Quality Assurance for Contrast Media

Parametric Release & New Annex 1

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Content

- Who we are - Introduction BIPSO & BRACCO
- Contrast Media for X-ray and MRI
- Aseptic vs. Terminal Sterilized
- Parametric Release
- New Annex 1 – Contamination Control Strategy

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Who we are - BIPSO GmbH

BIPSO = **B**racco **I**maging **P**harmaceutical **S**terile **O**perations

- Founded in 2011 through the transfer of a part of Nycomed GmbH to Bracco Imaging S.p.A.
- Long history in production of contrast media for X-ray back in the early ´80s (Solutrast)
- 2000-2003 Addition of magnetic resonance contrast media (ProHance & MultiHance)
- Sterile Filling Operations – Midsize Player serving global markets
- Sound Inspection History
- Part of BRACCO Group
- MAH is BRACCO

Bracco Group – Overview

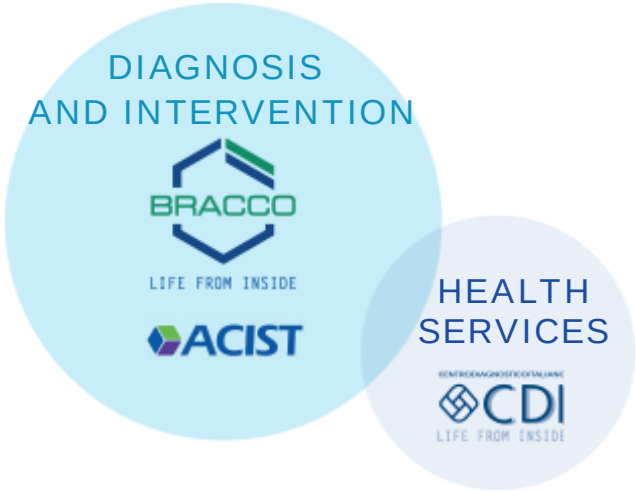
Italian **multinational**

Headquartered in Milan with **3 Business Units**:

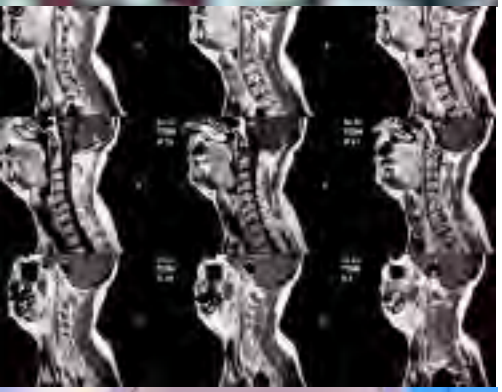
Bracco Imaging
International leader in diagnostic imaging

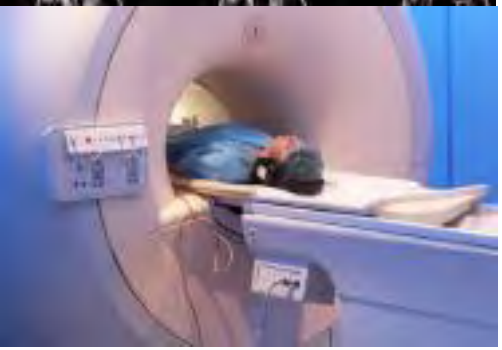
ACIST Medical systems
Leading company in systems for the administration of contrast media and advanced medical devices for cardiology

CDI – Italian Diagnostics Centre
Polyclinic facility in the sectors of prevention, diagnosis and rehabilitation



Bracco Group – Overview





- The Bracco Group operates **all over the world**
- Sales in more than **100 countries**
- Integrated Group with **private capital**
- **3,608 employees**
- Consolidated **turnover of € 1.5 billion euros**, 87% of which made in foreign markets
- Investment of **9,2% of reference turnover** in R&D for diagnostic imaging and advanced medical devices
- Portfolio comprising over **2,200 patents**
- **7 R&D centres and 9 Production units** in the world (Italy, Switzerland, USA, Germany, China, Japan, Canada)

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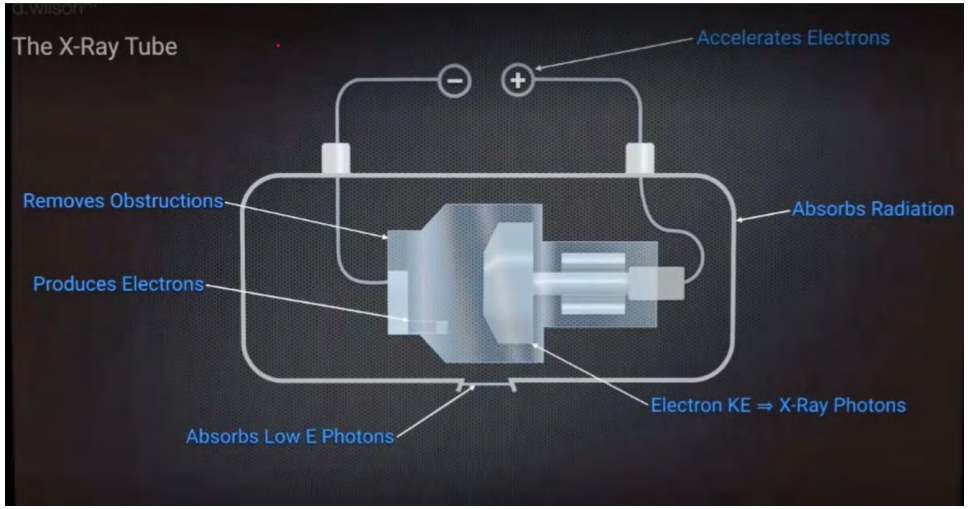
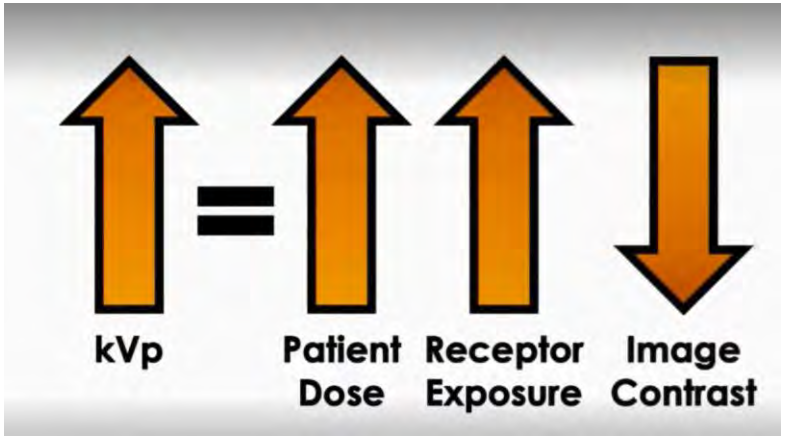
X-Ray Modality – Tube





X-Ray Tube:

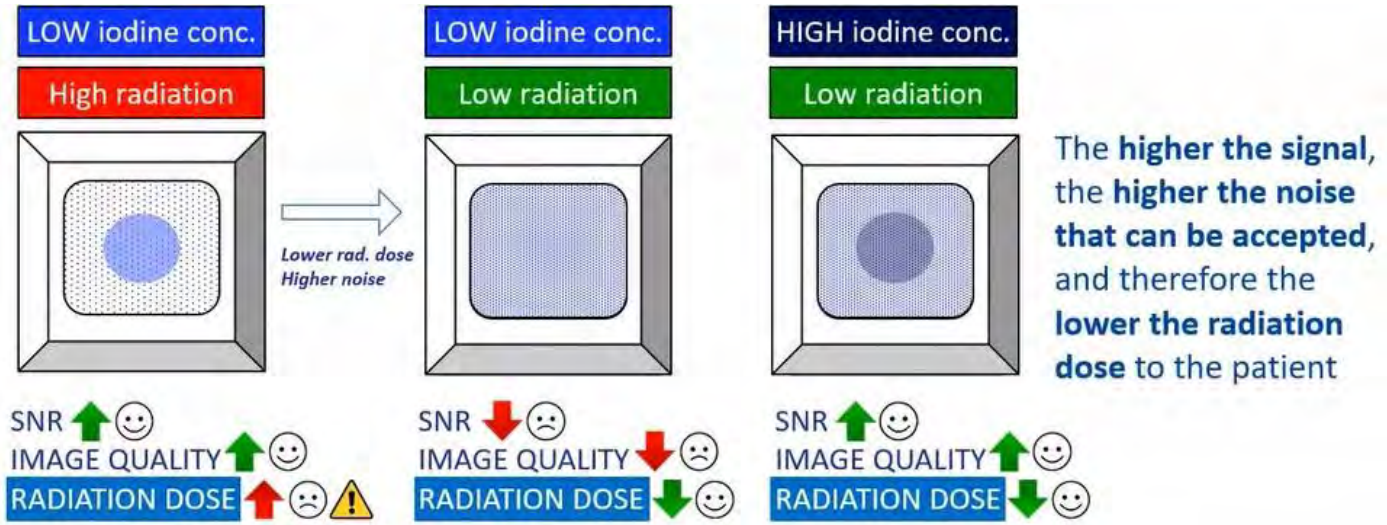
- Thermoionic emissions of electrons at Kathode, Energy release at rotating Anode (99% heat, 1% X-ray)
- Electrical potential determines X-ray energy (kVp)
- Tube insulated with lead
- X-ray beam passes Al window

X-Ray Modality – Image Contrast

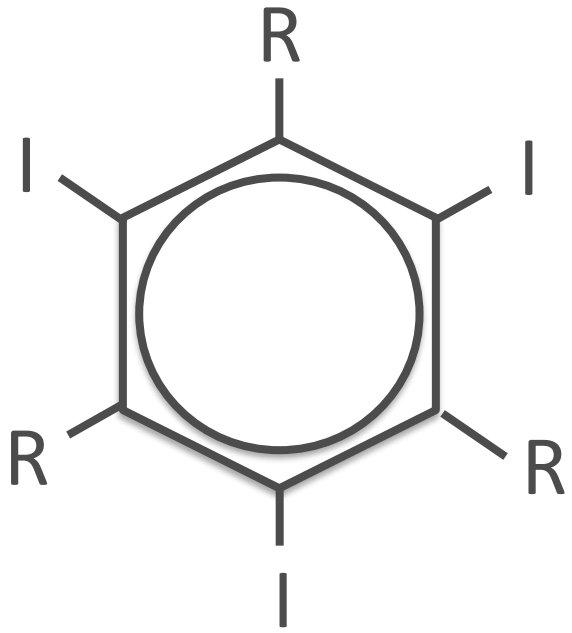
Function of the **Signal to Noise Ratio (SNR)** and **Density differences** of the object

Air Fat Soft Tissue Contrast Media Bone Metal

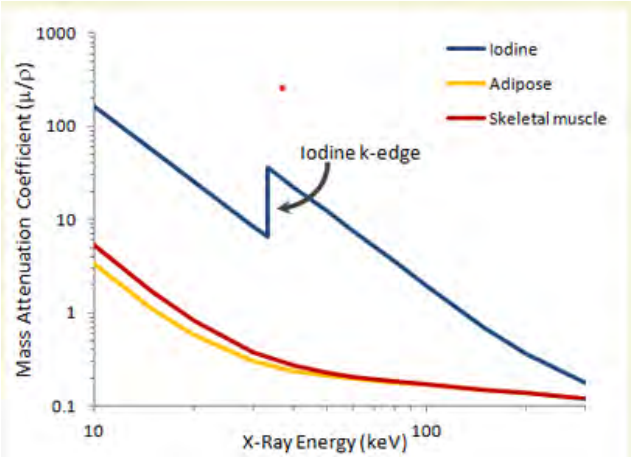
Positive **Contrast media** increases density by high **Iodine** concentration



Iodine Contrast Media



Iodine: high atomic no. 53
K-edge effect = sharp strong attenuation of X ray beam



Source: xrayphysics.com/attenuation.html

Tight binding of Iodine to benzene ring (= non toxic)
R compounds increase hydrophilic character of molecule
Pharmacodynamics: Parenteral application. Contrast media are excreted by glomerular filtration through the kidneys. Half-life approx. 120 minutes
Property is determined by **Solubility**, **Viscosity** and **Osmolality**

Isovue / Solutrast / Iopamiro

BRACCO
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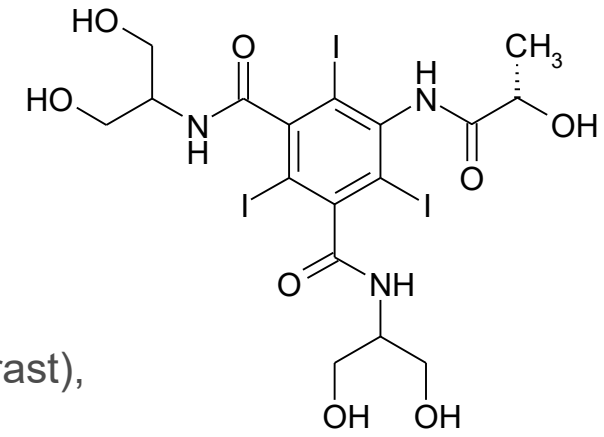
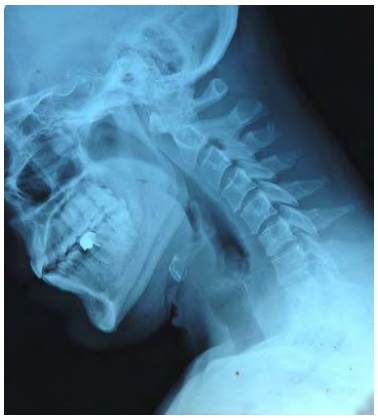
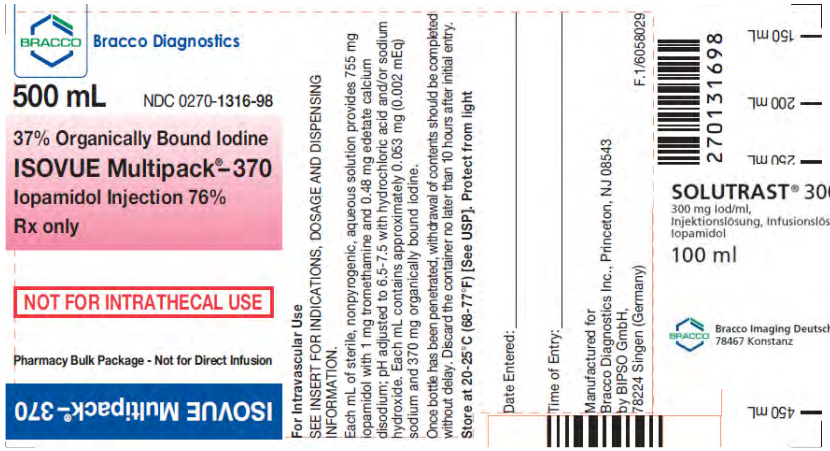
API: Iopamidol



Dosage:	200, 250, 300 and 370 mg Iodine/ml
Dosage forms:	Bottles/Vials
Filling volumes:	10 ml to 500 ml
Markets:	USA, Canada (Isovue), Germany (Solutrast), Austria (Iopamiro)
Active principle:	Contrast media for X-ray examination, contrast effect by organic bound iodine

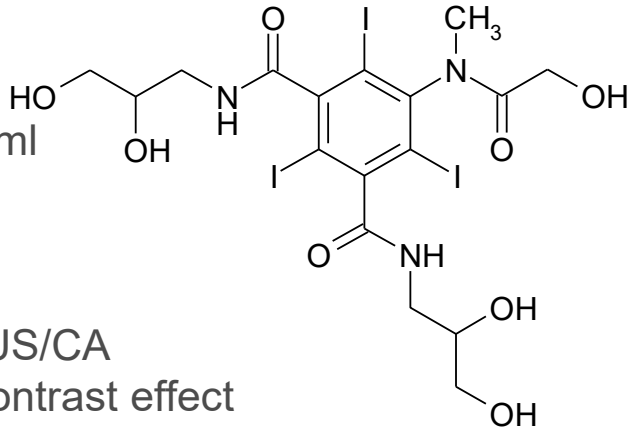
Manufacturing Process: terminal sterilized





Imeron / Iomeron

API: Iomeprol (= Isomer of Iopamidol)

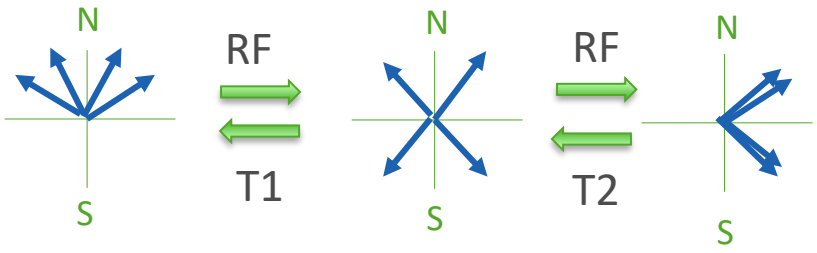


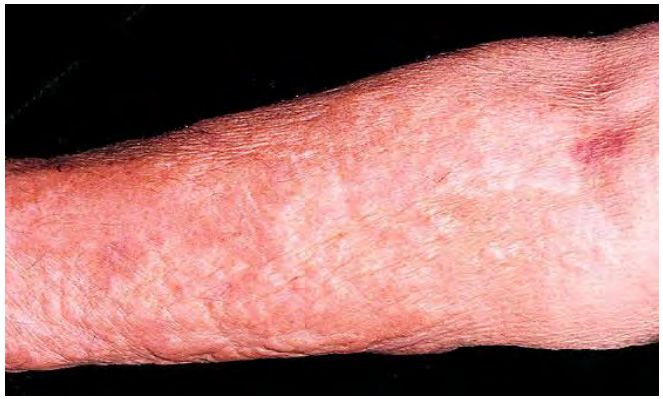
Dosage: 150, 200, 250, 300, 350, 400 mg Iodine/ml
Dosage form: Bottles and Vials
Filling volumes: 30 ml to 500 ml

Markets: Germany, many other countries except US/CA
Active principle: Contrast media for X-ray examination, contrast effect by organic bound iodine

Manufacturing Process: terminal sterilized, includes Ultrafiltration step

MRI Modality





MRI Contrast Media:

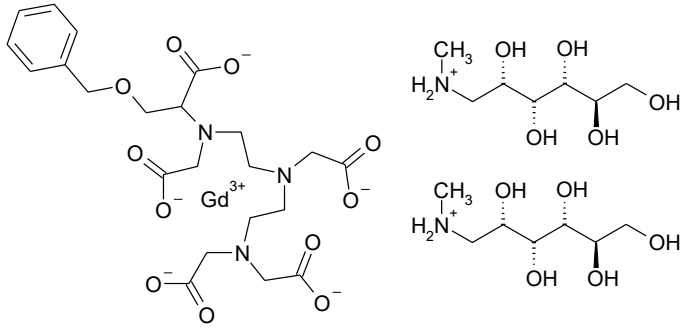
- **Increase T1 signal** by rapidly return protons to baselines (T1 Relaxation)
- Quickly regrow longitudinal magnetization
- **Gadolinium is paramagnetic at body temperature**
- Narrow concentration range for strong T1 signal
- **Gadolinium is toxic** (Gd (III) has same diameter as Ca (II), 0,99A)
- **Chelate complex**
- **Stability:** linear, nonionic < linear, ionic < macrocyclic nonionic
- **Regulatory restrictions** for linear chelates due to **NSF** (Nephrogenic Systemic Fibrosis, skin desease due to Gd accumulation in the body)
- **Pharmacodynamics**: Parenteral application. Contrast media are excreted by glomerular filtration through the kidneys. Eliminated with urine.

Multihance

API: Gadobenic acid, Dimeglumine salt

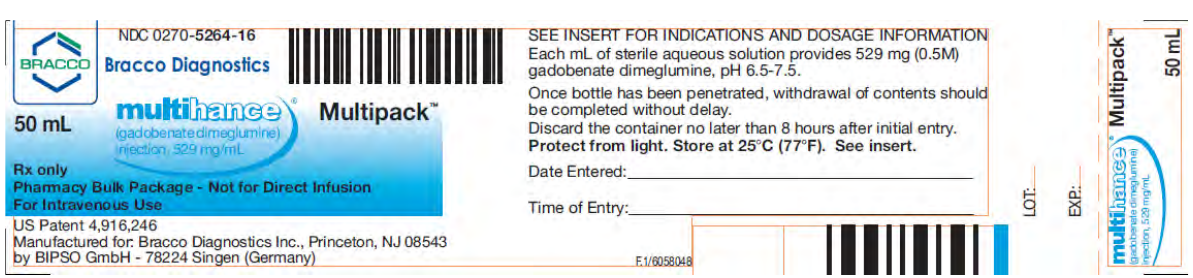
Dosage: 0,5 M
Dosage forms: Bottles, Vials
Filling volumes: 5 ml to 100 ml

Markets: (Germany), USA, Canada



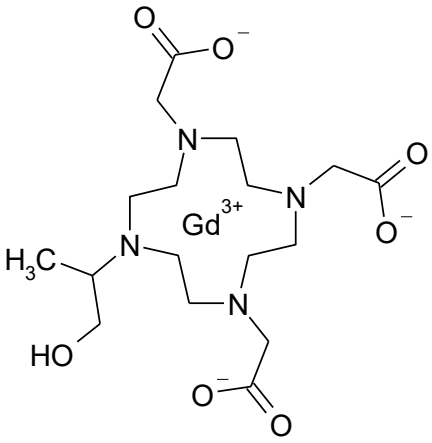
Active principle: MRT contrast media, effect by complexed paramagnetic Gd

Manufacturing process: terminal sterilized, includes API complex formation and Ultrafiltration step. Complex agent: BOPTA (Diethylentriamin-benzyloxypropionic acid tetraacetic acid)



Prohance

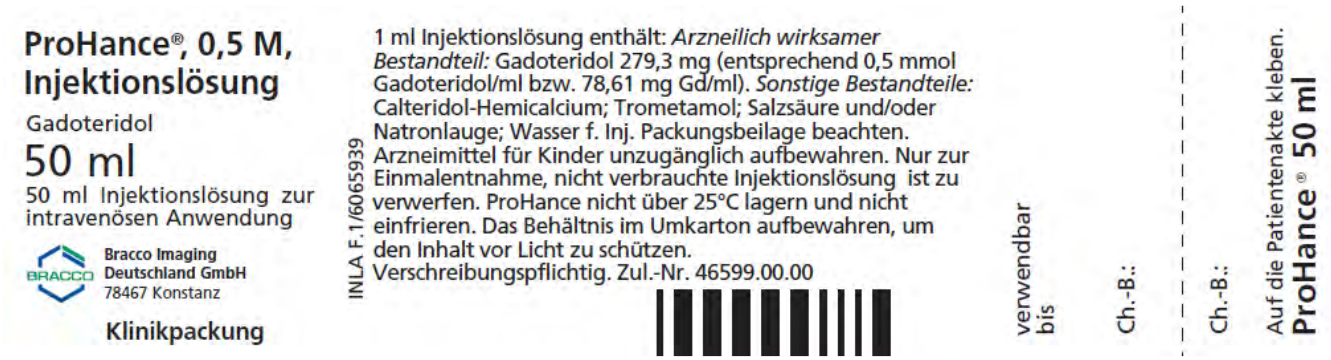
API: Gadoteridol

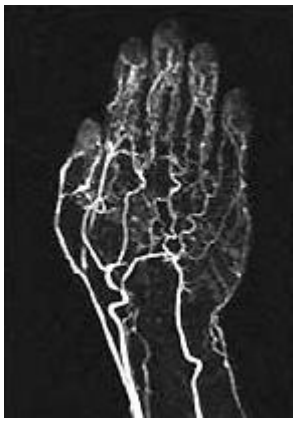


Dosage: 0,5 M
Dosage forms: Bottles, Vials, Syringes
Filling volumes: 5 ml to 100 ml (Bottles and Vials)
10 ml to 17 ml (Syringes)

Markets: EU, USA, Canada, Mexiko, Brasil, Uruguay, Japan, South Korea, China, Australia
Active principle: MRT contrast media, effect by complexed paramagnetic Gd

Manufacturing process: terminal sterilized





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Production of contrast media (1/3)

Weighing

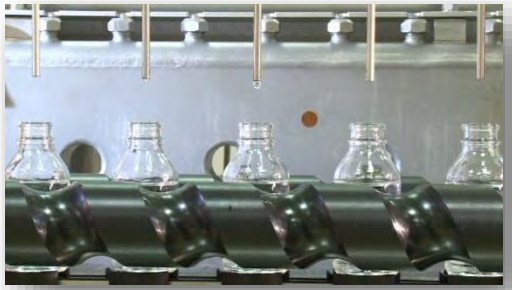
Producing solution

Filtration & monitoring

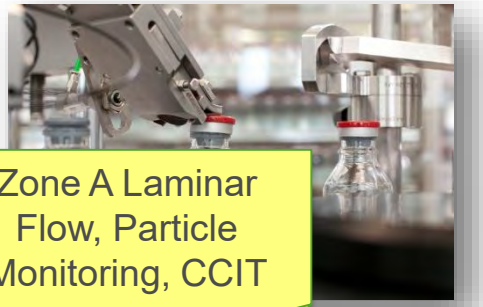
Zone C

UF, „Bioburden Reduction“ Filter (Sterile Filter)

Production of contrast media (2/3)



Filling & sealing



Zone A Laminar Flow, Particle Monitoring, CCIT

Terminal sterilisation

Bioburden Load, Sterility Tests **Parametric Release**

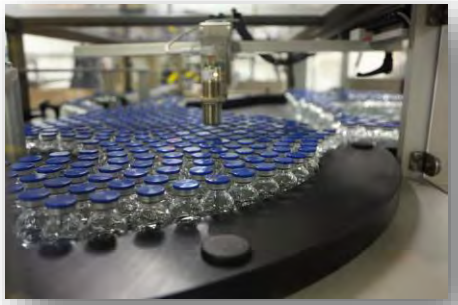
Transport to packaging department

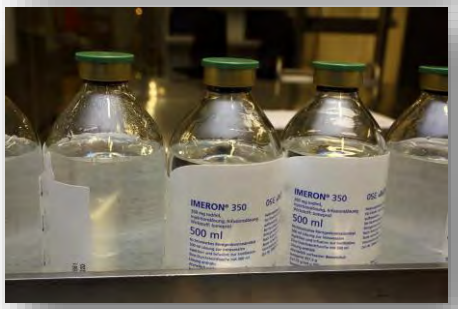
Production of contrast media (3/3)

Visual inspection

Labelling

Final packaging





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Parametric release – Definition and Regulatory Background

Parametric release can only be applied to products **terminally sterilized** in their **final containers.**

European Pharmacopoeia:
"When a **fully validated terminal sterilization method** by steam, dry heat or ionizing radiation is used, parametric release, that is the **release of a batch** of sterilized items based on **process data** rather than on the basis of submitting a sample of the items to sterility testing, may be carried out, subject to the **approval of the competent authority**."

→ **Type II Variation**

EU GMP Guide Vol. 4, Annex 17: Real Time Release Testing and Parametric Release, Dec. 2018
"Non-compliance with the specification for parametric release cannot be overruled by a finished product passing the test for sterility."

PIC/S Guidance on Parametric Release, 25 Sept 2007, PI 005-3
FDA Guidance of "Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes" (Feb. 2010).

Quality Must Be Built In – It Cannot Be Added On

Parametric release

Example 1: Recipe 7_FLASCHEN_10_BIS_250ML

No.	Step	Check parameter	value	Key parameter	CCP
1	Filling	chamber level		KP 1	
2	Heating up 1	Temperature reference bottle min.		KP 2	
3	Heating up 2	T difference between 2 reference Bottles (3 + 4)		KP 3	
4	Heating up 3	Temperature reference bottle min.		KP 4	
5a	**Sterilization**	**Temp. min.**			**CCP 1**
5b	**Sterilization**	**Temp. max.**			**CCP 2**
5c	**Sterilization**	**Time min.**			**CCP 3**
5d	**Sterilization**	**Time max.**			**CCP 4**
6	Cooling	Temperature reference bottle max.		KP 5	
7	Aeration 1	Chamber pressure			
8	Draining	Chamber level			
9	Aeration 2	Chamber pressure			

Further CCPs:
Bioburden before sterilization, Load Monitor (by Data logger) after sterilization

Parametric release

Load Monitor

- For each autoclave load a load monitor must be added to the products to challenge the sterilization program to be compliant with the requirements
- **The result of load monitor is one of the defined CCPs**
- Following questions to answer:
  - What kind of load monitor should be selected (Biological, **physical** or chemical indicator)? - **temperature logger**
  - How many indicators should be selected per sterilization run (1 – 3)? - **1**
  - Where should the monitors be placed on the racks? - **cold spot**
  - Distribution vs. penetration: must the load monitors be placed inside product solution or only inside the chamber? - **chamber (confirmed by validation)**
  - What would happen if defect, failure or missing result? - **tbd.**
  - How to assure the placement and reading of load monitors? - **tbd.**

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New Annex 1 - Contamination Control Strategy

A contamination control strategy is **a system that considers all the integral elements of pharmaceutical product manufacturing** (1). This is best achieved using quality risk management principles and supporting risk assessments for contamination control and monitoring (detectability of contamination event) (2).

Contamination control measures should be designed into each part of the production process and should include the use of contamination controls such as **cleaning, decontamination, sterilisation and transfer methods for primary packaging materials, consumables and intermediate product** that reduce the contamination risks...

The World Health Organisation has for Good Manufacturing Practice (GMP) defined contamination for pharmaceutical products as '**the undesired introduction of impurities of a chemical or microbial nature, or of foreign matter into or onto a starting material or intermediate during production, sampling, packaging, storage**.

New Annex 1 - Contamination Control Strategy

CCS addresses **mitigating actions** to **control risks** for

ICH Q9

- Microbial and Viral contamination
- Sterility assurance
- Chemical contamination
- Foreign matter particles (visible and sub visible)

Holistic approach comprising the entire **material flow processes** including **utilities** & **premises**.

Originally designed for **aseptic process** since statistical assurance cannot be provided.

Living process – living document!

Quality Must Be Built In – It Cannot Be Added On / Risk Based Approach

New Annex 1 - Contamination Control Strategy

Premises
Clean room design, qualification & monitoring (ISO 14644)
Contamination cascade (min. 10 Pa pressure differences for adjacent rooms of different grades)

Utilities
Water (Pharmaceutical grade, WFI, documented monitoring program for water systems (bioburden, endotoxins, TOC, conductivity)
Clean steam (defined chemical & endotoxin levels)
Compressed gases (including air supply): sterilizing grade filter at point of use, monitoring system (including air speed), backflow prevention

Barrier systems for equipment (RABS or Isolators): Qualification includes integrity testing, background environment, assessment of decontamination methods including contamination risk by disinfectant agents

Personnel & Process Qualification & Control - as usual (including **Media fill** for aseptic processes)

New Annex 1 - Contamination Control Strategy

How to approach?

CCS - Stand alone, controlled document

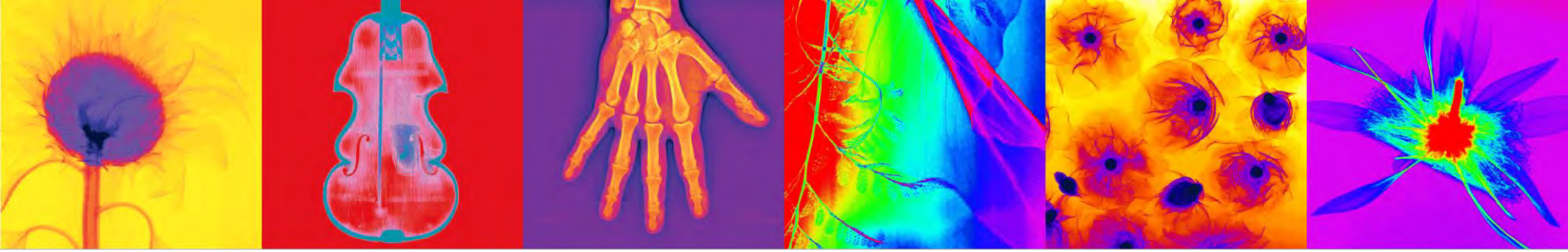
Prepared and regularly reviewed by **cross functional** team

Following principles and tools of ICH Q9 (Pharmaceutical Risk Management)

Change Control relevant

Inspection Readiness

Quality Must Be Built In – It Cannot Be Added On / Risk Based Approach



Do you have any questions?

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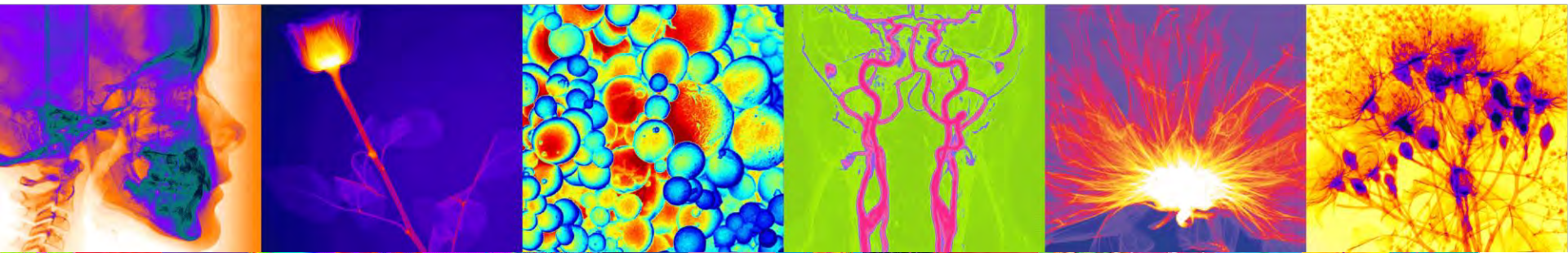

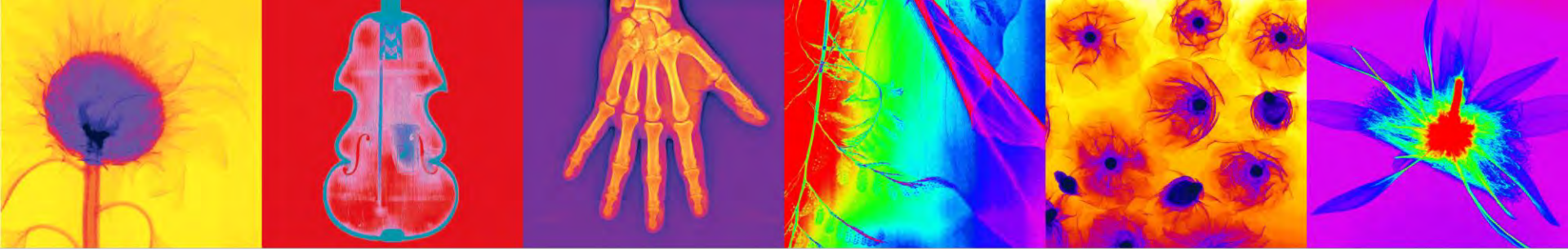

Special thanks to

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- **Gempex, for valuable support for CCS**

Thank You all for your attention

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