

How can we optimise the pharmaceutical analysis of radiopharmaceutical pediatric prescriptions?

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ABSTRACT

Objectives In France, dispensation is defined by the validation of a prescription associated with a pharmaceutical analysis, preparation of medication and provision of information necessary for proper use. There are very few data available in the literature that describe prescription analysis modality in radiopharmacy. The aim was to secure a place for paediatric prescription analysis in radiopharmacy by designing a flow chart validated by experts.

Methods Experts from different disciplines and health setups (ie, public, private) were selected to represent the various paediatric patient care processes. A review of the literature on pharmaceutical analysis and paediatric prescription in radiopharmacy was conducted. A Delphi approach comprising two rounds (Google Form survey) was used to validate the flow chart. Answers were graded according to a nine-point Likert scale for agreement. Open-ended questions allowed experts to comment on the propositions. A consensus between experts was reached if more than 70% of the experts agreed on an item and fewer than 30% disagreed.

Results Sixty-five experts were solicited: two oncopaediatricians, three nuclear medicine physicians, 46 radiopharmacists, three residents in radiopharmacy, one hospital pharmacist, five medical physicists, one pharmacy technician, two X-ray technicians and two patients who are pharmacists. The first round survey included a draft of the flow chart: 31 experts answered (48%). All professional disciplines were represented except pharmacy technician. The second round survey was sent with a new flow chart that had been improved by the experts' comments. After 3 weeks, 18 answers were obtained (28%). After the first round, consensus was obtained for each item. Experts gave a total of 97 comments. The second flow chart had three steps: regulatory aspects, patient data, and radiopharmaceutical data, and it was accompanied by descriptive text explaining the field of application.

Conclusion The resulting flow chart will secure the pharmaceutical analysis step for this special patient population.

INTRODUCTION

In France, radiopharmaceuticals are regulated by two items of legislations. First, they are covered by ionising radiation legislation. Second, as they are medication, they must be prescribed by a nuclear medicine physician and managed by a radiopharmacist, who must ensure the dispensing process, including pharmaceutical analysis of the prescription.¹ Radiopharmaceuticals can be used for diagnostic or therapeutic procedures. The effects of

low-dose radiation exposure, which are encountered during diagnostic procedures in nuclear medicine, are poorly understood although several studies have suggested an overestimation of the risk.^{2–5} Particular attention is required in radionuclide therapy due to high activities that are administered. Furthermore, children appear to be more sensitive to ionising radiation than adults.

As pharmaceutical analysis is an essential step in guaranteeing the safety of the medication process, the French Health Authority evaluate this criterion during the hospital certification process.⁶ The importance of the pharmacist's role in reducing the risk of errors in the paediatric population has been well described.^{7,8} Furthermore, the paediatric population has a higher risk of potentially dangerous medication errors than do adults.⁹ Pharmacokinetics is of particular importance in the paediatric population because of the physiological development from newborn to young adult,¹⁰ especially renal and skeletal immaturities, brown adipose tissue activation and membrane permeability. There are very few publications in the literature that describe the radiopharmaceutical circuit and safety modalities for children.

STUDY AIM

The aim of this study was to guarantee the safety of paediatric care processes by designing a radiopharmaceutical prescription analysis tool validated by experts.

ETHICS APPROVAL

Ethics approval was not required.

METHODS

A review of the literature was conducted by a radiopharmacist with over 10 years' practical experience and a hospital pharmacy resident who specialised in radiopharmacy. PubMed and ScienceDirect databases were consulted in successive iterations using the following MeSH keywords: (paediatric) pharmaceutical validation, (paediatric) pharmaceutical analysis prescription, paediatric prescription in nuclear medicine, radiopharmaceutical paediatric prescription, and paediatrics in nuclear medicine. Summaries of product characteristics and reference books^{11–14} were also consulted to retrieve paediatric recommendations for each radiopharmaceutical. Relevant articles in the French or English language from 2006 onwards were selected by the team.

To highlight several steps of the pharmaceutical analysis we chose a flow chart presentation. We validated the propositions by taking a Delphi



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approach.^{15 16} By questioning experts by means of successive questionnaires, this method allowed a convergence of opinion and a general consensus on topics. A first draft of a flow chart was designed and proposed to experts (online supplemental file 1). Their responses were analysed in order to improve the flow chart. Experts were selected to represent all the paediatric patient care processes from the examination or treatment prescription to the administration of radiopharmaceuticals. We solicited paediatricians who prescribe nuclear medicine examinations or treatments, nuclear medicine physicians who prescribe radiopharmaceuticals, radiopharmacists and residents in radiopharmacy who analyse and validate radiopharmaceutical prescriptions, hospital pharmacists who validate prescriptions for paediatric populations, pharmacy technicians and X-ray technicians who are in charge of the preparation and dispensation of radiopharmaceuticals, as well as patients who are pharmacists. The expertise of these individuals was essential in gaining an overall view of all the pharmaceutical processes.

A survey (Google Forms) was circulated by email. Answers were graded according to a nine-point Likert scale for agreement (1 = total disagreement and 9 = total agreement). Consensus was considered to be reached if more than 70% of the experts agreed on an item (score between 7 and 9) and fewer than 30% disagreed (score between 1 and 3). Open-ended questions allowed experts to comment on the propositions. Experts could also answer 'do not want to respond' or 'cannot respond' to each question.

The following data concerning the experts was also collected: profession, number of years of experience and conflicts of interest disclosures.

Experts had a 4-week deadline (first round) and a 3-week deadline (second round) by which to respond. Email reminders were sent 1 week before the deadline.

RESULTS

To create the first draft of the flow chart, a review of the literature was conducted to determine different steps of the prescription analysis. We categorised analysis criteria into five groups: examination or treatment planned, legal requirements of the prescription, patient data, radiopharmaceutical data, and dose preparation.

The first phase of the analysis concerned planned examinations or treatments and focused on premedication. We concentrated on thyroid blockage which is specific to some iodine radiopharmaceuticals. A blocking agent must be administered to patients at risk for thyroid accumulation of the drug: [123I] iobenguane, [131I]iodomethyl norcholesterol, [123I]ioflupane and [125I]iodinated human albumin. Several drugs are available to protect the thyroid: Lugol's iodine solution, potassium iodine tablets, sodium perchlorate tablets or oral solution.¹⁷ In France, Lugol's iodine solution 1% is often used for children because of its easy availability. For the second part of the analysis, we studied legislation requirements for a radiopharmaceutical prescription. According to the legislation, all the usual data relating to the non-radiopharmaceutical prescription must be checked. In addition, the dosage must be expressed in Becquerels (Bq). Four radiopharmaceuticals, which can be administered to children, must have specific plasma-derived medicinal product (PDMP) traceability: [125I]iodated human albumin, [99mTc] human nanocolloidal albumin, [99mTc]macroaggregated human albumin and [99mTc]human serum albumin. The physician has an obligation to inform the patient or their legal representative about any risks. The information concerning the prescription,

the dispensation and the administration must be archived for 40 years.

Patient data analysis was the third step of the first flow chart. We studied paediatric population physiological specifics, physiological changes during childhood and their consequences for radiopharmaceutical pharmacokinetics. Renal and hepatic functions are two examples of physiological modifications during childhood.⁵ In addition to these modifications, special attention is required for children with renal or hepatic failure. Most recommendations are due to the renal excretion of radiopharmaceuticals. In cases of renal failure, particular attention should be paid to three radiopharmaceuticals: [111In]pentetreotide is not recommended, and [99mTc]DMSA and [99mTc]oxidronate administration must be followed by a 6- to 24-hour delay before image acquisition to guarantee the quality of the examination. 18F-Fluorodeoxyglucose (18F-FDG) image quality is affected by a high background activity but administration is not contraindicated.

The fourth step concerns radiopharmaceutical contraindications and dosage. Summaries of product characteristics contained recommendations of contraindication for the paediatric population for all radiopharmaceuticals available in France. We recorded several radiopharmaceuticals containing pharmaceutical excipients with adverse events. Benzyl alcohol contained in [125I]iodinated human albumin, [67Ga]gallium citrate, [123I] iodine 123 iobenguane and [131I]iodomethyl norcholesterol may cause a 'gaspings syndrome'. The presence of ethyl alcohol in some radiopharmaceutical specialties (18F-FDG and [131I] iodomethyl norcholesterol) must be considered before administration. Other radiopharmaceuticals contain ethyl alcohol but are not indicated in children.¹¹

Summaries of product characteristics mention the dosage for the paediatric population. Different methods exist in nuclear medicine to calculate paediatric doses. Paediatric dosage is based on the age of the patient, weight, height or body surface area and must be adapted to acquisition. Dynamic acquisition requires higher doses than static acquisition. Camera technologies are evolving and the dose can be reduced without diminishing the image quality but minimum activity is needed to perform an adequate examination.¹¹ The European Association of Nuclear Medicine (EANM) developed a method to calculate the optimum administered activity for the paediatric population called EANM Paediatric Dosage Cards.¹⁸ The Paediatric and Dosimetry Committees of the EANM categorised radiopharmaceuticals into three classes: renal tracers are in class A, thyroid tracers in class C and other radiopharmaceuticals are in class B. To obtain the recommended dosage the baseline activity value has to be calculated using the multiples provided for each radiopharmaceutical class. Only six isotope radionuclides are referenced in dosage cards. The last step concerned recommendations provided by the radiopharmacist, which are useful for the preparation of the radiopharmaceutical (eg, the need for a specific medical device or volume of drugs according to the route of administration).

All the data were mentioned in the draft flow chart that was proposed to the experts.

Sixty-five experts were solicited: two oncopaediatricians, three nuclear medicine physicians, 46 radiopharmacists, three residents in radiopharmacy, one hospital pharmacist, five medical physicists, one pharmacy technician, two X-ray technicians and two patients who are pharmacists. The first round survey was composed of six questions and was associated with the first flow chart (online supplemental file 2). Questions focused on both form and content. Each question ended with space for comments.

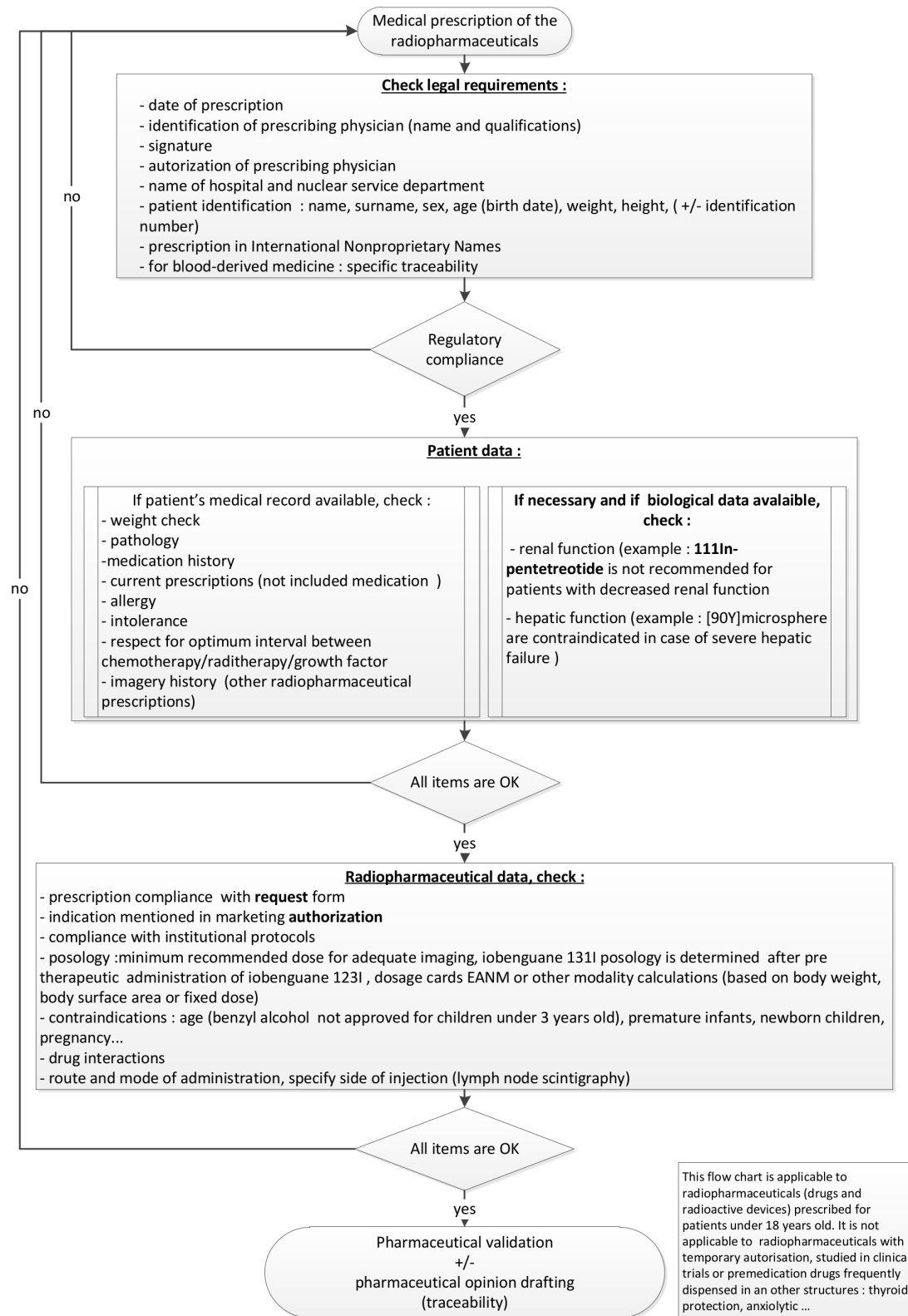


Figure 1 Flow chart for pharmaceutical analysis of radiopharmaceutical paediatric prescriptions. EANM, European Association of Nuclear Medicine.

Thirty-one experts answered (48%). All professional disciplines were represented except pharmacy technician. Average experience was 9 years (range, 6 months–25 years). No conflicts of interest were reported.

A consensus was obtained with the first round; however, nine experts wanted simplification and/or restructuring of the flow chart. These individuals proposed changing the chronology

of several items. Five experts wanted more detail in the part concerning information to the patient. According to the experts, several items were missing in the ‘legal requirements of the prescription’ step (date of the prescription and hospital) and in the ‘patient’ step (sex).

We removed the examination or treatment planning step and the recommendation for the preparation step from the flow

chart. We decided to have three steps in the new flow chart: regulatory aspects, patient data, and radiopharmaceutical data (online supplemental file 3). To keep the information about the two deleted steps linked to the prescription analysis, we wrote some introductory text defining the flow chart's scope and briefly describing the two removed steps. The text also described the legal considerations for pharmaceutical analysis in the paediatric population.

To ensure patient safety, a pharmacist can refuse to dispense a drug if he considers this necessary (Article 4235–61 of French Public Health Code) and has to immediately inform the prescribing physician of his refusal. The pharmacist also has to evaluate preparation feasibility: namely, supply of the radiopharmaceuticals, human and material resources for preparation, and quality control.¹⁹ Among other things, the pharmacist must check the French Nuclear Safety Authority (ASN) authorisation for the radionuclides and the maximum quantity allowed. After the analysis prescription process, recommendations should be provided to the person in charge of the preparation if necessary: syringe type (luer or luer-lock connection), volume of administration, and so on.

The flow chart, accompanied with the text, was proposed to the experts once again. The second round survey (six questions) was sent to the experts who answered the first survey (online supplemental file 2). Eighteen answers were obtained after 3 weeks (28%). After the first round, consensus was obtained for every item except one. Experts gave a total of 97 comments (first round: 60; second round: 37), of which 20 concerned the flow chart form.

After analysis of the second round, the introductory text was considered to be clear. Two experts thought that the text was too long. One expert considered the necessity of a pharmacovigilance conscious approach. Four experts considered checking every item in the patient file to be very difficult in daily practice.

Two experts wanted to add the unique patient identifier. Consensus was not reached for the item platelet count so we removed it.

Figure 1 shows the final flow chart composed of three steps instead of the initial five steps: regulatory aspects, patient data, and radiopharmaceutical data. Descriptive text explaining the fields of application introduced the flow chart and included important points regarding pharmaceutical analysis (box 1).

DISCUSSION

We focused on the paediatric population which has a higher risk of potentially dangerous medication errors compared with adults.

Peyronnet *et al*²⁰ and Potdevin *et al*²¹ have described how to secure the medication circuit but only limited data are concerned with the analysis prescription step in the paediatric population. Guérin *et al* have proposed criteria for the safety of the paediatric medication-use process that can be used in radiopharmacy,²² but several criteria specific to radiopharmaceuticals were not included in their study.

Some aspects of the analysis were not within the field of our study, in particular the traceability of the recommendations given by the pharmacist to the physician. Biechlin *et al*¹ have detailed modalities of prescription which could be electronic or paper-based. Wong *et al*²³ have described the advantages of electronic prescribing and computerised physician order entry. These systems generally contain some clinical decision support systems (eg, allergy alerts or drug dose suggestions and frequencies).

Box 1 Text explaining the fields of application introduces the flow chart and includes important points regarding pharmaceutical analysis.

Text accompanying the flow chart for the pharmaceutical analysis of radiopharmaceutical pediatric prescriptions

The dispensation of medication is defined in the Code de la Santé Publique (French Public Health Code) as the pharmaceutical acts associated with the delivery of medicine: pharmaceutical analysis of the medical prescription, supply of information and advice for correct usage of medication and preparation of doses to be administered.

This flow chart is applicable to radiopharmaceuticals (medication and implantable radioactive medical devices) prescribed for an examination or a treatment for patients under 18 years old. This flow chart does not concern medication prescribed under regulation, for clinical trials or delivered outside the hospital (thyroid blockers, anxiolytic drugs, etc.).

The following items are included in the preliminary request for pharmaceutical analysis of paediatric radiopharmaceutical prescription:

- ⇒ Fixed appointment (date, hours of the examination or treatment)
- ⇒ For a computerised prescription, parameters in relation to training (prescription for nuclear medicine physicians and pharmaceutical validation for radiopharmacists)
- ⇒ Availability of the medication
- ⇒ Availability of the medical devices necessary for the preparation
- ⇒ Testing of the equipment (flow hood)
- ⇒ Validation of documents (procedures, patient advice leaflet)
- ⇒ If possible, putting in place the specific circuit for the paediatric patient.

The pharmaceutical analysis is realised by means of three verification steps:

- ⇒ Presence of regulatory data (computerisation could secure this step)
- ⇒ Patient data
- ⇒ Medication data.

During the verification process, additional information may be required from the prescriber.

The pharmacist gives advice during the pharmaceutical analysis. This advice must be traceable. The article R 4235–61 of the Code de la Santé Publique states that the pharmacist should refuse to deliver medication if this is necessary in the interests of the health of the patient. The pharmacist should immediately inform the prescriber of his refusal and the action must be traceable.

Information is collected during pharmaceutical analysis and transmitted to the person in charge of the preparation of doses to be administered:

- ⇒ Choice of medical devices (eg, luer-lock syringe for central intravenous injection)
- ⇒ Incompatibility of the material

Specific procedures for preparation (example: respect of the number for aggregated human albumin).

During pharmaceutical analysis, the pharmacist can ask the prescribing physician for complementary information. The pharmacist gives an expert opinion which must be traceable.

In radiopharmacy we do not classify the analysis as does the French Society of Clinical Pharmacy (SFPC). Three levels of

analysis of prescription are defined according to the involvement of the clinical pharmacist.²⁴ This classification applies to therapeutic drugs but not to diagnostic radiopharmaceuticals. For SFPC, the first level is a simple analysis of the treatment prescription, the second level includes an analysis of all the different prescriptions, and the third level involves pharmaceutical monitoring. Access to the patient medical history is different in each health setup branch and the flow chart must be adapted to this constraint. Human resources should be linked to allow all possible checks to be made.

In France, any adverse event due to radiopharmaceuticals must be reported to the French health authority.²⁵ Different studies in various countries on the adverse reactions reveal their rarity.^{26–28} A robust pharmacovigilance system is essential and allows sharing of information. Such data will help radiopharmacists and other healthcare workers to improve patient care.

The Delphi approach was an easy means of reaching a consensus between experts from different disciplines and health setups (ie, public, private) and geographical locations. An unusual feature of the present study was that we solicited opinions from experts concerned with the steps in the medication circuit for paediatric patients. Paediatric patients themselves could not be surveyed. We also solicited opinions from patients who are pharmacists so as to have another viewpoint for the flow chart. Only one responded to the survey – a hospital pharmacist – and he shares the view of other participants on the flow chart.

The anonymity and confidentiality of responses were the most important advantages of this method, which help avoid potential confrontations between experts. The main drawback was the lack of discussion between experts.

The ratios of the various experts who participated in this study demonstrates their interest in the development of this tool. The flow chart is a tool to help pharmacists to standardise and secure the prescription analysis process. Dubois *et al* have previously demonstrated the importance of training in pharmaceutical analysis.²⁹

The introductory text is essential for understanding the flow chart and briefly explaining the different aspects of the pharmaceutical analysis that have been detailed previously. The developed tool is simple to understand.

CONCLUSIONS

We have created the first flow chart for radiopharmaceutical prescription analysis in paediatrics. The resulting tool is currently being used in our department and has allowed us to secure prescription analysis in radiopharmacy, which is an essential step in guaranteeing the safety of the medication process. The flow chart concept is proposed to software editors to improve their products and patient security.

What this paper adds

What is already known on this subject

⇒ Very few publications describe the radiopharmaceutical circuit and safety modalities for children.

What this study adds

⇒ We are proposing the first flow chart for radiopharmaceutical prescription analysis in paediatrics validated by experts.
⇒ This tool will secure prescription analysis in radiopharmacy.

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