

Site Master File

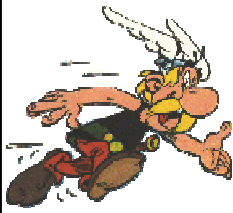


*All about the Site Master File
or
how to design your Pharmaceutical
facility?*

*Willem Meulenhoff
Pharmacist
UMC utrecht*



No Disclosures



Introduction

Willem Meulenhoff (1971)



- Production Pharmacist at NV Organon
- Head of the Production facility / Hospital Pharmacist at the University Medical Center Utrecht



Universitair Medisch Centrum
Utrecht

- GMP production game for hospital pharmacists (trainees) since 2005

UMC Utrecht



Mission of compounding unit UMCU: *Guarantee the availability of unique medicinal products*

1

"Guarantee the availability of unique medication"



Development of medicinal products

"Het formuleren en onderzoeken van geneesmiddelen die niet te koop zijn."



Production of these medicinal products

"Het op voorraad of patiëntspecifiek bereiden van geneesmiddelen conform de GMP (Good Manufacturing Practice)"



Delivery of medicinal products (selling)

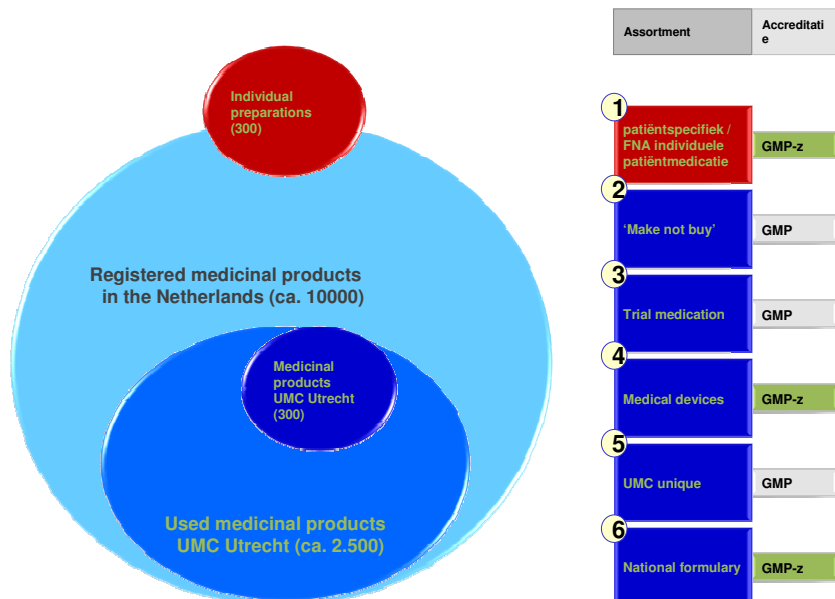
"Het verkopen van (uitsluitend de niet commercieel verkrijgbare) geneesmiddelen aan andere apotheken"



Provide knowledge on the preparation of medicinal products

"Het verstrekken van informatie, die andere apotheken of zorgverleners nodig hebben om medicatie voor hun patiënten te maken"

Of all used medicines in 12% in the UMC Utrecht is compounded by the production unit excluding the individual preparations

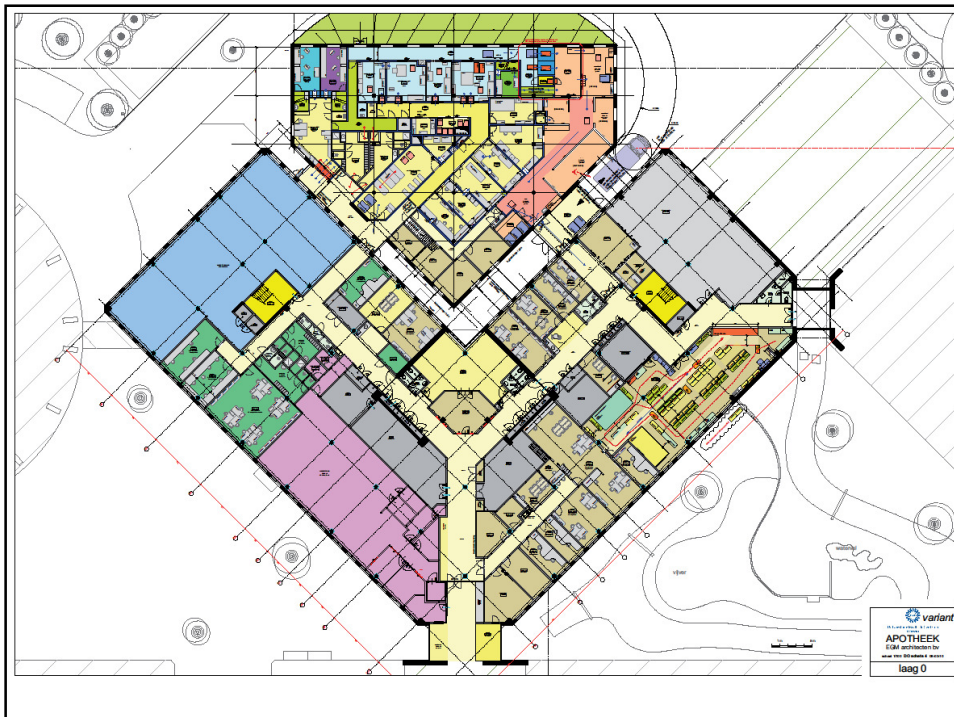


Production unit UMCU

- Sterile & non sterile production
 - 1000 batches a year
 - 15000 Cytotoxic preparations
 - 5000 individual preparations
- 25FTE, production staff
 - Incl 2.5 production pharmacist
 - Excl QP, QC, QA, logistic



- GMP license for production trial medication



Programme



- 1- Introduction
- 2- Site master file (content)
- 3- How to design a facility
- 4- Groupwork

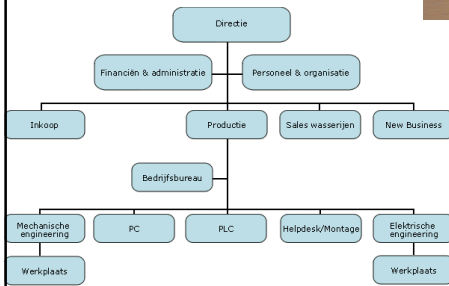
Groupwork

- Prepare a site master file containing
 - Mission, strategy and name of the organisation
 - Product lines
 - Number of batches
 - Batch size
 - Organogram
 - Technical infrastructure
 - Floor plan
 - Major equipment
 - Description of the quality system incl major procedures (optional)



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

<p>1</p> <p>"Guarantee the availability of unique medication"</p>	<p>Development of medicinal products</p> <p>"Het formuleren en onderzoeken van geneesmiddelen die niet te koop zijn."</p>
	<p>Production of these medicinal products</p> <p>"Het op eenmaal of periodiek basis bereiden van geneesmiddelen conform de GMP (Good Manufacturing Practice)"</p>
	<p>Delivery of medicinal products (selling)</p> <p>"Het verkopen van (substantie die niet commercieel verkrijgbaar) geneesmiddelen aan andere apotheken"</p>
	<p>Provide knowledge on the preparation of medicinal products</p> <p>"Het verstrekken van informatie, die andere apotheken of zorgverleners nodig hebben om medicatie voor hun patiënten te maken"</p>



Site master file

- A document useful for regulatory authorities to conduct GMP inspections



- PIC/S explanatory notes for industry on the preparation of a site master file



Site Master File

- Table of contents
 - General information
 - Manufacturing activities
 - Type of products
 - Description of the site
 - Outside assistance
 - Quality management system

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

Development of medicinal products
 "Het ontwikkelen en onderzoeken van geneesmiddelen die niet te koop zijn."

Production of these medicinal products
 "Het in overeenstemming met de goederenwet, de wet op de geneesmiddelen en de GMP (Good Manufacturing Practice) vervaardigen van geneesmiddelen die niet te koop zijn."

Delivery of medicinal products (selling)
 "Het verspreiden van geneesmiddelen die niet te koop zijn aan de apotheken en andere afnemers."

Provide knowledge on the preparation of medicinal products
 "Het verspreiden van informatie, die andere apotheken of zorgverleners nodig hebben om medicatie goed toe te passen in de praktijk."

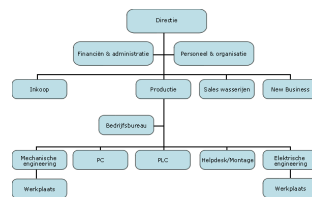
Afdeling	# medewerkers	# Charges	# productieslagen	# medewerkers	Ruimte behoefte per type ruimte in dagen		
					totale ruimte	ruimte	# dagen
Administratie	15500	0	0	1017	0	0	0
Biofarmacie	2245	31	26.5	26.5	26.5	0	0
De afvalafdeling	22014	0	113.1	0	113.1	0	0
Productie	4250	59	16.8	168.0	0	0	0
Keuken	22009	170	114.0	0	0	114.0	42.1
Logistiek	9418	252	87.7	157.0	0	0	87.0
Medicatie	19234	100	25.1	0	0	25.1	67.0
Werkplaats	18009	20	33.0	0	0	33.0	0
Totaal	38944	773	719.1	3279.0	414.1	182.0	120.0
Bezoeken				100			
Bezoeken				540	540	540	470

What you're doing

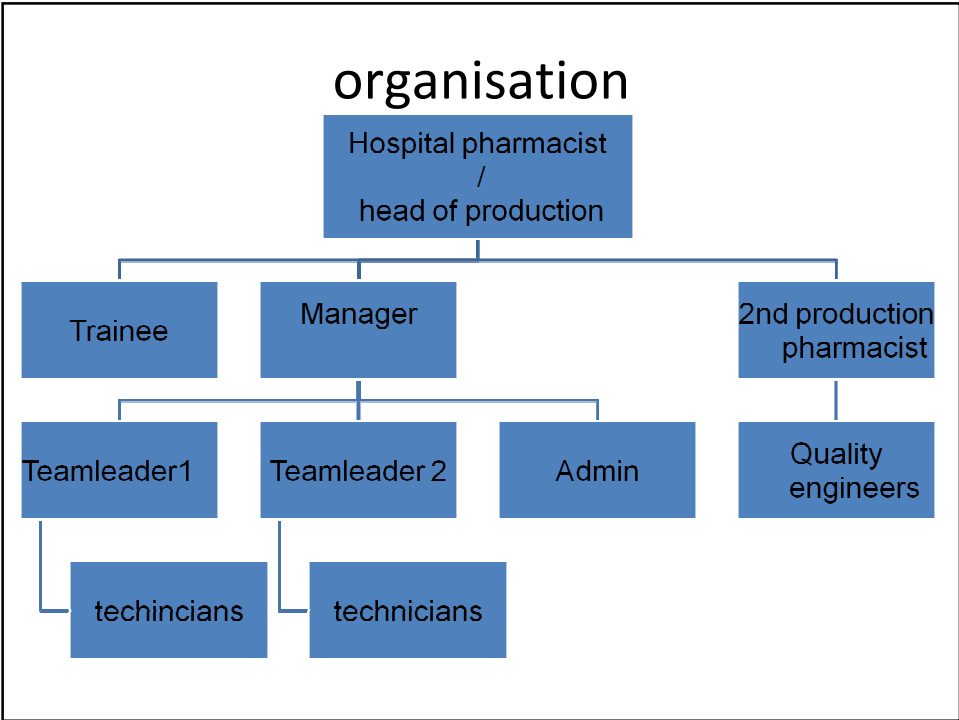
alle dagen zijn deze afnemers van boven: # Charges omzet alle 1 Charge per dag
 groot startaf idem, geconificeerd voor het softspan
 4. alle afnemers in tabel is netto bij berekening in meerder charges per dag kunnen, er wordt een deel uitgebracht per eigenlijke moet 114.42
 maar kan niet altijd vandaar wat ruimte
 oplossing voor ampren ki er rap wel in C maken
 mogelijk kloven een aantal nabehandelde producten in C en gaan niet naar B
 netto is gewoon alle productie 100 opgezet
 bruto is alle productie eigenaar naar boven en opgezet
 als er een wip tijde bij niet naar komt neemt aantal dagen in met n-ster bereiding af en dagen afweken toe
 Doelstelling

Site master file contents

- Personnel
 - Organisation chart
 - Qualifications and resp
 - Training
 - Health requirements
 - Personnel hygiene requirements & clothing



Who's is doing it



Site master file contents

- Premises and equipment
 - Plan of manufacturing area
 - Ventilation system
 - Water system incl sanitation
 - Maintenance programme
 - Equipment
 - Sanitation and cleaning

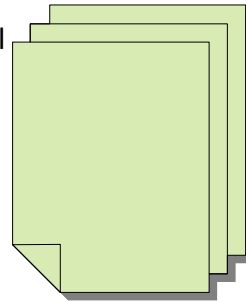
Where you're doing it

Site master file contents

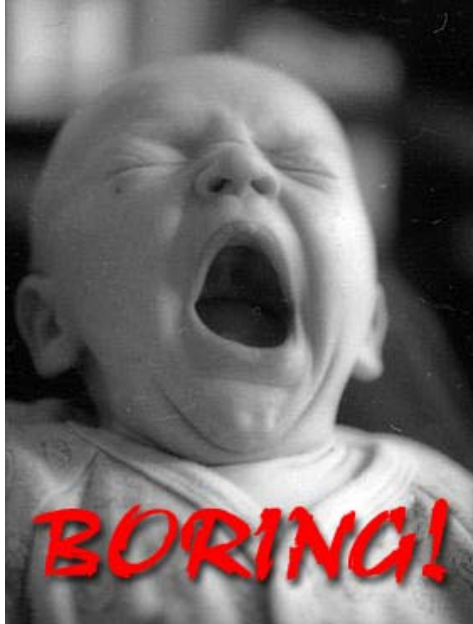
- Documentation
 - Arrangements for the preparation
 - Any other documents related to product quality
- Production
- Quality control
- Contract manufacture
- Distribution complaints and product recall
- Self inspection

What you're doing
Who's is doing it
Where you're doing it

How you're doing it



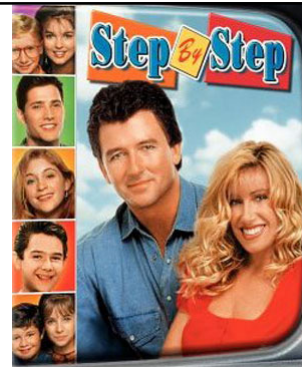
This baby says:



BORING!

Design step by step

- 1-Mission and strategy
- 2- Products to be made
- 3- Production proces
- 4- Capacity
- **5- Design**
- 6- Installations and equipment



Site Master File



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

<p>1</p> <p>Guarantee the availability of unique medicinal products</p>	<p>Development of medicinal products</p> <p>"Het formuleren en onderzoeken van geneesmiddelen die niet te koop zijn."</p>
	<p>Production of these medicinal products</p> <p>"Het op maatwerk of patiëntspecifiek bereiden van geneesmiddelen conform de GMP (Good Manufacturing Practice)"</p>
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	<p>Provide knowledge on the preparation of medicinal products</p> <p>"Het verstrekken van informatie, die andere apotheken of zorgverleners nodig hebben om medicatie voor hun patiënten te maken"</p>

1- Mission and strategy

- What is the mission of the production unit?
- What are the activities we are going to do?
- What sort of products are we going to make?



2- Products and service

- Product forms
- Batch size
- Customers
- Response time

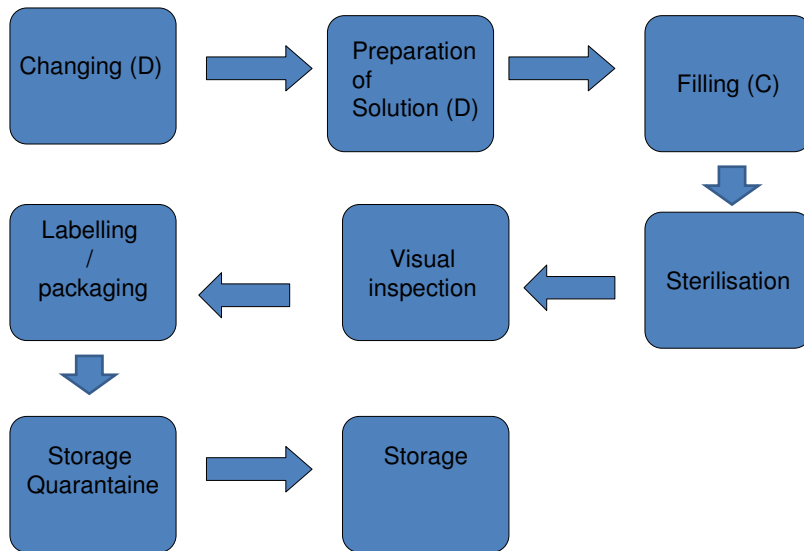


- These parameters define the different production processes of the unit

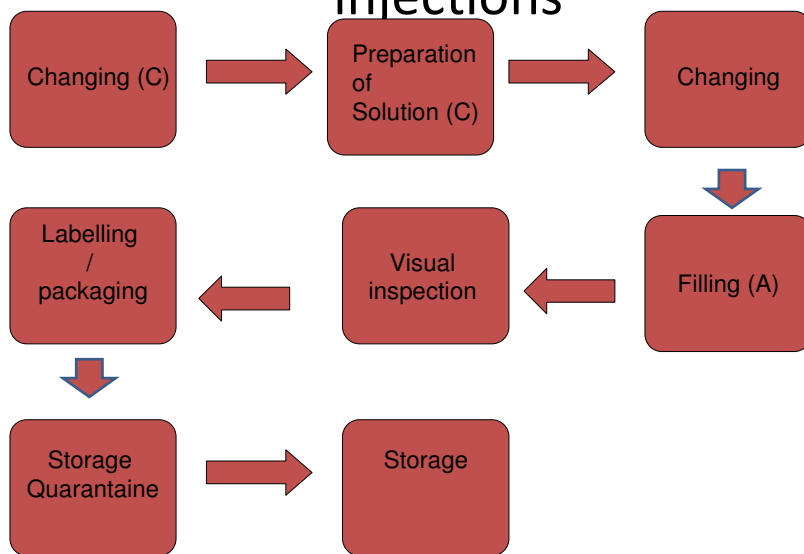
3- Design the production proces

- Define the different proces steps by location
- Example
- For the production of vials you need to have a process like
 - Assemble materials: Storage area for expipients and packaging materials
 - Get dressed: Gowning area
 - Prepare the solution:

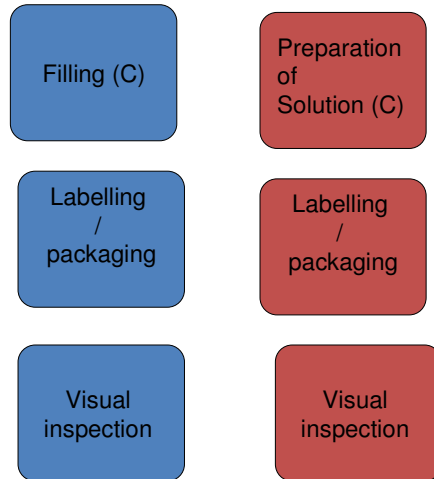
Production proces vials for inj



Production proces aseptic injections

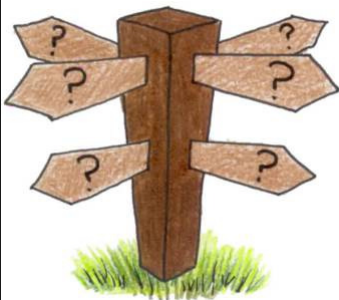


Combine different proceses



4- Determine capacity

- Number of rooms but also personel
 - night shifts
 - Qualification of staff
 - organogram



Where to start

- What are you going to make? (Mission, strategy and products)
- How are you making that? (proces)

Make an educated guess

- HOW MUCH?



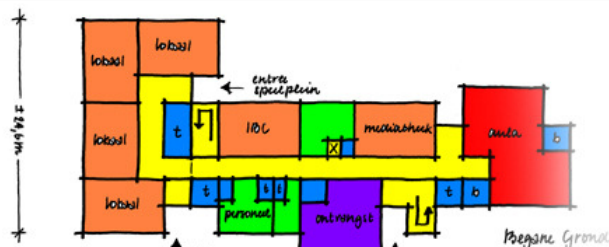
product omschrijving	# units	# batches	C	C days	Pack	Pack hours
ADENOSINE 30MG=10ML INJVL AMP10ML	3154		3 1	3	13	39
ADRENALINE 1MG/10ML INJECTIE			1 0,75	0,75	5	5
ADRENALINE 5ML=5MG INJ			1 0,75	0,75	5	5
ALCOHOL 96% INJ 5ML			1 0,6	0,6	3	3
BACLOFEN INTRATHECAAL 10MG=5ML	113		1 0,6	0,6	3	3
BLANCO HISTAMINE PROV.	414		1 0,6	0,6	4	4
CALCIUM CHLORIDE 5 MMOL = 10 ML INJVLST	4438		1 1	1	13	13
COBALTCHLORIDE 200 MICROG=2ML INFCONC	193		1 0,6	0,6	3	3
COCKTAIL INJ 2 ML	276		1 0,6	0,6	3	3
COFFEINE 10 MG = 1 ML INJVLST	1276		1 0,75	0,75	10	10
DEXAMETHASON 100 MG = 5 ML INJVLST			1 0,75	0,75	10	10
DEXAMETHASON 4MG/ML AMPUL 1ML	12782		3 1	3	30	90
ERGOMETRINE MAL 1ML=0,15MG INJ	609		1 0,75	0,75	5	5
FENOBARBITAL 20MG/ML INJECTIEVLST	1042		2 0,75	1,5	10	20
FENOL 5% IN OLIE INJ 5ML	167		1 0,6	0,6	3	3
FENOL 8% IN OMNIPAQUE INJ 5ML			1 0,6	0,6	3	3
FENYLEFRINE HCL 1ML = 10MG INJ	3121		3 1	3	13	39
FENYTOINE NA 250 MG = 5 ML INJVLST			1 0,75	0,75	10	10
FOLIUMZUUR 1MG = 1ML INJ	7225		2 1	2	13	26
FOSFAATBUFFER PH7,4 GLUC 0,5ML 1ML			1 0,75	0,75	5	5
FYSOSTIGMINE SALICYLAAT 1MG/ML AMP 2ML			1 0,6	0,6	3	3
HEPARINE 10000 IE=0,4ML ZONDER CONSERV	10339		2 1	2	30	60
HEPARINE IN FYS Z 1000E=10ML	31153		7 1	7	13	91
HEPARINE IN FYS Z 1000E=1ML INJ	6033		1 1	1	30	30
HEPARINE IN FYS Z 12,5E=5ML INJ	34673		5 1	5	26	130
HEPARINE IN FYS Z 250E=10ML INJ			1 1	1	13	13
HISTAMINE 0.25 MG/ML PROVOCATIE	412		1 0,6	0,6	4	4
HISTAMINE 0.5 MG/ML PROVOCATIE	426		1 0,6	0,6	4	4
HISTAMINE 1 MG/ML PROVOCATIE	449		1 0,6	0,6	4	4
HISTAMINE 16 MG/ML PROVOCATIE	252		3 0,6	1,8	3	9
HISTAMINE 2 MG/ML PROVOCATIE	834		2 0,6	1,2	4	8

	# units	# batches	# days	packaging	non sterile	D Class	C class	B class
ampoules	185458	94	76,6	1013		83	94	11
dermatics	2245	31	26,5	2	26,5	0	0	0
solutions	22914	82	116,1	9,5	116,1	0	0	0
LVP	42940	58	45,8	466,5		99	99	0
SVP	22299	179	114,3	355		0	114,3	42,1
Eyedrops	9418	202	67,7	157,5		0	67,7	67,7
tab&caps	85434	100	241,5	247	241,5			
supps	18936	29	30,6	29	30,6			
pack				1000				
TOTAL	389644	775	719,1	3279,5	414,7	182	375	120,8
# rooms				3	3		3	1
Occupation				54%	54%		49%	47%



5- make the global design

- Information to start the design
 - Proses flows: class of room and relationship
 - Capacity forecast: number of rooms / size



6- Add installations

- Air system
- Water
 - Tap water
 - Distilled water
 - Purified water
 - Cooling water
- Gases
- Autoclaves
- LAF cabinets



Groupwork

- Prepare a site master file containing
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