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SEMINAR COMPOUNDING PHARMACISTS

17 April 2019
Pakhuis De Zwijger, Amsterdam

health
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Hanneke Later-Nijland
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Agenda

Seminar

- Hanneke Later-Nijland, Axon Lawyers
  Compounding pharmacists: an overview of the legislation & case law. The recent letter by MinVWS
- Andras Kupecz, lawyer and patent attorney, Kupecz Intellectual Property
  The compounding exemption under patent law & compulsory licensing
- Peter Bertens, sr. policy advisor and projectleader, Association Innovative Medicines (**VIG**)
  The view of the VIG on compounding

Panel discussion

- Andras Kupecz, Kupecz Intellectual Property
- Peter Bertens, VIG
- Sandra de Wild-Chardonnens. Sector specialist & coordinator Life Sciences & Health, Netherlands Foreign Investment Agency (**NFIA**)
- Hanneke Later-Nijland, Axon Lawyers

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COMPOUNDING PHARMACISTS

10-11 December 2018
Pharma Biotech, Rome, Italy

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- Lawyer and pharmacist
- PhD, Clinical Pharmacokinetics
- Former inspector for Clinical Trials and Pharmacovigilance at the Netherlands Inspectorate for Healthcare (IGZ)
- Member editoral board, *Jurisprudentie Geneesmiddelenrecht,* Sdu
- Lecturer, Leiden University, Netherlands
- Areas of expertise: marketing authorizations, reimbursement, compliance, pharmacovigilance, clinical trials, compounding and advertising issues, product liability issues, market access and other regulatory issues, regulatory part of DD in M&A, advice as well as litigation (civil and administrative)

COMPOUNDING
(‘*MAGISTRALE BEREIDING*’)

Outline

1. What is compounding?
2. European legal framework re compounding & caselaw
3. European case law
4. Dutch legal framework re compounding & case law
5. AMC case CDCX & report IGJ
6. Letter by the Minister 9 April
7. Conclusion

What is it?

- No single definition, not even a single term:
  - Magistral and officinal preparation (*formula magistralis, formula officinalis*)
  - Extemporaneous preparation
  - Individually non-standardised preparations
  - Etc.

EUROPEAN LEGAL FRAMEWORK RE COMPOUNDING

EU Legal situation compounding

- No legal harmonization on European level, outside the scope of **Directive 2001/83/EC.**
- No binding regulation on European level.
- European legislation (Directive 2001/83/EC) requests manufacturing authorization and marketing authorization for bringing medicinal products onto the market but exempts compounding:

  Article 2(1) Dir 2001/83

  This Directive applies to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

  Article 3 Directive 2001/83/EC: Directive does not apply to any medicinal product (a) prepared in a pharmacy (b) in accordance with a medical prescription (c) for an individual patient (**magistral formula**) or in a pharmacy (a) in accordance with the prescriptions of a pharmacopoeia and (b) supplied directly to (c) patients of the pharmacy (**officinal formula**).

  Article 40 (2) Directive 2001/83/EC: A manufacturing authorization shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply (‘*verstrekking in het klein*’), by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.

- Further regulation on Member State level in accordance with **Resolution CM/Res(2016)**

Recitals Dir 2001/83

(3) The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.

(3) However, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community.

Resolution CM/Res (2016)1 Council of Europe

The Netherlands is signatory

- **Subject:** Quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients
- Noting that the preparation of medicinal products in pharmacies is not harmonised throughout Europe and falls under the national competencies of the States Parties to the Convention on the Elaboration of a European Pharmacopoeia;
- Not legally binding.
- Main points:
  - **Pharmacy preparations are not advisable if a suitable pharmaceutical equivalent with a marketing authorisation is available**
  - Risk assessment before preparation
  - Good Manufacturing Practice (GMP) Guidelines for high-risk preparations and PIC/S GPP Guidelines for low-risk preparations
  - Product dossier
  - Criteria for a marketing authorisation
  - Compliance with pharmacopoeial requirements

  - "If the preparation is carried out on **a scale comparable to the industrial level**, if distribution takes place and if an **authorised** medicinal product, or a pharmaceutical equivalent (see section 3.1), **is on the market**, the competent drug regulatory authorities should consider **establishing, if they have not already done so, the requirement for obtaining a marketing authorisation**, including full compliance with GMP, for pharmacy preparations (see note 1: refer to "high-risk preparation")."

  - "The professionals involved in patient care should jointly assume responsibility for determining whether a pharmacy preparation could be of added value. They should take into account the medical need of the patient.." *A pharmacist should be able to refuse a prescription for a pharmacy preparation **if a suitable pharmaceutical equivalent is available** on the national market, inform the physician that a suitable pharmaceutical equivalent is available and discuss with the physician if there is a specific need to dispense a pharmacy preparation*

  - With a view to **avoiding quality and safety differences between medicinal products prepared in pharmacies and those prepared on an industrial scale**, recommends that the governments of the States Parties to the Convention on the Elaboration of a European Pharmacopoeia adapt their regulations in accordance with the principles set out in the present resolution (..)

EUROPEAN CASE LAW

COMPOUNDING

The Abcur case

- Exception of art. 3 Directive 2001/83/EC should be interpreted **strictly** and the conditions are cumulative. The medical prescription must be issued and individual patient must be identified before the preparation of the medicine.

- Industrially prepared or manufactured by a method involving an industrial process demarcates the partition of the scope of the directive and the exception.

Abcur

(...) generally, provisions which are in the nature of exceptions to a principle must, according to settled case-law, be interpreted **strictly** [54]

Cumulative criteria for article 3(1) Dir 2001/83

1) Before the medicinal product is produced, a preceding medical prescription;
2) A prescription ‘for an individual named patient’, that needs to be identified before compounding;
3) It must be prepared specifically for a previously identified patient (no ‘subscription’ supply system)

Cumulative criteria for article 3(2) Dir 2001/83

1) prepared ‘in a pharmacy’;
2) ‘in accordance with the prescriptions of a pharmacopoeia’;
3) and ‘intended to be supplied directly**;**
4) to the patients served by the pharmacy in question’.

Hecht Pharma

Article 2(1) Dir 2001/83
This Directive applies to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

Exception in German Marketing of Medicines Law for preparation of up to 100 packages

Essential manufacturing steps carried out in a pharmacy as part of the normal pharmacy business producing in the course of one day up to 100 packages ready for dispensation and intended for supply under the existing pharmacy licence, cannot be regarded as prepared industrially or by industrial process

Commission/Poland

Court of Justice of the EU **(CJEU)** C-185/10 Commission v. Poland:

- *"(…) inasmuch that statutory provision dispenses with the requirement for a marketing authorization **(MA)** for medicinal products from abroad which have*
- *the same active substances;*
- *the same dosage, and*
- *the same form*
- *as those having obtained a MA in Poland,*

*on condition that the price of those imported medicinal products is competitive in relation to the **price** of the products having obtained such MA, (…) Poland has failed to fulfil its obligations under article 6 Dir 2001/83/EC, as amended"*

DUTCH LEGAL FRAMEWORK RE COMPOUNDING

Dutch situation

- Dutch Medicines Act
  - **Art. 18 par. 5:** *"not prohibited to prepare medicines without a license on a small scale if it is done for the purpose of direct dispensing at a pharmacy."*
  - **Art. 40 par. 3 sub a:** *"not prohibited to place medicines on the market on a small scale if it is done for the purpose of direct delivery at a pharmacy."*
- Decree Medicine Act:
  - **Art. 2:** Medicines prepared in a pharmacy (…) will only be dispensed when compliant with the standards of a Pharmacopoeia (European, if not available: national, U.S. or Japanese). Only sound components will be used for the preparation.

Regenboog pharmacy case

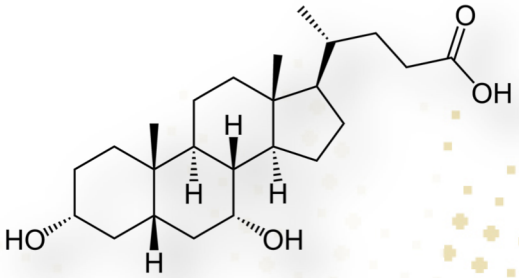
Compounded preparations should be:

- Customised compounding for the own “normal” patients of the pharmacy;

- 20.000 **tablets** per month for 300 pts, (who take 2 tablets a day, and who make up **0,25%** of the total number of methylphenidate using patients in the Netherlands)
- cannot be considered to be compounding at a small scale

AMC CASE (CDCA)

AMC case (CDCA)



- **April 2017:** Leadiant MA for CDCA for metabolic disorder CTX. Orphan exclusivity granted by EMA. No longer patented. CDCA was authorized for another indication until 2009.

  Price X 5.

- **April 2018:** AMC starts compounding **chenodeoxycholic acid (CDCA)** for 50 patients with **cerebrotendinous xanthomatosis (CTX).** N = 2 → 44 pts
- **May 2018:** Manufacturer of **CDCA**, Leadiant Biosciences, requests enforcement by Inspectorate for Healthcare
- Dutch Health Instpectorate (**IGJ**) concludes used raw materials are not compliant with European Pharmacopoeia standards
- **August 2018:** AMC stops manufacturing and recalls compounded **CDCA**
- **November 2018:** IGJ gave two warnings to AMC as to (i) using an API not complying quality standards and (ii) advertising compounded products

Conclusion IGJ

The Dutch Decree Medicinal act requires that compounded product comply with the regulations of the European Pharmacopeia (…). For the composition of the compounded product proper ingredients must be used.

CDCA - AMC did not comply with regulations Ph. Eur: impurities > 0,25%. No sound ingredients were used.

The process by AMC does comply with rules for compounding: they compound on a small scale on prescription without stock

Small scale:

- The pharmacist must dispense himself (no collegial delivery), [but delivery service]
- Provide information him-/herself;
- Have a medical treatment agreement in place

LETTER MINISTER
8 APRIL 2019

Explanation

1. The compounding takes place at a pharmacy, according a medical prescription for one patient or on stock for to be determined patients of the pharmacy;
2. The compounding complies with the Ph. Eur.;
3. The compounding serves ‘small scale’ dispensing

Ad 3.

- Dispensing to several to approx. 50 **unique patients** per month with long-term use of the medicinal product;
- Dispensing to approx. 150 pts per months with short-term use

The IGJ will take these numbers into account in her supervision & enforcement practice and will elaborate on these and publish policy rules.

Regenboog pharmacy case: 0,25%

"*The use of authorized medicinal products remains the starting point. Obviously, against a reasonable and acceptable price. If a financial arrangement has been concluded with me, in my view, there is a acceptable price of that particle medicinal product*."

Facts for the Netherlands:

- 2017: > €5 billion
- 7% state budget healthcare (€72 billion)
- 1,7% for expensive medicinal products

- Ranks 18th among EU Member States spending on medicinal products / citizen

“*Evolving circumstances: specialized compounding pharmacies*”

”*Larger scale*”

“*Hospitals merge and become larger*”

“*It is perceived that pharmacists also compound medicines that are on the market in an authorized form*.”

Evolving circumstances and practice should not lead to a different interpretation of laws and regulations.

Magistraal?

vs.

Total/year NL: 2,5% of all prescriptions

< 50 unique pts per month (long-term use)
< 150 pts per month (short-term use)
[*MinVWS*]

'*Eigen patienten*'
Patients of the pharmacy'

Delivery service
[*IGJ*]

Reimbursement

- Not arranged on a European level (outside of EUNetHa initiatives)
- **Netherlands**
  - As per 1 January 2019, compounded products may be charged, even if it concerns a prescribed Rx medicinal product (which has obtained a marketing authorization)
  - This also concerns ‘special’ compounding, *e.g.* when aseptic preparation, or working with hazardous materials is required, although from the view point of quality and efficiency, such compounding should take place in specialized pharmacies
  - However, whether the product is compounded by a dispensing care provider or by a compounding care provider on an individual prescription, the compounded quantity must correspond with the quantity needed to dispense the Rx medicinal product based on the individual prescription

Nederlandse Zorgautoriteit

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Wat zijn de belangrijkste wijzigingen in de regelgeving voor 2019?

In onze Beleidsregel prestatiebeschrijvingen voor farmaceutische zorg (BR/REG-19147) is de omschrijving van de zorgprestatie 'Bijzondere magistrale bereiding' aangepast.

Per 2019 mag de deelprestatie (bijzondere) magistrale bereiding in rekening worden gebracht, ook als het geregistreerde UR-geneesmiddel in de handel verkrijgbaar is.

As per 2019, (...) compounded preparation may be charged for, even when an authorized prescription-only medicinal product is available on the market

Conclusion (1)

- Obviously, the pricing of the so-categorized non-patented, yet expensive medicinal products have functioned as the trigger of the pragmatic interpretation of compounding;

- The Minister did clearly not pay attention to the relative effect of compounding for certain indications. This could lead to ”*good* orphan drug swiping”.

- In his view: expensive (‘*bad*’) drugs lead to “displacement” (‘*verdringing*’) of other necessary drugs.

- However, a more **focused** approach on the ‘expensives + non-innovative’ (‘*bad*’) group would:

(1) not lead to a ‘solution’ undermining the marketing authorisation system (‘50 Softenon babies, CBG-MEB ‘63)
(2) not lead to added safety risk for patients

Het Parool

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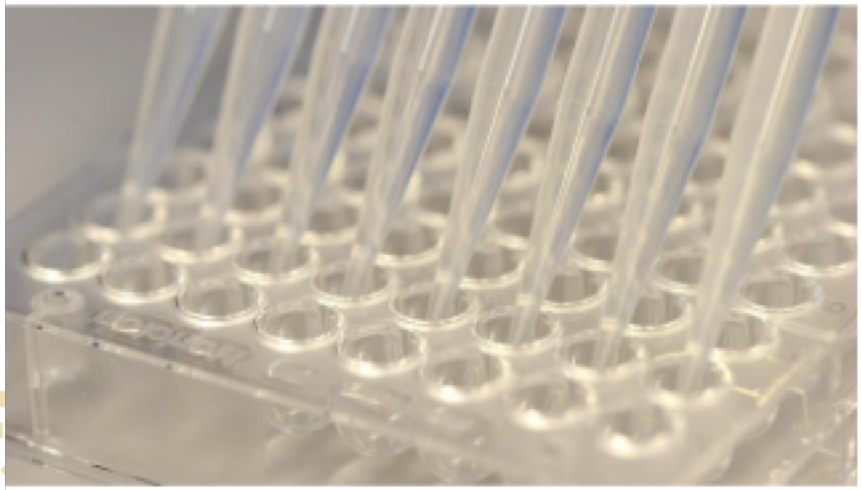
Patiënt VUmc mogelijk overleden door verkeerd medicijn



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Negen patiënten van het Amsterdam UMC locatie VUmc hebben begin deze maand een verkeerd medicijn toegediend gekregen. Mogelijk heeft dit bij één patiënt bijgedragen aan diens overlijden.

DOOR: HET PAROOL 15 MAART 2019, 15:50

De andere acht patiënten hebben er geen blijvende problemen aan overgehouden. Amsterdam UMC meldt niet om wat voor medicijn het gaat. Volgens het universiteitsziekenhuis zou een vergissing zijn gemaakt bij de bereiding van de medicatie.

United States Senate
HEALTH, EDUCATION, LABOR, AND PENSIONS COMMITTEE

The New England Compounding Center and the Meningitis Outbreak of 2012: A Failure to Address Risk to the Public Health

Committee Staff Report

November 15, 2012

On September 26, 2012, as a result of the rapid work of the Tennessee Department of Public Health and the Centers for Disease Control and Prevention (CDCP), an outbreak of an unusual strain of fungal meningitis was identified. Preservative free methylprednisolone acetate (MPA), administered via spinal injection, was quickly identified as a likely source of the infections. The MPA was traced back to a compounding pharmacy in Framingham Massachusetts, the New England Compounding Pharmacy Inc., doing business as the New England Compounding Center (NECC). The Food and Drug Administration (FDA) subsequently determined that three separate lots of MPA, totaling over 17,000 doses produced by NECC between May 21, 2012 and August 10, 2012, were contaminated with the *exserohilum rostratum* fungus.[i]

To date, NECC's failure to produce a sterile and safe product has led to more than 30 deaths and over 450 serious illnesses requiring treatment with high risk anti-fungal medications. The efforts of the CDCP and the Tennessee Department of Public Health allowed public health officials in 23 states to rapidly track and begin monitoring the approximately 14,000 possible recipients of the contaminated drug. But thousands of people around the country continue to

"The extra quality may cost more, but where are the limits?"

Slide by Martin van der Graaff,
Zorginstituut Nederland, ACP, 5 October 2018

Conclusion (2)

(3) Not lead to a negative investing climate for the Netherlands
(4) And thus, not to annihilate the effect of the EMA coming/being in Amsterdam

- Short-term aims have long-term effects
- Will the patients be adequately informed as legally required pursuant to WGBO (“inform about other available treatments”)
- Does compounding (when authorized on market) constitute “good care” pursuant to Wkkgz?
- Did the prescribers and pharmacists adequately think about and cover their (product-) liability? Are the professional liability insurers informed?

What to do if challenged?

1) Prepare enforcement request with IGJ (incl. recall at patient level):
2) Try to obtain the product (“second sample”)
3) Trace the suppliers of APIs
4) Collect all communication re the compounded product (advertising?)
   Discuss quality risks of compounded products with prescribers
5) Do not overlook product liability of pharmacists
6) Use media, with help of PR experts
7) Lobby

Ad 7. Is this the right time for lobbying in Brussels in order to start drafting interpretation protocols on the terminology in view of compounding, e.g. (i) small scale, (ii) direct use and (iii) patients of that pharmacy (‘*eigen patienten*’), (iv) normal pharmacy business (Hecht).
[Regulation CMR 2016/1; Recital (3) Dir; KNMP Bereiden 2016]

In de strijd om lagere medicijnprijzen is minister Bruins bereid ingrijpende maatregelen te nemen. Hij stelt voor om de periode waarop fabrikanten geneesmiddelen exclusief op de markt mogen brengen in te korten van 10 naar 5 jaar.

Minister Bruins voor Medische Zorg en Sport wil zijn voorstel volgende maand hoog op de agenda van de nieuwe Europese Commissie krijgen. "Er bestaat nu Europese regelgeving die farmaceuten 10 jaar lang het recht geeft middelen exclusief op de markt te brengen. Soms is dat te rechtvaardigen, maar heel vaak ook niet. Waarom moet een fabrikant 10 jaar lang een monopolie hebben, als er geen hoge investeringskosten zijn?"

The Dutch Minister for Medical Care proposes to shorten market exclusivity for medicinal products from 10 to 5 years. He intends to place his proposal high on the agenda of the new European Commission, next month.

Questions?

PROPOSITIONS

STELLINGEN

Extended compounding to curb the cost of medicines equals passing on safety risks to patients

Extended compounding is a short-term measure with long-term effects on the Dutch investment climate

Extended compounding is a short-term measure with long-term effects on patient access

Extended compounding to curb the cost of medicines lays off liability risks to compounding pharmacists

Interpretation by minister on ‘small scale’ to be qualified as ‘abuse of the compounding exemption’ (patent, regulatory)?

The solution to the compounding issue lies in ‘Europe’

this is the right timing for ‘interpretation protocol(s)’ for compounding