

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 = Bracco Imaging Pharmaceutical Sterile Operations

- 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

DIAGNOSIS
AND INTERVENTION



LIFE FROM INSIDE



HEALTH
SERVICES



LIFE FROM INSIDE



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)



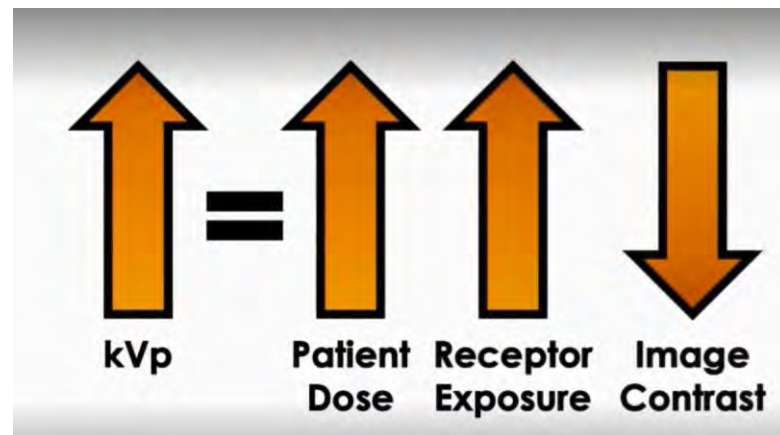
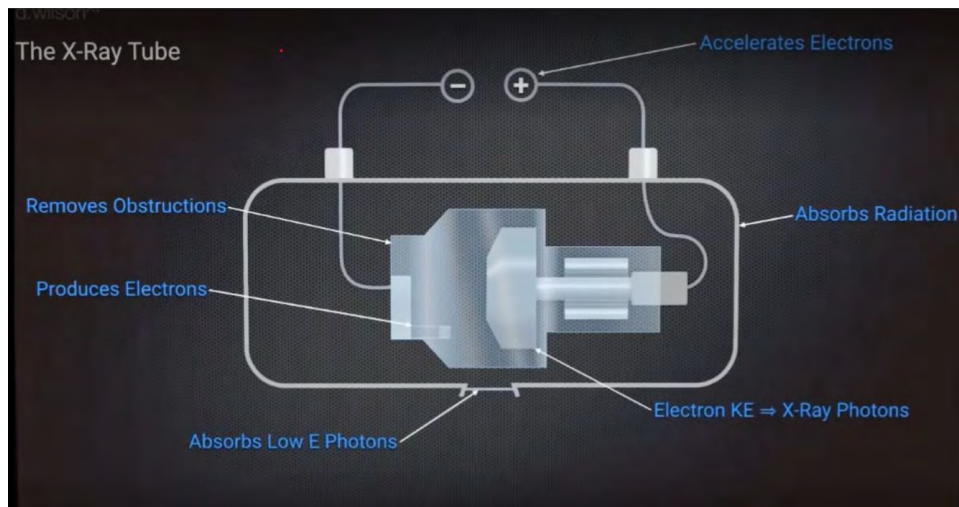
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X-Ray Modality – Tube



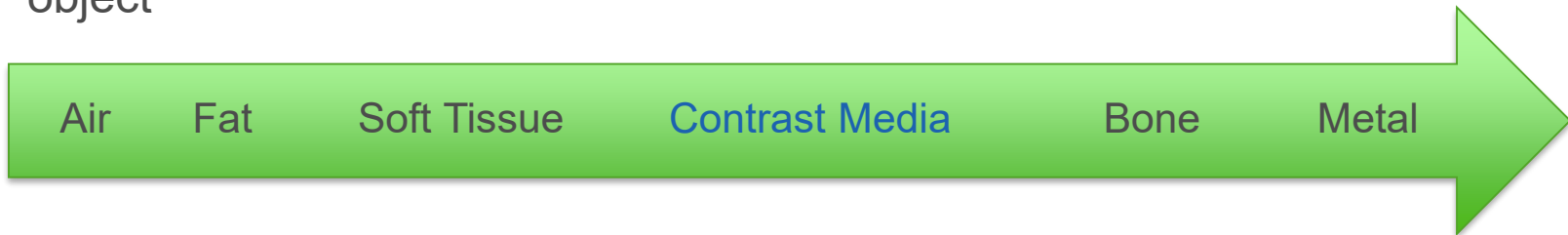
X-Ray Tube:

- 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

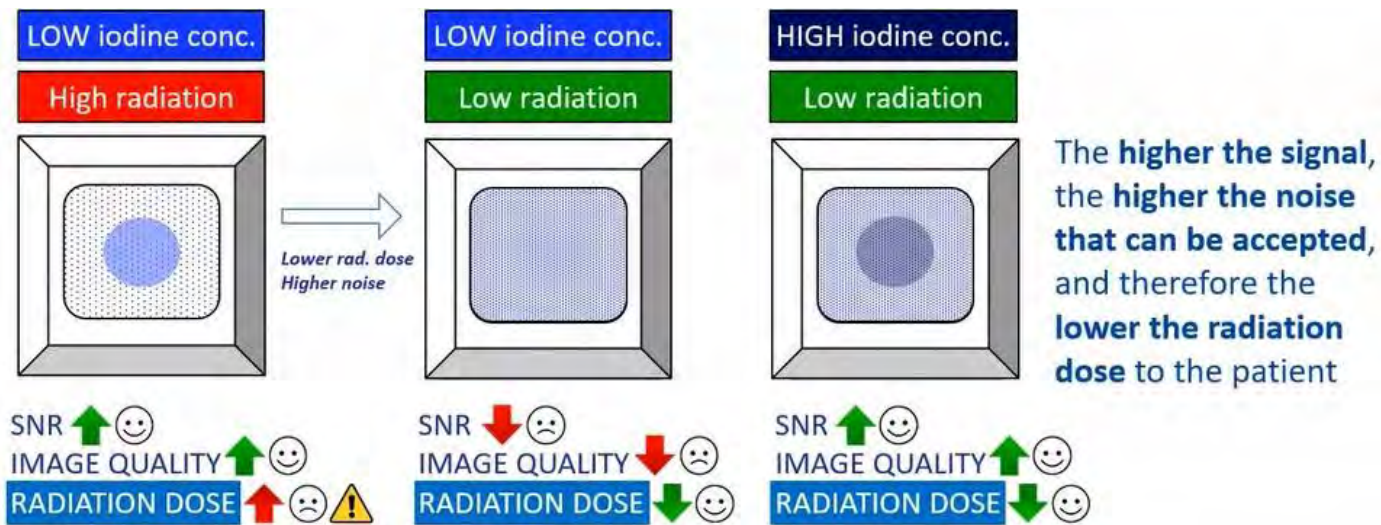


X-Ray Modality – Image Contrast

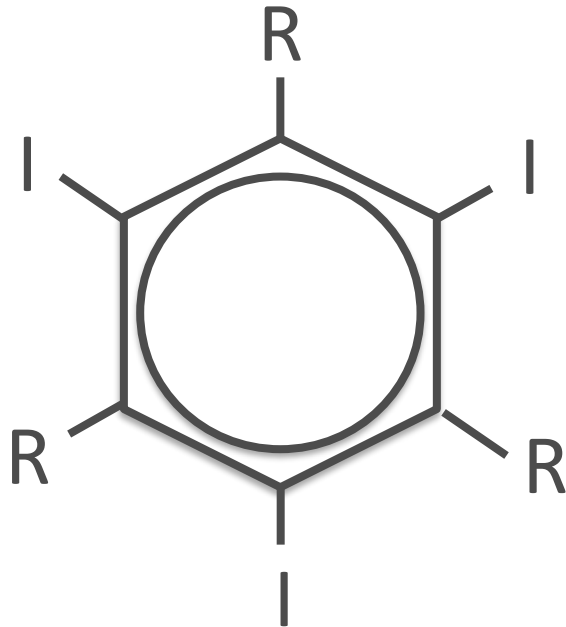
Function of the **Signal to Noise Ratio (SNR)** and **Density differences** of the object



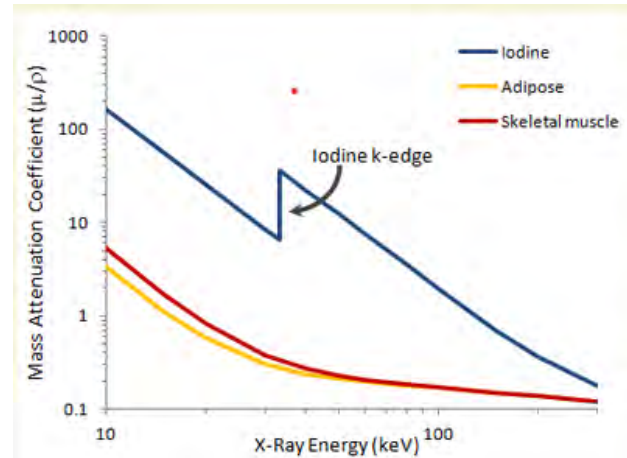
Positive **Contrast media** increases density by high **Iodine** concentration



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**



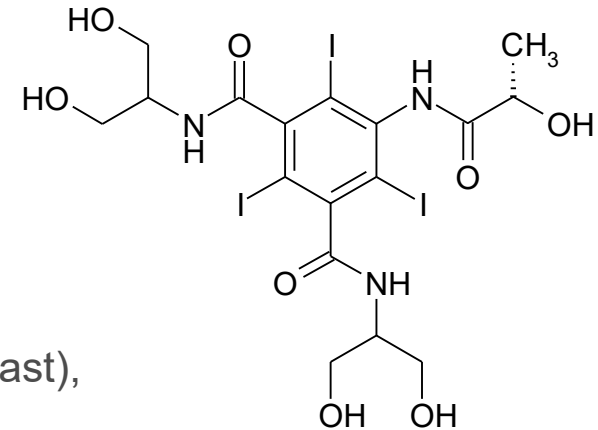
Isovue / Solutrast / Iopamiro

API: Iopamidol

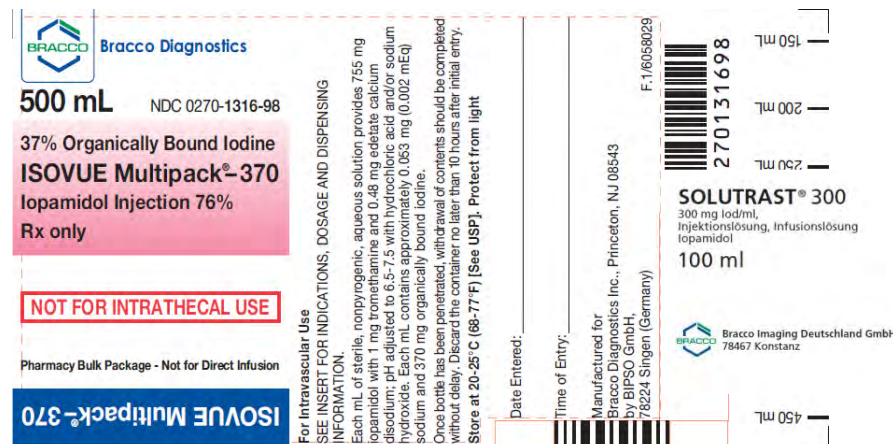
Dosage: 200, 250, 300 and 370 mg Iodine/ml
 Dosage forms: Bottles/Vials
 Filling volumes: 10 ml to 500 ml

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

The image shows the packaging for two contrast media products. On the left is the Isovue Multipack-370, a 500 mL bottle with a pink label. The label includes the Bracco logo, '37% Organically Bound Iodine', 'ISOVUE Multipack®-370', 'Iopamidol Injection 76%', and 'Rx only'. A prominent red box states 'NOT FOR INTRATHECAL USE'. Below this, it says 'Pharmacy Bulk Package - Not for Direct Infusion'. On the right is the Solutrast 300, a 100 mL bottle with a white label. The label includes the Bracco logo, 'SOLUTRAST® 300', '300 mg Iod/ml', 'Injektionslösung, Infusionslösung', 'Iopamidol', and '100 ml'. It also features a barcode with the number 270131698 and the text 'Manufactured for Bracco Diagnostics Inc., Princeton, NJ 08543 by BIPSO GmbH, 78224 Sillingen (Germany)'. A vertical label on the right side of the Solutrast 300 packaging indicates '500 ml' and '75 ml'.

SOLUTRAST® 300
 1 ml enthält: Arzneilich wirksamer Bestandteil Iopamidol 612 mg; Iodgehalt 300 mg/ml = 30 g Iod/100 ml. Weitere Bestandteile: Enthält Natriumverbindungen; Trometamol; Natriumcalciumedetat 2 H₂O; Salzsäure; Wasser für Injektionszwecke. 100 ml Injektionslösung zur intraarteriellen und intravenösen Anwendung. Lösung zur Instillation in Körperhöhlen, zur Infusion. Packungsbeilage beachten. Arzneimittel für Kinder unzugänglich aufbewahren. Vor Gebrauch auf Schwebstoffe prüfen. Lösung in einem Untersuchungsgang verbrauchen. Reste sind zu verworfen. Bei Raumtemperatur vor Licht und Röntgenstrahlen geschützt lagern. Zul.-Nr. 29273.01.00. Verschreibungsspflichtig.

Ch.-B.
 verwendbar bis
 ● 50 ml
 ● 75 ml



Imeron / Iomeron

API: Iomeprol (= Isomer of Iopamidol)

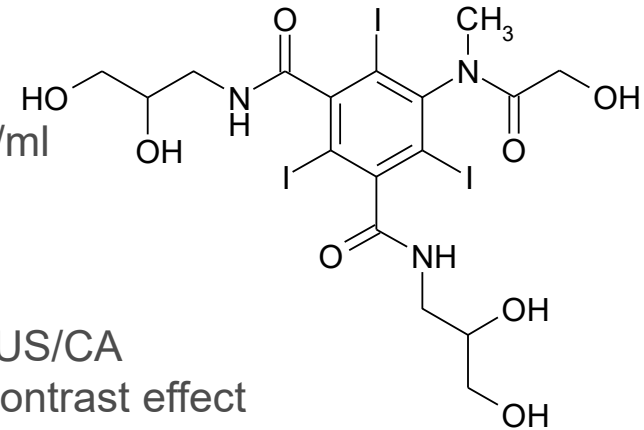
Dosage: 150, 200, 250, 300, 350, 400 mg Iodine/ml

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

IMERON® 300

300 mg Iod/ml,
Injektionslösung, Infusionslösung
Wirkstoff: Iomeprol

200 ml

Nichtionisches Röntgenkontrastmittel
200 ml Lösung zur intravasalen Injektion
und Infusion; zur Instillation.



IMERON® 300

Eine Durchstechflasche mit 200 ml Lösung enthält:

Arzneilich wirksamer Bestandteil:
Iomeprol 122,47 g (≙ 60g Iod = 300 mg Iod/ml)

Sonstige Bestandteile:

Trometamol; Salzsäure; Wasser f. Inj.

Packungsbeilage beachten.

Für Kinder unzugänglich aufbewahren.

Bei Raumtemperatur vor Licht und Röntgenstrahlen
geschützt lagern.

Nach Anbruch sofort verwenden.

Reste verwerfen.

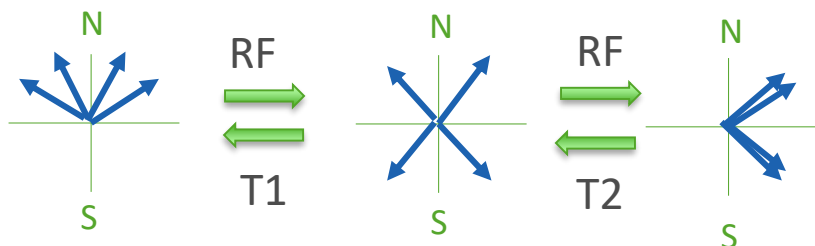
Verschreibungspflichtig

Zul.-Nr. 30699.03.00

INLA-F-1/601957/9



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 disease due to Gd accumulation in the body)
- **Pharmacodynamics:** Parenteral application. Contrast media are excreted by glomerular filtration through the kidneys. Eliminated with urine.

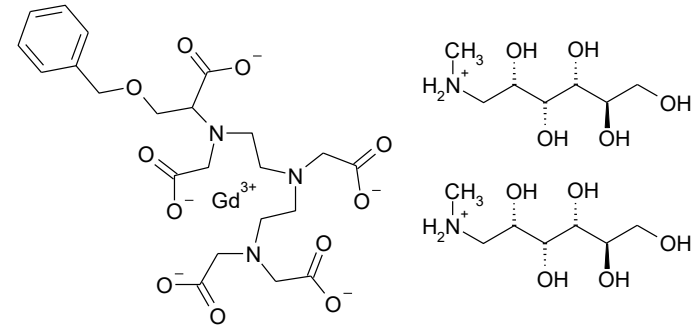


Multihance

API: Gadobenenic acid, Dimeglumine salt

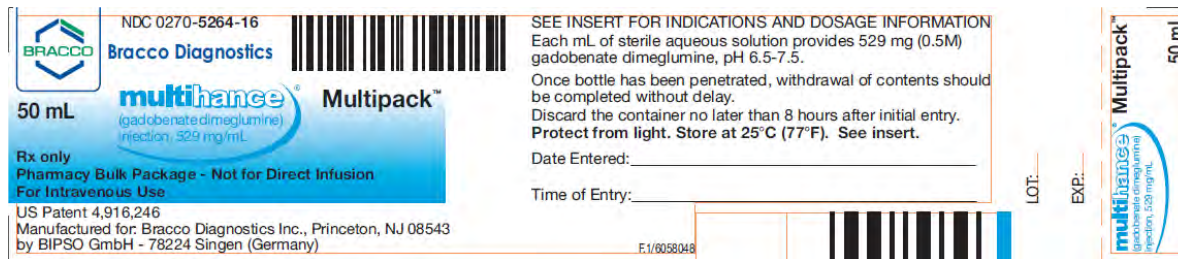
Dosage: 0,5 M
 Dosage forms: Bottles, Vials
 Filling volumes: 5 ml to 100 ml

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-**b**enzy**l**oxy**p**ropionic acid **t**etra**a**cetic acid)



The image shows the product packaging for Multihance Multipack 50 mL. The box is white with blue and red accents. It features the Bracco logo, the product name "multihance Multipack™", and the concentration "529 mg/mL". The text on the box includes: "NDC 0270-5264-16", "SEE INSERT FOR INDICATIONS AND DOSAGE INFORMATION", "Each mL of sterile aqueous solution provides 529 mg (0.5M) gadobenate dimeglumine, pH 6.5-7.5.", "Once bottle has been penetrated, withdrawal of contents should be completed without delay.", "Discard the container no later than 8 hours after initial entry. Protect from light. Store at 25°C (77°F). See insert.", "Date Entered: _____", "Time of Entry: _____", "LOT: _____", "EXP: _____", "US Patent 4,916,246", "Manufactured for: Bracco Diagnostics Inc., Princeton, NJ 08543 by BIPSO GmbH - 78224 Singen (Germany)", and "F.1/6058048".



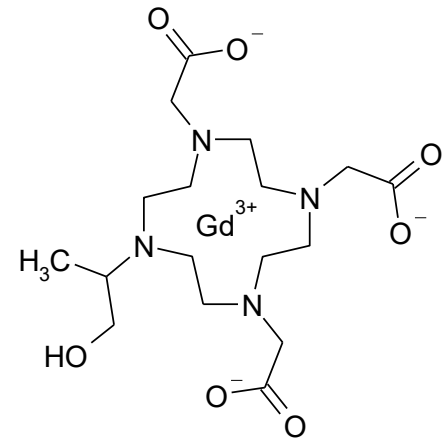
Prohance

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

ProHance® 0,5 M, Injektionslösung

Gadoteridol

50 ml

50 ml Injektionslösung zur intravenösen Anwendung



Klinikpackung

1 ml Injektionslösung enthält: *Arzneilich wirksamer Bestandteil:* Gadoteridol 279,3 mg (entsprechend 0,5 mmol Gadoteridol/ml bzw. 78,61 mg Gd/ml). *Sonstige Bestandteile:* Calteridol-Hemicalcium; Trometamol; Salzsäure und/oder Natronlauge; Wasser f. Inj. Packungsbeilage beachten. Arzneimittel für Kinder unzugänglich aufbewahren. Nur zur Einmalentnahme, nicht verbrauchte Injektionslösung ist zu verwerfen. ProHance nicht über 25°C lagern und nicht einfrieren. Das Behältnis im Umkarton aufbewahren, um den Inhalt vor Licht zu schützen. Verschreibungspflichtig. Zul.-Nr. 46599.00.00

INLA F.1/6065939



verwendbar
bis

Ch.-B.:

Ch.-B.:

Auf die Patientenakte kleben.
ProHance® 50 ml



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Production of contrast media (1/3)



Weighing



Zone C

Producing solution



Filtration & monitoring

UF, „Bioburden Reduction“ Filter
(Sterile Filter)



Production of contrast media (2/3)



Filling & sealing



Zone A Laminar Flow, Particle Monitoring, CCIT



Terminal sterilisation

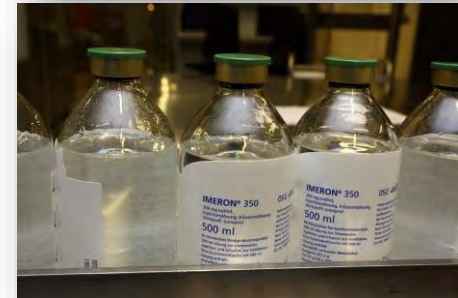
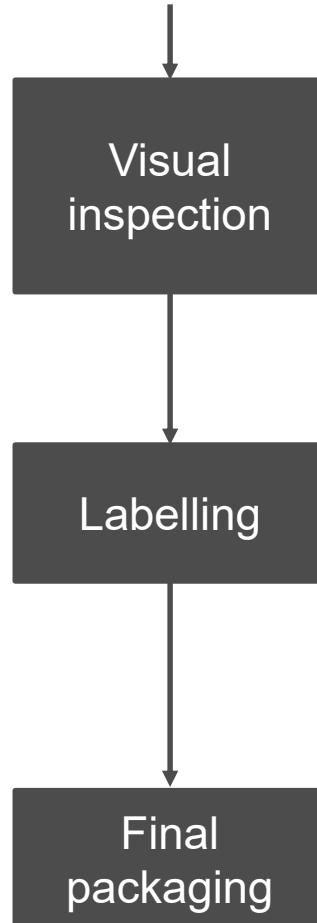
Bioburden Load, Sterility Tests
Parametric Release



Transport to packaging department



Production of contrast media (3/3)



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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

- 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

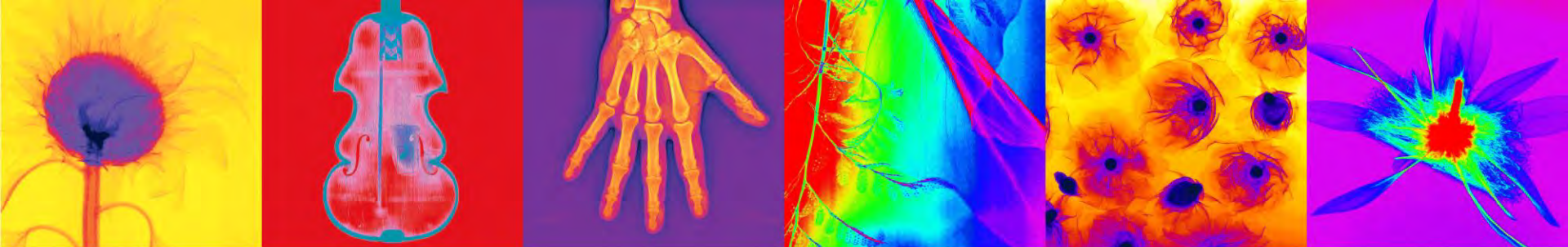
Following principles and tools of ICH Q9 (Pharmaceutical Risk Management)

Change Control relevant

Inspection Readiness

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

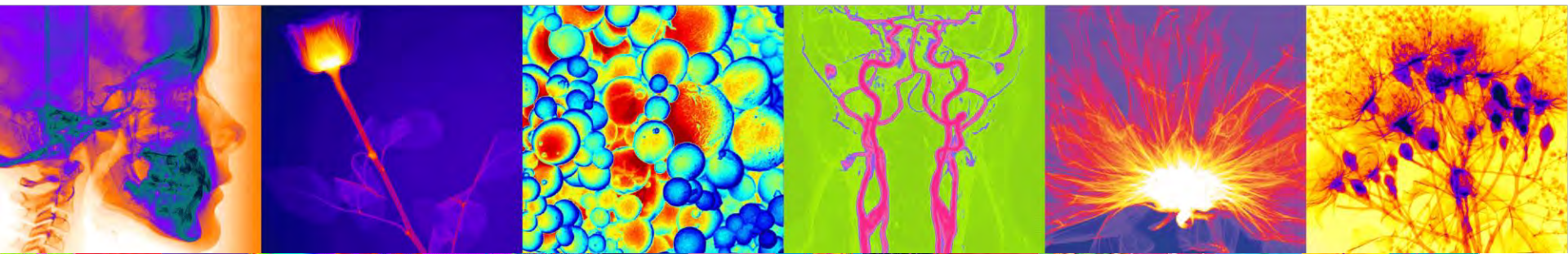


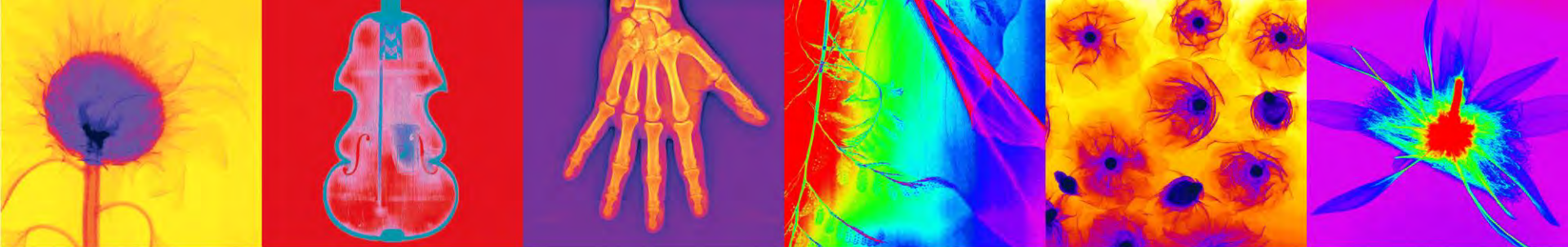


**Do you have
any questions?**



LIFE FROM INSIDE





Special thanks to

- **Maurizio Franchini, Global Marketing, Bracco**
- **Gempex, for valuable support for CCS**

Thank You all for your attention

