

Pharmacotherapy of unlicensed medicines prepared and distributed by Dutch pharmacies

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ABSTRACT

Introduction and objective In the Netherlands, preparing and distributing pharmacies (PDPs) are taking over a large proportion of pharmacy preparations. PDPs prepare and distribute medicinal products to dispensing pharmacies. Many pharmacies have stopped pharmacy preparation. However, this contravenes the Dutch Medicines Act and the European Union (EU) Directive 2001/83/EC on which Dutch law is based. This is because the medicinal products of PDPs are unlicensed and PDPs do not have a manufacturing licence.

Methods To solve the conflict with the Dutch Medicines Act, PDPs have since 2007 been authorised by the Dutch Health Care Inspectorate by means of a circular letter. This circular letter describes the qualitative conditions that must be fulfilled by PDPs. The circular letter's conditions state that PDPs must perform verifiable investigations to assess the availability, or not, of licensed pharmacotherapeutic alternatives (PA investigations) and to assess the pharmacotherapeutic rationale and the needs of the patient (PT investigations).

Results Regular visits were performed by the Dutch Health Care Inspectorate to check the compliance of PDPs with the circular letter. This article describes the results of these inspections for PA and PT investigations.

Conclusions The results of the inspections show that so far almost all PDPs inspected have complied with the PA and PT conditions of the circular level at system level. However, in a substantial proportion of cases, the rationale of the pharmacy-made products is insufficient or insufficiently documented.

the prescriptions of a pharmacopoeia that is intended to be supplied directly to the patients served by the pharmacy in question).¹ Although the scale of the operations of PDPs and the number of pharmacies they are supplying vary widely, these definitions of magistral and officinal formula refer to pharmacy preparation on a small scale, which does not usually correspond to the larger scale of a PDP.² This contravenes the Dutch Medicines Act because the medicinal products are unlicensed and PDPs do not have a manufacturing licence.³

There are, however, patients who need a pharmacy preparation because there is no licensed alternative available on the market. To solve the conflict with the Dutch Medicines Act, PDPs have been authorised by the Dutch Health Care Inspectorate by means of a circular letter since 2007.⁴ This circular letter, which was put before parliament by the Ministry of Health, Welfare and Sport, allows, under strict conditions, the preparation of unlicensed medicinal products in a preparing pharmacy and the distribution of these products to a dispensing pharmacy. The dispensing pharmacy can make an assessment concerning the pharmacotherapy, but the final responsibility for the preparation lies with the preparing pharmacy. PDPs are only accepted in particular cases when there are no alternatives that have marketing authorisation available for the patient, so there is a danger that there is no adequate treatment. If there is a pharmacotherapeutic alternative for the pharmacy-made product, the PDP is not allowed to prepare or distribute the product.

INTRODUCTION AND OBJECTIVE

The Medicines Act and the circular letter for preparing and distributing pharmacies (PDPs)

The Medicines Act in the Netherlands forbids the preparation and distribution of an unlicensed medicinal product by a PDP to a dispensing pharmacy. The latter pharmacy receives the prescription for a patient and provides the pharmacy preparation to the patient.

The Medicines Act in the Netherlands is based on European Union (EU) Directive 2001/83/EC. This Directive and thus the Medicines Act requires that no medicinal product may be placed on the market of a member state unless a marketing authorisation has been issued by the competent authorities of that member state.¹ The limited exceptions to this general rule are the magistral formula (any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient) and the officinal formula (any medicinal product prepared in a pharmacy in accordance with

Conditions for PDPs

PDPs are obliged to comply with the circular letter's conditions that:

- No licensed alternative medicinal product is available on the Dutch market;
- The pharmacotherapeutic rationale is demonstrated;
- Product dossiers are available for all products;
- Production complies with good manufacturing practice (GMP).

If PDPs do not fulfil these conditions, they have to stop the preparation and distribution of these unlicensed products.

The general requirements of the circular letter, background information concerning Dutch regulation and policies, selection of the PDPs, publication of inspection reports, and results of inspection visits related to the circular's conditions 'C' and 'D' (product dossiers and GMP) are presented in a separate article.⁵ The present article describes the compliance of Dutch PDPs with the requirement of the circular letter that a special need must be shown for the pharmacy preparation.

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Pharmacotherapeutic alternatives (PA) and pharmacotherapy (PT) investigation

PA and PT investigations are two requirements for PDPs that were introduced with the 2007 circular letter:

1. PA investigation, where the pharmacist has to investigate and document the availability of licensed pharmacotherapeutic alternatives and has to show evidence that none of these alternatives are available before the pharmacist makes the pharmacy preparation.
2. PT investigation, where the pharmacist performs investigations on the pharmacotherapeutic rationale and has to show documented evidence for the need for the pharmacy preparation.

Objective of the study

The aim of this study is to assess the overall compliance of PDPs with these two conditions, PA and PT investigations, of the circular letter. Regular visits have been performed since 2007 by the Dutch Health Care Inspectorate to check the compliance of PDPs with the circular letter. PDPs not complying were revisited until they complied. If they did not comply during repeated visits, then they had to stop their preparation and distribution activities.

This article describes the results of Dutch Health Care Inspectorate inspections carried out since 2007 for the PA and PT condition of the circular letter, including such measures as enforcement.

PDPs are responsible for the documented evidence concerning the PA and PT investigations for all products.

METHODS

The Inspectorate has developed an instrument to assess whether PDPs have carried out the PA and PT investigation adequately. Instructions were prepared by the associations of hospital and community pharmacists in order to teach PDPs how they could perform these investigations adequately. The interface between the pharmacists and the prescribers starts with the indication included in the PA/PT documentation. If there is uncertainty about a prescription or the indication, the pharmacist should contact the prescriber directly to clarify the matter.

Inspections to judge the evidence-based PA and PT documentation

One of the aims of the inspections was to assess whether the PDP complied with the circular letter's conditions for PA and PT. It needs to be demonstrated that the PDP is capable of performing and documenting the PA and PT investigations appropriately. In general, it was assessed whether the PDP had clear and unequivocal procedures on the one hand and whether the compliance with these procedures in daily practice was sufficient on the other hand.

To diminish inter-rater variability, assessments were carried out by inspectors who were trained and who were able to use table 1 where the scores from 1 to 4 are clearly defined.

Score for PA investigation at system level as assessed during PDP inspection

The assessment by the Inspectorate of the PA investigations carried out by the PDP consisted of three items to be scored:

1. The procedure for assessing pharmacotherapeutic alternatives;
2. The criteria for the pharmacotherapeutic alternative included in the procedure;

Table 1 Assessment scores

1 (absent)	The standard is absent; the standard is not followed and is not available in a documented form.
2 (available)	The standard is demonstrably available, but it is not followed consistently. The written procedures are available, but not all employees involved in PA investigation are aware of the procedures.
3 (operational)	The standard is operational and is followed consistently. All employees working with the standard are aware of the written procedures, but a regular evaluation or adjustment does not take place.
4 (guaranteed)	The standard is guaranteed and followed consistently. The employees are well aware of the written procedures. Moreover, regular evaluation takes place and, if needed, adjustment.

3. The investigation of licensed pharmacotherapeutic alternatives based on a random check by the Inspectorate of the forms for selected products.

The score for each of these three items could vary from 1 to 4, as shown in table 1.

Based on observations and information gained during the visit to the PDP, the Inspectorate assessed each item to be scored as adequate if that item scored at least 3. A score of 4 is the level of quality to be strived for, but this score was not always assessed during the inspection visits.

The result for the circular letter's condition relating to PA was considered to be sufficient if a score of at least 3 was given for each of the three above items to be scored. This means that the PDP has clear procedures and instructions on how to perform the PA investigation and that it follows these in daily practice.

Score for PT investigation at system level as assessed at the PDP inspection visit

The assessment by the Inspectorate of the PT investigations carried out in the PDP consisted of three items to be scored:

1. The procedure for assessing the pharmacotherapeutic rationale;
2. The assessment of the pharmacotherapeutic rationale for a stock preparation, based on a random check by the Inspectorate of the forms relating to a sample of selected products;
3. The minimum requirement for the level of evidence for prepared stock preparations distributed to other pharmacies.

For assessment of the pharmacotherapeutic rationale, PDPs use a classification scheme that ranges from A1 (a high level of evidence) to D8 (the lowest level of evidence).⁶ A1 refers to systematic reviews consisting of at least some investigations of A2 level that consistently show evidence. A2 refers to a randomised, double-blind, controlled clinical trial of sufficient magnitude and consistency. D4 refers to evidence-based advice from national associations of specialists or national associations of pharmacists. D8 reflects a low level of evidence; the pharmacotherapeutic treatment in this case is only based on the individual insights of treating physicians without objective clinical evidence.

The minimum requirement for a PDP is D4 for the distribution of stock preparations. This implies that there is evidence-based, country-wide consensus for application of the product for that particular indication.

The score for each of these three items could vary from 1 to 4, as shown in table 1.

The result for the circular letter's condition relating to PT was considered to be sufficient if a score of at least 3 was given for

each of the three items. This means that the PDP has clear procedures and instructions on how to perform the PT investigation and that it follows these.

RESULTS

In 2007 and 2008, the Inspectorate selected the PDPs to be visited based on a questionnaire that was sent to all pharmacies. A risk-based approach was applied in the sense that the PDPs with the highest number of dispensing pharmacies—that is clients—were visited first. The reason for this is that, in the case of a possible product defect, the consequences are greater if the product is distributed to more pharmacies. There was a large variation in the group of PDPs visited, but, for all PDPs, the number of dispensing pharmacies was at least 10. Nearly all PDPs that dispensed their products to at least 10 dispensing pharmacies have been inspected. However, changes in the status of PDPs occur continuously, which means that the planning of the visits has to be adapted regularly. At present, there are still PDPs that decide to stop either their preparation or their distributing activities or both. The Inspectorate has performed repeated inspections at most of the PDPs that did not comply with the conditions of the circular letter. PDPs that stopped distribution to dispensing pharmacies were visited to verify that they had, in fact, stopped.

Overall compliance of PDPs with the circular letter's conditions at system level

The results of the surveillance of the Inspectorate show that compliance with the circular letter's conditions has increased significantly and consistently since 2007. On 1 November 2014, almost all PDPs distributing their products to more than 10 dispensing pharmacies had been visited by the Inspectorate. Of these, 18 complied and three nearly complied with the circular letter's conditions, while 10 had stopped distribution to dispensing pharmacies for various reasons. The progress made was possible because of the efforts of different stakeholders including the PDPs themselves, the associations of PDPs, and the Dutch Health Care Inspectorate. A more detailed description of the overall compliance with the circular letter's conditions can be found in a separate article.⁵

Compliance of PDPs with the PA and PT conditions of the circular letter at system level

The PDPs are obliged to document the results of their PA and PT investigations for all products. By means of these PA and PT investigations, the pharmacist documents the added value of the unlicensed pharmacy preparation. The PDP uses primary criteria⁷ such as efficacy, tolerability and safety, and secondary criteria⁷ such as their experience with the product and how easy it is to use, in order to draw comparisons between the pharmacy preparation and the licensed alternative.

Examples are patients who are allergic to lactose or other ingredients of the registered product, or patients who need a lower dose than the registered dose of a medicinal product.

On 1 November 2014, 20 of 21 PDPs visited had fulfilled the PA condition of the circular letter at system level. Nineteen of the 21 PDPs had complied with the PT condition at system level. For these complying PDPs, the procedures for PA and PT are available and are followed consistently in daily practice. There were two PDPs that did not comply with the PA or PT condition. Their PA and PT documentation needed improvement.

The reports of the Inspectorate's visits to PDPs aimed to assess the quality assurance system the PDP had set up to comply with the conditions of the circular letter. How the

PDP's system functioned in daily practice was checked by the Inspectorate by means of a random check of the forms of selected products. If these forms were not available, or if they contained significant omissions, then the Inspectorate scored as insufficient the functioning of the PDP at system level.

Compliance of PDPs with the PA and PT conditions of the circular letter at the level of the product

We describe above how the Inspectorate assessed the compliance of PDPs with the conditions of the circular letter at system level. This assessment by the Inspectorate included a check on the functioning of the system in PDPs in daily practice for a selection of products made during the visits.

Apart from the inspection aimed at assessing the quality assurance system for PA and PT, the Inspectorate also requested in 2011 that all PDPs send a list containing the complete range of products, including the actual numbers distributed per product. The product lists of all PDPs were reviewed and discussed by the Inspectorate in order to find 'clear' violations of the circular letter's conditions. If the Inspectorate had concerns that those products might not fulfil the conditions of the circular letter, then the PDP was requested to send them the PA and PT documentation. This request was based on a number of criteria.

- The number of units or packages distributed. Products with the highest numbers were selected preferably, as indicated in the list submitted by the PDPs.
- Products which, in the opinion of the Inspectorate, were possibly obsolete or dangerous.
- Availability of licensed alternatives on the Dutch market.
- Combination products that raised questions in the minds of the Inspectorate.

The Inspectorate received the PA and PT documentation of the products it selected from the PDPs. It then sent these to the National Institute for Public Health and the Environment (RIVM) to be assessed. The conclusions of the RIVM were discussed by the Inspectorate with the PDP during the inspection visits. If, as in some cases, there was a clear pharmacotherapeutic rationale for the product, then the PA and PT documentation had to be improved. However, with other products, the PDP had to stop production and distribution altogether.

The results of the assessments of the RIVM are published in a report on the RIVM website.⁸

Results of the PA and PT documentation of PDPs' products

It is clear that PDPs had difficulty making accurate PA and PT documentation. The following deviations in PA and PT documentation were found during the inspections.

- ▶ No comparison was made or documented with licensed pharmacotherapeutic alternatives.
- ▶ The comparison with other pharmacotherapeutic alternatives only consisted of products with the same compound.
- ▶ No comparison was made with other administration routes of the licensed alternatives.
- ▶ A ready-to-use (RTU) product was found with a higher dose than that recommended by the Formulary of Dutch Pharmacists (FNA) without justification or evidence offered for the higher dose recommended.
- ▶ The indication for the product was missing.
- ▶ The advantages of a combination product containing two licensed medicinal products over separate application of the two licensed products were not adequately documented.
- ▶ The pharmacotherapeutic rationale of thyroid powder of animal origin (thyroideum) was not demonstrated while pharmacotherapeutic alternatives are available on the market.

- ▶ Evidence for the usefulness of the product for the indication was missing.
- ▶ The level of evidence for the pharmacotherapeutic rationale as assessed by the PDP was inadequate or missing.
- ▶ Documentation, including data from the literature, on the indication claimed for the product was not adequate to draw conclusions on its efficacy and safety.
- ▶ An unequivocal concentration for the product was missing.
- ▶ The starting material for the pharmacy preparation was not described in the product dossier.
- ▶ The advantage or added value of the product over the licensed alternative was inadequately documented in the product dossier.
- ▶ There was no proof that the D4 level, constituting a national consensus, was achieved.

Shortcomings were reported back to the PDP, with the request that they should either take adequate measures to correct the shortcomings or stop distribution of the pharmacy preparation. Measures taken by the PDPs were checked during subsequent visits.

DISCUSSION

Concerning the circular letter's condition with regard to PA, the terms 'licensed pharmacotherapeutic equivalent' and 'licensed pharmacotherapeutic alternative' are used. Some PDPs focus on therapeutic equivalents and look for registered products with exactly the same active ingredient, the same dose, and the same administration route. In recent years the views have changed in the sense that different compounds may be interchangeable as long as the indication is the same and the prescribing physician takes responsibility for the prescription.

The term 'therapeutic alternative', however, is difficult to define for the whole population. This is because what is an alternative for the majority of patients may not be an alternative for the minority who are insensitive or hypersensitive to that specific medicinal product. The pharmaceutical industry cannot always take into account the needs of smaller patient categories. A pharmacy preparation with another chemical substance for the same indication is sometimes unavoidable.

Sometimes the dose is a reason to opt for the pharmacy preparation, as the number of patients who need a lower or higher dose than the range of the registered alternative appears to be increasing. Thus, there is a need for more individualised therapy, which cannot always be covered through licensed medicinal products. Examples of patient categories where another dose may be needed are children and patients with impaired kidney function, including the elderly.

The criteria to be used for comparison with registered alternatives, as well as for the added value of the pharmacy preparation, are subdivided by the pharmacists into primary and secondary criteria,⁷ suggesting that the weight of primary criteria for the individual patient is higher than that of the secondary criteria. Secondary criteria could be seen as soft criteria, but it is difficult to draw general conclusions for all patient categories. For example, 'ease of use' may be extremely important for patients with rheumatoid arthritis who may encounter difficulties in the handling of medicines, whereas this aspect may be of negligible importance for other patient categories.

There are PDPs that specialise in aseptic preparation and dispensing of parenteral medicines with a marketing authorisation which cannot be administered directly to patients—that is, they are not presented in ready-to-administer (RTA) form. For these medicines in particular, patient safety and medication safety are crucial topics in healthcare institutions.⁹ The last steps in the

process of individualising treatment with licensed medicinal products for patients sometimes need to be performed in a pharmacy or sometimes on the ward of a hospital. This may be carried out on the wards by employees who also have other tasks to perform and who do not always have a quiet environment in which to prepare the product or perform a complicated calculation. Therefore some hospital pharmacies and some PDPs offer the service of making so-called RTU and RTA¹⁰ products:

1. RTU is defined as an injection containing the active drug in solution at the required concentration and volume in a vial. The injection is then transferred to a final container, such as a syringe, infusion bag or elastomeric device, for administration to the patient.
2. RTA is defined as an injection containing the active drug in solution at the required concentration and volume, presented in the final container, such as a syringe, infusion bag or elastomeric device, and is ready to be administered to the patient.

As a consequence of RTU and RTA, the further processing of the product in the hospitals is simplified. This means a reduced number of preparatory steps in the process, a reduced need for calculations and no need for dilution. Reconstitution of parenteral medicinal products should preferably take place in a pharmacy assuming that the requirements concerning the safe preparation of sterile products can be fulfilled. Pharmacy services such as RTU and RTA may reduce risks on the hospital wards and improve patient safety.

Some pharmacy preparations are based on development activities carried out at the FNA. This means that the PDP can rely partly on FNA knowledge as long as the pharmacist can guarantee following exactly the procedure and processing proposed by the FNA, including having the correct equipment and expertise. Validation activities can simply be added to the already available FNA knowledge and can be simplified for FNA products.

Sometimes a pharmacy preparation is a second- or third-choice treatment. PDPs are only allowed to make these products if it can be shown that first-choice and/or second-choice treatments for this indication have failed or have given demonstrable adverse events. The pharmacist should be able to prove that the use of the product conforms to this treatment schedule.

During the inspections, the product, thyroideum, was encountered in one of the PDPs. The choice of this product was seen as being irrational, because licensed pharmacotherapeutic alternatives are available on the market. The preparation and distribution of thyroideum to dispensing pharmacists is forbidden because this is not in accordance with the circular letter's conditions. There may be a limited place for thyroideum. It may only be used for those patients with a demonstrably unfavourable reaction to the registered alternatives. More details concerning the position of the Dutch Inspectorate can be found on its website.¹¹

Another case that the Inspectorate has encountered during inspections is the topic of methotrexate syringes. The pharmaceutical company distributing the licensed methotrexate syringes enlarged the dose range of licensed syringes. When these additional syringes offering a new dose became available on the market, the preparation activities of some PDPs had to be stopped. More details on the position of the Dutch Ministry and Inspectorate can be found on the website.¹²

CONCLUSIONS

Almost all PDPs inspected complied with the PA and PT conditions of the circular letter on a systematic level. The report of the RIVM,⁵ however, shows that the rationale of the pharmacy-made products is insufficient or insufficiently documented in a substantial proportion of cases.

There is a national acceptance by hospital and community pharmacists, together with other important organisations in healthcare, to only make pharmacy preparations with a favourable pharmacotherapeutic rationale for which no licensed pharmacotherapeutic alternative is on the market.

PA and PT documentation of PDPs still requires attention. PA and PT documentation of a PDP should be available for all products and should show the added value for the patient.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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