The art of building and maintaining a quality portfolio in diagnostics

ASCOmed
Customer Seminar
Sychrov, April 26./27. 2018

Dr. Jörg Ruppert
Director Business Strategy

Normative References

CERTIFICATE

DQS Medizinprodukte GmbH

hereby certifies that the company

ORGENTEC Diagnostika GmbH
Carl-Zeiss-Straße 49
55129 Mainz
Germany

has implemented and maintains a **Quality Management System**.

Scope:
Design, development, manufacturing and distribution of in-vitro diagnostic medical devices and in-vitro diagnostic analyzers used in the diagnosis of autoimmune diseases comprising rheumatology, thrombosis, ANCA/vasculitis, thyroid, gastroenterology, diabetes diagnosis and infections diseases

Through an audit, documented in a report, it was verified that the management system fulfills the requirements of the following standard:

ISO 13485 : 2003

Certificate registration No.	014965 MP23CMDR
Certificate unique ID	170519413
Effective date	2011-08-16
Expiry date	2014-08-15
Frankfurt am Main	2011-05-26

SCC Accredited CB-MS
OCSM Accredité CCN

Frank Gralchen
Managing Director

Sigrid Uhlemann
Product Manager

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DQS Medizinprodukte GmbH is a CMDCAS (Canadian Medical Devices Conformity Assessment System) recognized registrar.

Certificate

mdc medical device certification GmbH
certifies that

ORGENTEC Diagnostika GmbH
Carl-Zeiss-Straße 49
55129 Mainz
Germany

with the distribution sites

ORGENTEC Hungary Kft.
Aradi Vértanúk utca 45
H2060 Bicske
Hungary

ORGENTEC Austria GmbH
Hausfeldstraße 90
A2232 Deutsch-Wagram
Austria

for the scope

design, development, manufacturing and distribution of in-vitro diagnostic medical devices, reagents, controls and analyzers/instruments used in the diagnosis of autoimmune and infectious diseases

has introduced and applies a

Quality Management System

The mdc audit has proven that this quality management system meets all requirements of the following standard

EN ISO 9001

Quality management systems – Requirements

(ISO 9001:2008)

Valid from	2011-08-15
Valid until	2014-08-14
Registration no.	1632.57.11/0
Report no.	E 1632.57 / 2011-08-15
Stuttgart	2011-08-15

Head of Certification Body

medical device certification mdc

DAkkS Deutsche Akkreditierungsstelle D-ZM-16032-01-01

mdc medical device certification GmbH
Kriegerstraße 6
D-70191 Stuttgart, Germany
Phone: +49-(0)711-253597-0
Fax: +49-(0)711-253597-10
Internet: http://www.mdc-ce.de

For electronic publication only

Ressources

Top management determines and provides resources needed:

Human resources (15 staff in QC, 2 QM)

Infrastructure

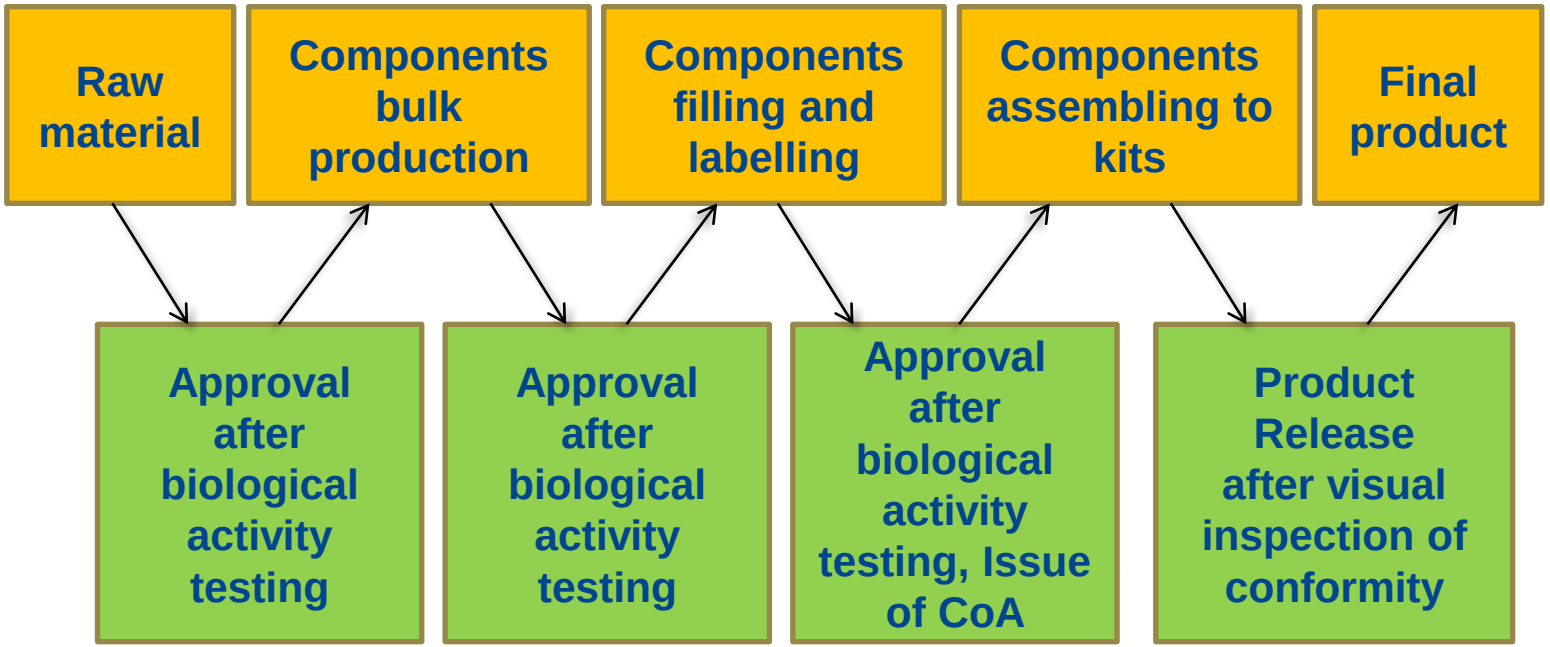
Work Environment

Product Realization

Production process

For every step in the production process there has to be a check & approval by quality control

Product Realization



After Market Survey

- Customer satisfaction is key
- Measurement, analysis, improvement
- Communication via direct contact with customers (customer trainings, trade fairs, newsletters,
- ORGENTEC homepage, E-mail questionnaire)

Recording of any customer inquiry or complaint

Quality assurance programs

- **regular participation in major national and international quality assurance programs since 1994**
  - **- UK NEQAS (Great Britain)**
  - **- DGKL-RfB (Germany)**
  - **- Instand e.V. (Germany)**
  - **- CAP (USA)**
  - **- RCPA (Australia)**
  - **- ÖQUASTA (Austria)**

Successful participation in quality assurance programs confirms the high efficiency and consistency of ORGENTEC autoimmune tests:

Consistency ratio: 98.2 % in 2017

CAPA – Corrective Action / Preventive Action

Any Problem, Complaint or Non Conformity :
Defect Product or Insufficient Process

WHAT is a CAPA System

Improvements to an organization's processes taken to eliminate causes of non-conformities or other undesirable situations.

CAPA is a concept which focuses on the systematic investigation of the root causes of identified problems or identified risks in an attempt to prevent their recurrence (for corrective action) or to prevent occurrence (for preventive action).

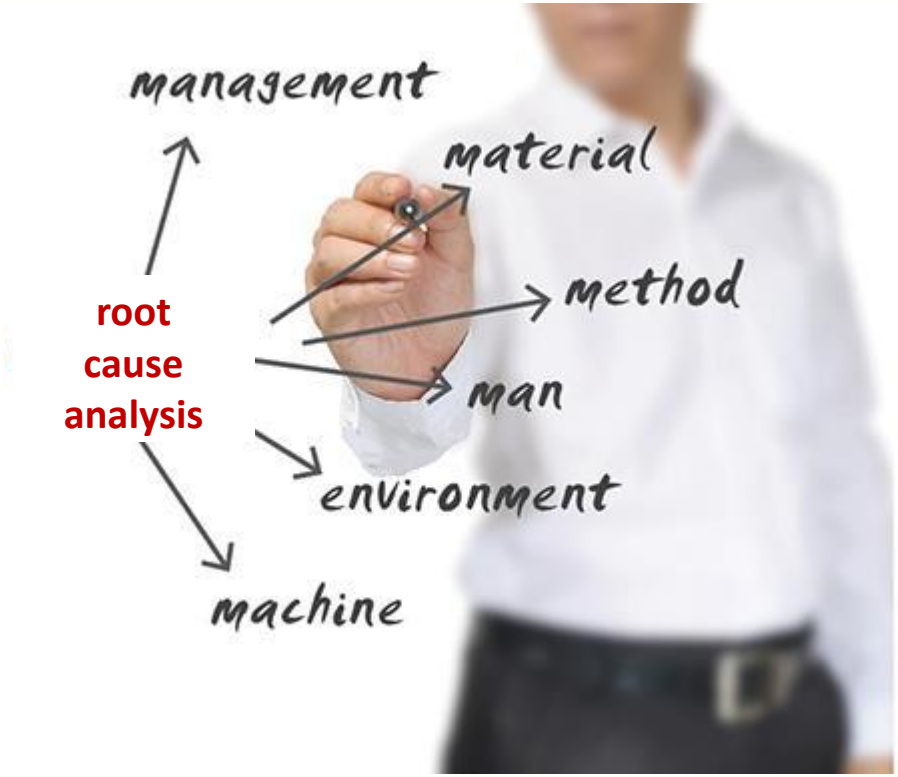
Corrective actions are implemented in response to customer complaints, unacceptable levels of product non-conformance, issues identified during an internal audit, or adverse or unstable trends in product and process monitoring. Preventive actions are implemented in response to the identification of potential sources of non-conformity.

We have to differentiate between:

- Correction
- Corrective action
- Preventive action

Project “COOR* Prevention“ in a CAPA form

open brainstorming and root cause analysis needed



- stability of strip?
- stability of single component/s
- stability of antigen?
- effect during production
- effect by Alegria instrument?
- effect by shipping/handling?
- effect at customer?
- effect in instrument?
- …..

- * Calibrator Out Of Range*

COOR Prevention – Data overview

1. CAPA's Name: COOR Prevention

2. Project members and function:

Project Team	Function
Christian Löbke	Project leader, QM
Barbara Mansi	Reviewer
Anna Schneider	Project coordinator
Kelly Pitts	Project Sponsor
Ulrich Leinfelder	Investigator QC
Martina Klemm-Manns	Investigator Production

3. Project goal:

a) Identify product quality related causes for COOR occurrence

b) Improve product quality to reduce COOR occurrence

COOR Prevention – Data overview

4. Identify most QCF affected parameters:

ORG 209 Anti-SS-B

ORG 215G Anti-Cardiolipin IgG

ORG 229G Anti-Phospholipid Screen IgG

ORG 221G Anti-beta-2-Glycoprotein I IgG

ORG 215S Anti-Cardiolipin Screen

Additional data available?

- Complaint/refund data
- QC performance data (retainer kit run-time)

COOR Prevention – Data overview

5. Error tree/ fault tree analysis

to identify and prioritize critical causes which could contribute to the QCF occurrence:

Plastic Material
Instable Antigen Coating
Instable antigen Blocking
TMB Substrate
Pipetting Protocol
c/o Setpoint
Reader Software
Enzyme Conjugate
Contaminations
Liquid Exchange

COOR Prevention – Data overview

6. Prioritize potential problems

7. Investigation

Investigation:
a) investigation plan (products, experiments, controls, describe analysis)
b) investigate!
c) document outcome / report
d) Review of outcome, define next steps

8. Root cause found?

Define actions, do risk analysis

9. Implement actions

10. Perform effectiveness check

Complaint review, QC data review, 1-2 year after implementation

COOR Status

Decrease of COOR with 10 key-products by 50-75% !

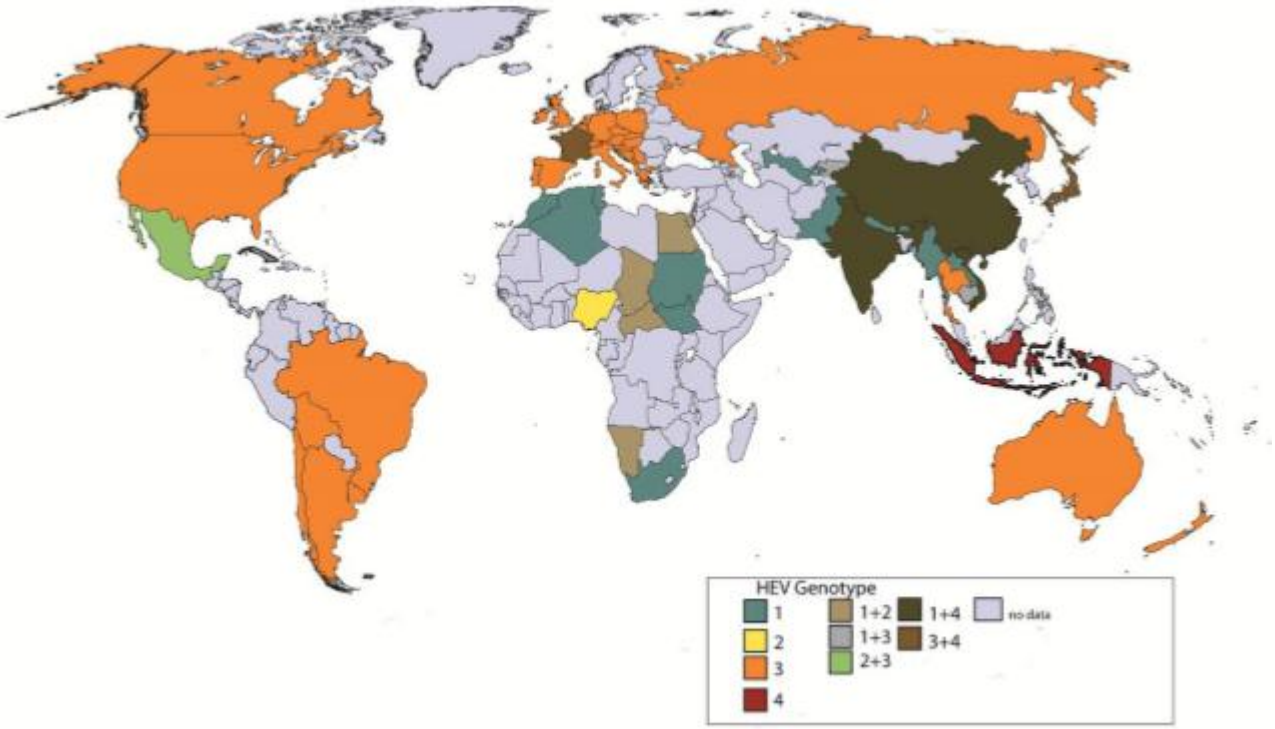
ORGENTEC product availablity

- *Thorough review and optimization of processes in R&D and production*
- *In parallel preparation for requirements of new IVD-R*
- *Significant increase in demand*
- *All of the above require re-organization of production*
- *Dependency on specialty-vendor for production: Vendor-problems become ORGENTEC-problems become customers problems.*
  Action: ORGENTEC established new safeguard measures
- *All together numerous internal updates and improvements causing a transient situation of increased backorder.*
- *Backorder List already shortened by half*
- *We do realize that as long as key products like CCPhs, EBV IgM, and Vitamin D currently are on the list – many partners will be concerned*
- *Goal: Minimize backorder-list to „usual“ small numbers by 06_2018*
- *Be ready for future demand and regulations*

Thank you for your trust !

Hepatitis E Virus (HEV)

Prevalence HEV genotypes



Excerpt from:
http://www.who.int/immunization/sage/meetings/2014/october/1_HEV_burden_paper_final_03_Oct_14_yellow_book.pdf

Review

Hepatitis E Seroprevalence in Europe: A Meta-Analysis

Johannes Hartl [1,*], Benjamin Otto [1], Richie Guy Madden [2], Glynn Webb [2], Kathy Louise Woolson [2], Levente Kriston [3], Eik Vettorazzi [4], Ansgar W. Lohse [1], Harry Richard Dalton [2,†] and Sven Pischke [1,2,†]

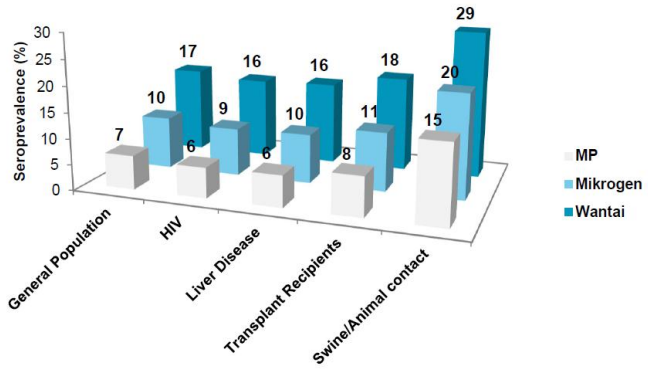


Figure 2. The relationship between anti-HEV IgG seroprevalence rates and the assay employed in different study cohorts. The difference between Wantai (WT) vs. Mikrogen (MG) and WT vs. MP was statistically significant after adjusting for study cohort (WT vs. MG: $p < 0.05$; WT vs. MP: $p < 0.001$).

Table 3. Calculated seroprevalence rates for the general population.

Title	Abbott	Adaltis	Dia.Pro	Mikrogen	MP	Other	Wantai
Austria	1.9% *	0.7% *	6.6% *	8.9% *	3.9% *	9.3% *	13.9%
Belgium	4.5% *	2.5% *	10.9% *	13.8% *	7.4% *	14.3%	19.7% *
Czech Republic	1.5% *	0.5% *	5.9%	8.1% *	3.3% *	8.5% *	12.9% *
Denmark	4.8%	2.8%	11.4%	14.3%	7.8%	15.2%	19.8%
France	12.0% *	8.7%	21.1% *	24.7% *	16.3%	25.4%*	31.9%
Germany	2.6%	1.1% *	7.8% *	10.3%	4.8%	10.8%	29.5%
Italy	0.1% *	0.1% *	2.4%	3.9% *	0.9% *	4.1%	7.5%*
Netherlands	1.8%	0.6% *	6.4%	8.7% *	3.7%	9.1%	27.0%
Spain	2.2%	0.9% *	7.1%	9.5% *	4.3%	10.0%*	14.7%
Switzerland	1.8% *	0.6%*	4.2%	8.8%	4.2%	9.2%	21,2%
UK	1.4% *	0.4% *	5.7% *	7.9% *	3.2%	8.3% *	12.7%

* For combinations of seroassays and countries for which reported seroprevalence rates were not determined, the seroprevalence was calculated using a restricted maximum likelihood estimator model (R statistical platform and The metafor Package).

Why is it that difficult determine the correct seroprevalence of Hepatitis E Virus infections?

Clinical picture and symptoms of a hepatitis E virus infection

- **Acute hepatitis E**
  weakness, arthralgia, myalgia, vomiting
  icterus, pruritus, colorless feces, dark urine
  lab findings: elevated transaminases, bilirubin, alkaline phosphatase, gamma-GT

  Severe symptoms may appear in patients with pre-existing liver diseases and pregnant women

- **Chronic hepatitis E (with genotype 3)**
  mainly with immunosuppressed and transplant patients
  more aggressive compared to HBV and HCV

- **Extra-hepatic manifestations**
  nervous system and kidneys

But: 99% of infections are clinically unapparent!

Situation in industrialized countries

- Hepatitis E was formerly known an imported, travel-associated infection caused by HEV genotype 1, 2, or 4 infections.
- Now the autochthonous prevalence of genotype 3 is proven.
- Antibody prevalence varies between countries.
- Main source of infection: pork, boar, dear - direct contact or under-cooked meat.

Diagnostics

- A **clinical** differentiation between a type E hepatitis and other viral (or autoimmune) hepatitis is not possible.
- Lab diagnosis is needed for differentiation.
- HEV infections are typically analyzed by proof of IgM (acute) and IgG (acute or past).
- Acute HEV infections can be diagnosed by PCR too (important when immunocompromised), which is accepted as gold-standard method.
- Antibody detection methods are ELISA, blot, and rapid assays.

There are big differences between the various kits in the market regarding sensitivity and specificity!

They are caused by:

- choice of recombinant antigens (chosen ORF and genotype)
- cut off adjustment
- antigen purity

Coated antigen with Alegria tests

- ORG 921G Anti-Hepatitis E Virus IgG ORF2 of genotypes 1 and 3
- ORG 921MX Anti-Hepatitis E Virus IgM Abs. ORF2 of genotypes 1 and 3

genotypes 1 antigen is cross-reactive with genotype 2

genotypes 3 antigen is cross-reactive with genotype 4

All HEV genotypes are detected with the Alegria assays!

alegria 3™

Hybrid technology for automation in specialty diagnostics

Mainz, 2018/04/

alegria 3 ™

- *Next Generation Automation by ORGENTEC*
  - *Hybrid: Alegria® & CLIA technology*
  - *Primary tube handling*
  - *All parameters available at launch*
  - *Targeted at mid-sized laboratories*
  - *Fully TLA (total laboratory automation) compliant*

alegria 3 ™

- *Ease of use diagnostics solution*
  - *Up to 800 tests per day*
  - *Full flexibility with serum, CSF and stool parameters for each patient sample*
  - *2-D Bar code reader*
  - *ELISA and CLIA detectors*
  - *Continously load and empty while running*

alegria® Platform

- *Full Compatibility Between Generations*
  - *Strips can be used interchangeably*
  - *ELISA technology with correlating results*
  - *Proven SMC® technology*

alegria 3 TM - Compartments

alegria 3 TM - Insertion of Plates

- *Alegria plates (12 strips) can be loaded from the front*
- *Up to 36 plates per load*
- *All parameters can be combined even within a plate/frame*
- *Cooled storage*
- *Continuous loading*
- *Resource monitoring with loading instructions for plates and buffers*

Usability

Easy Menu


alegria 3
RUNNING
ADMIN.
LOG OUT
TEMPERATURE
SCHEDULING
HOME
SAMPLERACKS
SUPPLIES
WORKLIST
OFF
Worklist
In Progress
Queued
Inactive
54%
Tests In Progress: 256
Tests In Queue: 33
Sampleracks
1 Available sampleracks
8 Free sample positions
Samplerack ready to be loaded
ABCDEFGH
Time to next available samplerack: 00:02:33
Supplies
Luminol
System Fluid
Wash buffer
Test Plates
Liquid Waste
Distillled Water
Solid Waste
Dillution Plates
Pipette Tips
Est. tests: 202
Est. time: 02:23:45
Est. tests: 41
Est. time: 00:40:45
Est. tests: 202
Est. time: 02:23:45
Est. tests: 21
Est. time: 00:03:45
Est. tests: 50
Est. time: 00:38:12
Est. tests: 202
Est. time: 02:23:45
Est. tests: 202
Est. time: 02:23:45
Est. tests: 129
Est. time: 01:03:45
Est. tests: 20
Est. time: 00:08:12

Under Development: External Quality Control Sera

- Sets with Positiv-/Negativ-Controls
- Parameter-specific
- For IDD and AID
- Use like a patient sample
- Identification while inserting the rack
- Option to use one sample rack for controls
- Applicable for Alegria® (1)

alegria 3

Yes, we can hardly wait…!