only after exhaustive trials. Manufactured to the highest standards and prescribed only after a consultation with a professional who has spent many years qualifying to practise, they are finally dispensed by another well-qualified professional, in strictly regulated conditions. That is the theory and, of course, in the vast majority of cases, the reality.

However, it isn’t always so. On occasion, decisions can and have been made that exploit loopholes and subjectivities, in the above system. A doctor may decide to prescribe to a twelve year old, a product unlicensed for use in children, because there is no licensed alternative. A clinician may decide that, as two medicines seem at first sight similar, an unlicensed one might do the same job as a licensed one (particularly if the former is much cheaper).

A hospital may decide to use a general skin cleaner for pre-operative skin-disinfection if the regulations are so vague that it can avoid the cost of a licensed skin disinfectant.

Tragically, people have died, as Adverse Event Reporting Systems can fail to pick up critical side effects.

In January 2011, the EMA published a study[ii] in which it stated that 45-60% of medicines prescribed to children were unlicensed or off-label. The highest rates were in very young or severely ill children. The EMA is developing an inventory of paediatric needs, in an effort to find a solution to this situation. In the meantime, doctors are, quite reasonably, treating children with what they have available.

In France, a medicine for treating obesity in diabetic patients was, until it was finally banned, routinely prescribed for general weight loss in non-diabetic patients. The French authorities estimate resultant deaths at a minimum of 500, with 3500 hospitalisations.[iii]

In each of the following case studies, we shine the spotlight on a specific, yet different, example of what can happen when the medical model outlined in the first paragraph above, fails, leaving those with the biggest vested interest, patients, at risk.

The Risky Regulatory Loophole

When a patient signs a pre-operative release form, there is perhaps an even stronger bond of trust than in any other clinical setting. The patient trusts, implicitly, that the treatment will be the very best available. It is assumed that equipment, medicines or other substances used prior to, during or following surgery, are appropriately licensed. EU and Member State regulations seem to support that view but, as the EAASM has discovered, even here, a "medicine" is not always a medicine. It appears that unlicensed products are being routinely used in pre-operative settings. We believe that there are clear reasons why this is totally unacceptable and, here, we examine the regulatory loophole that places patients at risk at their time of greatest vulnerability – on the operating table.

Setting the Standard

There are three main substances used for patient pre-operative skin preparation – traditional Idophors, Alcohol, and Chlorhexidine (or combinations thereof). Chlorhexidine gluconate is highly recommended by at least 17 organizations and initiatives, with 11 specifically advocating a 2% formulation.[iv] This includes the recently-updated UK High Impact Interventions document.[v] The only such preparation holding a UK Marketing Authorisation is ChloraPrep®.

A study published in the New England Journal of Medicine[vi] states that Preoperative skin cleansing with chlorhexidine-alcohol (ChloraPrep®) is superior to cleansing with povidone-iodine for preventing surgical-site infection after clean-contaminated surgery

To License or Not to License?

By law, before a medicine is placed on the market, it must be given a marketing authorisation (product licence) by a medicines regulator (MHRA in the UK). The MHRA also inspects the factory where the medicine is to be made, to make sure that supplies will be of a uniformly and consistently high standard. The licensing system is designed to:

- ★ guarantee that all those involved are answerable for their actions
- ★ ensure that processes, supplies, and quality can be thoroughly monitored
- ★ enable swift corrective action to be taken when needed

The MHRA has also stated that "The consequences of using even simple medical devices outside their intended purpose can be serious."[vii] An update to MHRA guidance published on 18 June 2008 is quite clear on which products require marketing authorisation: "wipes/swabs containing antiseptics/antimicrobials such as chlorhexidine, iodine, cetrimide and similar will remain as medicinal products and therefore will continue to require a marketing authorization (MA)."[viii]

The licensing requirement appears to be clear. However, a loophole exists which seriously compromises patient safety, enabling unlicensed products to be used for pre-operative skin disinfection. Products **intended** for the disinfection of humans may be regulated as biocides or medicinal products, depending upon their intended purpose. According to the MHRA, those considered to be medicinal products will require a MA.

- ★ Disinfectant products intended for use by the general public or by healthcare professionals for **hand cleansing** etc are usually considered to be biocides
- ★ Products **specifically intended** as surgical scrubs for use prior to operative procedures are usually considered as medicinal products
- ★ **Disinfectant products intended to be used on patients** are considered to be medicinal products (including swabs, solutions to disinfect wounds, and topical antiseptics)

Products that are **intended** to be used as multi-purpose hard surface disinfectants / cleansers and / or general environmental disinfectants would be likely to come within the regulations covering biocides.

There is no provision under the regulations for a product to be indicated for use on humans AND for general purpose use OR for use on medical devices.

The MHRA considers that such products should be marketed separately under the different sets of legislation, be that medicines, biocides or medical devices. However, there is currently **NO REQUIREMENT TO DO SO. This means that products unlicensed for use as skin disinfectants prior to invasive medical procedures, can be (and are) used as such.** The issue is further clouded by unclear, ambiguous product labeling, which allows unlicensed product to circumvent the **"intention"** measure. In reality, products intended for use as biocides, are drifting beyond their **intended** use, into an area that, should require a licence. They are intended for use as general disinfectants/cleansers, but are being promoted and used for pre-operative skin disinfection. That is both wrong, and dangerous.

Why is this a Patient Safety Risk?

During treatments and procedural techniques, professionals, having a duty to ensure the delivery of safe and therapeutic care, are required to act in the best interests of their patients and to minimise risks at all times. **Using unlicensed, unsuitable products for pre-operative skin disinfection, unwittingly or otherwise, without the knowledge of the healthcare provider and fully informed consent of the patient, destroys the vital bond of trust between clinician and patient.**

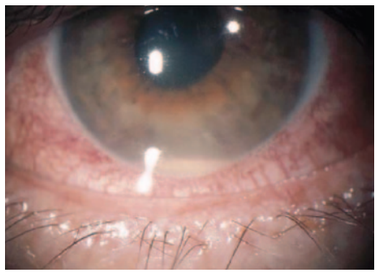
Choosing an unlicensed product in this setting removes the vital checks and balances provided by the regulatory process. There is no pharmacovigilance, none of the burden of proving safety or efficacy that is necessary with a licensed product alongside the appropriate and ongoing quality control during manufacture.

Age Related Blindness

In the EU, the legislation is very clear. A medicine MUST have a Marketing Authorisation for a particular indication if it is to be promoted to treat it. The European Medicines Agency not only defines the type of disease to be treated. It also defines the type of patient to be treated. The historical reason lies within the Thalidomide™ story, where that medicine caused severe harm to unborn babies. The legislation was therefore established with only one very clear principle in mind: safeguarding patient safety. Very limited exceptions apply to the above-mentioned rule of authorized medicines (e.g. use of unlicensed medicines in authorized clinical trials). None of them applies in this case. The licensed medicines have been considered by the EU agencies as adequate treatments for age-related blindness.

Neovascular (wet) age-related macular degeneration is probably the leading cause of blindness in the elderly population in the developed world. It is a disease which slowly impairs the eyesight but it is not a deadly disease. Yet many doctors – instead of using the licensed product - are using a medicine (Avastin™) designed for use in seriously ill cancer patients, to treat patients with age-related blindness. Avastin™ is not available in the right dosage and it is not supposed to be injected in the eye. Physicians are deciding themselves upon the "right" dosage, changing the dosage and refilling the product into syringes. Doctors or hospitals sometimes may also decide to store the leftover product (although it is not designed for storage after opening) and use the leftovers on other patients. Such behaviour brings with it additional risks of infection or contamination of the product.

It is extremely worrying that this practice of unlicensed use is also undermining the incentives by companies to research new medicines and to test the safety of innovative products designed to fight blindness. But most importantly, this practice endangers patient safety:



Between 2007 and 2009, newspapers reported clusters of adverse reactions – including complete vision loss - in the eye following injections of the unlicensed product directly into the eye, in Australia (19 cases), Austria (8 cases), Germany (5 cases), Canada (105 cases) and Portugal (6 cases). There are also published indications of a higher risk of stroke and other problems.[ix] But the full extent remains unknown.

Regulatory authorities carefully assess and approve products according to efficacy, safety and quality. Off-label use bypasses those checks & balances, and undermines the systems for measuring adverse events. The EAASM believes that it is reasonable to ask why a healthcare provider would embark on such a course of action.

Why is this happening?

The answer is money. Cost differentials between licensed and unlicensed substitutes can be significant (reflecting the research costs, time and effort to test the safety/efficacy of the medicine and market it, and in part simply because hospitals and doctors carry little of the risk and none of the costs of assessing the long term safety of the product in clinical trials). In this case, "compounding" (breaking up a single dose into several doses) creates considerable cost savings.

Health Authorities, keen to save money, are encouraging such unlicensed use and, by definition, the circumventing of the need to obtain Marketing Authorisations. It's easy to draw the conclusion that this compromises two things – the regulatory framework in Europe, and patient safety. Indeed, the European Medicines Agency (EMA) has stated its dissatisfaction with the practice.

> **For a Member State to encourage the use of a pharmaceutical for an indication for which it is not licensed, would be a breach of EU legislation**
>
> Thomas Lönngren, former Executive Director, EMA, when in office[x]

Of course, budget-driven, off-label use is inconsistent with the European Courts' consistent statements that the protection of public health should be given precedence over economic considerations. Ultimately, any therapeutic decision should be made with the full involvement of the patient. Specifically, if a licensed medicine is available, then the patient should be told, enabling that patient to make a fully informed choice.

Single Use? - Not Necessarily So...

In recent years, great advances in design, manufacture and use of medical devices have provided enormous patient benefit during surgery and treatment. However, important safety, ethical and legal concerns arise when devices, **originally designed and labeled for single use,** are, despite the manufacturers' express instructions, refurbished, repackaged and reused. This practice is undertaken mainly for the alleged economic benefit of the users' institutions, usually hospitals.

The refurbishment of single use devices involves cleansing, sterilising, re- packaging and otherwise fixing them to render them as close as possible to their original quality, performance and functionality. However, such processes are rarely adequate enough to eliminate the risks of cross-infection, and can often cause deterioration of the component materials.

The white plastic tip of a linear cutter has become separated slightly, exhibiting a crack and blood and body fluid residues.

The use of refurbished single use devices can lead to an increase in hospital acquired infections (HAI), one of Europe's most serious medical challenges. In addition, it can potentially cause harm or death to the patient by infection or mechanical breakdown.

Reprocessed catheter tip contaminated with proteins from previous patients. Image- Eucomed

The practice is considered ethically insupportable, since patients are placed at unnecessary risk, are uninformed and their interests are subordinated to hypothetical and unsubstantiated economic benefits to the user, usually a hospital. The economic benefits, if any, are seen to be overestimated. The costs of dealing with HAI, additional complications, administrative overheads and eventual litigation are rarely calculated or included in total cost:benefit analyses.[xi]

In much of Europe the practice is heavily discouraged, but not universally illegal; exceptions to this rule are France, Spain, Italy and Portugal. Although current EU directives do not prevent a so-called refurbishment industry from re-selling refurbished single use devices, the practice is condemned by the World Health Organisation.

The safest and most unambiguous method for ensuring that there is no risk of residual infectivity on surgical instruments is to discard and destroy them by incineration ... this strategy should be universally applied to those devices and materials that are designed to be disposable. (WHO)[xii]

Medical ethics is based on the principles of beneficence (a duty to promote good and act in the best interest of the patient and the health of society) and non-maleficence (the duty to do no harm to patients). Information should be disclosed whenever it is considered to be material to the patient's understanding of his or her situation. Medical ethics also require that patients be fully informed of the risks and benefits of medical procedures. [xiii]

It is difficult to see how this basic principle can be reconciled with a practice that both carries with it serious patient safety risks and the condemnation of the major global healthcare arbiter (WHO). The patient safety risks associated with the re-use of single use medical devices are extremely serious, and are several. They include:

- ★ The potential for cross-infection
- ★ The inability to clean and decontaminate devices
- ★ The residues from chemical decontamination agents
- ★ The alteration of component materials
- ★ The mechanical failure of devices
- ★ Reactions to endotoxins
- ★ Removal of biologics
- ★ Removal of prions

A third party refurbished EP catheter resulting in an insufficient heart valve. As the electrodes separated the heart valve was locked between the electrodes. Image- Eucomed

The reuse of single use devices is reported (by the refurbishment industry) to deliver significant cost savings to healthcare systems.[xiv] The argument against, is that the cost reduction potential is immensely exaggerated, as it doesn't factor in costs associated with increased patient safety risks. The body representing 4500 medical technology companies active in the diagnosis, prevention, treatment and amelioration of disease and disability, is Eucomed. It has compiled and conducted exhaustive research into the cost:benefit of this practice and concludes:

Only the purchasing department will benefit financially. Such benefits may have some indirect positive impact on patient care. However, it remains that any beneficial impact accruing to a particular patient is outweighed by the increased risks.

Eucomed's research documents horrendous incidents where re-used devices have failed, leading to, inter alia, repeat surgery, coma, heart attack and death. The organization has now called for Europe-wide measures to ensure patient safety is no longer compromised by the repeated use of single use devices.[xv] In the interests of patient safety, our primary objective, **the EAASM supports this call, particularly given the wider societal costs associated with the possible proliferation of hospital acquired infections.**

Patient Choice Means Patient Safety

This report documents three very different cases where a single issue, that of cost, has compromised the very basis of the Hippocratic Oath, "First do no harm". To ensure that the safety and well-being of patients are the paramount considerations for all treatment decisions, we call on:

1. **Policy-makers at national and European level** to introduce clarifying legislation in order to close regulatory loopholes which allow patient safety to be put needlessly at risk by allowing the use of unlicensed medical products although there is no medical need for such use;

2. **European and national product safety agencies** to intervene swiftly whenever healthcare providers are using unlicensed products despite licensed products being the safer and medically adequate alternative;

3. **Associations of healthcare providers** to set clear standards for their members under which conditions the use of unlicensed products is warranted (i.e. medical reason);

Either through taxes, insurance, or directly, patients pay for the healthcare they receive. Regardless of any economic consideration, it is unacceptable that, in order to cut costs, they be asked to risk paying a much higher price, with their health, well-being or even life.

For further details of the case studies summarised in this report, please use the 2d data-matrix codes below. Using any smartphone, download the scanlife app from your app store (if you already have a scanner app, you may skip this step). Scan the code for the case study you wish to find out more about and your smartphone browser will open and automatically access the information.

To find out more about the risky regulatory loophole that allows unlicensed medicinal products to be used in pre-operative settings, scan this code, or visit the following link
http://www.eaasm.eu/When_is_a_medicine_not_a_medicine/Unlicensed_product_use_in_preoperative_settings

For more information on the implications in age-related blindness of the use of unlicensed medicine, use this code or visit here
http://www.eaasm.eu/When_is_a_medicine_not_a_medicine/Off_label_use_of_medicine

For further information about the re-use of single use medical devices, scan this code or visit this link
http://www.eaasm.eu/When_is_a_medicine_not _a_medicine/Reuse_of_single_use_devices

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