

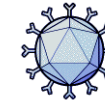
VIVO
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General Presentation

vivo Science GmbH

vivo Science GmbH
Fabrikstraße 3
48599 Gronau
Germany

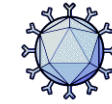
lab@vivoscience.de
www.vivoscience.de
Fon: +49-(0)2562-8170-0



Location

Gronau / Westfalia
(near Enschede / NL)
Germany

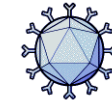




History

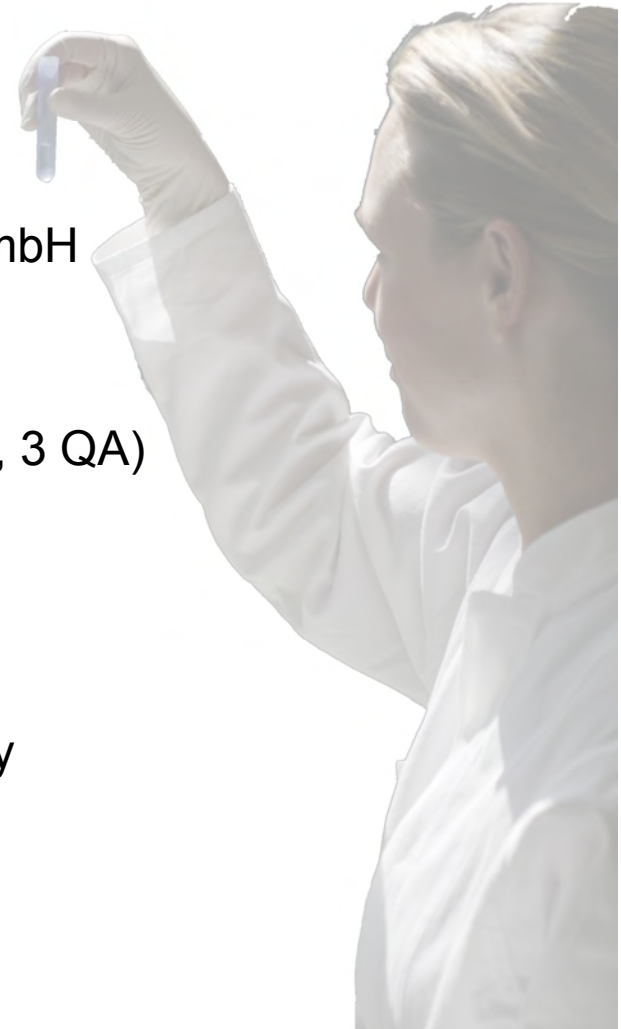
- 2001 founded as **PARA BioScience GmbH**
- 2004 **GLP** certificate granted (renewed 2012)
- 2006 merger with **NewLab BioQuality AG** as legally independent affiliate (GmbH)
- 2007 **GMP** certificate granted (renewed 2012)
- 2008 private acquisition by Dr. Jürgen Schumacher and Stefan Fischer, independent company renamed to **vivo Science GmbH**

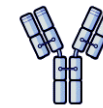
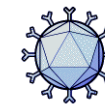




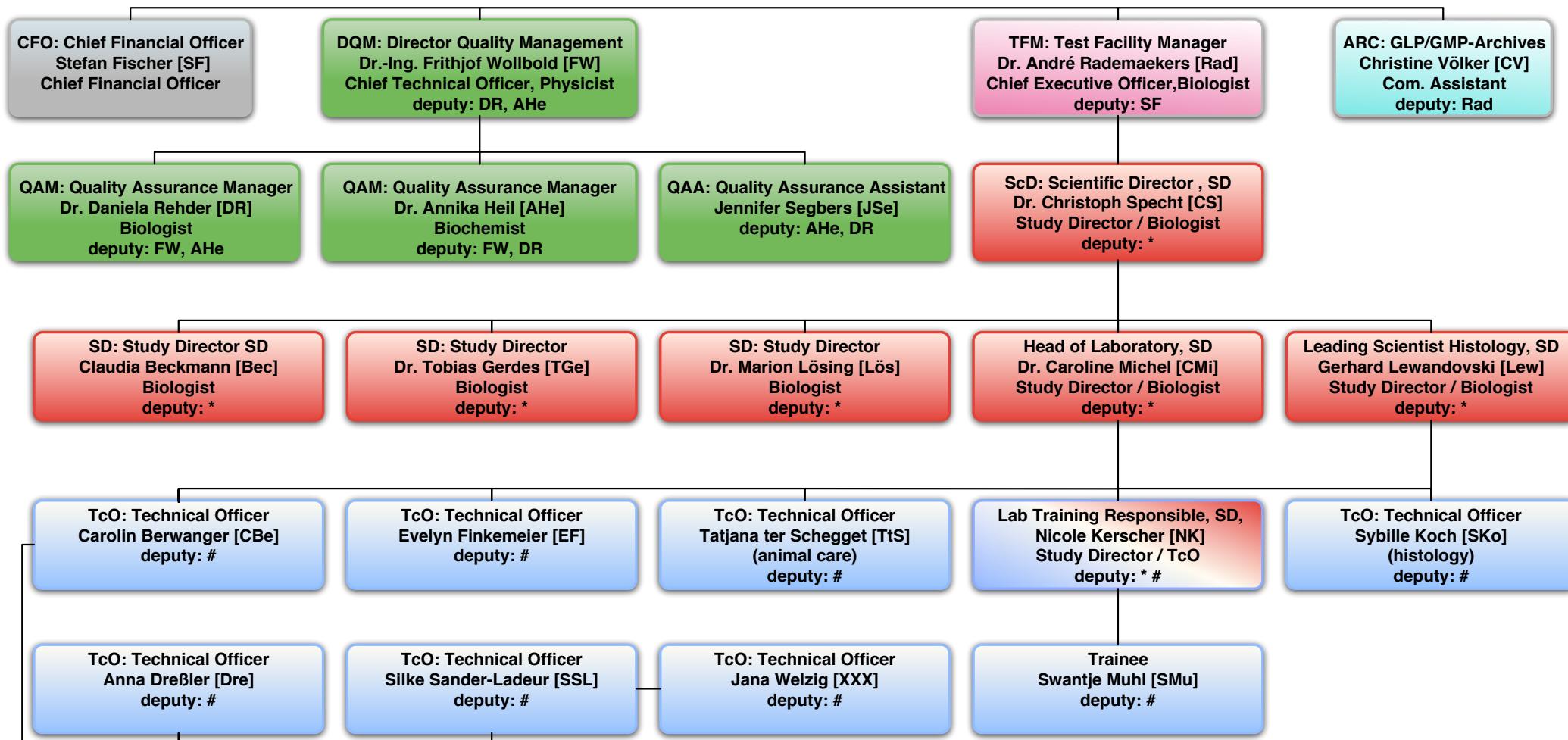
Facility overview

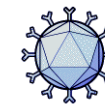
legal form	privately held, independent company, GmbH
site area	> 900 sqm
no. of employees	21 (6 study directors, 9 technical officers, 3 QA)
years of service	11
main sales market	central Europe, India
main customers	pharma, biotechnology, chemical industry
quality status	GLP, GMP
workload in 2011	50 GLP studies, 115 GMP assays





Organisation chart



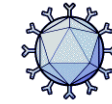


Facility construction



Labs

- 5 animal labs (IVC[S2] / SPF / Standard)
- standard bio-lab
- biosafety level S2 lab
- radioisotopes lab
- histology lab
- 2 GxP archives (documents / materials & el. data)



Contract Research / Services

Immunology [GLP]

- Cell-based and humoral immune response
- Immunotoxicity
- Immunogenicity
- Vaccination studies
- Potency tests
- Tumourigenicity studies

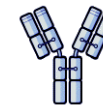
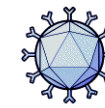
Toxicology [GLP]

- Toxicity *in-vivo* studies acc. to EMA or OECD

Viral Safety [GMP]

- Tests of cell substrates and cell-lines on adventitious viruses





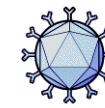
Immunotoxicity testing [GLP]

According to ICH - S8

species: mouse/rat

Standard testing:

- Monitoring of clinical signs
- Haematology / Clinical chemistry
- General pathology / Histopathology
- Cell-mediated immunity
 - ✓ Flow-cytometry of B and T cell subsets
 - ✓ Mitogen stimulation assays for B and T cells
 - ✓ Natural killer cell activity
 - ✓ Quantitation of phagocytic ability
- Humoral-mediated immunity
 - ✓ Humoral responses to T-dependent antigen (primary and secondary)
 - ✓ Humoral responses to T-independent antigens (primary)



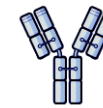
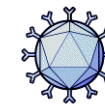
Immunogenicity testing [GLP]

As recommended by ICH - S6 for *BIOLOGICALS*

species: mouse/rat/guinea pig

Advanced testing:

- Delayed-type hypersensitivity response (DTH)
- Acute systemic // active/passive cutaneous anaphylaxis (ASA // ACA/PCA)
- Mixed leukocyte response (MLR)
- Local lymphnode assay (LLNA)
- antigen dependent proliferation of primed lymphocytes (3H-thymidine incorporation)
- antigen dependent cytokine production of primed lymphocytes
- quantitation of antigen-specific antibodies (ELISA, hemagglutination, ...)
- quantitation of antigen/allergen-specific immunoglobulines (IgE, IgG,...) (ELISA)
- detection of glomerular immune complexes/autoantibodies
- Cytotoxic T lymphocyte (CTL) cytolysis against allogeneic tumour cells



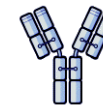
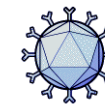
Other *in-vivo* safety tests [GLP]

EMA (Pharmaceuticals) (e.g.)

- CPMP/SWP/1042/99 Note for Guidance on Repeated Dose Toxicity
- CPMP/SWP/465/95 Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines
- CPMP/3097/02 Note for Guidance on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Drug Substance
- CPMP/SWP/2145/00 Note for Guidance on Non-Clinical Local Tolerance Testing of Medicinal Products

OECD (Chemicals) (e.g.)

- 402 Acute Dermal Toxicity
- 407 Repeated Dose 28-day Oral Toxicity Study
- 408 Repeated Dose 90-Day Oral Toxicity Study
- 410 Repeated Dose Dermal Toxicity: 21/28-day Study
- 414 Prenatal Developmental Toxicity Study
- OECD 420 Acute Oral Toxicity - Fixed Dose Method
- 421 Reproduction/Developmental Toxicity Screening Test
- 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test
- 423 Acute Oral toxicity - Acute Toxic Class Method
- 425 Acute Oral Toxicity: Up-and-Down Procedure
(*others on request*)



in-vivo assays [GMP]

According to: PTC (1993), Q5A (CPMP/ICH/295/95) and European Pharmacopoeia 2.6.16 "Tests for extraneous agents in viral vaccines for human use"

Viral safety studies on:

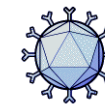
- Adult mice
- Suckling mice
- Guinea pigs
- Embryonated eggs
- Hamsters

Embedded assays:

- MAP (analysis by P.I.) incl. LDH
- HAP (analysis by P.I.)

In preparation: European Pharmacopoeia 2.7.15 "Assay of Hepatitis B Vaccine (rDNA)"

- Immunization of mice and serum sampling (*currently performed under GLP*)



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QA system

- April 2004


GLP – first inspection by local monitoring authorities in March 2004 on (immuno-) toxicity and immunogenicity studies.

Second re-inspection successfully accomplished in May 2012

- June 2007

GMP – inspection on *in vivo* analysis for adventitious viruses in cell lines and substrates. Planned: other related *in vivo* lot release tests

Second re-inspection successfully accomplished in May 2012



Ministerium für Arbeit, Gesundheit und Soziales
des Landes Nordrhein-Westfalen

Fürstenwall 25, 40219 Düsseldorf Aktenzeichen II A 5 – 31.11.38.02

**Gute Laborpraxis/Good Laboratory Practice
GLP-Bescheinigung/Statement of GLP Compliance
(gemäß/according to § 19b Abs. 1 Chemikaliengesetz)**

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 88/320/EG wurde durchgeführt in: Assessment of conformity with GLP according to Chemikaliengesetz and Directive 88/320/EEC at:

Prüfeinrichtung/Test facility Prüfstandort/Test site

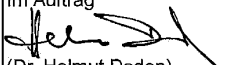
NewLab BioQuality GmbH *
Fabrikstr. 3
48599 Gronau


Prüfungen nach Kategorien	Areas of Expertise
Kategorie 2	category 2
Prüfungen zur Bestimmung der toxikologischen Eigenschaften	toxicity studies
Kategorie 9	category 9
Immuntoxikologie und Immunogenität in vitro und in vivo	Immunotoxicology and Immunogenicity in vitro and in vivo
Datum der Inspektion	Date of Inspection
23. bis 24. April 2008	on 23 until 24 April 2008

Die genannte Prüfeinrichtung befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht. The above mentioned test facility is included in the national GLP Compliance Programme and is inspected on a regular basis.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können. Based on the inspection report it can be confirmed, that this test facility is able to conduct the aforementioned studies in compliance with the Principles of GLP.

Düsseldorf, den 24. Juli 2008
Im Auftrag


(Dr. Helmut Deden)


Dienstsiegel/official-seal

Certificate of GMP-Compliance for a Pharmaceutical Laboratory according to sect 14 (4) of the German Drug Law

GMP Certificate No. 25/2012 , reference number
24.5.1-204

The company
vivo Science GmbH
Fabrikstraße 3
48599 Gronau

with the following laboratory

Fabrikstraße 3
48599 Gronau

has been approved according to sect 14 para 4 of the German Drug Law to perform quality testing on medicinal products for human use. This approval covers the following testing procedures:

- *In vivo analysis for adventitious viruses according to European Pharmacopolia and ICH Q5A*

On the basis of the knowledge gained during latest GMP-inspection of this laboratory, which was conducted on 05/22/2012 it is certified that the company complies with the requirements of the EC Good Manufacturing Practices regarding the testing procedures listed above.

This certificate remains valid for three years from the date of the last inspection.

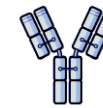
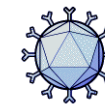
This English translation is for reference only. It is not part of the official certificate.

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14.06.2012

*signature of the
certifying officer*

* certificate also valid for vivo Science GmbH,
GLP certificate of 2012 pending



SOPs: combined **GLP** / **GMP** QA system (Modules)

ORG Organisation

DOC Documents

STO Storage

TAS Training and Safety

QAM Quality Management

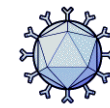
CAD Changes and Deviations

EQU Equipment

MAT Materials

ATM Analytical Test Methods

currently 117 SOPs

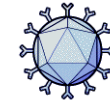


GLP / GMP - Quality Assurance Program

- GLP/GMP-compliance monitoring
- GLP/GMP-training and registration of training records
- Audit and distribution of SOPs
- Audit of **study plan** / **Assay Protocol for Clients**
- Audit of raw and calculated data
- Audit of **study report** / **Certificate of Analysis**
- Selfinspections (study- / facility- / processbased / in-life)
- Approval of qualification- and validation documents
- Approval of changes (Change Control)
- Approval of Deviations (Deviation Control, CAPA)
- Audit of Failure Investigations (failure analysis, OOS, OOT)
- Audit of subcontractors

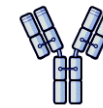
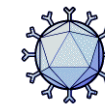
Selfinspections: 2009: 55 / 2010: 100 / 2011: 112

Audits by customers: 2008: 10 / 2009: 4 / 2010: 2 / 2011: 5



GLP / GMP Testing - Workflow

- Quotation
- Order
- Order Confirmation
- Contract (CDA / umbrella agreement / individual contract)
 - study plan / Assay Protocol for Clients
 - Approval of study plan / assay
 - Test Item Submission Form
 - Shipment
 - Receipt of shipment
 - Preparation of study folder, lab work sheet, lab records
 - Performance of study / assay
 - Changes, Deviations, Out of Specification
 - Doublecheck, QA statement
- Delivery of study report / Certificate of Analysis

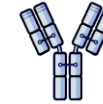
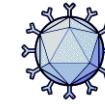


vivo Science housing standards

TABLE 1: Recommended Space for Commonly Used Group-Housed Laboratory Rodents in the AAALAC recommendations, the ETS123 and NewLab's SOP MAT-3-0007.

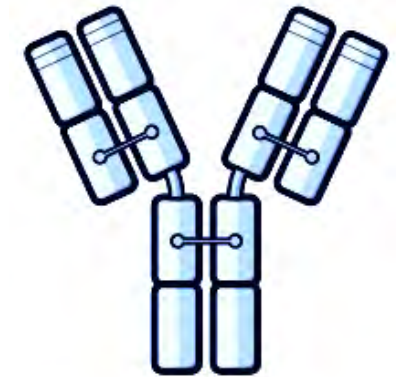
Animals	Weight, g	cage sizes: Floor Area/Animal / Height					
		AAALAC reomm.		ETS123 Appendix A		Newlab SOP MAT-3-0007*	
Mice	<10	38,7	12,7	60	12	80	13,9
	Up to 15	51,6	12,7	60	12	80	13,9
	Up to 25	77,4	12,7	70	12	80	13,9
	>25	96,8	12,7	80-100	12	80	13,9
Rats	<100	109,7	17,8	200	18	333	24,5
	Up to 200	148,4	17,8	200	18	333	24,5
	Up to 300	187,1	17,8	250	18	333	24,5
	Up to 400	258,1	17,8	350	18	333	24,5
	Up to 500	387,1	17,8	450	18	n.a.	
	>500	451,6	17,8	600	18	n.a.	
Hamsters	<60	64,5	15,2	150	14	200	15
	Up to 80	83,9	15,2	200	14	200	15
	Up to 100	103,2	15,2	200	14	200	15
	>100	122,6	15,2	250	14	200	15
Guinea pigs	<350	387,1	17,8	350-500	23	500	24
	>350	651,6	17,8	500-900	23	750	24

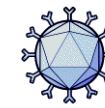
*Standard Operating Procedure No. MAT-3-0007 „Tierbeschaffung, Haltung und Pflege“



Legal Permissions (Germany)

- „Gute Laborpraxis“ nach ChemG* -GLP- (weltweit anerkannt)
- „Gute Herstellungspraxis“ nach AMG** -GMP- (weltweit anerkannt)
- Arbeiten gem. Tierschutzgesetz (Modellorganismen für Sicherheitsuntersuchungen)
- Arbeiten gem. Gentechnikgesetz S1 (neue, gentechnisch veränderte Wirkstoffe)
- Arbeiten gem. Infektionsschutzgesetz S2 (Überprüfung auf Virenkontamination)
- Arbeiten gem. Strahlenschutzverordnung (für immunologische Spezialprüfungen)
- Anerkannter Ausbildungsbetrieb (bislang 4 Azubis)





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Your direct contact partners



Test Facility Management

Dr. André Rademaekers

++49 2562 8170 11



Director Quality Management

Dr.-Ing. Frithjof Wollbold

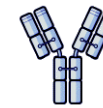
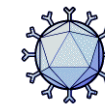
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Scientific Director

Dr. Christoph Specht

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Thanks for your attention!