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BEAM 2010 - ASPECTS OF COMPOUNDING

PRODUCT DESIGN

Reinout C.A. Schellekens, PharmD, RHPh, QP

Head Clinical Drug Production and Development

Department of Hospital and Clinical Pharmacy

University Medical Center Groningen, The Netherlands

r.c.a.schellekens@apoth.umcg.nl

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DISCLOSURE STATEMENT

- Nothing to disclose

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LEARNING OBJECTIVES

- Be able to develop a hospital prepared product and its packaging
- Able to design a new product with an understanding of the concept "quality by design"

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CONTENT

1. Introduction
2. Pharmaceutical development
   - Product design
   - Process development
   - Development in practice
3. Case study
4. Take home message

INTRODUCTION

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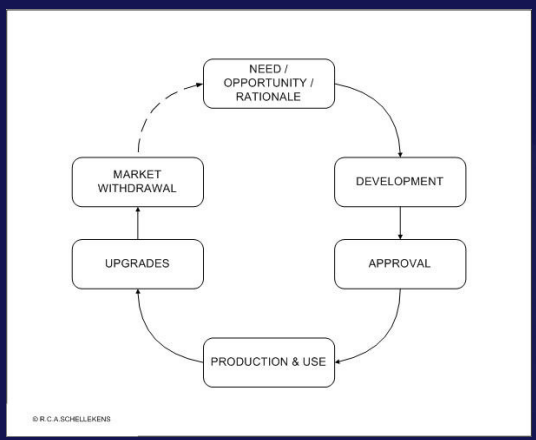
LIFE CYCLE OF A DRUG PRODUCT



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INDUSTRY VERSUS PHARMACY ?

- 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

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INDUSTRY VERSUS PHARMACY ?

- 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. ??-??

www.ejhp.org

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[1], B Greijdanus[1], DRA Uges, PharmD, PhD, RHPh[1], RCA Schellekens, PharmD, MSc, RHPh[1]

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INDUSTRY VERSUS PHARMACY ?

- Different regulatory environment

	Industry manufacturing	Pharmacy compounding
Approval	Regulatory authority	Doctor / Pharmacist
Production process	GMP (2001/83/EG, §46)	Professional standards
Product specifications	Registration file	Pharmacopoeia
Release	Qualified Person	Pharmacist
Distribution	National / International	Local / National
Vigilance	Mandatory + Regulated	Local policy
Information	SPC + Package leaflet	Local policy

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DEVELOPMENT OF PHARMACY-PREPARED PRODUCTS

- Relevant differences between industry and pharmacy developing products for health care
  - Policy
  - Development characteristics
  - Regulatory environment

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PHARMACEUTICAL DEVELOPMENT

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PHARMACEUTICAL DEVELOPMENT

- 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

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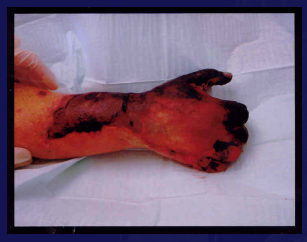
WHAT IS "QUALITY" OR "INTENDED PERFORMANCE" ?

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

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QUALITY IS BUILT INTO DRUG PRODUCTS ...

- ... through a comprehensive understanding of:
  - The intended therapeutic objectives; patient population; route of administration; and pharmacological, toxicological, and pharmacokinetic characteristics of a drug
  - Chemical, physical, and biopharm. characteristics of a drug
  - Design of a product and selection of product components and packaging based on drug attributes listed above
  - The design of manufacturing processes using principles of engineering, material science, and quality assurance

FDA, PAT Guideline

DIFFERENT APPROACHES

	Traditional approach (Minimal approach)	Enhanced approach (QbD approach)
Overall pharmaceutical development	•Mainly emperical •Developmental research often conducted one variable at a time	•Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs •Multivariate experiments to understand product and process •Establishment of design space •PAT tools utilised

SO PHARMACEUTICAL DEVELOPMENT ...

- ... considers both product and process development
- ... is based on thorough knowledge of pharmacology, biopharmacy, pharmaceutical technology, material science, engineering, quality assurance, analytical chemistry, biotechnology, microbiology ...

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PRODUCT DESIGN

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PHARMACOTHERAPEUTIC RATIONALE

- primary criteria
  - mechanism of action
  - efficacy
  - safety
- secundary criteria
  - experience
  - user friendliness
    - added value of dosage form or formulation (taste, local toxicity)
  - (QoL)

Tabel 2
Indeling van de literatuur naar mate van bewijs

A1	systematische reviews die ten minste enkele onderzoeken van A2-niveau betreffen, waarbij de resultaten van afzonderlijke onderzoeken consistent zijn
A2	gerandomiseerd vergelijkend klinisch onderzoek van goede kwaliteit (gerandomiseerde dubbelblind gecontroleerde trials) van voldoende omvang en consistentie
B	gerandomiseerde klinische trials van matige kwaliteit of onvoldoende omvang of ander vergelijkend onderzoek (niet-gerandomiseerd, vergelijkend cohortonderzoek, patiëntcontroleonderzoek)
C	niet-vergelijkend onderzoek
D	meningen van deskundigen gebaseerd op of in de vorm van D1 t/m D8:
D1	registratiegegevens van producten met hetzelfde farmacon, die in de handel zijn in Nederland, de Europese Unie, de Verenigde Staten, Canada of Japan
D2	gepubliceerde landelijke consensus: *Farmacotherapeutisch Kompas*, *Dermatica op recept*, NHG-standaarden, CBO-standaarden
D3	handboeken: naast algemene farmacotherapeutische handboeken is voor apotheekbereidingen waardevol het *Neues Rezeptur Formularium*
D4	advies van landelijke deskundigen: specialistenverenigingen, de Werkgroep farmacotherapie en geneesmiddeleninformatie van de KNMP
D5	aantoonbaar besluit van het FTTO waarbij het proces van besluitvorming volgens een vaste procedure is verlopen
D6	lokaal advies geneesmiddelencommissie of formularium-commissie van het ziekenhuis
D7	eigen inzicht van de individuele behandelaars (arts en apotheker) met onderbouwing van objectieve (klinische) gegevens
D8	eigen inzicht van de individuele behandelaars (arts en apotheker) zonder onderbouwing met objectieve (klinische) gegevens

Maurer et al, PW, 2009

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FACTORS TO CONSIDER

- Components
  - API, excipients, container
- Physicochemical properties
  - pK_a, solubility, melting point, hygroscopicity, stability, molecular weight, interactions (container & excipients), particle size, polymorphism,
- Biopharmaceutical properties
  - Biopharmaceutic classification system, Lipinsky's rule, dose number

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MANUFACTURABILITY

- Occupational safety
- Cleanability
- Cross-contamination
  - highly sensitising material (β-lactam antibiotics)
  - biological preparations (live microorganisms)
- Operational capacity
- Technical capacity
  - selection of sterilisation process
  - manual vs automated compounding (scale-up issues)

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OVERAGE

- Overages
  - Use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged.
  - Only accepted if degradation products have no or limited toxicity.
- Stability overage
- Process overage

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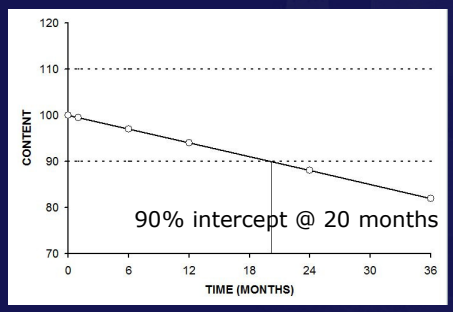
STABILITY (1)

- Stability studies
  - Chemical, physical and microbiological aspects
- Understand your drug product !
  - Mechanism of decomposition
  - Adsorption phenomena
  - Gas permeability of plastics
    - PET vials lose 6% water in 2 years (@ room temperature)
- Determine end-of-shelf-life specifications
  - Drug substance and critical excipients (preservatives!)

STABILITY (2)

- Initial stability testing
  - Accelerated versus shelf-life testing

- Assign end-of-shelf-life spec
- Assign release spec
- Assign expiry term
- What to decide for a new batch?
  - If content = 110%
  - If content = 95%



STABILITY (3)

- Surveillance testing
  - Fixed interval versus selected date approach

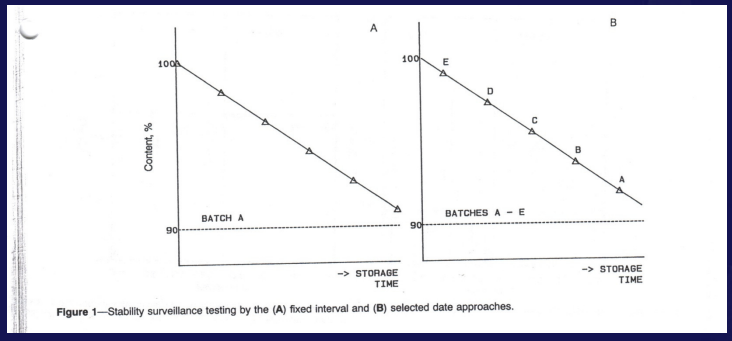


Figure 1—Stability surveillance testing by the (**A**) fixed interval and (**B**) selected date approaches.

De Kleijn, Lakeman, J Pharm Sc, 1993

PROCESS DEVELOPMENT

EXPERIMENTAL DESIGN

- Univariate experimental design
  - Traditional approach
  - Result: fixed process
- Multivariate experimental design
  - Factorial design or design of experiments approach
  - Also considers interaction between formulation variables
  - Result: range for process parameters

DESIGN OF EXPERIMENTS (DoE)

Available online at www.sciencedirect.com
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International Journal of Pharmaceutics 285 (2004) 65–75
international journal of pharmaceutics

Process characterisation, optimisation and validation of production of diacetylmorphine/caffeine sachets: a design of experiments approach

Marjolein G. Klous[a,*], Bastiaan Nuijen[a], Wim Van den Brink[b,c], Jan M. Van Ree[b,d], Jos H. Beijnen[a,e]

[a] Department of Pharmacy and Pharmacology, Slotervaart Hospital, P.O. Box 90440, 1006 BK Amsterdam, The Netherlands
[b] Central Committee on the Treatment of Heroin Addicts, Utrecht, The Netherlands
[c] Department of Psychiatry, Academic Medical Centre, University of Amsterdam, The Netherlands
[d] Department of Pharmacology and Anatomy, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, The Netherlands
[e] Faculty of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

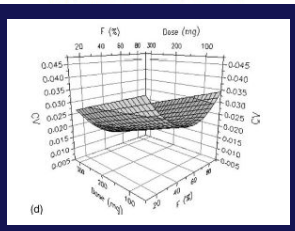

Table 2
Experiment design matrix (replicate runs: 3/17, 4/5, 11/16)

Run no.	D	AuS	AgS	F	DI
1	1	−1	−1	−1	−1
2	0.5	−0.5	−0.5	−0.5	0.5
3	−1	1	−1	1	−1
4	1	1	−1	1	−1
5	1	1	−1	1	−1
6	−1	1	1	−1	−1
7	0.5	−0.5	0.5	−0.5	0.5
8	−1	−1	−1	1	1
9	0	−1	1	−1	1
10	−0.5	0.5	0.5	−0.5	0.5
11	0	0	0	0	0
12	−0.5	−0.5	0.5	−0.5	0.5
13	1	1	1	1	1
14	1	1	1	−1	−1
15	1	−1	−1	1	1
16	0	0	0	0	0
17	−1	1	−1	1	−1
18	1	1	−1	−1	1
19	0.5	0.5	0.5	−0.5	0.5
20	−1	1	1	1	1
21	−1	−1	1	1	−1
22	−1	−1	−1	−1	−1
23	1	−1	1	1	−1
24	−1	1	−1	−1	1

D, dose; AuS, auger speed; AgS, agitator speed; *F*, hopper fill level; and DI: dose interval. Numbers represent the coded parameter settings: 1 for the maximum of the selected range, −1 for the minimum of the selected range, etc.

DEVELOPMENT IN PRACTICE

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DEVELOPMENT POLICY

- Develop local "pharmaceutical development procedure"
- This procedure should cover:
  - scope
    - magistral or officinal preparations - reconstitution
  - pharmacotherapeutic aspects
  - technological aspects
  - product file & review & approval
  - clinical evaluation
  - Product Quality Review

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UMCG APPROACH (1)

- Three principles
  1. Project management
     - appointment of project leader (= pharmacist)
  2. Structured process
     - 7 phases
     - structured product file
     - template "development file"
  3. Monitoring of progress

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UMCG APPROACH (2)

- Seven phases determining work flow
  1. pharmacotherapeutic rationale
  2. feasability study
  3. product & process concept & go / no-go decision
  4. experiments, pilot and validation batch, stability
  5. review & approval
  6. introduction
  7. clinical evaluation

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CASE STUDY

Bupivacaine-sufenta RTA

solution for epidural infusion

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IMPROVING SAFETY IN POST-OP ANALGESIA …

- Bupivacain / Sufentanil solution for epidural infusion is applied as post-op analgesia
- Marcain®, Sufenta forte® and NaCl 0,9% are admixed in a ratio of 12,5:1:36,5 into a perfusor syringe 50 mL
- Considerations:
  - Epidural space is immuno-incompetent
  - Preparation in uncontrolled areas
  - Preparation syringe by syringe is inefficient
  - 12.000 syringes used / year
- Request: develop a RTA-solution at comparable cost

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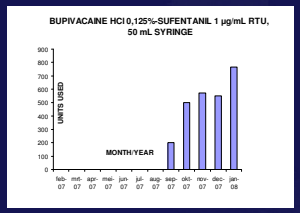
IMPROVING SAFETY IN POST-OP ANALGESIA …

- 2007: Bupi-sufentanil RTA in prefilled syringes
  - Qualification of the syringe as a storage device (#)
  - Process development
  - Process validation
  - Product design
- 2010: Bupi-sufentanil RTA (durante parte)



Dillingh et al, in progress

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CONCLUSION & TAKE HOME MESSAGE

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ADDED VALUE OF NEW PRODUCT DESIGN

- Meet local request for better drug treatment
  - Unique population
  - Orphan diseases
  - Increased patient safety
  - Decreased workload on the ward
  - Availability (in emergency situations)
- Meet local requests for IMPs
- Increased knowledge
  - Optimize existing products
  - Enhance future product development

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TAKE HOME MESSAGE

- New pharmacy-prepared drug products increase the added value of a compounding department for your patients
- Pharmaceutical development:
  - considers both product design and process development
  - requires broad pharmaceutical knowledge
  - needs to be organized and managed
- Group work
  - Develop own policy on pharmaceutical development (product group)
  - (Put into practice for your product)