Inspectorate surveillance of preparing and distributing pharmacies in The Netherlands

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ABSTRACT

Introduction and objective The preparation of medicines in pharmacies is essential for accommodating the individual needs and medical conditions of patients in Europe and beyond. This article describes the state of pharmacy preparation in preparing and distributing pharmacies (PDPs) in the Netherlands. The Medicines Act in the Netherlands is based on the European Union Directive 2001/83/EC, which forbids a PDP from preparing and distributing unlicensed medicinal products to dispensing pharmacies. In order not to obstruct patient care, the Dutch Inspectorate has sent a Circular Letter on large-scale preparation to all Dutch pharmacists. This Circular describes the qualitative conditions that must be fulfilled by the PDPs. The aim of this study was to assess the overall compliance of Dutch PDPs with the conditions of the Circular. These conditions are: an absence of licensed pharmacotherapeutic alternatives, rational pharmacotherapy, a product dossier for all products and compliance with Good Manufacturing Practice (GMP). **Methods** PDPs are obliged to fulfil the conditions of the Circular. If PDPs do not fulfil these conditions, then they have to stop preparing and distributing medicinal products. A questionnaire was sent to all Dutch pharmacies to get information about the number of PDPs and the number of pharmacies served by each PDP. The instrument that was used in this observational study to assess the compliance of the PDPs with all conditions of the Circular is described.

Results The results of the inspections until now show that on 1 November 2014, 18 out of 21 PDPs fulfilled the four conditions of the Circular. Only minor deficiencies were found with 3 out of 21 PDPs. Twenty out of the 21 PDPs visited fulfilled the condition concerning the absence of pharmacotherapeutic alternatives and 19 out of 21 PDPs visited complied with the condition of rational pharmacotherapy. Nineteen out of the 21 PDPs visited fulfilled the Circular condition that a product dossier was available for all products. All of the 21 PDPs visited complied with GMP. Regular visits, at least every 3 years, were performed by the Inspectorate to check the compliance of the PDPs with the Circular. The publication of the inspection reports on the website of the Inspectorate allowed, probably, many PDPs to be better prepared. The inspection visits showed that the PDPs have invested in compliance with the conditions of the Circular.

Conclusions Most of the PDPs fulfilled the requirements of the Circular. The Inspectorate is in consultation with the Ministry of Health, Welfare and Sport about how to proceed with the question of PDPs and the conditions they have to fulfil. Recent European case law will have to be taken into account.

INTRODUCTION AND OBJECTIVE

The Medicines Act and the Circular for preparing and distributing pharmacies

The Medicines Act in the Netherlands is based on the European Union (EU) Directive 2001/83/EC, which forbids an unlicensed medicinal product being prepared and distributed by a preparing and distributing pharmacy (PDP). PDPs prepare medicinal products in their pharmacy and distribute these products to a dispensing pharmacy. The dispensing pharmacy receives the prescription for a patient and provides the pharmacy preparation, made by another pharmacy, to the patient.

In the Netherlands, a pharmacy consists of premises that are coherent and connected.¹ By law, it is obliged to have a pharmacy at each address where a stock of medicines is kept. Therefore, a PDP that prepares and distributes medicinal products to dispensing pharmacies belonging to the same legal entity has to fulfil the conditions of the Circular.

There are, however, patients who need a pharmacy preparation because there is no adequate licensed alternative medicinal product available on the market.² 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 that medicinal product. Strict reinforcement of the Medicines Act by the Inspectorate is not considered an option because this would impede the availability of these essential medicines.

Since 2007, the PDPs have been permitted by the Inspectorate by means of a Circular.³ This Circular was supported in parliament by the Ministry of Health, Welfare and Sport. It is obliged to fulfil the conditions of the Circular. If the PDPs do not fulfil the conditions of the Circular then they have to stop the preparation and distribution of their medicinal products.

The trend is towards pharmacies stopping with pharmacy preparation and transferring these activities to PDPs.² In general, routine preparation on a large or a more frequent scale, with the use of specific equipment and expertise, provides a better product quality assurance.

The Inspectorate monitors these developments in order to ensure that the principle of market authorisation for medicinal products, as described in the EU Directive 2001/83/EC and implemented in the Dutch Medicines Act, is not undermined. This Act⁴ requires that medicinal products that are available on the Dutch market are evaluated in advance for their efficacy, safety and quality by the Dutch Medicines Board or European Medicines Agency and that a marketing authorisation is granted, if appropriate, for these medicinal products. This Act⁵ also requires that medicinal products are prepared under a

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manufacturing licence. However, limited exceptions exist. One such is the preparation and dispensing of the medicinal products on a small scale by a pharmacist in his or her pharmacy.^{5,6} Usually, the larger scale of a PDP excludes it from this exception, which is geared towards small-scale preparation in a pharmacy.

Conditions for PDPs

In the Circular, the Inspectorate explains that PDPs are obliged to fulfil the following conditions:

- A. No licensed alternative medicinal product is available on the market.
- B. The pharmacotherapeutic rationale is demonstrated.
- C. Product dossiers (PDs) are available for all products.
- D. Production complies with Good Manufacturing Practice (GMP).

Advertising is forbidden

The Circular³ states that neither the PDP nor the dispensing pharmacy is allowed to advertise for unlicensed medicines. This is a logical consequence of the EU Directive 2001/83/EC, which is implemented through the Dutch Medicines Act.⁷

Compliance with these conditions is assessed during inspections by the Inspectorate. If these conditions are not fulfilled by the PDP then the PDP has to stop the preparation and the distribution of its medicinal products.

Objective of the article

The aim of this study was to assess the overall compliance of the PDPs with the conditions of the Circular. These conditions are: an absence of licensed pharmacotherapeutic alternatives (PA), rational pharmacotherapy, a PD for all products and compliance with GMP. Regular visits were performed by the Inspectorate to check the compliance of the PDPs with the Circular. 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 the Dutch Health Care Inspectorate programme operating since 2007 for each of the conditions of the Circular, including such measures as enforcement.

CONSULTATIONS WITH PROFESSIONAL ASSOCIATIONS

Consultations between the Inspectorate and the associations of pharmacies, including hospital pharmacies

The Inspectorate has conducted periodic consultations with the associations of pharmacies, including hospital pharmacies, which began immediately after the Circular came into force. These consultations were aimed at the details of the conditions of the Circular and its implementation.

The associations of pharmacists have developed guidelines and tools⁸ for pharmacists on:

1. How to investigate and document the availability of registered PA and to show evidence that none of these alternatives is available before the pharmacist makes the pharmacy preparation. PA investigation.
2. How to perform investigations on the pharmacotherapeutic rationale and to show documented evidence for the need for the pharmacy preparation. Pharmacotherapeutic rationale (PT) investigation.
3. How to compile an adequate PD, for stock preparations and for standardised individual preparations. PD investigation.
4. How to comply with GMP.

Frequently asked questions and answers, published by the Inspectorate

There was a need, expressed by community pharmacists and hospital pharmacists, for further clarification of the conditions

of the Circular. Therefore, the Inspectorate has put answers to frequently asked questions on its website.⁹

METHODS

Questionnaire aimed at achieving transparency

Because there is no notification requirement for PDPs in the Dutch Medicines Act, the Inspectorate has sent a questionnaire to all pharmacies in 2007 and 2008 asking them about the status of their preparation activities, as far as it concerned the distribution of unlicensed pharmacy-made medicines to other pharmacies. The results of the questionnaire were used to perform risk-based inspections. The PDPs that served the highest number of dispensing pharmacies were given the highest priority when arranging visits. The reason for this is that, in the case of a possible product defect, the consequences are higher if the product is distributed to more pharmacies.

The questionnaire was sent in 2007 and 2008 to 2480 Dutch pharmacies, including 81 hospital pharmacies. The response to the questionnaire was 99% for hospital pharmacies and 94% for community pharmacies. There were 379 PDPs:

- 7 pharmacies (2%) distributed their products to more than 100 other pharmacies
- 8 pharmacies (2%) to 51–100 other pharmacies
- 9 pharmacies (2%) to 21–50 other pharmacies
- 23 pharmacies (6%) distributed the products to 11–20 other pharmacies
- the remainder of the PDPs (88%) distributed their products on a smaller scale to fewer than 10 pharmacies.

Twenty-eight of these 47 (60%) pharmacies were hospital pharmacies.

Surveillance by the Inspectorate

The Inspectorate has been responsible for overseeing PDPs compliance with the conditions of the Circular since 2007. To perform the visits, the Inspectorate has developed an instrument to assess whether the PDPs fulfilled the four conditions of the Circular. The assessment of the Inspectorate was based upon an instrument that assessed PA, PT and PD (A–C) and GMP (D):

A. The documentation of the PA investigation:

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

1. The procedure for assessing PA.
2. The criteria for the PA included in the procedure.
3. The investigation of licensed PA based on a random check by the Inspectorate of the forms for some selected products.

The score for each of these three items could vary from 1 to 4, as it is shown in the table below:

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 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.

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

B. The documentation of the PT investigation:

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

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 that were distributed to other pharmacies.¹⁰

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

The result for the Circular's condition relating to PT was assessed 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 the PDP follows these.

C. The PDs, PD investigation:

The assessment by the Inspectorate of the PDs consisted of the following items to be scored:

1. The procedure for the assessment of the technical and pharmaceutical aspects.
2. The procedure for PDs.
3. The format for PDs.
4. The assessment of the quality of the PD.
5. The availability of PDs for the products made, based on a random check by the Inspectorate of the PDs relating to a sample of selected products.

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

The result for the Circular's condition relating to PDs was assessed sufficient if a score of at least 3 was given for each of these items. This means that the PDP has clear procedures and instructions on how to make a PD and that the PDP follows these.

D. GMP:

The Circular states that GMP compliance is one of the conditions for a PDP. All parts of GMP¹¹ had to be assessed during the inspection visits at the PDPs.

The deficiencies of the PDP concerning GMP were classified on the basis of the following definitions:

► Critical deficiency:

A deficiency which has produced, or leads to a significant risk of producing, a product which is harmful to the patient.

► Major deficiency:

A non-critical deficiency:

which has produced, or may produce, a product, which does not comply with its product dossier;

or

which indicates a major deviation from the EU GMP;

or

which indicates a failure to carry out satisfactory procedures for the release of batches;

or

a combination of several "other" deficiencies, none of which on their own may be major, but which may, together, represent a major deficiency and should be explained and reported as such.

► Other deficiency:

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

A deficiency may be 'other' either because it is judged as minor, or because there is insufficient information to classify it as a major or critical.

The result for the Circular's condition GMP was assessed insufficient for the PDP if one critical deficiency was found or if there were more than five major deficiencies. GMP was assessed sufficient if there were five or fewer than five major deficiencies.

Advertising

The Inspectorate has investigated the websites of the PDPs and, if considered necessary, an advertising inspector was added to the inspection team. This was considered necessary if the website of the PDP contained elements of advertising.⁷

Publication of inspection reports

The inspection reports of all PDPs were published on the website of the Inspectorate (<http://www.igz.nl>) in accordance with a specific procedure communicated to the PDPs in advance.

RESULTS

There was a large variation in the types of PDPs which we visited, but nearly all those who dispensed their products through at least 10 dispensing-only pharmacies, were inspected.

However, changes in the status of the PDPs occur continuously, which means that the planning of the visits has to be adapted regularly.

The results of the Inspectorate's system surveillance

1. Compliance with the conditions of the Circular relating to the whole system.

The Inspectorate had to perform repeated inspections since the results of the first inspection visits of the PDPs were disappointing because they did not comply with the conditions of the Circular. Moreover, the capacity for these inspections had to be increased. In the meantime, the consultations with the professional associations continued as normal. During these first inspection visits enforcement measures were taken in one PDP. In this, PDP risks were seen for patient care because essential GMP safety measures for the preparation of sterile products were assessed as insufficient. Therefore, the sterile preparations of this PDP were halted temporarily until the PDP had implemented all the necessary safety measures.

In the years 2012–2014, the Inspectorate performed repeated inspections at most of the PDPs that did not comply with the conditions of the Circular. In total 34 PDPs were visited. The status concerning the 34 PDPs on 1 November 2014 was as follows:

- Eighteen PDPs complied with all conditions of the Circular.
- Three PDPs complied with GMP, but there were some minor deficiencies concerning the other conditions of the Circular.

These PDPs will be inspected again until they fulfil all the conditions of the Circular.

- ▶ One PDP distributed only licensed products, which were reconstituted at the PDP for direct use by the patient, in a small region. It was difficult to assess, therefore, whether the conditions of the Circular applied.
- ▶ For another PDP, the inventory did not predominantly consist of medicinal products, so an inspection had to be planned together with the Netherlands Food and Consumer Product Safety Authority.
- ▶ Ten PDPs had stopped distribution of the medicinal products to dispensing pharmacies because they could not fulfil the conditions of the Circular or because they considered it not feasible to make the necessary investments. Verification visits were performed by the Inspectorate in order to check whether these PDPs had, in fact, stopped distribution.
- ▶ One PDP prepared its products through a company which did not possess a manufacturing licence. This is forbidden by the Dutch Medicines Act, for which reason the Inspectorate took enforcement measures to stop this practice.

On 1 November 2014, there were 13 new PDPs. The reports of these inspection visits were not included in this observational study because the reports were not yet finished (seven PDPs) or because the visits were not yet carried out (six PDPs).

These results show that 18 out of 21 PDPs complied with all conditions of the Circular. Only three of these PDPs required more than one inspection visit. Only minor deficiencies were found with 3 out of 21 PDPs. The publication of the inspection reports on the website of the Inspectorate allowed, probably, many PDPs to be better prepared. The inspection visits showed that the PDPs have invested in compliance with the conditions of the Circular.

1.1 The conditions of the Circular concerning PA and PT investigations of the system.

The PDPs are obliged to document the results of their PA and PT investigations for all products. On 1 November 2014, 20 out of the 21 PDPs visited fulfilled the PA condition and 19 out of 21 PDPs visited complied with the PT condition. The details about this requirement of the Circular will be presented in a separate publication.¹⁰

1.2 The conditions of the Circular concerning the systematic use of a PD.

The PDPs should have a PD available for all their products, stock preparations and standardised individual preparations, in order to document the quality by design of the pharmacy preparation. The topics to be covered in a PD are described on the website of the Inspectorate and in the resolution on pharmacy preparation of the Council of Europe.^{2,9}

As of 1 November, 19 out of the 21 PDPs visited fulfilled the PD condition of the Circular. For two PDPs, significant improvements were made concerning the PDs, but the documentation still showed deficiencies that required further improvement.

At the request of the Inspectorate, the National Institute for Public Health and the Environment has performed descriptive research concerning the quality of the PDs.¹² Its report states that the quality of the PDs and the information contained in them is, in general, reasonably good. One of the recommendations of the National Institute for Public Health and the Environment report is to make a fixed format for the content of the PDs since a large variation was found in the content of the dossiers, especially in PDPs among the community pharmacies. In addition, the documentation should demonstrate that all items of the PD, such as validations and stability data, have been

completed. There is, therefore, a clear basis for the overall conclusion that the PD of a particular product of a PDP is complete before distribution takes place to dispensing pharmacies.

1.3 The conditions of the Circular Letter concerning GMP

As of 1 November 2014, all of the 21 PDPs visited complied with GMP.

DISCUSSION

Current situation

There is a broad consensus in the Netherlands concerning the conditions of the Circular.⁸ The GMP condition seemed the most difficult requirement to comply with, but all of the 21 PDPs visited had complied in 2014.

The initial results in 2011 had been disappointing, but in 2014 the inspections showed a clear improvement in the compliance with the conditions of the Circular. The progress made was possible due to the efforts of the different stakeholders. These were as follows:

- ▶ The PDPs have invested in compliance measures, in many cases hiring external experts to accelerate the process.
- ▶ The associations of hospital pharmacies and community pharmacies have developed tools and other information materials to support pharmacies.
- ▶ The Inspectorate has increased the capacity of the inspection programme. It performed repeated inspections until the required level of quality was achieved. The Inspectorate took reinforcement measures where needed.

Additional findings during the inspections

GMP is considered an appropriate quality standard for pharmacy preparation in PDPs.² The risks of possible product defects that might occur at PDPs and its implications for the patients being treated are substantial. Emphasis should therefore be given to all efforts to prevent these risks.

Given the character and the scale of the pharmacy preparations, there may be situations that GMP cannot be declared applicable. This could, for example, be the case if the preparation in the PDP of a specific medicinal product is on a small scale. If GMP has not been declared as a clear requirement for a given situation in a PDP, then the Dutch Pharmacy Standard¹³ could, if necessary, be considered to be an appropriate standard. However, this is only for that specific situation and could here be backed up by the three other conditions contained in the Circular.

Some points of attention have been addressed during and after the inspection visits.

1. Product defects and recalls: In general, PDPs do not possess a system for addressing product defects, quality complaints, mistakes and other signals warning of possible problems with their products. There have been recalls by PDPs in the case of deviations from the PDs, but, given the relatively low number of recalls, the awareness around this topic may have to be increased. Internal exercises at PDPs to test their ability to trace either batch and lot numbers or the dispensing pharmacies to which the products were distributed, and then to recall the products, are of crucial importance.
2. Pharmacovigilance: There may be products distributed by the PDP, where the balance between efficacy and safety is questionable. Therefore, it is important that dispensing pharmacies that receive medicinal products from the PDP report safety problems to the PDP. The PDP should be capable of gathering and evaluating information about their products such as that concerning adverse events or warning signals in

order that appropriate measures can be taken in case of safety problems.

- Responsibilities: The responsibilities of the pharmacies concerned here, the PDPs and the dispensing pharmacies, are, in general, laid out in a contract. However, the description of the different tasks and responsibilities such as reporting adverse events and product defects, the surveillance of medication and with regard to patient information, needs attention.

CONCLUSIONS

A circular is a temporary measure usually only accepted in anticipation of a new law. However, there is a dilemma here. On the one hand, the Dutch Medicines Act and the EU Directive 2001/83/EC, on which it is based, aims to protect public health by means of a system of marketing authorisations and manufacturing licenses. On the other hand, the preparation of unlicensed medicines in pharmacies is indispensable for patients with special needs, in particular if an appropriate licensed medicine is not available on the market.

What this paper adds

What is already known on this subject?

- The Medicines Act in the Netherlands is based on the European Union (EU) Directive 2001/83/EC, which forbids an unlicensed medicinal product being prepared and distributed by a preparing pharmacy (preparing and distributing pharmacies (PDPs)) to a dispensing pharmacy—that is one which dispenses the medicinal product to the patient.
- There are, however, patients who need a pharmacy preparation because there is no adequate licensed alternative medicinal product available on the market.
- Since 2007, the PDPs have been permitted by the Inspectorate by means of the Circular. This Circular allows, under strict conditions, preparation of unlicensed medicinal products in a preparing pharmacy and distribution of these products to a dispensing pharmacy.
- The PDPs are only permitted if they fulfil the strict conditions of the Circular: absence of licensed pharmacotherapeutic alternatives, rational pharmacotherapy, compilation of a product dossier and compliance with Good Manufacturing Practice.

What this study adds?

- The results of the inspection programme of the Dutch healthcare Inspectorate show that most of the PDPs fulfil the conditions of the Circular at a systematic level.
- The Inspectorate is in consultation with the Ministry of Health, Welfare and Sport about how to proceed with the question of PDPs and the conditions they have to fulfil. Recent European case law concerning the interpretation of the EU Directive 2001/83/EC will have to be taken into account.

PDPs have been permitted in the Netherlands since 2007 so long as they fulfil the conditions of the Circular.³ The Circular allows, under strict conditions, the preparation of unlicensed medicinal products in a preparing pharmacy and then their distribution to a dispensing pharmacy. If PDPs do not fulfil these conditions, then they have to stop preparing and distributing medicinal products.

The results of the inspections until now indicate that most of the PDPs fulfil the conditions of the Circular. Compliance of the PDPs with these conditions was checked by the Inspectorate through regular visits. However, changes in the status of the PDPs occur continuously, which means that the planning of the visits has to be adapted regularly.

The Inspectorate is in consultation with the Ministry of Health, Welfare and Sport about how to proceed with the question of PDPs and the conditions they have to fulfil. Recent European case law will have to be taken into account.¹⁴

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