Development of sterile medicinal products in Dutch hospital pharmacy

SEHP
2011

Santiago de Compostella

Universitair Medisch Centrum
Utrecht

Introduction

- **Willem Meulenhoff (1971)**
  - Production Pharmacist at NV Organon (MSD)
  - Head of the Production facility / Hospital Pharmacist at the University Medical Center Utrecht, the Netherlands
  - GMP production game for hospital pharmacists (trainees) since 2005
  - EAHP 2010: all about the site master file

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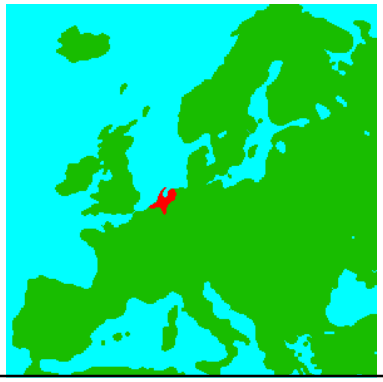
Introduction



The Netherlands

- 16 million inhabitants
- 3000 Pharmacists
- 100 Hospitals
- 500 hospital pharmacists

Programme

1- Introduction
2- History of compounding in dutch hospitals
3- Development of drug products

Why, what and how

Take home message

- "Pharmacists can play an important role in the availabillity of drugs for rare diseases"

Introduction

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UMC Utrecht

- University Hospital
  - Care
  - Research
  - Education
- 1000 beds
- 10000 employees

introduction

Hospital Pharmacy

- 150 employees
- Clinical pharmacy
- Therapeutic drug monitoring & toxicology laboratorium
- Pharmacy satelites in Childrens hospital and ICU
- Production unit

" Picture of hospital pharmacy"

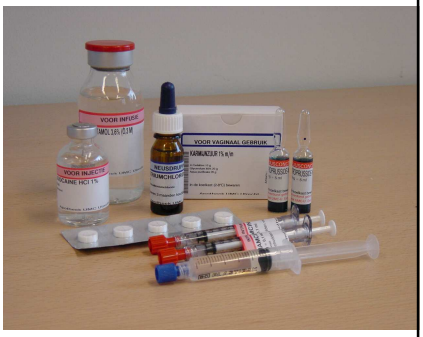
Hospital pharmacy

- Pictures
- Laboratorium
- ICU
- Clinical pharmacy
- Cytotoxic compounding
- Sterile production
- Non steriel vessels
- ampoules

Introduction

Production

- Preparation
- Formulation



Mission of production unit UMCU:
Guarantee the availability of unique medicinal products

1 *"Guarantee the availability"*

Development of medicinal products

"formulation of not available drugs"

Production of medicinal products

"individual or stock preparation and compounding, conform GMP (Good Manufacturing Practice)

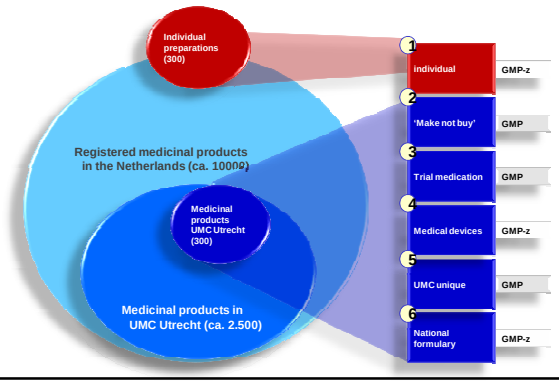
Delivery of medicinal products (selling)

"selling of drugs to other pharmacies"

Provide knowledge on the preparation of medicinal products

"share knowledge on the preparation of medicines to other pharmacies to gurantee continuous pharmaceutical care"

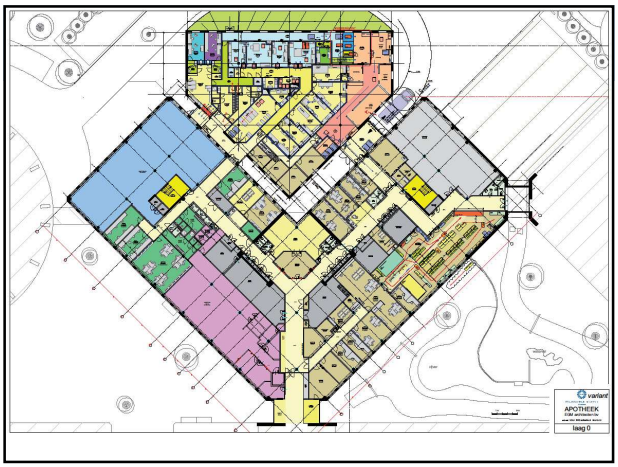
Of all used medicines 12% is compounded by the production unit



Production unit UMCU

Key numbers

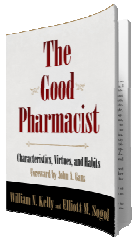
- Sterile & non sterile production
  - 1000 batches a year
  - 15000 Cytotoxic preparations
  - 5000 individual preparations
- 30 FTE, production staff
  - Incl 3 production pharmacist
  - QP, QC, QA, logistic
- GMP license for production trial medication



Introduction

- pictures
- Van de nieuwbouw en de oudbouw

- Pharmacists make medicines available!!!



Pharmacists can play an important role in the availability of medicines for rare diseases

- **European stimulation measures**
- EC141/2000 and EC1901/2006: Economical and regulatory incentives for pharmaceutical industries to stimulate the development of orphan drugs and pediatric drugs

- Where is the pharmacist?

An example: orphan drugs?

- Orphan Drug: for the diagnosis, prevention or treatment of a rare disease (OD)
- Rare disease: EU definition:
  - chronic progressive or life-threatening
  - prevalence < 5 in 10,000
- Worldwide millions of patients affected

Introduction orphan drugs
Obstacles for development

- Small market
- Clinical trials
  Too expensive

EC141/2000: Economical and regulatory incentives for pharmaceutical industries to make development cheaper

Guardian Unlimited

Read today's paper

Special report Medicine and health

EU loophole sends drug prices soaring

Doctors say companies are exploiting regulations on life-saving treatments for patients with rare diseases

Sarah Boseley, health editor
Monday June 24, 2002
The Guardian

The prices of cheap, life-saving treatments for rare children's diseases are being increased by drug companies to levels where hospitals can barely afford them.

The companies are exploiting EU regulations concerning "orphan drugs" - drugs which are of benefit to fewer than five per 10,000 people - despite the rules being put in place in order to encourage the invention of new medicines.

Two children in Middlesbrough were hospitalised and put on

Relevance of compounding
Case

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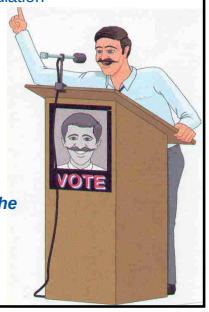
- Orphan Europe: Wilzin® tablet zincacetate formulation
- Pharmacy: oral liquid zincsulfate FNA formulation
- Ucyclyd Pharma: Ammonul®
- Pharmacy: sodiumbenzoate

- Over 10% of the orphan drugs (800) can be or is already made by pharmacists!



Pharmacists can play an important role in the availability of medicines for rare diseases

A short history of compounding in the netherlands

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Overview

- Until 1996 every pharmacy could do some preparations
- Until 2006 all hospital pharmacies could do sterile preparations
- Now about 25 hospital pharmacies Produce everything for all 100 hospitals

A short history of compounding in the netherlands

Regulations

- To manufacture medicines you have to:
  - have an GMP license
  - have an market authorisation for your product

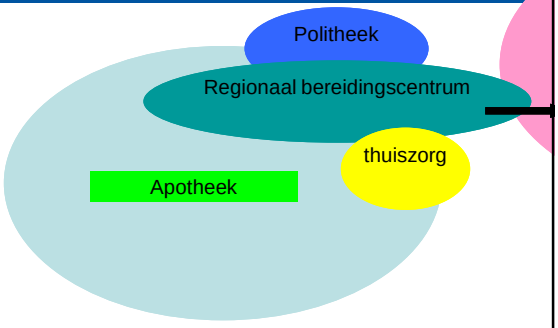
Unless you're a pharmacist...
.....and its for your patient (care)

A short history of compounding in the netherlands

Regulations

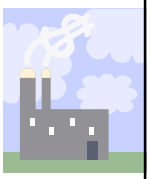
- If there is a need for a certain product it is allowed to pharmacies sell medicines without market autorisation if
  - GMP
  - no commercial alternative
  - There is a productdossier to substantiate product quality

A short history of compounding in the netherlands



Good Manufacturing Practice

- GMP is logic



- Production is business
- GMP is not the goal, its just a way to get there

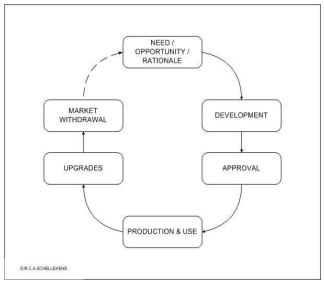
Development of new medicinal products

LEARNING OBJECTIVES
- Able to develop a hospital prepared “quality product”
- Able to design a new product with an understanding of the concept "quality by design“

Development of new products in hospitals: policy

- Aim = health care
- Policy in compounding:
  - Product is not-registered
  - Product registered but not available
  - Product is therapeutically relevant
  - Product is not available in required (dosage) form
- Complementary to pharmaceutical industry

LIFE CYCLE OF A DRUG PRODUCT



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Product life cycle hospital pharmacy

Farmacotherapeutical ratio

Commercial product

Individual preparation

Batch preparation

Standardised individual preparation

Productdossier

Product life cyclepharmaceutical industrie

New target / diseases

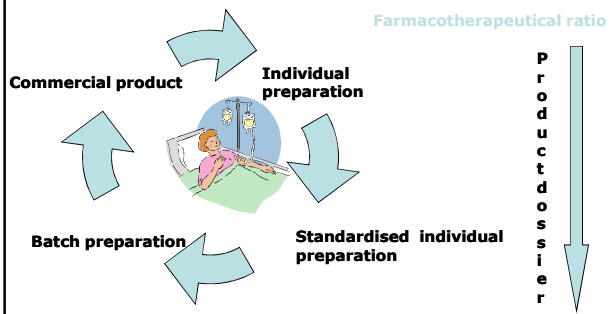
Research & Development

generic

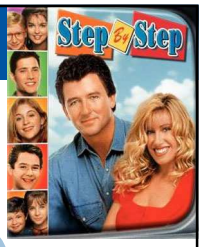
Registration & marktintroduction

Registrationdossier

Product life cycle hospital pharmacy



The development proces

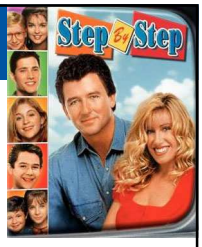


STEP BY STEP

- 1-Rationale (WHY)
- 2- Design (WHAT)
- 3- Pharmaceutical development of prod
- 4- Development of proces
- 6- Clinical testing
- 7- Introduction

It starts with the patient and the question: why?

The development process

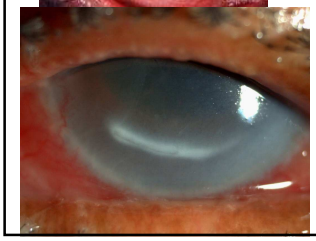


- **1-Rationale**

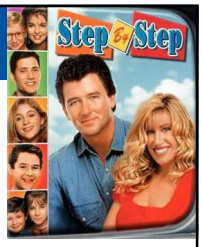
Why do we make this product?
Questions to be asked?
  - Risk for the patient
  - Alternatives
  - Safety
  - Effective
  - Quality

- Eyedrops antibiotic or anti mycotic

The development process



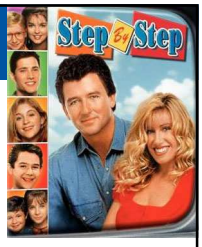
The development proces



- 1-Rationale (WHY)
- **2- Design (WHAT)**

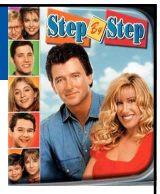
- Questions to be asked
  - How is the product going to be used?
  - What are the user requirements?
  - How is going to look like?

The development proces: Design



- Examples
  - **Sterile ice for transplantation**
  - **Glutaraldehyde solution**
  - **Intravitreal injections**

The development proces



- 1-Rationale (WHY)
- 2- Design (What)
- **3- Pharmaceutical development of product (WHAT)**

- Specify the pharmaceutical properties of the product
  - Sterile
  - Osmotic value
  - pH
  - particles?
  - Dosage & volume
  - Required stability

To determine the properties that may effect safety of efficacy:
"QUALITY BY DESIGN"

PHARMACEUTICAL DEVELOPMENT

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- ICH Q8 (R2) (EMEA/CHMP/167068/2004)
  - The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.
  - Scope:
    - Drug product submission for marketing authorisation
    - Not: pharmacy-prepared drug products
    - Not: IMPs

AN EXAMPLE OF BAD DESIGN

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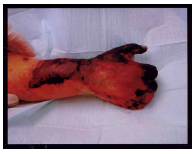
Toepassing en risico's van trometamol

Complicatie: weefselnecrose

Bij de behandeling van acidose kan het nodig zijn gebruik te maken van alkalische middelen, zoals trometamol. Maar de toepassing van trometamol kan ernstige consequenties hebben.

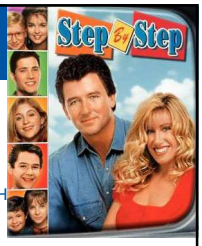


- Trometamol 3.27% solution for infusion
  - isotonic but pH = 11
- Local toxicity of parenterals:
  - pH + buffercapacity
  - Osmolality

- New composition:
  - Trometamol
  - Glacial ac. acid
  - WFI
  - pH=8.5

Heijman et al, PW, 2000

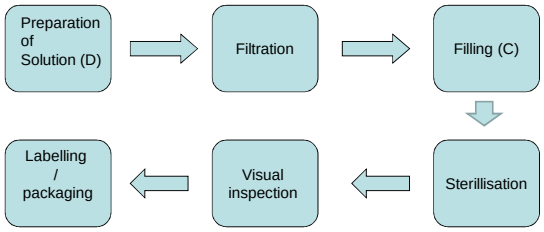
The development process



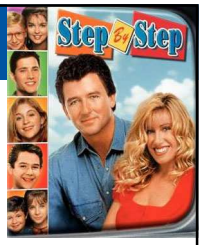
- 1-Rationale (WHY)
- 2- Design (WHAT)
- 3- Pharmaceutical development of product (WH
- 4- **Development of process (HOW)**

Parenteral drugs:
- if possible thermal sterilisation
- If possible in line filtration

Production process vials for inj: the basics



The development process



Pictures of in line filtration
Picture of ampoule machine and cabin
Picture of autoclave

The development process

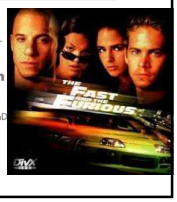
- Development characteristics:
  - New combination of known drug substance, known compounding process, known dosage form and strength
  - Develop for limited number of patients (sometimes one patient)
  - Limited development time: months to hours (!)

The European Journal of Hospital Pharmacy Science Volume 12 • 2006 • Issue 6 • P. ??-??

1781-7595 /26

Rapid development of pharmacy prepared labetalol injection as the solution for Trandate drug discontinuity

JWC Alffenaar, PharmD, MSc, RPh[1], J van der Heiden, PharmD, MSc, RPh[1], R E Herder[2], B Greijdanus[1], DRA Uges, PharmD, PhD, RHPh[1], RCA Schellekens, PharmD, MSc, RHPh[1]



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The development process

Formulation

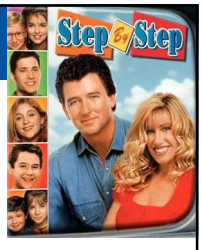
To establish the preparation method and composition based on:

- Literature
- Expericience in other pharmacies
- Physical & chemical data
- Test productions

The development process

Problems:

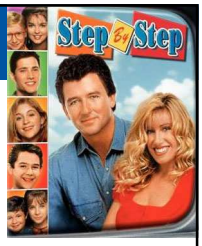
- Thermal instable products
- Thermal instable packaging
- Dry products
- Suspensions



Alternatives to thermal sterilisation

- Sterilisation with gamma radiation
- Aseptic preparation

The development process



Picture gamma
Picture B room
Picture frozen eyedrop

The development process

- **Process validation**
- to prove that the critical steps in the process are guaranteed
- to consistently deliver the intended performance of the product.

- Specify the process and its components
- Risk analysis
- Determine possible critical parameters
- Testing of critical parameters
- Conclusion

A QUALITY PRODUCT

The development process

Process validation
An example

Filtration | Filling (C) | Sterillisation

Content before and after filtration
Content before and after sterilisation

The development process

- Stability testing
  - Fixed interval
  - cluster

A QUALITY PRODUCT ALSO AT THE END OF SHELFLIFE

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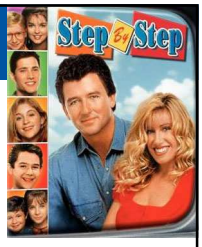
The development process

- Stability testing
  - “example of fixed and of cluster”

A QUALITY PRODUCT ALSO AT THE END OF SHELFLIFE

50

The development process



STEP BY STEP

- 1-Rationale (WHY)
- 2- Design (WHAT)
- 3- Pharmaceutical development of product
- 4- Development of proces
- 6- **Clinical testing**

Most of the times no clinical testing

The development process

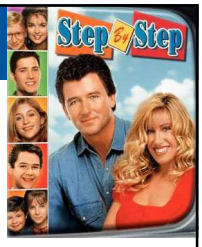
No clinical testing:
- A known active substance
- Use (administration) is known from literature of registration data

Clinical testing
- A new or relatively unknown substance
- A new route of administration
- No literature data
- The product itself is subject of investigation (the aim is not care)

The development process

An example
Intrathecal methylprednisolonacetate injection
Toxicity studie (animal)

The development process



STEP BY STEP

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- 7- **Introduction**

It ends with the patient

The development process

It ends with the patient:
- Results of development are considered
- Efficacy – Safety – Quality

This balance is different in care vs industry

The development process

This balance is different in care vs industry

The pharmacist can make the difference

“Pharmacists can play an important role in the availabillity of drugs for rare diseases”