Quality requirements for nanomedicines: which role for the European Pharmacopoeia?

7-8 June 2022

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Introduction Session

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Cancer Nanomedicine

- Principles, Progress, Products, Problems, Prospects -

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Quality requirements for nanomedicines: which role for the European Pharmacopoeia?

7-8 June 2022, Strasbourg, France

Key Question :

How to make cancer nanomedicines vs. How to make them work ?

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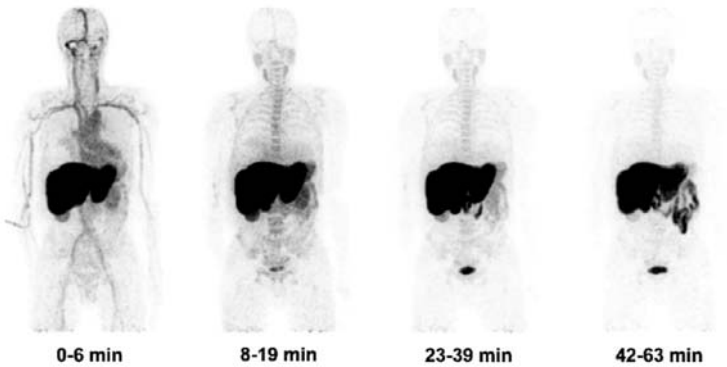
Principles

Drug Delivery to Tumors

is very inefficient

PET Imaging of ^{11}C-Docetaxel in a Patient with Mesothelioma

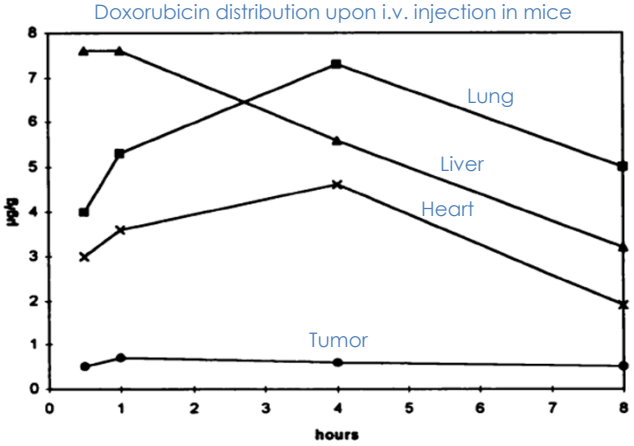


Van der Veldt et al, EJNMMI 2010

Drug Delivery to Tumors

is very inefficient

Doxorubicin distribution upon i.v. injection in mice



Bosslet et al, Cancer Res 1998

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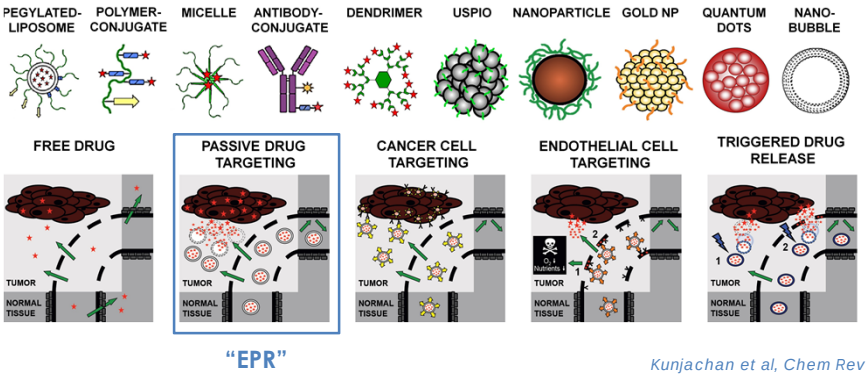
Cancer Nanomedicine

- 1-100(0) nm drug delivery systems
- Protect the drug from the body
- Protect the body from the drug
- Increase efficacy + reduce toxicity



Kunjachan et al, Chem Rev 2015

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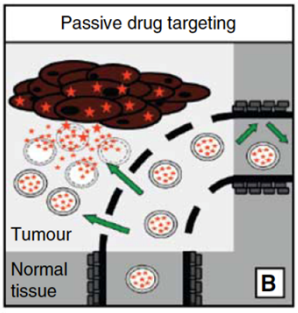
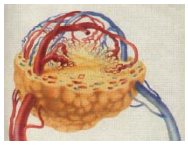
EPR : Enhanced Permeability and Retention

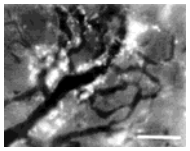
- High blood vessel density +
- High vascular permeability +
- Lack of lymphatic drainage →

=> Efficient accumulation of long-circulating nanomedicines in tumors

Hiroshi Maeda, 1986







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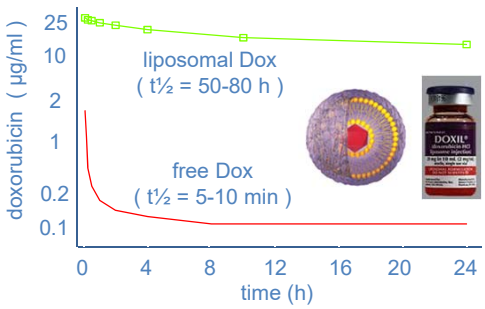
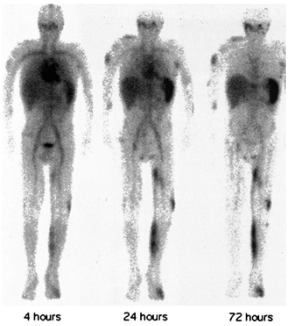
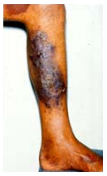
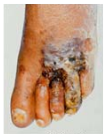
Nanomedicine Tumor Targeting in Patients









in Kaposi sarcoma: Improved efficacy vs. ABV => 1 CR + 60/133 PR vs. 31/125 PR

Reduced toxicity => Less cardiomyopathy, nausea, alopecia

Gabizon et al, Cancer Res 1994

Harrington et al, Clin Cancer Res 2001

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Products

Nanomedicines in the Clinic

- In 2016 : 51 nanomedicine approved and 77 in clinical trials
- 15 nanocrystals, 15 polymer-drugs, 10 liposomes, 8 inorganic
- Only approx. 10 nanomedicines approved for cancer therapy

Pharm Res
DOI 10.1007/s11095-016-1958-5

EXPERT REVIEW

Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date

Daniel Bobo[1,2,3,4] · Kye J. Robinson[4,5] · Jiaul Islam[2,4,5] · Kristofer J. Thurecht[1,2,4] · Simon R. Corrie[1,2,4,5]

Bobo et al, Pharm Res 2016

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Nanoparticles in the Clinic

Received: 5 August 2019 | Revised: 22 August 2019 | Accepted: 23 August 2019
DOI: 10.1002/btm2.10143

Check for updates

REVIEW

BIOENGINEERING & TRANSLATIONAL MEDICINE

Nanoparticles in the clinic: An update

Aaron C. Anselmo[1] | Samir Mitragotri[2]

- Up until 2016 : **25** nanoparticles approved by FDA/EMA
  45 additional NP technologies in clinical trials
- From 2016-2019 : **3** new NP approved, **15** new NP in trials
  75 new trials with existing but not-yet-approved NP
- From 2019-2021 : **2** new NP approved, **35** new NP in **55** new trials
  30 new trials with existing but not-yet-approved NP

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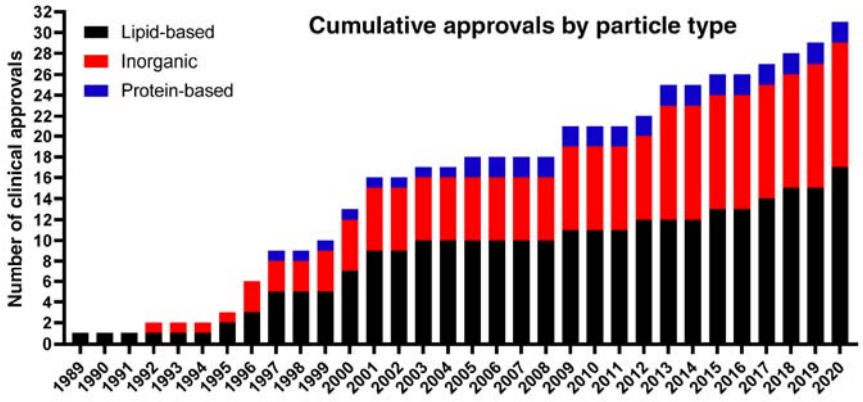
Nanoparticles in the Clinic

In 2020 : Excl. nanocrystals, ADC and PEG/polymer-drugs



Anselmo et al, BioTM 2021

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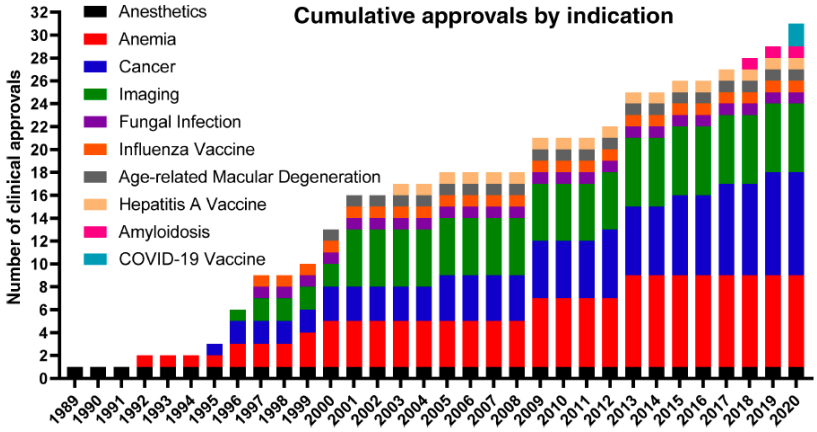
Applications of NP in the Clinic



Anselmo et al, BioTM 2021

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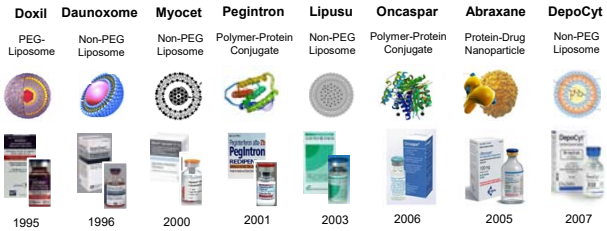
Cancer Nanomedicines in the Clinic



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Problems

The Cancer Nanomedicine Controversy

The Cancer Nanomedicine Controversy

Advanced Drug Delivery Reviews
Volume 65, Issue 1, January 2013, Pages 80–88
Advanced Drug Delivery: Perspectives and Prospects

Cancer nanomedicines: So many papers and so few drugs! ☆

Vincent J. Venditto, Francis C. Szoka Jr.

ACS Nano 2020, 14, 12281−12290

What Went Wrong with Anticancer Nanomedicine Design and How to Make It Right

Duxin Sun,* Simon Zhou, and Wei Gao

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The Cancer Nanomedicine Controversy

ACS Publications C&EN CAS

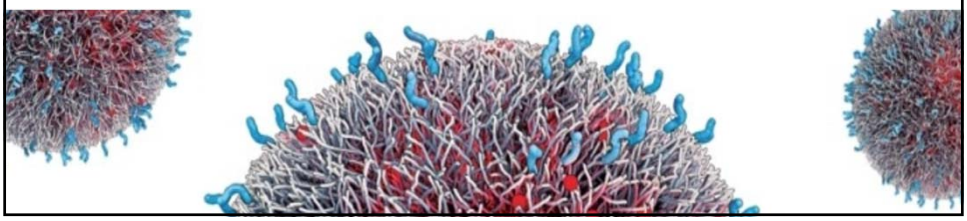
c&en CHEMICAL & ENGINEERING NEWS

TOPICS MAGAZINE COLLECTIONS VIDEOS JOBS

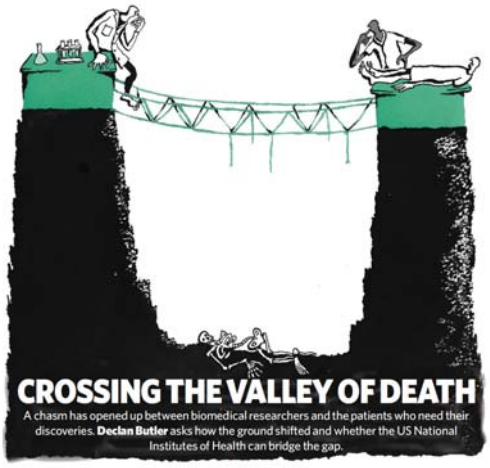
Does nanomedicine have a delivery problem?

Experts debate controversial paper that suggests delivery efficiencies for cancer nanomedicines are low and not improving

By ***Michael Torrice***



How to improve cancer nanomedicine delivery and translation?



Butler, Nature 2008

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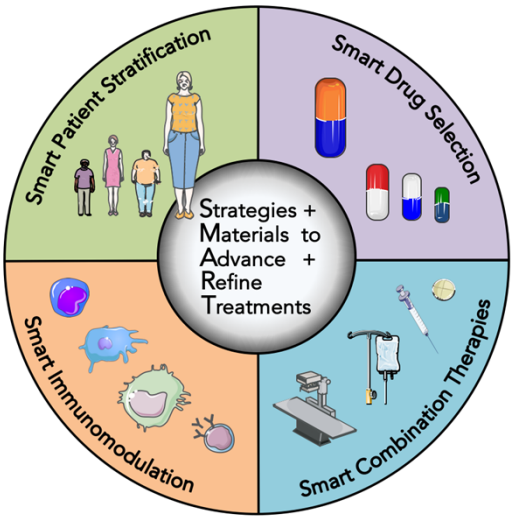
Strategies to Improve Cancer NM Performance and Translation



Van der Meel et al, Nat Nano 2019

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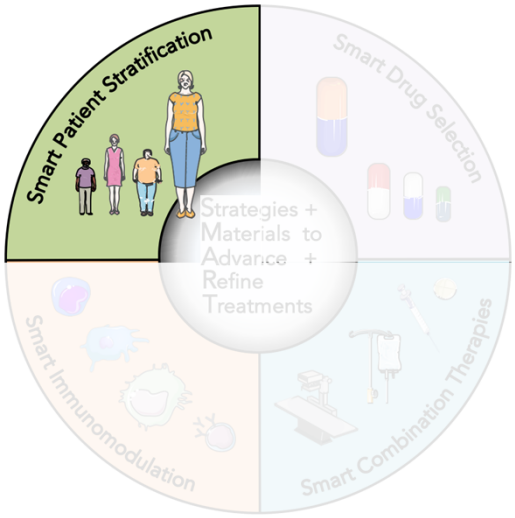
Strategies to Improve Cancer NM Performance and Translation



Van der Meel et al, Nat Nano 2019

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Some More Controversy

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review article

To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine?

F. Danhier

Université catholique de Louvain, Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, Avenue Mounier, 73 bte B1 73.12, 1200 Brussels, Belgium

Danhier. JCR 2016

(848 citations)

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Some More Controversy

A B S T R A C T

Tumor targeting by nanomedicine-based therapeutics has emerged as a promising approach to overcome the lack of specificity of conventional chemotherapeutic agents and to provide clinicians the ability to overcome shortcomings of current cancer treatment. The major underlying mechanism of the design of nanomedicines was the Enhanced Permeability and Retention (EPR) effect, considered as the "royal gate" in the drug delivery field. However, after the publication of thousands of research papers, the verdict has been handed down: the EPR effect works in rodents but not in humans! Thus the basic rationale of the design and development of nanomedicines in cancer therapy is failing making it necessary to stop claiming efficacy gains via the EPR effect, while tumor targeting cannot be proved in the clinic. It is probably time to dethrone the EPR effect and to ask the question: what is the future of nanomedicines without the EPR effect? The aim of this review is to provide a general overview on (i) the current state of the EPR effect, (ii) the future of nanomedicine and (iii) the strategies of modulation of the tumor microenvironment to improve the delivery of nanomedicine.

Danhier. JCR 2016

(848 citations)

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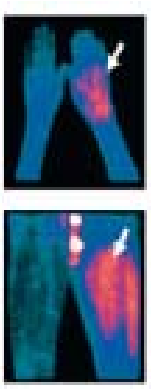
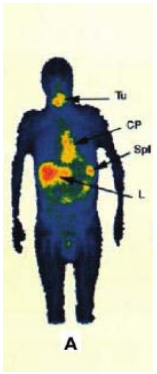
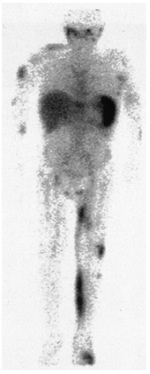
Nanomedicine Tumor Targeting in the Clinic

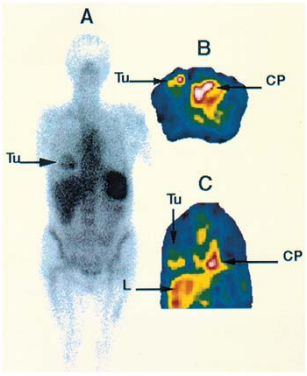
- Definitely **NOT** absent in patients



Koukourakis et al
Acta Oncol 2000







Harrington et al, Clin Cancer Res 2001

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Nanomedicine Tumor Targeting in the Clinic

- Definitely **NOT** absent in patients
- Highly variable : 2.7 - 53.0 %ID/kg

Table 3 Patient details: histology, stage, and results of gamma camera imaging and estimated tumor uptake from ROI analysis

Patient	Tumor	Stage	Whole body scan	SPECT	Total % injected dose[a]	% ID/kg[b]
1	SCC[c] bronchus	T4N0M0	Positive	Positive	1.7	12.5
2	SCC bronchus	T4N0M0	Positive	Positive	1.6	25.4
3	Breast (ductal)	T4N2M1	Negative	Negative		
4	SCCHN	T3N2M0	Positive	Positive	3.5	46.8
5	Breast (ductal)	T4N1M0	Positive	Positive	0.3	2.7
6	Breast (ductal)	T4N2M1	Positive	Positive	1.5	3.9
7	Breast (ductal)	T3N2M0	Positive	Positive	1.7	9.5
8	SCCHN	T4N0M0	Positive	Positive	0.7	24.2
9	SCCHN	T3N1M0	Positive	Positive	1.0	32.0
10	SCC cervix	FIGO IIIB	Negative	Positive	NA	NA
11	Breast (ductal)	T4N2M0	Positive	Positive	1.4	5.2
12	SCC bronchus	T2N0M1	Negative	Negative		
13	SCCHN	T3N2M0	Positive	Positive	0.6	9.0
14	SCCHN	T3N0M0	Positive	Positive	1.6	53.0
15	SCC bronchus	T3N0M1	Positive	Positive	2.6	16.7
16	Glioma (AA)	Inoperable	Negative	Positive	NA	NA
17	Glioma (GBM)	Inoperable	Negative	Positive	NA	NA

Harrington et al, Clin Cancer Res 2001

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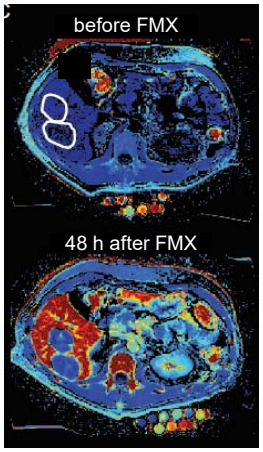
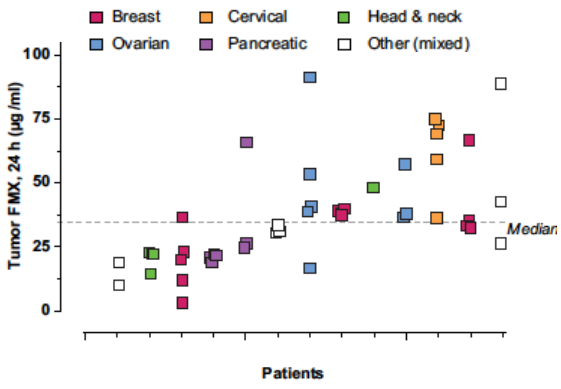
Imaging-based Patient Stratification

Clinically used iron oxide NP as companion diagnostic





Ramanathan et al, Clin Cancer Res 2017

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Imaging-based Patient Stratification

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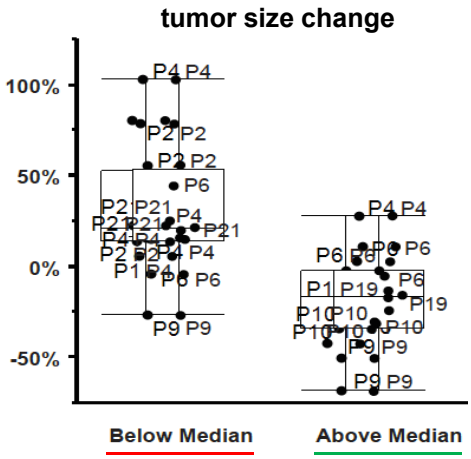

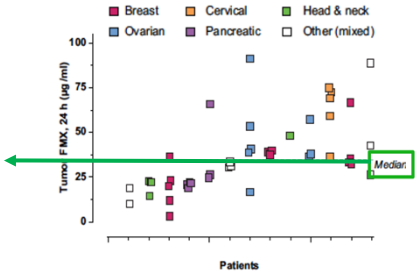

Ramanathan et al, Clin Cancer Res 2017

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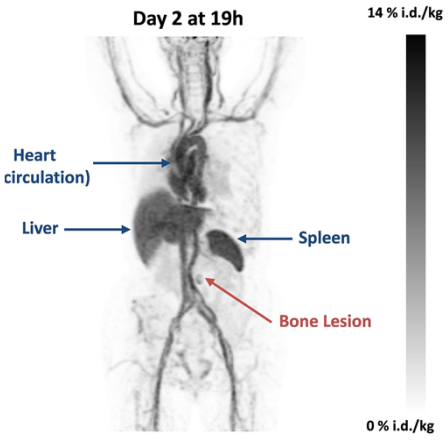
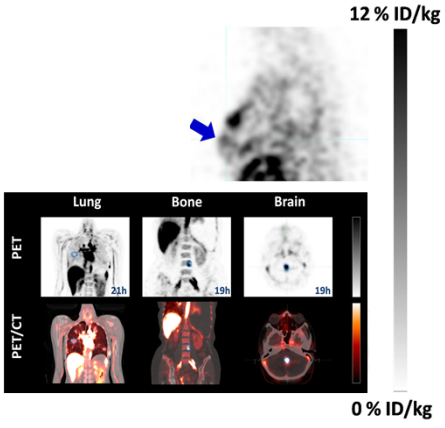
Imaging-based Patient Stratification

Theranostic approach : ^{64}Cu-Dox-liposomes





Lee et al, Clin Cancer Res 2017

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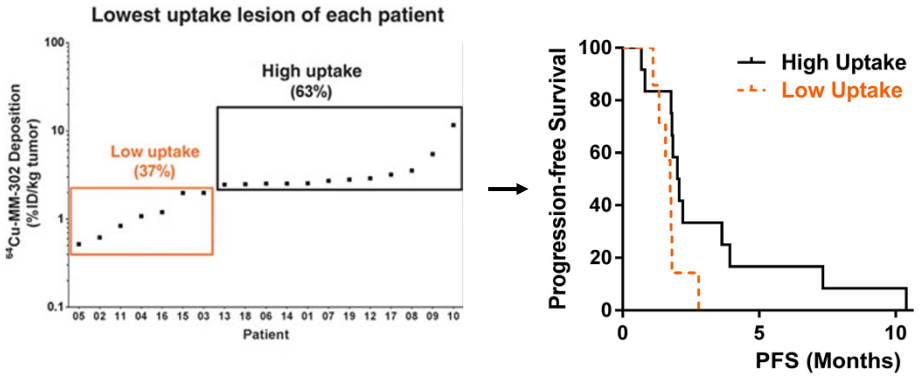
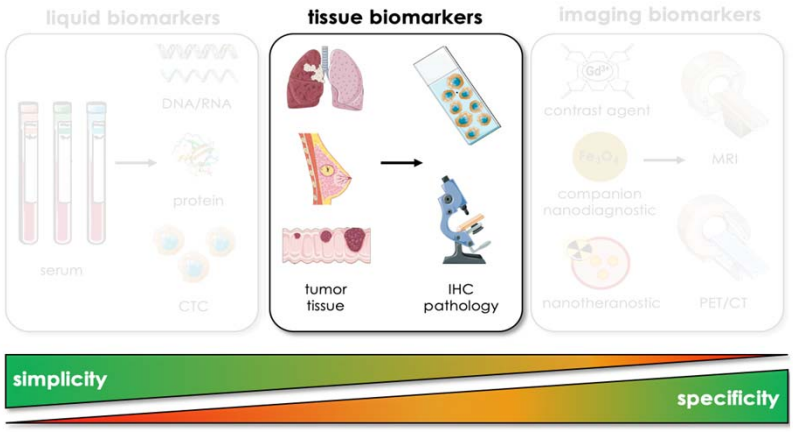
Imaging-based Patient Stratification

Theranostic approach : ^{64}Cu-Dox-liposomes



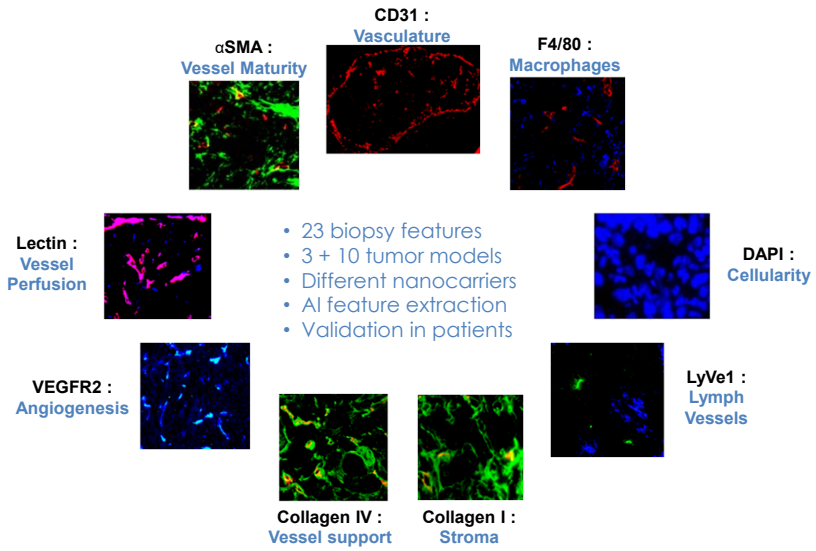
Lee et al, Clin Cancer Res 2017

Biomarkers for Patient Stratification



Van der Meel et al, Nat Nano 2019

Towards Biopsy Biomarkers for Patient Stratification



May, Hare et al, in prep

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Metastasis

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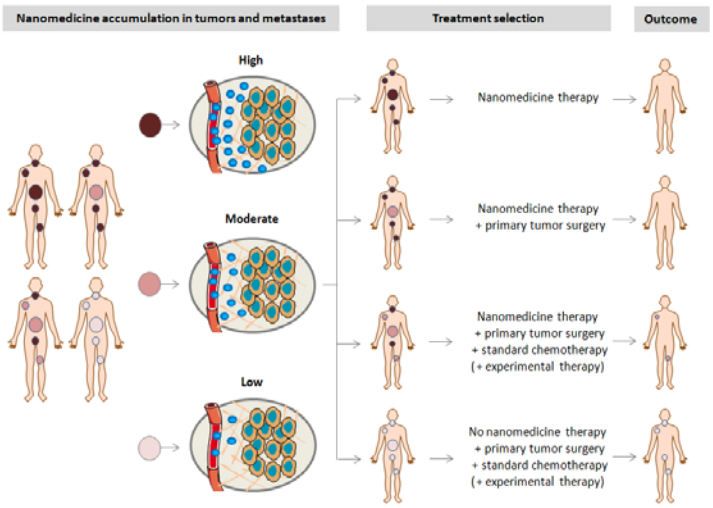
Imaging biomarkers are needed in patients with metastases



Ojha et al, EODD 2015

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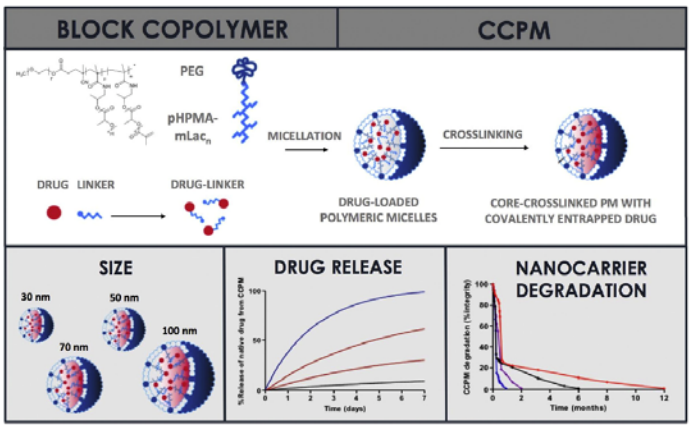
Metastasis Targeting with CCPM

Core-crosslinked PEG-b-PHPMA-Lac$_n$ polymeric micelles



Cristal Therapeutics

Hu et al, JCR 2016

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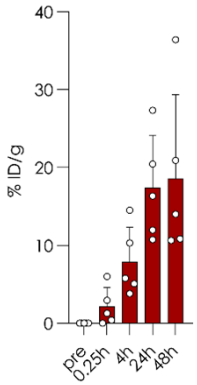
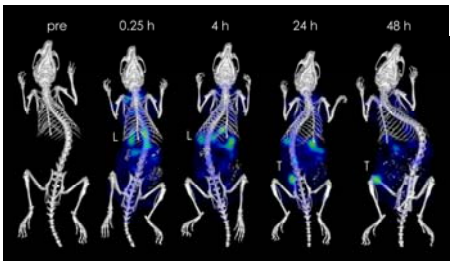
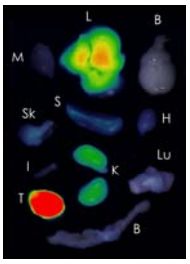
Primary Tumor Targeting with CCPM

in 4T1 triple-negative breast cancer







Biancacci et al, JCR 2020

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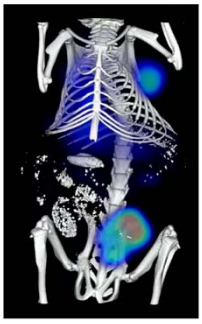
Imaging Metastasis Targeting with CCPM

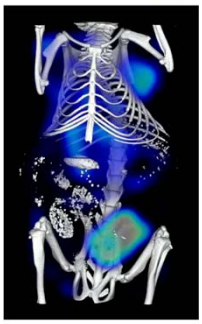
in 4T1 triple-negative breast cancer

organs (CT)

cancer cells (FMT_{680})



micelles (FMT_{750})



Rizzo et al, in prep

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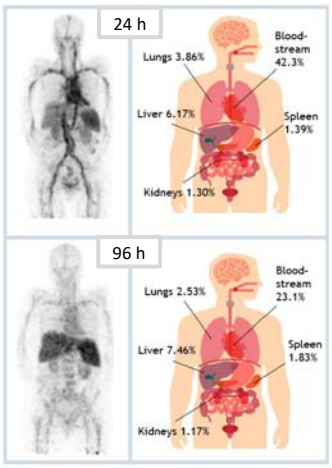
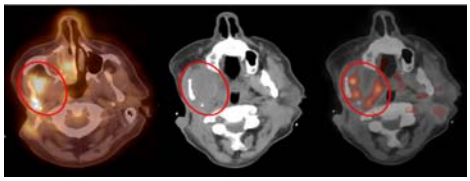
Imaging Metastasis Targeting in Patients

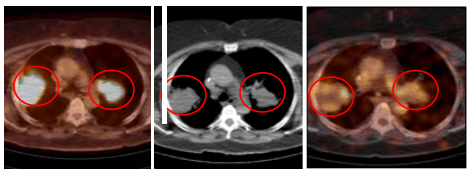
^{89}Zr-DTX-Micelles



^{18}FDG-PET CT ^{89}Zr-DTX-Micelles



Retromandibular Metastasis (Myoepithelioma)



Lung Metastases (Colorectal Cancer)

Miedema et al, Adv Mater 2022

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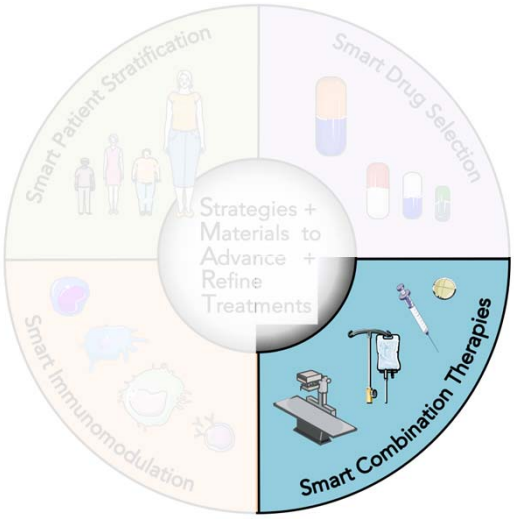
Prospects

ExMI

Strategies to Improve Cancer NM Performance and Translation



ExMI

Corticosteroid Nanomedicines

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review

Liposomal corticosteroids for the treatment of inflammatory disorders and cancer

Burcin Ozbakir [a,1], Bart J. Crielaard [a,b,1], Josbert M. Metselaar [d], Gert Storm [a,d,*], Twan Lammers [a,c,d,*]

[a] Department of Pharmaceutics, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands
[b] Department of Pediatrics-Hematology/Oncology, Weill Cornell Medical College, 515 E71st Street, 10021 NY, USA
[c] Department of Experimental Molecular Imaging, RWTH - Aachen University, Helmholtz Institute for Biomedical Engineering, Pauwelsstrasse 30, 52074 Aachen, Germany
[d] Department of Controlled Drug Delivery, MIRA Institute for Biomedical Engineering and Technical Medicine, University of Twente, 7500 AE Enschede, The Netherlands

Ozbakir et al, JCR 2014

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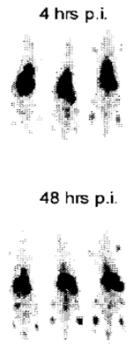
Targeting Inflammation

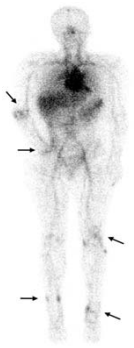
Inflammatory lesions and infections also display "EPR"

^{111}In-Liposomes in RA



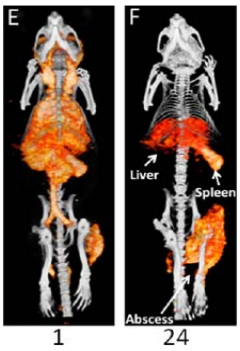
Metselaar et al, Arthr Rheum 2003

^{111}In-Liposomes in RA



Boerman et al, UMCN

^{111}In-Liposomes in SA



Van der Geest et al, JCR 2015

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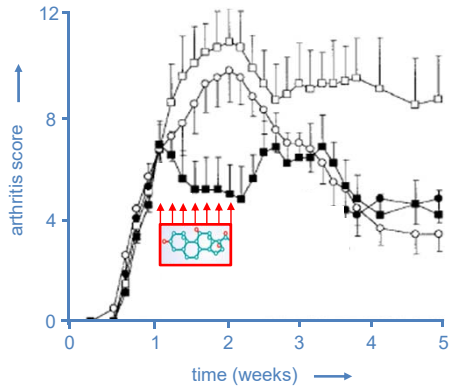
Corticosteroid Nanomedicines

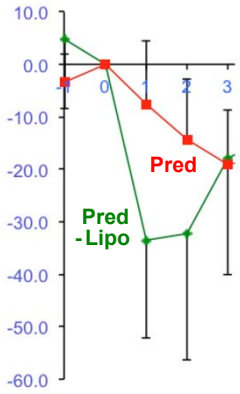
For treating rheumatoid arthritis

Arthritis score in AIA rats



Ozbakir et al, JCR 2014

DAS28 score in RA patients



Metselaar et al, JCR 2022

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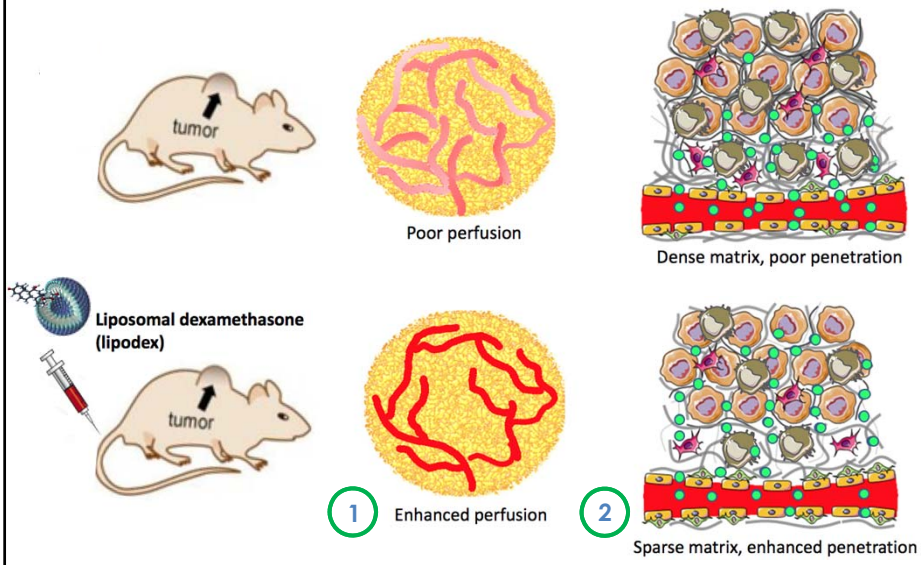
Tumor Priming with Corticosteroid Nanomedicines



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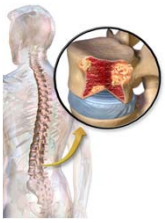
Clinical Translation

Corticosteroid Liposomes

Phase III	:	Rheumatoid Arthritis
Phase II	:	Inflammatory Bowel Disease
Phase I	:	Atherosclerosis, Uveitis
Phase I	:	Multiple Myeloma (@ RWTH)

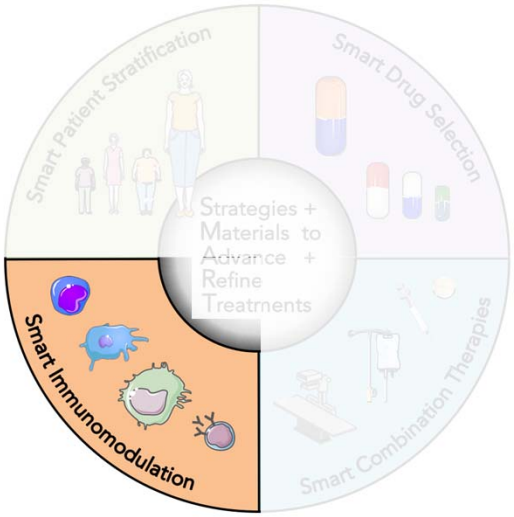


enceladus

RWTH AACHEN UNIVERSITY
Medizinische Fakultät
Center for Translational & Clinical Research (CTC-A)

ExMI

Strategies to Improve Cancer NM Performance and Translation



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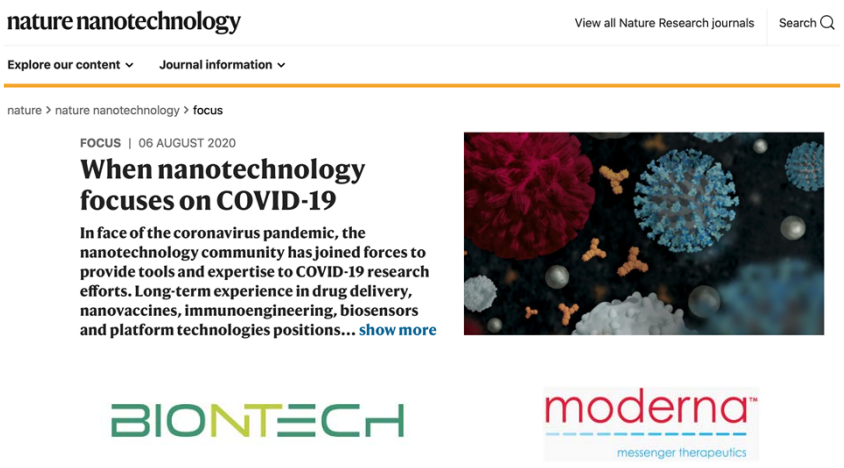
Nanomedicine for Immunotherapy Applications



BIONTECH

moderna
messenger therapeutics

ExMI

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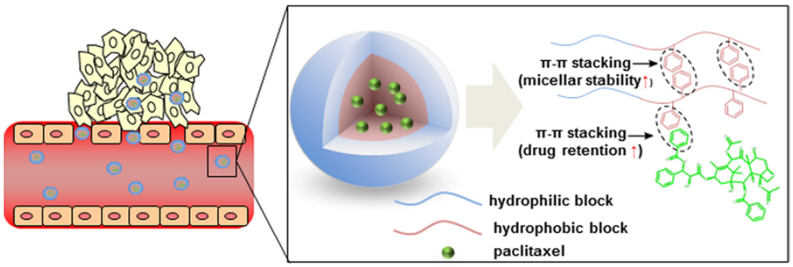
Picelles

Π-Π stacking stabilized polymeric micelles : PEG-PHPMA-Bz



ExMI

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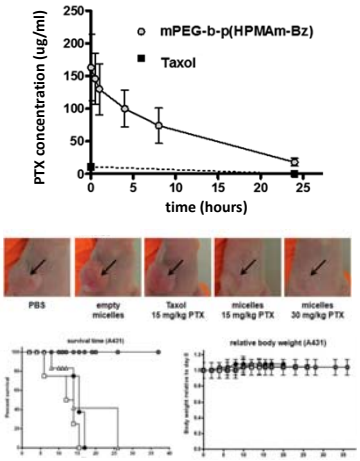
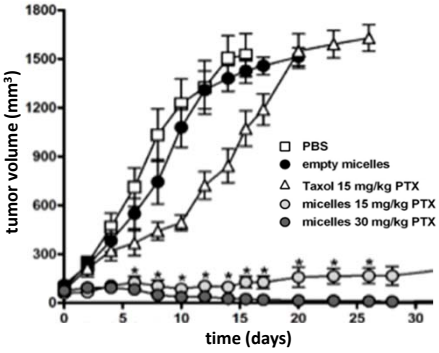
PTX-Picelles

Paclitaxel delivery in skin and breast cancer models





Shi et al, ACS Nano 2015

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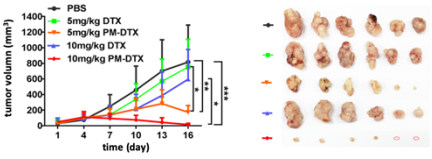
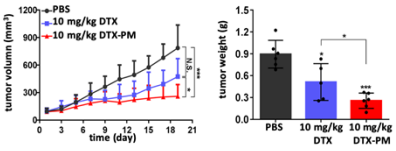
DTX-Picelles

Docetaxel delivery in advanced GI cancer models

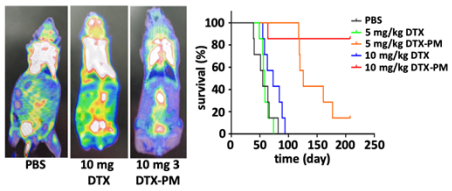
subcutaneous CDX model of gastric cancer



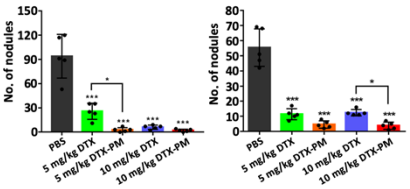
subcutaneous PDX model of colon cancer



intraperitoneal metastasis model of gastric cancer



lung metastasis model of gastric cancer



Liang et al, Biomaterials 2021

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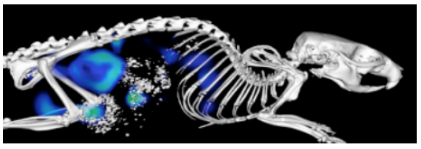
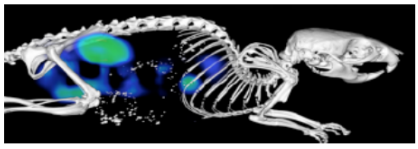
Theranostic Picelles

For patient stratification

low tumor accumulation

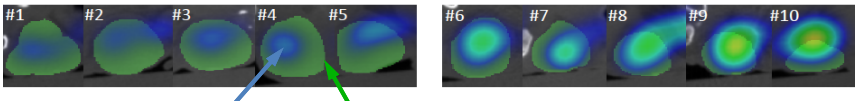


high tumor accumulation



low accumulation => poor efficacy

high accumulation => good efficacy



Tumor accumulation Tumor size

Biancacci et al, Adv Sci 2022

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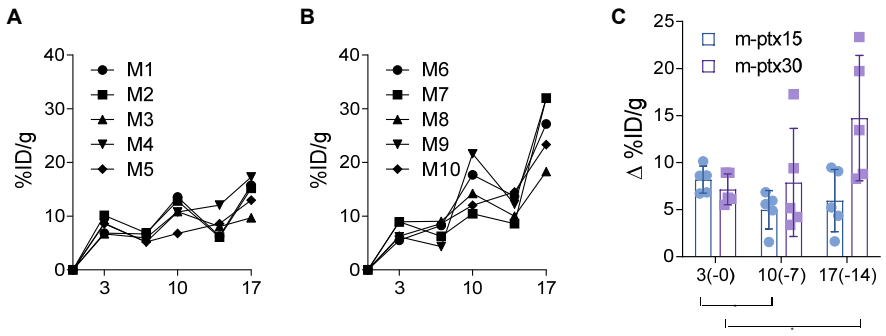
Theranostic Picelles

Monitoring EPR effect dynamics during nano-taxane treatment

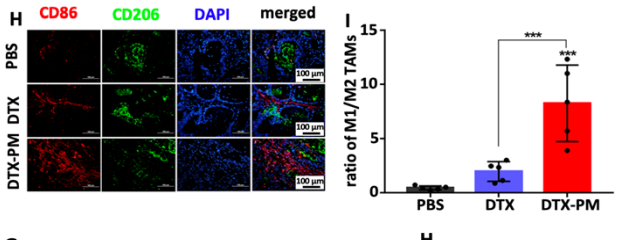


Biancacci et al, Adv Sci 2022

Immunotherapy-Promoting Picelles

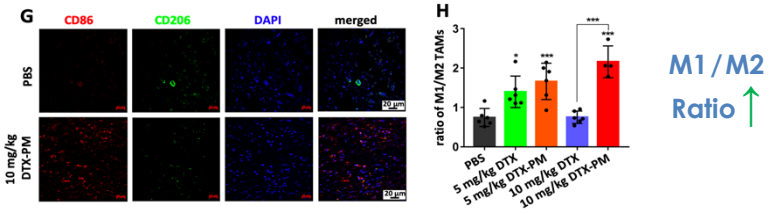
help to prime the tumor microenvironment

Gastric CDX



M1 / M2 Ratio ↑

Colon PDX



M1 / M2 Ratio ↑

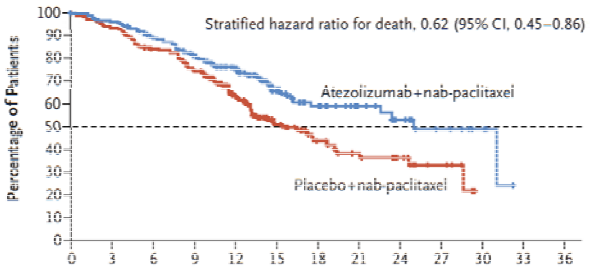
Liang et al, Biomaterials 2021

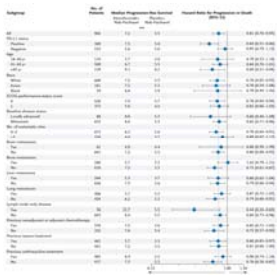
Promoting Immunotherapy using Taxane-Nanomedicines

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel
in Advanced Triple-Negative Breast Cancer





Schmid, NEJM 2018

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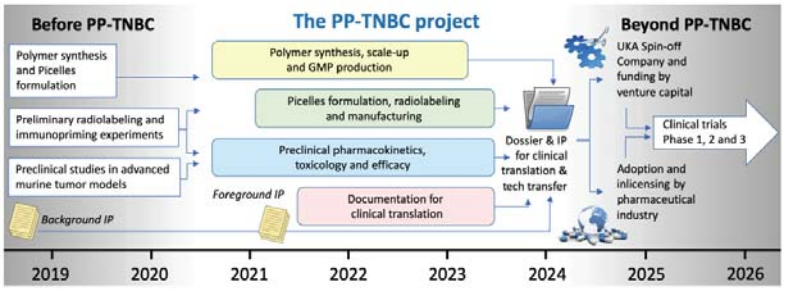
PP-TNBC

Image-guided and Immunotherapy-promoting
Paclitaxel-**P**icelles for Metastatic **TNBC** Therapy

Bundesministerium für Bildung und Forschung

eu2020.de

ARDENA



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Summary

- NM improve drug performance and therapeutic index
- Various NM platforms have shown good results in patients
- NM tumor targeting is highly heterogeneous and dynamic
- Smart (pragmatic and realistic) protocols for stratification
- Future: Combination therapies, Nano-immunotherapy

tlammers@ukaachen.de

erc STW-KWF EuroNanoMed3 Federal Ministry of Education and Research DFG GRK2375 SFB/TRR57 SFB1066 KFO5011

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THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

A short introduction to the European Pharmacopoeia (Ph. Eur.)

Emmanuelle Charton & Dirk Leutner, EDQM, Council of Europe

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Structure

- Council of Europe and EDQM
- The European Pharmacopoeia: content and structure
- Flexibility offered the European Pharmacopoeia
- The European Pharmacopoeia: elaboration process
- Gene therapy products: a case study
- Advertisement
- Target outcome of the event

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Council of Europe and EDQM

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The Council of Europe: the EDQM's parent organisation

- Founded in 1949
- Headquarters in Strasbourg, France
- 46 MEMBER STATES

- The oldest pan-European organisation dedicated to fostering co-operation in Europe
  - Promotes DEMOCRACY
  - Protects THE RULE OF LAW
  - Protects HUMAN RIGHTS

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About the EDQM

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

The **E**uropean **D**irectorate for the **Q**uality of **M**edicines and HealthCare (EDQM)

- A Directorate of the **Council of Europe**
- Work is based since 1964 on the European Pharmacopoeia Partial Agreement

… contributing to public health and access to **good quality medicines and healthcare in Europe**.

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Networks and collaboration

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EDQM and COVID-19: some initiatives

EDQM co-ordinates the EU OMCL Network, including the Official Control Authority Batch Release (OCABR) process,

- INDEPENDENT control of biological medicines such as vaccines by testing batches before they reach the patient.
- Testing by an OMCL is recognised by all Members and beyond (saving time and resources by reducing re-testing)

Specific impact

- Guidelines for testing of first COVID-19 vaccine available in November 2020,
- COVID-19 vaccines released immediately, without delay, following marketing authorisations from EMA from Dec 2020
- Between December 2020 and now, more than **2200 batches** / **billions of doses of vaccine released** through the network by **6 of the OCABR OMCLs**

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EDQM and COVID-19: some initiatives

Regional

Work performed by EDQM/Ph. Eur. Commission and the network of experts

Guidance produced on recombinant viral-vectored vaccines to fill a gap

Pharmacopoeial texts relevant for COVID-19 on antivirals, vaccines and other relevant medicines together with training materials

Global

Collaboration with pharmacopoeias and regulatory authorities from around the world

Group of world pharmacopoeias (e.g. India, Mexico, USA, Japan, WHO, Vietnam) chaired by EDQM worked on monographs on medicinal products potentially of interest for COVID-19

Participation in the Regulatory Advisory Group from COVAX: to promote reliance on the European OCABR process worldwide

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European Pharmacopoeia in 2022

- Protecting public health – one common compulsory standard
- Applied by all licencing authorities
- Legally binding quality standards for all medicinal products

- Mandatory on the same date for all Members
- 40 Members (39 Member States & EU; latest member: Albania 2020)
- 30 Observers (5 European, 23 non-European countries, TFDA, WHO; latest Observer: Mexico 2020)
- 10th Edition (including Supplement 10.8: contains **2462 monographs (including dosage forms), 383 general texts** (including general monographs and methods of analysis) and about **2850 descriptions of reagents**.

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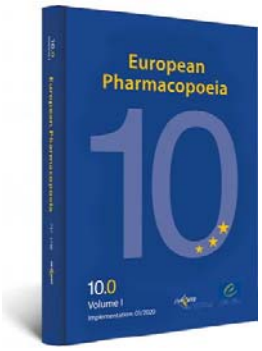
European Pharmacopoeia Reference Standards

Chemical Reference Substances,
Biological Reference Preparations,
Herbal Reference Standards and Reference Spectra invoked in the texts of the European Pharmacopoeia are



- **an integral part of the** official quality standard;
- **alone authoritative** in case of arbitration;
- **adopted** by the European Pharmacopoeia Commission;
- **available** from EDQM.

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The European Pharmacopoeia: content and structure

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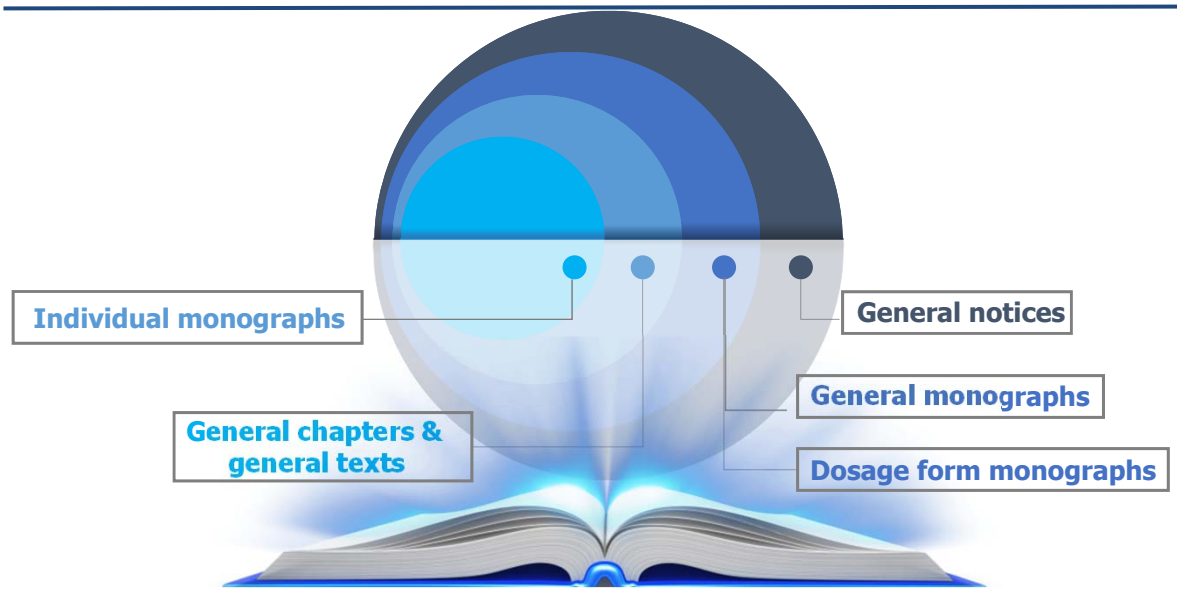
Ph. Eur.: Content and structure



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Content and structure of the Ph. Eur.

- ✓ Alternative methods
- ✓ Validation of methods
- ✓ Implementation of methods
- ✓ Compliance with the pharmacopoeia

General notices

General chapters

- ✓ General methods & texts
- ✓ Editorial convenience
- ✓ Not mandatory "*per se*"
- ✓ Part of the standard when referred to in a monograph
- ✓ **Can be used** when there is no monograph

- ✓ Vaccines for human use 0153
- ✓ Pharmaceutical Preparations 2319
- ✓ Dosage form monographs
  - Parenteral preparations

General monographs

Individual monographs

- ✓ 60 Vaccine individual monographs
- ✓ Iron sucrose concentrated solution (under elaboration)
- ✓ Cholesterol
- ✓ Squalene
- ✓ Polysorbate 20, 80

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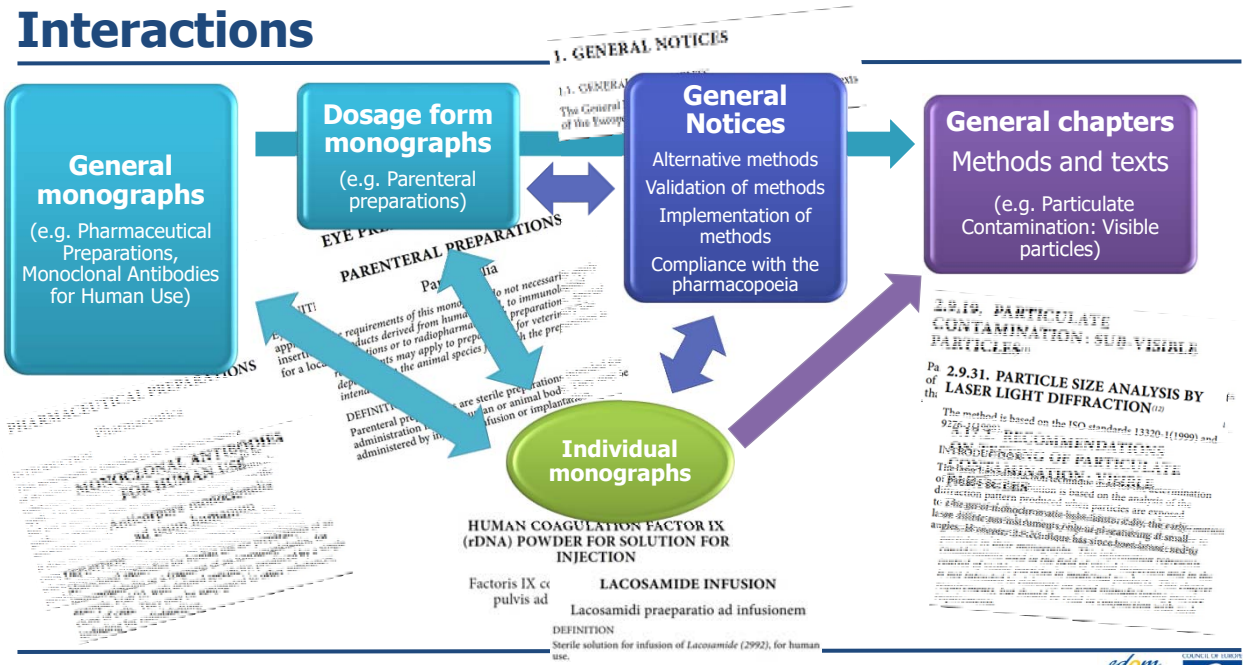
Interactions



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Example: Parenteral Preparations (0520)

- ✓ Generally applicable to all injections and infusions
- ✓ Need and efficiacy for antimicrobial preservation
- ✓ Particulate contamination
  - visible particles (2.9.20)
  - sub-visible particles (2.9.19)
- ✓ Sterility (2.6.1)
- ✓ Bacterial Endotoxins – pyrogens
- ✓ Uniformity requirements (2.9.40 or 2.9.6)
- ✓ Extractable Volume
- ✓ Release of active substance for modified release and implants

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Selected General Chapter

- ✓ Nuclear Magnetic Resonance Spectrometry (2.2.33, 2,264)
- ✓ PSD by LLD (2.9.31)
- ✓ Infrared Spectrophotometry (2.2.24)
- ✓ Sterility (2.6.1)
- ✓ pH (2.2.3)
- ✓ Size-exclusion chromatography (2.2.30)
- ✓ Osmolality (2.2.35)
- ✓ Recommendations: visible particles (5.17.2)
- ✓ PSD by DLS (2.9.50), upcoming, draft published

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Flexibility offered by the European Pharmacopoeia

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Demonstration of compliance with the Ph. Eur.

... and flexibility

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The way(s) to compliance - Flexibility

1.1.2.2

(1) An article is of Ph. Eur. quality if it complies with all of the requirements stated in the monograph. This does not im... cribed in a monograph when assessing compl... may obtain assurance that an article is of Ph. Eu... ol strategy and data derived, for example, from validation studies of the manufacturing process.

(1) WAIVING OF TESTS

In certain monogra... hat the analytical procedu... e replaced by a suitable, validated proc... e' procedure), subject to approval by the competent authority.

NEW **EXAMPLE PROCEDURE**

(2) An en...) and/or real-time releas... sting alone. Real-time r... thus not precluded by the ...

(2) REAL-TIME RELEASE TESTING

(3) Reduction of animal testing: the Ph. Eur. is committed to phasing out the use of animals for test purposes, in accordance with the 3Rs (Replacement, Reduction, Refinement) set out in the European Convention for the Pr... Scientific Purposes. In demonstrating compl... y consider establishing additional system... the competent authority, the choice of tests performed to assess compliance with the Ph. Eur. when animal tests are prescribed is established in such a way that animal usage is kept to a minimum.

(3) SUPPORTING THE 3Rs

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Flexibility #1: Waiving of tests

1.1.2.2

Compliance ≠ Performance of test

prerequisite — not a prerequisite

Tests may be omitted based on:

- **Design and control strategy**
- **Process knowledge** : validation studies of the manufacturing process or other suitable justification

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Additional flexibility: Example procedure

1.1.2.2

NEW

In certain monographs, identified by the statement

'*The following procedure is given as an example*'

✓ the analytical procedure has been validated for the intended purpose;

A

Implement & use the example procedure

OR

B

Replacement by another suitable **validated** procedure

No need to demonstrate equivalence to the procedure in the monograph

subject to approval by the competent authority.

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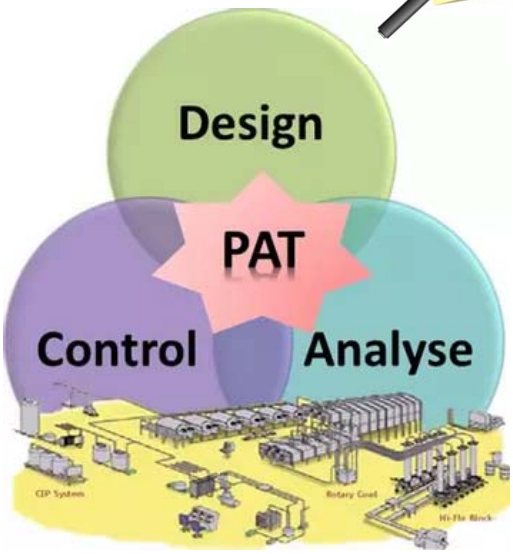
Flexibility #2: RTRT and PAT

1.1.2.2

"An **enhanced approach to quality control** could utilise process analytical technology (**PAT**) and/or **real-time release testing** (including parametric release) strategies as **alternatives to end-product testing alone**. Real-time release testing in circumstances deemed **appropriate by the competent authority** is thus **not precluded by the need to comply with the Pharmacopoeia**."



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The European Pharmacopoeia: elaboration process

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Basis for Monographs

- ✓ Mandatory texts
- ✓ Monographs take account of all currently approved products
- ✓ Approved specifications are the main basis backed up by batch data and stability data
- ✓ Draft monographs are checked by users and regulatory authorities at Pharmeuropa stage
- ✓ Policy for monograph elaboration is given in:

  Technical Guide for the Elaboration of Monographs
  (available on the EDQM website
  https://www.edqm.eu/documents/52006/66555/02-technical-guide-elaboration-monographs-7th-edition-2015.pdf)

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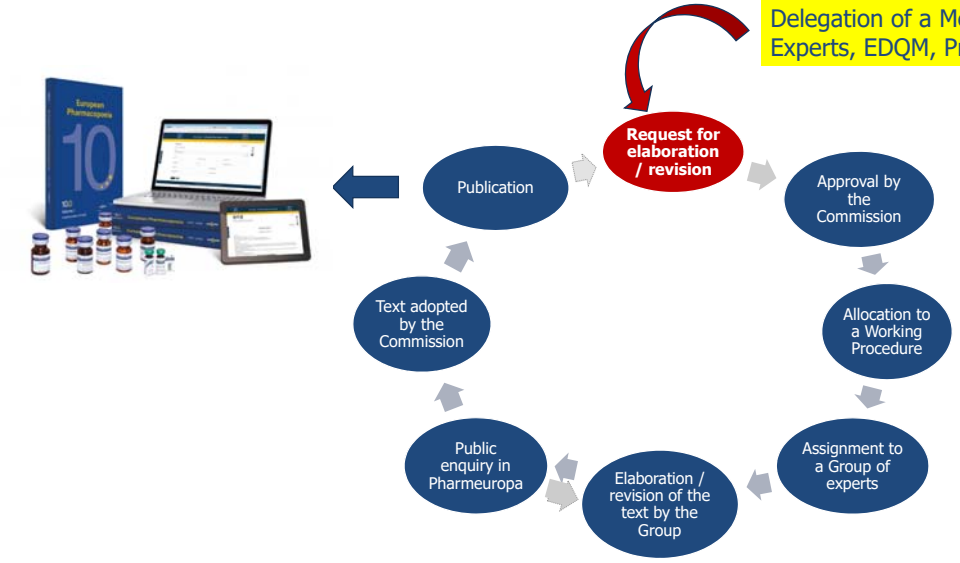
Elaboration or Revision of a text

Request

Delegation of a Member State
Experts, EDQM, Producers



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Proposing a new monograph

⇨ Contact the EDQM or your National Pharmacopoeia Authority

- ✓ **Initial data**: countries (in Europe) where the product is approved
- ✓ **Data package**:
  - Current specification
  - Analytical procedures (SOPs)
  - Corresponding validation reports
  - Batch data (release and stability)
  - Justification for spec., list of potential impurities, [pharmaceutical development data]
  - Samples of the [medicinal product], substance and impurities

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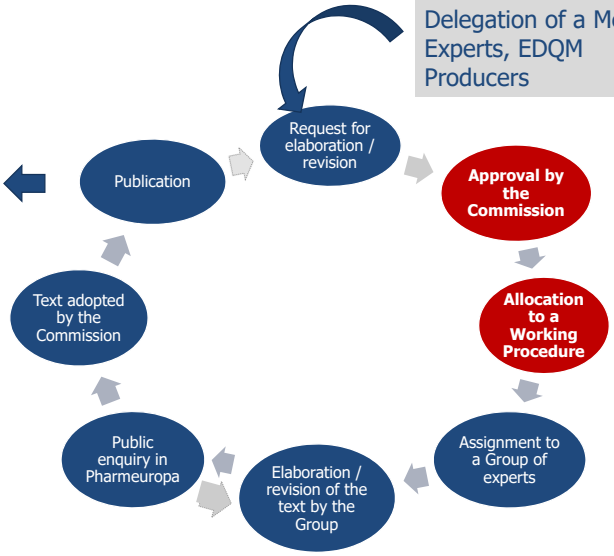
Elaboration or Revision of a Text



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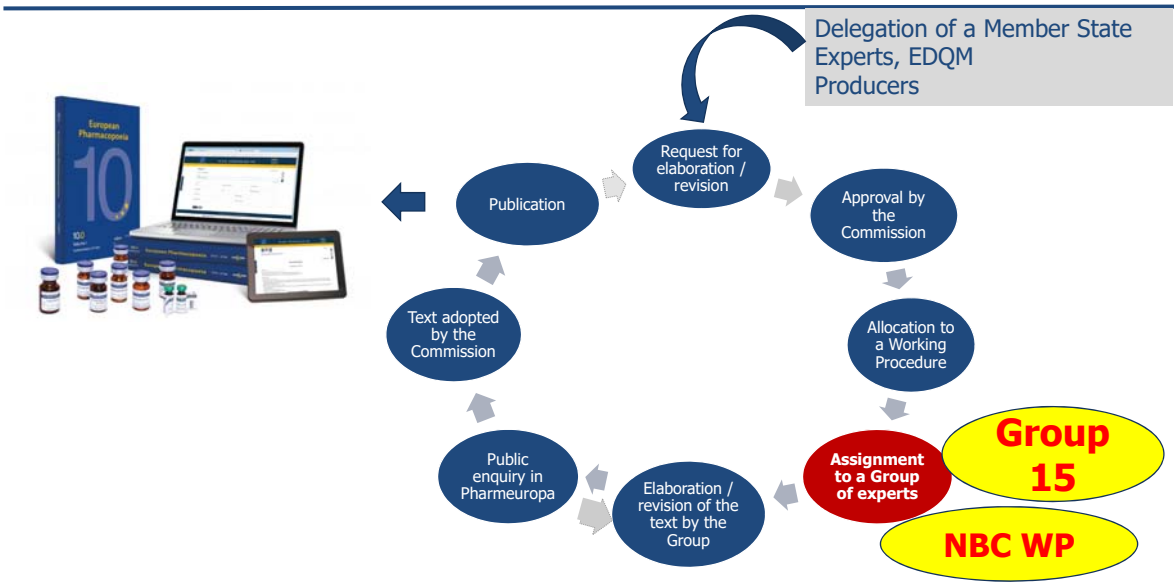
Elaboration or Revision of a Text



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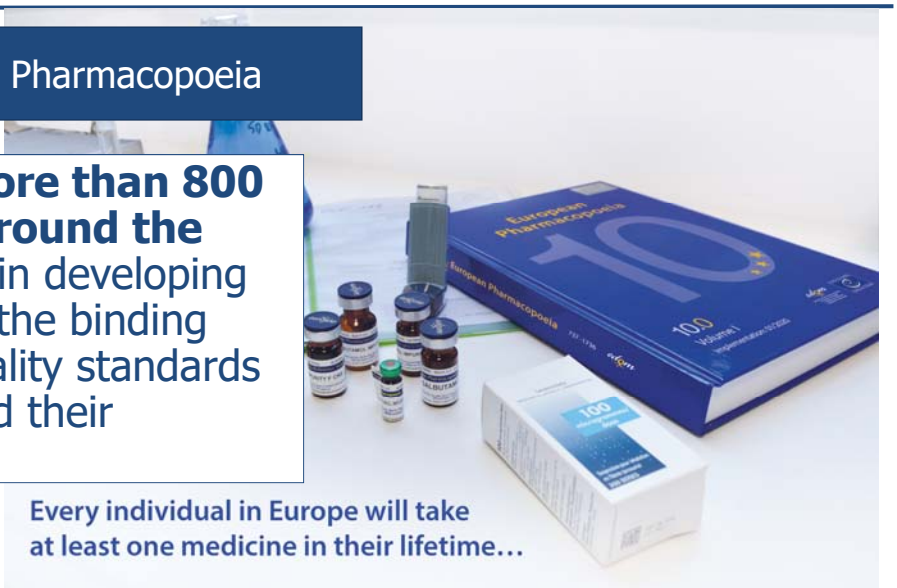
60 Groups of Experts and Working Parties

The European Pharmacopoeia

At the EDQM, **more than 800 experts from around the world** take part in developing and maintaining the binding documentary quality standards for medicines and their ingredients.



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Elaboration or Revision of a Text

Delegation of a Member State
Experts, EDQM
Producers

Request for elaboration / revision

Approval by the Commission

Allocation to a Working Procedure

Assignment to a Group of experts

Elaboration / revision of the text by the Group

Public enquiry in Pharmeuropa

Text adopted by the Commission

Publication

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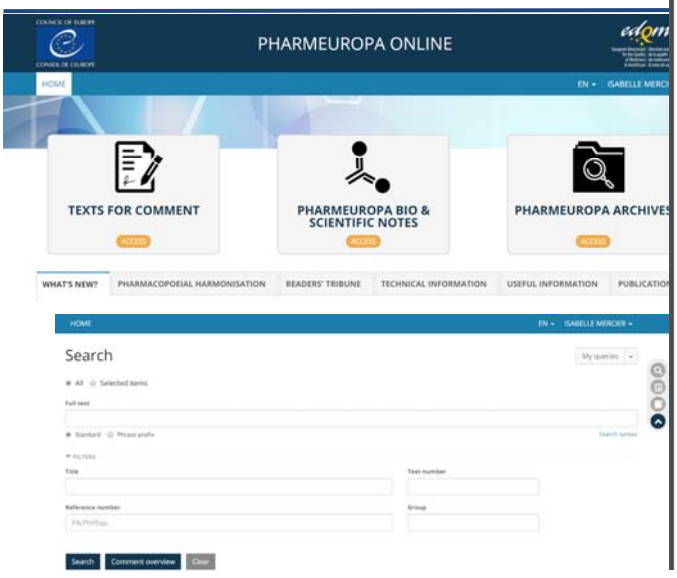
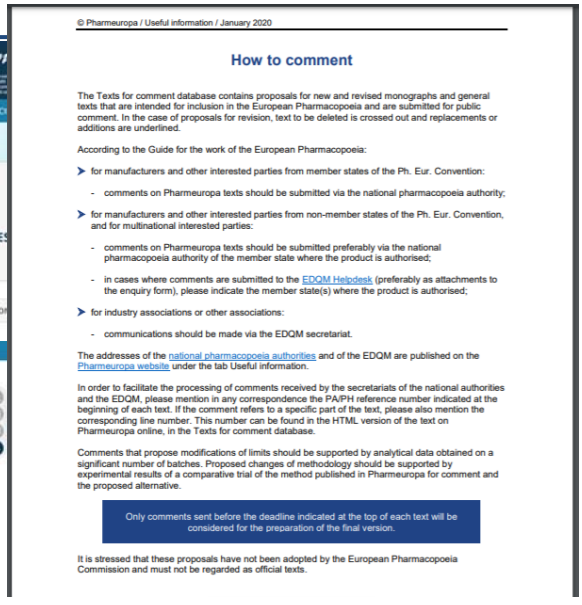
How to Comment?!





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How to comment

The Texts for comment database contains proposals for new and revised monographs and general texts that are intended for inclusion in the European Pharmacopoeia and are submitted for public comment. In the case of proposals for revision, text to be deleted is crossed out and replacements or additions are underlined.

According to the Guide for the work of the European Pharmacopoeia:

- for manufacturers and other interested parties from member states of the Ph. Eur. Convention:
  - comments on Pharmeuropa texts should be submitted via the national pharmacopoeia authority;
- for manufacturers and other interested parties from non-member states of the Ph. Eur. Convention, and for multinational interested parties:
  - comments on Pharmeuropa texts should be submitted preferably via the national pharmacopoeia authority of the member state where the product is authorised;
  - in cases where comments are submitted to the EDQM Helpdesk (preferably as attachments to the enquiry form), please indicate the member state(s) where the product is authorised;
- for industry associations or other associations:
  - communications should be made via the EDQM secretariat.

The addresses of the national pharmacopoeia authorities and of the EDQM are published on the Pharmeuropa website under the tab Useful information.

In order to facilitate the processing of comments received by the secretariats of the national authorities and the EDQM, please mention in any correspondence the PA/PH reference number indicated at the beginning of each text. If the comment refers to a specific part of the text, please also mention the corresponding line number. This number can be found in the HTML version of the text on Pharmeuropa online, in the Texts for comment database.

Comments that propose modifications of limits should be supported by analytical data obtained on a significant number of batches. Proposed changes of methodology should be supported by experimental results of a comparative trial of the method published in Pharmeuropa for comment and the proposed alternative.

Only comments sent before the deadline indicated at the top of each text will be considered for the preparation of the final version.

It is stressed that these proposals have not been adopted by the European Pharmacopoeia Commission and must not be regarded as official texts.

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Elaboration or Revision of a Text

Delegation of a Member State
Experts, EDQM
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Text adopted by the Commission

Publication

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Ph. Eur. Commission

Ph. Eur. Commission

Composed of :
- 39 Member States
- European Union
- 30 Observers:
  - 5 European countries
  - 23 non European countries
  - Taiwan Food and Drug Administration (TFDA)
  - World Health Organization (WHO)

Presidium
- Chair
- 2 vice-chairs
- Ph. Eur. Secretariat

Presidium Meetings + Meeting of Chairs of Groups of Experts

Contributors:
- National Pharmacopoeia Authorities
- Competent Authorities
- Industry
- OMCL Network

Groups of Experts | Working Parties

- One delegation per Member State / Observer
- Three sessions a year
- Texts are adopted by **unanimous** vote
- Composition of groups of experts decided by Ph. Eur. Commission
- Since 2016: open to experts throughout the world

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Gene therapy products: a case study

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Gene transfer medicinal products for human use (5.14)

General chapter

Recombinant vectors
Genetically modified cells

- Plasmid vectors for human use
- Bacterial cells used for the manufacture of plasmid vectors for human use
- Adenovirus vectors for human use
- Poxvirus vectors for human use

GTP WP

Addition of:

- Retroviridae-derived vectors for human use
- Adeno-associated virus vectors for human use

General revision to consider recent developments in the field

Addition to WP 2000 — **Adoption** 2005 — **Revision #1** 2008 — **GTP WP reinstatement** 2018 — **Revision #2** 2019

GTMPs in Europe

Glybera, IMLYGIC, Strimvelis, YESCARTA, LUXTURNA, KYMRIAH, Zynteglo

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NOW

General chapter
Gene transfer medicinal products for human use (5.14)

- Definition, Production
  - *Recombinant vectors*
  - *Genetically modified cells*
- Plasmid vectors for human use
- Bacterial cells used for the manufacture of plasmid vectors for human use
- Adenovirus vectors for human use
- Poxvirus for human use
- Adeno-associated-virus vectors for human use
- Retroviridae-derived vectors for human use

Sections reproduced directly from 5.14
Section reproduced from 5.14 with limited changes
Revised sections originating from 5.14
Newly drafted sections

FUTURE?

General monograph
Gene therapy medicinal products for human use (3186)

- Definition
- General requirements on:
  - the Production of GTMPs
  - *Recombinant vectors*
  - *Genetically modified cells*
- *Genetically modified autologous human cells*
- *Adeno-associated-virus vectors for human use*
- *Oncolytic herpes simplex virus for human use*

General chapter
Additional information on gene therapy medicinal products for human use (5.34)

- *Plasmid vectors for human use*
- *Bacterial cells used for the manufacture of plasmid vectors for human use*
- *Genetically modified bacterial cells for human use*
- *Adenovirus vectors for human use*
- *Poxvirus vectors for human use*
- *Retroviridae-derived vectors for human use*

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Before we conclude…

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Call for experts 2022-2025

Why become a Ph. Eur. expert?

- Provide a **vital and invaluable contribution** to the elaboration and maintenance of Ph. Eur. texts **by taking part** in the work of the Ph. Eur.
- **Expand** your knowledge of the Ph. Eur. and the European regulatory system
- **Network** with peers and other professionals with various backgrounds and from all over Europe and beyond
- Help **shape** Ph. Eur. texts, internationally-recognised quality standards for medicines
- **Share** information and experience

Nomination process now open to all experts!

- **Ph. Eur. member states**: via your respective pharmacopoeia authorities.
- **Non Ph. Eur. member states**: via EDQM Helpdesk service.

Visit EDQM website: Join the network!

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Celebrating the 11th Edition… see you again in September?

Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition
International Conference
19-21 September 2022
Strasbourg, France

Registration open

This three-day conference will delve into numerous in-depth topics around the work of the **European Pharmacopoeia**, and much more…

Take a closer look at the programme

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Target outcome of the event

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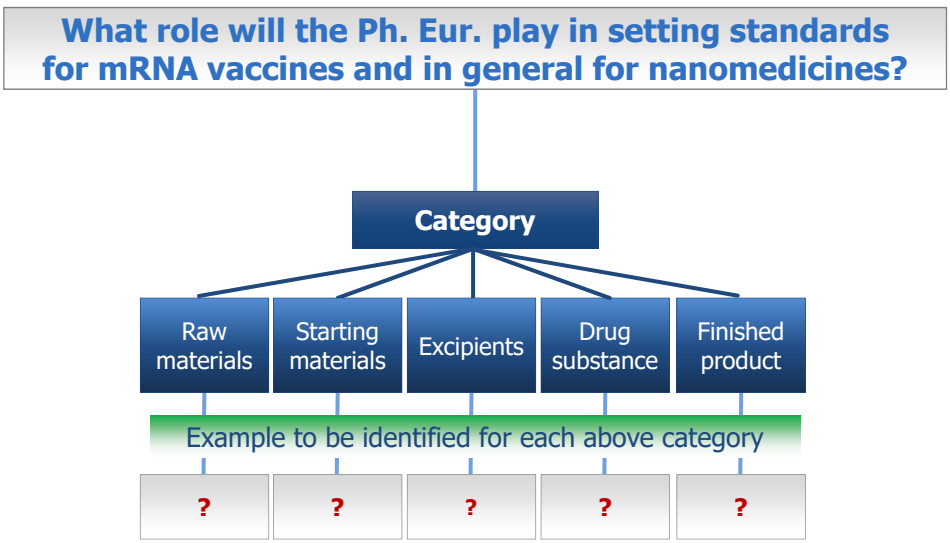
Target outcome of the event



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Target outcome of the event

What role will the Ph. Eur. play in setting standards for mRNA vaccines and in general for nanomedicines?

Format

- Individual monographs
- General monographs
- General chapters
- Reference standard

Question to be addressed for each example identified above

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Target outcome of the event (continued)

If a general chapter: in what detail?

- Guidance document
- "Toolkit" (list of methods)
- Detailed analytical procedure

If an excipient monograph: what approach?

- **Revision** of existing individual monograph(s) → to cover a grade suitable for the manufacture of nanomedicines
- **Elaboration** of new excipient monograph(s) (LNP component)

Reference Standards

.....

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Target outcome of the event

Interactive Session: What does the future hold?

The floor will be yours!

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Thank you for your attention

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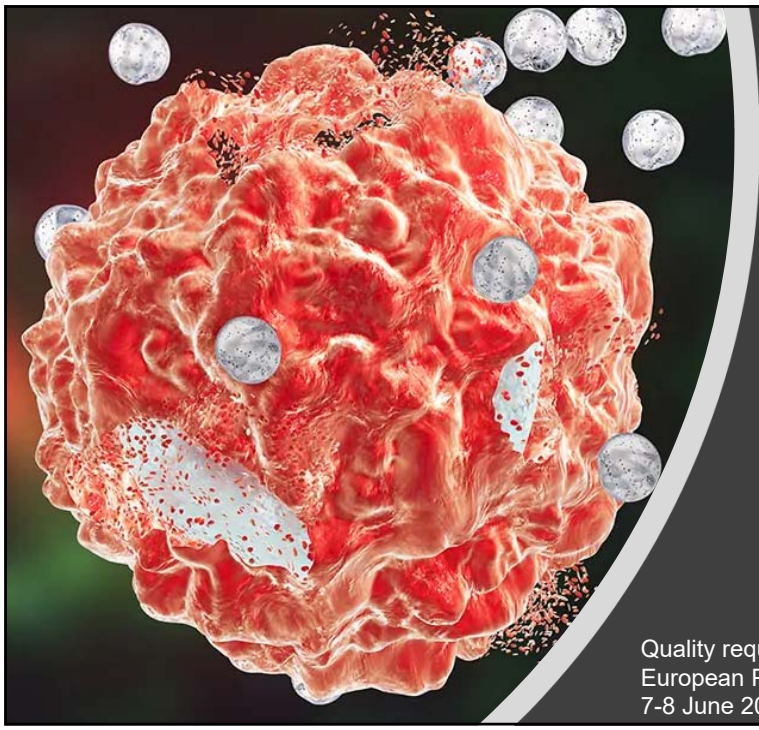


Nano-related activities at the Ph. Eur.: The Non-Biological Complex working party

Gerrit Borchard, PharmD, PhD

School of Pharmaceutical Sciences
University of Geneva
Switzerland

Quality requirements for nanomedicines: which role for the European Pharmacopoeia?
7-8 June 2022, Strasbourg, France

Declaration of interests

- Member of the Non-Biological Complex Drug (NBCD) Working Group, a non-profit organisation managed by Lygature (Utrecht, NL)
- Member of the cientific Advisory Board of EU projects EU-NCL and REFINE
- Consultant for TEVA (former) and VIFOR Pharma (Glattbrugg, CH, current)

European Directorate for the Quality of Medicines & HealthCare (EDQM)

- A Council of Europe Directorate, based on the Convention on the Elaboration of a *European Pharmacopoeia* (PA, 1964)
  - Mission: to contribute to a basic human right: access to good quality medicines and healthcare

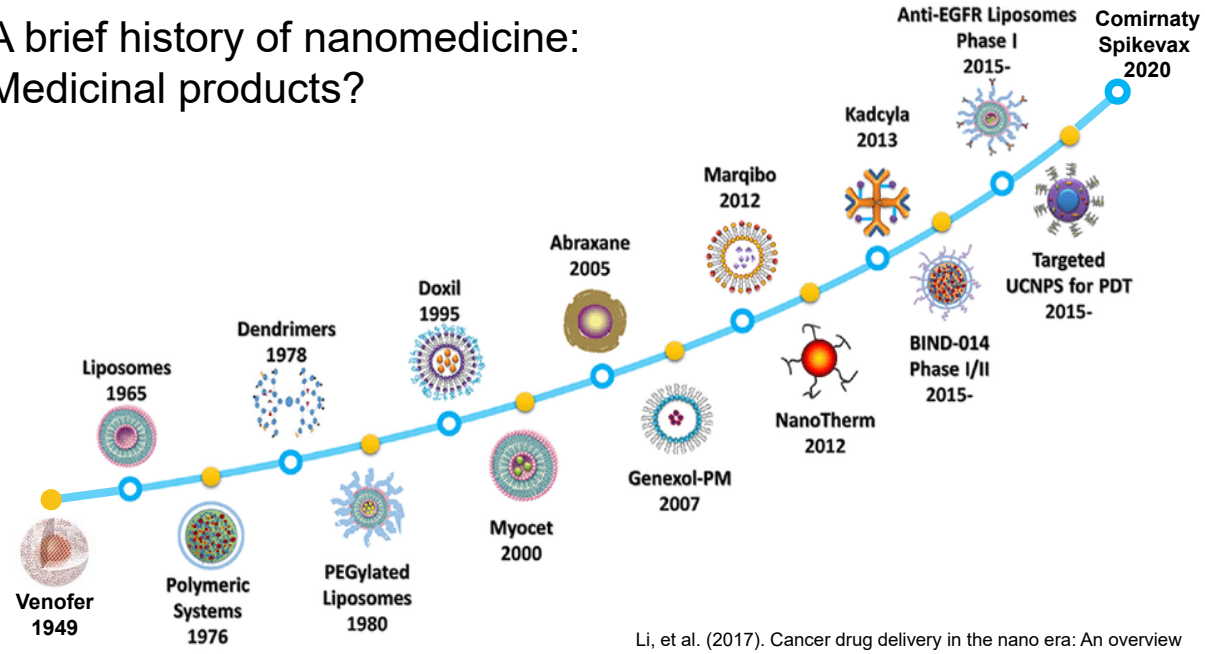
edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

The European Pharmacopoeia (Ph. Eur.)

- Protecting public health - one **common compulsory standard**
- The Ph. Eur. is the **official pharmacopoeia** in Europe
- The Ph. Eur. is **complemented by national pharmacopoeias** for texts of interest to only one Member State
- **Mandatory** at the same date in 39 Member States (CoE) and the EU (decision of Ph. Eur. Commission).
- Legally binding **quality standards** for ALL medicinal products, i.e. raw material, preparations, dosage forms, containers,…

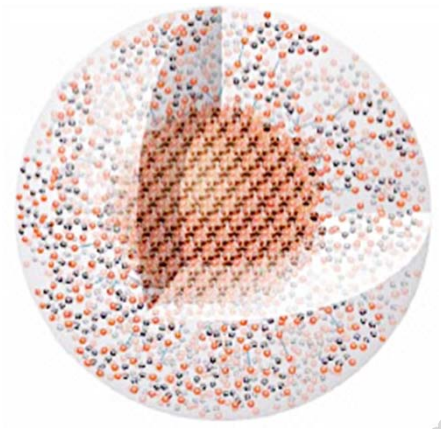
A brief history of nanomedicine: Medicinal products?



Li, et al. (2017). Cancer drug delivery in the nano era: An overview and perspectives. Oncology Reports. 38. doi: 10.3892/or.2017.5718.

Non-Biological Complexes (NBC) Working Party

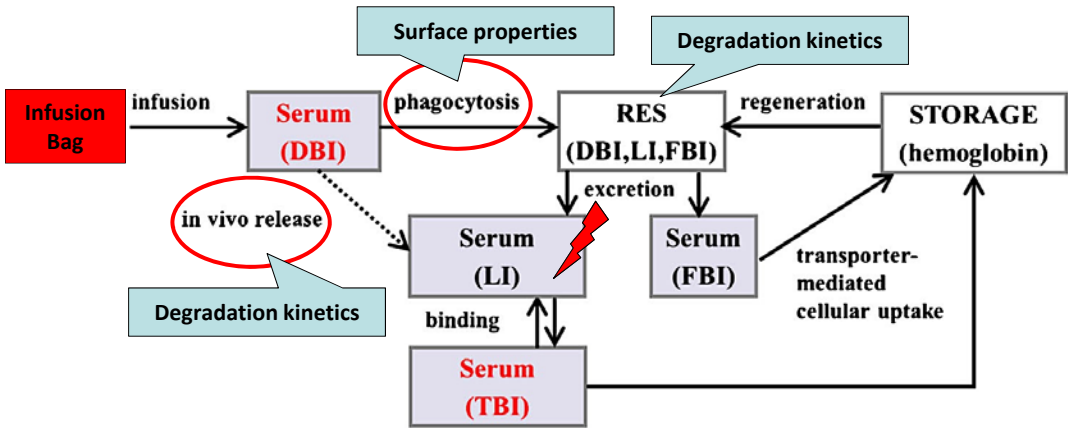
- Created in June 2011 based on an initiative by SwissMedic and following the decision of the Ph. Eur. Commission to add on its work programme the elaboration of a monograph on ***Iron sucrose concentrated solution***.
- Elaboration of monographs on **non-biological complexes** (e.g., nanoparticle solutions, like for example iron sucrose concentrated solution) allocated to the group by the Commission.
- Members from academia, industry (originator, follow-on), regulatory authorities and public research institutes



Why Iron Sucrose (IS)?

- Used in treatment of iron deficiency in chronic kidney diseases (CKD), chronic heart failure, inflammatory bowel disease (IBD), obstetrics and gynecology, etc.
- On the European market since 1949, replacing iron dextran (used since 1900), US introduction in 2000
- Several follow-on products approved ("Iron sucrose similars", ISS)
- Nano-sized polynuclar iron cores coated with a layer of sucrose, stabilized at pH 11
- Side effects related to labile iron -> ROS creation, other?

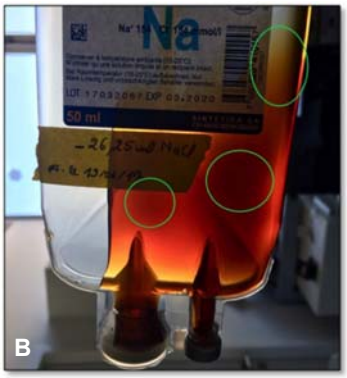
PK of iron sucrose upon i.v. infusion



RES: reticulo-endothelial system, DBI: drug bound iron, LI: labile iron, FBI: ferritin-bound iron, TBI: transferrin-bound iron

Modified from: Zheng, et al., AAPSJ, 2017

IV iron products infusion bags



- Viscosity issues: difficulties in mixing with saline (A, B)
- Differences in color between Ferrasil and Feromax (C)

Di Francesco, E. Sublet, G. Borchard, Nanomedicines in clinical practice: are intravenous iron sucrose ready-to-use solution[9] interchangeable? Eur. J. Pharm. Sci. (2019) doi: 10.1016/j.ejps.2019.02.012.

Monograph draft Iron Sucrose Concentrated Solution

Definition, Content, Production, Characters, Identification

Tests:

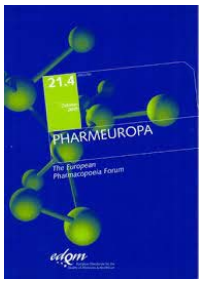
- pH
- Alkalinity
- Fe^{2+} content
- Reduction potential
- Labile iron
- Chloride
- Molecular mass distribution
- Particle size distribution
- Turbidity point
- Total iron

- Method development
- Round robin tests (WP members)
- Logistics by EDQM
- Regular meetings

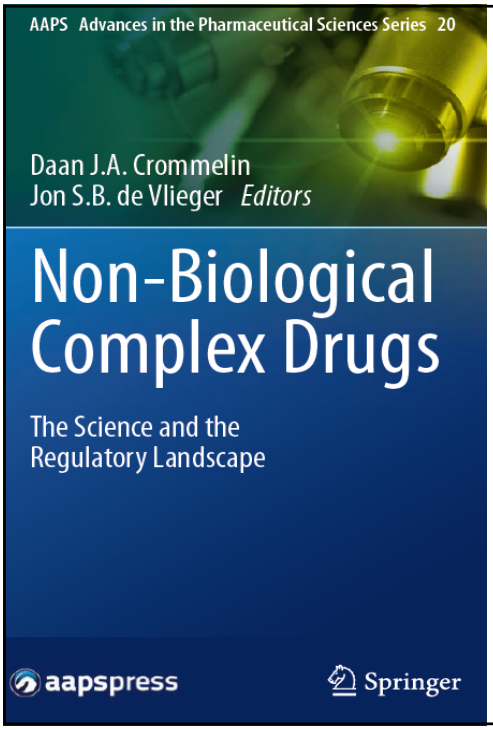
Storage, Labelling

Monograph draft Iron Sucrose Concentrated Solution

Next steps:



- Finalisation of draft monograph
- Publication in **Pharmaeuropa** for public comments
- **National Pharmacopoeia Authorities** process the comments received
- **European Pharmacopoeia Secretariat** compiles the comments sent
- **NBC working party** examines the comments and revises the monograph
- The draft is proposed to the **European Pharmacopoeia Commission**
  - adopts the monograph if necessary with slight modification
  - implementation date about 1 year after the adoption of the monograph
- Ph. Eur. (3 revisions/year): Publishes about 6 months later



Non Biological Complex Drugs working group

Book for AAPS series 'Advances in the Pharmaceutical Sciences':

'non biological COMPLEX DRUGS; the science and the regulatory landscape'

Released mid 2015, available through Springer:

http://www.springer.com/gp/book/9783319162409

Ph. Eur. standards in the field of vaccines and perspectives for new vaccine classes including mRNA vaccines

Svein Rune Andersen

Scientific Director – Vaccines

Norwegian Medicines Agency

Statens legemiddelverk

Ph. Eur. Group of Experts 15 – Human Vaccines and Sera

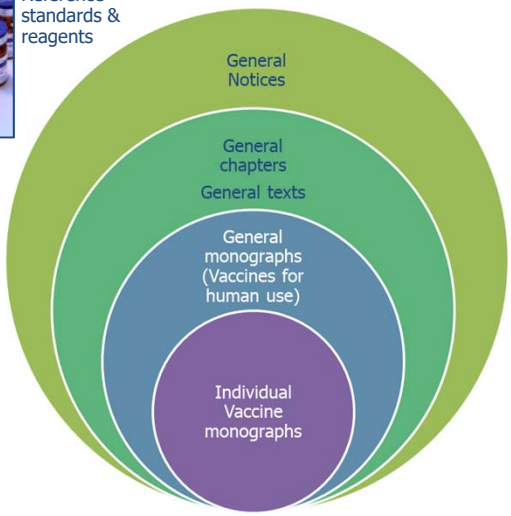
- Elaborate texts (monographs and general chapters/texts) related to vaccines and sera for human use
- The group consists of ca 30 experts (NRAs, national control labs & industry) with expertise in analytical methods related to the QC of vaccines and sera and in development of control methods
- Observers from US FDA, Health Canada, TGA, Taiwan FDA…

Statens legemiddelverk

Ph. Eur. standards for vaccines

- European Pharmacopoeia 10.8
  - European Pharmacopoeia 10.8
    - 00 Introduction
    - 01 General notices
    - 02 Methods of analysis
    - 03 Materials for containers and containers
    - 04 Reagents
    - 05 General Texts
    - 06 General Monographs
    - 07 Dosage forms
    - 08 Vaccines
    - 09 Immunosera
    - 10 Radiopharmaceutical preparations and st...
    - 11 Sutures
    - 12 Herbal drugs and herbal drug preparations
    - 13 Homoeopathic preparations
    - 14 Monographs A-C
    - 15 Monographs D-K

Reference standards & reagents



Technical guide for the elaboration of monographs on vaccines
(not part of Ph. Eur.)

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General chapters supporting vaccine monographs

1) General chapters on analytical methods

- European Pharmacopoeia 10.8
  - European Pharmacopoeia 10.8
    - 00 Introduction
    - 01 General notices
    - 02 Methods of analysis
    - 03 Materials for containers and containers
    - 04 Reagents
    - 05 General Texts
    - 06 General Monographs
    - 07 Dosage forms
    - 08 Vaccines
    - 09 Immunosera
    - 10 Radiopharmaceutical preparations and st...
    - 11 Sutures
    - 12 Herbal drugs and herbal drug preparations
    - 13 Homoeopathic preparations
    - 14 Monographs A-C
    - 15 Monographs D-K

General methods	Chapter number
Biological tests	
Tests for extraneous agents in viral vaccines for human use	*2.6.16*
Test for neurovirulence of live virus vaccines	*2.6.18*
Residual pertussis toxin	*2.6.33*
Biological assays	
Assay of diphtheria vaccine (adsorbed)	*2.7.6*
Assay of pertussis vaccine (whole cell)	*2.7.7*
Assay of tetanus vaccine (adsorbed)	*2.7.8*
Assay of hepatitis A vaccine	*2.7.14*
Assay of hepatitis B vaccine (rDNA)	*2.7.15*
Assay of pertussis vaccine (acellular)	*2.7.16*
In vivo assay of poliomyelitis vaccine (inactivated)	*2.7.20*
Flocculation value (Lf) of diphtheria and tetanus toxins and toxoids (Ramon assay)	*2.7.27*
Immunonephelometry for vaccine component assay	*2.7.35*

Limit tests
Free formaldehyde *2.4.18*

Assays e.g.
- Aluminium in adsorbed vaccines *2.5.13*
- Phenol in immunosera and vaccines *2.5.15*

Etc...

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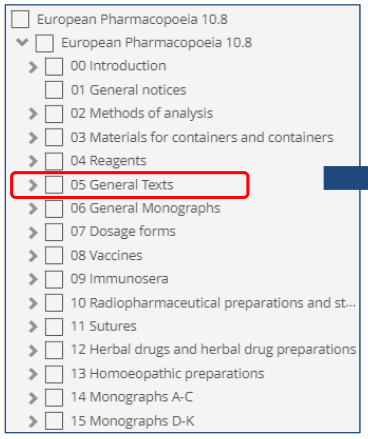
General chapters supporting vaccine monographs

2) General texts (substrates for propagation, carrier proteins, 3Rs…)



General texts	Chapter number
Chicken flocks free from specified pathogens for the production and quality control of vaccines	5.2.2
Cell substrates for the production of vaccines for human use	5.2.3
Carrier proteins for the production of conjugated polysaccharide vaccines for human use	5.2.11
Substitution of *in vivo* methods by *in vitro* methods for the quality control of vaccines	5.2.14

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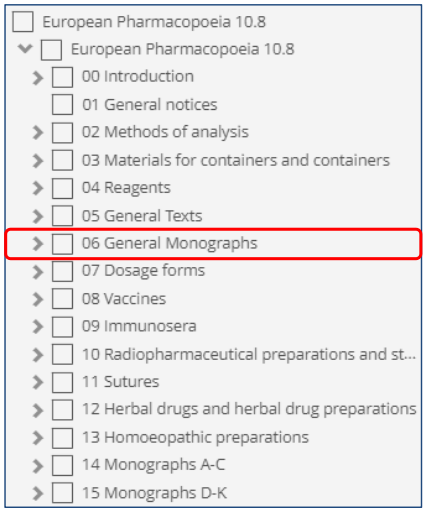
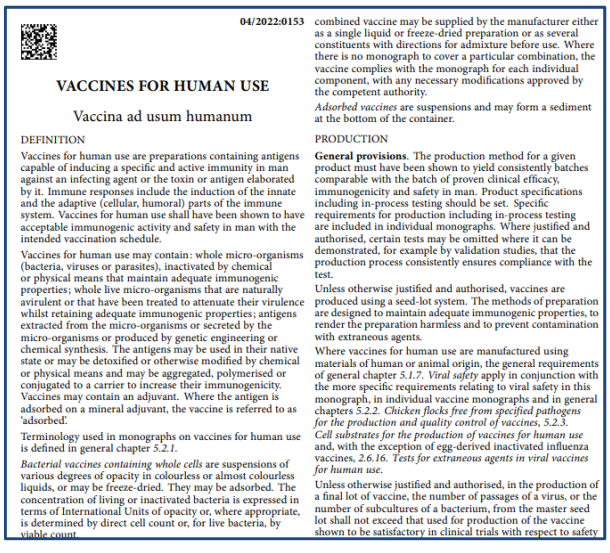
General monograph *Vaccines for human use* (0153)





04/2022:0153

VACCINES FOR HUMAN USE

Vaccina ad usum humanum

DEFINITION

Vaccines for human use are preparations containing antigens capable of inducing a specific and active immunity in man against an infecting agent or the toxin or antigen elaborated by it. Immune responses include the induction of the innate and the adaptive (cellular, humoral) parts of the immune system. Vaccines for human use shall have been shown to have acceptable immunogenic activity and safety in man with the intended vaccination schedule.

Vaccines for human use may contain: whole micro-organisms (bacteria, viruses or parasites), inactivated by chemical or physical means that maintain adequate immunogenic properties; whole live micro-organisms that are naturally avirulent or that have been treated to attenuate their virulence whilst retaining adequate immunogenic properties; antigens extracted from the micro-organisms or secreted by the micro-organisms or produced by genetic engineering or chemical synthesis. The antigens may be used in their native state or may be detoxified or otherwise modified by chemical or physical means and may be aggregated, polymerised or conjugated to a carrier to increase their immunogenicity. Vaccines may contain an adjuvant. Where the antigen is adsorbed on a mineral adjuvant, the vaccine is referred to as 'adsorbed'.

Terminology used in monographs on vaccines for human use is defined in general chapter *5.2.1.*

Bacterial vaccines containing whole cells are suspensions of various degrees of opacity in colourless or almost colourless liquids, or may be freeze-dried. They may be adsorbed. The concentration of living or inactivated bacteria is expressed in terms of International Units of opacity or, where appropriate, is determined by direct cell count or, for live bacteria, by viable count.

combined vaccine may be supplied by the manufacturer either as a single liquid or freeze-dried preparation or as several constituents with directions for admixture before use. Where there is no monograph to cover a particular combination, the vaccine complies with the monograph for each individual component, with any necessary modifications approved by the competent authority.

Adsorbed vaccines are suspensions and may form a sediment at the bottom of the container.

PRODUCTION

General provisions. The production method for a given product must have been shown to yield consistently batches comparable with the batch of proven clinical efficacy, immunogenicity and safety in man. Product specifications including in-process testing should be set. Specific requirements for production including in-process testing are included in individual monographs. Where justified and authorised, certain tests may be omitted where it can be demonstrated, for example by validation studies, that the production process consistently ensures compliance with the test.

Unless otherwise justified and authorised, vaccines are produced using a seed-lot system. The methods of preparation are designed to maintain adequate immunogenic properties, to render the preparation harmless and to prevent contamination with extraneous agents.

Where vaccines for human use are manufactured using materials of human or animal origin, the general requirements of general chapter *5.1.7. Viral safety* apply in conjunction with the more specific requirements relating to viral safety in this monograph, in individual vaccine monographs and in general chapters *5.2.2. Chicken flocks free from specified pathogens for the production and quality control of vaccines*, *5.2.3. Cell substrates for the production of vaccines for human use* and, with the exception of egg-derived inactivated influenza vaccines, *2.6.16. Tests for extraneous agents in viral vaccines for human use*.

Unless otherwise justified and authorised, in the production of a final lot of vaccine, the number of passages of a virus, or the number of subcultures of a bacterium, from the master seed lot shall not exceed that used for production of the vaccine shown to be satisfactory in clinical trials with respect to safety

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General monograph *Vaccines for human use* (0153)

Pharmacopoeial requirements for vaccines:

→ Given in general monograph *Vaccines for Human Use* and individual vaccine monographs

General Monograph *Vaccines for Human Use* :

- Provisions apply to all vaccines, including those for which there is no individual monograph
- General requirements for production, testing, storage, and labelling
- Essential requirements which supplement and expand on requirements contained in the monographs for specific vaccines
- Requirements usually not repeated in individual monographs

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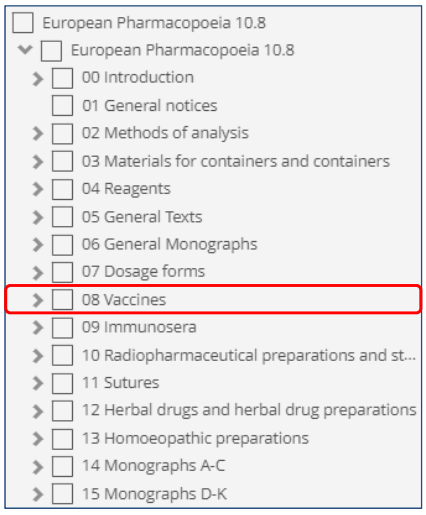
Individual vaccine monographs

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ROTAVIRUS VACCINE (LIVE, ORAL)

Vaccinum rotaviri vivum perorale

07/2022:0158

INFLUENZA VACCINE (SPLIT VIRION, INACTIVATED)

Vaccinum influenzae inactivatum ex virorum fragmentis praeparatum

DEFINITION

PRODUCTION

VIRUS PROPAGATION AND HARVEST

MONOVALENT POOLED HARVEST

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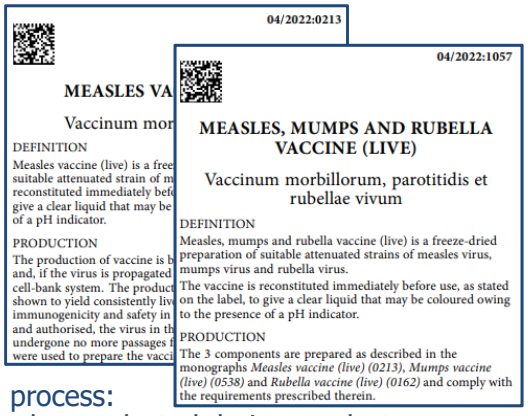
Individual vaccine monographs

- Monographs are elaborated for single type vaccines (e.g. Measles vaccine) & combined vaccines (e.g. MMR vaccine)
- The quality standards attained by vaccines already on the market are taken into consideration during the elaboration of a new monograph
- Content:

  - Production (essential features of the manufacturing process: points to be addressed for vaccine production; tests to be conducted during product development, routinely on intermediates and on each vaccine batch)
  - Identification tests, Tests (batch tests with limits), Potency assay
  - Storage, Labelling



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MEASLES VA

Vaccinum mor

DEFINITION

Measles vaccine (live) is a free
suitable attenuated strain of m
reconstituted immediately bef
give a clear liquid that may be
of a pH indicator.

PRODUCTION

The production of vaccine is b
and, if the virus is propagated
cell-bank system. The product
shown to yield consistently liv
immunogenicity and safety in
and authorised, the virus in th
undergone no more passages f
were used to prepare the vacci

04/2022:1057

MEASLES, MUMPS AND RUBELLA VACCINE (LIVE)

Vaccinum morbillorum, parotitidis et rubellae vivum

DEFINITION

Measles, mumps and rubella vaccine (live) is a freeze-dried preparation of suitable attenuated strains of measles virus, mumps virus and rubella virus.

The vaccine is reconstituted immediately before use, as stated on the label, to give a clear liquid that may be coloured owing to the presence of a pH indicator.

PRODUCTION

The 3 components are prepared as described in the monographs *Measles vaccine (live) (0213)*, *Mumps vaccine (live) (0538)* and *Rubella vaccine (live) (0162)* and comply with the requirements prescribed therein.

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Options to describe quality requirements for vaccines in Ph. Eur. – summary

- General monograph *Vaccines for human use* (0153)
  - Requirements apply to <u>all</u> vaccines
- When more detailed information is needed:

  Individual vaccine monographs (ca 60, e.g. IPV monograph)
  - General provisions on production + testing requirements/limits for drug substance and drug product
  - Legally binding
  - Requirements: «the smallest common denominator»

    ➔A new monograph should not render already approved vaccines incompliant

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Options to describe quality requirements for vaccines in Ph. Eur. – summary (cont'd)

- General Texts:
  - Only mandatory if referred to in a monograph (unless otherwise stated)
  - E.g. Chapter 5.2.11 *Carrier proteins for production of conjugated polysaccharide vaccines*
- General Chapters on analytical methods (tests and assays):
  - Potency assays: e.g. for Tetanus or Hepatitis A vaccines (2.7.8, 2.7.14)
  - Viral safety tests: e.g. *Tests for extraneous agents in viral vaccines* (2.6.16)
  - Pyrogen test: e.g. *Monocyte-activation test* (2.6.30)
- Substance monographs, e.g. monographs on vaccine adjuvants (or other excipients)
  - Squalene, MPL, $Al(OH)_3$, $AlPO_4$ (under elaboration)

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Pharmacopoeial standards for mRNA vaccines: where to start?

What is needed for mRNA vaccines?

- Nucleic acid-based vaccines are currently not covered by the General monograph *Vaccines for human use*
  - Group 15: work in progress to update the general monograph to take into account new vaccine classes including mRNA vaccines and viral-vectored vaccines
    --> First important step to cover mRNA vaccines in the Ph. Eur.
- Would a general text (non-binding) on mRNA vaccines be useful?
  - Acknowledge the need for flexibility in the context of a quickly evolving field
  - E.g. control strategy for this class of vaccines; (nano-)formulation aspects?
- Specific analytical methods? Need for physical standards (reference standards)?
- Monographs on components of the lipid nanoparticles?

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