Medicines & Healthcare products Regulatory Agency

MHRA

Coroner Dr Philip Barlow
The Office of Her Majesty's Coroner
for the County of Northamptonshire
Constabulary Block One Angel
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30 September 2021

Medicines & Healthcare products Regulatory Agency

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Dear Dr Barlow

Reference: Mr Andrew Cook

I write with reference to your Regulation 28 letter following the inquest into the sad death of Mr Andrew Cook.

Following the inquest and our report to your office dated 28 May 2021, you requested that we take action to prevent similar events of this kind occurring in the future.

I have taken the opportunity to provide supporting information to the statements as well as respond to the request for action to be taken for each of the Matters of Concern raised.

Matters of Concern:
You have expressed the following matters of concern:

Concern 1: Polyethylene Glycol (PEG) allergy is rare but may be under-reported. PEGs are ubiquitous and more research into their effect as allergens is required.

Concern 2: Whether the existence, dose and molecular weight of PEG should be made clear on medical product information (such as the Instructions for Use, data sheets, packaging and marketing information).

- The existence of PEG in the equipment (in this case, the Sion and Sion Blue guidewires manufactured by Asahi Intecc) was not apparent from the packaging or product information available to the clinicians.
- PEGs are available in various molecular weights. There was expert evidence that reaction to PEG may depend on the dose and exact molecular weight to which an individual is exposed.
- It was acknowledged that labelling can have negative effects and therefore needs to be considered with care. Labelling also requires coordination with other national regulators.

Concern 3: There is inconsistency and potential confusion in nomenclature. For example, PEG can be referred to as "Macrogol", "polyethylene oxide" (PEO) or "polyoxyethylene" (POE). Nomenclature may also vary between countries. There was evidence that clinicians reviewing product information in urgent situations are not aware of the various synonyms.

Response to Matters of Concern

This information should be read in combination with MHRA's report dated 28 May 2021.

Concern 1: general comments
The MHRA receives approximately 20,000 medical device adverse incidents per year across a wide variety of issues. In our report to HM Coroner dated 28 May 2021 we reference 10 suspected reports received by MHRA since 2006, including the report that was the subject of this inquest.

Underreporting affects all types of medical devices. Underreporting can be particularly relevant to events involving suspected allergic / adverse reactions. These types of event may be complicated by several factors, e.g. a patient may have been exposed to more than one potential allergen from more than one source, one or more allergens may go unrecognised or the adverse reaction may not be immediate.

One major area of the MHRA's responsibilities is to collect, analyse, monitor, and act on information relating to safety concerns from a range of data sources including relevant published research and scientific literature papers. Whilst there has been some scientific literature produced over the last 15 years which has reported on PEG/macrogol exposure and its potential to elicit allergic type adverse reactions, the overall relative number has been very modest and limited to patient specific case studies. Of these, only a few have reported clinical events potentially linked to medical device use.

Manufacturers are required to work to keep the safety and performance of their devices under continual review through pro-active risk management procedure, an ongoing process of post market surveillance (PMS) which forms a vital phase of the device lifecycle.

Some examples of PMS include**:** Adverse incident logging, investigation and failure analysis; post CE-market clinical trials; user feed-back; device tracking/implant registries; expert user groups ("focus groups"); and literature reviews.

Please see MHRA actions in response to this Concern.

Concern 2: general comments
As detailed in our report to HM Coroner dated 28 May 2021, seventeen medical device manufacturers were contacted and questioned about their awareness of PEG and its association with allergy and other forms of adverse reaction; their post market surveillance (PMS) data; and approach used on PEG labelling. The majority reported having little concern regarding PEG and its potential as an allergen. They reported receiving minimal adverse incident reports concerning allergy/adverse reactions and no confirmed reports of PEG exposure leading to adverse events.

Nonetheless, manufacturers of such devices will often comply with relevant key designated international standards to show they comply with relevant requirements of the regulations to place a device on the market. One such standard is ISO 14971 *Medical devices – Application of risk management*, which requires the manufacturer to undertake a process of "Risk Analysis", "Risk Evaluation" and "Risk Control". In general, it requires the device (including the chosen materials) be evaluated for its safety, quality, and performance. It also requires that the associated Risk Management Report is updated regularly to ensure relevant new detail (signals) through the "real-world" clinical experience of using the device feeds into a risk assessment to ensure risks are minimised and the benefits outweigh these risks. Another relevant key standard is ISO 10993 *Biological evaluation of medical devices, which states that f*ollowing risk analysis and evaluation and the implementation of risk controls, it is necessary to review the findings of these preceding activities and to document the residual risk and to decide on any further disclosure of such residual risks, for example through appropriate labelling, cautions or warnings.

In general, the manufacturer is responsible for the information accompanying their medical device. This information should provide comprehensive, informative, and clear detail on how to use the device safely. Any precautions / warnings to be taken or noted before or during use of the device should be evident and clear. Additional detail may be included under the “indications” and “contra-indications” sections of the IFU where appropriate. This is a requirement under current legislation, as well as the relevant global ISO standards listed above.

Where PEG/macrogol and its derivatives are used in the forming / construction and final product of a medical device, where it may exist as either a major / functional ingredient or minor, trace / residue component or ingredient, the manufacturer should bring awareness of the presence of this chemical, as well as highlighting its potential as a trigger for allergy in some people, via device labelling.

There are a number of issues relating to PEG within this case which would influence labelling requirements; in order to explore and understand these and ensure the labelling benefits patients and healthcare providers, we will engage with stakeholders to seek expert advice on the form and extent of the labelling needs. A range of issues will be explored including for example whether there should be emphasis or priority for certain types/class of device and type/risk of anticipated exposure to PEG.

Please see MHRA actions in response to this Concern.

Concern 3: general comments
The variation in name / identification for PEG/macrogol seems to have evolved organically and is often linked to common international regional vernacular or usage with certain groups of products e.g. medicines, cosmetics, industrial items, as well as the particular discipline or field of interest e.g. medical, industrial or pure sciences (chemistry, biochemistry etc.).

There is no specific legislative labelling requirement that instructs medical device manufacturers on how to decide upon the most appropriate nomenclature where more than one common name exists for an ingredient / chemical.

It is likely that a manufacturer would opt for an identification that is perceived to be in common usage or reference (globally), however, as is the case with PEG, the situation is compounded by regional and subject / discipline variations. A further complication is the potential use of registered trade names assigned by several bulk chemical supplying industries.

Please see MHRA actions in response to this Concern.

PEG in medicinal products
Whilst the product at issue is a medical device, the MHRA also regulates medicinal products and they were also discussed at the inquest.

The legislation covering the labelling and packaging of medicines is a separate and different regime in some aspects from that in relation to medical devices. Medicines legislation recognises the need for excipients within a formulation to be transparent and these are listed qualitatively in the statutory product information for all medicines. In addition, Macrogol or PEG of various molecular weights is prevalent as a pharmaceutical excipient in more than 8000 medicinal products authorised in the United Kingdom. The nomenclature of this product is set out in the World Health Organisation of International Non-proprietary Names as *‘macrogol’* and this is how this excipient will appear in the medicines’ product information although in some cases both macrogol and PEG may be declared.

There are guidelines on those excipients which have adverse effects in-their-own-right and the information which must be included. There is the separate issue of the potential for PEG to cause an adverse effect in-its-own-right. The document which sets out which compounds need to be included on the labelling of all medicines is derived from Article 65 of Council Directive 2001/83/EC and is a

publication from the Commission. Macrogol (PEG) is not currently listed as an excipient of known effect. There are no specific warnings given in the Patient Information Leaflet on its effects

Though the current medical device legislation does not specify the need for all ingredients to be named/listed, it does instruct manufacturers to label any warnings or precautions to take, as well as information to be given to avoid certain risks. This would include labelling those ingredients that could possibly induce an allergic reaction. However, please see MHRA action points concerning medical device legislation under "Concern 2".

Actions taken or planned by the MHRA in response to the Matters of Concern

Concern 1:

1. Patient safety is our highest priority. It is mandatory for manufacturers of medical devices to report certain incidents to MHRA. We encourage patients and healthcare professionals to report safety concerns to MHRA through our voluntary Yellow Card scheme. We run a number of campaigns to promote awareness of reporting by patient, public and healthcare professionals, so that we can take action to help to reduce the risk of similar incidents happening again.
2. As part of the medical device legislation, manufacturers are required to monitor, collect, and review safety data on their devices in the post market phase. Through our ongoing regulatory work with UK Approved Bodies (UK ABs - independent assessment/certification bodies) the MHRA will continue to ensure that manufacturers meet their legislative obligations.
3. We recognise the need to raise awareness of this safety issue to patients, public and healthcare professionals relating to medical devices and medicines.

    - The MHRA plan to launch a Devices Safety Information (DSI) webpage specifically on PEG/macrogol in medical devices to highlight its potential to illicit allergic type reactions, and to raise awareness of nomenclature variations.
    - We also plan to issue a Drug Safety Update (DSU) that links directly to the DSI webpage (above) to reinforce this message as well as raise awareness of the different names for PEG compounds in medicines.

    To further publicise these safety messages, the MHRA will utilise relevant patient representative groups, major medical professional societies/colleges, and appropriate healthcare manufacturer trade associations to further publicise this safety issue. In combination with standard alerts to subscribers of our safety message webpage, this will ensure a greater reach to patients, public and health care system.

Concern 2:

1. The MHRA will work with UK ABs to communicate the importance for appropriate clear labelling with respect to PEG.
2. We will continue to engage with relevant stakeholders, in particular the medical device manufacturers, to develop clear guidelines on labelling requirements for PEG/macrogol.
3. Concerning the need for additional detail on the labelling of PEG regarding the its molecular weight and amount/quantity used, we will need to undertake a longer-term programme of review. The MHRA will discuss these points with patient representative groups, clinical experts, and industry.
4. The MHRA will continue to perform ongoing appraisal of the current medical devices and medicines UK legislation with regards to expectations on minimum labelling requirements relating to ingredients.

    On 16 September we launched a public consultation on future of medical device regulation; giving everyone the opportunity to contribute to the improvement of the regulatory framework and therefore patient safety in the future. https://www.gov.uk/government/consultations/consultation-on-the-future-regulation-of-medical-devices-in-the-united-kingdom

    In particular – under Chapter 3 : Economic Operators (Section 6.4) : *The MHRA considers that the UK medical devices regulations could be amended to provide further detail to the existing*

essential requirements and to add further essential requirements in line with technological progress and international best practice to deliver public and patient safety benefits. Examples of how the essential requirements could be amended include: More detail on the information that should be provided with the medical device, ***including a requirement to list ingredients/component parts which are known allergen/sensitisers****.*

5. MHRA will seek to discuss labelling requirements with other regulators internationally, to ensure any future UK requirements do not adversely or significantly conflict with other global requirements that could compromise UK patient safety.
6. Where necessary and appropriate, the MHRA will communicate and share information with other national regulators to protect patients worldwide.

Concern 3:

We will review the challenges relating to nomenclature.

1. MHRA will engage with global stakeholders such as the World Health Organisation (WHO) and the International Medical Device Regulators Forum (IMDRF) on PEG nomenclature. For example, WHO has a "*constitutional mandate to develop, establish and promote international standards with respect to biological, pharmaceutical and similar products*" and as such manage the International Non-proprietary Names Programme and Classification of Medical Products. The IMDRF is tasked with accelerating international medical device regulatory harmonization and convergence.
2. As described under "Concern 2", the MHRA will discuss labelling requirements with other regulators internationally, to ensure any future UK requirements do not adversely or significantly conflict with other global requirements that could compromise UK patient safety.

Conclusion

The MHRA will continue to collect and review information from a range of data sources on PEG exposure including via our adverse incident (Yellow Card) reporting system and database, as well as independent scientific publications. This information will form part of an ongoing review in which we will seek views of external experts, that will aid us in the development of labelling advice for PEG in medical devices and medicines, specifically the balance of benefits and risks to patients and other users of medical devices.

We will raise the profile of PEG/macrogol, in particular its presence in some medical devices, as well as associated allergy risks and nomenclature variability, working with relevant stakeholders where appropriate.

The MHRA will appraise the feedback received from the public consultation of the UK medical devices legislation including the Chapter relating to labelling so that we may create a world-leading regime that continues to prioritise patient safety. These actions combined with the measures above, will minimise risk associated with PEG allergy while ensuring continued access to devices from those patients who will benefit.

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Dr [redacted]
Chief Safety Officer, MHRA