SLOVENSKO FARMACEVTSKO DRUŠTVO
SEKCIJA BOLNIŠNIČNIH FARMACEVTOV

15. mednarodni simpozij Sekcije bolnišničnih farmacevtov pri SFD

15. International Symposium of the Section of Slovenian HP at the Slovenian Pharmaceutical Society

ASEPTIČNA PRIPRAVA ZDRAVIL – VČERAJ, DANES, JUTRI

Aseptic drug preparation – yesterday, today, tomorrow

ZBORNIK PREDAVANJ

7. november 2023, Domus Medica, Ljubljana

Strokovno-organizacijski odbor simpozija:

dr. Aljaž Sočan – predsednik SBF

Vesna Bizjak

mag. Franci Tratar

Simona Mitrović

Bernarda Emeršič

Marijana Fortuna Lužar

Danila Hriberšek

Anja Soukup

Tajda Miharija Gala

KOLOFON:

e-Zbornik 15. mednarodnega simpozija Sekcije bolnišničnih farmacevtov pri SFD

ASEPTIČNA PRIPRAVA ZDRAVIL – VČERAJ, DANES, JUTRI, 2023

Za interno uporabo!

Zbrala: Bernarda Emeršič, mag. farm., spec.

Uredila: dr. Andrijana Tivadar, mag. farm., generalna sekretarka SFD

Dostop: www.sfd.si

Založnik:

SLOVENSKO FARMACEVTSKO DRUŠTVO

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ZBORNIK 15. mednarodnega simpozija

Sekcije bolnišničnih farmacevtov pri SFD

Ljubljana, 7. november 2023

KAZALO

PROGRAM SIMPOZIJA

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7. november 2023, Domus Medica, Ljubljana, Dunajska cesta 162, 1000 Ljubljana

Ura	Naslov in predavatelj/ica/Title and speaker
8:00–9:00	**Prihod udeležencev in registracija**/ Registration
9:00–9:05	**Uradna dobrodošlica in odprtje simpozija**/ Official wellcome and Symposium opening **Aljaž Sočan**, predsednik Sekcije bolnišničnih farmacevtov/ President of the Section of Slovenian Hospital Pharmacists
9:05–9:35	**Nekoč in danes: Zgodovina aseptične priprave zdravil**/ Historical overview of aseptic preparation **prof. dr. Mirjana Gašperlin**, mag. farm., Fakulteta za farmacijo/ Faculty of Pharmacy
9:35–10:05	**EU Legislation - Experience from The Netherlands**/ Evropska zakonodaja- izkušnje iz Nizozemske **Paul Le Brun,** PharmD, PhD, Associate professor
10:05–10:35	**Aseptična priprava zdravil v bolnišnični lekarni v luči zakonodajnih zahtev**/ Medicines preparation in a hospital pharmacy and legislative requirements mag. **Andrej Ferlan,** mag. farm., spec.
10:35–10:55	**Aseptična izdelava v farmacevtski industriji**/ Aseptic preparation in the pharmaceutical industry Boštjan Kmet, mag. farm.
10:55–11:00	**Razprava**/ Discussion
11:00–11:30	**Odmor**/ Coffee break
11:30–12:15	**Current activities in modern hospital environment in The Netherlands**/ Aktivnosti v sodobnem bolnišničnem okolju na Nizozemskem **Paul Le Brun,** PharmD, PhD, Associate professor
12:15–12:25	**Čisti prostori bolnišnične lekarne SB Murska Sobota**/ Clean room in Hospital Pharmacy in General Hospital Murska Sobota **Simona Mohar Karakatič,** mag. farm., spec., SB Murska Sobota
12:25–12:35	**Avtomatizirana priprava citostatikov**/ Automated preparation of cytotoxics **Jure Dolenc,** mag. farm., Onkološki Inštitut Ljubljana
12:35–12:45	**Aseptična priprava radiofarmakov**/ Aseptic preparation of radipharmaceuticals **dr. Aljaž Sočan, mag. farm., spec.,** UKC Ljubljana
12:45–13:00	**Aseptična priprava v lekarni na primarnem nivoju**/ Aseptic preparation in community pharmacy **Lidija Vrbovšek, mag. farm., spec.**, JZ Celjske lekarne

Ura	Naslov in predavatelj/ica/Title and speaker
13:00–13:30	**Vabljeno predavanje**/ Invited lecture **Contamination – a hidden risk of everyday items used in the aseptic units/ Ko**ntaminacija pri delu v aseptičnih prostorih **Rufus Smith**, MSc, Senior Pharmacist
13:30–15:00	**Kosilo**/ Lunch
15:00–15:30	**Risk assessment in daily practice/** Ocena tveganja v vsakodnevni praksi **Paul Le Brun,** PharmD, PhD, Associate professor
15:30–15:50	**Koliko stane kakovost? /** What is the price of Quality? dr. **Mateja Tršan**, mag. farm., spec., UKC Ljubljana
15:50–16:10	**Vpliv racionalizacije dela in stroškov na kakovost in ceno izdelka**/ The impact of labor and cost rationalization on product quality and price **Simona Mitrović, mag. farm., spec., Lidija Vrbovšek, mag. farm., spec., Simona Mohar Karakatič,** mag. farm., spec.,
16:10–16:30	**Vabljeno predavanje**/ Invited lecture **Is it enough being done to prevent contamination in the cleanrooms?**/ Ali delamo vse, da preprečimo kontaminacijo v čistih prostorih? **Rufus Smith**, MSc, Senior Pharmacist
16:30–17.00	**Odmor**/ Coffee break
17.00–17:15	**Satelitsko predavanje**/ Sponsored lecture **– Amgen** **Pogled na podobna biološka zdravila: zdravilo BEKEMV**/ A view on biosimilars: BEKEMV **Tomislav Laptoš, mag. farm., spec.**
17:15–17:30	**Satelitsko predavanje**/ Sponsored lecture **– Ecolab** **Dezinfekcija in sporocidna rotacija pri čiščenju aseptičnih prostorov**/ Desinfection and sporocidal rotation in clean rooms **Juš Žagar, univ. dipl. kem.**
17:30–18:10	**Kratek povzetek in panelna razprava s predavatelji**/ Short conclusion and panel discussion vodi **Simona Mitrović, mag. farm., spec., UKC Ljubljana**
18:10–18:15	**Zaključne besede in zahvala**/ Conclusion of the symposium **Aljaž Sočan**, predsednik Sekcije bolnišničnih farmacevtov/President of the Section of Slovenian Hospital Pharmacists

LZS je programu simpozija dodelila 6,5 licenčnih točk za pasivno udeležbo za magistre farmacije z licenco in 4 licenčne točke za aktivno udeležbo.

Nekoč in danes: Zgodovina aseptične priprave zdravil

Historical overview of aseptic preparation

prof. dr. Mirjana Gašperlin, mag. farm.

NEKOČ IN DANES: ZGODOVINA ASEPTIČNE PRIPRAVE ZDRAVIL)

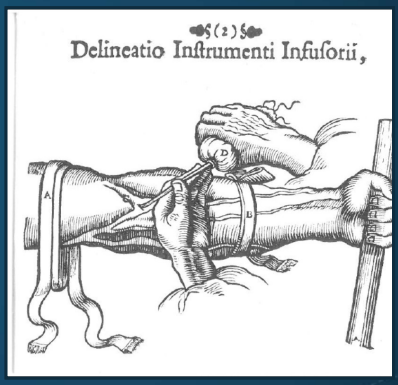
PROF. DR. MIRJANA GAŠPERLIN
FAKULTETA ZA FARMACIJO UNIVERZA V LJUBLJANI

ASEPTIČNI POSTOPEK, KOT GA POZNAMO DANES, JE REZULTAT RAZVOJA VEČ PODROČIJ

- Načini aplikacije
- Vsebniki in naprave
- Tehnologija procesa
- Standardi & regulativa
- Mikrobiologija

KAKO SE JE ZAČELO ?

- Opazovanje pikov insektov in kač, smrti zaradi zastrupljenih puščic
- 17. stoletje
  - 1616 opis cirkulacije krvi (Wiliam Harvey)
  - 1656 sir Christphoper Wren uspava psa z injiciranjem morfija
  - 1662 uspešen poskus injiciranja zdravila ljudem
-



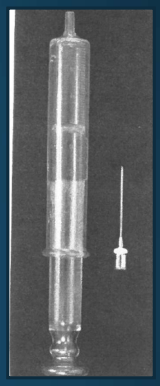
MIKROSKOP

Antonie Van Leeuwenhoek 1632 - 1723

- Suknar, trgovec & prirodoslovec iz Delfta
- Oče mikroskopa - izdelal naj bi okrog 400 mikroskopov in 500 leč, ohranjenih je še 9 primerov
- Prvi je opazil očem nevidne organizme, kar je kasneje omogočilo razumevanje infekcij in tlakovalo pot metodam za uničenje mikrorganizmov
- .

KAKO SE JE ZAČELO ?

- 1836 LaFaregue zdravi nevralgije tako, da prebode kožo z lanceto, namočeno v morfij
- 1844 Alexsander Wood von Edinburg - prvi uspešno aplicira zdravilo subkutano
- **2. polovica 19. stoletja** - L. Pasteur, J. Lister in I. Semmelweis – pionirji uvajanja antisepse na področju medicine



LOUIS PASTEUR 1822 -1895

..

... med drugim

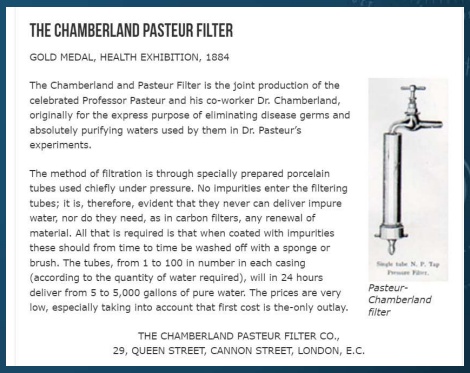
1862 objavi, da MO povzročajo različne bolezni, kar vodi kasneje do procesa pasterizacije

Potrdi, da toplota uniči MO, kar tlakuje pot k sterilizaciji s toploto

Skupaj s R. Kochom velja za očeta bakteriologije

CHARLES CHAMBERLAND 1851 - 1908

- Pasteurjev učenec in sodelavec
- Avtor prvega avtoklava
- Razvije vrsto filtrov, danes poznanih kot Chamberland-Pasteur- jevi filtri.



THE CHAMBERLAND PASTEUR FILTER

GOLD MEDAL, HEALTH EXHIBITION, 1884

The Chamberland and Pasteur Filter is the joint production of the celebrated Professor Pasteur and his co-worker Dr. Chamberland, originally for the express purpose of eliminating disease germs and absolutely purifying waters used by them in Dr. Pasteur's experiments.

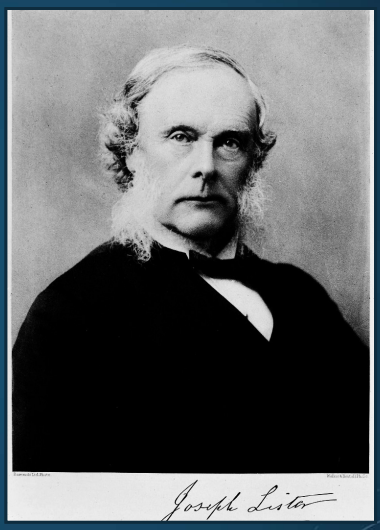
The method of filtration is through specially prepared porcelain tubes used chiefly under pressure. No impurities enter the filtering tubes; it is, therefore, evident that they never can deliver impure water, nor do they need, as in carbon filters, any renewal of material. All that is required is that when coated with impurities these should from time to time be washed off with a sponge or brush. The tubes, from 1 to 100 in number in each casing (according to the quantity of water required), will in 24 hours deliver from 5 to 5,000 gallons of pure water. The prices are very low, especially taking into account that first cost is the-only outlay.

Pasteur-Chamberland filter

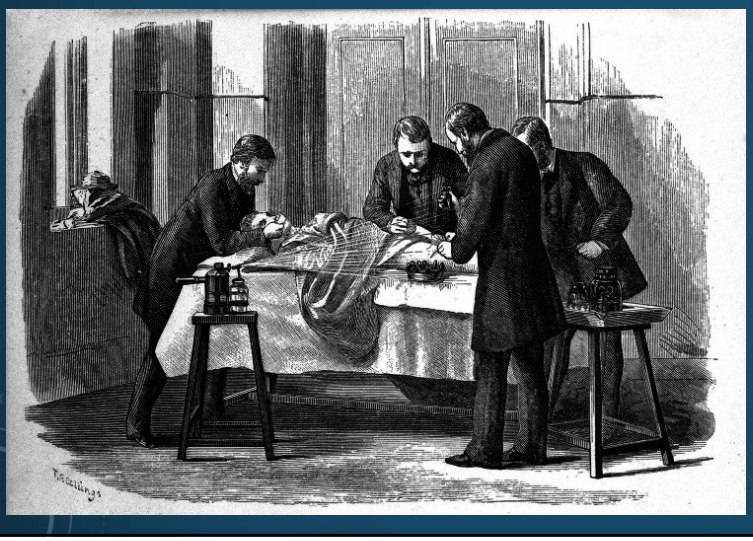
THE CHAMBERLAND PASTEUR FILTER CO.,
29, QUEEN STREET, CANNON STREET, LONDON, E.C.

JOSEPH LISTER 1827-1912

- Velja za očeta moderne antiseptične kirurgije
- Z aplikacijo Pasteurjevih odkritij v mikrobiologiji v kirurško prakso je bistveno pripomogel k zmanjšanju infekcij ran
- »No germs – no infection – no disease«



LISTERJEVA ANTISEPTIČNA METODA & NAPRAVE



Napravi za razprševanje fenola

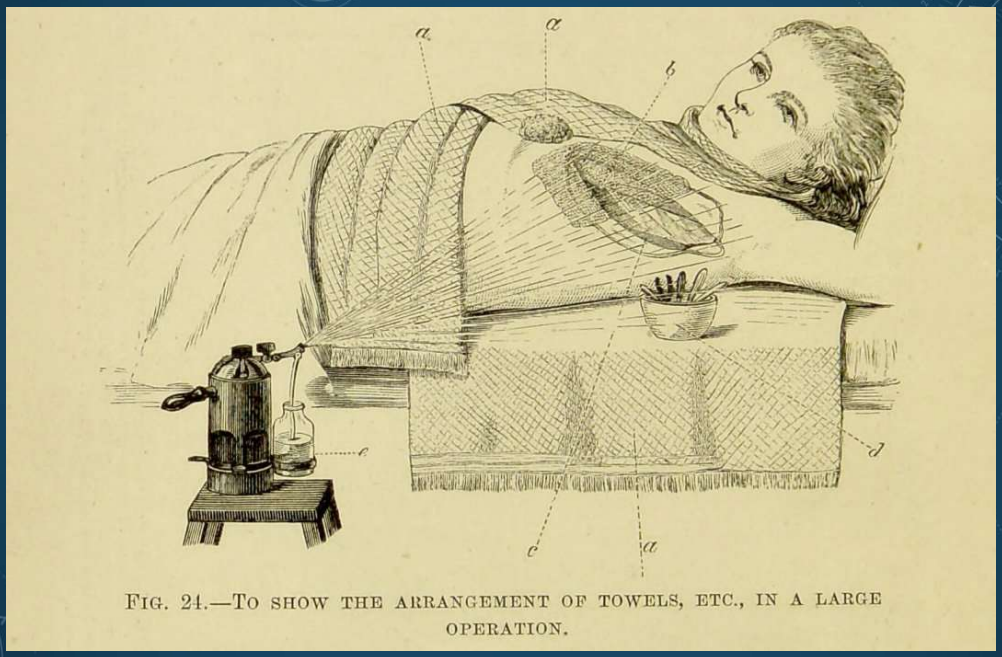
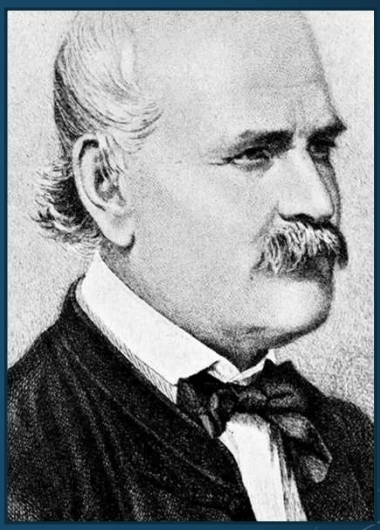


FIG. 24.—TO SHOW THE ARRANGEMENT OF TOWELS, ETC., IN A LARGE OPERATION.

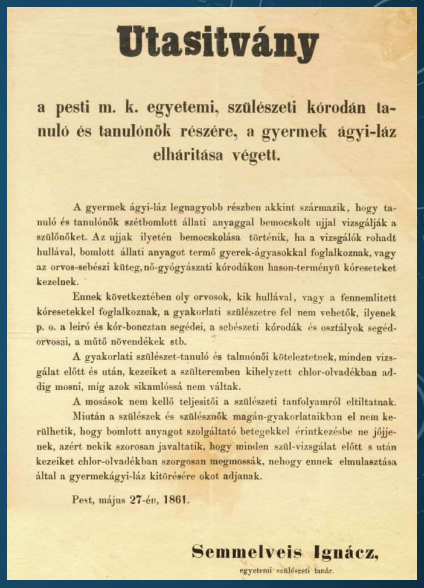
IGNAC SEMMELWEIS 1818 - 1865

- Forgotten data on the introduction of aseptic techniques*
- Danes znan kot rešitelj mater zahvaljujoč zahtevi po obveznem umivanju rok za zdravstveno osebje v raztopini klora
- Pionirska odkritja
- Spor z medicinsko fakulteto na Dunaju
- Po njem se imenuje največja univerza na Madžarskem



T. Doby. Hist Phil.Life Sci 9. 1987

Semmelweisova navodila ¨¨Instruction to the Medical Students Studying at the Maternity Hospital of the Hungarian Royal University of Pest to Prevent Childbed Fever¨, obešena na vrata porodnišnice 1861



Utasitvány

a pesti m. k. egyetemi, szülészeti kórodán tanuló és tanulónök részére, a gyermek ágyi-láz elháritása végett.

A gyermek ágyi-láz legnagyobb részben akkint származik, hogy tanuló és tanulónök szétbomlott állati anyaggal bemocskolt ujjal vizsgálják a szülőnőket. Az ujjak ilyetén bemocskolása történik, ha a vizsgálók rohadt hullával, bomlott állati anyagot termő gyerek-ágyasokkal foglalkoznak, vagy az orvos-sebészi küteg, nő-gyógyászati kórodákon hason-terményü köreseteket kezelnek.

Ennek következtében oly orvosok, kik hullával, vagy a fennemlitett köresetekkel foglalkoznak, a gyakorlati szülészetre fel nem vehetők, ilyenek p. o. a leiró és kór-boneztan segédei, a sebészeti kórodák és osztályok segéd-orvosai, a mütő növendékek stb.

A gyakorlati szülészet-tanuló és talmunői köteleztetnek, minden vizsgálat előtt és után, kezeiket a szülteremben kihelyzett chlor-olvadékban addig mosni, míg azok sikamlóssá nem váltak.

A mosások nem kellő teljesitői a szülészeti tanfolyamról eltiltatnak.

Miután a szülészek és szülésznők magán-gyakorlatnikban el nem kerülhetik, hogy bomlott anyagot szolgáltató betegekkel érintkezésbe ne jöjjenek, azért nekik szorosan javaltatik, hogy minden szül-vizsgálat előtt s után kezeiket chlor-olvadékban szorgosan megmossák, nehogy ennek elmulasztása által a gyermekágyi-láz kitörésére okot adjanak.

Pest, május 27-én, 1861.

Semmelveis Ignácz,
egyetemi szülészeti tanár.

OD ANTISEPSE K ASEPSI

- Suha toplota in sterilizacija s paro kot alternativa kemijskim sredstvom, uvedba avtoklava
- Konec 19. stoletja
  - Evropa: na osnovi Kochovih raziskav Gustav Neubert uvede sterilizacijo in aseptične metode v operacijske dvorane, Ernst von Bergmann sterilizira s paro operacijske instrumente (1885)
  - ZDA: William Stewart Haltsted uvede sterilna oblačila, dezinfekcijo operacijskih prostorov, sterilne rokavice (1898)

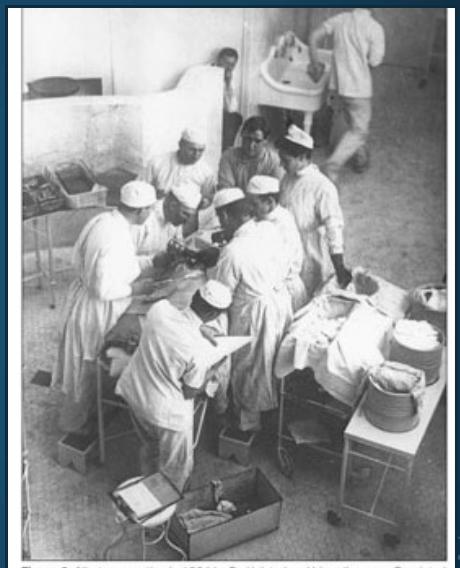
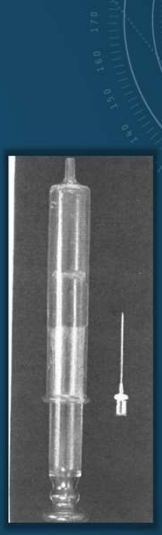
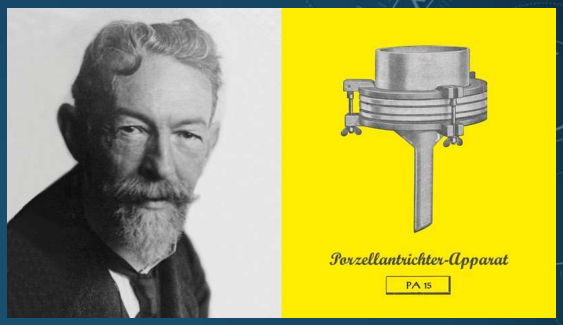


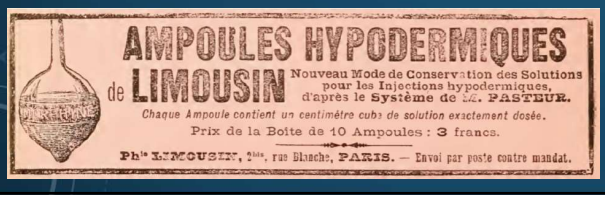
Figure 2. All-star operation in 1904 by Dr. Halsted and his colleagues. Reprinted with permission of the Alan Mason Chesney Medical Archives of The Johns Hopkins Medical Institutions. Next to Dr. Halsted are Dr. Joseph Bloodgood, Dr. Hugh Young, and Dr. Harvey Cushing. Directly across from Dr. Halsted is Dr. John

NAZAJ K ZDRAVILOM – KONEC 19. STOLETJA

- Zamik uvajanje antisepse/asepse na področju parenteralne terapije
- Materiali, iz katerih so bile brizge, niso dopuščali sterilizacije s toploto, raztopine so bile termolabilne
- Priprava raztopin na mestu z raztapljanjem tablet na segreti žlički
- Pomemben napredek:
  - Richard A. Zsigmondy & Bachmann razvijeta metodo za komercialno proizvodnjo filtrov iz celuloznega nitrata in lansirata pojem membranski filter (1918)
  - S. Limousin izumi ampulo







NEKAJ POMEMBNIH MEJNIKOV V ZADNJIH 100 LETIH

- 1942 sušenje z zamrzovanjem postane metoda za sterilizacijo farmacevtskih izdelkov
- 1933 patentiran etilenoksid, od leta 1960 množična uporaba za sterilizacijo v bolnišnicah
- 1940 odkritja, ki so omogočila komercialno uporabo sterilizacijo z radiacijo v poznih 50-ih letih
- 1940 koncept LAF komor, obremenjenih s HEPA filtri, ki omogoči sterilno delovno okolje
- 1974 FDA uvede koncept validacije za procesov za proizvodnjo sterilnih izdelkov
- 1977 koncept »clean in place« (CIP)
- Sistemi za enkratno uporabo (singe –use systems)


????
Izolatorji & RABS
TRENDI
Single – use tech
Robotizacija
Biofarmacevtiki & ATMPs
Avtomatizacija & AI

EU Legislation - Experience from The Netherlands

Evropska zakonodaja- izkušnje iz Nizozemske

Paul Le Brun, PharmD, PhD, Associate professor

Leids Universitair Medisch Centrum

EU Legislation - Experience from The Netherlands

Legislation and preparation in pharmacies

Paul Le Brun, PharmD, PhD
Hospital pharmacist-clinical pharmacologist

Ljubljana November 7, 2023

Conflict of interest: Nothing to disclose

Agenda

GMP and other relevant legislation

GMP and Preparation in European (hospital) pharmacies

Interpretation of GMP in Dutch hospital pharmacies

GMP and other relevant legislation

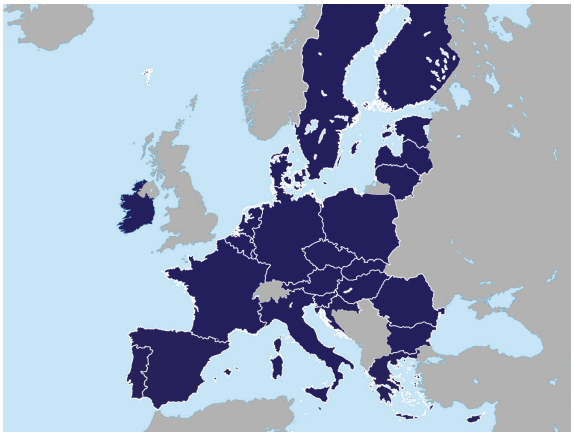
EU GMP, annexes
PIC/s documents
Ph Eur monography: Pharmacy preparation
Resolution on good preparation practices

NB: a rather boring subject but don't worry we will only discuss highlights ☺

GMP

Since 1989 EU GMP
Why: numerous incidents → to protect the public
Directive from the European commission
Law in 27 EU member states
Product: safety
Not for personnel safety

Recently new Annex 1 and most relevant Contamination Control strategy (CCS)



GMP: when applicable?

Industry?
Yes: The principles of GMP and the detailed guidelines are applicable to all operations which require the authorisations referred to in Article 40 of Directive 2001/83/EC, in Article 44 of Directive 2001/82/EC and Article 13 of Directive 2001/20/EC, as amended.

(hospital) pharmacies?
Yes: They (the principles) are also relevant for pharmaceutical manufacturing processes, such as that undertaken in hospitals.
But……

PIC/s documents

PIC/s: Pharmaceutical Inspection Co-operatic ıe

PIC/S aims at harmonising inspection procedures worldwide by developing common standards in the field of GMP

PE009: GMP for industry with a marketing authorisation

PE010: GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS (GPP)

PE 010

National legislation and regulatory policies laid down by the relevant competent authority should always be referred to when determining **the extent** to which the provisions laid down in this document are **binding.**

E.g. Premises for aseptic preparations states class A in a class B background and *any **justification** for background environments of a **lesser grade** should be based on a documented risk assessment which should be performed with great care.*
Possible factors which could be considered in such a risk assessment include:

- *Time between preparation and use*
- *Use of a closed system*
- *Nature and composition of product*

Pharmacy preparations regulation: Resolution CM/ResAP(2011) and CM/Res(2016)2

- Pharmacy preparations are indispensable for accommodating the special needs of individual patients in Europe.
  - ➢ Pharmacists can legally prepare medicinal products in the pharmacy by virtue of their professional education, professional licence and licensing of the pharmacy's premises.
- No marketing authorization is required for pharmacy preparations (magistral and officinal formula).
- Balance between European legislation and national legislation of the member state.
- The preparation of medicinal products in pharmacies is not harmonized throughout Europe and falls under the competency of **national health authorities**.

See: https://search.coe.int/cm/pages/result_details.aspx?objectid=090000168065c135

European rules for pharmacy preparations; main topics

Production quality

- **GMP Guide** is a reference for an appropriate quality system for 'high- risk preparations'.
- **PIC/S GPP** Guide is a reference for 'low- risk preparations'.

High and low risk preparations:

Resolution CM/Res(2016)1 and 2 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients

Contains a model for a risk assessment which taks into account:

- ➢ Type of preparation
- ➢ Amount
- ➢ Pharmacological effect
- ➢ Preparation process
- ➢ Supply

GMP: when applicable in (hospital) pharmacies

The principles are applicable!

Fully applicable or room for interpretation?

Three situations:

- Investigational medicinal products (IMP's)
- ATMP's
- Interpretation in Dutch hospital pharmacy

IMP's Until January 31, 2022:

Preparation (and import) of IMP's according EU directive 2011/20/EU:

- Manufacturing license is required
- GMP is applicable

Preparation includes not only the process starting with raw materials but also (re)packging and (re) labeling of batches of medicines to be used in a clinical trial.
Exemptions: reconstitution and dispensing

Consequence: only a few pharmacies were able to acquire a licence and a GMP certificate (premises, quality system, training, organisation, QP ….)

IMP's, since January 2022

EU directive 2011/20/EU was replaced by regulation EU 536/2014: the European Clinical Trial Regulation (ECTR) (still valid until 2025 for trial submitted before January 31, 2022)

Goal: simplify and facilitate research

Consequences:
A manufacturing license is still necessary for preparation and import of IMP;s **BUT NOT for**

a) Relabeling and repackaging of IMP's within healthcare organisations (e.g. hospitals) under responsibility of a pharmacist to be used by healthcare organisations participating in the trial within a member state
b) Preparation of radiopharmaceuticals used as diagnostics in a trial under the same conditions as in a)
c) Magistral or officinal preparation of IMP's under the same conditions as in a)

ECTR and GMP

GMP is **not** required in case of the situations described in the previous slide when a manufacturing license is not necessary.

But: *appropriate and proportionate requirements and the processes are subject to regular inspections.*

So it depends on the national authorities which standards are applicable.
For The Netherlands it was agreed to accept the **GMP-hospital pharmacy** (GMP-H; to be discussed later)

GMP and ATMP's

Licensed products

- Centrally regulated; reconstitution

Clinical trials

- As a manufacturer
  - For ATMPs, mainly academic-based manufacturing
- As a site in a clinical trial

Unlicensed medicines

- Non-routine manufacture (hospital exemption)

New GMP for ATMP since May 2018

EudraLex
The Rules Governing Medicinal Products in the European Union
Volume 4
Good Manufacturing Practice

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

GMP for ATMP's : not much room for interpretation

17 chapters

1. Introduction
2. Risk-based approach
3. Personnel
4. Premises
5. Equipment
6. Documentation
7. Starting and raw materials
8. Seed lot and cell bank system
9. Production
10. Qualification and validation
11. Qualified person and batch release
12. Quality Control
13. Outsourced activities
14. Quality defects and product recalls
15. Environmental control measures for ATMPs containing or consisting of GMOs
16. **Reconstitution of product after batch release**
17. Automated production of ATMPs

Room for interpretation? Not much…

Reconstitution

16.14. The manufacturer, or –as appropriate- the sponsor or marketing authorisation holdershould describe the reconstitution process, including equipment to be used and requirements at the site of administration

GMP like but not specific

Professional statements

The use of goggles: obligatory according to GMP rules but provides more risks in ATMP handling because of process controls with a microscope: therefor, we state not to use goggles wich was accepted

Interpretation of GMP

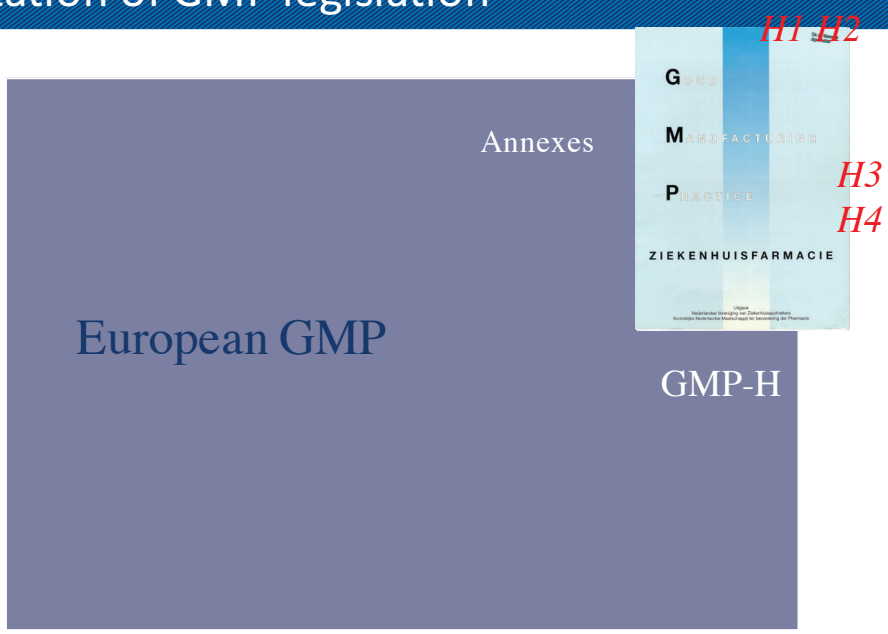
About 30 ago: EU GMP

BUT: processes are different; large scale versus individual
E.G : Aseptic **manufacturing** versus Aseptic **handling**!

1996 GMP-H (Co-production with the Dutch regulatory authorities)

Aseptic handling is the procedure to enable sterile products to be made ready to administer using closed systems'
(EU Resolution CM/Res(2016)2)

Interpretation of GMP legislation



Purpose: to allow GMP to be realized on any type and level of manufacturing of medicines within hospital pharmacy

GMP hospital pharmacy

GMP-H provides necessary supplemental information on specific topics that have not been described within GMP, such as

- Product design
- Different processes
- Small batches of products
- Drug manufacturing for individual patients
- Large variety and diversity of products
- Products with a short shelf life
- Aseptic preparation (GMP-H3) Class A workbench in class D background

USP <1116>

USP, "USP <1116> Microbiological Control and Monitoring of Aseptic Processing Environments," USP 35 vol. 1 2012a, 2012: pp. 697-707.

"It is not possible to maintain a manufacturing environment that is sterile. ***In any environment where human operators are present microbial contamination is inevitable***.

Best clean room environment design and operating practices cannot prevent the shedding of microorganisms into the environment by human operators

Thus, an expectation of zero contamination at all locations during every aseptic processing operation is technically wrong and unrealistic."

Conditions in GMP-H chapter aseptic handling

Differentiation on the basis of **four aspects**:

1. Complexity of the handling of the product
2. Magnitude of product protection
3. Personnel and working method
4. Validation and monitoring

Process

Differentiation on the basis of microbiological contamination:

Simple aseptic preparations (e.g. withdraw from ampoule)

Complex aseptic preparations (e.g. parenteral nutrition)

Product protection

Three levels of product protection

limited product protection (ward)

increased product protection (satellite)

maximum product protection (pharmacy)

Conditions for GMP-H

Levels of product protection	Clothing and hand hygiene	Working area	Background space	Air treatment of the background space
Limited product protection	Clean clothing every day new single use gloves for each session Hand hygiene	Work surface cleaned and disinfected for each session	Quiet	No requirements
Increased product protection	Clean trouser suit every day, new sterile gloves, hair covering, mouth/nose mask for each session; hand hygiene	Horizontal LAF cabinet, biohazard workbench or isolator with overpressure	Separate; limited accessibility; clean	No requirements
Maximum product protection	Clean trouser suit every day, new sterile gloves, hair covering, mouth/nose mask for each session; special shoes; hand hygiene	Horizontal LAF cabinet	Separate; limited accessibility; clean, airlock, smooth finish	Grade D
		Biohazard workbench		Grade D
		Isolator with overpressure		No requirements

Shelflife

Complexity	Product protection	Personnel	Validation and monitoring	Maximum shelf life of the prepared product before administration		Shelf life from start of administration to end administration	
				Time	Condition	Time	Condition
Simple	Limited product protection	Training, method and supervision appropriate to the degree of product protection, see Tables 2 and 3	Appropriate to the degree of product protection, see Table 3	8 hours	Room temperature	24 hours	Room temperature
	Increased product protection			7 days	2-8 °C	24 hours	Room temperature
	Maximum product protection			1 month	2-8 °C	7 days	Room temperature
Complex	Maximum product protection			7 days	2-8 °C	7 days	Room temperature

Take home messages

GMP principles are always applicable

Interpretation is possible especially for IMP's, reconstitution of ATMP's and specific pharmacy preparations like aseptic handling

Interpretation is based on **risk analysis, research and monitoring** (to be continued in todays third presentation)


ANY
QUESTIONS
?

Aseptična priprava zdravil v bolnišnični lekarni v luči zakonodajnih zahtev

Medicines preparation in a hospital pharmacy and legislative requirements

mag. Andrej Ferlan, mag. farm., spec.

Izdelava aseptičnih zdravil v bolnišnični lekarni v luči zakonodajnih zahtev

Slovensko farmacevtsko društvo
Sekcija bolnišničnih farmacevtov Slovenije,
Ljubljana, 7.11.2023

Andrej Ferlan
Solutiones d.o.o.

Vsebina

- Zakonodajne osnove za izdelavo/pripravo aseptičnih zdravil
- GMP skladnost
- Ključne točke skladnosti z določili GMP/Dodatkom 1, Dodatkom 15
- Odprta vprašanja

Zakonodajne osnove

Nacionalna zakonodaja, ki temelji na:

- Council of Europe, EDQM
- Pharmacy preparations: Resolution CM/Res on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients
  - PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments

Ocena tveganja

- Ocena tveganja lekarniško izdelanih/pripravljenih zdravil
- Glede populacije pacientov (omejena uporaba zdravil)
  - Majhna
- Glede zadevnega pacienta/pacientov
  - Velika

Resolucija

Svet Evrope (potrebno je vzeti v obzir):

- Pacienti imajo posebne potrebe glede na starost, zdravstveno stanje, individualne posebnosti in okoljske faktorje
- Industrijsko pripravljena zdravila ne morejo vedno v celoti pokriti teh potreb
- Lekarniško izdelana zdravila predstavljajo pomemben faktor pri farmacevtski skrbi v EU
- Pacienti z vso pravico pričakujejo, da bodo zdravila kakovostna, varna in učinkovita ne glede na mesto izdelave/priprave

Resolucija

Moderna zasnova Resolucije, temelji na oceni tveganja

- Parametri (in primeri):
  - Vrsta pripravka (parenteralni pripravki = 5)
  - Količina letno pripravljenih enot (Zelo malo = 1, velike količine = 5)
  - Farmakološki učinek aktivne učinkovine (Zelo močne učinkovine = 5 – citostatiki, močne učinkovine = 3, šibke učinkovine = 1)
  - Proces priprave (aseptično polnjenje = 5)
  - Distribucija (samo notranji odjemalci = 1)

Resolucija

- Določena metodologija ocene tveganja in specifikacije

  - Izdelki nizkega tveganja (PIC/S vodilo)
  - Izdelki visokega tveganja (GMP)

- Osnovni pogoji in pogoji okolja ENAKI
  - Kvalifikacija/klasifikacija čistih prostorov
- Velike razlike glede obremenitve procesa

Parametri (primeri)

- Sistem kakovosti
  - Obvladovanje tveganj, QRM, odstopi/deviacije na primer odstopi pri re-validaciji aseptičnega polnjenja (Media Fill)
  - Kontrolna strategija kontaminacije CCS
- Osebje
  - Kvalifikacija osebja (validacija aseptičnega postopka)
- Dokumentacijski sistem
  - Obseg
  - Ukrepi za zagotovitev celovitosti podatkov, Data Integrity
    - Validacija računalniško podprtih sistemov

Parametri (primeri)

- Sistem stalnega nadzora pogojev okolja!!!
  - Obseg
  - Oprema nadzora in kalibracija opreme
  - Celoten čas procesa
  - Trendiranje podatkov in prepoznava trendov
- Re-kvalifikacije (prostori, oprema)
  - Pogostnost, strogost
- Stopnja validacije procesa!!!
  - Glede na izdelek (procesna validacija, klasična)
  - Glede na vključene postopke (na primer tehtanje, raztapljanje, prenos tekočin…)
  - Validacija aseptičnega procesa
  - Validacija VSEH procesov sterilizacije

GMP, Dodatek 1

- Manufacture of Sterile **Medicinal Products**
  Proizvodnja sterilnih **zdravil**
- Sprejet na Komisiji 22.08.2022, stopi v veljavo: 25.08.2023
- Zmanjšanje kontaminacije glede **delcev**, **mikroorganizmov** in **pirogenov/endotoksinov**

Farmacevtski sistem kakovosti

- Izjemen poudarek sistemu kakovosti
- Pristop obvladovanja tveganj QRM
- Vse odločitve morajo biti utemeljene
- Večja fleksibilnost

GMP, Dodatek 1

Nadzor okolja in procesov

- Razlika med kvalifikacijo in rednim monitoringom(!)
- „Tekoč rutinski nadzor“ (On-going Routine Monitoring) v odvisnosti od dizajna sistema
- Postavitev meja ukrepanja (večnivojsko)
- Pregled in trendiranje rezultatov
- Zahteve za validacijo aseptičnega procesa Aseptic Process Simulation APS

GMP stopnje čistote

4 stopnje čistote:

- Razred A: Območje proizvodnje z velikim tveganjem
  - območje polnjenja
  - območje odprtih ampul in vial, namestitev zapork
  - območje vzpostavitve aseptične povezave
  - Izolatorji, RABS
  - Enakomerna hitrost zračnega toka - od 0,36 do 0,54 m/s (lahko manj za izolatorje)
  - Direktne človeške intervencije zmanjšati na minimum
- Razred B: Za aseptično pripravo in polnjenje je razred B neposredna okolica območja razreda A
  - Ne velja za izolator
- Razreda C in D: Čisti prostori za manj kritične stopnje izdelave sterilnih izdelkov

Kontrolna strategija nadzora kontaminacije

Contamination Control Strategy CCS

- Znotraj sistema kakovosti, nova zahteva
- Cela vrsta povezanih ukrepov in mer za zmanjšanje tveganj glede delcev (vidnih in nevidnih), endotoksinov/pirogenov in mikroorganizmov
  - Učinkovitost vedno obravnavamo kot **celoto**
- Definiranje kritičnih kontrolnih točk, nadzornih sistemov in nadzor učinkovitosti postopkov
- Kombinacija vseh mer mora zagotoviti robustno zaščito pred kontaminacijo

Kontrolna strategija nadzora kontaminacije

- Dokument je potrebno redno pregledati in po potrebi posodabljati
  - Mora spodbujati stalne posodobitve proizvodnih tehnologij in kontrolnih sistemov
- Učinkovitost CCS mora biti del vodstvenega pregleda
- Vpliv sprememb na CCS
- Pri razvoju CCS je potrebno upoštevati:
  - Načrtovanje obrata, procesov in dokumentacije
  - Prostore, opremo, oskrbne sisteme
  - Vhodne kontrole materialov, in-procesne kontrole
  - Vsebnike in zaporne sisteme

Kontrolna strategija nadzora kontaminacije

- Potrjevanje dobaviteljev in ponudnikov storitev
  - Ključni materiali, opreme za enkratno uporabo SUS, sterilizacija komponent…
- Upravljanje zunanjih izvajalcev (sterilizacija!)
- Obvladovanje procesnega tveganja, procesna validacija
- Validacija procesa sterilizacije
- Preventivno vzdrževanje (tveganje za kontaminacijo)
- Nadzorni sistemi, vključno s hitrimi alternativnimi metodami (znanstveno utemeljeno)
- Čiščenje in dezinfekcija
- Preventivni mehanizmi: trendiranje, iskanje izvorne napake, CAPA, orodja preiskav
- Stalno izboljševanje

Odprta vprašanja

- Ali je določila in interpretacijo GMP in Dodatka 1 mogoče zagotoviti v bolnišnični lekarni?
  - Število izdelkov!
  - Posamična ali maloserijska izdelava/priprava (sicer opisano v Dodatku 1)
  - Relativno nizko znanje glede izdelka in procesa (pogostnost, velikost „serije“)
  - Celotna obremenitev z zahtevami in v luči razpoložljivih virov
    - Dodana vrednost (finančna)
    - Javne finance
  - ….

Odprta vprašanja

- Regijski centri z visoko stopnjo GMP?
  - Distribucija v skladu z GDP
  - Razdelitev pogače?
- Uhajanje strokovnosti iz lekarn (splošno) z specializacijo določenih bolnišničnih lekarn
- Samooskrbnost
  - Izredni dogodki

Odprta vprašanja

- Lastnik bolnišnic je država!
- Določitev strategije glede izdelave sterilnih/aseptično izdelanih/pripravljenih zdravil
  - Stroka, LZ, SFD
  - Na nivoju države
- Zahteva za vzpostavitev OSNOVNIH zahtev glede aseptične izdelave (minimum)
  - PIC/S vodilo in zahteve za redne nadzorne sisteme
- Usklajen pogled glede strategije in regulatorne skladnosti
  - Zaščita pacienta
- Odgovornost farmacevta

Aseptična izdelava v farmacevtski industriji

Aseptic preparation in the pharmaceutical industry

Boštjan Kmet, mag. farm.

Aseptični procesi v farmacevtski industriji

Boštjan Kmet

November 2023

KRKA
Living a healthy life.

Vsebina

Proizvodnja sterilnih izdelkov:

- Dejavniki, ki vplivajo na sterilnost izdelka
- Vrednotenje aseptičnih posegov
- Metode sterilizacije in dezinfekcije
- Validacije

Izzivi v proizvodnji

2.5 The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxin) as well as particulate (e.g. glass and other visible and sub-visible particles).

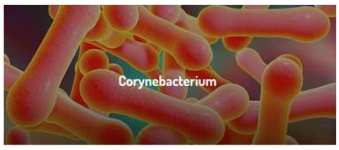
Osebje- človeški mikrobiom

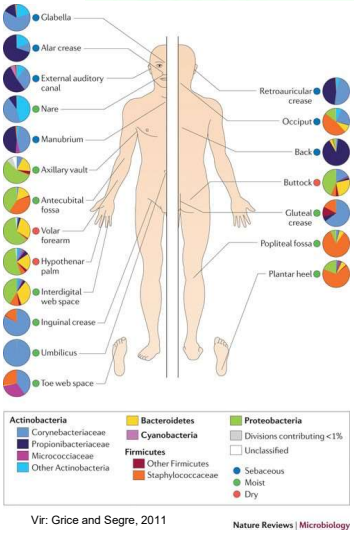
- ~ 30-40 bilijonov mikrobnih celic v človeškem telesu (bakterije, virusi, glive)
- koža, usta, prebavni trakt,…
- ~ bilijon mikrobnih celic na človeški koži
- 1-3 % teže človeka.

Bakterije na koži

- Koža: 1000 vrst bakterij
- 5 milijonov bakterij/cm^2 kože
- Predeli z večjim izločanjem sebuma na obrazu

(80 milijonov bakterij/cm^2)





Vir: Grice and Segre, 2011

Nature Reviews | Microbiology

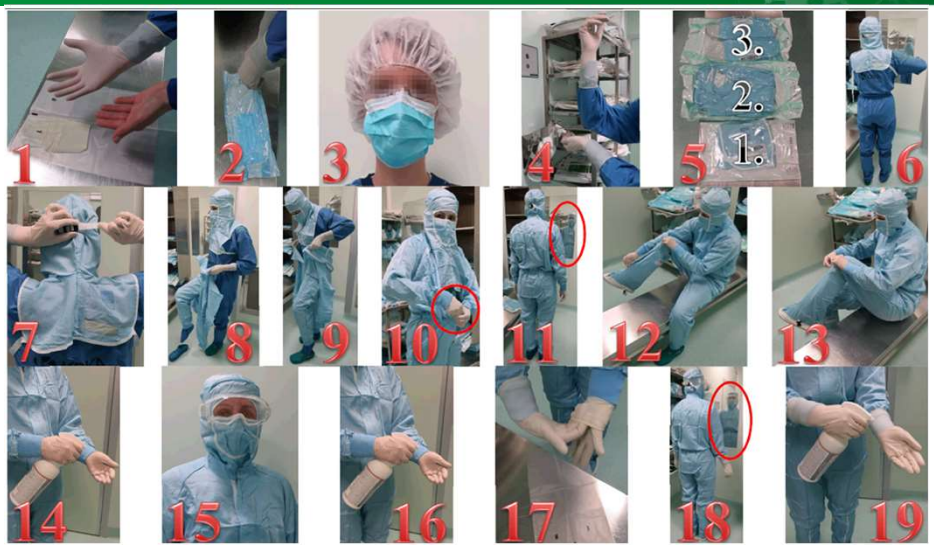
Vstop v čiste prostore

1. garderoba

2. garderoba

Vstop v čiste prostore

3. garderoba



Vzorčenje osebja

Razredi čistosti v čistih prostorih

- Razred čistosti A: kritično območje za operacije z visokim tveganjem (npr. aseptično polnjenje, odprta primarna embalaža ali za aseptične povezave). Običajno takšne pogoje zagotavlja sistem laminarnega pretoka zraka znotraj RABS ali izolatorjev. Poseganje s strani operaterjev je omejeno.
- Razred čistosti B: okolje razreda čistosti A
- Razred čistosti C in D: prostori, ki se uporabljajo za izvajanje manj kritičnih stopenj v proizvodnji sterilnih izdelkov.

Okolje/prostori

- Spremljanje 0,5 µm/m^3 in 5 µm/m^3
- Hitrost zraka: 0,36-0,54 m/s na delovni površini
- Mikrobiološki monitoring
- Neprekinjeno delovanje klimatskega sistema
- Sistem nadtlakov

Table 1: Maximum permitted total particle concentration for classification

Grade	Maximum limits for total particle ≥ 0.5 µm/m^3		Maximum limits for total particle ≥ 5 µm/m^3	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not specified [a]	Not specified [a]
B	3 520	352 000	Not specified [a]	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [b]	29 300	Not predetermined [b]

Table 2: Maximum permitted microbial contamination level during qualification

Grade	Air sample CFU/m^3	Settle plates (diameter 90 mm) CFU/4 hours [a]	Contact plates (diameter 55 mm) CFU/plate
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

Okolje/prostori

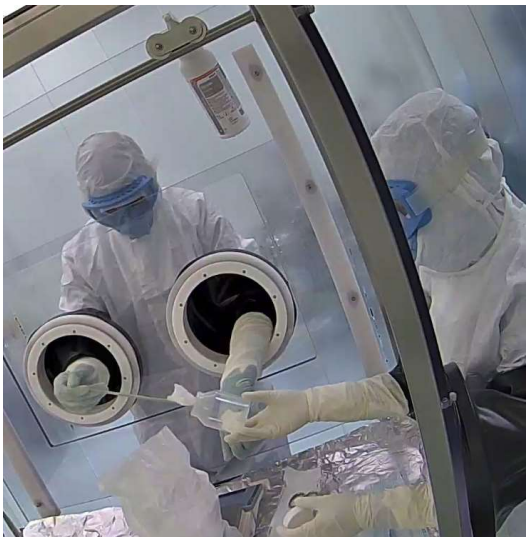
- Laminarni tok zraka

Polnilna linija

Priprava suspenzij

- Suspenzije- ni sterilne filtracije končne suspenzije

- Sterilen API
- Vzorčenje API
- Aseptična priprava



Vrednotenje aseptičnih posegov

Aseptični posegi so predpisani, trenirani in dokumentirani.

Ocena tveganja; izračun stopnje tveganja

- Čas trajanja korektivnega posega,
- Način poseganja (z orokavičeno roko, RABS rokavico, s pinceto ali orodjem)
- Oddaljenost kritične točke (lokacija izdelka med delovanjem stroja)

Poseg: zamenjava polnilne igle

Vrednotenje tveganj pri izvajanju aseptičnih posegov – polnilna linija [redacted]

UKREPI ZA ZMANJŠANJE TVEGANJA	KRITIČNOST
• Poseg izvajamo ob upoštevanju aseptične tehnike. • Operater A nadene 3. par sterilnih rokavic. • Upoštevamo vlogo operaterja A in B. • Uporaba sterilnega orodja, za enkratno uporabo. • Vzorčenje orodja po posegu. • Dezinfekcija orodja po posegu. • Menjava MKB plošč. • Delitev na novo spremnico. • Dezinfekcija površin stroja nad katerim smo posegali. • Vzorčenje rok operaterja A po posegu nato odstrani 3. par rokavic. • IPK kontrola višine zataljevanja. • IPK kontrola polnilnega volumna • Delitev na novo spremnico. • Zavržemo prve napolnjene injekcije iz vsakega polnilnega mesta. Naslednje prve napolnjene ampule iz vsakega polnilnega mesta po ena so vključene v reden vzorec za test sterilnosti nove spremnice in jih ustrezno označimo. • Simulacija pri validaciji aseptičnega polnjenja. • Poseg zabeležimo v ZOP.	Poseg izvajamo z roko faktor = [redacted] Trajanje posega več kot 120s, faktor = [redacted] Poseg z roko nad kritičnim mestom faktor = [redacted] Izračun kritičnosti = [redacted] Ocena kritičnosti- tvegan (kritičen) poseg

Poseg: zamenjava polnilne igle

Vrednotenje tveganj pri izvajanju aseptičnih posegov – polnilna linija [redacted]

POSEG	OPIS POSEGA	POSTOPEK IZVEDBE
AK 08 Menjava in nastavitev polnilne ali zaplinjevalne igle	• Stroj ustavimo in odstranimo ampule iz polnilnega dela stroja in zaključimo polnjenje spremnice. • Poseg izvajamo ob odprtih vratih polnilne št. 4 ali 5 ali obojih. • Operater B dezinficira roke sebi in operaterju A s sterilnim dezinfekcijskim pršilom ter odpre ovoj s sterilnim rokavicam. **Operater A nadene 3. par sterilnih rokavic**. Operater B s sterilnim dezinfekcijskim pršilom dezinficira roke operaterju A. • Operater na panelu odklene vrata polnilne kabine in odpre vrata št.4 ali 5 ali obojih. • **Operater A pred posegom v polnilni kabini odstrani MKB plošče in izpostavi nove. Dezinfekcija rok.** • Operater A odstrani silikonsko cev iz igle in jo drži proti polnilni kabini v čim bolj navpični legi. Z drugo roko odstrani iglo ter jo poda operaterju B. Če vijaka ne more odviti z roko, uporabi univerzalni ključ iz nosilca v polnilni kabini. • Operater B odpre sterilizacijski rokav/alu ovoj z novo sterilno polnilno/zaplinjevalno iglo. • Operater A odvzame sterilno iglo zavito v tyvec zaščitno vrečko/alu foljo, na iglo namesti silikonsko cev, odstrani tywec zaščito/alu foljo ter iglo namesti na držalo za igle ter pričvrsti. Če uporabimo ključ, ga vzorčimo, dezinficiramo s sterilno brezprašno krpico, omočeno s sterilnim dez. sredstvom in vrnemo na nosilec v polnilni kabini. • Operater B z ročico pripelje ampule na transportno pot pod igle. • Nato operater B dezinficira roke operaterju A in sebi ter odpre sterilizacijski rokav s sterilnim orodjem za nastavitev igel. • Operater A po aseptičnem postopku vzame orodje iz sterilizacijskega rokava in nastavi pozicijo in višino igle. • **Vzorčimo roke operaterja A**, operater B s sterilnim dezinfekcijskim pršilom dezinficira roke operaterju A. • Operater B odpre sterilizacijski rokav s sterilno brezprašno krpo. Operater A vzame krpo iz rokava, operater B jo omoči s sterilnim dezinfekcijskim pršilom. • Operater A dezinficira površine stroja nad katerimi je posegal in spodnji fiksni del polnilnega stroja. • **Operater A po posegu v polnilni kabini odstrani MKB plošče in izpostavi nove**. • Po končanem posegu operater B zapre vrata polnilnega stroja, operater A odstrani 3. par rokavic in s dezinficira roke. • **Prvih pet napolnjenih injekcij iz vsake igle zavržemo (40 ali 50 injekcij). Začnemo s polnjenjem nove spremnice**. • **Naslednje prve napolnjene ampule iz vsakega polnilnega mesta po ena so vključene v vzorec za test sterilnosti nove spremnice zato jih ustrezno označimo.** • V kolikor smo menjali ali spreminjali pozicijo zaplinjevalne igle, pred nadaljevanjem polnjenja izvedemo **IPK kontrolo zaplinjevanja**. Če smo menjali polnilno iglo, pa **IPK polnilnega volumna**. • Poseg zabeležimo v ZOP. *Med poseganjem laminarni tok piha iz smeri polnilne kabine proti operaterju. Ni zračnega toka s strani operaterja proti polnilni kabini. Rezervne igle pred sterilizacijo zavijemo v tyvec zaščitne vrečke/alu folijo in nato zaščitimo v dvojne steril. rokave/alu folijo. Kontaktni del igle, na kateri namestimo silikonsko cev ni pokrit, da lahko namestimo silikonsko cev nanj, brez da bi se dotikali igle. Iglo v fazi nameščanja silikonske cevi drži zavito v tyvec vrečko/alu foljo kar omogoča, da se operater ne dotika neposredno stičnega dela igle. Med izvajanjem posega operater A drži silikonsko cev proti polnilni kabini, tako da ni smeri zračnega toka iz operaterja proti odprtim stičnim delom med nameščanjem nove igle. Laminarni tok zraka prehaja mesto posega tj. polnilno cev in iglo, nato se izpiha na sprednjo stran stroja iz polnilne kabine. Tok zraka poteka proti zunanjosti, ni gibanja zraka od operaterja proti sterilnim stičnim delom.*	1. Zaključimo polnjenje spremnice, transportne poti odstranimo vse injekcije. 2. Dezinfekcija rok operaterja A in operaterja B, operater A nadene 3. par sterilnih rokavic. 3. Operater B odpre vrata polnilne kabine. 4. Operater A zamenja MKB plošče, dezinfekcija rok . 5. Operater A izvede poseg. 6. Če uporabimo orodje, ga vzorčimo in dezinficiramo. 7. Vzorčenje rok operaterja A. 8. Operater A izvede dezinfekcijo pod mestom poseganja. 9. Operater A zamenja MKB plošče. 10. Operater B zapre vrata polnilne kabine, operater A odstrani 3. par rokavic, dezinfekcija rok. 11. Prve napolnjene injekcije zavržemo. 12. Začnemo s polnjenjem nove spremnice, prve ustrezne napolnjene injekcije označimo in vključimo v test sterilnosti nove spremnice. 13. Izvedemo IPK kontrola zaplinjevanja ali polnilnega volumna. 14. Poseg zabeležimo v ZOP.

www.krka.biz

Poseg: zamenjava polnilne igle

Hitrost x 2,0

Čiščenje in dezinfekcija

Dnevno in tedensko čiščenje

- Priprava raztopine dezinfekcijskega sredstva (sterilna filtracija)
- Omakanje krp
- Dvovedrni sistem
- Vnos pripomočkov za čiščenje
- Stene- od zgoraj navzdol
- Tla- od bolj čistih proti manj čistim prostorom

Menjava dezinfekcijskega sredstva

- Odstranjevanje predhodnega
- Uporaba sporocidnega dezinfekcijskega sredstva
- VHP* biodekontaminacija čistih prostorov

(*Vaporized Hydrogen Peroxide)

Vnos v razred čistosti B/A

Metode dezinfekcije/ dekontaminacije

- Primopredajna komora
  - VHP
  - Brisanje s sporocidnimi dezinfekcijskimi sredstvi + prepihovanje

Metode sterilizacije

- Avtoklaviranje
- Sterilizacijski in depirogenizacijski tunel
- Suhi sterilizator
- Sterilna filtracijska linija

Validacije

EU-GMP, Annex 1, Manufacture of Sterile Products

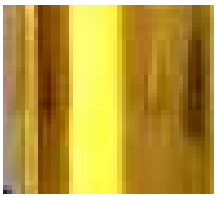
8.36 All sterilisation processes should be validated. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilised and its sterilisation. Before any sterilisation process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired sterilising conditions in all parts of each type of load to be processed should be validated notably by physical measurements and where appropriate by Biological Indicators (BI). For effective sterilisation, the whole of the product, and surfaces of equipment and components should be subject to the required treatment and the process should be designed to ensure that this is achieved.

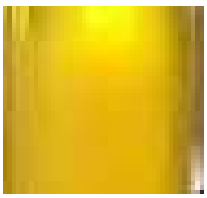
Validacija aseptičnega polnjenja

APS (aseptic process simulation); »worst case« pogoji

- proizvodnja aseptičnih izdelkov; vključevanje vseh kritičnih situacij, ki bi lahko vplivale na sterilnost;
- vsa rokovanja in posegi, do katerih lahko pride med proizvodnjo;
- »worst case« parametri (npr. maksimalni čas stanja raztopine v filtracijski posodi, minimalni in maksimalni volumen ampul, hitrost polnjenja).
- vse skupine osebja (vse izmene) za aseptično polnjenje.
- maksimalni časi stanja sterilizirane opreme
- maksimalno število prisotnega osebja v čistih prostorih, kjer se odvijajo rutinski aseptični postopki.
- Vsaka oseba vključena v validacijo aseptičnega polnjenja vsaj dvakrat letno.
- Vsaka nova oseba, ki izvaja aseptično pripravo, mora biti udeležena vsaj pri treh uspešnih simulacijah aseptične priprave (zaporedne, ki jih izvaja ta oseba), preden lahko prične samostojno izvajati aseptične priprave.

Kriterij: Po inkubaciji v nobeni ustrezno napolnjeni AMPULI ne sme biti rasti. Vsaka okužena z gojiščem napolnjena ampula pomeni neuspešen APS.





Ključni poudarki

Zagotavljanje sterilnosti je velik izziv.

1. Stalno raziskovati in ugotavljati tveganja kontaminacije z mikroorganizmi in razvijati kontrolno strategijo

2. Spremljati napredke v tehnologiji in skladnost z GMP Annex 1 ter drugimi smernicami

3. Osebje: glavni vir mikrobiološke kontaminacije;
   - ozaveščanje in izboljševanje vedenja v čistih prostorih.


KRKA
Living a healthy life.

Current activities in modern hospital environment in The Netherlands

Aktivnosti v sodobnem bolnišničnem okolju na Nizozemskem

Paul Le Brun, PharmD, PhD, Associate professor

Leids Universitair Medisch Centrum

Preparation of medicinal products in Dutch hospital pharmacies

15. mednarodni simpozij Sekcije bolnišničnih farmacevtov pri SFD

Paul Le Brun, PharmD, PhD
Hospital pharmacist-clinical pharmacologist

Ljubljana November 7, 2023

Nothing to disclose

Healthcare in The Netherlands

90 hospitals divided over 120 locations

30.000 bed (=3/1000 inhabitants)

75 hospital pharmacies

Almost all with outpatient pharmacy facilities

NVZA: Dutch Association of Hospital Pharmacist

600 hospital pharmacist

100 hospital pharmacist in training

120 pharmacist not (yet) in training

Many technicians

Hospital Pharmacy education

High School level 3 (6 years)

Pharmacy BSc + MSc (6 years)

Apply for a job as a trainee (25/year)

Specialisation 4 years (PharmD)

About 30% PhD

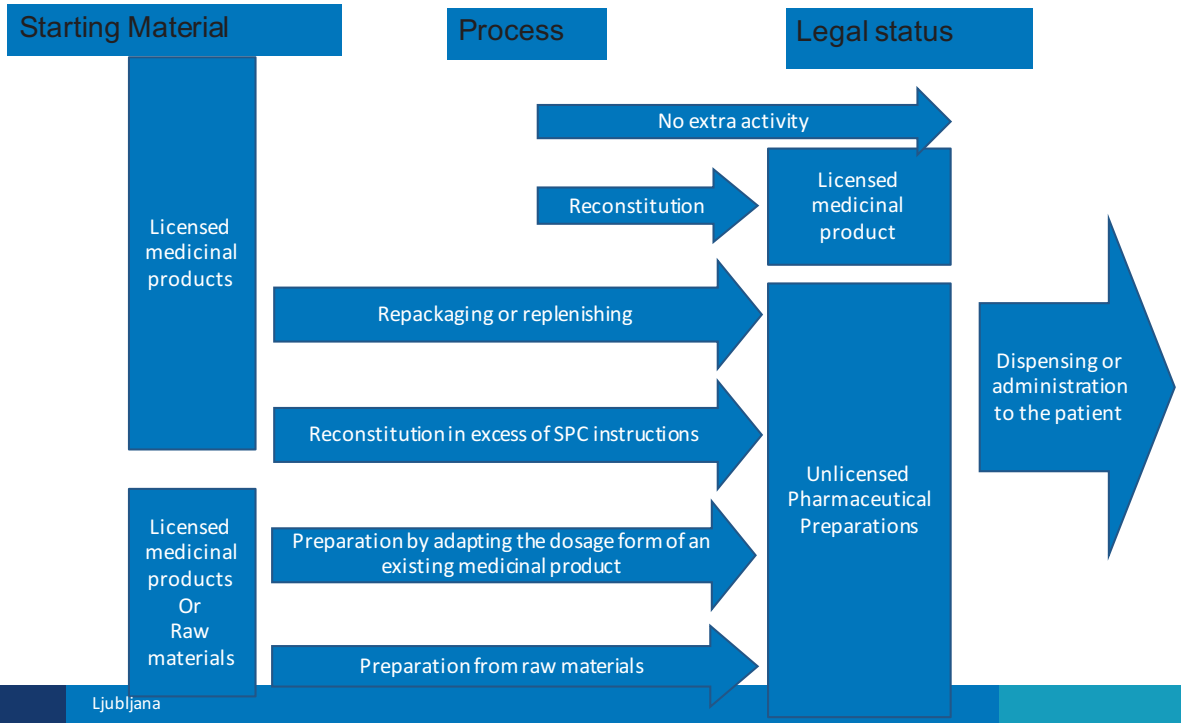
Some further specialisation like MBA/MHA/Clinical pharmacologist/Epidemiology etc

Full member Specialist staff

Involved with everything that has to do with medicines (Many committees)

And involved with preparations!

Preparations and actual legal status

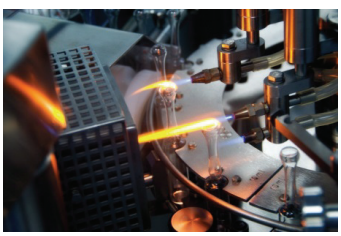


Preparation: 'History' 1980-1995

Small and Large scale preparation in most hospital pharmacies

Main driving forces:

- *Therapy*
- *Availability*
- *Application*
- *Economy*



Afb. 43: Een apotheker, die op een fornuis zijn stropen e.d. kookt.
Achter de gevels van Delft

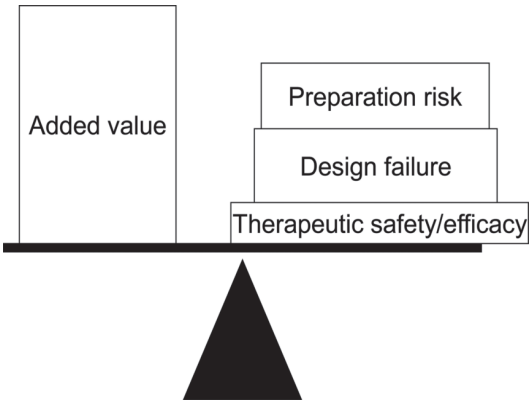
Preparation after 1995

Policy in manufacturing:

- *Therapeutically relevant*
- *Not available in required administration form*

Conditions

- *Not commercially available*
- *Not for economic reasons*



Driving forces:

- *awareness and legislation (EU GMP and PIC/s guidelines)*

Consequences

- *Rationalization and centralization*
- *Delivery between pharmacies, compounding centres, 'commercial pharmacies'*

Legislation

Geneesmiddelenwet (Law on medicines; Medicine act)
No medicines on the market without a market authorisation
One legal exemptions:

- Preparation in a pharmacy prescribed by a phycisian for your own patients

One tolerated exemption:

- **Deliveries between pharmacies are allowed:**
  - GMP
  - Productfile (therapy)
  - No equivalent product in the market
  - Pharmacovigilance
  - Notification

Consequences for Dutch hospital pharmacies

	Local level	National level
Preparation prior to use	All hospital pharmacies	Not yet
Extemp. preparation	Most hospital pharmacies	Commercial pharmacies
Batch preparation	Some (25) hospital pharmacies	Few (10) hospital pharmacies/ commercial pharm.

Some actual examples of pharmacy preparations (Netherlands)

SDD (selective decontamination) capsules (*several hospitals*)
Cannabis oil (*one community pharmacy*)
Hydrochlorothiazide mixture for children (*several pharmacies and also commercial pharmacies*)
Lisinopril mixture for children (*several pharmacies and also commercial pharmacies*)
Sildenafil mixture for children (*several pharmacies and also commercial pharmacies*)
Ethanol in dextrose infusion fluid (*several hospital pharmacies*)
Amifampridine (3,4-diaminopyridine) tablets (*one hospital pharmacy*)
Phenelzine tablets (*one community pharmacy*)

Reasons for preparation: therapeutic need and registered product not available

‘Lost’ dosage forms (after development in pharmacies)

From pharmacy preparation to commercial product:

- Midazolam RTU
- Caffeine injection
- Inhalation solutions of antibiotics
- Atropine injection → RTA
- Ephedrine injection → RTA
- CDCA → orphan medicine

In general an advantage ☺

Sometimes an unacceptable increase in costs ☹

Agreement with authorities about small scale preparation of commercially available medicines (countervailing effect)

Medicine development: why in Europe?

Increasing dependency on Asia:

- 80% of active pharmaceutical ingredients are sourced from India and China

- 40% of finished medicines sold in Europe come from China and India

- China and India produce 60% of the world’s paracetamol, 90% of its penicillin and 50% of its ibuprofen

- COVID: anaesthetics, antibiotics, muscle relaxants and other medicines : stocks run out

Uncertainty in delivery : public health risk

Medicine development in hospitals; examples

Orphan drugs

Orphan drugs:

CDCA

Sildenafil (Pulm hypertension)

Drug repurposing

Drug repurposing

In several therapeutic areas

Proof of principle studies in hospitals

Ready to Administer dosage forms

Future: what are other trends in medicines with impact for preparation

- **Focus on patient safety**
- **Personalised medicine**
- Increasing complexity of medicines
  - ATMP's
  - Nanomedicines , Biologicals, Radiopharmaceuticals
  - Phage therapy
- **New technol**ogies
  - Robotics
  - 3D printing

Costs

Patient safety and preparation: Why do we need RTU/RTA

Medication errors regarding reconstitution and possible failures in the reconstitution process

• Reconstitution of the wrong dose

• Calculation errors leading to administration of the wrong dose and/or at the wrong concentration or rate

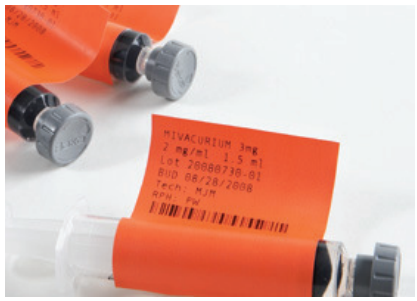
• Incorrect reconstitution (insufficient mixing, incomplete dissolution, use of the wrong diluent)

• Incompatibility between diluent, infusion, other medicinal products or administration devices

Risk of microbiological contamination

AND lack of personnel!

Examples



Adrenalin
Cefamandol
Cefotaxim
Ceftazidim
Dobutamin
Dopamin
Phenylephrine
Furosemide
Glucose 5%
Heparine
Insulin
Potassium chloride
Midazolam
Midazolam / Morphine
Morphine
NaCl 0,9%
Nitroglycerin
Nitroprusside
Noradrenalin
Propofol

Semi automatic filling

Patient safety: Reorganise the preparation prior to use
A risk based approach where, who and how

Central:

- high risk medication/process
  - Patient
  - Technician
- Efficiency: RTU, RTA

Satellite

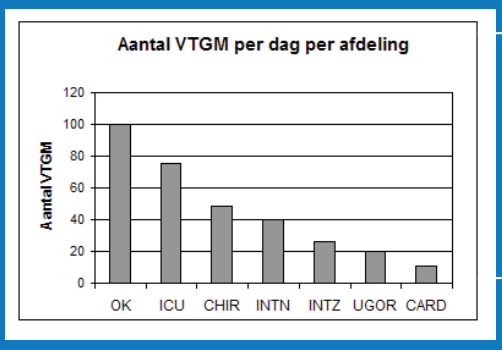
- As much as possible
  - Quality
  - Efficiency

Patient bed

- Immediate use

Good Reconstitution Practices; outcome RA

process



Complex Reconstitution (< 10%) = Pharmacy → RTU or RTA dispensed by pharmacy

Simple reconstitution > 90% → RTA dispensed by pharmacy

Simple reconstitution > 90% → On the ward? Minimal requirements → Education Handbook Training If not: pharmacy

Good reconstitution practices supported by EDQM

Development in legislation:

2016: A resolution on good reconstitution practices (Resolution CM/Res(2016)2 was prepared to improve safety of reconstitution in clinical areas

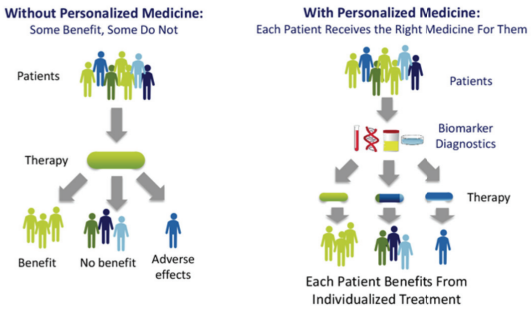
Adopted by the Committee of Ministers on June 1st, 2016 (37 Member States parties to the Ph. Eur. Convention

Recommendation (soft law) to member states to adapt their regulations in accordance with the provisions in the Resolution, taking into account the national frameworks.

See: https://www.edqm.eu/en/d/162941

Personalised medicines and preparation

Precision medicines for patients with shared disease markers

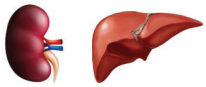


Classical preparation of 'individual medication'

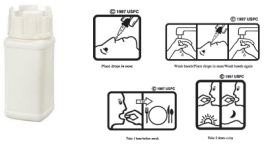
- Adjustment of dosage forms
  - Special groups (children, elderly)
- Individual preparations
  - Dermatological preparations
  - Special compositions because of allergy to components

Why do we need individual pharmacotherapy

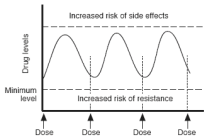
organ function



drug use



drug levels



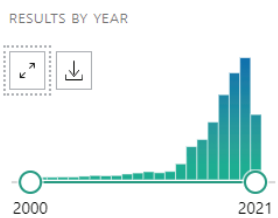
special populations

drug interactions

co-morbidity

Innovative Research; 3D printing of tablets

Pubmed: 3D printing pharmaceutical
(20 juni 2021)



Pharm Res (2018) 35: 176
https://doi.org/10.1007/s11095-018-2454-x
EXPERT REVIEW

3D Printing in Pharmaceutical and Medical Applications – Recent Achievements and Challenges

Witold Jamróz · Joanna Szafraniec · Mateusz Kurek · Renata J.

Review Article

3D Printing technologies for drug delivery: a review

Leena Kumari Prasad & H.
Pages 1019-1031 | Received 31 Aug
13 Dec 2015
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Drug Discovery Today
Volume 23, Issue 8, August 2018, Pages 1547-1555

Review
Post screen

Reshaping drug development printing

Atheer Awad, Sarah J. Trenfield, Alvaro Goyanes, Simon Gaisf

International Journal of Pharmaceutics
Volume 567, 15 August 2019, 118471

Direct powder extrusion 3D printing: Fabrication of dr... single-step proc...

Trends in Pharmacological Sciences

Review

3D Printing Pharmaceuticals: Drug Development to Frontline Care

Sarah J. Trenfield,[1] Atheer Awad,[1] Alvaro Goyanes,[2] Simon Gaisford,[1,2] and Abdul W. Basit[1,2,*]

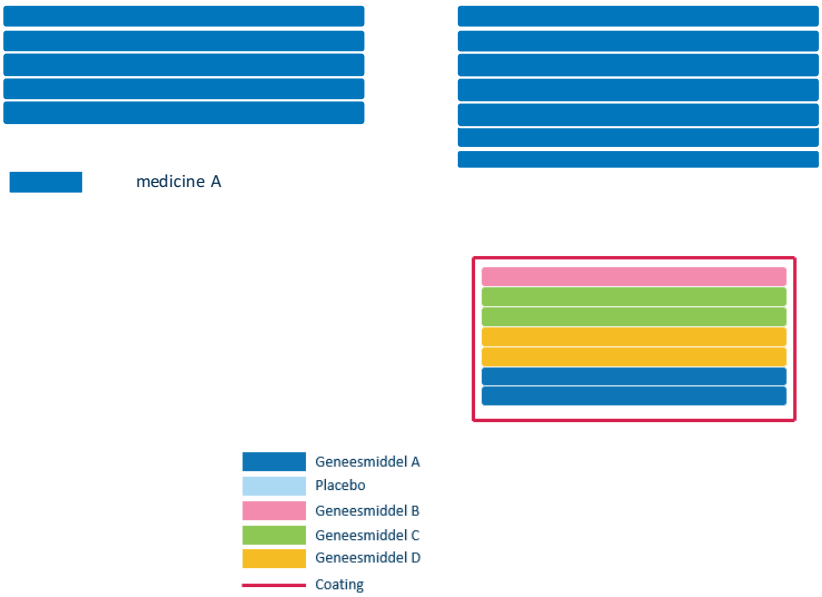
International Journal of Pharmaceutics
Volume 603, 15 June 2021, 120694

3D printed furosemide and sildenafil tablets: Innovative production and quality control

I. Lafeber [a], J.M. Tichem [a], N. Ouwerkerk [b], A.D. van Unen [b], J.J.D. van Uitert [b], H.C.M. Bijleveld-Olierook [a], D.M. Kweekel [a], W.M. Zaal [a], P.P.H. Le Brun [a], H.J. Guchelaar [a], K.J.M. Schimmel [a]

Show more

3D printing = flexibility



Interesting? E.g. Polypharmacy

- Poly-tablet: to date disadvantage:
  - fixed combination, inflexibable

- 3D printed poly-tablet:
  - Adjust individual dosages

Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. J Control Release. 2015 Nov 10;217:308-14

Siyawamwaya M, du Toit LC, Kumar P, Choonara YE, Kondiah P, Pillay V. 3D printed, controlled release, tritherapeutic tablet matrix for advanced anti-HIV-1 drug delivery. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2018

Interesting? E.g. Children

Licensed medicines:
- Too large to swallow
- Wrong dosage

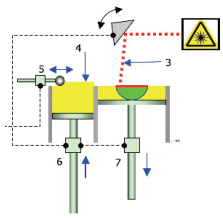
Oral medication:
- taste
- Side effects of excipeints

Children prefer minitablets[1]

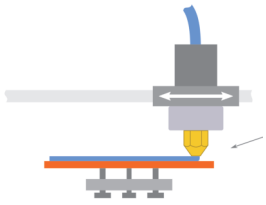
[1] Van Riet-Nales DA, de Neef BJ, Schobben AFAM, Ferreira J, Egberts TCG, Rademaker CMA. Acceptability of different oral formulations in infants and preschool children. Arch Dis Child 2013 Sep;98(9):725-731

Techniques

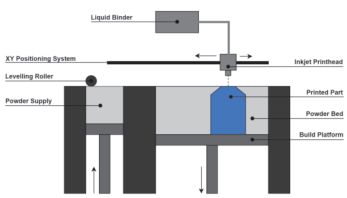
Selective laser sintering



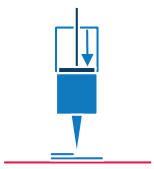
Fused deposition modelling



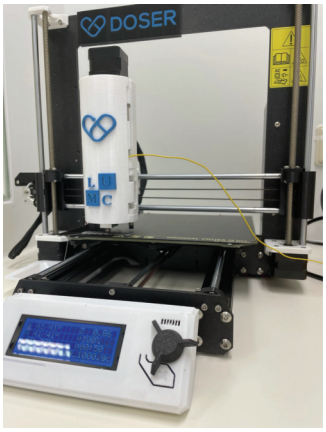
Binder jetting

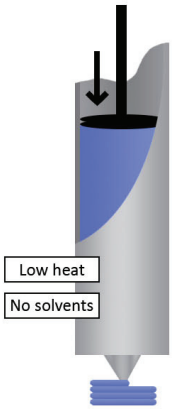


Semi-solid extrusion

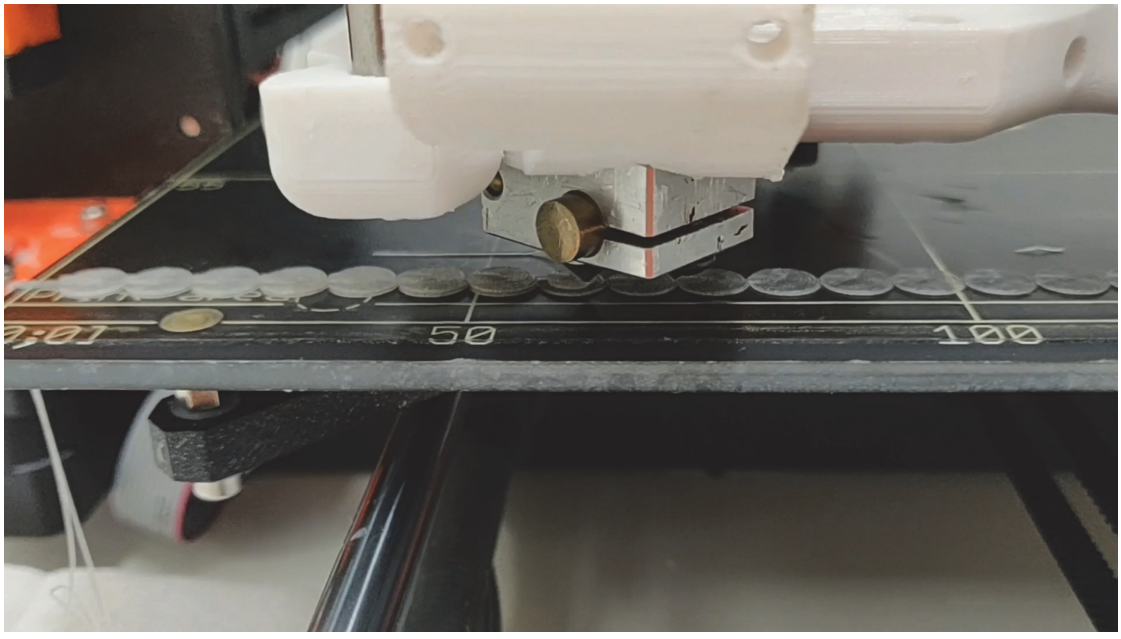


Which technique do we use?

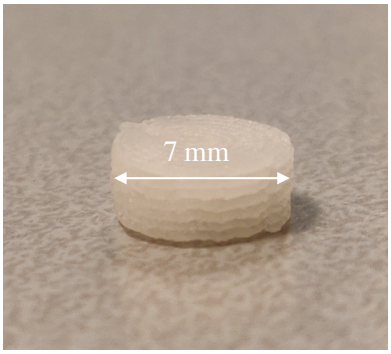




Impression of 3D printer LUMC

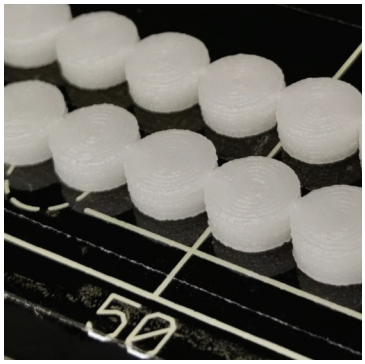


What are we preparing already?

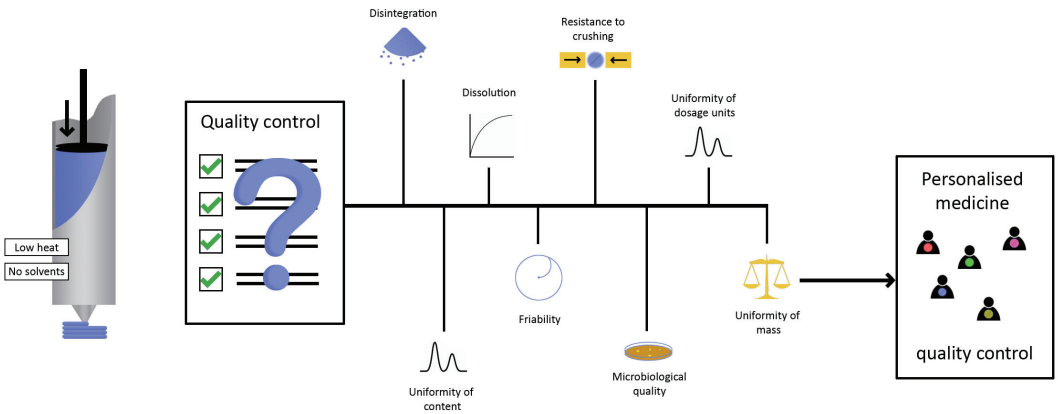


- Furosemide (2 mg; 10 mg)
- Sildenafil (4 mg; 7 mg; 10 mg)

- Aplication for children:
- Excisting formulations:
  - fluids
  - High dose tablets



Are 3D printed tablets comparable to licensed products? Research: Quality Control



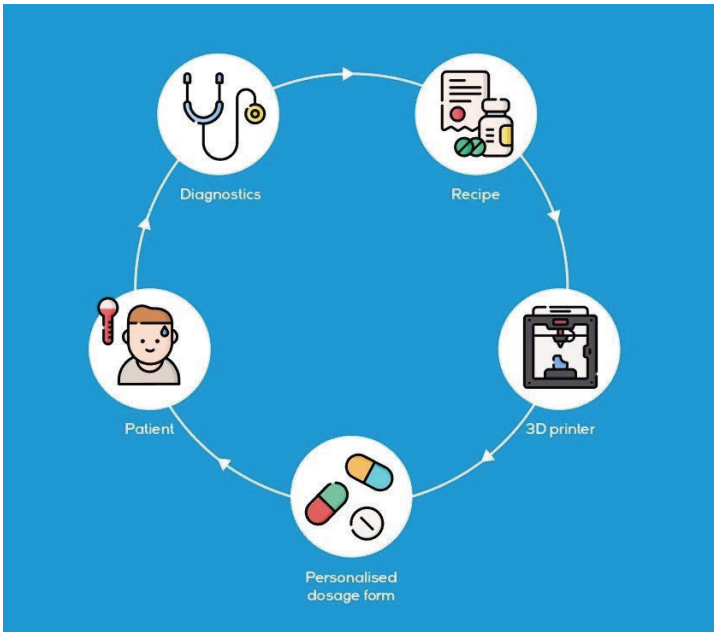
What are our objectives

- Optimise the 3D Printer
  - Multiple nozzles
  - Software optimisation
    - Simple interface
    - GAMP compliant

- Optimise the formulation

- In vivo study
  - Pharmacokinetics and Bioequivalency (published)
  - Proof of principle personalised 3D

Near future???



New technologies in preparation: Robotics

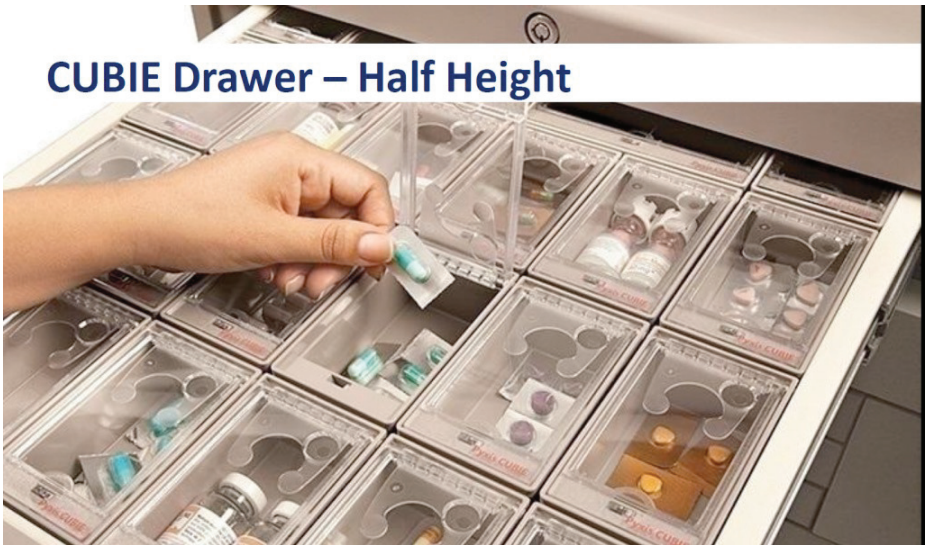
Preparation of parenterals is complex with high risks

- Labour intensive: Safety and health of staff
- Product quality: errors, contamination, variability, controls
- Efficiency and productivity
- Lack of workforce

Automation (robotics) might be a logic solution but keep in mind scope (URS), costs, validation, training, integration with order entry …)

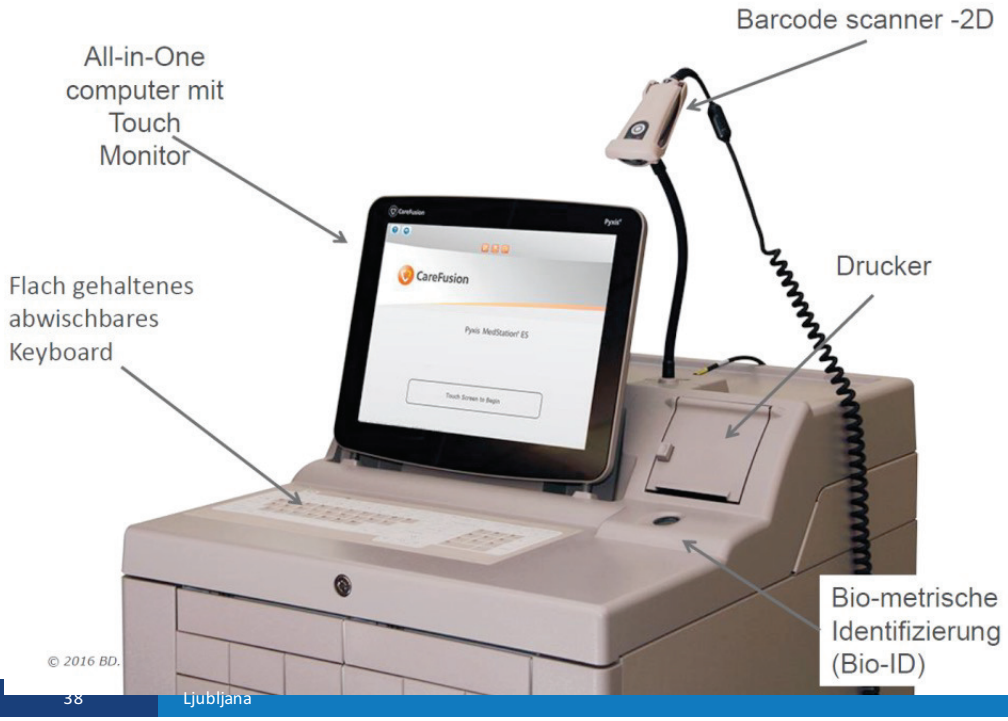
(Semi)Automated Logistics

Electronic distribution – single dose/single unit dose



Pyxis MedStation® ES system

Electronic distribution



Examples for cytostatic preparation

L.Soumoy, Jean-Daniel Hecq Automated Compounding of Intravenous Therapy in European Countries: A Review in 2019. https://doi.org/10.1515/pthp-2019-0008

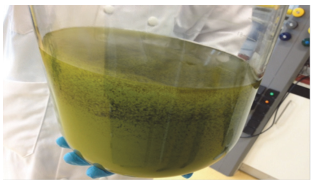
Complex and personalised: peptides
Facilities chemical synthesis

1. 3 peptide synthesizers

2. Purification and analysis (HPLC/UPLC-MS)

3. Aseptical vialing and lyophilization (class A in B cleanroom, CIP/SIP)

Personalised: Fluorescent imaging agents



Labels….

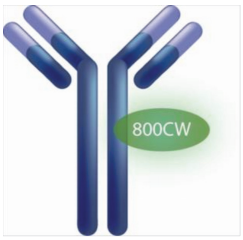
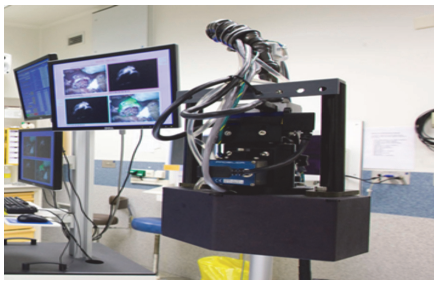


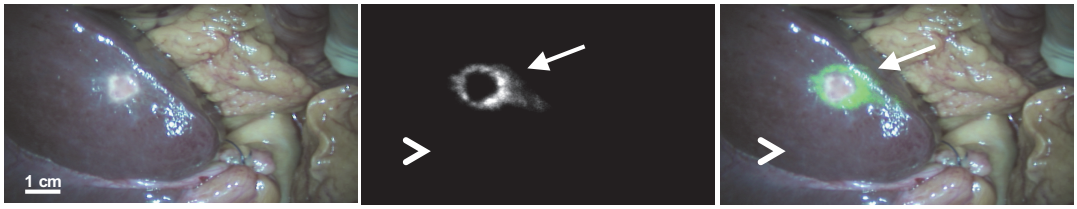
Image-guided surgery

Advanced camera systems for optical imaging



Visual | Fluorescent signal | Integrated

Direct visualization during resection



Partners: LUMC Surgery/Radiology, Harvard Center for Molecular Imaging

CMI Center for Molecular Imaging *Seeing is Curing™*

Take home messages

Preparation is a unique and indispensable competency of the pharmacist

Merging of pharmacies will continue and improve quality and cost effectiveness

RTU's and RTA's are required as much as possible to improve patient safety

Personalised complex medicines; classic preparation and a new challenge like ATMP's, peptides

Robotics and 3D printing will support preparation

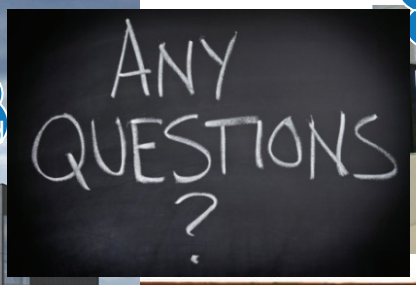
Product care requires product knowledge and is part of clinical treatment

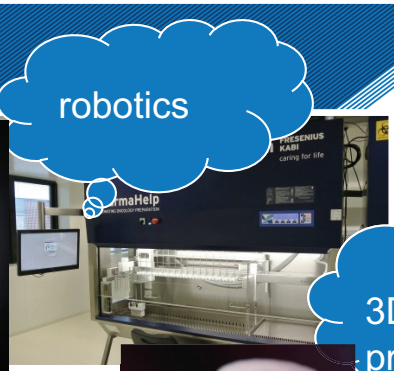
Education is paramount! Invest in skills and technology

A bright future for hospital preparations lays ahead!!

Information: Onze GMP-faciliteit

Email: pphlebrun@icloud.com

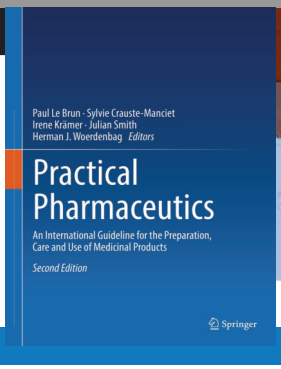


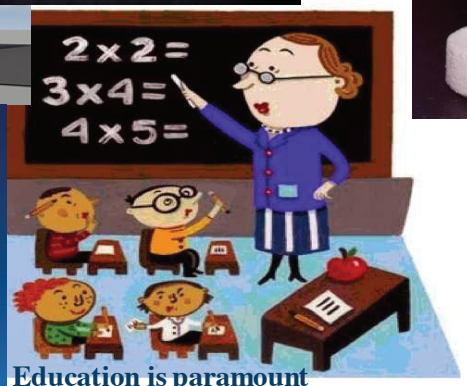


Personalised medicines

ATMP

RTA's





Education is paramount

Čisti prostori bolnišnične lekarne SB Murska Sobota

Clean room in Hospital Pharmacy in General Hospital Murska Sobota

Simona Mohar Karakatič, mag. farm., spec., SB Murska Sobota

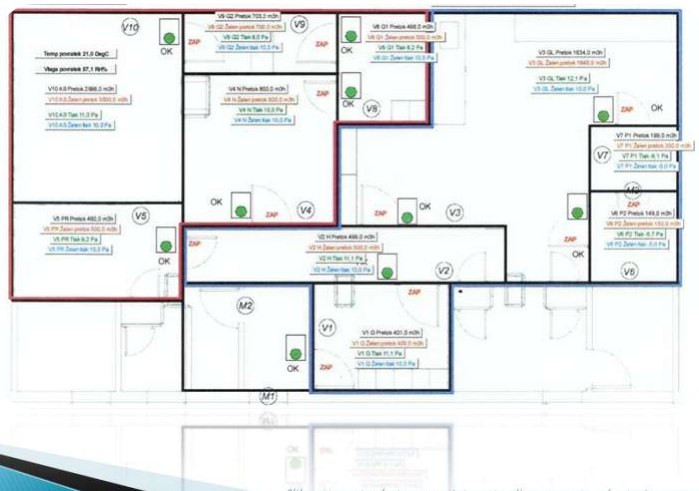
ČISTI PROSTORI BOLNIŠNIČNE LEKARNE SB MURSKA SOBOTA

Simona Mohar Karakatič, mag. farm., spec.

Simpozij Sekcije bolnišničnih farmacevtov
07.11.2023, Ljubljana

Priprava zdravil:

- poteka v čistih prostorih
- prostori so ločeni od okolice
- ločen prostor magistralne in aseptične priprave zdravil



Slike so prosto dostopne na internetu ali pa posnete od avtorja prezentacije.

Preprečevanje navzkrižnega onesnaženja v čistih prostorih:

- z ustreznimi organizacijskimi in tehničnimi ukrepi
- priprava nesterilnih magistralnih izdelkov poteka v magistralnem laboratoriju
- priprava aseptičnih zdravil poteka v prostorih aseptike
- namenski prostori za shranjevanje
- pomivanje posode in ovojnine v pomivalnici
- čiščenje prostorov in opreme po predpisanih postopkih
- upoštevanje načel Dobre proizvodne prakse.

Slike so prosto dostopne na internetu ali pa posnete od avtorja prezentacije.

Osebne poti:

- vstop v čiste prostore dovoljen le s pooblaščeno kartico

- prehodi med prostori so nadzorovani s posebnim sistemom odpiranja vrat in nadzorom vstopa "Interlock"

- upoštevanje načel Dobre proizvodne prakse

- uporaba zaščitnih oblačil in ostalih osebnih zaščitnih sredstev

Slike so prosto dostopne na internetu ali pa posnete od avtorja prezentacije.

Materialne poti:

- prostor za sprejem vhodnih materialov

- prenos vhodnih materialov v prostore magistralnega laboratorija in aseptike preko materialne zapore

- prenos vhodnih materialov in gotovih izdelkov v in iz prostora aseptike preko materialne zapore

Slike so prosto dostopne na internetu ali pa posnete od avtorja prezentacije.

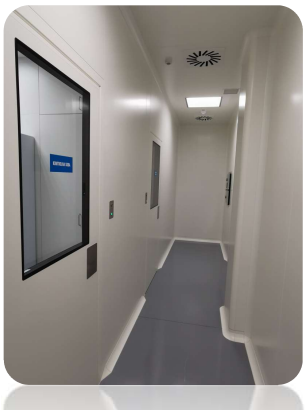
Dokumentacija:

- sprejem materiala: analizni izvidi, varnostni listi, dnevniki
- evidence nadzora opreme in prostorov
- evidence čiščenja opreme in prostorov
- poročila o izdelavi izdelkov
- specifikacije izdelkov
- dnevniki izdelanih izdelkov s pregledi
- ...

Slike so prosto dostopne na internetu ali pa posnete od avtorja prezentacije.

Priprava zdravil v SBMS:

- izdelki po naročilu za potrebe bolnišnice
- priprava zdravil za pogodbene odjemalce



Slike so prosto dostopne na internetu ali pa posnete od avtorja prezentacije.

Priprava zdravil v SBMS:

- naročila oddelkov,
- rekonstitucija bioloških zdravil,
- naročila mobilnega paliativnega tima,
- naročila zunanjih lekarn…

Slike so prosto dostopne na internetu ali pa posnete od avtorja prezentacije.

SPLOŠNA BOLNIŠNICA MURSKA SOBOTA
RAKIČAN, Ulica dr. Vrbnjaka 6, 9000 Murska Sobota

HVALA ZA VAŠO POZORNOST!

Slike so prosto dostopne na internetu ali pa posnete od avtorja prezentacije.

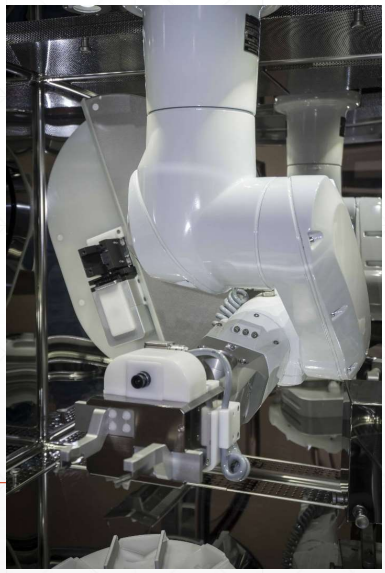
Avtomatizirana priprava citostatikov

Automated preparation of cytotoxics

Jure Dolenc, mag. farm., Onkološki Inštitut Ljubljana

ASEPTIČNA PRIPRAVA ZDRAVIL – VČERAJ, DANES, JUTRI

AVTOMATIZIRANA PRIPRAVA CITOSTATIKOV



15. Mednarodni simpozij Sekcije bolnišničnih farmacevtov pri SFD

Jure Dolenc, mag. farm.

7. Nov 2023

PROTITUMORNA TERAPIJA

- **Visoko rizična zdravila!** -> Individualno odmerjanje
- Pogosto nizka stabilnost -> Sprotna priprava
- Proces od naročila, preko priprave, dostave in do aplikacije pacientu na oddelku.
- **NAPAK NE SME BITI!**
  - Pravilno zdravilo,
  - v pravilnem odmerku,
  - pravilnemu pacientu,
  - ob pravem času
- VARNOST:
  - Pacienta
  - Zaposlenih

APOTECA chemo

- Razbremenitev osebja (repetitive strain injury)
- Povečanje kapacitet
- **Varnost za paciente;** natančnost odmerjanja, avtomatizirani varnostni mehanizmi
- **Varnost zaposlenih;** zmanjšanje potencialne izpostavljenosti rizičnim učinkovinam

Postavitev, inštalacija in zagon: julij 2020

APOTECA chemo

Prednosti

- ↓Izpostavljenost protitumornim učinkovinam
- Dodatni nivoji varnosti priprave (z ustrezno podporo)
- Visoka ponovljivost in natančnost (odmerki)
- Razbremenitev osebja (RSD - ponavljajoče poškodbe zaradi gibov)

Slabosti

- Počasnost
- Težavno čiščenje
- Občasne Okvare, okornost sistema
- Stroškovna učinkovitost?

PRIPRAVA KEMOTERAPIJE (‚*COMPOUNDING*')

- Individualizirano odmerjanje in priprava v bolnišničnih lekarnah

- cca. 50 različnih zdravil
- 50-200 pripravkov na dan

OSNOVNE KOMPONENTE

- Območje za Pripravo
- Koš za citotoksične odpadke

- **VIDEO**
- Območje za nalaganje/razklada nje materiala

Mikrobiološki Vidik – pregled Literature

- „Območje polnjenja z robotsko roko dosega vse zahteve za čistost razreda A po EU GMP“

Sabatini L, Paolucci D, Marinelli F, *et al;* Microbiological validation of a robot for the sterile compounding of injectable non-hazardous medications in a hospital environment; *European Journal of Hospital Pharmacy* 2020;**27:**e63-e68.

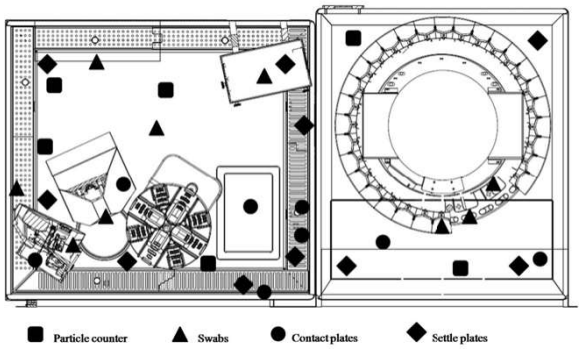


Figure 3 Environmental monitoring sample map.

Mikrobiološki Vidik – LAF vs Robot

LAF*

- 2x rokavice
- Osnova: maska, lasna kapa,
- Kombinezon
- Obujke
- Kapuca

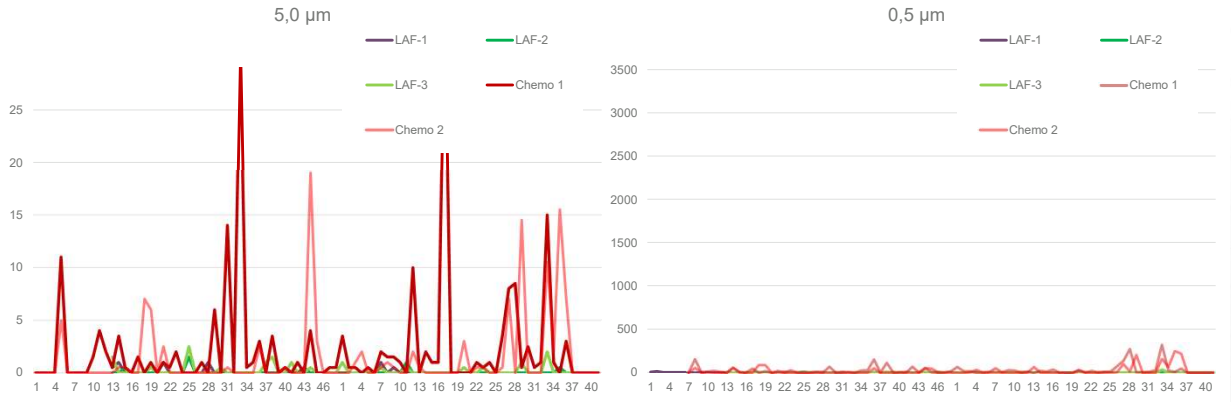
Robot*

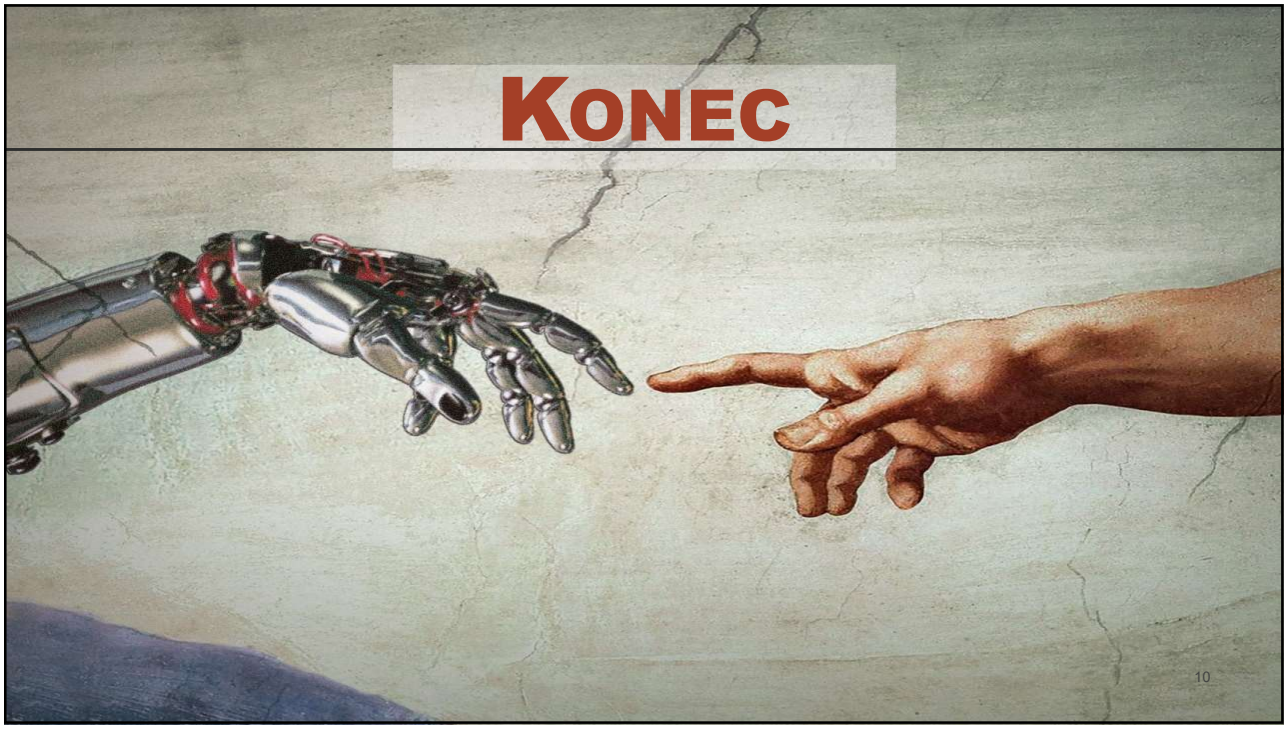
- 1x rokavice
- Sterilni brezprašni plašč

- *Režim čiščenja je enak za vse čiste prostore
- Oba postavljena v enake čiste prostore z enakimi izhodiščnimi pogoji

Mikrobiološki Vidik – LAF vs Robot

- Primerjava rezultatov meritev št. Delcev
- LAF in robota postavljeni v enake pogoje v mirovanju; razred B po EU GMP
- Razlike v resnici posledica razlik v internih standardih oblačil





Aseptična priprava radiofarmakov

Aseptic preparation of radipharmaceuticals

dr. Aljaž Sočan, mag. farm., spec., UKC Ljubljana

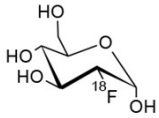
klinični center ljubljana
University Medical Centre Ljubljana

ASEPTIČNA PRIPRAVA RADIOFARMAKOV
ASEPTIC PREPARATION OF RADIPHARMACEUTICALS

dr. ALJAŽ SOČAN, mag.farm.,spec.
radiofarmacevtska lekarna, Klinika za nuklearno medicino

RADIOFARMAK - ZDRAVILO

POSEBNOSTI:



- **odprti vir ionizirajočega sevanja**
- kratek rok uporabnosti (dnevi, ure, minute)
- nimajo farmakološkega učinka
- sproščeni v promet, preden so končani vsi testi nadzora kakovosti
- majhne serije
- odmerek se s časom zmanjšuje
- **parenteralne raztopine (90%)**

ZAHTEVE

IZPOLNJEVANJE ZAHTEV **ZAKONODAJE IZ PODROČJA FARMACEVTSKIH IZDELKOV**

- Zakon o zdravilih
- Zakon o opravljanju lekarniške dejavnosti
- Pravilnik o opravljanju Radiofarmacevtske lekarniške dejavnosti
- Pravilnik o radiofarmacevtskih izdelkih
- cGRPP (current Good Radiopharmacy Practice) smernice EANM
- PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments

IZPOLNJEVANJE ZAHTEV **ZAKONODAJE IZ PODROČJA VARSTVA PRED IOS**

- Zakon o varstvu pred ionizirajočimi sevanji in jederski varnosti
- Pravilnik o obveznosti izvajalca sevalne dejavnosti in imetnika vira ionizirajočih sevanj
- Pravilnik o uporabi virov sevanja in sevalni dejavnosti

POGOJI DELA

- izdelava sterilnih farmacevtskih izdelkov mora izpolnjevanjevati posebne zahteve z namenom **minimiziranja tveganja** mikrobiološke, kontaminacije z delci in pirogeni
- izrednega pomena sta **znanje in izkušenost** ter odnos v procesu udeleženega **osebja**
- nujno je **izpolnjevanje zahtev QA** (Quality Assurance - zagotavljanje kakovosti)
- izdelava mora potekati po striktno določenih in **validiranih** metodah priprave in postopkih
- zanašanje na terminalno sterilizacijo izdelka, ter teste končnega izdelka ni sprejemljivo

"čisti prostori" namenjeni izdelavi sterilnih farmacevtskih izdelkov so glede na zahtevane značilnosti okolja razdeljeni na **4 razrede (A, B, C, D)**

	Maximum permitted number of particles/m3 equal to or above			
Grade	At rest (b)		In operation	
	0,5µ m	5µ m	0,5µ m	5,0µ m
A	3 500	0	3 500	0
B(a)	3 500	0	350 000	2 000
C(a)	350 000	2 000	3 500 000	20000
D(a)	3 500 000	20 000	not defined (c)	not defined (c)

	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m³	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Vsaka operacija proizvodnega procesa med izdelavo zahteva okolje ustrezne čistosti, z namenom minimiziranja kontaminacije (delci, mikrobiološka) izdelka ali uporabljanih materialov

POGOJI DELA, RADIOFARMACEVTSKA LEKARNA (1)

Radiofarmacevtska lekarniška dejavnost se glede na način in obseg dela deli na naslednje razrede in ravni:

Razred 1 obsega prevzem in izdajo registriranih radiodiagnostikov.

Razred 2 obsega prevzem radiofarmacevtskih izdelkov, **pripravo in izdajo radiofarmakov** za diagnostiko in zdravljenje, vključno s paliativnim, **iz registriranih radiofarmacevtskih izdelkov**, pripravljenih skladno z navodili proizvajalca ter **radiooznačevanje avtologni krvnih celic** in se deli na:

- **Raven 2A** obsega pripravo in izdajo radiofarmakov za diagnostiko in zdravljenje, vključno s paliativnim iz registriranih radiofarmacevtskih izdelkov, pripravljenih skladno z navodili proizvajalca.
- **Raven 2B** obsega radiooznačevanje avtologni krvnih celic z registriranimi radiofarmaki, v skladu z navodili proizvajalca, po zaprtem postopku.

Razred 3 obsega prevzem radiofarmacevtskih izdelkov, **pripravo in izdajo radiofarmakov** za diagnostiko in zdravljenje, vključno s paliativnim, ter **vključno z neregistriranimi radiofarmaki, radiooznačevanje celic** in se deli na:

- **Raven 3A** obsega pripravo iz komponent in radionuklidnih predhodnikov, kontrolo kakovosti in izdajo radiofarmakov za diagnostiko(vključno s PET) in zdravljenje.
- **Raven 3B** obsega radiooznačevanje celic.

Pravilnik o pogojih za opravljanje radiofarmacevtske lekarniške dejavnosti ((Uradni list RS, št. 82/18)

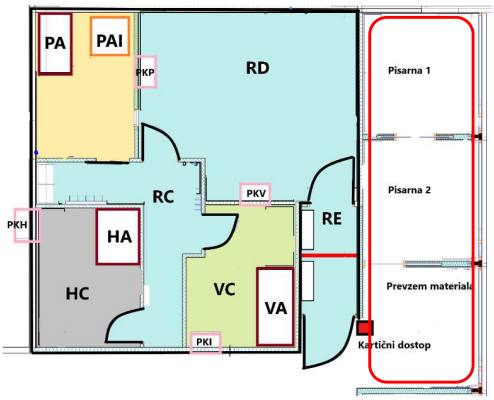
POGOJI DELA, RADIOFARMACEVTSKA LEKARNA (2)

- **Prostori**, v katerih se rokuje z ali se v njih shranjujejo radiofarmacevtski izdelki, so **del nadzorovanega območja sevanja** in so opremljeni z označbami v skladu s predpisi s področja varstva pred ionizirajočimi sevanji ter z merilniki hitrosti sevanja in merilniki površinske kontaminacije.
- Radiofarmacevtski izdelki se shranjujejo v skladu z **navodili proizvajalca, veljavno farmakopejo** in v skladu z **načeli dobre skladiščne**, **dobre lekarniške** in **dobre radiofarmacevtske prakse**.
- Nepooblaščenim osebam se onemogoči dostop do zalog radiofarmacevtskih izdelkov v radiofarmacevtski lekarni.
- Za shranjevanje virov sevanja, ki se ne uporabljajo več, je na voljo **poseben prostor**, v skladu s predpisi s področja varstva pred ionizirajočimi sevanji

PROSTORI RADIOFARMACEVTSKE LEKARNE V UKCL:

NEKONTROLIRANO OBMOČJE:

- Nekontrolirano območje, **kontrolirano z vidika opravljanja sevalne dejavnosti, ni definirana stopnja čistote zraka in niso spremljani pogoji** (tlačna razlika, temperatura, relativna vlaga.)
- Brez kartičnega dostopa.
- Pisarni in predprostor, kjer vršimo prevzem materiala (iz skladišča UKC).
- V prostoru je izključevalec osebne kontaminacije.



Slika 1. Shema prostorov radiofarmacevtske lekarne KNM. V čistih prostorih (od kartičnega dostopa dalje) **oznake prostorov A, B, C, D hkrati pomenijo stopnje čistote posameznega prostora**.

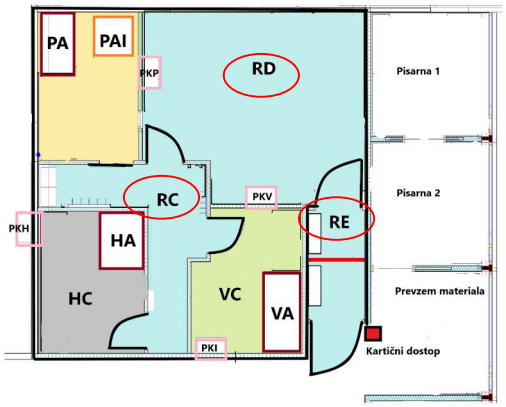
PROSTORI RADIOFARMACEVTSKE LEKARNE UKCL:

Čisti prostori:

SKUPNI PROSTORI:

- Prostor za vstop osebja ter preoblačenje in preobuvanje ter vnos materiala v čiste prostore radiofarmacevtske lekarne: **RE** (radiofarmacija – E)
- centralni prostor RL - izvedba postopkov kontrole kvalitete, shranjevanje materialov, kompletov za pripravo RF, staranje radiofarmakov za test na sterilnost**: RD** (radiofarmacija – D)
- prostor za preoblačenje 2. nivoja, preobuvanje in razkuževanje, predprostor do prostorov 2. nivoja: **RC** (radiofarmacija – C)

drugem nivoju pa v **TRI LOČENE SKLOPE**



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PROSTORI RADIOFARMACEVTSKE LEKARNE UKCL:

SKLOP VROČI:

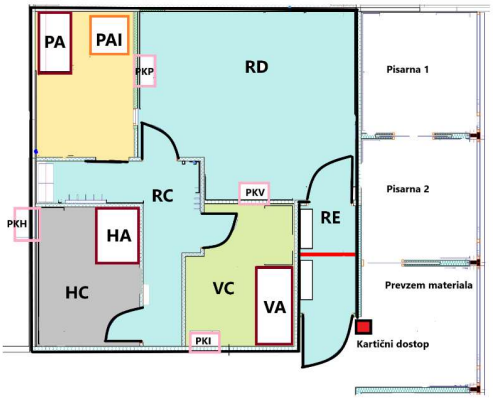
- prostor, v katerem se nahaja komora z laminarnim pretokom zraka (LAF) za pripravo radiofarmakov MC 18-2-Pb:VC (vroči – C)
- delovni volumen LAF komora MC 18-2-Pb:VA (vroči – A) – LAF komora

SKLOP HEMATOLOGIJA:

- prostor, v katerem se nahaja LAF komora za pripravo radiofarmakov SMBC 122 AV/Pb: HC (hematologija – C)
- delovni volumen LAF komore SMBC 122 AV/Pb: HA (hematologija – A) – LAF komora

SKLOP PET:

- prostor, v katerem se nahajata PET izolator in LAF komora: PC (PET – C)
- delovni volumen PET izolatorja: PAI (PET – izolator) in LAF komore: PAI (PET – izolator)



Slika 1. Shema prostorov radiofarmacevtske lekarne KNM. V čistih prostorih (od kartičnega dostopa dalje) **oznake prostorov A, B, C, D hkrati pomenijo stopnje čistote posameznega prostora**.

PROSTORI RADIOFARMACEVTSKE LEKARNE UKCL:

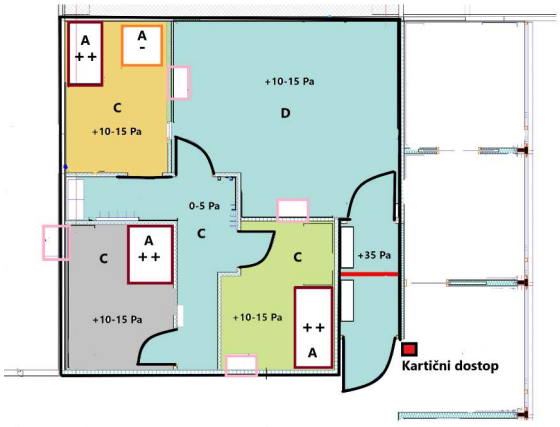
Tlačne razlike:

IZPOLNJEVANJE ZAHTEV **ZAKONODAJE IZ PODROČJA FARMACEVTSKIH IZDELKOV**

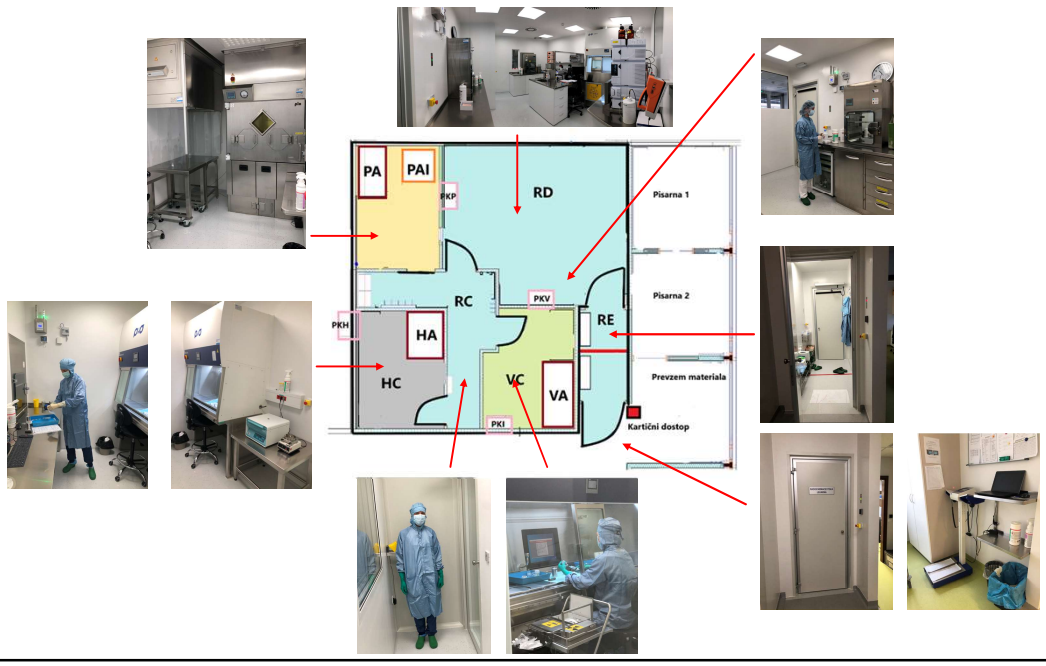
Čisti prostori morajo biti pozitivni glede na sosednje, manj čiste prostore (**nadtlak**)

IZPOLNJEVANJE ZAHTEV **ZAKONODAJE IZ PODROČJA VARSTVA PRED IOS**

Območje priprave mora biti relativno pod negativnim tlakom glede na okolico (**podtlak**)



Slika 2. Shema čistih prostorov radiofarmacevtske lekarne KNM. Na shemi so označene stopnje čistote (A-D, EU GMP) posameznih prostorov in razlike tlakov. ++ pomeni višji tlak, - pomeni podtlak.



HVALA ZA VAŠO POZORNOST

Aseptična priprava v lekarni na primarnem nivoju

Aseptic preparation in community pharmacy

Lidija Vrbovšek, mag. farm., spec.

ASEPTIČNA PRIPRAVA V LEKARNI NA PRIMARNEM NIVOJU

Aseptic preparation in community pharmacy

Lidija Vrbovšek, mag. farm., spec.
JLZ Celjske lekarne

15. mednarodni simpozij Sekcije bolnišničnih farmacevtov pri SFD
Ljubljana, november 2023

STERILNA MAGISTRALNA ZDRAVILA

- Sterilne FO:
  - za oko (kapljice, mazila)
  - raztopine za inhaliranje
  - parenteralne raztopine v elastomernih črpalkah
  - drugo (tekoče dermalne FO za poškodovano kožo,..)
- Postopek priprave:
  - aseptična priprava
  - filtracija (0,22 µm filter)

- **kakovost mag. zdravila = kakovost industrijskega zdravila**
- zdravila visokega tveganja

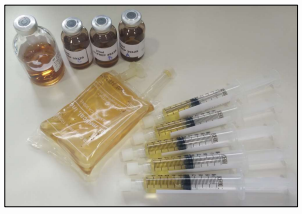
PREDPISI ZA MAGISTRALNO PRIPRAVO SRERILNIH ZDRAVIL

- **ŠE V PRIPRAVI! Dobra lekarniška praksa, usklajena z dobro prakso PICS/GPP s poglavjem o sterilni pripravi zdravil**

- PICS/GPP
- EU GMP, priloga 1
- Ph. Eur. 11th
- USP-797
- Standard ISO14644-1…

OSEBJE

- odgovorna oseba za pripravo magistralnih zdravil
- **usposobljeno** za pripravo sterilnih FO
  - validacija aseptičnega postopka
    Klerkit® Universal Operator Broth Transfer Validation Kit



- SOP: *Priprava sterilnih zdravil v lekarni*
- IN: *Preverjanje usposobljenosti farmacevta za delo v čistem prostoru*
- *Zapisnik priprave sterilnih zdravil v lekarni*

CELJSKE LEKARNE	ZAPISNIK NADZORA PRIPRAVE STERILNIH ZDRAVIL V LEKARNI	Oznaka dokumenta: CL-LEK-SOP-II-13-2.0 Stran 1 od 2

Nadzor opravil:	Nadzorovana oseba (operater):	Datum:

Nadzorovani postopek	OPOMBE	Ustreza: DA/NE
1. Umivanje in razkuževanje rok		
2. Brisanje in priprava materiala na pladnje za prenos v čisti predprostor		
3. Vstop v čisti predprostor-lepljiv predpražnik		
DELO V PREDPROSTORU		
4. Razkuževanje rok s sterilnim alkoholom.		
5. Pravilna namestitev sterilne maske (preko nosu in ust).		
6. Pravilno rokavičenje.		
7. Priprava in razkuževanje materiala za vnos v čisti prostor (postopek spray-wipe-spray)		
• vse površine dovolj omočene		
• pravilno prebrisavanje		
• ustrezen čas - 2 minuti po razprševanju		
8. Odstranjevanje zaščitne folije z zamaškov infuzijskih plastenk ali stekleničk		
9. Pravilno oblačenje kombinezona		
10. Namestitev prevlek za obuvala		
11. Vstop v čisti prostor-lepljiv predpražnik		
DELO V KOMORI		
12. Kontrola tehtnice		
13. Razkuževanje komore		
14. Vnos materiala v komoro		
15. Dvojno rokavičenje, zamenjava rokavic, razkuževanje rokavic		
16. Odstranjevanje odpadkov		
17. Beleženje nateht, označevanje med pripravo		
18. Dobra aseptična tehnika		
• počasni gibi		
• rezanje in ne trganje		
• preprečevanje mikrobiološke in navzkrižne kontaminacije		

CELJSKE LEKARNE	ZAPISNIK NADZORA PRIPRAVE STERILNIH ZDRAVIL V LEKARNI	Oznaka dokumenta: CL-LEK-SOP-II-13-2.0 Stran 2 od 2

Nadzorovani postopek	OPOMBE	Ustreza: DA/NE
• Pravilen postopek priprave:		
✓ črpalk		
✓ kapljic za oko/inhalacij		
✓ mazil za oko		
19. Medprocesne kontrole – pH, bistrost, homogenost…		
20.Čiščenje in razkuževanje komore po končanem delu		
POSPRAVLJANJE ČISTEGA PROSTORA IN PREDPROSTORA		
21. Odstranjevanje odpadkov – ločevanje odpadkov		
22. Čiščenje in razkuževanje delovnih površin, pladnjev za prenos materiala		
23. Razkuževanje tal		
DOKUMENTACIJA IN OZNAČEVANJE		
24. Pravilno izpolnjen spremni list		
25. Pravilno označevanje zdravila		

Skupna ocena nadzora: opravil DA / NE

Komentar:

Podpis nadzorne osebe: Podpis operaterja: Podpis vodje lekarne:

OSEBJE

- osebna higiena in čistoča
- brez: nalezljivih bolezni
  nakita in dekorativne kozmetike
- **sterilna zaščitna oprema**:
  - nesterilna podkapa
  - **maska**
  - **rokavice (dvojne nitrilne)**
  - **kombinezon**
  - **obujki**
- pisna navodila za pravilo umivanje/razkuževanje rok in oblačenje
- kontrola pravilnega oblačenja kombinezona

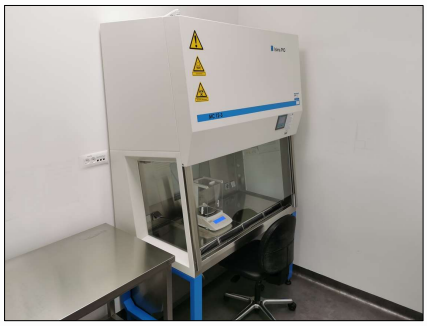
OKOLJE

PROSTOR

- fizično ločen od ostalih prostorov
- gladke površine
- dovod filtriranega zraka (HEPA H14)
- klasificiran
- nadtlačna razlika (10-15 Pa)
- število menjav zraka na uro
- dnevni nadzor T in vlage, tlaka
- vstop 1-2 x dnevno
- čist

KOMORA

- validirana (letno preverjanje)
  - ➢ štetje delcev
  - ➢ število menjav zraka na uro
  - ➢ hitrost pretoka zraka na delovnih mestih
  - ➢ kontrola integritete filtrov HEPA
- čista



ČIŠČENJE IN DEZINFEKCIJA prostora in komore

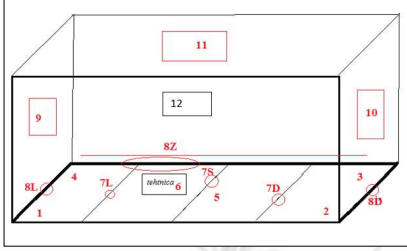
- *Navodilo za čiščenje, razkuževanje in vzdrževanje prostorov in LAF komore za pripravo sterilnih zdravil*
  - ➢ definiran časovni plan (dnevno, tedensko, mesečno, polletno)
  - ➢ uporaba sterilnih: čistil
    brezprašnih krpic
    omočenih mop-ov
  - ➢ usposobljenost osebja

- *Evidenca čiščenja, razkuževanja in vzdrževanja prostorov in LAF komore za pripravo sterilnih zdravil*

MIKROBIOLOŠKI NADZOR

- kontrola mikrobiološke ustreznosti:
  - prostor
  - osebje
  - aparature
  - zrak
  - posoda in pribor
  - sterilizacija
  - gotova mag. zdravila

A) Shematski prikaz odvzema vzorcev v LAF komori



1	Delovna površina – levo spredaj
2	Delovna površina – desno spredaj
3	Delovna površina – desno zadaj
4	Delovna površina – levo zadaj
5	Delovna površina – sredina
6	Tehtnica
7S	Stičišče delovna površina – sredina
7D	Stičišče delovna površina – desno
7L	Stičišče delovna površina – levo
8D	Stičišče delovna površina – stena - desno
8L	Stičišče delovna površina – stena – levo
8Z	Stičišče delovna površina – stena – zadaj
9	Leva stena
10	Desna stena
11	Zgoraj
12	Zadnja stran komore

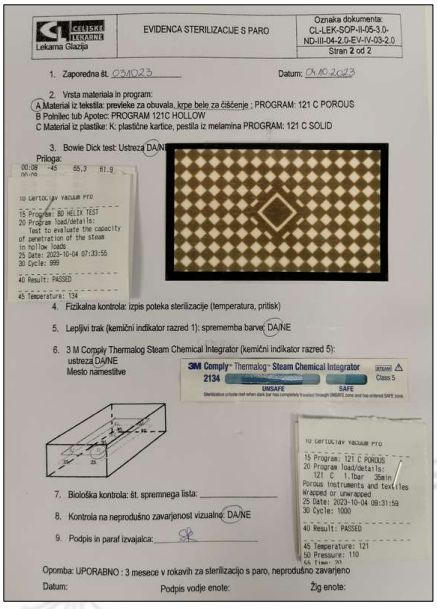
- SOP: *Mikrobiološka kontrola priprave sterilnih zdravil*
- Navodilo*: Preverjanje mikrobiološke kakovosti gotovih mag. zdravil*

STERILIZACIJA POSODE IN PRIBORA

- s toploto
- z vodno paro

- preverjanje ustreznosti z indikatorji:
  - fizikalni
  - kemijski
  - biološki

- dokumentiramo


EVIDENCA STERILIZACIJE S PARO

Oznaka dokumenta: CL-LEK-SOP-II-05-3.0-ND-III-04-2.0-EV-IV-03-2.0

Stran 2 od 2

1. Zaporedna št. 25102023 Datum: 24.10.2023
2. Vrsta materiala in program:
A Material iz tekstila: prevleke za obuvala, krpe bele za čiščenje ; PROGRAM: 121 C POROUS
B Polnilec tub Apotec: PROGRAM 121C HOLLOW
C Material iz plastike: K: plastične kartice, pestila iz melamina PROGRAM: 121 C SOLID
3. Bowie Dick test: Ustreza DA/NE
Priloga:
4. Fizikalna kontrola: izpis poteka sterilizacije (temperatura, pritisk)
5. Lepljivi trak (kemični indikator razred 1): sprememba barve DA/NE
6. 3 M Comply Thermalog Steam Chemical Integrator (kemični indikator razred 5): ustreza DA/NE
Mesto namestitve
3M Comply™ Thermalog Steam Chemical Integrator 2134 Class 5 UNSAFE SAFE
7. Biološka kontrola: št. spremnega lista:
8. Kontrola na neprodušno zavarjenost vizualno: DA/NE
9. Podpis in paraf izvajalca:
Oporaba: UPORABNO : 3 mesece v rokavih za sterilizacijo s paro, neprodušno zavarjeno
Datum: Podpis vodje enote: Žig enote:

OBVLADOVANJE TVEGANJA

- vse našteto
- **kratki roki uporabnosti**
- **za posameznega pacienta** ali manjšo skupino pacientov
- uporaba industrijsko pripravljene sterilne vode za injekcije (raztopine)
- lipofilne podlage (mazila)
- sterilni vsebniki z ozkimi vratovi
- takojšnje polnjenje in zapiranje

ZAKLJUČEK

- nova DLP
- centraliziran postopek priprave sterilnih mag. zdravil
- možnosti izboljšav (prostori, monitoring,…)
- preskrbljenost prebivalstva

SmartCon GMP čisti prostori

ZA POPOTNICO…

»Največja nevarnost za vse nas ni v tem, da bi si svoj cilj postavili previsoko in ga ne bi dosegli, ampak v tem, da si postavimo cilj prenizko in ga dosežemo.«

Michelangelo

Hvala za pozornost!

Contamination – a hidden risk of everyday items used in the aseptic units

Kontaminacija pri delu v aseptičnih prostorih

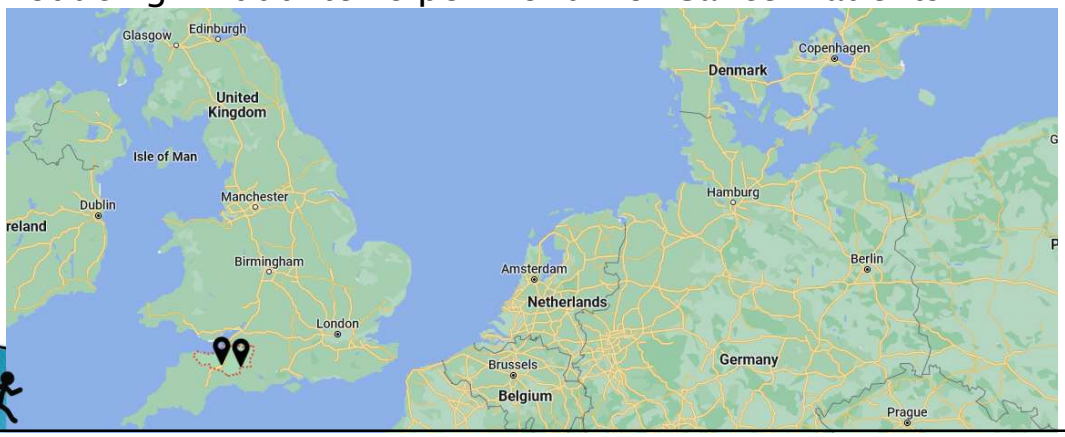
Rufus Smith, MSc, Senior Pharmacist

Contamination In Clean Rooms – A hidden risk in everyday items

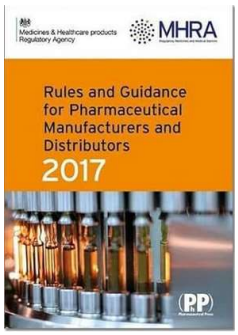
Rufus Smith
Pharmacist

Thank you for inviting me

- Accountable Pharmacist for Somerset in England
- Two Aseptic Units at Two hospitals
- Producing >2000 items per month for Cancer Patients



Clean Room Standards – The Why

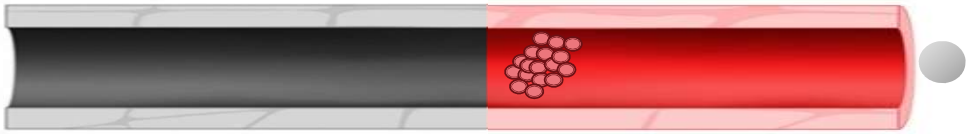


- Standards on Particular Contamination
  - MHRA
  - ISO
- Regardless of standard – you might know the person being treated
- Loss of function or Complication (infection) – Immunosuppression
- Infection/Contamination is important regardless of drug cost

Class	Maximum particles/m³ [a]						FED STD 209E equivalent
	≥0.1 µm	≥0.2 µm	≥0.3 µm	≥0.5 µm	≥1 µm	≥5 µm	
ISO 1	10[b]	[d]	[d]	[d]	[d]	[e]	
ISO 2	100	24[b]	10[b]	[d]	[d]	[e]	
ISO 3	1,000	237	102	35[b]	[d]	[e]	Class 1
ISO 4	10,000	2,370	1,020	352	83[b]	[e]	Class 10
ISO 5	100,000	23,700	10,200	3,520	832	[d,e,f]	Class 100
ISO 6	1,000,000	237,000	102,000	35,200	8,320	293	Class 1,000
ISO 7	[c]	[c]	[c]	352,000	83,200	2,930	Class 10,000
ISO 8	[c]	[c]	[c]	3,520,000	832,000	29,300	Class 100,000
ISO 9	[c]	[c]	[c]	35,200,000	8,320,000	293,000	Room air

Clean Room Standards – The Why

- Contamination can be microorganisms or non-viable particles
  - Pulmonary embolism
  - Granuloma (viable contamination)
  - Systemic Inflammatory Response Syndrome (SIRS)
- Numbers Game – Reducing the Risk of a Contaminated Product and keeping us out of the press and out of court.



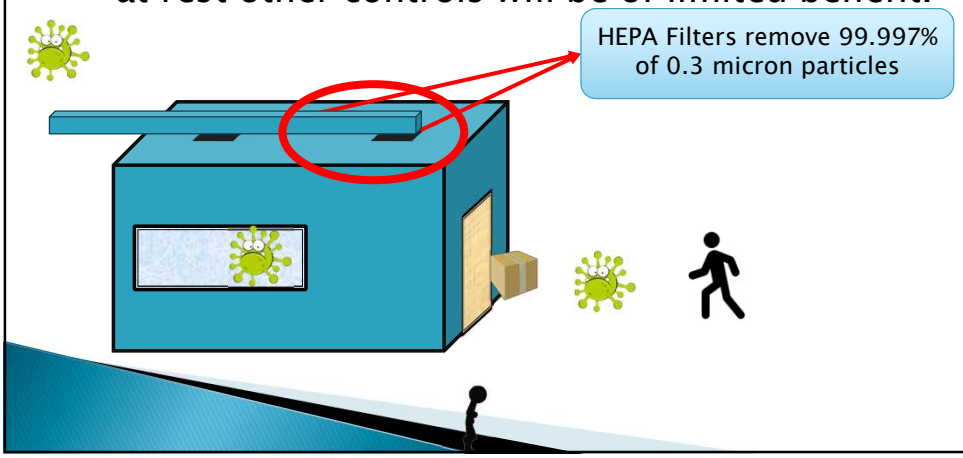
ADVERTISER & TIMES

NHS fined £45,000 after 'basic' mistakes caused medication overdose

By Jon Waller - 12 December, 2019

The Clean Room

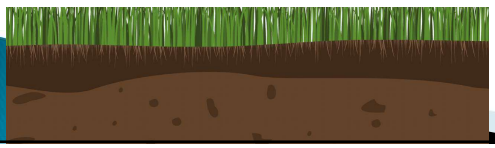
- Build with engineering controls
- First and most important step. If you don't have a clean room at rest other controls will be of limited benefit.

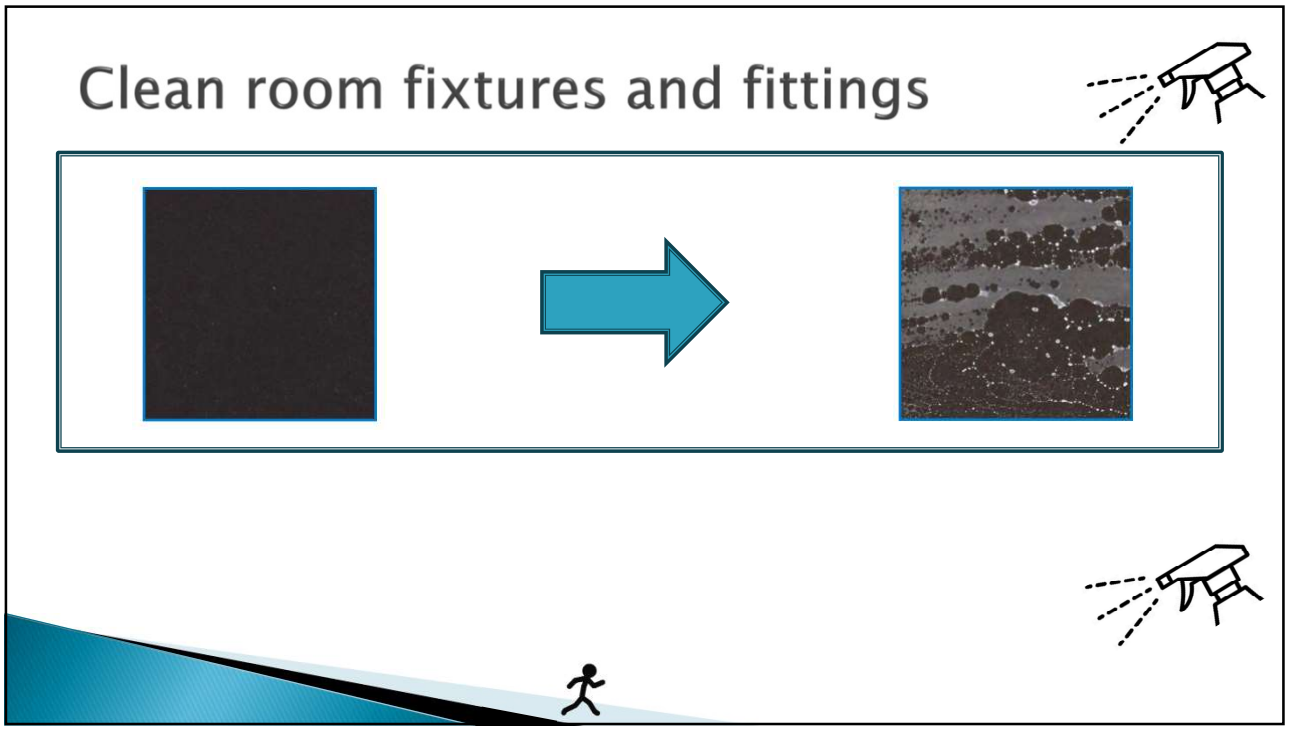


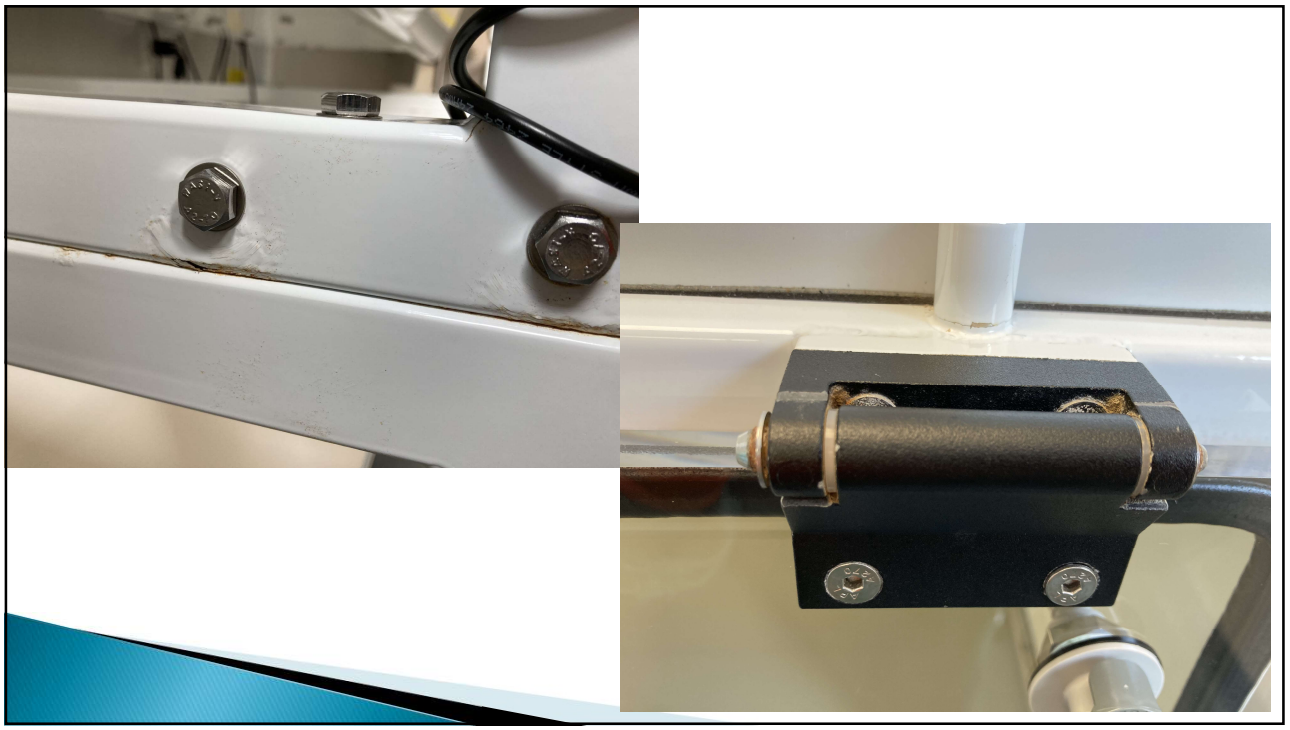
Clean room fixtures and fittings

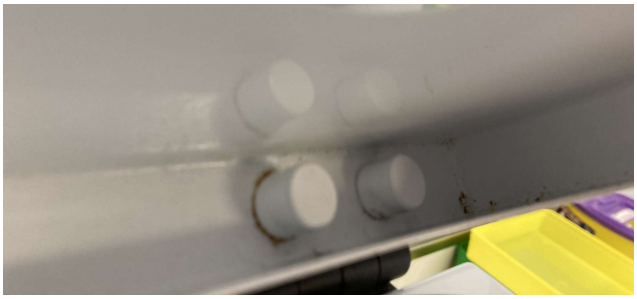
- Cleanroom is an expensive build
- Plan to last long-term, at least >20+ years
- 2014 3 Babies died & 21 infected with Bacillus Cereus (soil, vegetation, food)
- Spore forming bacteria
- MHRA decided the need to switch from IMS to sporicidal cleaners
- Constant cleaning with chlorine or peroxide based solutions
  → Rust (anything with a screw) → Hard to clean surfaces
  → Residue build up

Clean room fixtures and fittings



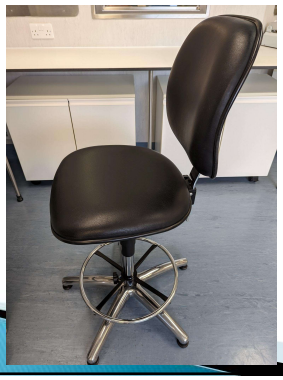

Clean room fixtures and fittings





Clean room furniture

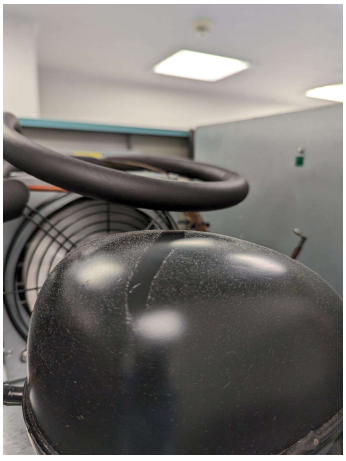
- Wooden furniture
  - Impossible to clean
  - Laminated Chipboard, lamination can fail
- Cleanroom Chairs
- Stools

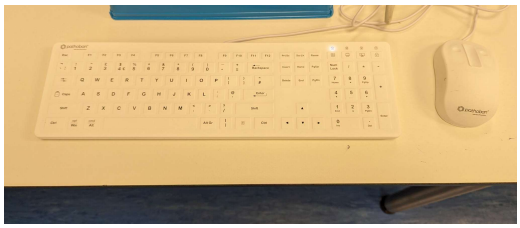


Cleanroom Equipment

- Don’t have anything in the cleanroom you don’t need
- Fridges
  - Easy to clean:
    - Covered
    - On Wheels
  - Condensation
- Light boxes
- PC’s – Wipe clean keyboard and mouse
- Sleeve Pressure Monitor
- Filling pumps & compounding equipment
- Phone

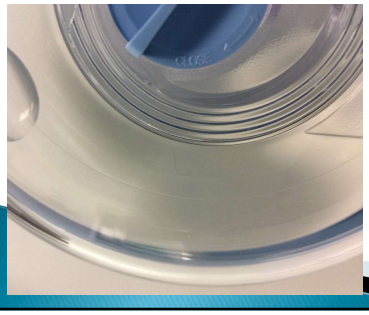
Cleanroom Equipment

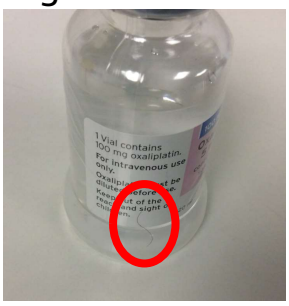




Clean Room Materials

- Packaging
  - Paper machines provide conditions favourable for growth of microbes. Main contaminants of paper and board belong to *Bacillus* and *Paenibacillus*.[1]
- Paper – Essential to operation
- Manufacturer Failures – Particles can carry microorganisms

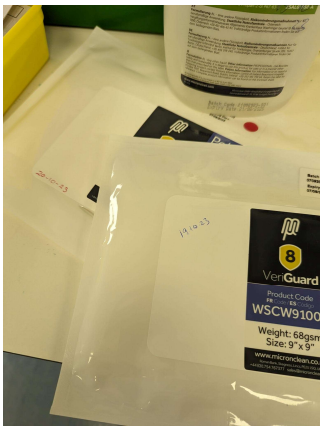




1. SUOMINEN, I., SUIHKO, M.-. and SALKINOJA-SALONEN, M., 1997. Microscopic study of migration of microbes in food-packaging paper and board. *Journal of industrial microbiology & biotechnology*, **19**(2), pp. 104-13.

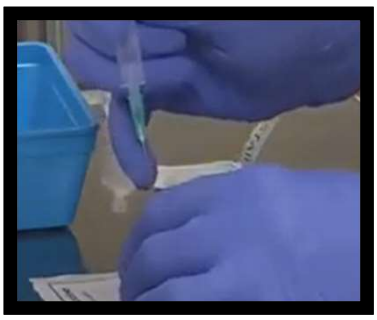
Clean Room Materials

- Pens – High touch item, how often are they cleaned?
- Alcohol? Sprays
  - Record a date opened on the item
  - Wipes dry out
- Stickers versus Staples

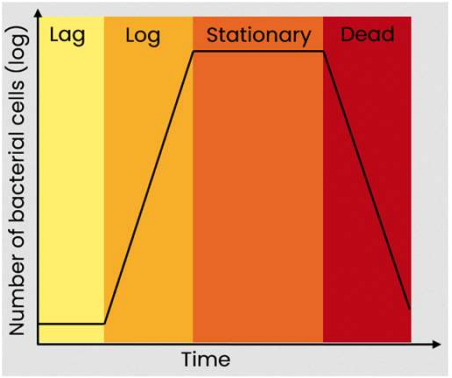


Technique and Training

- Knowing the risks is only half the story
- Consistency in good manufacturing practice
- Worst case you produce a non-sterile product
- Time & Temperature become important




Pfizer COVID-19
0.3 ml
Lote EH9899
Expiration:12/16/2


Lag
Log
Stationary
Dead
Number of bacterial cells (log)
Time

Thank You

Risk assessment in daily practice

Ocena tveganja v vsakodnevni praksi

Paul Le Brun, PharmD, PhD, Associate professor

Leids Universitair Medisch Centrum

Aseptic preparation and risk assessment in daily practice

15. mednarodni simpozij Sekcije bolnišničnih farmacevtov pri SFD

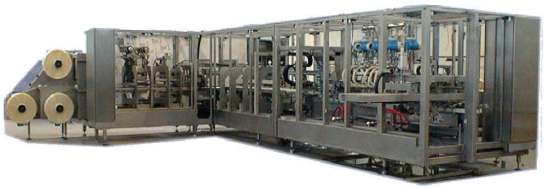
Paul Le Brun, PharmD, PhD
Hospital pharmacist-clinical pharmacologist

Ljubljana November 7, 2023

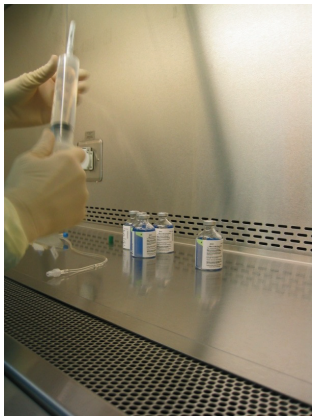
Nothing to disclose

Room for interpretation?

industry



hospital



Conditions for GMP-H

Levels of product protection	Clothing and hand hygiene	Working area	Background space	Air treatment of the background space
Limited product protection	Clean clothing every day new single use gloves for each session Hand hygiene	Work surface cleaned and disinfected for each session	Quiet	No requirements
Increased product protection	Clean trouser suit every day, new sterile gloves, hair covering, mouth/nose mask for each session; hand hygiene	Horizontal LAF cabinet, biohazard workbench or isolator with overpressure	Separate; limited accessibility; clean	No requirements
Maximum product protection	Clean trouser suit every day, new sterile gloves, hair covering, mouth/nose mask for each session; special shoes; hand hygiene	Horizontal LAF cabinet	Separate; limited accessibility; clean, airlock, smooth finish	Grade D
		Biohazard workbench		Grade D
		Isolator with overpressure		No requirements

GMP-H

Advantages:

- Economic (premises and maintenance)
- Environment (materials, HVAC)

- But interpretation needs foundation: validation, monitoring, risk assessment, and research

Validation

The aseptic method should be validated by repeating the procedures with an appropriate nutrient medium

In large-scale aseptic manufacturing a large number of units is involved, so it can be demonstrated that the probability of microbiological contamination is less than 0.1%.

For smaller quantities it is sufficient to scale down repetition of the manufacturing with the nutrient medium to the size of the batch

For aseptic preparations this method gives insufficient information. After all, the batch consists of one or several units (individual preparations)

For this sort of procedure the system of continuous sampling has been developed

Process simulation and continuous validation

The End-of-Session Broth Test
Microbiological Monitoring
Operator Broth Transfer Validation Test

Data?

Database ‘Microbio’

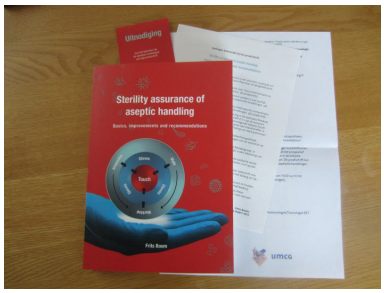
A web based programme for processing, evaluation and assessing microbiological controls during aseptic handling

Microbiological limits

Microbiological controls of aseptic handling in Dutch hospital pharmacies: results, limits, and methods for assessing. Frits A. Boom, Paul P. H. Le Brun, Stefan Boehringer, Madeleine Sirks, Daan J. Touw

Published online by European Journal of Pharmaceutical Sciences, June 2022.

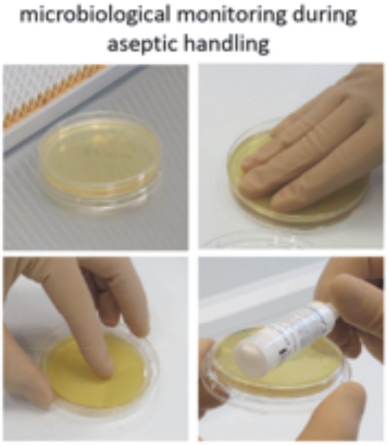
Thesis of Frits Boom is available: https://doi.org/10.1016/j.ejps.2022.106228.

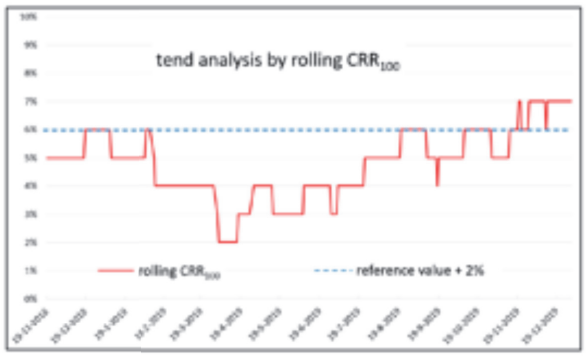


Monitoring data

Number of cfu's of growth/no growth

Contamination recovery rate: is the percentage of samples that show any microbial recovery, irrespective of the number of cfu





Contamination Recovery Rate (CRR) = percentage of samples contaminated by ≥ 1 cfu.

Microbiological limits

Limits for Aseptic Process Simulation (APS) and MM are described in EU GMP Annex 1 but

End of Session Broth Test' (ESBT) instead of APS in combination with assessing aseptic techniques which means that each operator should APS during training. This test has to be repeated at least once a year.

A limit for ESBT can be set at one sample with growth out of 1000 samples.

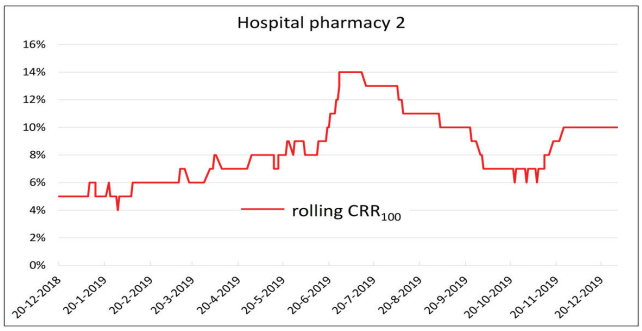
MM we use cfu count and CRR; A CRR of < 10% as well as a mean cfu count of < 1 cfu are used as limits in the MM procedures for aseptic handling in the Netherlands.

Data analysis by reference values and rolling CRR100

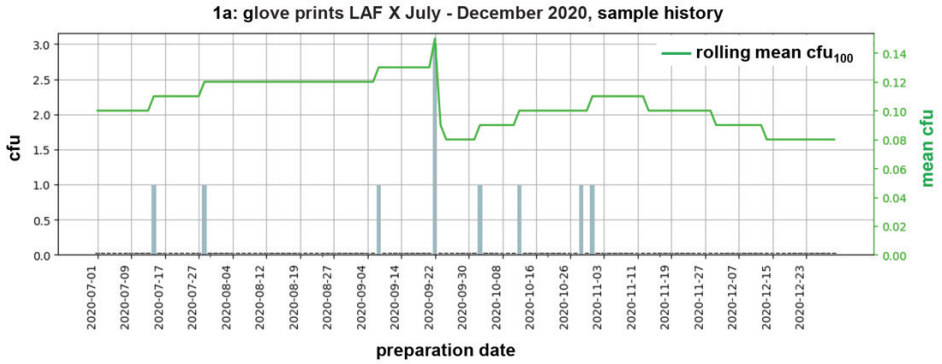
Reference value of air sampling, glove prints and work top prints of each LAF or SC by using MM results from the last year or years (at least 250 samples).

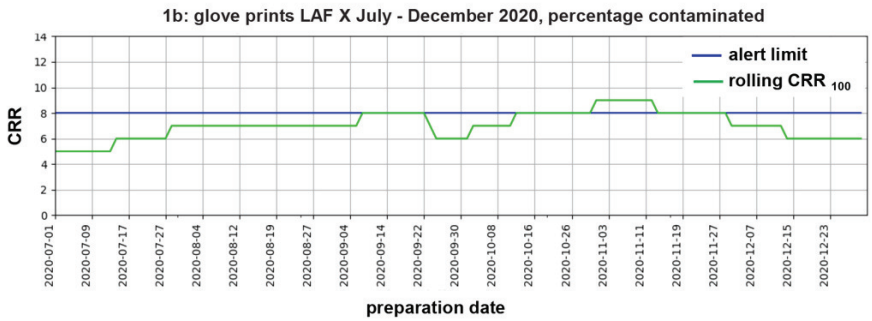
A rolling CRR_{100} diagrams of each kind of MM of each LAF/SC updated regularly

If a rolling CRR_{100} exceeds over the reference value + 2% (percentage point), during one month or longer, actions are needed



Sample history (1a) and percentage contaminated (1b).





Risk identification

The exact relationship between the results of APS and MM and the risk of non-sterility is not known.

Therefore, to improve sterility assurance, additional research is needed to identify risk sources and quantify the risk of non-sterility and how to mitigate this risk.

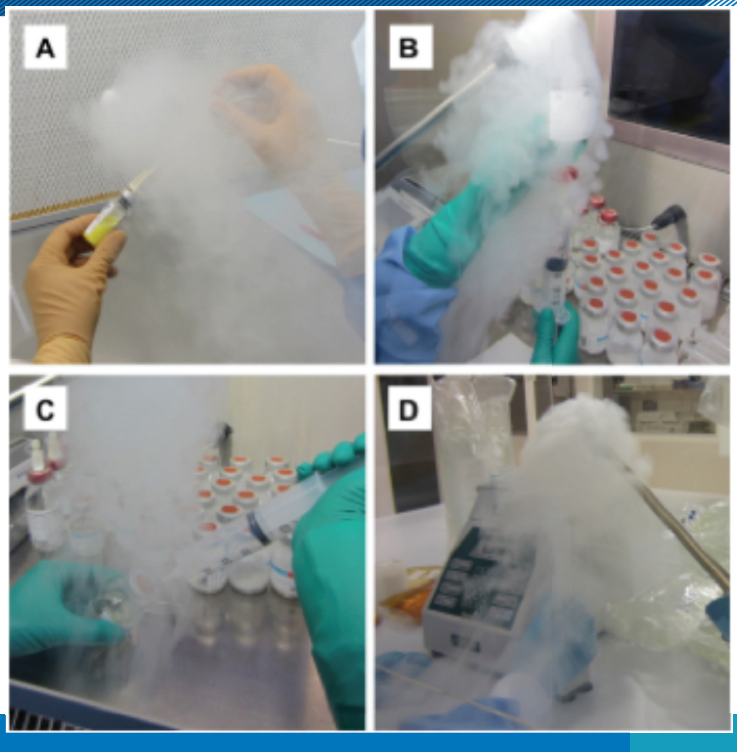
Aseptic handling: risk sources of non sterility

Work Area: air, worktop LAF/SC and wall and ceiling LAF/SC;

Transfer of Materials: materials with a sterile surface and materials with a non-sterile surface;

Operator: Operators' hands, Operators' forearms and working procedures.

Visualization of risks



Transfer and desinfection of materials

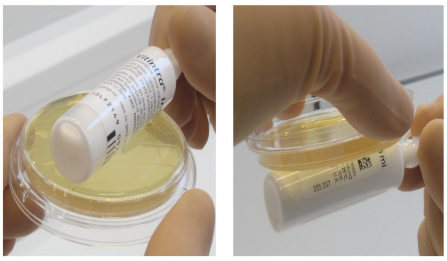
Transfer is not standardised

Two types of materials

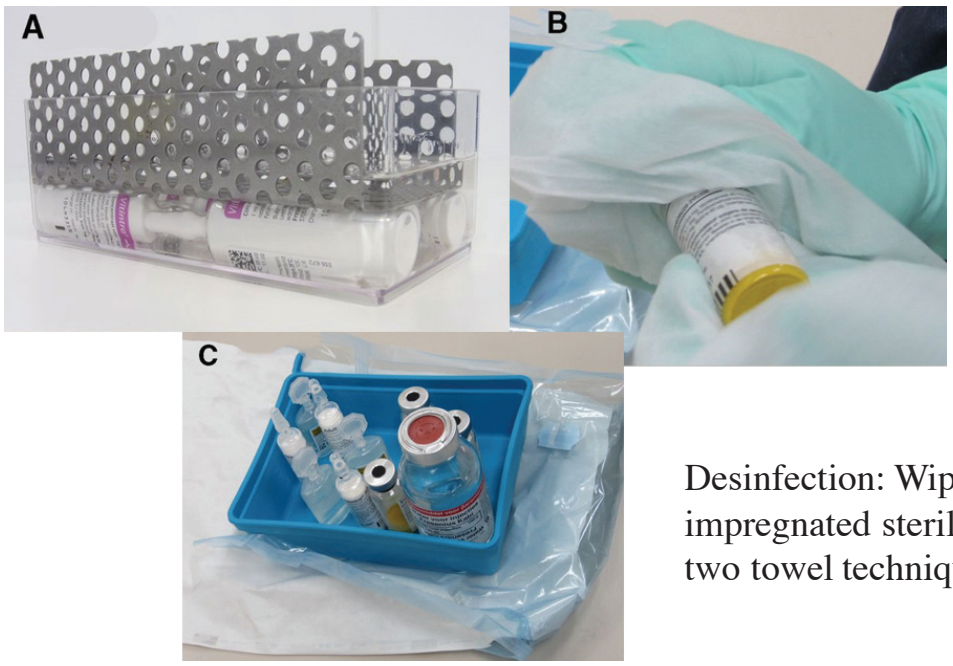
- Sterile materials wrapped and sterilised in an outer layer

- Materials with a non sterile surface like ampoules, vials

Determination of bioburden: contact plates



Desinfection procedures

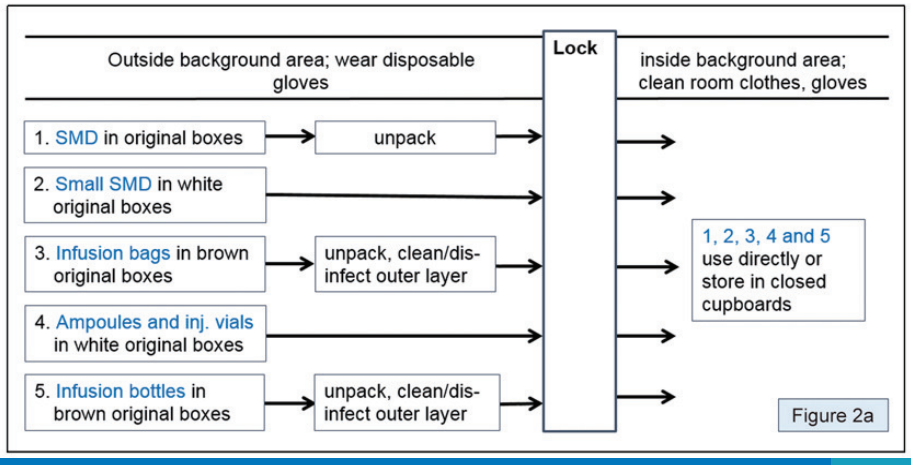


Desinfection: Wiping with alcohol impregnated sterile wipes and two towel technique

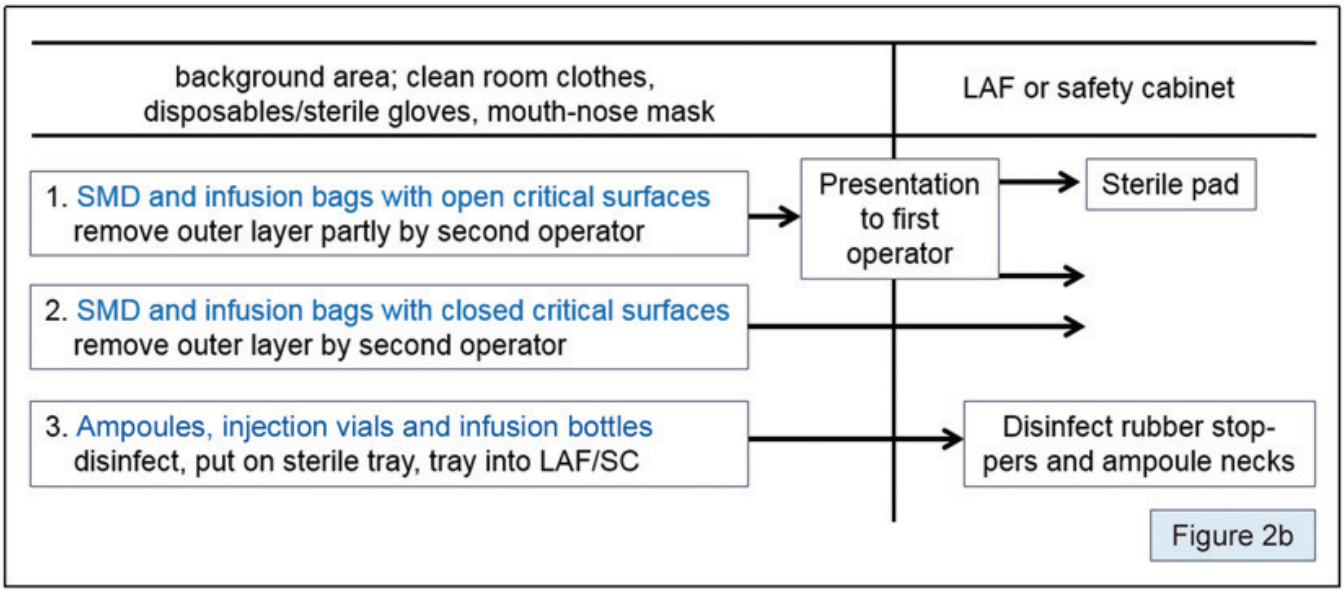
Transfer into background class D

Transfer: Unpack from box in front of material lock and keep sterile materials in original packaging and open in front of LAF

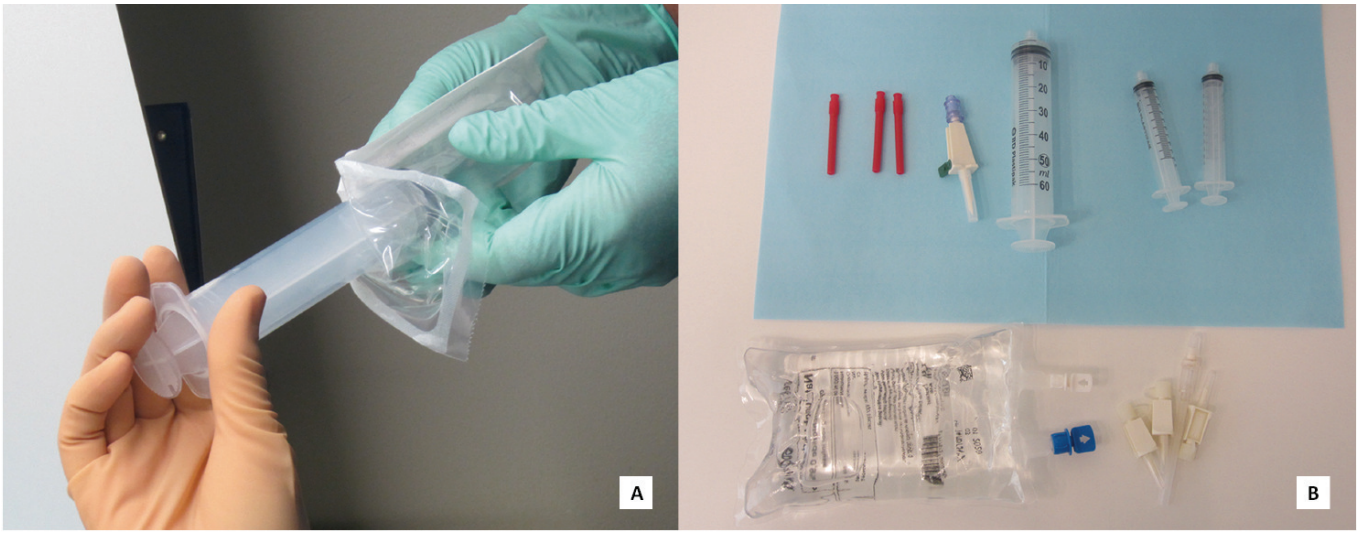
Non sterile materials like ampoules: transfer in their box into background area



Transfer into working area class A



Transfer example and location in working area



Sources of risk of non-sterility during aseptic handling.

code	Description
A	Air in LAF/SC
B	Worktop LAF/SC
C	Wall and ceiling LAF/SC
D1	Materials with a sterile surface (tubes, syringes, needles, infusion bags etc.)*
D2	Critical spots such as the opening of tubes, syringe tips, needles, septa of infusion bags
E1	Materials and equipment with a non-sterile surface (ampoules, vials, bottles etc.)*
E2	Critical spots such as vial stoppers, ampoule necks
F	Operators' hands
G	Operators' forearms
H	Working procedure

Risk assessement

	sources of risk	risk reduction in 10 hospital pharmacies	remaining risk in 10 hospital pharmacies	S	O	D	RPN
A	Air	LAF/SC checked once or twice a year by particle measurements, airflow velocity and HEPA filter integrity in at rest condition; daily monitoring by settle plate	chance of environment around work zone at rest not in accordance with Grade A air	5	1	2	10
			materials and equipment disturb the unidirectional airflow and can block first air at critical spots	5	2	3	30
B	Worktop LAF/SC	disinfection before each work session by wiping with ethanol or isopropyl alcohol 70% impregnated wipes; disinfection is registered in a log; daily monitoring by contact plate	contamination by materials used during preparation	5	3	3	45
C	Wall and ceiling LAF/SC	daily surface disinfection by wiping with ethanol or isopropyl alcohol 70% impregnated wipes; disinfection is registered in a log	unlikely	5	1	1	5
D1	Materials with a sterile surface (sterile devices and infusion bags)	unwrap in front of LAF/SC	parts of outer layer inside LAF/SC	5	2	3	30
D2	Critical spots (syringe tips, needles and the opening of tubes)		contact of critical spots with the worktop of LAF/SC	5	4	3	60
E1	Materials and equipment with a non-sterile surface (ampoules, vials, bottles)	disinfection by wiping with ethanol or isopropyl alcohol 70%	high surface bioburden before disinfection	5	3	3	45
			disinfection improperly done	5	4	4	80
			recontamination of disinfected materials	5	3	3	45
E2	Critical spots (vial stoppers and ampoule necks)	additional disinfection in LAF/SC by wiping with sterile ethanol or isopropyl alcohol 70%	additional disinfection improperly done	5	3	4	60
F	Operators hands	sterile gloves, which are changed at least every hour; daily monitoring by glove print 5 fingers	glove damage	5	2	3	30
			surface contamination during putting on gloves	5	2	3	30
			surface contamination during preparation	5	3	3	45
G	Operators forearms	cleanroom clothing which is changed every day	surface contamination of the worktop	5	2	3	30
H	Working procedure	working with two operators; SOP; operators trained in aseptic techniques by broth simulations every year; process validation by broth simulation [8]	deviation from SOPs	5	3	3	45
			touching critical spots	5	4	4	80
			a. crossflow: blocking first air at critical spots	5	2	3	30
			or b. downflow: blocking first air at critical spots	5	3	3	45

Risk control

	sources of risk and risk reduction in 10 hospital pharmacies	remaining risk in 10 hospital pharmacies	S	O	D	RPN	additional risk reduction (1)	remaining risk	S	O	D	RPN	additional risk reductions (2)	remaining risk	S	O	D	RPN
A	**Air;** LAF/SC checked once or twice a year by particle measurements, airflow velocity and HEPA filter integrity in at rest condition; daily monitoring by settle plate	chance of environment around work zone at rest not in accordance with Grade A air	5	1	2	10	non-viable particle counting in work zone at rest at least quarterly	unlikely	5	1	1	5						
		materials and equipment disturb the unidirectional airflow which can result in blocking first air at critical spots	5	2	3	30	correct position of materials after investigations by airflow visualization in worst case situation	incorrect position of materials still exists	5	2	2	20	position of materials is regularly audited	unlikely	5	1	1	5
B	**Worktop LAF/SC;** disinfection before each work session by wiping with ethanol or isopropyl alcohol 70% impregnated wipes; disinfection is registered in a log; daily monitoring by contact plate	contamination by materials used during preparation	5	3	3	45	disinfection before each new prepared dosage form	risk of no proper disinfection still exists	5	2	2	20	disinfection is regularly audited	unlikely	5	1	1	5
C	**Wall and ceiling LAF/SC; d**aily surface disinfection by wiping with ethanol or isopropyl alcohol 70% impregnated wipes; disinfection is registered in a log	unlikely	5	1	1	5												

Questionnaire to be used in an audit

		critical (C)	judgment
	Operators clothing and hygiene		
1	Wrist watches, jewellery and cosmetics should not be worn		
2	Wash hands		
3	Disinfect hands		
4	Change clothes; prevent contact between cleanroom clothes and floor		
5	Wear face mask and gloves before entering background area		
6	Disinfect hands during each glove change		
	Set up		
7	Check background area		
8	Switch on LAF/SC on working mode		
9	Disinfect by wiping inside LAF/SC		
10	Wipes well impregnated		
11	Register disinfection in a log		
12	Collect all necessary materials for the preparation		
13	Remove tear off caps		
14	Check collected materials in according to the preparation document	C	
15	Sign the preparation document for collecting and controlling the materials		
16	Collecting and controlling done by different operators	C	
17	Materials with a non-sterile surface: disinfection by wiping in accordance with disinfection procedure	C	
18	Wipes well impregnated		
19	Disinfected materials are placed in a sterile tray on a sterile surface (see [1], figure 1)		
20	Disinfect gloves regularly		
	Set up by primary operator		
21	Remove gloves and disinfect hands		
22	Put on sterile sleeves (outside LAF/SC)		
23	Put on sterile gloves without chance of outside contamination	C	
24	Check sterile gloves after putting on for tears or gaps		
	Transfer materials into LAF/SC		
25	Secondary operator: disinfect gloved hands, unwrap sterile pad partly in front of LAF/SC and present sterile site to primary operator		
26	Primary operator: place sterile pad on the right place inside LAF/SC		
27	Materials with a sterile surface Secondary operator: unwrap partly in front of LAF/SC and present sterile site to primary operator	C	
28	No wrapped surface inside LAF/SC		
29	Primary operator: places SMD with open critical spots (open tubes, syringes and needles) on the sterile pad and full capped SMD as well as infusion bags outside the sterile pad (see chapter 3 figure 1)	C	
30	Secondary operator: present tray with disinfected materials to primary operator		
31	Primary operator: disinfected materials inside LAF/SC. Beware of: • keeping first air on critical spots • enough space to perform the preparation		
32	Primary and secondary operator work as a team		
	Preparation (primary operator)		
33	Open settle plate		
34	Enough distance between work location and LAF/SC front		
35	Unload the tray with disinfected materials; keep the tray inside LAF/SC for sampling waste during preparation		
36	Disinfect vial stoppers and ampoule necks (critical spots) in accordance with disinfection procedure by wiping; wait at least 30 sec before puncturing stopper	C	
37	Keep critical spots from sterile materials and materials with a non-sterile surface always in first air		
38	Execute aseptic manipulations in first air	C	
39	Enough distance between fingers and critical spots on materials	C	
40	Non-touch working technique	C	
41	Glove disinfection every 15 minutes	C	
42	Keep SMD with open critical spots on the sterile pad; no other materials on this pad	C	
43	Collect waste in empty tray		
44	Keep hands inside LAF/SC		
45	Keep LAF/SC well organized		
46	No social talks during preparation		
	After preparation		
47	Primary and secondary operator: transfer finished product outside LAF/SC		
48	Secondary operator: label product immediately after transfer	C	
49	Primary operator: Surface monitoring by contact plate (contact time at least 3 sec)		
50	Primary operator: glove print 5 fingers (contact time each finger at least 3 sec)		
51	Make LAF/SC empty and disinfect worktop by wiping		
52	Glove change or glove disinfection if a next preparation will follow		

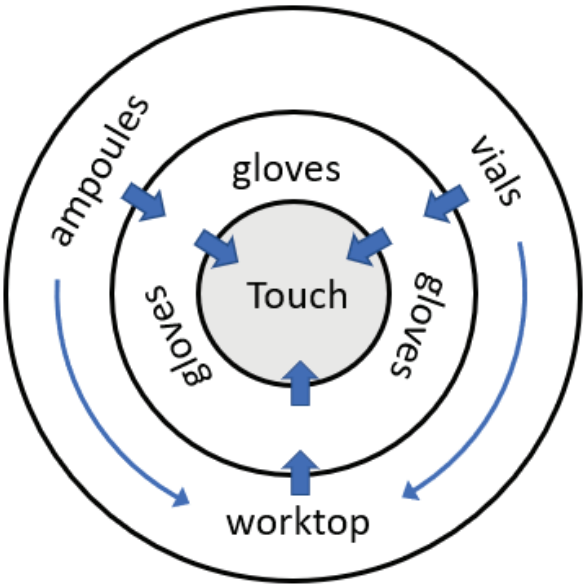
Risk assessment in daily practice of 7 hospitals

Hospital pharmacy 3		risk assessment after initial audit						results after final assessment					
	sources of risk	risk reduction	remaining risk after first audit	S	O	D	RPN 1	additional risk reduction	remaining risk	S	O	D	RPN 2
A	Air	SC checked once a year by particle measurements, airflow velocity and HEPA filter integrity in at rest condition; daily air sampling by settle plate	1. chance of environment around work zone at rest not in accordance with Grade A air	5	1	2	10	no	chance of environment around work zone at rest not in accordance with Grade A air	5	1	2	10
			2. materials and equipment disturb the unidirectional airflow and can block first air at critical spots	5	2	3	30	no	materials and equipment disturb the unidirectional airflow and can block first air at critical spots	5	2	3	30
B	Worktop SC	disinfection before each work session by wiping with ethanol 70% impregnated wipes; daily monitoring by contact plate	1. disinfection forgotten; contamination by materials used during preparation	5	3	3	45	disinfection at the beginning of a working day is registered in a log	contamination by materials used during preparation still excists	5	3	2	30
C	Wall and ceiling SC	daily surface disinfection by wiping with ethanol 70% impregnated wipes	1. disinfection forgotten	5	1	2	10	disinfection at the beginning of a working day is registered in a log	unlikely	5	1	1	5
D1	Materials with a sterile surface (sterile devices and infusion bags)	unwrapping in front of SC	1. contaminated outer layer	5	4	2	40	all operators in background area wear disposable gloves; original boxes are unpacked in front of lock with gloved hands; materials are used directly and/or stored in closed cupboards	transfer and storage is not audited	5	1	2	10
			2. parts of outer layer inside SC	5	3	2	30	aseptic transfer is regularly audited and both operators correct each other	no aseptic transfer into SC by presentation	5	2	1	10
D2	Critical spots (syringe tips, needles and the opening of tubes)		1. contact of critical spots with the work top of SC	5	4	3	60	putting down syringes, needles and open tubes on a sterile pad in SC; use of sterile pad is regularly audited; both operators correct each other	unlikely	5	1	1	5
E1	Materials and equipment with a non-sterile surface (ampoules, vials, bottles)	disinfection by wiping with ethanol 70% impregnated wipes	1. high surface bioburden before disinfection	5	3	3	45	ampoules and vials are transferred in their original boxes into the background area; materials are used directly and/or stored in closed cupboards	no periodical surface bioburden determination before disinfection; transfer and storage is not audited	5	1	3	15
			2. disinfection improperly done	5	4	4	80	thorough wiping by completely impregnated wipes; disinfection is regularly audited and both operators correct each other	no validated disinfection procedure; no regular surface monitoring of disinfected materials	5	2	3	30
			3. recontamination of disinfected materials	5	4	2	40	measures to prevent recontamination; measures to prevent changing disinfected and non-disinfected materials; measures are regularly audited and both operators correct each other	unlikely	5	1	1	5
E2	Critical spots (vial stoppers and ampoule necks)	additional disinfection in SC by wiping with sterile ethanol 70%	1. additional disinfection improperly done	5	3	4	60	precisely described and improved second disinfection technique; additional disinfection is regularly audited; both operators correct each other	still no assurance of a sterile surface	5	1	2	10
F	Operator's hands	sterile gloves, which are changed at least every hour; daily glove print by settle plate	1. glove damage	5	3	3	45	gloves integrity is tested immediately after putting them on and during processing; glove handling is regularly audited; both operators correct each other	unlikely	5	1	1	5
			2. surface contamination during putting on gloves	5	3	3	45	no	surface contamination during putting on gloves	5	3	3	45
			3. surface contamination during preparation	5	4	2	40	no	surface contamination during preparation	5	4	2	40
G	Operator's forearm	wearing cleanroom clothing which is changed every day	1. surface contamination of the worktop	5	3	2	30	operator wears sterile sleeves which are changed after every session	unlikely	5	1	1	5
H	Working procedure	working with two operators during processing; SOPs; operators trained in aseptic techniques; aseptic process simulation with a broth solution	1. deviation from SOPs	5	3	3	45	accurate and up to date SOPs (enough details, univocal text); working according to SOPs is regularly audited; both operators correct each other	unlikely	5	1	1	5
			2. touching critical spots	5	4	4	80	additional training in non-touch working; non-touch working is regularly audited; both operators correct each other	chance of touch still excists	5	2	2	20
			3. SC (downflow), blocking first air at critical spots	5	3	3	45	prevention of blocking first air is regularly audited; both operators correct each other	chance of blocking first air still excists	5	2	1	10
							780						290

Conclusion from RA, RC and audit

- Systematic and science-based reduction of the risks of non-sterility can be done by using a checklist with risk reducing measures and an RA and RC template.
- Prospectively, the relevance of each risk reducing measure can be demonstrated by RPN calculations.
- Of all risk reducing measures, a yearly audit of all operators has the greatest impact on reducing the risk of non-sterility.
- Microbiological controls are an important part of the overall assurance of product quality.

Transfer of micro organisms



Research

Sterility assurance of aseptic handling: basics, improvements and recommendations
Frits Boom

https://research.rug.nl/en/publications/sterility-assurance-of-aseptic-handling-basics-improvements-and-r

https://research.rug.nl/files/569358418/Complete_thesis.pdf

Prerequisite for the future: EDUCATION

Is the new generation ready for the future challenges?

International Journal of Pharmaceutics 514 (2016) 11–14

Contents lists available at ScienceDirect

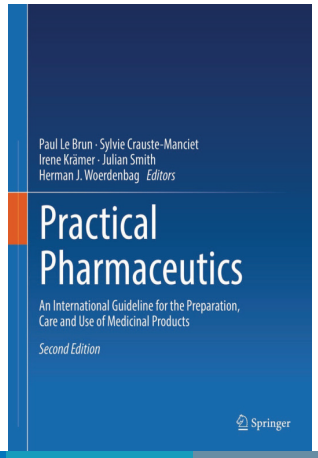
International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Commentary

Pharmacy preparations: Back in the limelight? Pharmacists make up your mind!☆

Daan J.A. Crommelin[a,*], Yvonne Bouwman-Boer[b]



Current curricula pay too little attention to technology

Competences and skills

Product knowledge <-> Product care <-> Patient care

Koliko stane kakovost?

What is the price of Quality?

dr. Mateja Tršan, mag. farm., spec., UKC Ljubljana

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KOLIKO STANE KAKOVOST?

dr. Mateja Tršan, mag.farm., spec.
Oddelek za zagotavljanje in kontrolo kakovosti
Lekarna UKCL

1

UVOD

Magistralna in maloserijska sterilna proizvodnja v bolnišnični lekarni je po zahtevah glede kakovosti **podobna farmacevtski industriji**, pomembno pa se **razlikuje** glede **proizvodnih pogojev, opreme in števila osebja...**

...in finančnih sredstev.

8

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VSEBINA

- ❑ Prostori
- ❑ Oprema
- ❑ Osebje
- ❑ Vhodne surovine
- ❑ Ovojnina
- ❑ Čiščenje in dezinfekcija
- ❑ Ocena tveganja
- ❑ Procesna validacija
- ❑ Dokumentacija
- ❑ Monitoring – analiza trendov

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PROSTORI našega ekosistema

4 čisti prostori (Clean room)

kvalifikacija prostora
1x letno
4x 900 €
3.600 €

- Oddelek za pripravo parenteralnih raztopin
- Oddelek za popolno parenteralno prehrano
- Oddelek za pripravo zdravil iz nevarnih učinkovin
- Oddelek za pripravo pripravkov za oči in terapijo bolečine

10

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OPREMA v ekosistemu

Oprema za proizvodnjo:

- 7 brezprašnih komor - LAF
- 1 biološko varna komora - BVK

kvalifikacija komore
1x letno
8x 360 €
2.880 €

11

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OPREMA

Oprema za kontrolo kakovosti:

kalibracija
1x 240 €
240 €

- Vzorčevalnik zraka – SAS duo
- Aparat za testiranje bakterijskih endotoksinov – Endosafe PTS™

validacija
3x 890€
2.670 €

12

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PROSTORI IN OPREMA

Oprema	Količina	Stroški
Prostori	4	3.600,00 €
Komore (LAF, BVK)	8	2.880,00 €
SAS-duo	1	240,00 €
Endosafe PTS	3	2.670,00 €
Skupaj		**9.390,00 €**

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OBSEG DELA za ohranjanje ekosistema

VZORCI

vsi vzorci (izdelki in prostori)	9.875
mikro vzorci (izdelki in prostori)	**7.767**
mikro izdelki	**3.899**
mikro prostor	**3.868**
vse analize skupaj	16.662

OPREMA

pH meter	3.319
denzitometer	208
titrator	2.527
spektrofotometer	48
HPLC	616
polarimeter	76
tehtnica	846
vodna kopel	68
endosafe	**687**
vzorčevalnik zraka	**132**
luminometer	**500**
skupaj	9.027

PREGLED ANALIZ PO SKUPINAH STERILNIH IZDELKOV

Parenteralne raztopine in sterilni izdelki za zunanjo uporabo
- vsaka serija sterilnost, apirogenost (6-7 serij na dan)
- dnevno: zrak LAF – izpostavitev
- mesečno: odtisi površin, zrak aktivno

Popolna parenteralna prehrana in citostatična terapija
- dnevno: zrak LAF – izpostavitev, 2 izdelka na testiranje sterilnosti
- tedensko: odtisi rok
- mesečno: odtisi površin, zrak aktivno

Očesni izdelki in terapija bolečine
- dnevno: zrak LAF – izpostavitev, izdelki po protokolu (cca 2/dan)
- mesečno: odtisi površin, zrak aktivno

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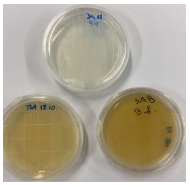
MATERIALI

Sedimentacijske plošče s TSA

Zrak - izpostavitev - na snažnost - **LAF**
2.424x 3,89 €
9.429,36 €

RODAC plošče (Replicate Organism Detection And Counting) s tremi različnimi gojišči:
- Bakterije
  - TSA (Tryptic Soy Agar)
- Glive
  - Sabouraud
  - G18 gojišče - Dichloran glycerol agar

Bakteriološki nadzor zraka **s presesavanjem**
44 x 7,78 €
342,19 €



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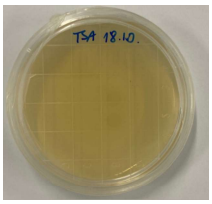
MATERIALI

RODAC TSA za površino



Snažnost površin z odtisi **RODAC TSA**
804 x 7,78 €
6.255,12 €

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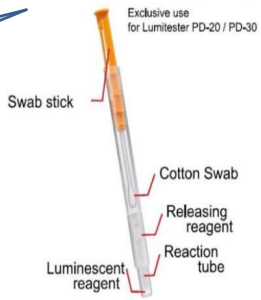
MATERIALI

Lumitester PD 30

Bris površine
300 x 2,85 €
855 €

LuciPac Pen



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FARMACIA, 2019, Vol. 67, 6
https://doi.org/10.31925/farmacia.2019.6.11 ORIGINAL ARTICLE

THE ATP BIOLUMINESCENCE METHOD: AN ALTERNATIVE APPROACH FOR MONITORING CLEANLINESS IN HOSPITAL PHARMACY CLEANROOMS

MATEJA TRŠAN [1]*, KATJA SEME [2], STANKO SRČIČ [3]

Evaluation of ATP bioluminescence for monitoring surface hygiene in a hospital pharmacy cleanroom

Mateja Tršan[a,*], Matej Vehovc[a], Katja Seme[b], Stanko Srčič[c]

[a] University Medical Centre Ljubljana Pharmacy, Quality Assurance and Quality Control Department, Zaloška cesta 7, SI-1000 Ljubljana, Slovenia
[b] University of Ljubljana, Faculty of Medicine, Institute of Microbiology and Immunology, Zaloška cesta 4, SI-1000 Ljubljana, Slovenia
[c] University of Ljubljana, Faculty of Pharmacy, Department of Pharmaceutical Technology, Aškerčeva cesta 7, SI-1000 Ljubljana, Slovenia

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MATERIALI

Endosafe PTS™

Določanje vsebnosti bakterijskih endotoksinov

Kromogena kinetična metoda

BET
687 x 50 €
34.350,00€

20

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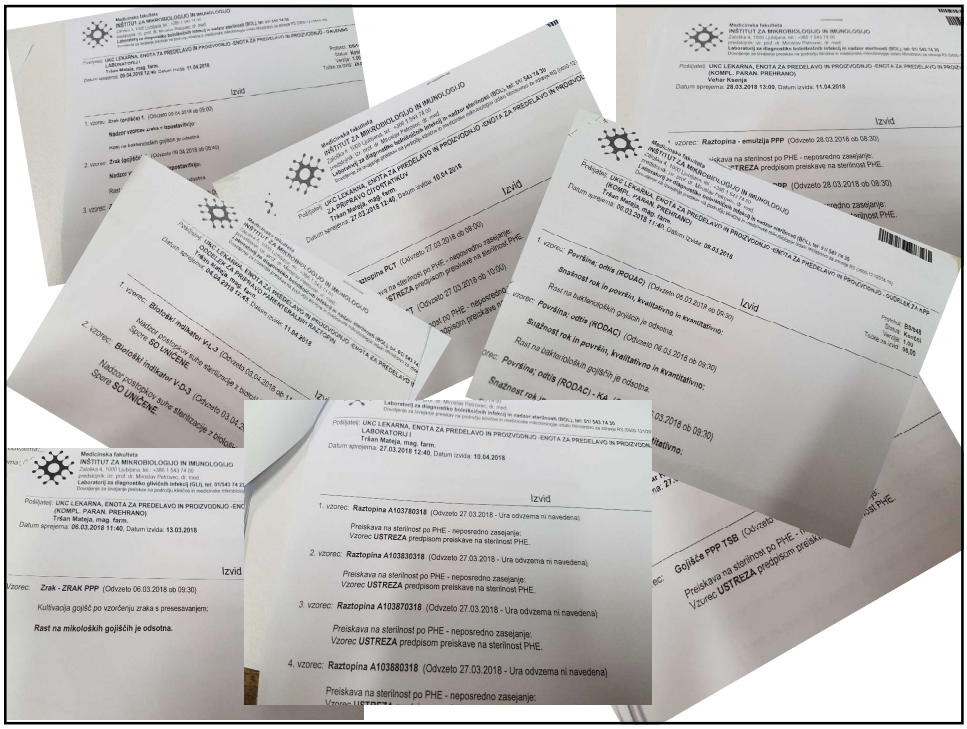

LETNI STROŠKI ZA MIKROBIOLOŠKE ANALIZE

Storitev	Količina	Stroški
Sterilnost Ph.Eur. - membranska filtracija	126	3.191,68 €
Sterilnost Ph.Eur. - neposredno zasejanje	2.638	16.705,66 €
Preiskava na snažnost	122	948,79 €
Identifikacija **MALDI -TOF**	686	7.621,46 €
Kontrola snažnosti površin z odtisi **RODAC**	804	6.252,71 €
Zrak - izpostavitev - na snažnost	2.424	9.425,72 €
Sterilnost različnih predmetov	18	119,99 €
Kultivacija gojišč po vzorčenju zraka s presesavanjem	42	793,25 €
Bakteriološki nadzor **zraka s presesavanjem**	44	342,19 €
Plesni-identifikacija 2 (+ mikroskopska preiskava	2	46,42 €
Mikroskopska preiskava, različna barvanja	6	17,06 €
Glive - kultivacija in izolacija	4	57,28 €
Kontrola postopkov sterilizacije z **biološkimi indikatorji**	220	1.466,52 €
Antibiogram, 6-12 antibiotikov	2	20,00 €
Glive - mikroskopska preiskava	52	231,09 €
Skupaj	**7.190**	**47.239,83 €**

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LETNI STROŠKI ZA MIKROBIOLOŠKE ANALIZE

Storitev	Količina	Stroški
Test **BET**	687	34.350,00 €
ATP površine	300	855,00 €
ATP voda	200	570,00 €
Skupaj	**1.187**	**35.775,00 €**

23

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LETNI STROŠKI SKUPAJ

Kvalifikacija prostorov in opreme
9.390 €

Letni stroški za mikrobiološke analize (IMI+UKC)
83.000 €

Skupaj 92.390 €
cca. 100.000 €

24

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- ☑ **upoštevanje standardov in smernic**
- ☑ uporaba **kakovostnih surovin**
- ☑ uporaba **standardiziranih postopkov**
- ☑ oprema
- ☑ validacija, kvalifikacija, certifikacija
- ☑ vzorčenje
- ☑ materiali

- ❑ **čisti prostori**
- ❑ osebje – potencialen vir kontaminacije
- ❑ osebje – izobraževanje

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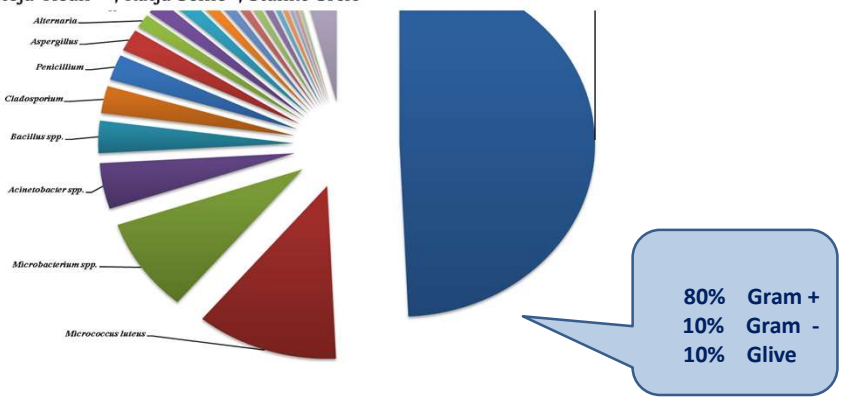
MIKROBIOTA našega ekosistena

Original article

The environmental monitoring in hospital pharmacy cleanroom and microbiota catalogue preparation

Mateja Tršan [a,*], Katja Seme [b], Stanko Srčič [c]



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človeško telo:
10 trilijonov celic in
100 trilijonov bakterijskih celic razmerje:
1:10

intrinzični in
ekstrinzični
faktorji

27

Hvala za pozornost

28

Vpliv racionalizacije dela in stroškov na kakovost in ceno izdelka

The impact of labor and cost rationalization on product quality and price

Simona Mitrović, mag. farm., spec., Lidija Vrbovšek, mag. farm., spec., Simona Mohar Karakatič, mag. farm., spec.,

Vpliv racionalizacije dela in stroškov na kakovost

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

Simona Mitrovič, mag.farm.,spec.

SPLOŠNA BOLNIŠNICA MURSKA SOBOTA
RAKIČAN, Ulica dr. Vrbnjaka 6, 9000 Murska Sobota

Simona Mohar Karakatič, mag.farm.,spec.

CELJSKE LEKARNE

Lidija Vrbovšek, mag.farm.,spec.

Simpozij Sekcije bolnišničnih farmacevtov
7.11.2023, Ljubljana

Kako zmanjšati stroške v aseptiki?

VRSTE STROŠKOV /na dan		Lekarna UKCL	Lekarna SBMS	Lekarna Celje		
		24 dni /mesec (+sobota)	260 dni = 21,6 dni/mesec	260 dni = 21,6 dni/mesec		
STERILNA OBLEKA	cleanroom obleka: 2+1 oseba	57,82 €	30 - 120 €	31,09 €	STERILNA OBLEKA	Sterilni: plašč, maska, rokavice, obujki, maska, (podkapa)
	maska, kapa, rok (2 para): 2+1 oseba	10,00 €	5 - 15 €			
LETNA VLIDACIJA	PROSTOR +BVK : 500+400=800 eur	2,50 €	4 €	1,92 €	VALIDACIJA	Komora, (prostor)
MIKRO PROSTOR	prostor+laf+odtisi+spore+presesavanje zraka: 171 eur/mesec	8,55 €	9,50 €	12,94 €	MIKROBIOLOGIJA	TSA, SDA gojišča (za prostor, komoro in osebje) in analiza vzorcev
MIKRO VZORCI	60 vzorcev	26,72 € /dan	/	4,83 €	STERILIZACIJA	Letna validacija (avtoklav sterilizator), rokavi za sterilizacijo, indikatorski trakovi, kemični indikatorji (termalog S, Bowie Dick)
ČIŠČENJE obleka	1 oseba: cleanroom obleka, kapa, maska, rokavice	21,08 €	30 €	57,18 €	ČIŠČENJE	Sterilni alkohol, peroksid, nevtralni detergent, biocid A, mopi, suhe krpice, incidin, biocidni predpražniki, obleka (1x tedensko)
ČIŠČENJE IN RAZKUŽVANJE TAL	biocidni predpražnik, dezinfek sredstva in pripomočki	11,37 €	19 €			
ČIŠČENJE IN RAZKUŽVANJE POVRŠIN + VNOS MATERIALA	sterilni etanol v razpršilu+ krpice+ etanol 500ml KC-I	34 €				
POTROŠNI MATERIAL	Clean room brizge, igle, filtri cca= 20 eur	20 - 40 €	5 - 10 €	48,51 €	POTROŠNI MATERIAL	Brizge, igle, filtri
	skupaj	193 - 213 €	102,5 - 207,5 €	156,47 €		
PRIMERJAVA	IZDELANO ŠT. PRIPRAVKOV / dan	67-100 kd / dan	5 - 50 kd / dan	11 kd / dan		
	CELOKUPNI STROŠEK / kd	3,2 € - 2,13 € / kd	41,5 € - 4,15 € / kd	6,99 € / kd Če ZZZS ne bi pokril stroškov zaščitne opreme in potrošnega materiala: 14,22€ / kd		

Vpliv racionalizacije dela in stroškov

Organizacija naročanja = 1x vstop v aseptiko = nižja cena oblačenja

Centralizacija dela = večje število pripravkov = porazdelitev stroškov

Stroški potrošnega materiala in dezinficiensov = clear pack = kvaliteta

Hvala za pozornost!

1. Pacienti z vso pravico pričakujejo, da bodo zdravila kakovostna, varna in učinkovita ne glede na mesto priprave = preskrbljenost prebivalstva = Focus on patient safety
2. Reasons for preparation: therapeutic need and registered product not available
3. Ali je določila in interpretacijo GMP in Dodatka 1 mogoče zagotoviti v bolnišnični lekarni?
4. Centraliziran postopek priprave sterilnih magistralnih zdravil: regijski centri z visoko stopnjo GMP?
5. Zahteva za vzpostavitev osnovnih zahtev glede aseptične izdelave (minimum): nova DLP?
6. Koliko stane kakovost? Importance of RA and RC!
7. A bright future for hospital preparations lays ahead!!

Is it enough being done to prevent contamination in the cleanrooms?

Ali delamo vse, da preprečimo kontaminacijo v čistih prostorih?

Rufus Smith, MSc, Senior Pharmacist

Is Enough Being Done to Prevent Contamination in Clean Room

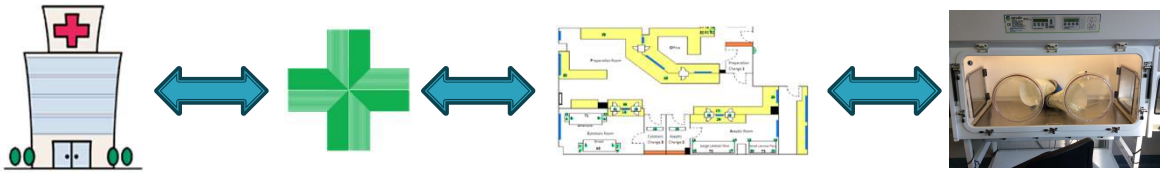
Rufus Smith
Pharmacist

The Nº1 Contamination Risk

- People = 99% of all microorganisms detected in clean rooms
- Person will shed >1,000,000 organisms per hour[1]
- Can't remove the person
- Covering up versus Practicality
  - Time Pressures
  - Staff Comfort – Temp + Sweating
  - Ease of Use
  - Cost per item

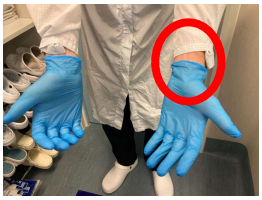
1. J.Agalloco & J.E.Akers Aseptic Processing: A vision of the Future. J.Pharm. Technol. Aseptic Processing s16-23 (2005)

Stepped Approach



Average BSA = $2m^2$
=40,000cm
Shedding 1,000,000 microorganisms per hour

Visible skin = 1cm x 18cm x 2 wrists = 36cm
=900 microorganisms per hour

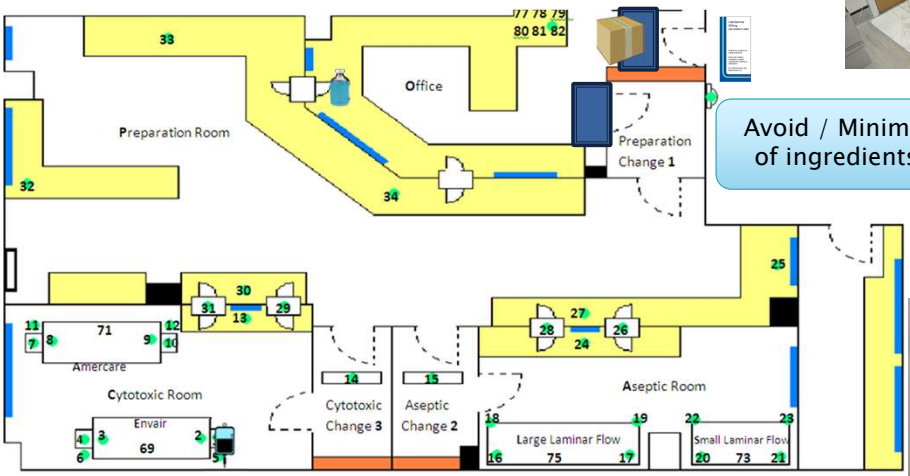


Human Processes

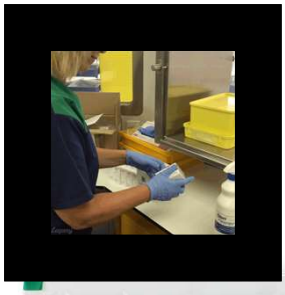
- FDA – "A well-designed aseptic process minimizes personnel intervention. As operator activities increase in an aseptic processing operation, the risk to the finished product sterility also increases"[1]
- Human performance is Variable
  - Training / Coaching / Supervision
  - Monitoring
  - Multiple successful broth tests does not ensure a sterile product

1. Food and Drug Administration, Guideline on Sterile Drug Products Produced by Aseptic Processing (FDA, Rockville, MD, 2004)

Decontamination Through the Unit

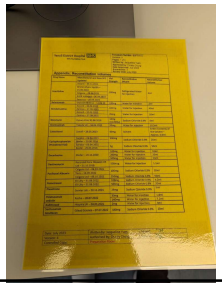


Avoid / Minimise crossover of ingredients & Products



Essentials

- Paper – Prescriptions & Worksheets
- Drive to electronic systems hasn't removed paper
- Practicality of paper versus electronic tablets not the same, yet!
- Cleanroom paper, worth the cost?
- For procedures required in the unit can they be laminated?



Future

- Gas sterilisation
  - Will be more effective than current spray & wipe
  - Increased cost
  - Not full proof, still need existing practices to not strain the system
- Minimizing the human requirement – Compounding Robots?
  - Cost
  - Validation
  - Speed
  - Still need human to load
  - Reliability
  - Very complex process for variety of products

Thank You

Satelitsko predavanje/ Sponsored lecture – Amgen

Pogled na podobna biološka zdravila: zdravilo BEKEMV/ A view on biosimilars: BEKEMV

Tomislav Laptoš, mag. farm., spec.

Pogled na podobna biološka zdravila: zdravilo BEKEMV

A view on biosimilars: BEKEMV

Simpozij Sekcije bolnišničnih farmacevtov – 07. 11. 2023

Tomi Laptoš, mag. farm., spec.
UKC Ljubljana, Lekarna

Razkitje

Avtor nima navzkrižja interesov.

Predavanje je sponzoriralo družba Amgen. Sponzor ni posegal v vsebino predavanja.

Izjava o omejitvi odgovornosti

Sponzor predavanja je družba Amgen.

Predstavljene terapevtske sheme in pristopi zdravljenja so izbira lečečega zdravnika.

Družba Amgen priporoča uporabo svojih zdravil le v skladu z zadnjim odobrenim Povzetkom glavnih značilnosti zdravila (SmPC).

Ekulizumab

Indikacije

- Paroksizmalna nočna hemoglobinurija – PNH
- Atipični hemolitično-uremični sindrom – aHUS
- Refraktarna generalizirana miastenija gravis
- Specifične oblike nevromielitisa vidnega živca

Mehanizem delovanja

- Vezava na beljakovino humanega komplementa C_5 in zaviranje aktiviranja terminalnega komplementa → intravaskularno hemolizo, trombotično mikroangipatijo, ipd.

Farmacevtska oblika

- Koncentrat za raztopino za infundiranje

Povzetek glavnih značilnosti zdravila Soliris - https://www.ema.europa.eu/

Podobna biološka zdravila včasih

- Razkorak v percepiji (glede na male molekule)
- Nezaupanje v stroki
- Pomanjkanje kliničnih izkušenj

Deležniki

- Deležniki z izkušnjami na področju bioloških zdravil
- Ustrezna analizna preskušanja
- Regulatorni vidiki

https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview
https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars
https://www.jazmp.si/humana-zdravila/podobna-bioloska-zdravila/

Kje dobiti osnovne informacije?

https://www.jazmp.si/humana-zdravila/podobna-bioloska-zdravila/
https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_sl.pdf

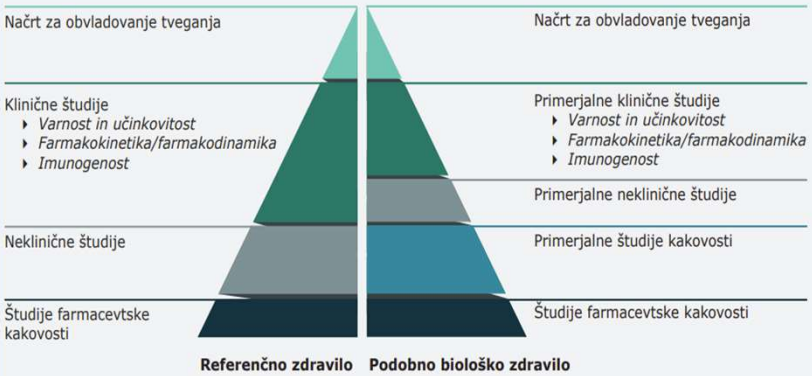
Značilnosti podobnih bioloških zdravil

Preglednica 1. Značilnosti podobnih bioloških zdravil

Visoka podobnost referenčnemu zdravilu	Podobno biološko zdravilo ima fizikalne, kemijske in biološke lastnosti, ki so zelo podobne lastnostim referenčnega zdravila. Med njim in referenčnim zdravilom lahko obstajajo manjše razlike, ki pa niso klinično pomembne v smislu varnosti ali učinkovitosti.
Odsotnost klinično pomembnih razlik v primerjavi z referenčnim zdravilom	Razlik v doseganju kliničnih izidov ne pričakujemo. Klinične študije, ki so podlaga za odobritev podobnega biološkega zdravila, morajo potrditi, da morebitne razlike ne bodo vplivale na varnost in učinkovitost.
Variabilnost biološko podobnega zdravila je strogo zamejena	Manjša variabilnost je dovoljena izključno, kadar znanstveni dokazi izkazujejo odsotnost njenega vpliva na varnost in učinkovitost podobnega biološkega zdravila. Dopustni razpon variabilnosti za podobno biološko zdravilo, je enak razponu, ki je dovoljen med serijami referenčnega zdravila. Doseže se z zanesljivim proizvodnim postopkom, ki zagotavlja, da imajo vse serije zdravila dokazano kakovost.
Enaki strogi standardi kakovosti, varnosti in učinkovitosti	Podobna biološka zdravila so odobrena na podlagi enako strogih standardov kakovosti, varnosti in učinkovitosti, ki se uporabljajo za katero koli drugo zdravilo.

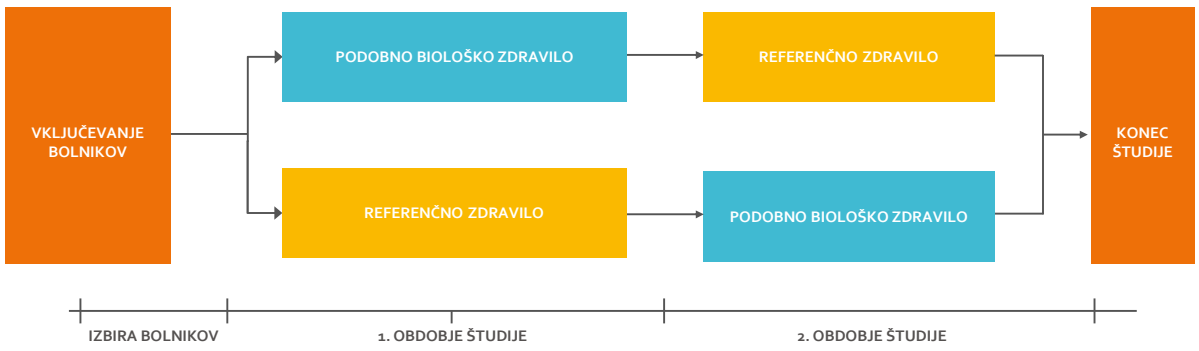
Zahteve za odobritev PBZ

Slika 4. Primerjava zahtevanih podatkov za odobritev podobnega biološkega zdravila v primerjavi z referenčnim zdravilom



https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_sl.pdf

Kako poteka primerjalna klinična študija podobnega biološkega zdravila z referenčnim zdravilom?



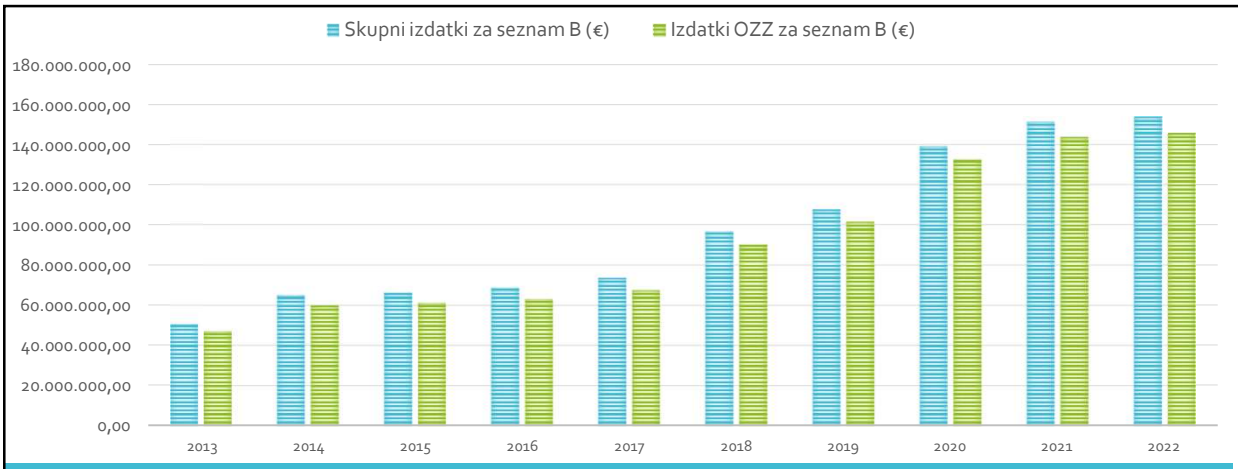
Kulasekararaj A, et al. Poster presented at: American Society of Hematology Annual Scientific Meeting; December 10-13, 2022; New Orleans, USA.

Praksa danes

- Zgodnejše umeščanje (podobnih) bioloških zdravil v protokole
- Več indikacij, ekstrapolacija indikacij
- Veliko kliničnih izkušenj

Finančni vidik

- Naraščajoči stroški (za vsa zdravila)
- Vzdržnost zdravstvenih sistemov
- Vpliv na oblikovanje cen



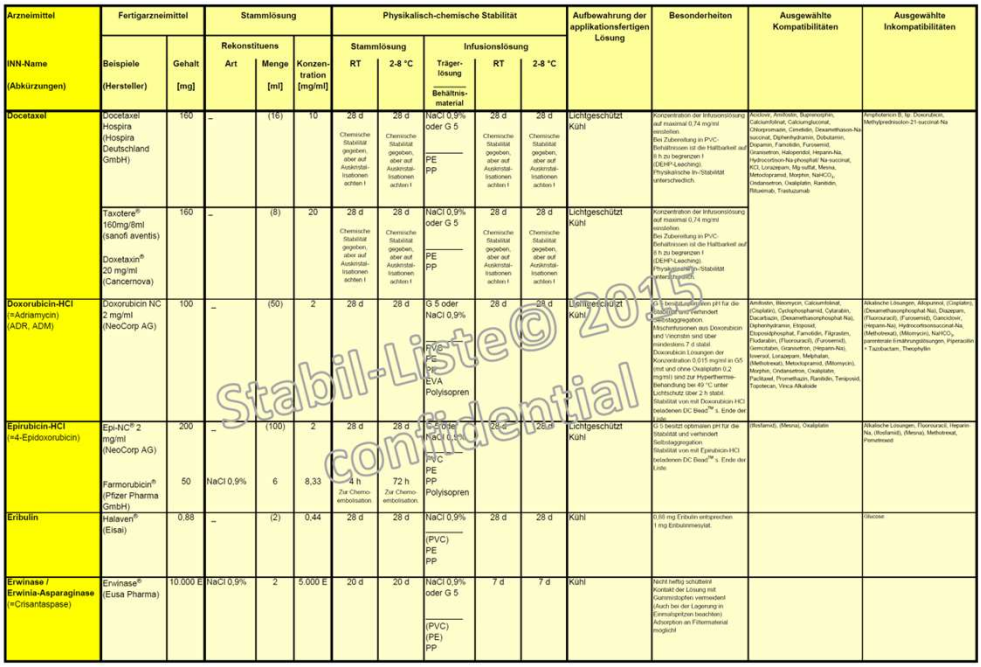
Poraba liste B

Zanesljivost preskrbe

- Časovno breme
- Zamik obravnave
- Povečanje stroškov

Vidik bolnišničnega farmacevta

- Optimicija uporabe (javni razpisi)
- Centralizirana priprava in zagotavljanje sledljivosti (bioloških) zdravil
- Stabilnost osnovne raztopine in farmacevtske pripravka



Arzneimittel	Fertigarzneimittel		Stammlösung			Physikalisch-chemische Stabilität				Aufbewahrung der applikationsfertigen Lösung	Besonderheiten	Ausgewählte Kompatibilitäten	Ausgewählte Inkompatibilitäten
			Rekonstituens			Stammlösung		Infusionslösung					
INN-Name (Abkürzungen)	Beispiele (Hersteller)	Gehalt [mg]	Art	Menge [ml]	Konzentration [mg/ml]	RT	2-8 °C	Trägerlösung / Behältnismaterial	RT	2-8 °C			
Docetaxel	Docetaxel Hospira (Hospira Deutschland GmbH)	160	–	(16)	10	28 d Chemische Stabilität gegeben, aber auf Asepsis/Stabilisationen achten!	28 d Chemische Stabilität gegeben, aber auf Asepsis/Stabilisationen achten!	NaCl 0,9% oder G 5 / PE PP	28 d Chemische Stabilität gegeben, aber auf Asepsis/Stabilisationen achten!	28 d Chemische Stabilität gegeben, aber auf Asepsis/Stabilisationen achten!	Lichtgeschützt Kühl	Konzentration der Infusionslösung auf maximal 0,74 mg/ml einstellen. Bei Zubereitung in PVC-Behältnissen ist die Haltbarkeit auf 6 h zu begrenzen! (DEHP-Leaching). Physikalische In-Stabilität unterschiedlich.	Acidose, Amifostin, Buprenorphin, Calciumfolinat, Calciumgluconat, Chlorpromazin, Cimetidin, Dexamethason-Na-succinat, Diphenhydramin, Dobutamin, Dopamin, Famotidin, Furosemid, Granisetron, Haloperidol, Heparin-Na, Hydrocortison-Na-phosphat/-Na-succinat, KCl, Lorazepam, Mg-sulfat, Mesna, Metoclopramid, Morphin, $NaHCO_3$, Ondansetron, Oxaliplatin, Ranitidin, Rituximab, Trastuzumab	Amphotericin B, Ig, Doxorubicin, Methylprednisolon-21-succinat-Na
	Taxotere® 160mg/8ml (sanofi aventis) / Doxetaxin® 20 mg/ml (Cancernova)	160	–	(8)	20	28 d Chemische Stabilität gegeben, aber auf Asepsis/Stabilisationen achten!	28 d Chemische Stabilität gegeben, aber auf Asepsis/Stabilisationen achten!	NaCl 0,9% oder G 5 / PE PP	28 d Chemische Stabilität gegeben, aber auf Asepsis/Stabilisationen achten!	28 d Chemische Stabilität gegeben, aber auf Asepsis/Stabilisationen achten!	Lichtgeschützt Kühl	Konzentration der Infusionslösung auf maximal 0,74 mg/ml einstellen. Bei Zubereitung in PVC-Behältnissen ist die Haltbarkeit auf 6 h zu begrenzen! (DEHP-Leaching). Physikalische In-Stabilität unterschiedlich.		
Doxorubicin-HCl (=Adriamycin) (ADR, ADM)	Doxorubicin NC 2 mg/ml (NeoCorp AG)	100	–	(50)	2	28 d	28 d	G 5 oder NaCl 0,9% / PVC PE PP EVA Polyisopren	28 d	28 d	Lichtgeschützt Kühl	G 5 benötigt Injektion pH für die Stabilität und verhindert Selbstaggregation. Mischinfusionen aus Doxorubicin und Vincristin sind über mindestens 7 d stabil. Doxorubicin Lösungen der Konzentration 0,015 mg/ml in G5 (mit und ohne Oxaliplatin 0,2 mg/ml) sind zur Hyperthermie-Behandlung bei 49 °C unter Lichtschutz über 2 h stabil. Stabilität von mit Doxorubicin HCl beladenen DC Bead™ s. Ende der Liste.	Amifostin, Bleomycin, Calciumfolinat, (Cisplatin), Cyclophosphamid, Cytarabin, Dacarbazin, (Dexamethasonphosphat-Na), Diphenhydramin, Etoposid, Etoposidphosphat, Famotidin, Filgrastim, Fludarabin, (Fluorouracil), (Furosemid), Gemcitabin, Granisetron, (Heparin-Na), Irinotecan, Lorazepam, Melphalan, (Methotrexat), Metoclopramid, (Mitomycin), Morphin, Ondansetron, Oxaliplatin, Paclitaxel, Promethazin, Ranitidin, Teniposid, Topotecan, Vinca-Alkaloide	Alkalische Lösungen, Alkopurinol, (Cisplatin), (Dexamethasonphosphat-Na), Diazepam, (Fluorouracil), (Furosemid), Ganciclovir, (Heparin-Na), Hydrocortisonsuccinat-Na, (Methotrexat), (Mitomycin), $NaHCO_3$, parenterale Ernährungslösungen, Piperacillin + Tazobactam, Theophyllin
Epirubicin-HCl (=4-Epidoxorubicin)	Epi-NC® 2 mg/ml (NeoCorp AG) / Farmorubicin® (Pfizer Pharma GmbH)	200 / 50	– / NaCl 0,9%	(100) / 6	2 / 8,33	28 d / 4 h Zur Chemoembolisation	28 d / 72 h Zur Chemoembolisation	G 5 oder NaCl 0,9% / PVC PE PP Polyisopren	28 d	28 d	Lichtgeschützt Kühl	G 5 benötigt optimalen pH für die Stabilität und verhindert Selbstaggregation. Stabilität von mit Epirubicin-HCl beladenen DC Bead™ s. Ende der Liste.	(Reviamid), (Mesna), Oxaliplatin	Alkalische Lösungen, Fluorouracil, Heparin-Na, (Reviamid), (Mesna), Methotrexat, Pemetrexed
Eribulin	Halaven® (Eisai)	0,88	–	(2)	0,44	28 d	28 d	NaCl 0,9% / (PVC) PE PP	28 d	28 d	Kühl	0,88 mg Eribulin entsprechen 1 mg Eribulinmesylat.		Glucose
Erwinase / Erwinia-Asparaginase (=Crisantaspase)	Erwinase® (Eusa Pharma)	10.000 E	NaCl 0,9%	2	5.000 E	20 d	20 d	NaCl 0,9% oder G 5 / (PVC) (PE) PP	7 d	7 d	Kühl	Nicht heftig schütteln! Kontakt der Lösung mit Gummistopfen vermeiden! (Auch bei der Lagerung in Einmalspritzen beachten) Adsorption an Filtermaterial möglich!		

Parameter	Referenčno zdravilo	Zdravilo BEKEMV
Rok uporabnosti	30 mesecev	36 mesecev
Shranjevanje neodprte viale na sobni T	3 dni	7 dni
Farmacevtski pripravek	24 ur	14 dni pri T 2-8 °C + 48 ur pri sobni temperaturi (poliolefinske vrečke) 48 ur pri T 2-8 °C (PVC vrečke)

Stabilnost

Povzetek glavnih značilnosti zdravila Bekemv - https://www.ema.europa.eu/

Povzetek

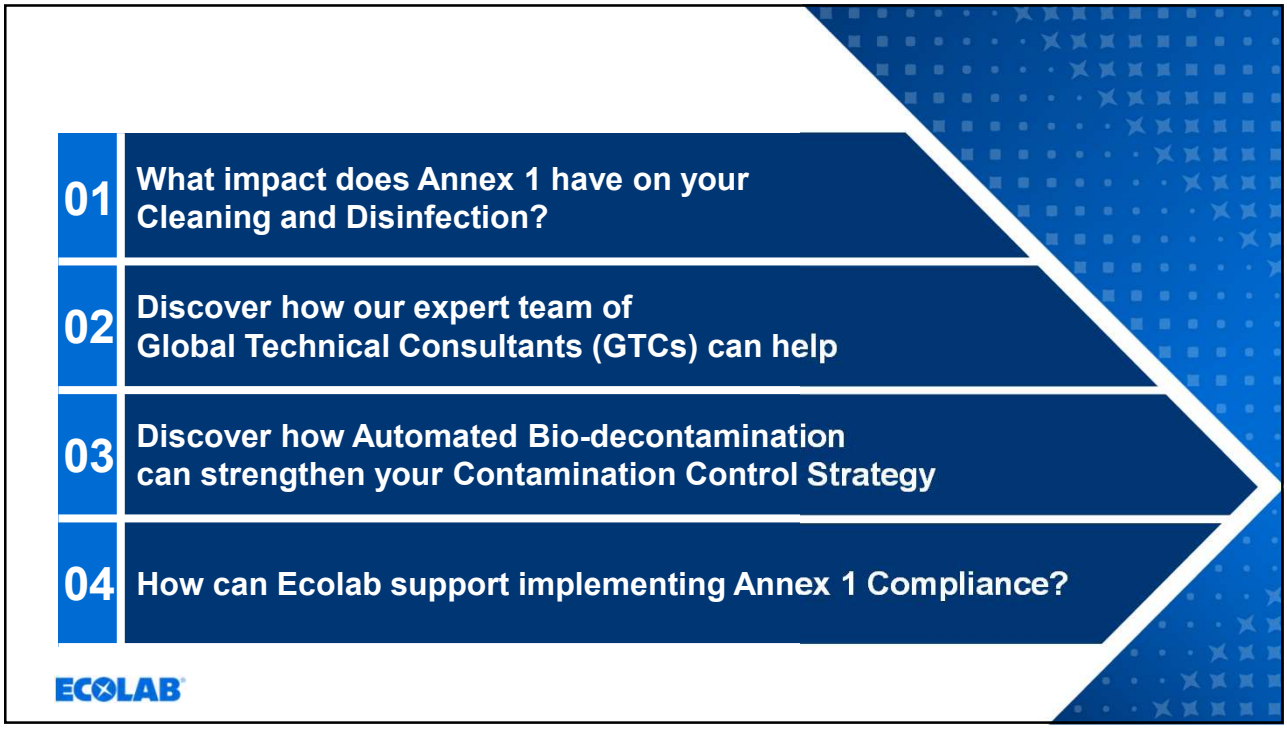
- Dokazani kakovost, varnost in učinkovitost
- Prihranek za zdravstveni sistem
- Novosti v razvoju oblike (lahko) nudijo dodatne prednosti pri rokovanju z zdravilom

Satelitsko predavanje/ Sponsored lecture – Ecolab

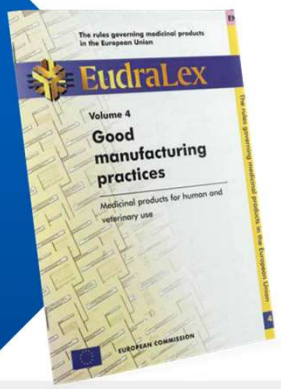
Dezinfekcija in sporocidna rotacija pri čiščenju aseptičnih prostorov/ Desinfection and sporocidal rotation in clean rooms

Juš Žagar, univ. dipl. kem.


Take control
of Annex 1
Build your roadmap to compliance in
cleaning, disinfection and bio-decontamination
ECOLAB


01
What impact does Annex 1 have on your
Cleaning and Disinfection?
02
Discover how our expert team of
Global Technical Consultants (GTCs) can help
03
Discover how Automated Bio-decontamination
can strengthen your Contamination Control Strategy
04
How can Ecolab support implementing Annex 1 Compliance?
ECOLAB

What impact does Annex 1 have on your Cleaning and Disinfection?



Annex 1 has been modified to reflect the change in technology within recent years, to harmonise with ICH chapters on Quality Risk Management and Pharmaceutical Quality System, and to provide greater clarity for interpretation of the content.

TIMELINE

AUGUST 2023

As from **August 2023**, audits will be conducted according to last Annex 1 revision

ECOLAB

Annex 1 - focus points

Contamination Control Strategy (CCS)

Product Selection

Residue Management

Disinfectant Rotation

Validation

Education & Training

ECOLAB

4

Contamination Control Strategy

Contamination Control Strategy (CCS)

"The development of the Contamination Control Strategy (CCS) requires detailed technical and process knowledge… Eléments to be considered within a CCS should include… xiii. Cl Cleaning and disinfection."

Ref Eudralex Vol 4. Annex1, 2.5

How our Global Technical Consultants can help

Ecolab provides a comprehensive assessment service of your cleaning and disinfection contamination control practices:

- Conduct an in-depth review of your cleaning & disinfection activities
- Document the risks to your cleanroom contamination control and assess their impact
- Provide with a detailed risk assessment report outlining compliance gaps and approaches for resolution

ECOLAB 5

Product Selection

Product Selection

"Disinfectants and detergents used in grade A and grade B areas should be sterile prior to use. Disinfectants used in grade C and D may also be required to be sterile where determined in the CCS…"

Ref Eudralex Vol 4. Annex1, 2.5

"If the disinfectants and detergents are supplied "ready-made" then results from certificates of analysis or conformance can be accepted subject to successful completion of the appropriate vendor qualification"

Ref Eudralex Vol 4. Annex1, 2.5

How our Global Technical Consultants can help

Made in cleanrooms, for cleanrooms, Ecolab's range of Contamination Control solutions is designed to facilitate compliance:

- Bespoke cleaning and disinfection regimes can be provided
- Sterile and ready-to-use formats manufactured to the principles of GMP supplied with certificate of analysis for every batch
- Support is provided for the Vendor Qualification process

ECOLAB 6

Residue Management

Residue Management

"For disinfection to be effective, prior cleaning to remove surface contamination should be performed. Cleaning programmes should effectively remove disinfectant residues."

Eudralex Vol 4. Annex 1, 4.33

How our Global Technical Consultants can help

With our portfolio of low residue products and detailed scientific data, Ecolab provides proactive support to help manage your risk from residues:

- Comprehensive data package to manage residues removal prior disinfection
- Ecolab can provide a residue management program in compliance with Annex 1 regulation
- Low residue products and automated bio-decontamination equipment can be provided to minimize residue risks proactively, throughout the facility

ECOLAB 7

Disinfectant Rotation

Disinfectant Rotation

"More than one type of disinfecting agent should be employed to ensure that where they have different modes of action, their combined usage is effective against bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent."

Eudralex Vol 4 Annex 1, 4.33

How our Global Technical Consultants can help

Ecolab designs bespoke cleaning and disinfection regimes to suit the contamination control needs of your facility:

- Disinfectant agents can be proposed after review of contamination risks and EM data within the facility
- Specific recommendations can be made to address high risk activities such as material transfer
- Ecolab has a comprehensive portfolio of sporicidal solutions for manual disinfection and log-6 automated Bio-decontamination

ECOLAB 8

What is rotation and why

Rotation as booster to Contamination Control

What is daily disinfectiant needed and why is not enough?

- Good operator acceptance
- Better material compatibility
- Easy setup and handling
- Broad usage possible
- Good Residue management technology

Effectiveness is not on all microorganisms

Quote from David Keen:

"We all wish to have a perfect disinfectant that would:

- kill all kinds of microorganisms
- smell like Chanel perfume
- perfect material and operator compatibility

Unfortunately not possible ☺

Rotation is "harsh" approach to eliminate microorganisms that could survive daily disinfectant.

ECOLAB 9

Difference between Daily Disinfectant and Sporicidal Agent

Table 1: EN Test methods and Results for Klercide Low Residue Quat Concentrate

Test	Test Type	Claim	Organism	Strain	Pass Criteria	Test Result
EN 1276:2009	Suspension Test	Bactericidal	P. aeruginosa	ATCC 15442	≥ Log 5 reduction in 60 min	Pass in 5 minutes
			E. coli	ATCC 15036		
			S. aureus	ATCC 6538		
			E. hirae	ATCC 10541		
EN 1650:2008 +A1:2013	Suspension Test	Yeasticidal	C. albicans	ATCC 10231	≥ Log 4 reduction in 60 minutes	Pass in 5 minutes
EN 14476:2013 +A2:2019	Suspension Test	Virucidal against enveloped viruses	Vacciniavirus	Modified Vacciniavirus Ankara (MVA)	≥ Log 4 reduction in 60 minutes	Pass in 5 minutes

Test	Test Type	Claim	Organism	Strain	Pass Criteria	Result
EN 13697:2001	Surface Test without mechanical action	Bactericidal and/or Yeasticidal	P. aeruginosa	ATCC 15442	≥ Log 4 reduction in 60 minutes	Pass in 5 minutes
			E. coli	ATCC 15036		
			E. hirae	ATCC 10541		
			S. aureus	ATCC 6538		
			C. albicans	ATCC 10231	≥ Log 3 reduction in 60 minutes	Pass in 5 minutes
EN 13697:2015 +A1:2019	Surface Test without mechanical action	Bactericidal and/or Yeasticidal	P. aeruginosa	ATCC 15442	≥ Log 4 reduction in 60 minutes	Pass in 15 minutes
			E. coli	ATCC 15036		
			E. hirae	ATCC 10541		
			S. aureus	ATCC 6538		
			C. albicans	ATCC 10231	≥ Log 3 reduction in 60 minutes	Pass in 30 minutes
EN 16777:2018	Surface Test without mechanical action	Virucidal against enveloped viruses	Vacciniavirus	Modified Vacciniavirus Ankara (MVA)	≥ Log 4 reduction in 60 minutes	Pass in 30 minutes

Table 1: EN Test Methods and Results for Klercide Sporicidal Active Chlorine

Test	Test Type	Claim	Organism	Strain	Pass Criteria	Test Result
EN 1276:2009	Suspension Test	Bactericidal	P. aeruginosa	ATCC 15442	≥ Log 5 reduction in 60 minutes	Pass in 5 minutes
			E. coli	ATCC 15036		
			S. aureus	ATCC 6538		
			E. hirae	ATCC 10541		
EN 1650:2008 +A1:2013	Suspension Test	Fungicidal or Yeasticidal	C. albicans	ATCC 10231	≥ Log 4 reduction in 60 minutes	Pass in 5 minutes
			A. brasiliensis	ATCC 16404		
EN 13704:2002	Suspension Test	Sporicidal	B. subtilis	ATCC 6633	≥ Log 3 reduction in 60 minutes	Pass in 5 minutes
EN 13704:2018	Suspension Test	Sporicidal	B. subtilis	ATCC 6633	≥ Log 3 reduction in 60 minutes	Pass in 5 minutes
EN 14476:2013 *EN 14476:2007	Suspension Test	Virucidal	Murine Norovirus	Strain S99 Berlin	≥ Log 4 reduction in 60 minutes	Pass in 1 minute
			*Poliovirus	Type 1 strain LSc-2ab		
			*Adenovirus	Type 5 strain Adenoid 75		
EN 14476:2013 +A1:2015/ prA2:2016	Suspension Test	Virucidal against murine Parvovirus	Murine Parvovirus, Minute virus of mice (MVM)	Strain crawford	n.a.	≥ Log 4 in 1 minute

ECOLAB 10

Difference between Daily Disinfectant and Sporicidal Agent

Liquid	Stress	Weight Change (%)	Thickness Change (%)	Comments
316 stainless steel	0	< 0.01	0	
	+	< 0.01	0	
304 stainless steel	0	< 0.01	0	
	+	< 0.01	0	
Aluminium	0	- 0.03	0	
	+	- 0.03	0	
PVC coated mild steel	0	- 0.01	0	Slight corrosion at edges
	+	- 0.02	0	Slight corrosion at edges
Acrylic	0	+ 0.44	+ 0.35	
	+	+ 0.47	+ 0.38	
Vinyl	0	+ 1.03	+ 0.1	
	+	+ 1.10	+ 0.2	
Trespa	0	+ 0.91	+ 0.32	

Liquid	Stress	Weight Change (%)	Thickness Change (%)	Comments
316 stainless steel	0	- 0.29	0	Slight corrosion at edges
	+	- 0.26	0	Slight corrosion at edges
304 stainless steel	0	- 0.35	0	Slight corrosion at edges
	+	- 0.32	0	Slight corrosion at edges
Aluminium	0	- 1.24	0	Moderate surface corrosion
	+	- 1.16	0	Moderate surface corrosion
PVC coated mild steel	0	- 0.18	0	Slight corrosion at edges
	+	- 0.21	0	Slight corrosion at edges
Acrylic	0	+ 0.29	+ 0.04	None
	+	+ 0.31	+ 0.04	None
Vinyl	0	+ 0.34	+ 0.11	None
	+	+ 0.29	+ 0.08	None
Trespa	0	+ 0.62	+ 0.11	None
Vinyl	0	+ 0.58	+ 0.10	None

ECOLAB

11

Validation

Validation

"Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions."

Eudralex Vol 4 Annex 1, 4.34

How our Global Technical Consultants can help

Easing the burden of validation, Ecolab's team of Global Technical Consultants provides the resource and expertise to manage the challenges of disinfectant validation that you face.

- Ecolab's Disinfectant Validation Portal is available for customers, to ease the burden of on-site testing
- Advising and coordinating with accredited contract testing laboratories, reviewing draft protocols and results
- Consulting on rationales for regulatory approvals
- Provide bespoke automated Bio-decontamination solution quick and easy to validate thanks to Geobacillus stearothermophilus biological indicators
- and log-6 automated Bio-decontamination

ECOLAB

12

Education and Training

Education & Training

"This training should include the basic elements of microbiology and hygiene, with a specific focus on cleanroom practices, contamination control, aseptic techniques.."

Eudralex Vol. 4 Annex 1, 7.3

How our Global Technical Consultants can help

A wide range of educational materials and hands-on training is available to assist with learning needs:

- Ecolab's technical consultants deliver a wide range of industry relevant educational materials
- Practical trainings such as application techniques are available
- On-site bespoke workshops are provided to broaden knowledge and increase awareness of the criticality of cleaning and disinfection

ECOLAB 13

How can Ecolab support implementing Annex 1 Compliance?

ECOLAB 14

Discover Ecolab's Change Management programme

Compliance with the updated Annex 1 may drive the need to change the cleaning and disinfection practices within your facility.

Our team of Global Technical Consultants can support you through the process with a customised end-to-end change management plan that suits your specific needs

RISK ASSESSMENT → SUPPLIER ASSURANCE → PRODUCT SELECTION → VALIDATION → IMPLEMENTATION

ECOLAB

ECOLAB®

PROTECTING WHAT'S VITAL™

ZAHVALA

Zahvaljujemo se vsem, ki so omogočili in podprli naš simpozij!

Sponzorji srečanja

Zapis življenja oblikujemo v življenjsko pomembna zdravila

V družbi Amgen smo prepričani, da so odgovori na najbolj pereča medicinska vprašanja zapisani v besedah naše DNA. Smo pionirji na področju biotehnologije in svoje globoko razumevanje govorice teh besed uporabljamo za ustvarjanje življenjsko pomembnih zdravil – zdravil, namenjenih neizpolnjenim potrebam bolnikov z resnimi boleznimi za dramatično izboljšanje njihovega življenja.

SI-AMC-0322-00001

AMGEN®

Amgen zdravila d.o.o.
Ameriška ulica 2, Ljubljana, Slovenija
www.amgen.si