BRIEF FOR ADVISERS ON ISSUE OF THE MANUFACTURE OF 'SOLUTION 18'

Introduction

1. Senior Counsel on behalf of the Raychel Ferguson family, Mr Michael Topolski Q.C., provided a note to the Inquiry dated 19th August 2010. Mr Topolski raised a number of issues regarding the scope of the Inquiry, including an issue regarding hypotonic intravenous saline solution (4% dextrose/0.18% saline) or "Solution 18":

   *"It would also be very helpful to know whether the Inquiry accepts that the examination of the relationship **(if any)** between medical practitioners and/or administrators and the manufacturers of Solution 18 is regarded as falling within the Inquiry's terms of reference. It seems to me that whether or not there is or was any kind of commercial tie-in that at its lowest may have encouraged some to prescribe this Solution 18 as opposed to any other fluid, should be the proper subject of investigation and inquiry."*

2. The Chairman of the Inquiry, Mr John O'Hara Q.C. responded to this point in his opening statement at the Progress Hearing held at Banbridge Courthouse on Wednesday 9th March 2011, stating as follows:

   "One other specific issue which was raised with us on behalf of the Ferguson family is about the manufacture of Solution 18 and connections between the manufacturers and the hospitals, whether there are any commercial considerations which affected that or, I guess by extension, improperly affected that. In response to this issue being raised with us we have made contact with the Medicines and Health Care Products Regulatory Agency and the European Medicines Agency, and we are engaging with them and with our expert advisers to determine whether this is an issue which the Inquiry should add to the issues to be investigated. If the advice we receive is that it should well then it will be added, if it isn't we will explain why it is not being included. Anyone who wants to can come in and make representations on that."

3. As indicated in the Chairman's remarks above, Ms Anne Dillon, Solicitor to the Inquiry, wrote to the Medicines and Health Care Products Regulator Agency (MHRA) and the European Medicines Agency (EMA) on 24th September 2010, requesting the following:

   "I would be grateful if you would provide me with any information you hold pertaining to the use of a hypotonic intravenous solution, namely 4% dextrose/0.18% saline. In particular, I would be grateful if you would advise me of the following:

   1. Whether you are aware of any literature dealing with the product's contra-indications.

2. *The date and details of any report made to you regarding the use and or safety of the solution. I am aware of only one report, made in September 2001 by Dr Robert Taylor of the Royal Belfast Hospital for Sick Children."*

4. The MHRA responded by letter of 4th October 2010 and the EMA responded by letter of 7th December 2010.

Response of the MHRA

5. The MHRA provided Summaries of Product Characteristics (SPCs) for the three 0.18% saline/4% dextrose solutions that are currently available on the UK market. SPCs are produced by the marketing authorisation holder and approved by the MHRA and contain information on how to use the product as well as contraindications and warnings about adverse effects. These SPCs are attached.

6. According to the MHRA, the three 0.18% saline/4% dextrose solutions that are currently available on the UK market (as of 4th October 2010) are:

- Sodium Chloride 0.18% and Glucose 4% Solution for Infusion BP (marketed by Baxter Healthcare Ltd)
- Steriflex No.18 or freeflex (marketed by Fresenius Kabi Ltd)
- Sodium Chloride 0.18% and Glucose Intravenous Infusion (marketed by Fresenius Kabi Ltd)

Response of the EMA

7. The EMA stated in December 2010 that it had not evaluated any solution for infusion of sodium chloride 0.18% and dextrose 4% for authorisation purposes. Such products were authorised in individual EU Member States, in accordance with their national authorisation purposes. Safety concerns regarding this product were not discussed by the Pharmacovigiliance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) of the EMA.

Reports received by the MHRA regarding suspected adverse reactions

8. The MHRA stated that there have been 2 reports through the Committee for the Safety of Medicine/MCA Yellow Card Scheme (YCS) of suspected adverse reactions associated with this solution:

(1) A female of unknown age who underwent abdominoplasty and died on 28th January 1999. The Reaction Text indicates that the female had

been infused by 3000 ml of glucose/saline and 500ml Haemaccel. When the batch was tested by the hospital, results indicated the batch did not contain sodium. It was indicated that this individual died as a result of a cerebral oedema caused by a post-operative infusion.

(2) A report of the Raychel Ferguson case by Dr. Robert Taylor of RBHSC. Dr Taylor had reported the case to the Medicines Control Agency by letter of 1st October 2001.

9. As a result of the latter report, Dr Katherine Cheng of the Medicines Control Agency produced a Safety Review paper in October 2001 on Hyponatraemia and 4% Dextrose/0.18% Saline in Children for the Committee on Safety of Medicines Working Group on Paediatric Medicines. (A copy is attached). At that time there were four marketing authorisation holders in the U.K. (paragraph 7 of Dr Cheng's report):

- Baxter Healthcare Ltd
- Maco Pharma (UK) Ltd
- Fresenius Kabi Ltd (this bears the same authorisation number as the third solution indicated at paragraph 6, ie Sodium Chloride 0.18% and Glucose Intravenous Infusion)
- Galen Research Laboratories

10. The Working Group met and discussed Dr Cheng's paper on 21st November 2001. They were asked to advise on whether they considered hyponatraemia and 4% dextrose / 0.18% saline in children to be a safety concern, whether there was any concern for children in situations other than after surgery, whether there was any concern for children in situations other than after surgery, whether there were specific indications for this particular solution in paediatric practice and whether there should be any changes to SPCs.

11. The Working Group advised that:

(1) There is a risk of hyponatraemia and electrolyte imbalance with the use of all IV fluids

(2) There was a risk of hyponatraemia with the use of this solution in situations other than surgery e.g. diahorrea and vomiting

(3) The solution is used as a standard maintenance fluid in paediatric practice and was designed specifically to provide maintenance requirements of dextrose and saline

(4) The crucial issue was careful monitoring of fluid balance in the post-operative period, with particular attention in avoiding fluid if the patient was oliguric (a physiological response to surgery)

(5) There should be no changes to product information

(6) The Working Group considered that the issue of hyponatraemia related more to clinical practice rather than to medicines regulation

Reports received by the EMA regarding suspected adverse reactions

12. The EU database for spontaneous reports (EudraVigilance) for adverse reactions reported with solution for infusion of sodium chloride 0.18% and dextrose 4% had one report relating to this solution between 1 January 1995 to 26 November 2010. The report dated 12th August 2010 related to a non-EEA country and relates to a male patient aged 49 years old who died after he given 1000ml infusion for intraperitoneal use.

Requirements

13. As can be seen from the Chairman's remarks in his opening statement to the Progress Hearing above, the Inquiry Team require written advice from the Expert Advisers as to whether the issues raised by Michael Topolski Q.C. regarding the manufacture and marketing of Solution 18 fall within the Terms of Reference of the Inquiry.

14. The Inquiry Team would therefore like your advice and comments on the following issues:

(1) The likelihood, if any, of a connection between the manufacturers of Solution 18 and hospitals/trusts/medical personnel that might have affected, or improperly affected, any decision on appropriate fluid administration

(2) Whether there are any commercial benefits from using a Solution 18 product in preference to a less hypotonic intravenous solution, for example, half-normal saline (0.45% saline + 4% glucose) or normal saline (0.9% saline + 5% glucose).

(3) Whether there are any commercial benefits from using a particular Solution 18 product from one manufacturer in preference to using another Solution 18 product from a different manufacturer

(4) The relative costs of Solution 18, half-normal saline and normal saline solutions

(5) The procedure and effectiveness of reporting of adverse effects from medication or solutions to the MHRA through ADROIT (Adverse Drug Reactions Online Information Tracking)

(6) Whether there is any significance or investigation required into the Yellow Card Scheme report of January 1999

(7) Whether further information needs to be sought to answer the above issues effectively, and if so, who can provide said information including:
- whether the Inquiry should seek information from the British National Formulary (BNF), the Royal Pharmaceutical Society (RPS), or Solution 18 manufacturers to seek literature from the time of each child's death
- whether the Inquiry should revert back to the MHRA to seek literature from the time of each child's death
- whether the Inquiry should ask Dr Katherine Cheng (or any more suitable person) to provide a background paper on Solution No.18

(8) Whether any of these issues should be included in the work of the Inquiry

15. Your advice and comments should be provided in the form of a referenced Report.

KEY ACCOMPANYING DOCUMENTS

(i) Letter from Professor Kent Woods, CEO, Medicines and Healthcare products Regulatory Agency to Anne Dillon, Inquiry Solicitor dated 4th October 2010 with accompanying SPCs, and reports of adverse reactions associated with Solution 18

(ii) Letter from Thomas Lonngren, Executive Director, European Medicines Agency dated 7th December 2010 with accompanying EudraVigilance search result

(iii) Safety Review paper prepared by Dr Katherine Cheng of the Medicines Control Agency in October 2001 on Hyponatraemia and 4% Dextrose/0.18% Saline in Children for the Committee on Safety of Medicines Working Group on Paediatric Medicines

(iv) Minutes of meeting on 21st November 2001 of the Committee on Safety of Medicines Working Group on Paediatric Medicines