City of Hope®

PIPAC ESSENTIALS

Regulatory Background of PIPAC in the U.S.

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Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

The off-label/investigational use of Cisplatin, Doxorubicin, Mitomycin-C, Oxaliplatin, and Taxanes will be discussed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

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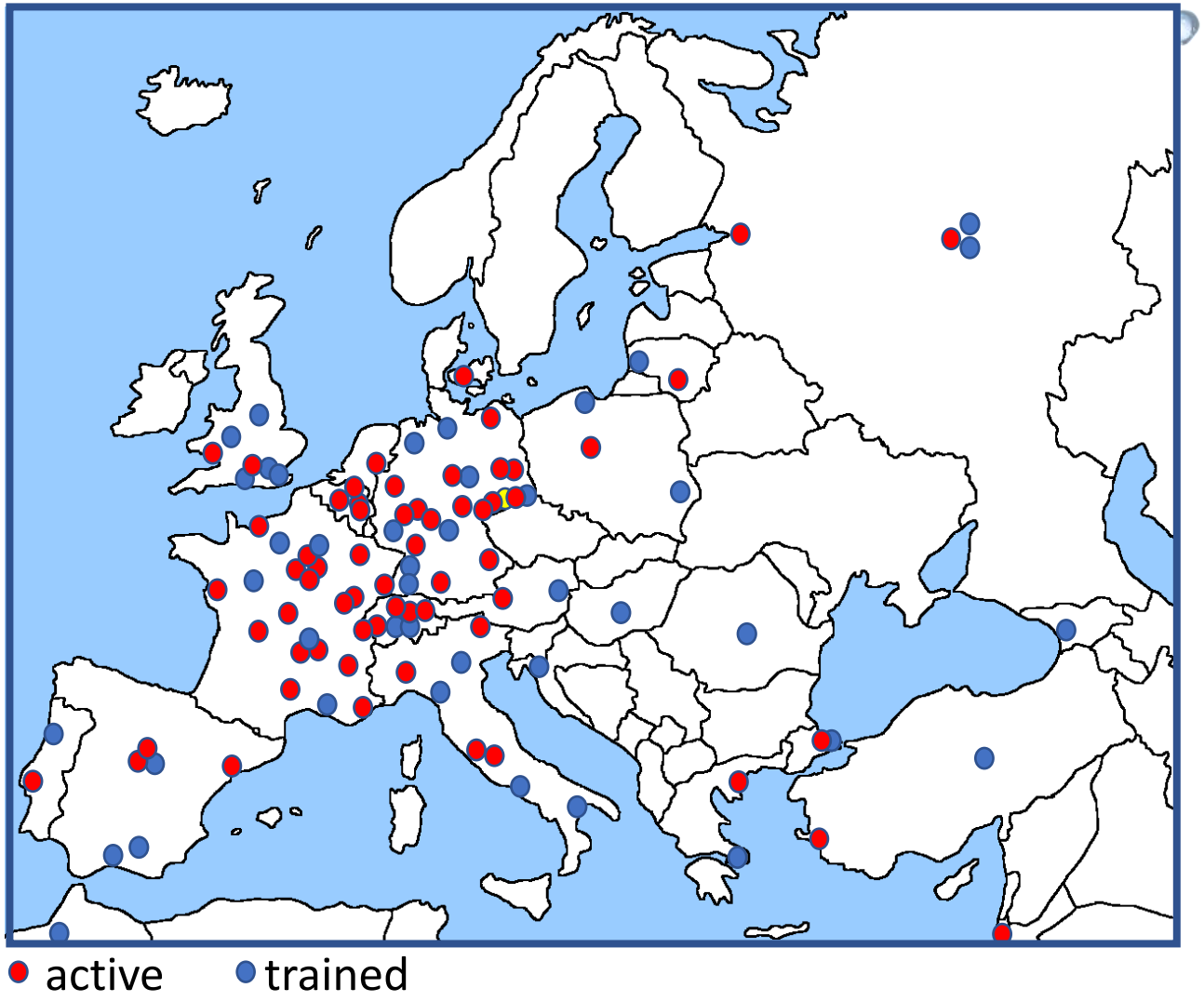
PIPAC in Europe



January 2020

Source: Capnomed GmbH

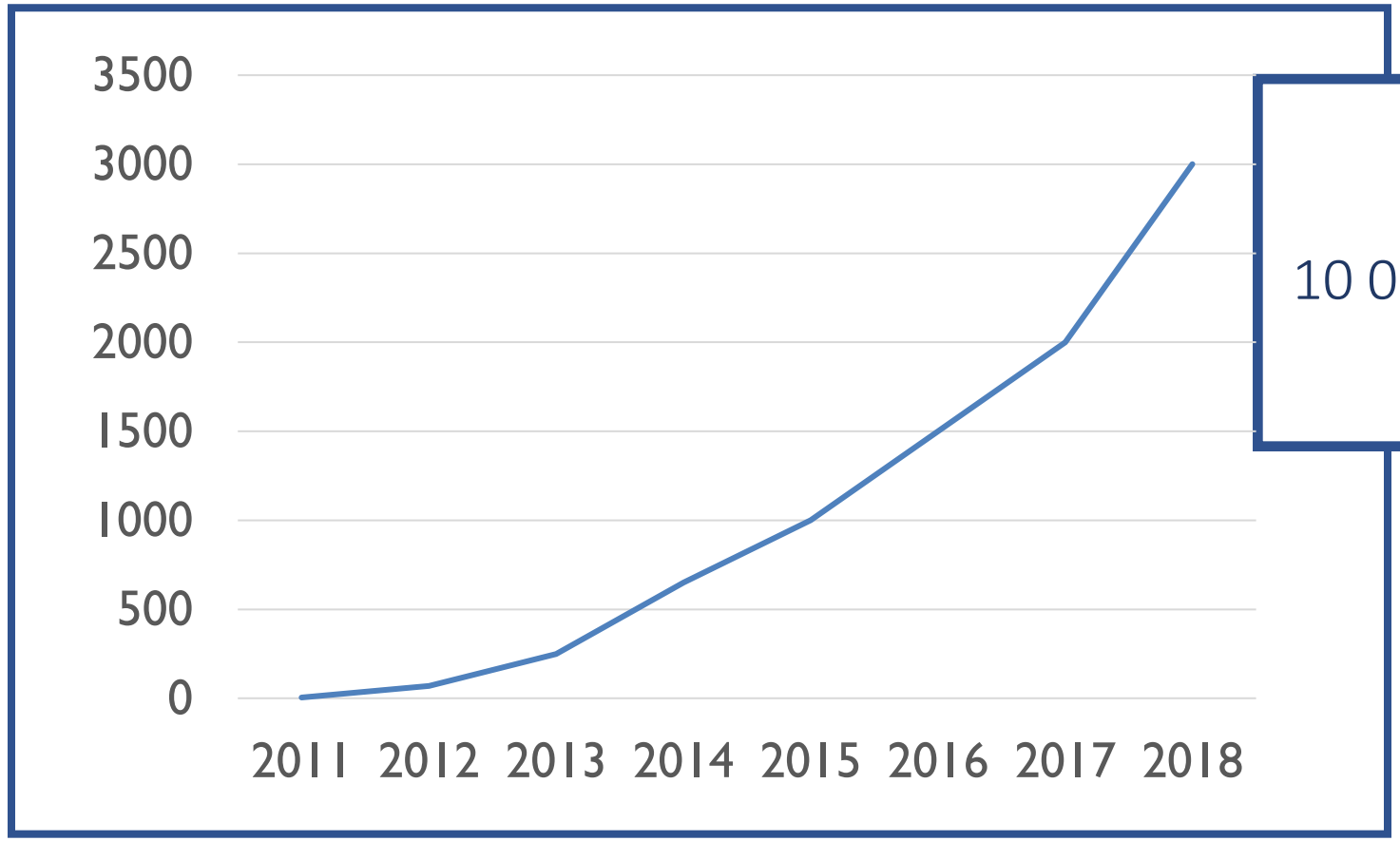
PIPAC in the World

January 2020

Source: Capnomed GmbH

active trained

PIPAC: Number of Procedures

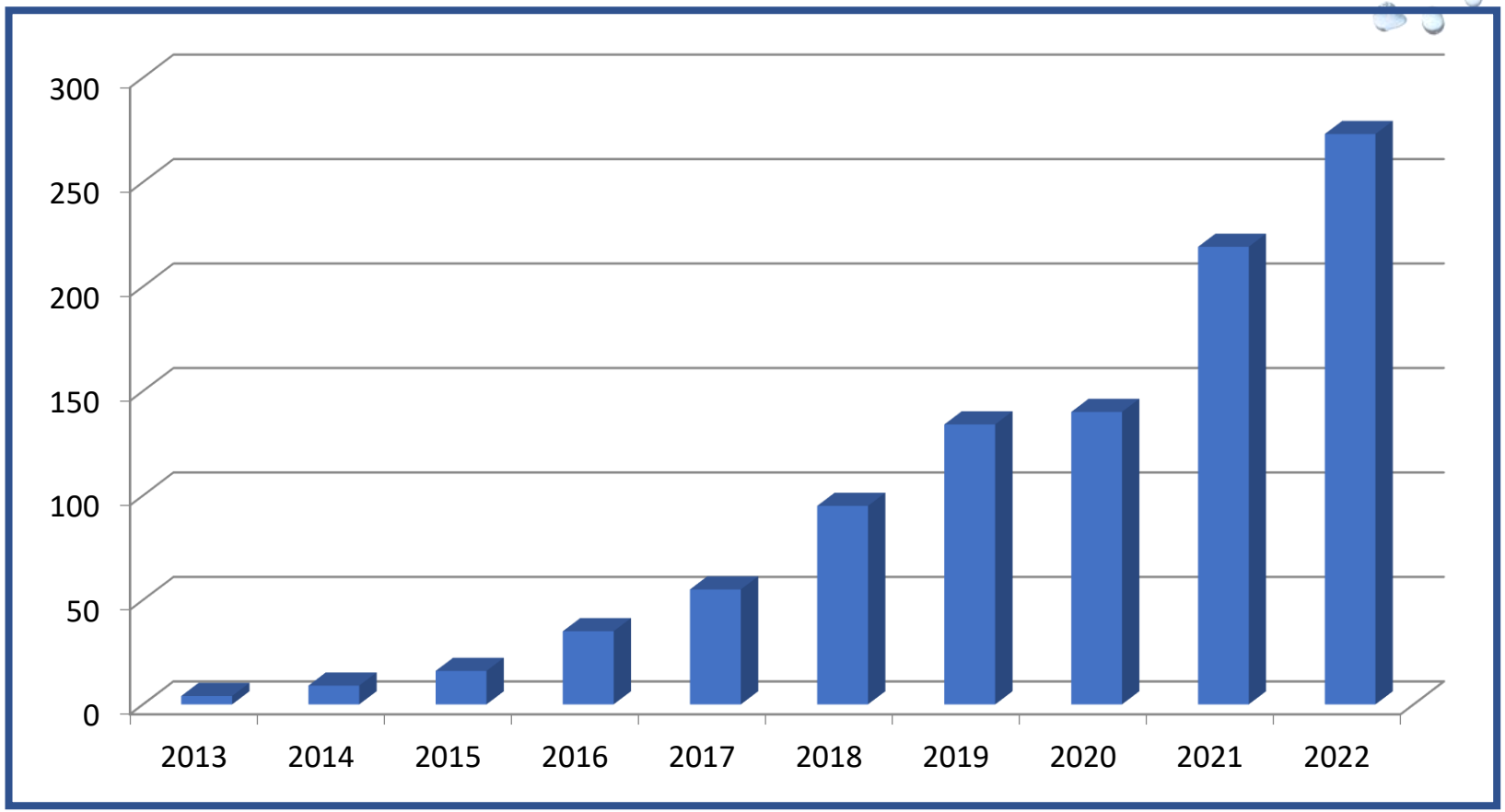


August 2021

10 000 PIPAC Procedures

Source: Capnomed GmbH

PIPAC: Number of Publications



PubMed September 2022

Regulatory Framework: Background

Development of PIPAC → implementation of an innovative therapy into clinical practice

- Highly regulated environment
  - Ethical framework: Helsinki declaration
  - Various laws: drug act, medical device act, workers protection act, data protection act, etc.
  - Various regulations: ICH-GCP (International Council for Harmonization of Good Clinical Practice), NIOHS (National Institute for Occupational Safety & Health), etc.
  - Various countries
- Economical framework
  - Reimbursement modalities

Medical Device: Regulatory Status

Aerosolizer (Capnopen®) is CE certified (class 2A)

- for intracavitary delivery of solutions
- intended use was not required at that time

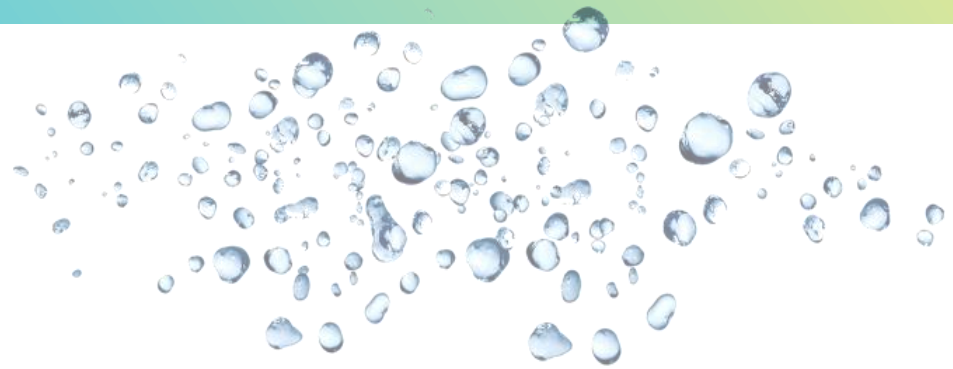
Aerosolizer is not (yet) FDA-approved

- Class III High-risk device
- Combined IDE/IND granted by FDA to Mayo Clinic and City of Hope
- Current Phase I trial with City of Hope, Mayo Clinic, Northwell Hospital

What is "Off-label Use" ?

- Off-label = the use of medicinal products outside of the drug-approved indication.
  - Often a last treatment opportunity for patients with cancer
  - 2/3 of drugs in modern oncology are administered off-label
- Used for a disease/condition that it is not approved to treat
  - Chemotherapy for one type of cancer, but used for a different type
- Given via a different modality
  - Approved as a capsule, but given as an oral solution
- Given at a different dose
- Off-label use of FDA-approved drugs is not regulated, but is legal in the United States
  - Not legal for drug companies to market their drugs for off-label use

Angio-injectors are Used "Off-label"



High-pressure angio-injectors

- were developed for intravenous delivery of contrast medium
- most devices CE and FDA certified class 2B
- for diagnostic purpose only

NOT approved for delivering chemotherapeutic drugs

- therefore "off-label use" for:
  - chemoembolization
  - intraarterial chemotherapy
  - PIPAC
- chemotherapy explicitly excluded by the instructions for use

Most IP Drugs are Applied "Off-label"

- **Oxaliplatin (off-label)**
  - Mostly for PM of colorectal and appendiceal origin
    - 92 mg/m2 body surface, derived from HIPEC with 80% dose reduction
    - 4 dose-finding studies to determine the optimal dosage

  NCT03172416 – Singapore: 120mg/m^2 (final Dose, not reaching the MTD)
  NCT03294252 – Nantes (together with iv 5FU): 90mg/m^2 (Dose-limiting toxicity)
  NCT02604784 – Turin: 135mg/m^2 (final Dose, not reaching the MTD)
  NCT03246321 – Eindhoven (ePIPAC, together with iv 5FU): 92mg/m^2

- **Doxorubicin and Cisplatin (off-label)**
  - For all indications (PM of ovarian, gastric, HBP origins, DMPM)
    - Evidence-based dosage: doxorubicin is 2.1 mg/m^2 and for cisplatin 10.5 mg/m^2 *Tempfer, Gynecol Oncol. 2018*
    - 1 dose-finding study NCT02604784 – Turin: doxorubicin is 6mg/m^2 + cisplatin 30 mg/m^2

Most IP Drugs are Applied "Off-label"

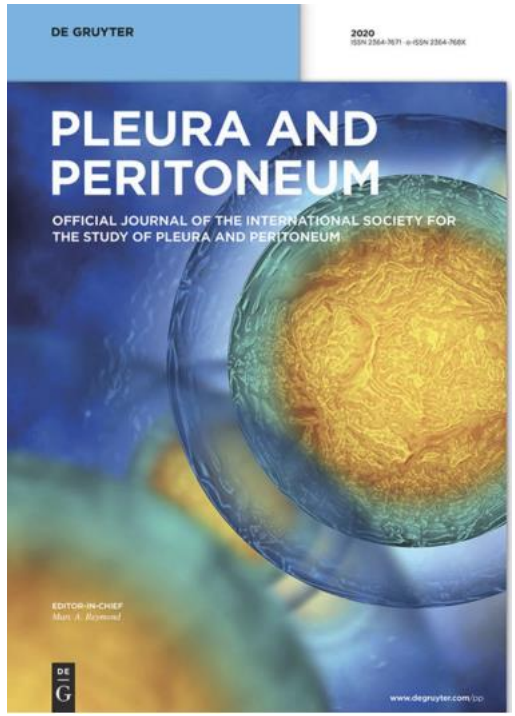
- **Taxanes (nab-paclitaxel) (off-label)**
  - NCT03304210 - phase I-II trial for PM of GI and ovarian origin – Ghent (140mg/m^2)
  - NCT04000906 - nab-paclitaxel + Cisplatin – Geneva (recruiting as of 9/2021)

- **Mitroxantron (approved for IP delivery)**
  - Older drug used in the 80s, rarely used for IP chemotherapy

- **Mitomycin-C (off-label)**
  - Currently used for IP chemotherapy (HIPEC)
  - Used in PIPAC in patients with confirmed allergy to platinum compounds, dose 1.5 mg/m^2 (Alyami M, EJSO 2017)
  - **Ongoing US dose finding study for colorectal/appendiceal cancer – 7mg/m^2 - 25mg/m^2**

- **Acetylcystein and bromelaine (approved for IP delivery)**
  - European Medicines Agency-Orphan drug designation for IP delivery in PMP obtained 2018
  - Feasibility studies together with PIPAC ongoing

Most IP Drugs are Applied "Off-label"

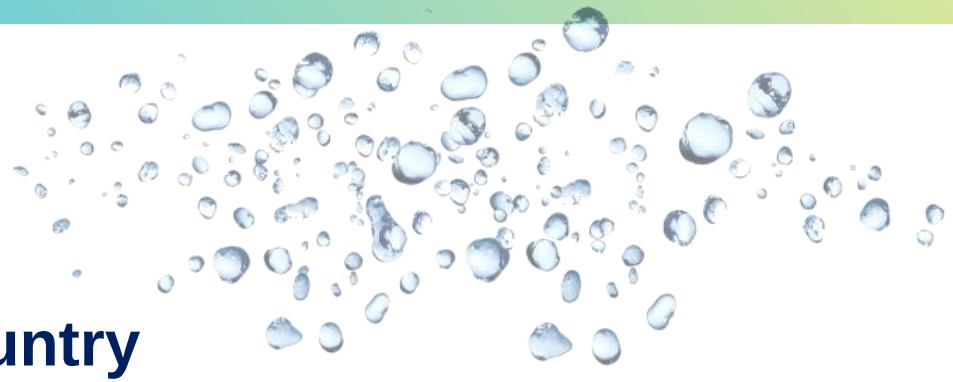


Olivia Sgarbura*, Clarisse Eveno, Mohammad Alyami, Naoual Bakrin, Delia Cortes Guiral, Wim Ceelen, Xavier Delgadillo, Thanh Dellinger, Andrea Di Giorgio, Amaniel Kefleyesus, Vladimir Khomiakov, Michael Bau Mortensen, Jamie Murphy, Marc Pocard, Marc Reymond, Manuela Robella, Koen P. Rovers, Jimmy So, S.P. Somashekhar, Clemens Tempfer, Kurt Van der Speeten, Laurent Villeneuve, Wei Peng Yong and Martin Hübner

Consensus statement for treatment protocols in pressurized intraperitoneal aerosol chemotherapy (PIPAC) Pleura and Peritoneum 2022; 7(1): 1–7

- 2-day hybrid consensus meeting in July 2021; 22 experts
- 3-round Delphi process
- Doxorubicin (2.1 mg/m2) and cisplatin (10.5 mg/m2) combination – 91%
- Oxaliplatin at 120 with reduction to 90 mg/m2 (frail patients) – 73%
- PIPAC-Ox in combination with 5-FU – 77%
- Mitomycin-C and Nab-paclitaxel were favored as alternative regimens.

Is PIPAC a Drug or a Medical Device?



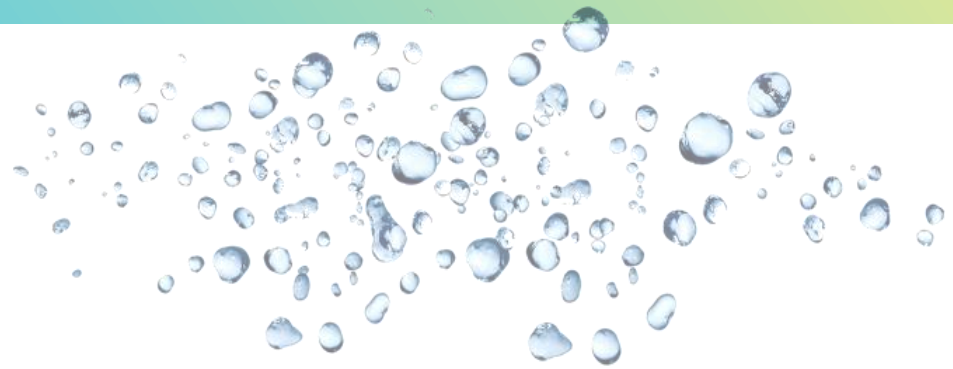
The regulatory answer differs depending on the country

- Germany: PIPAC development and clinical use is governed by the Federal Drug Act (AMG), not the Medical Devices Act (MPG)
  - Federal Drug Agency responsible for drugs and medical devices
- At EU level, European Medicine Agency (EMA) is only responsible for drugs, not for medical devices.
- USA: PIPAC is using a novel device to deliver chemotherapy in a novel method
  - Combined device (Class III – high-risk) need IND (investigational new drug) and IDE (investigational device exemption) approval, followed by clinical trials.

Reimbursement of "Off-label" Therapies

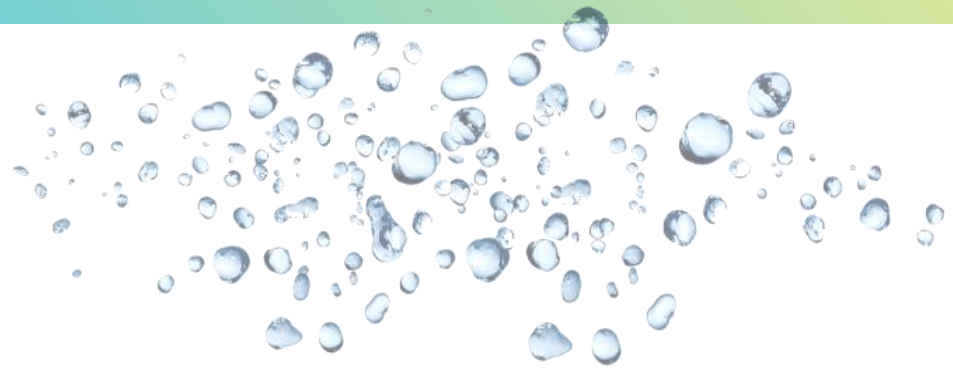
- Some resistance of insurance plans to reimburse for off-label use
  - Judged "experimental" or "investigational"
- Federal legislation in US requires insurers to cover medically appropriate cancer therapies
  - Includes off-label use if treatment has been studied and published
  - 2008 Medicare rules changed to liberalize use of off-label cancer drugs

Off-label Use: Legal Aspects



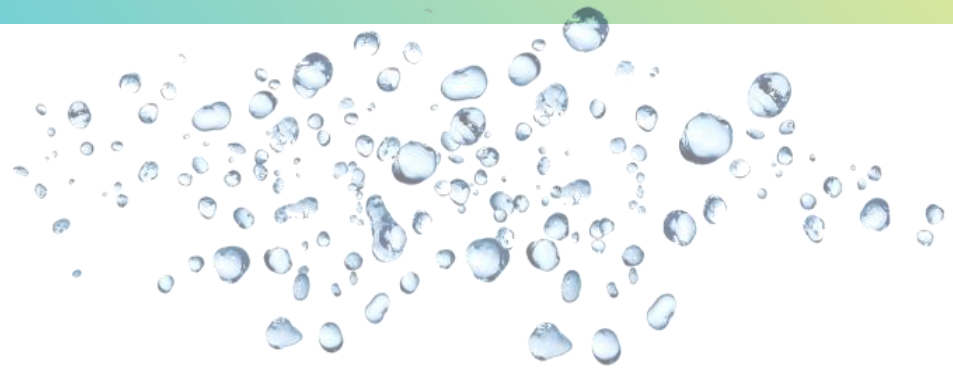
- FDA does not regulate the practice of medicine
  - “practice” refers to interventions designed to solely enhance the well-being of an individual patient and has a reasonable expectation of success.
- Can prescribe approved drugs for off-label use, as long as it does not qualify as ”research”
  - “research” is designated as an activity designed to test a hypothesis, permit conclusions to be drawn, and to contribute to generalizable knowledge.
- Risk of liability is related to informed consent and negligence

Off-label Use: Legal Aspects



- Limitation of liability and protection against malpractice
  1. Patient's knowledge that drug is prescribed for off-label use
  2. Motivated by desire to diagnose, treat, and directly benefit the patient for whom the drug is prescribed.
  3. Based on the MD's own expert medical opinion
  4. Supported by reputable peer reviewed literature reflecting sound scientific evidence
  5. Generally supported by the opinions of the physician's local colleagues.

Conclusion



- PIPAC is growing worldwide, and now available (on trial) in the United States.
  - Increasing number of clinical trials and published articles

- Injector and drugs approved, but are “off label”
- Aerosolizer is not yet FDA approved

- Consensus statement for treatment protocols for PIPAC outlines expert opinion to guide treatment