PIPAC ESSENTIALS

Principles of Capnoperitoneum and PIPAC Technology

Marc A. Reymond, MD, MBA

Professor of Surgery, University of Tübingen, Germany

Director, National Center for Pleura and Peritoneum

Disclosures

- CEO/Owner of Capnomed GmbH
- CEO/Owner of Capnopharm GmbH

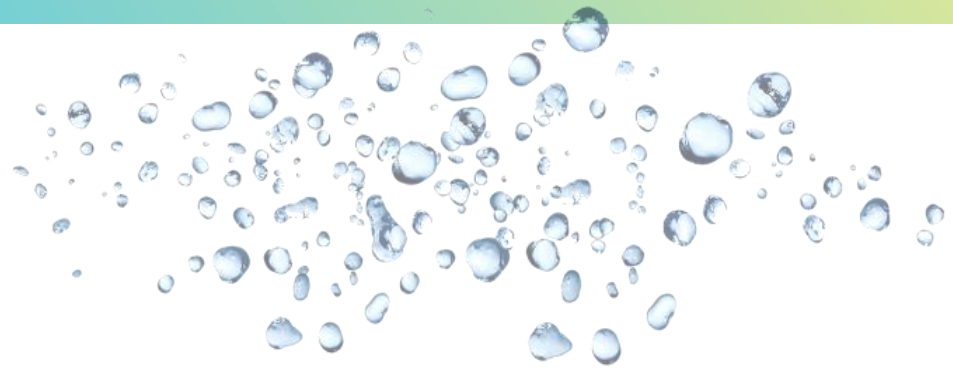
These disclosures have been deemed as irrelevant, as this presentation is:

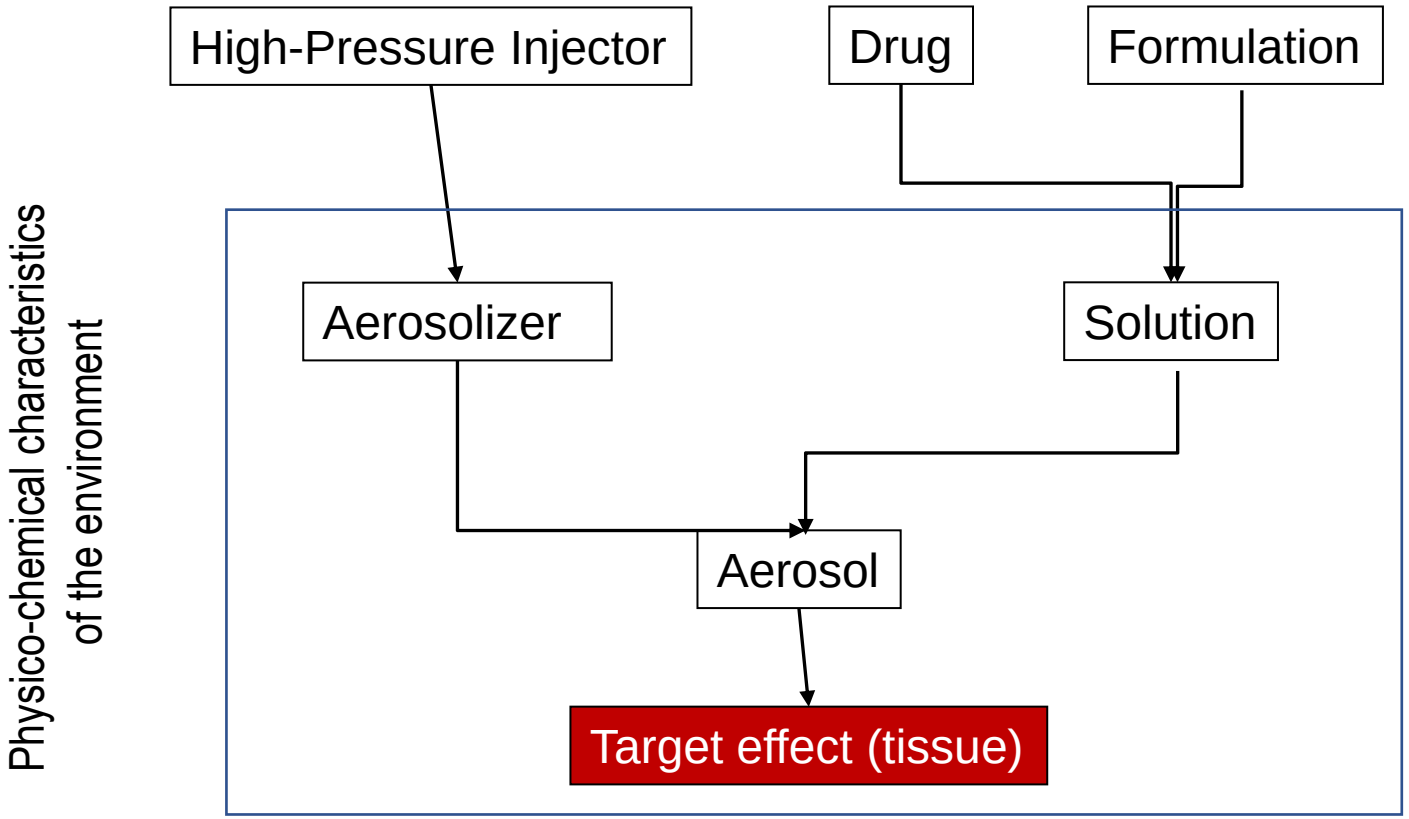
- Limited to basic science research, such as pre-clinical research and drug discovery, or the methodologies of research, and I will not make care recommendations.
- Intended to teach the safe and proper use of medical devices, and I will not recommend whether or when a device is used.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

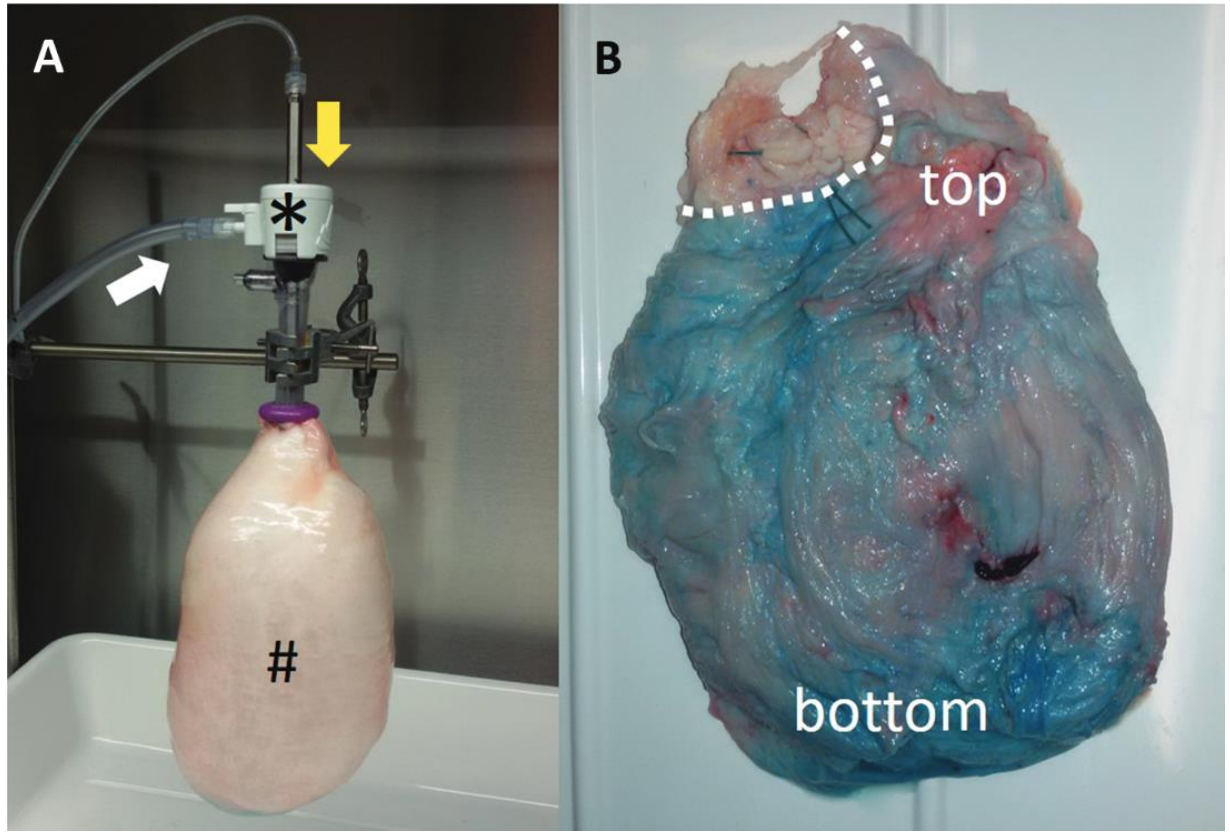
The off-label or investigational use of Cisplatin, Doxorubicin, nab-Paclitaxel, and Oxaliplatin will be addressed.

PIPAC Optimization: Quality-by-Design Approach





Inverted Bovine Urinary Bladder (IBUB) Model



Optimal model for optimization of aerosol repartition/ tissue contact time
Similar volume with abdomen, serosa inside.
Homogeneous biological test system, fully saturated with humidity.
Can be heated in a water bath.

Schnelle et al, Pleura Peritoneum 2017

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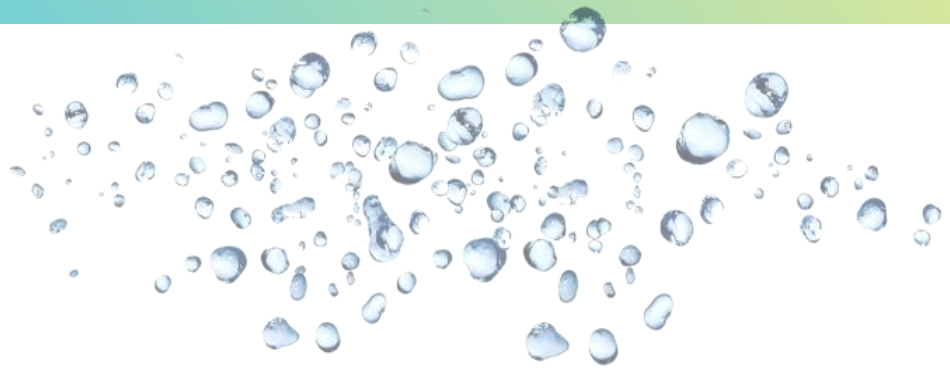
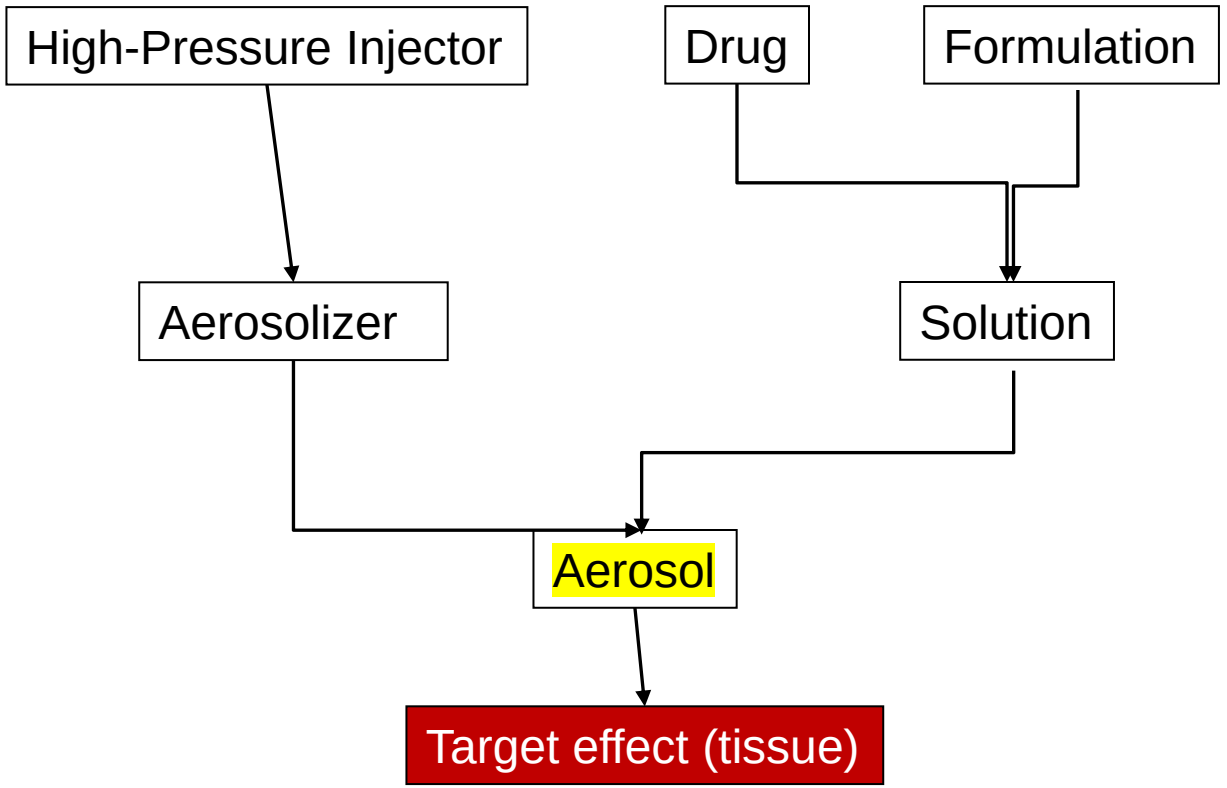
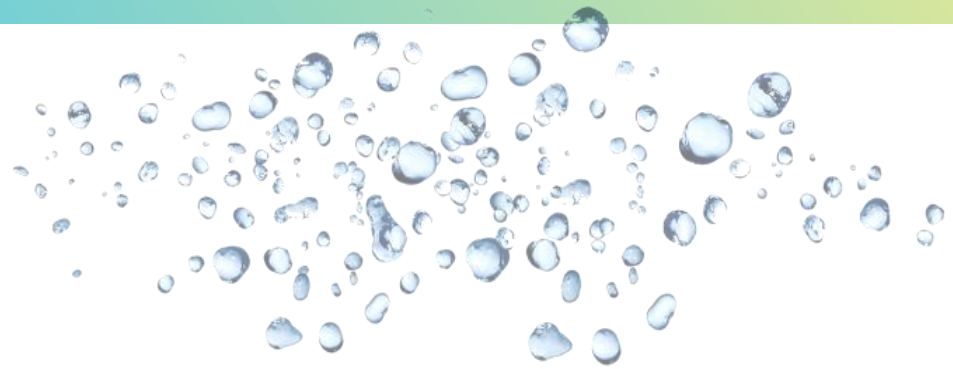
Optimizing the Aerosol





Aerosol: Definition and Physical Properties



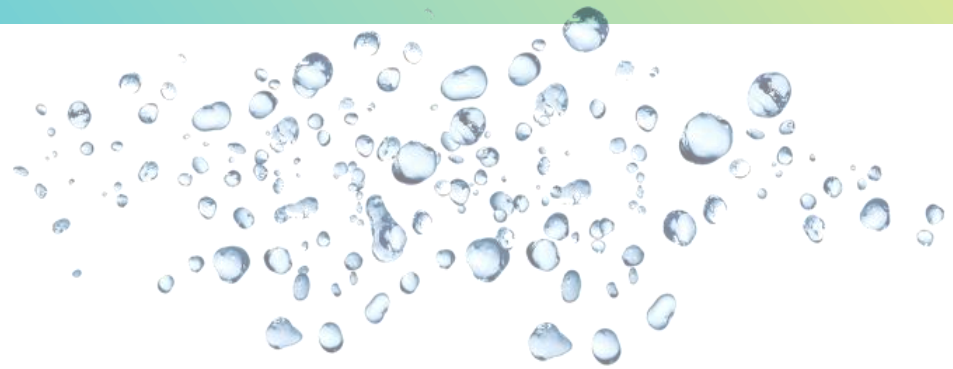
Aerosol:

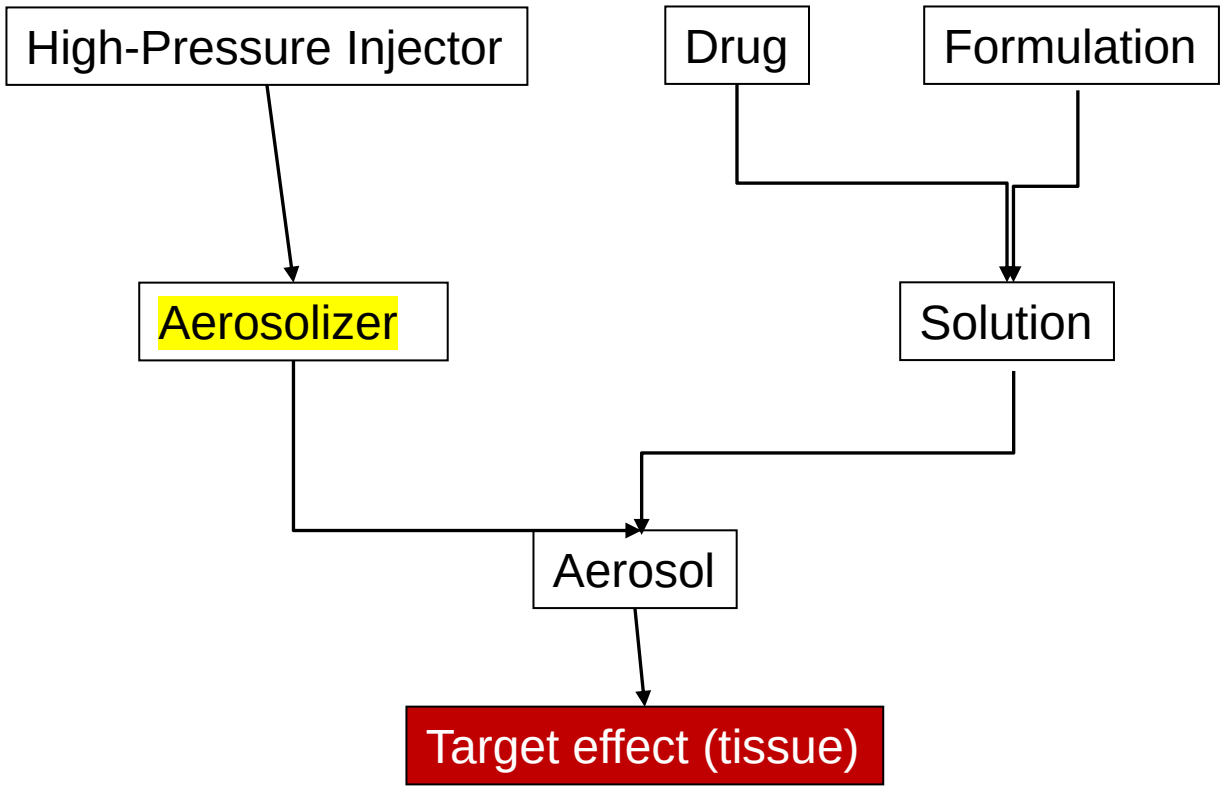
Suspension of fine solid particles or liquid droplets in a gas (here: CO_2)

Aerosol is defined by the size distribution of the droplets
- most medical aerosols are polydisperse (multiple droplet sizes)
- most medical aerosols have a droplet size between 5-30 µm

Main mechanisms of deposition
- sedimentation (gravitation, with time)
- impaction (flow-dependant)

Effect on the Target Tissue: Role of the Nebulizer





Current Aerosolizer, Design and Function

A single device on the market

- Capnopen®, Capnomed, Zimmern, Germany

Nozzle aerosolizer (diameter 9 mm)

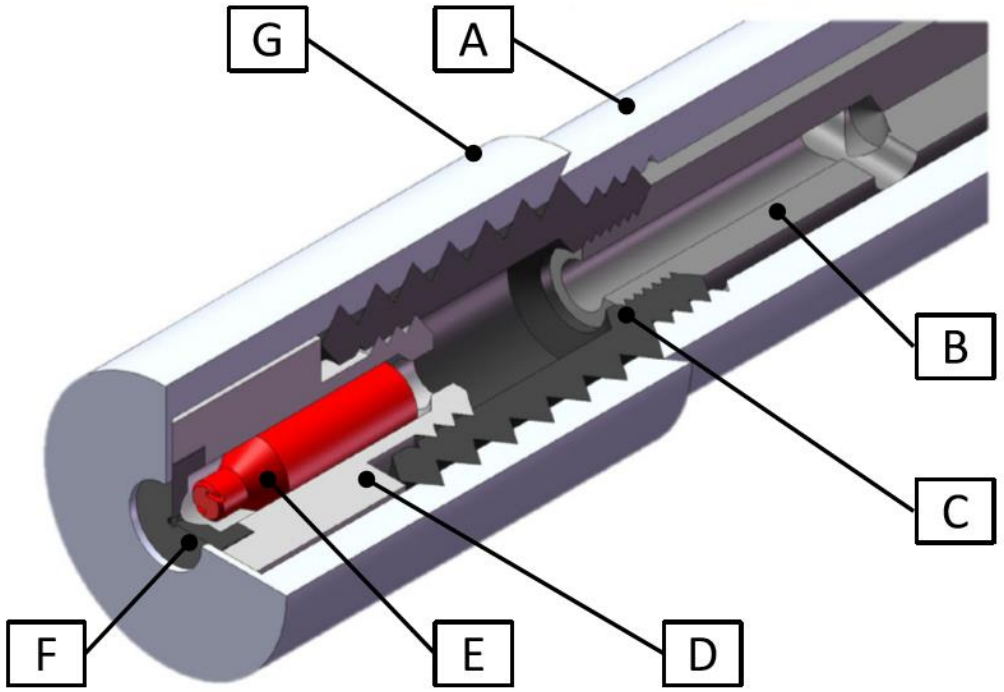
- Angle of aerosolization 60 degrees

Device aerosolizes droplets into the existing capnoperitomeum

- no gas flow

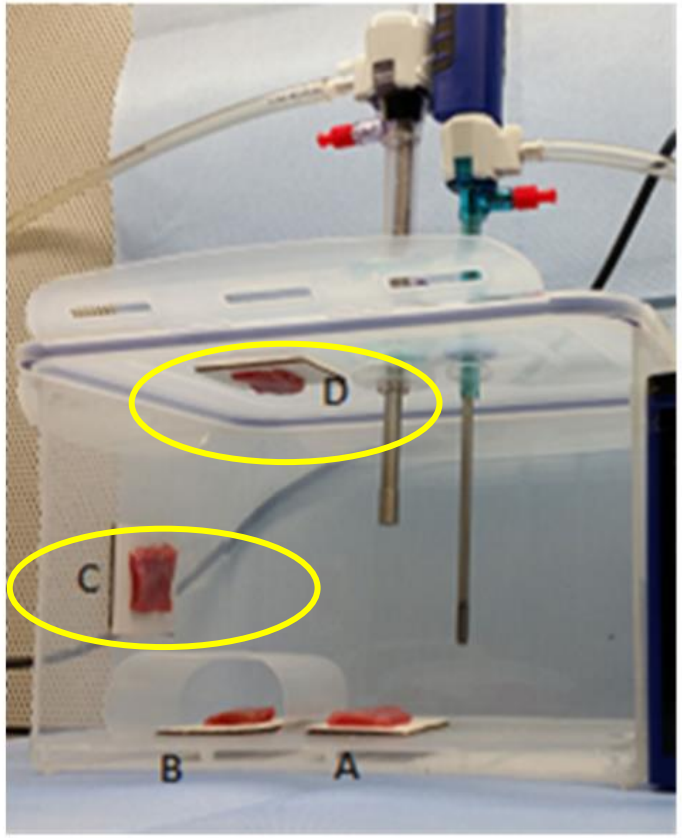
Able to aerosolize a large range of substances and solutions without loss of activity

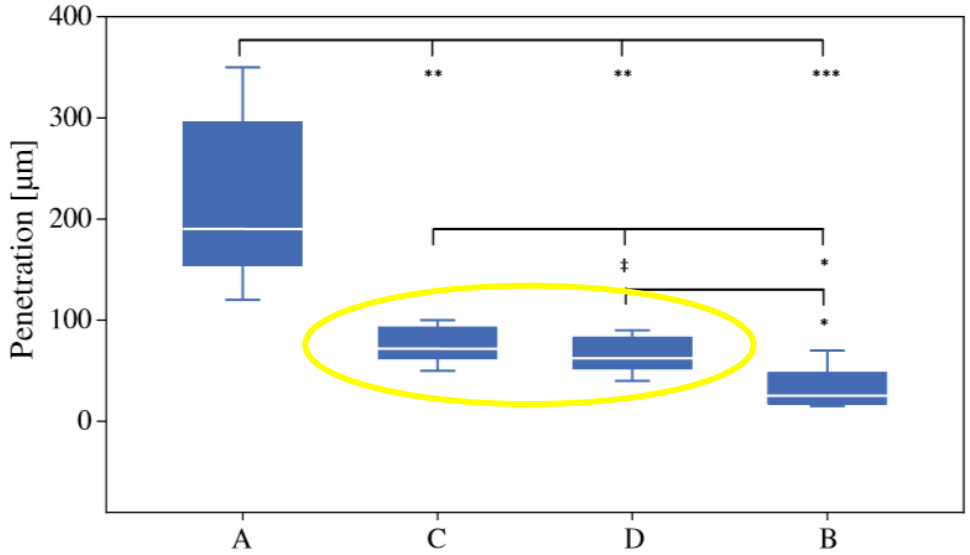
- drugs, nanos, genes, viruses, adhesive substances and even cells



Göhler et al Surg Endosc 2016; Minnaert AK Macromol. Biosci. 2017; Solass W et al Surg Endosc 2013; Ceelen W et al Pleura Peritoneum 2018;

Aerosol: Spatial Distribution





Plastic box model

Human peritoneum

Drug: doxorubicin

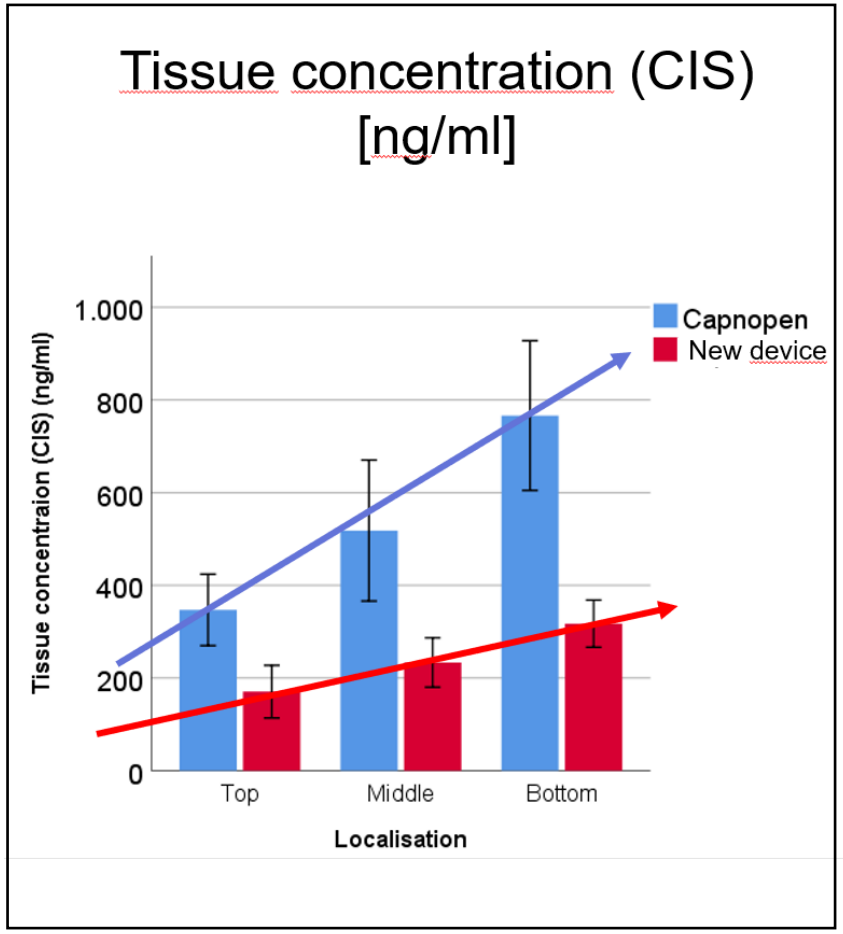
A gradient in depth of tissue penetration is observed from the top to the bottom

The difference between the lateral wall and the ceiling is not significant

Khosrawipour et al 2015

Next-Generation Aerosolizer

- Multi-head injector
- Prototype/demonstrator delivered
- Biological testing completed
- Much better homogeneity of repartition
- CE certification process ongoing



IBUB ex-vivo model

Bovine peritoneum

Drug: cisplatin

Capnomed, patent pending
Sautkin I et al, submitted

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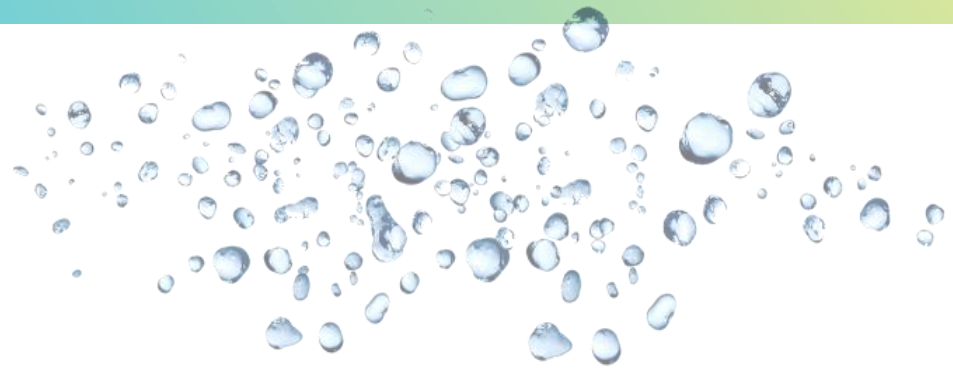
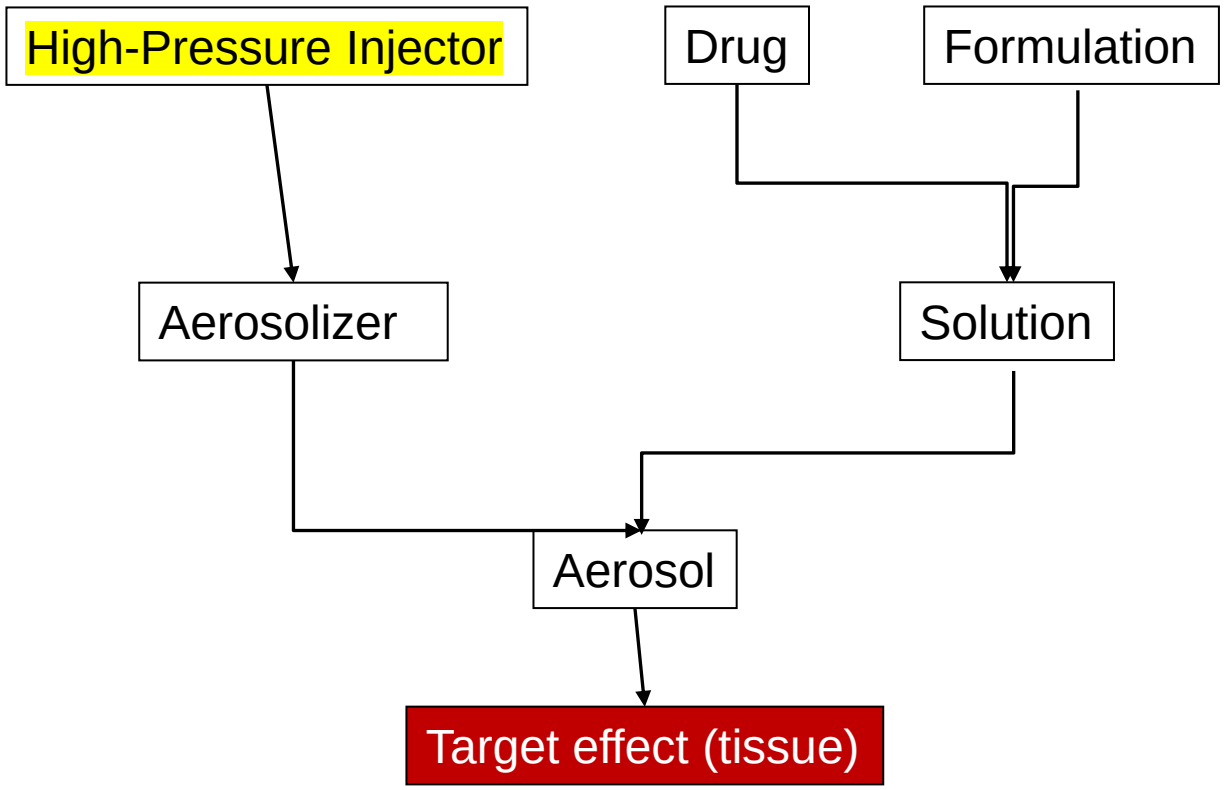
Role of the Angioinjector





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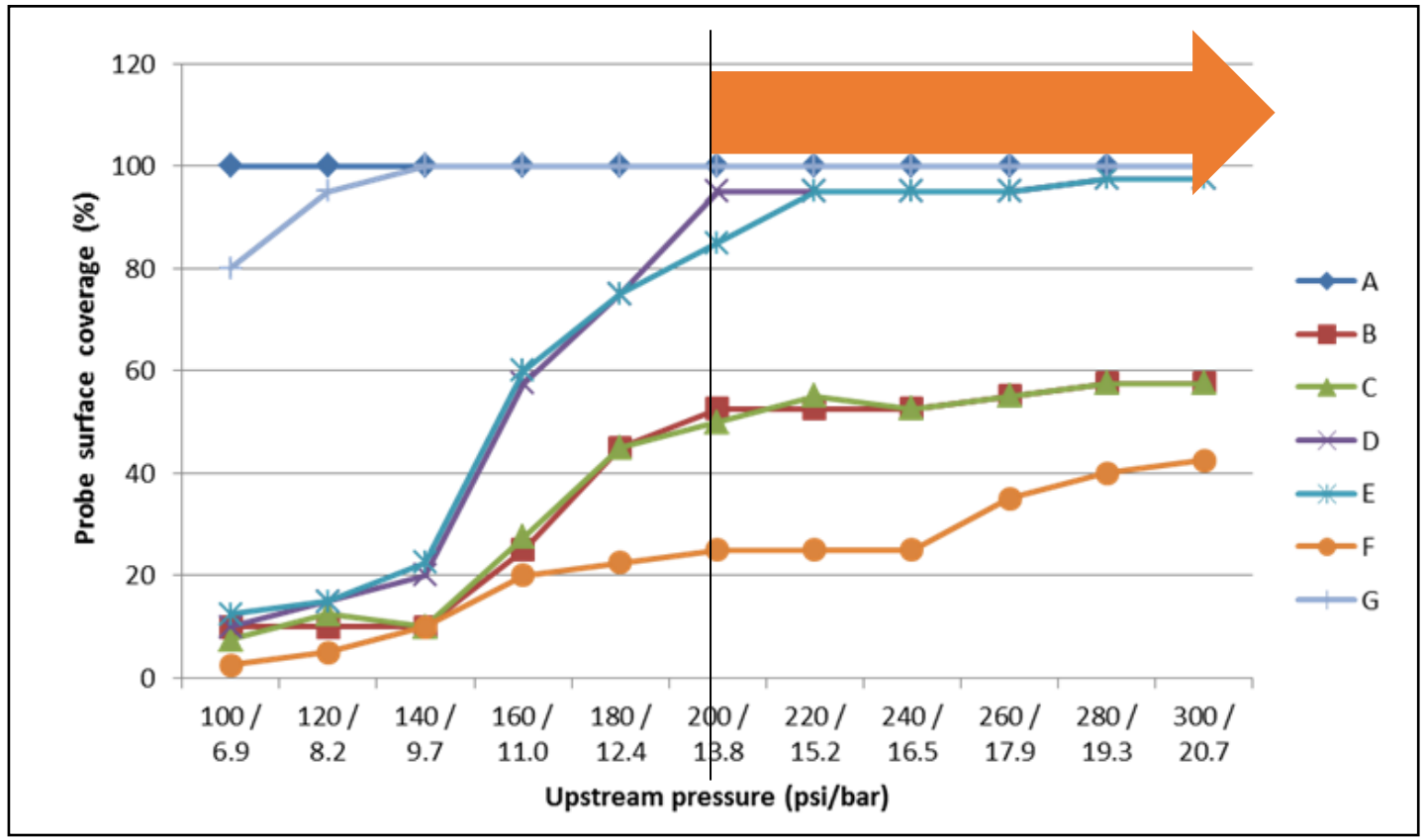

Plastic box model

Room temperature

Spatial distribution of the aerosol is depending upon driving pressure.
The upstream pressure applied by the angioinjector onto the aerosolizing device.
should be between 13 and 20 bar

Data: Reger Medizintechnik

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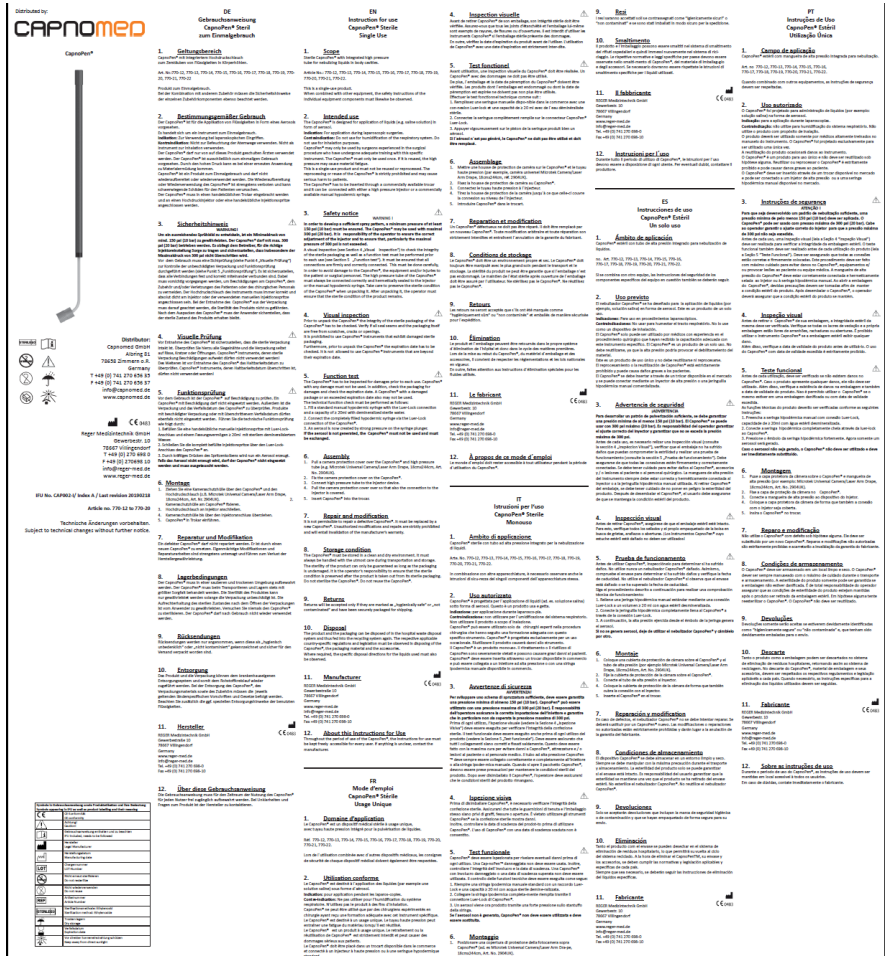
Recommendation by Manufacturer



3. Safety notice

WARNING !

In order to develop a sufficient spray pattern, a minimum pressure of at least 150 psi (10 bar) must be ensured. The CapnoPen® may be used with maximal 300 psi (20 bar). It is responsibility of the operator to ensure the correct adjustment of the injector and to ensure that, particularly the maximal pressure of 300 psi is not exceeded.

Cave:

Pressure is determined by flow rate (and resistance):

Typical flow rate: 0.5-0.7ml/s

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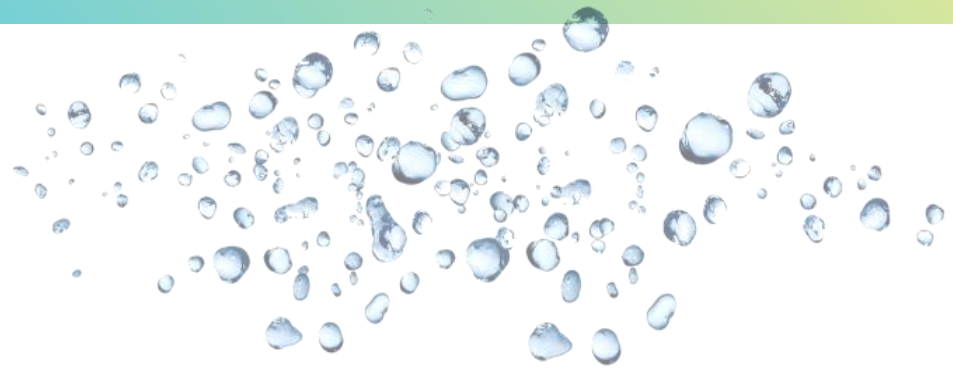
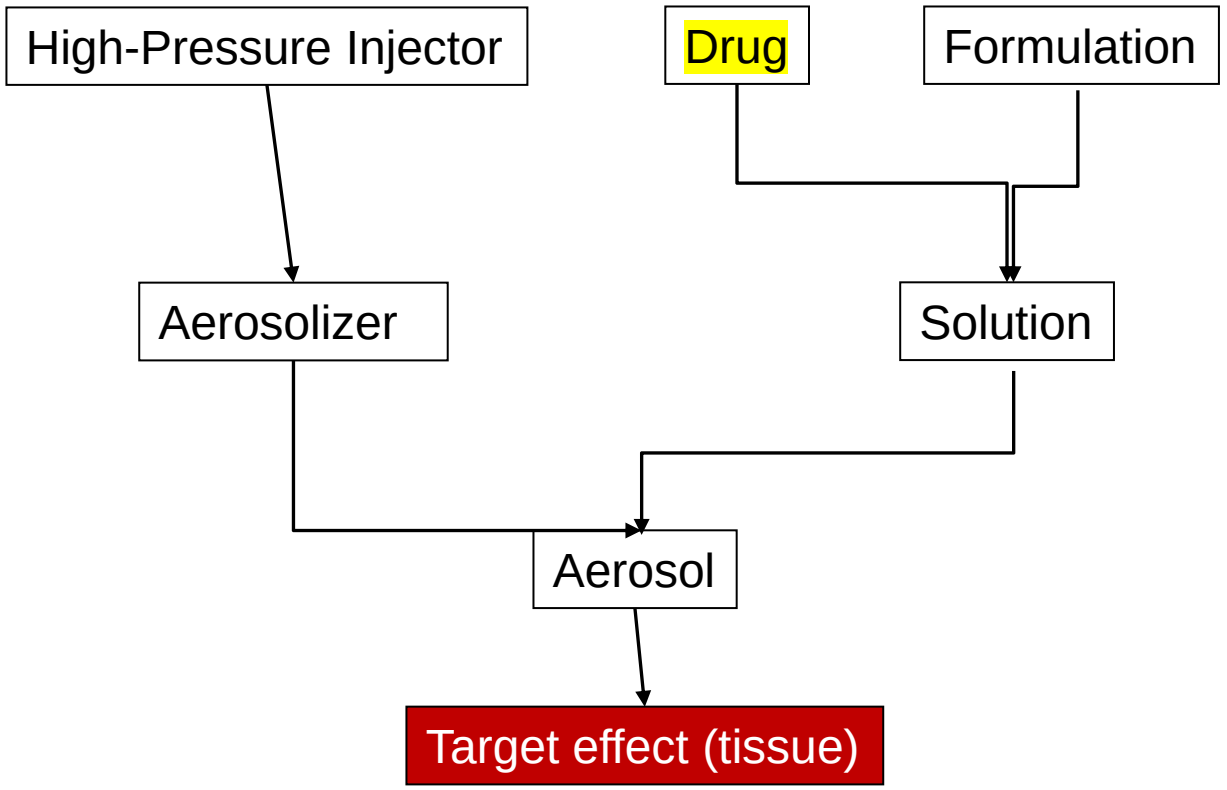
Role of the Drug in the Target Effect





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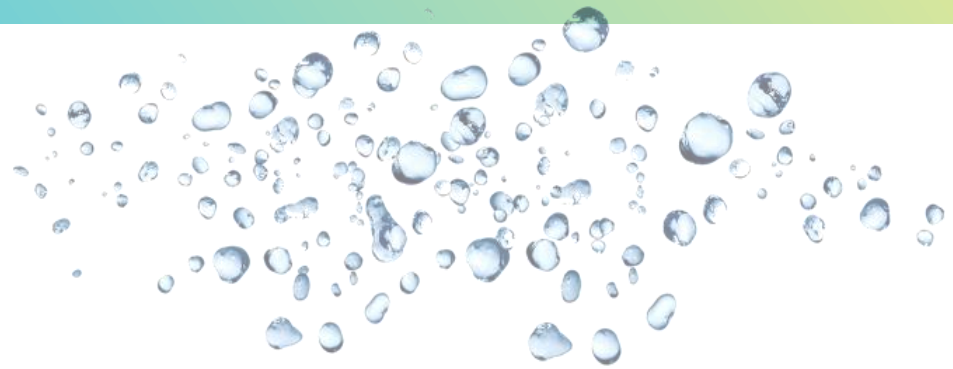
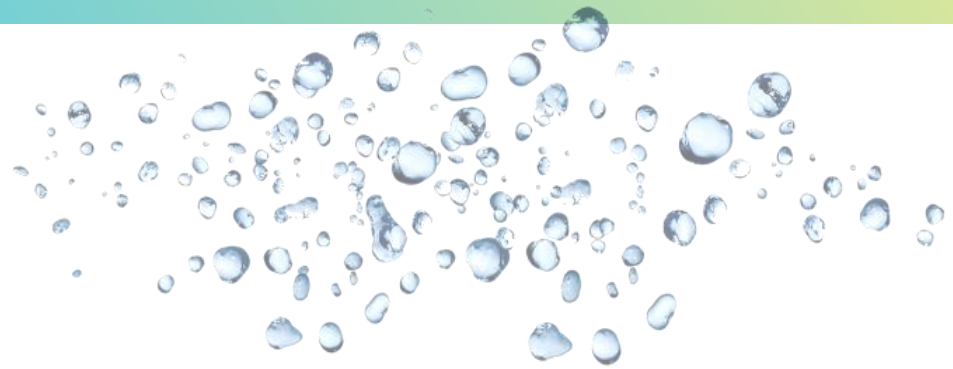


- Acetylcystein and bromelaine (approved)
  - EMA and FDA Orphan drug designation for IP delivery in PMP obtained 2018
- Taxanes (nab-paclitaxel) (off-label)
  - Ongoing phase I-II trial for PM of GI and ovarian origin (NCT03304210)
- Mitroxantron (approved for IP delivery)
  - Older drug used in the 1980ies, currently not used for IP chemotherapy

Role of the Drug on the Target Effect



- Oxaliplatin (off-label)
  - PM of colorectal and appendiceal origin
    - Dosage of 92 mg/m^2 body surface, derived from HIPEC with 80% dose reduction
    - 4 dose-finding studies to determine the optimal dosage: NCT03172416, NCT03246321 (ePIPAC, together with 5FU), NCT03294252 (together with 5FU), NCT02604784.

Ox : 90, 92, 120, 135 ?

- Doxorubicin and Cisplatin (off-label)
  - For all other indications (PM of ovarian, gastric, HBP origins & mesothelioma)
    - Evidence-based dosage: doxorubicin is 2.1 mg/m^2 body surface and for cisplatin 10.5 mg/m^2 body surface (Tempfer et al 2018).

D/C : 2.1/10.5
√

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Defining the Optimal Dose for PIPAC Ox

	PIPOX study	NUH study	Turin Study
RP2D	90mg/m2	120mg/m2	135mg/m2
Study design	3+3	3+3	Continual Reassessment Method
DLT defined	Any grade III or IV toxicity or unexpected post-operative complication.	Any grade 3 toxicity	Not defined
Predefined dose levels	90, 145, 200, 255, 300	45, 60, 90, 120	100, 135, 155
No of included patients	10	17	6
Repeated PIPAC	10	8	No
sCT	Yes	No	No
Grade 3 toxicity	Nausea, neutropenia, anemia, hypersensibility to Pt, hemorrage, obstruction	Acute pancreatitis in the 1st dose level,	No
Origin of PM	Gastric, CRC+App	Gastric, CRC+App, HPB	Gastric, CRC+App, HPB
Criticism	Hypersensitivity considered as a DLT while it is not dose-dependent Neutropenia usually excluded from other studies or used as a combined parameter.	DLT not attained Last level not doubled (n=3)	DLT not clearly defined Very limited no of patients included Last dose level not doubled (inclusions stopped because of insurance issues)

Courtesy by O Sgarbura

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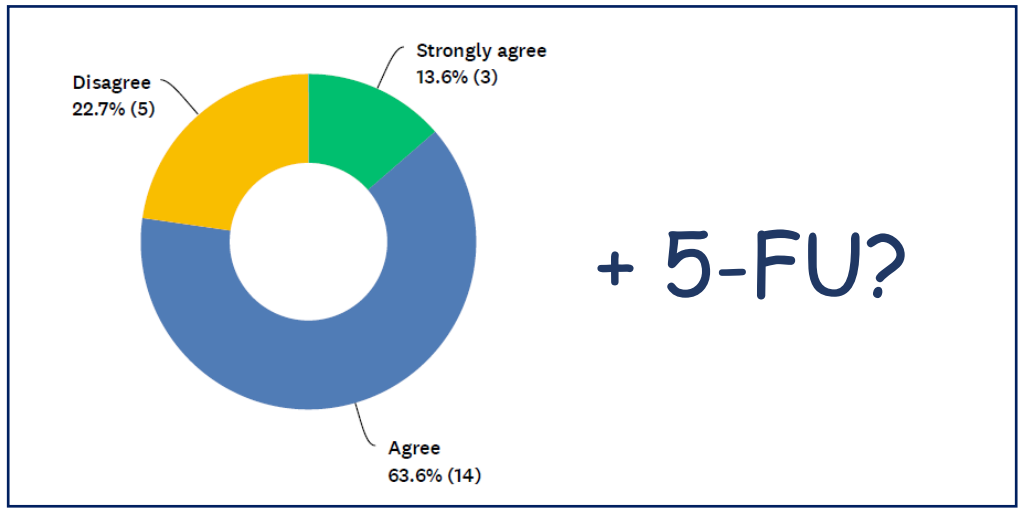
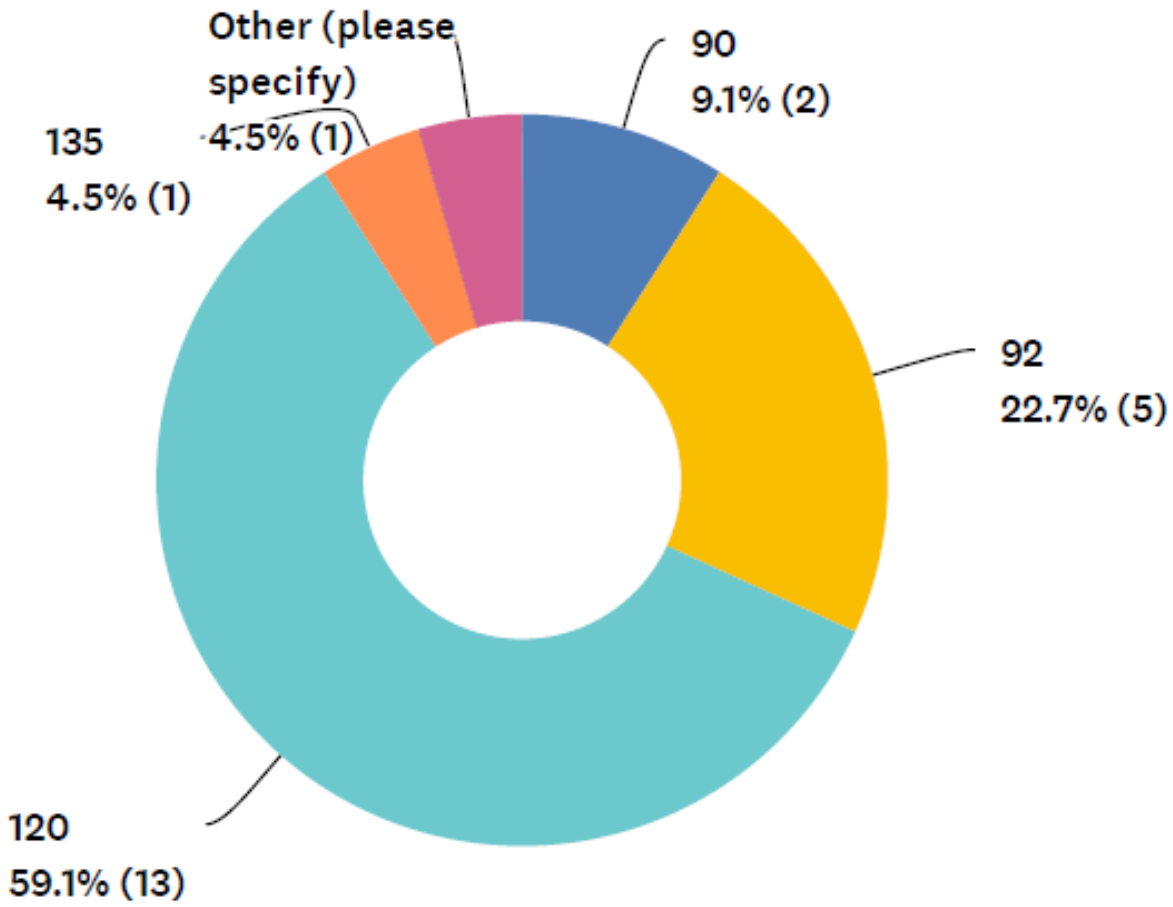
PIPAC consensus meeting 02-03 July 2021, Paris
ISSPP
INTERNATIONAL SOCIETY FOR THE STUDY OF PLEURA AND PERITONEUM - 2018 -

Paris Proposal for PIPAC-Ox

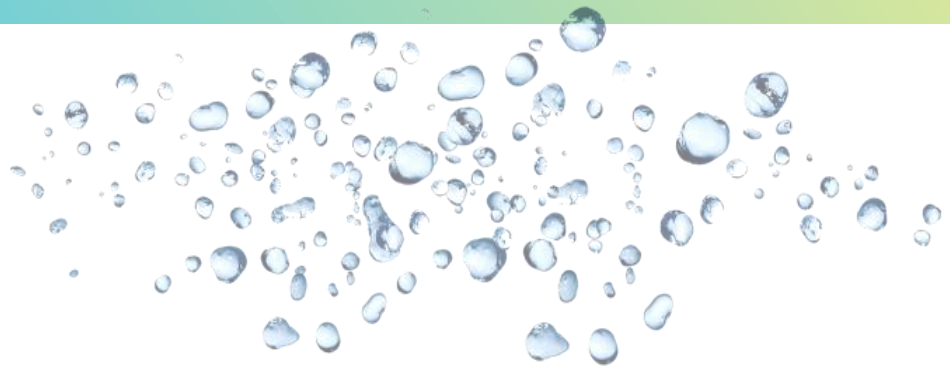
The recommended dose for routine clinical use / PIPAC course material and outside clinical trials should be… (mg/m2):

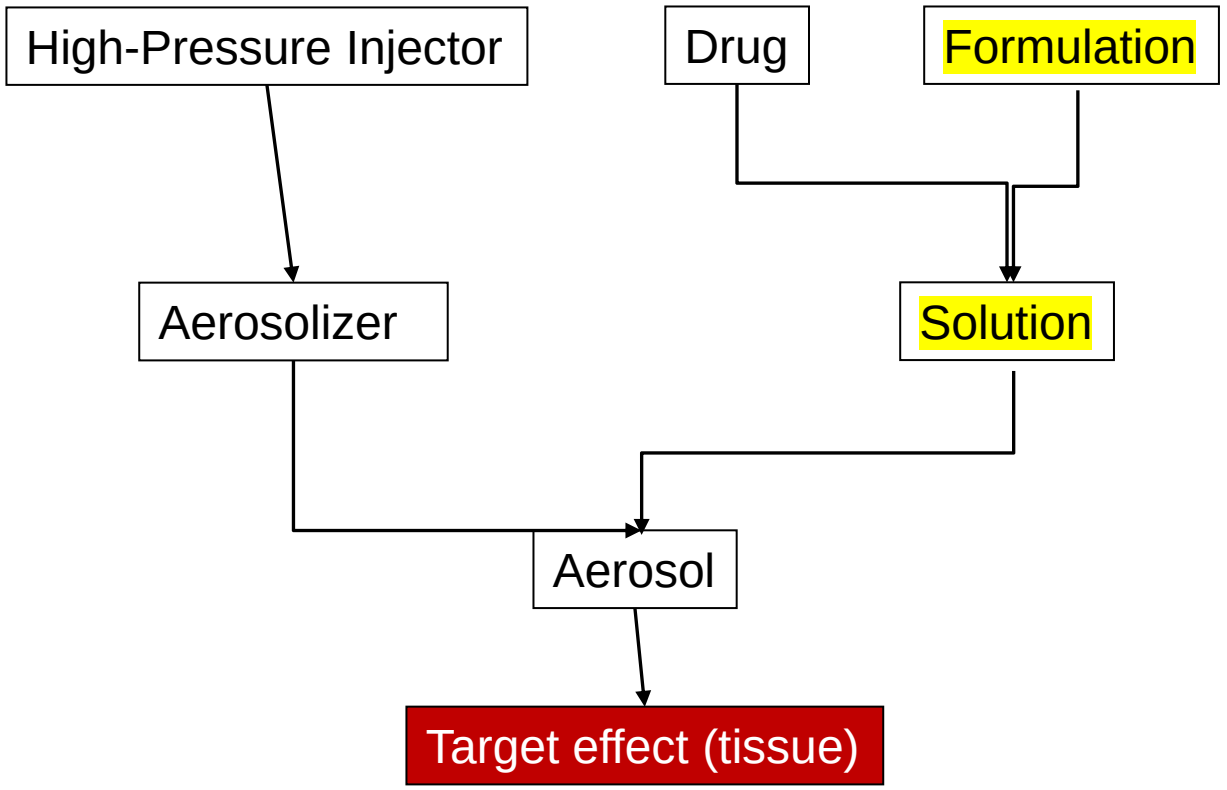


+ 5-FU?



Role of the Formulation

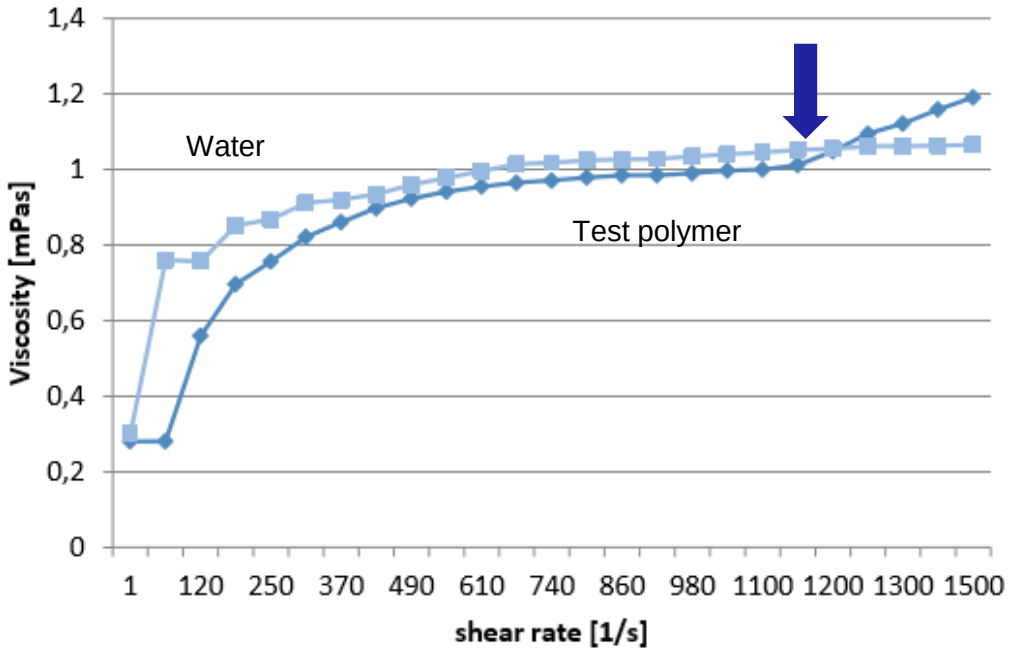




Effect of Formulation on Target Effect

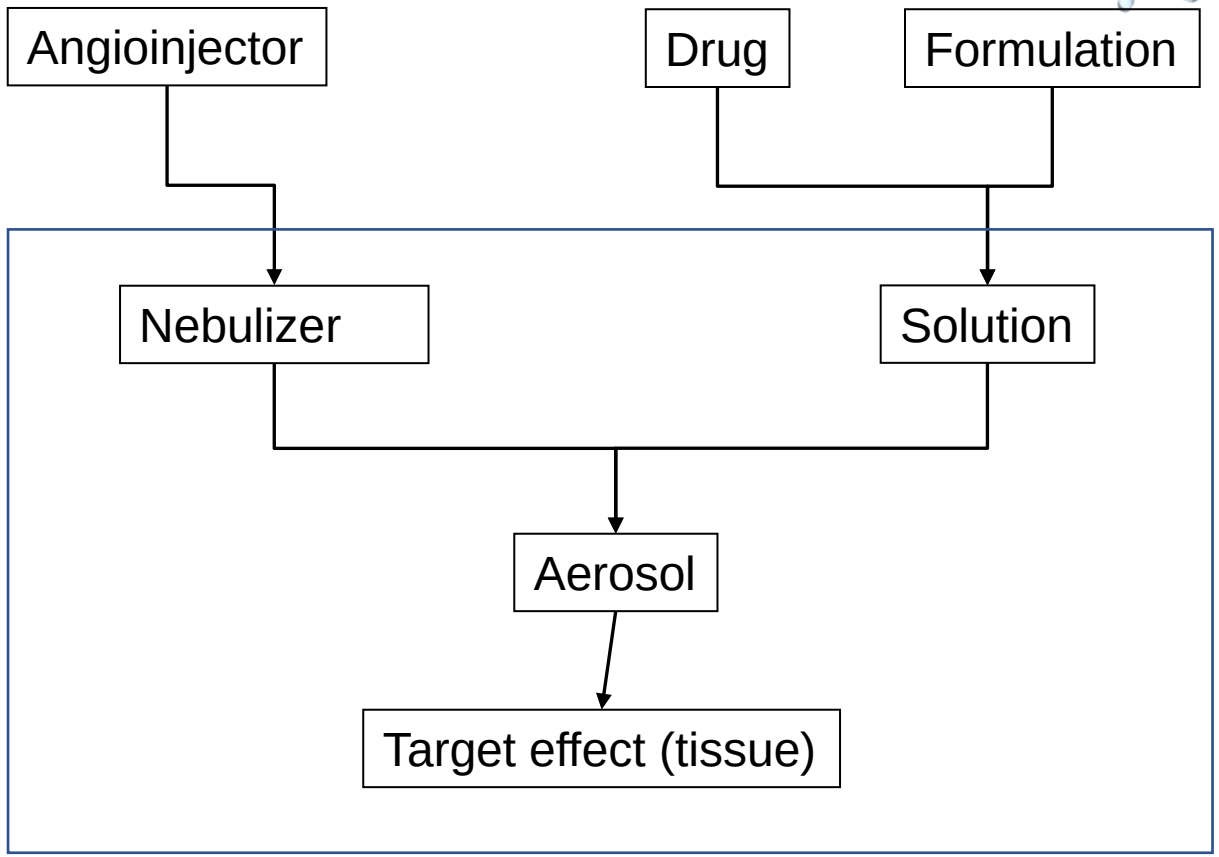
Specific formulations for IP drug delivery are largely missing.

This emerging research field offers significant opportunities for optimizing PIPAC.



For each excipient concentration a flow curve/ rheogram is used to describe rheological properties.

Role of the Environment for Enhancing Target Effect

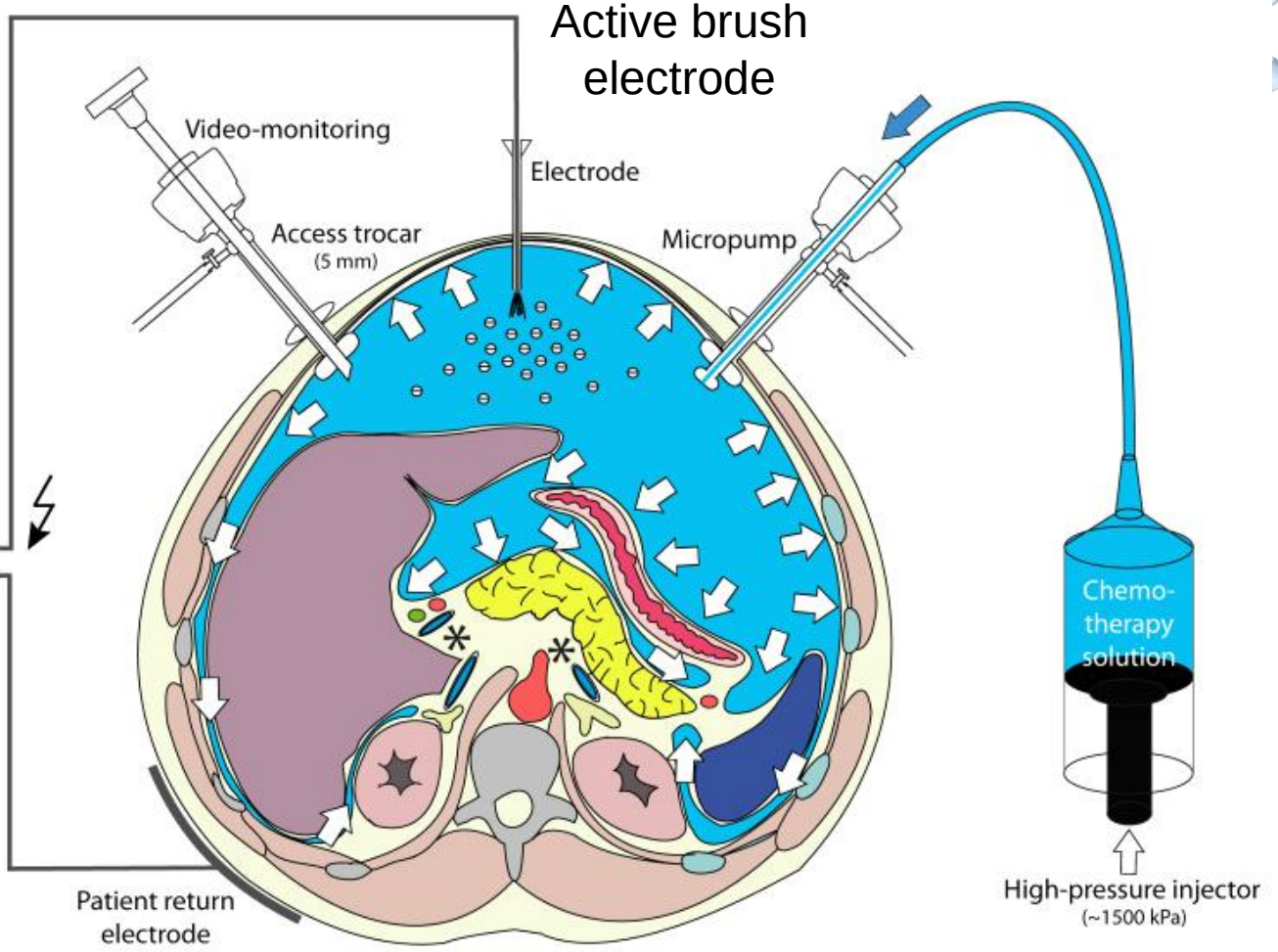


Electrostatic Precipitation PIPAC (ePIPAC)

Active brush electrode

Generator unit (Voltage 7500–9500 V, current = 10 μA)

Ultravision®
Alesi Surgical Ltd
Cardiff, UK



Patient return electrode

Kachkeeva T et al, Ann Surg Oncol 2016, Demtröder et al Pleura Peritoneum 2016

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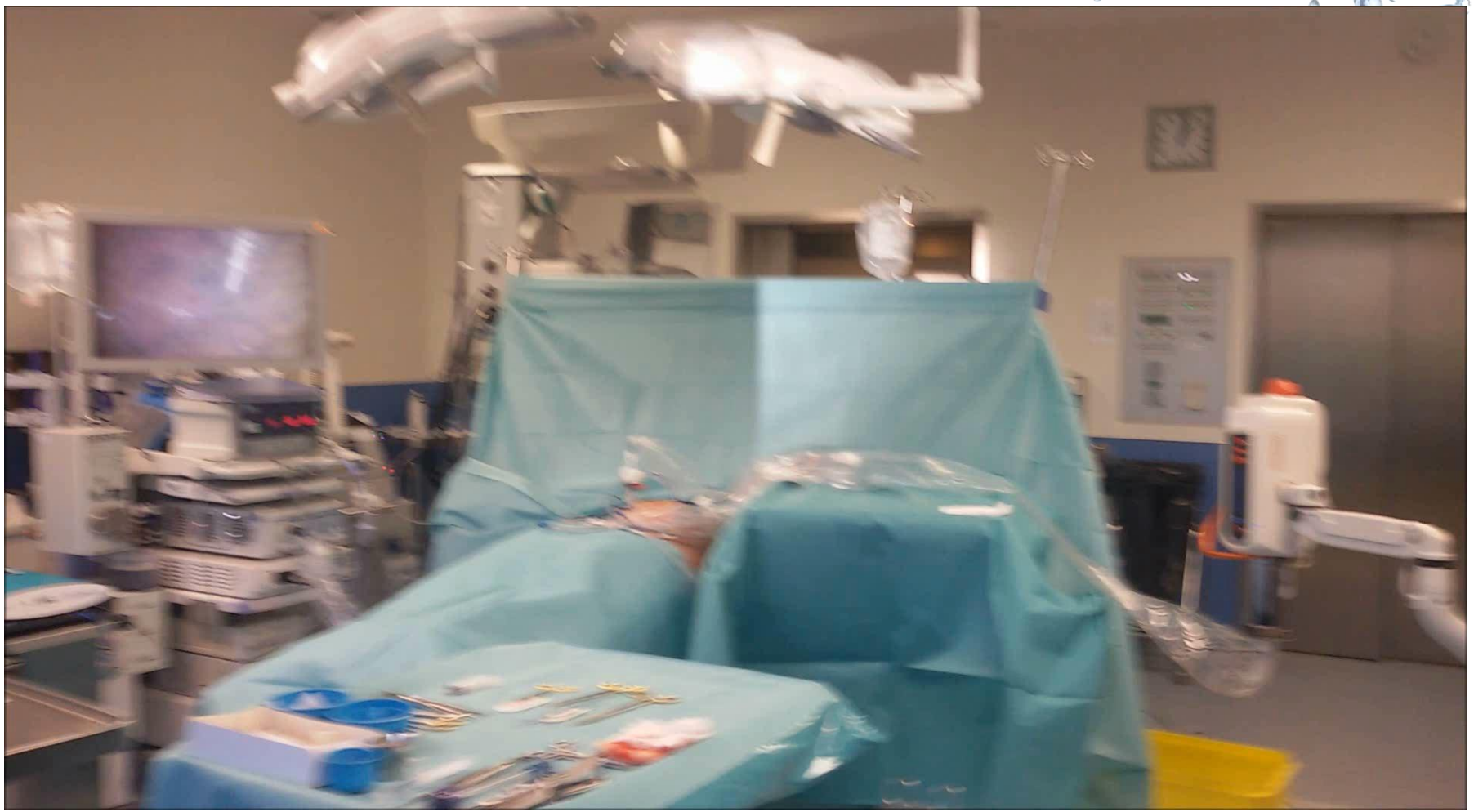
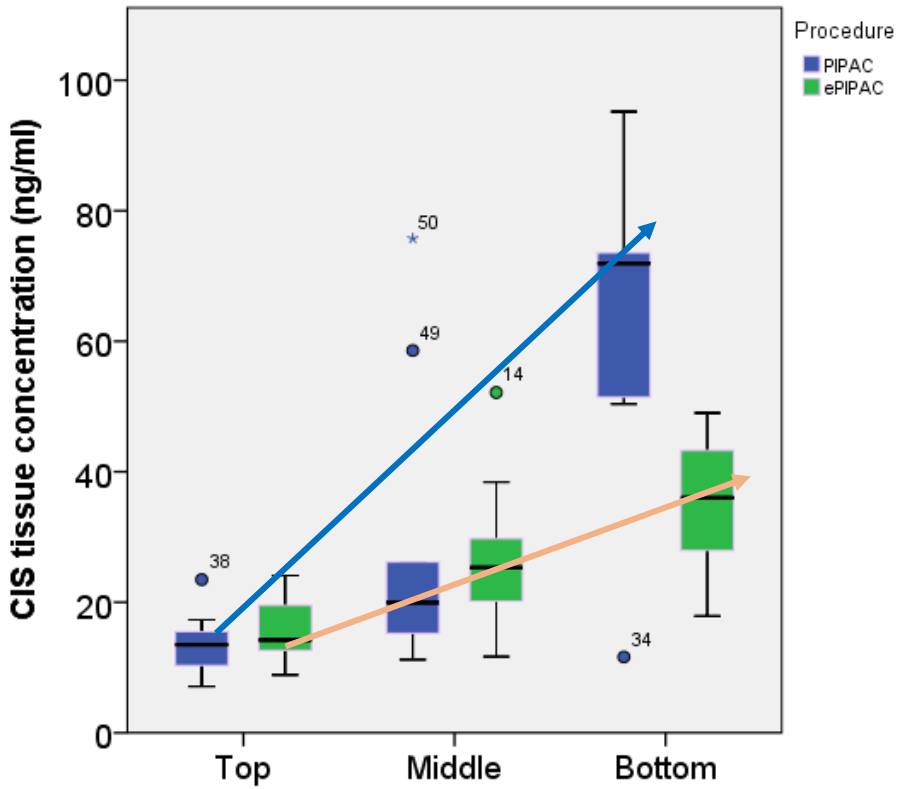
ePIPAC



Video: courtesy of M.A. Reymond

Potential Advantages (In Vitro Data Only)

- improves homogeneity of spatial distribution
- increases significantly depth of tissue penetration
- allows reduction of operating time



Sautkin I et al, submitted

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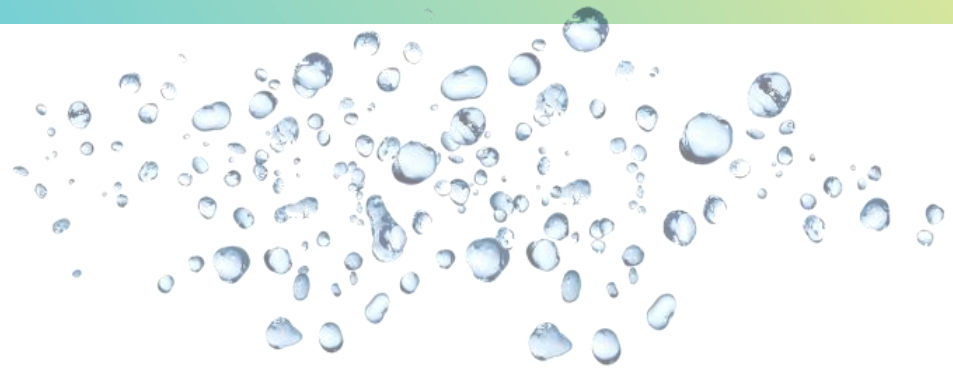
ePIPAC- Clinical Evidence



- Willaert et al.
- N=48; 135 ePIPAC

- No grade 4/5 toxicity
- Anemia 10%, nausea 4%, vomiting 5% (grade 1-3)

- For those received 3 PIPAC (n=28)
  - 11 responders
  - 2 stable disease
  - 15 non-responders

ePIPAC was safe and well-tolerated

Eur J Surg Oncol 2019

ePIPAC- Clinical Evidence

- Graversen et al.
- ePIPAC 1 minute duration
- N=33, 65 PIPAC
- Adverse events: Minimal

CTCAE grade					
ePIPAC	1	2	3	4	5
1	14	23	3	0	0
2	9	15	2	0	0

- 4 disease progression

1 minute ePIPAC was safe but tumor response was inadequate

Eur J Surg Oncol 2020

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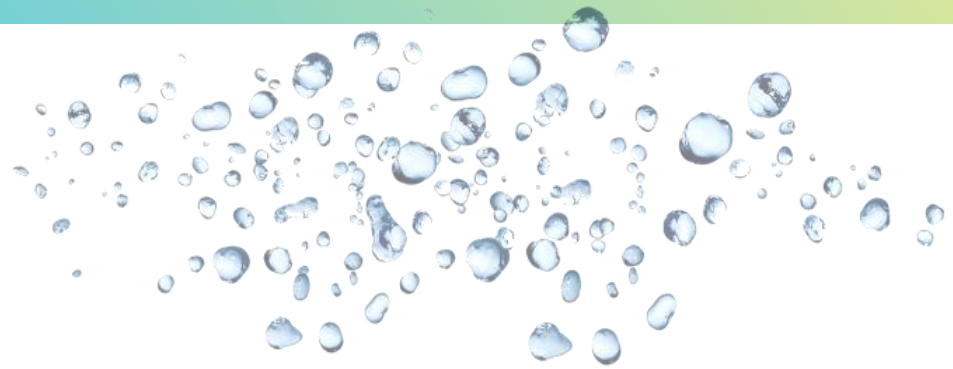
Take Home



- PIPAC is a drug delivery system
  - This is considered as a **drug-device combination**
  - In fact there are several components
- Target effect on the tissue is determined by the drug, not the device
  - Different from a shaver during arthroscopy, for example
- Optimizing target effect on the tissue requires optimization of the whole system