



## Speakers



Dr Martin Becker  
IDT Biologika



Martin Dearden  
ECA Visual Inspection  
Group



Dr Helmut Gaus  
WinSol, previously  
Boehringer Ingelheim



Roland Koch  
Gasporex



Felix Krumbain  
Roche



Christof Langer  
OSConsulting



Dr Daniel Müller  
GMP-Inspector



Dr Tobias Posset  
Roche



Dr Brian Turnquist  
Boon Logic

# Control of Parenterals

Container/Closure Integrity Testing  
Visual Inspection Systems



Live Online Conferences on 6 & 7/8 October 2020



## Highlights

### Container-/Closure Integrity Testing, Live Online Conference on 6 October 2020

- Pharmacopeial Requirements for the CCI testing
- GMP Requirements regarding CCIT
- Overview CCI Testing Technologies
- Online vs. Offline Testing
- Case Study: CCI Testing of Prefilled Syringes
- Case Study: CCI Testing of Ampoules
- Case Study: CCI Testing of Vials

### Visual Inspection Systems, Live Online Conference on 7/8 October 2020

- Pharmacopeial Requirements for Visual Inspection
- GMP Requirements regarding Visual Inspection
- Manual Inspection
- Semi-Automated Inspection
- Fully-Automated Inspection
- Test Sets: Preparation, Handling and Usage
- Re-Inspection of Defect Fractions
- Trending and Monitoring of Inspection Data
- AQL Testing and Batch Release
- Unsupervised Machine Learning: new concept for automated visual inspection

## Objective

Different products and different container types require different testing methods: this event aims at giving an overview of the different CCI testing systems which are applied during production and as part of the quality control system. Apart from technical aspects the regulatory requirements on CCI testing will be highlighted as well as the applicability of inline and offline testing.

## Background

An intact container closure system, which is the sum of packaging components that protect the dosage form, is the pre-requisite for a safe and sterile drug product. The CC system protects the product from microbial contamination and also from exposure to gases or water vapour or the loss of solvent. Container Closure integrity testing is therefore a regulatory requirement and it is part of the whole life cycle of a sterile drug product.

Initially this testing was performed as part of the initial development of the packaging system and the system's suitability verified in stability studies including on-going stability. Over the years, the expectation was raised to perform batch by batch verification with latest trends to 100% inline or offline testing wherever possible.

We will discuss and answer questions like:

- What are the current and upcoming GMP- and compendial requirements in the US / EU / RoW?
- Will container closure integrity testing change to 100% inline testing?
- What does the Annex 1 require?
- How do we have to define 'tight'?
- Which testing technologies are available and suitable?
- Is blue dye testing still a standard? And how does modern blue dye testing look like?
- CCI testing of prefilled syringes
- CCI testing of lyo & liquid vials
- CCI testing of ampoules

## Target Audience

This conference is directed at specialists and executives from the areas engineering and production and QA dealing with the implementation and operation of systems for the container/closure-integrity testing of sterile medicinal products.

## Moderator

Christof Langer

## Programme

### Container Closure Integrity Testing of Sterile Drug Products – Requirements, Expectations and Exaggerations

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- Container Closure Integrity during development, qualification and stability testing
- Regulatory, Pharmacopoeial and GMP requirements
- System integrity versus container damages
- Patient risks – do we need batch by batch testing?
- Industrial best practices

### Expectations of a GMP-Inspector regarding to Container/Closure Integrity Testing

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- Regulatory documents on container / closure integrity testing (an overview)
- Testing methods for CCIT & validation strategies
- Current situation on CCIT in pharmaceutical industry & challenges
- Inspection findings & experience

### Overview of Container/Closure Integrity Testing Technologies

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The presentation gives a complete overview of the different aspects of leak testing to do CCIT in the pharmaceutical production. The systems presented can be used for the CCIT of vials, ampoules, syringes, BFS, IV bags, blisters etc.

- Leak, leak rate and the relevant physical units
- Leak test methods
  - Pressure change methods (vacuum, pressure and LFC)
  - Head Space Analysis using TDLAS
  - Helium Leak Test and other Mass Spectroscopy Systems
  - High Voltage Leak Detection (HVLD)
  - Force Sensing Technology
- Capabilities and examples of the different methods
- How to select the right method
- How to generate positive controls

### Case Study: 100% Testing of Vials

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- System setup
- Validation
- Routine operation

### 100% inline CCI Testing of Ampoules

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- High Voltage inline testing: method description
- Integration in the production process
- Limits of the system
- Qualification of the system
- Validation
- Routine Operation

### Integrity Testing of Prefilled Syringes

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- Sampling plan
- He-leak testing
- Limitations of the He-leakage test
- Cross validation with mCCI

## Objective

Main topic of this course is the detection of defects like particles in injectables and their evaluation during batch release. Besides the current regulatory requirements with regards to particulate matter, routine 100% inspection of injectables will be addressed. Manual inspection as well as automated inspection systems will be covered, including validation, training, defect categories, AQL testing, trending and batch release considerations.

## Background

In most cases particles found in parenteral medicines will lead to a quarantined product or even to the recall of the product – as we have seen in the last years in the cases of several pharmaceutical companies. Responsible staff in charge will have to start root cause analysis to find the source of the particles and will have to do an evaluation of batches already shipped.

There is still confusion within the global pharmaceutical industry with regard to the requirements for testing for visible particles. After the USP chapters <790> and <1790> were published, things have become much clearer, at least for the US. But still, lots of questions arise, e.g. concerning re-testing, detection capabilities and revalidation of inspection systems.

Furthermore there has been a recognisable trend towards automated inspection machines throughout the last years. The challenge for pharmaceutical companies is to find a suitable machine for their products and to determine reasonable inspection parameters during qualification and validation. But also during routine process there are questions arising like re-testing and the usage of test-sets, doing AQL-Testing as well as the adjustment of parameters of the vision systems.

We will address those topics during the conference and discuss and answer questions on

- The latest compendial requirements concerning particulate matter
- Compliance with the revised Annex 1
- Training and qualification of operators in the manual inspection
- Validation and operation of an automated inspection system
- Trending and monitoring of visual inspection data
- Correct AQL testing as part of the batch release
- Re-inspection of defect fractions
- Usage of artificial intelligence in visual inspection

## Target Audience

This course is directed at staff from sterile operations, that is production, quality assurance and engineering. But also suppliers of primary packaging materials and inspections technology are target group of this event.

## Moderator

Dr Tobias Posset, Roche Diagnostics & Chairman of the ECA Visual Inspection Group

## Programme

### Regulatory Requirements for the Visual Inspection of Parenterals

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- Compendial Requirements
  - 100% visual inspection & AQL testing
  - PharmEur, USP, JP - similarities and differences
- News from the Annex 1 revision
- Risk Management Considerations

### Expectations of a GMP Inspector regarding Visual Inspection

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- Regulatory documents on visual inspection of parenterals (an overview)
- Manual inspection, semi-automated inspection (personnel, working place, equipment, training & qualification)
- Automated inspection (incl. validation strategy)
- Routine operations, AQL testing, handling of (r)jects
- Inspection findings & experience

### Manual Visual Inspection – Theory and Practical Aspects

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- Probabilistic nature of visual inspection
- Defect categorisation
- Differentiation of test kits for training, qualification and routine
- Qualification and training of personnel
- Standardisation of working conditions in manual inspection
- Usage of the Knapp and the modified Knapp test

### Automated Visual Inspection – from Setup to Routine Use

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- Limitations of automated inspection
- Setting up a qualification strategy for automated systems
- Cross validation during the PQ phase of an automated system
- Importance of particle detection rates
- System suitability, requalification and revalidation
- Inspection of defect fractions
- The Roche Inspection systems: manual, semi-automated and fully automated inspection

### Requirements, Composition, and Handling of Test Sets

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- Definition of defect categories
- Set-up and composition of a test set
- Test sets and their use for training, qualification and routine
- Handling and release of test sets
- Documentation

## Re-Inspection of Defect Fractions in Visual Inspection

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Different scenarios will be covered such as:

- Re-inspection or additional inspection of “grey-channel” units from (semi-) automated inspection
- Re-inspection in case of exceeding alert limits or AQL failures
- Focused re-inspection
- Inspection approaches in case of investigations due to unexpected particles (e.g., to determine frequency of occurrence of visible particles when particles are found during release/stability testing)

## Automated Visual Inspection Based on Unsupervised Machine Learning

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- Vector segmentation using unsupervised machine learning
- Characterizing variation using computer vision
- Learning normal variation in defect-free bottles
- Visual inspection via anomaly detection

## Particle Testing and the Correlation with Trending and Batch Release

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- Why do we Monitor (What is it all about)
- Data and measurement
- The AQL trap
- Improvement process map
- Investigation and routine analysis,
- Release Process. “To AQL or not to AQL that is the Question”
- Product release: “Falling off a log”

## Speakers



**Dr Martin Becker**  
IDT Biologika

Dr Becker is group leader in project management at IDT. Before he has been Head of Technical Operations and Head of Production Sterile Operations at Siegfried Hameln. He previously held also different positions in analytical development, quality assurance, and production at IDT and Sandoz.



**Martin Dearden**  
M&F Pharma Quality Solutions

Martin holds Degree level qualifications in Applied Biology and also Immunology and Microbiology. He was Senior Director at UCB S.A. and as the UCB Corporate Microbiologist responsible for microbiological standards and strategy and for 5 years Vice President of Global Quality for PaxVax Berna in Switzerland. Now he is Director of M&F Pharma Quality Solutions Ltd. Independent Pharmaceutical and Biotechnology sector consultants.



**Dr Helmut Gaus**  
WinSol & former Director Quality Control at Boehringer Ingelheim

Dr Gaus was Head of Quality Control Service at Boehringer Ingelheim, Biotechnology. He has also been working as Vice President Quality Control and Qualified Person for Novartis Generics, Vetter-Pharma and Rentschler Biotechnologie. In 2018 he founded his own company WinSol.



**Roland Koch**  
Gasporex

Roland Koch has 25 years' experience in the development and implementation of technologies and systems for the GMP regulated industry (Differential Pressure Measurements, Tunable Laser Absorption Spectroscopy, HVLD, Force Sensor Technology and NDIR). He is at GASPOROX AB in Lund (SE) as a Senior Sales and Application Engineer.



**Felix Krumbein**  
Roche Diagnostics

Felix Krumbein studied optotechnics and image processing and has been responsible for the implementation of GMP-compliant imaging-tools. Now he is head of Inspections-Systems-Support at Roche Mannheim where he is responsible for the qualification of visual inspection systems.



**Christof Langer**  
OSConsulting

Christof Langer studied Biotechnology and is certified Risk Manager as well as a Lean Six Sigma Black Belt. He has been working as Managing Director at Baxter BioScience, responsible for Operations. Since 2009 he runs his own consultancy business.



**Dr Daniel Müller**  
GMP Inspector Germany

Daniel Müller is head of a local GMP inspectorate in Germany. Since 2001 he has been working as GMDP inspector, conducting national inspections as well as EMA- and overseas inspections. He is member of Germany's expert groups 'biotechnology & tissue' and 'quality assurance'.



**Dr Tobias Posset**  
Roche Diagnostics

Tobias Posset studied Biochemistry and Chemistry. He is heading the Production Support unit in the Pharma Production at Roche in Mannheim. Herein he is responsible for the IPCs, the particle laboratory, the automated visual inspection and the coordination of the manual inspection training. He is also chairman of the ECA Visual Inspection Group.



**Dr Brian Turnquist**  
Boon Logic

Dr Turnquist has worked in machine learning for the past twenty years developing numerous novel algorithms for automatically clustering biological signals in real-time. Turnquist is CTO of Minneapolis tech start-up, Boon Logic and is a tenured professor at Bethel University.

## CCI Testing of Parenterals

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### Date Live Online Conference

Tuesday, 6 October 2020, 09.00 – 18.00h

### Fees (per delegate, plus VAT)

ECA Members € 790

APIC Members € 890

Non-ECA Members € 990

EU GMP Inspectorates € 495

The conference fee is payable in advance after receipt of invoice.

## Visual Inspection Systems

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### Date Live Online Conference

Wednesday, 7 October 2020, 09.00 – 16.45 h

Thursday, 8 October 2020, 08.30 to approx. 16.30 h

### Fees (per delegate, plus VAT)

ECA Members € 1590

APIC Members € 1690

Non-ECA Members € 1790

EU GMP Inspectorates € 995

The conference fee is payable in advance after receipt of invoice.



### Would you like to save money?

Book both courses and save € 300 in total  
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## Registration

Via the attached reservation form, by e-mail or by fax message. Or you register online at [www.gmp-compliance.org](http://www.gmp-compliance.org).

## Presentations/Certificate

The presentations will be made available to you prior to the Live Online Conferences as PDF files. After the event, you will automatically receive your certificate of participation.

## Conference language

The official conference language will be English.

## Organisation and Contact

ECA has entrusted Concept Heidelberg with the organisation of this event.

### CONCEPT HEIDELBERG

P.O. Box 10 17 64  
69007 Heidelberg, Germany  
Phone +49(0)62 21/84 44-0  
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### For questions regarding content please contact:

Dr Robert Eicher (Operations Director) at  
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### For questions regarding organisation:

Mr Rouwen Schopka (Organisation Manager) at  
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schopka@concept-heidelberg.de.

## GMP/GDP Certification Scheme

Building on your education the ECA GMP/GDP certification programmes provide you with the appropriate supplement to acquire this qualification. Simply choose any three courses within the programme according to your professional interest. Your certificate is then valid for two years. To renew it, you can pick any training from the ECA courses and conferences list within that two-years period – allowing you to broaden your knowledge in GMP and GDP compliance.



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D-69007 Heidelberg  
GERMANY

### Reservation Form (Please complete in full)



Visual Inspection Systems, Live Online Conferences on 6 & 7/8 October 2020  
 CCI testing of Parenterals, Live Online Conference on 6 October 2020  
 Visual Inspection Systems, Live Online Conference on 7/8 October 2020

Title, first name, surname

Department

Company

Important: Please indicate your company's VAT ID Number

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#### General terms and conditions

- If you cannot attend the conference you have two options:
1. We are happy to welcome a substitute colleague at any time.
  2. If you have to cancel entirely we must charge the following processing fees:
    - Cancellation until 2 weeks prior to the conference 10 %
    - Cancellation until 1 week prior to the conference 50 %
    - Cancellation within 1 week prior to the conference 100 %
- CONCEPT HEIDELBERG reserves the right to change the materials, instructors,

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