Medicines & Healthcare products
Regulatory Agency

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Dr Julian Morris
Senior Coroner
London Inner South
Southwark Coroners Court
1 Tennis Street
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By email: [redacted]

Reference: [redacted]

8 January 2025

Dear Dr Morris,

Regulation 28 Report: Deaths of babies Yousef Al-Kharboush, Oscar Barker and Aviva Otte

Thank you for your Regulation 28 Report of 15 November 2024 in which you asked the Medicines and Healthcare products Regulatory Agency (MHRA) to provide a response following the inquest into the sad deaths of babies Yousef Al-Kharboush, Oscar Barker and Aviva Otte. We would like to extend our sincere sympathies to the families and loved ones of Yousef, Oscar and Aviva for their loss.

I am writing in relation to the concerns raised in your report where you considered that the MHRA should take action to prevent similar events of this kind occurring in the future.

Role of MHRA in the regulation of the manufacture of unlicensed medicines
The MHRA is an executive agency of the Department of Health and Social Care and is responsible for the regulation of medicinal products, medical devices, and blood components for transfusion in the UK. We take all reasonable steps to protect public health and safeguard patients, the public and users.

The MHRA is responsible for the licensing regime which permits the supply of unlicensed medicines under Regulation 167 of The Human Medicines Regulations 2012 (‘the Regulations’).

Regulation 167 provides an exemption from the need for a marketing authorisation for a medicinal product which is:

a) supplied in response to an unsolicited order;
b) manufactured and assembled in accordance with the specification of a person who is a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber; and
c) for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient.

Under this regime the unlicensed medicinal products (commonly described as "specials") may only be supplied in order to meet the special needs of an individual patient. Responsibility for deciding whether an individual patient has "special needs" which a licensed product cannot meet should be a matter for the doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber responsible for the patient's care.

Licensing the manufacture of medicinal products

In accordance with Regulation 17 of the Regulations, the manufacture of medicinal products requires a licence granted by the MHRA. There are a number of different licence types, depending on whether manufacture is of licensed medicines, unlicensed medicines or investigative medicinal products (clinical trials medicines). Licences are granted to the would-be licence holder once they have demonstrated that their facility and quality systems are able to operate in accordance with Good Manufacturing Practice (GMP). Assurance of this is obtained by on-site inspections by MHRA GMP Inspectors during the licence application phase and is then maintained via the conditions of the licence.

Once a licence is granted, MHRA inspectors will periodically inspect the facility to ensure GMP compliance is maintained. The MHRA operates a risk-based strategy to determine inspection periodicity, with the frequency of inspection being dependent on the type of medicines which are manufactured and the manufacturer's record of compliance. The MHRA's escalation procedures in instances where critical deficiencies are identified involve the Agency's Inspection Action Group (IAG). The IAG is a non-statutory, multi-disciplinary group which advises the MHRA on the requirement for regulatory or restrictive licensing action, usually following the identification of critical deficiencies at inspection[1].

The Section 10 exemption

Section 10 of the Medicines Act 1968, as amended, provides scope for exemptions from the requirement to hold a manufacturer's licence or marketing authorisation in defined circumstances. A pharmacist (or any person working under their supervision in a registered pharmacy), hospital pharmacy, or a pharmacy in a care home service or health centre to whom the Section applies may: prepare, assemble or dispense a medicinal product in accordance with a prescription given by a practitioner. Facilities that are preparing or assembling medicinal products under a Section 10 exemption fall outside the responsibility of MHRA.

The preparation of medicines under Section 10 in NHS hospital pharmacies remains an essential enabler for patient care, including such activities as parenteral nutrition, cancer chemotherapy, clinical trials and innovative advanced therapy medicinal products. NHS England (NHSE) has oversight of the quality assurance of NHS hospital pharmacies in England operating in accordance with Section 10. The 2020 Department of Health and Social Care report "Transforming NHS pharmacy aseptic services in England" made the specific recommendation to strengthen the accountability and responsibility of Trusts operating s10

[1] https://www.gov.uk/government/groups/inspection-action-groups

facilities regarding the unlicensed preparation of aseptic medicines and the importance of the ability of NHS hospital pharmacies to operate safely under Section 10 was emphasised by the NHS.

Matters of concern

You have expressed the following issues as matters of concern and I address each of the matters of concern within the remit of the MHRA below:

1. There is no requirement for a section 10 exempt entity to report any of its findings to the MHRA or indeed to other Trusts or the industry in general if an adverse event occurs.
2. The current reporting structures (for a section 10 entity) involve reporting to NHSE and the CQC but the threshold or necessity for such reporting appears unclear and, in essence, up to the Trust.
3. There may be times when section 10 entities reach conclusions which would assist the wider industry and help to assist both other Trusts and commercial organisations in assessing their own risks and improving the provision of highly specific medication to a group of vulnerable patients.
4. The same may also be true of commercial organisations but they have the power of the MHRA controlling and effecting recalls and actions and the wider dissemination of information.

Requirement to report adverse events to MHRA

It may be helpful to first clarify the situation in respect of the reporting of adverse events (interpreted as manufacturing errors). Part 5 of the Regulations places an obligation on the holder of any manufacturer's licence to inform the licensing authority (MHRA) immediately when they become aware of any defect which could result in a recall. This is coordinated using the MHRA's Defective Medicines Report Centre (DMRC) but it is noted that, at the point of recall the emphasis is on dissemination of appropriate information to facilitate a recall and not, necessarily, the root cause of the defect. Investigations carried out by the licence holder will be reported to the MHRA at a later date.

The Regulations also require that the licence holder implements a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network. Medicines extemporaneously prepared under Section 10 are done so in accordance with a prescription, so there would not be the possibility of a recall. The statutory requirement to inform the MHRA of defective medicines and/or report adverse events does not apply to medicines prepared under Section 10.

Section 64 of the 1968 Medicines Act relates to protection for the purchaser of medicines products noting that 'No person shall, to the prejudice of the purchaser, sell any medicinal product which is not of the nature or quality demanded by the purchaser'. This strict liability offence is mitigated only if extraneous matter present is an inevitable consequence of the manufacture of the medicine or if the addition or abstraction of a substance was not carried out fraudulently and did not injuriously affect the composition of the product[2].

The MHRA accepts that whilst there is not a requirement *to* report, nor is there a 'threshold', this is not a barrier to incidents being reported particularly in the context of Section 64. The

[2] https://www.legislation.gov.uk/ukpga/1968/67

NHSE's 'Assurance of Aseptic Preparation of Medicines Guidance' of 2023 states, at Appendix 3, that in instances of *serious* incidents the MHRA will investigate incidents where civil or criminal prosecutions may result. Our interpretation of this guidance is that while not a requirement, it is incumbent on Trusts to report instances where serious incidents may have occurred in their Section 10 NHS Pharmacy facility to the MHRA. The MHRA intends now to further communicate this expectation to facilities operating under the s10 exemption (see below).

Following the outcome of the inquest, the MHRA has discussed this with NHSE officials who advised they will review this Guidance to make it clearer that, where investigations of incidents in a Section 10 facility identify learnings which may not result in enforcement action, but which could impact licensed manufacturers, this should also be communicated without delay to the MHRA. It is anticipated that this would be done following escalation from the Trust to either NHSE or Care Quality Commission (CQC). It will mean that the MHRA can be contacted for reasons other than to take enforcement action, which is the message from the current guidance which needs to be clearer. The initial emphasis is on NHSE but this message will be expanded as soon as is practical and communicated to the devolved governments (see timescales below).

Communicating information on adverse events to other Trusts, wider industry and commercial organisations

The MHRA agrees there are potential scenarios where it could be important to promptly share information about a defective medicine prepared under a Section 10 exemption, and how the risk should be minimised, with licensed manufacturers. This will be done by the MHRA using existing and established mechanisms for communicating to licence holders. In regard to the sharing of information from the licensed manufacturing sector, the MHRA has established via the DMRC lines of communication to share information regarding defective medicines with the NHS compounding community (which includes Section 10 NHS hospital pharmacies) which are in addition to the reporting of defective medicines detailed above.

This is achieved via attendance at NHS Pharmacy QA Committee meetings (DMRC is a member), and which can also be via email correspondence on an *ad hoc* basis using the established membership. This Committee is made up of UK-wide NHS regional quality assurance leads, one of whom is appointed as chair. While this Committee facilitates communication in both directions, NHSE has indicated that there should be an additional approach which would be directly under its governance. It is our expectation that this will be covered in Memoranda of Understanding with NHSE and equivalent mechanisms with devolved governments (see below).

Accordingly, the MHRA will work with NHSE with a view to implementing a memorandum of understanding to enable appropriate categorisation and mutual dissemination of actionable safety information and learning from incidents at both an executive and operational level. The MHRA is also exploring with NHSE enabling better sharing of information with Trusts whose Section 10 NHS hospital pharmacy is under compliance monitoring by the NHS Specialist Pharmacy Services (SPS) and under the oversight of the MHRA's IAG which, as noted above, is MHRA's escalation route where critical failings in GMP are identified and the need for regulatory action against a licence may be required.

This plan also builds on work which is already being implemented to share common understanding of processes and procedures regarding the auditing of Section 10 NHS hospital pharmacies (SPS) and inspecting of licensed facilities (MHRA).

As detailed above there is a legal requirement for the holder of any manufacturer's licence, be they commercial organisations or NHS Trusts, to notify MHRA and work with us to instigate an appropriate recall. While the matter in question relates to NHS pharmacy units, the MHRA notes that the Section 10 exemption is not limited to NHS sites. Registered pharmacies (i.e. retail/commercial pharmacies) are under the jurisdiction of the General Pharmaceutical Council (GPhC) in Wales Scotland and England and the Pharmaceutical Society of Northern Ireland (PSNI) for Northern Ireland.

The MHRA already has Memoranda of Understanding with the GPhC and PSNI and will use these (including updating, as necessary) to highlight the need to ensure formal exchange of information related to the preparation of Section 10 medicines. Similarly, the MHRA will enter into dialogue with the CQC which regulates other healthcare settings in England e.g. independent hospitals and their equivalents, as these may also prepare medicines under the Section 10 exemption and should also be included in the planned programme of increased clarification of roles and responsibilities, information exchange and learnings.

Timescales for action:

- The MHRA will publish an update to the sector detailing issues raised by this case and our intentions to address the concerns (by the end of March 2025).
- The MHRA will agree and implement a memorandum of Understanding (MoU) with NHSE for routine updates (e.g. sites identified as high risk, increased oversight or under regulatory restriction) and also the dissemination of *ad hoc* learnings from incidents (by end of June 2025).
- The MHRA will inform devolved governments of this requirement to improve information exchange as soon as practical and agree an approach in line with that for the NHSE MoU (by end of September 2025).
- The MHRA will remind GPhC and PSNI of their responsibilities regarding commercial pharmacies and with CQC regarding the independent hospitals (by end September 2025).

I would be happy to discuss this proposed plan of action with you if that would be helpful.

Yours sincerely,

[redacted]

[redacted]
Chief Executive
Medicines and Healthcare products Regulatory Agency
E: [redacted]