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

November 2015

Location

Gronau / Westfalia
(near Enschede / NL)

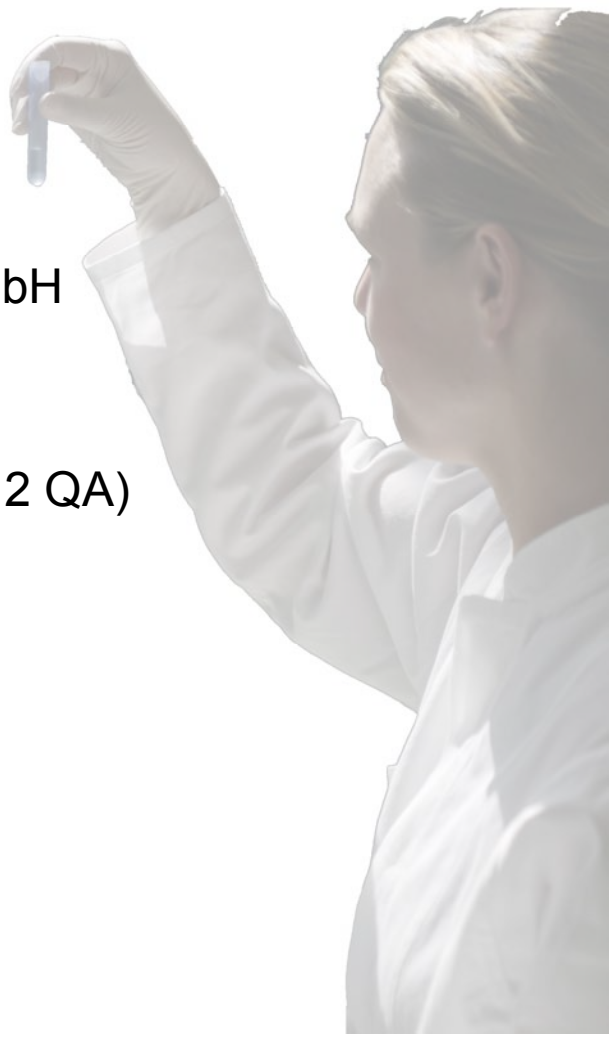
Germany

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 2015)
2008	private aquisition by Dr. Jürgen Schumacher and Stefan Fischer, independent company renamed to vivo Science GmbH

Company overview

legal form	privately held, independent company, GmbH
site area	approx. 1000 sqrm
no. of employees	20 (6 study directors, 9 technical officers, 2 QA)
years of service	14
main sales market	Europe, India
main customers	pharma, biotechnology, chemical industry
quality status	GLP, GMP



Facility

- 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
- Biosimilarity

Toxicology [GLP]

- *in-vivo* toxicity tests acc. to EMA or OECD (incl. DART)

Testing of Medical Devices [GLP]

- Tests according to ISO 10993

Assay validation [GLP]

- Method transfer, proof of concept
- Validation of Analytical Procedure [ICH Q 2 (R1)]

Viral Safety [GMP]

- Tests of cell substrates and cell-lines on adventitious viruses *in vivo*

Potency Testing [GMP]

- *in vivo* potency testing of (recombinant) vaccines

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 lymph node assay (LLNA)
- antigen dependent proliferation of primed lymphocytes (3H-thymidine incorporation)
- antigen dependent cytokine production of primed lymphocytes
- quantification of antigen-specific antibodies (ELISA, hemagglutination, ...)
- quantification of antigen/allergen-specific immunoglobulines (IgE, IgG,...) (ELISA)
- detection of glomerular immune complexes/autoantibodies
- Cytotoxic T lymphocyte (CTL) cytolysis against allogeneic tumour cells
- Detection of Anti-Drug-Antibodies (ADA)
- Tissue Cross-Reactivity (TCR)

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.)

species: mouse/rat

- 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
- 416 Two-Generation Reproduction Toxicity Study
- 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
- 443 Combined Chronic Toxicity/Carcinogenicity Studies

(others on request)

Medical Devices [GLP]

According to ISO 10993

species: mouse/rabbit

- ISO 10993-3 Genotoxicity, carcinogenicity and reproductive toxicity
- ISO 10993-4 Selection of tests for interaction with blood
- ISO 10993-5 Tests for in vitro cytotoxicity
- ISO 10993-6 Tests for local effects after implantation
- ISO 10993-7 Ethylene oxide sterilization residuals
- ISO 10993-10 Tests for irritation and skin sensitization
- ISO 10993-11 Tests for systemic toxicity

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"

Virus 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.)

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

- *in vivo* potency testing of (recombinant) vaccines

QA system

- April 2004

GLP – inspection on toxicity studies and immunotoxicity and immunogenicity studies.

Re-inspections successfully accomplished in 2008 and 2012

- June 2007

GMP – inspection on *in vivo* analysis for adventitious viruses.

Re-inspections successfully accomplished in 2009, 2012, 2015

- July 2013

GMP – certificate expanded on *in vivo* potency testing of (recombinant) vaccines.

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

Fürstenwall 25, 40219 Düsseldorf — Aktenzeichen III 5 – 31.11.38.03

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 2004/9/EG wurde durchgeführt in:

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 2004/9/EEC at:

☒ Prüfeinrichtung/Test facility ☐ Prüfstandort/Test site

vivo Science GmbH
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48599 Gronau

Prüfungen nach Kategorien (gemäß ChemVwV-GLP Nr. 5.3/OECD guidance)	**Areas of Expertise** (according ChemVwV GLP Nr. 5.3/OECD guidance)
Kategorie 2 Prüfungen zur Bestimmung der toxikologischen Eigenschaften	category 2 toxicity studies
Kategorie 9 Immuntoxikologie und Immunogenität in vitro und in vivo	category 9 Immunotoxicology and Immunogenicity in vitro and in vivo

Datum der Inspektion
23. Mai 2012

Die/Der genannte Prüfeinrichtung/Prüfstandort befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung/ diesem Prüfstandort die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

Date of Inspection
23rd May 2012

The above mentioned test facility/ test site is included in the national GLP Compliance Programme and is inspected on a regular basis.

Based on the inspection report it can be confirmed, that this test facility/test site is able to conduct the aforementioned studies in compliance with the Principles of GLP.

Düsseldorf, 04.06.2013
Im Auftrag
(Dr. 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. 14/2013 , reference number 24.05.03-154

The company

vivo Science GmbH
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48599 Gronau

with the following laboratory

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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 Pharmacopoia and ICH Q5A*
- *In-vivo potency testing of (recombinant) vaccines*

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.

25.07.2013 signature of the certifying officer

Dr. Arno Terhechte
Regierungspharmaziedirektor
Tel: +49(251)411-3121
Fax: +49(251)411-2137

seal of the certifying authority

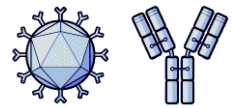
SOP system

SOPs: combined GLP / GMP QA system (modules)

ORG	Organisation
DOC	Documents
STO	Storage and Archive
TAS	Training and Safety
QAM	Quality Management
CAD	Changes and Deviations
EQU	Equipment
MAT	Materials
ATM	Analytical Test Methods
HST	Histology

currently 121 SOPs

GLP / GMP - QA 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 documents (DQ, IQ, OQ, PQ)
- Approval of analytical test methods validation
- Approval of changes (Change Control)
- Approval of Deviations (Deviation Control, CAPA)
- Audit of Failure Investigations (failure analysis, OOS, OOT)
- Audit of subcontractors

Selfinspections: 2009-2015: 55 / 100 / 112 / 127 / 134 / 77 / 103 (ongoing)
Audits by customers: 2009-2015: 4 / 2 / 5 / 2 / 7 / 1 / 2 (ongoing)

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

GMP-Testing

Contract

Approval of assay

- Assay Protocol for Clients
- Acceptance Form

Test Item Submission Form

transfer of relevant data

Laboratory Work Sheet

SOP

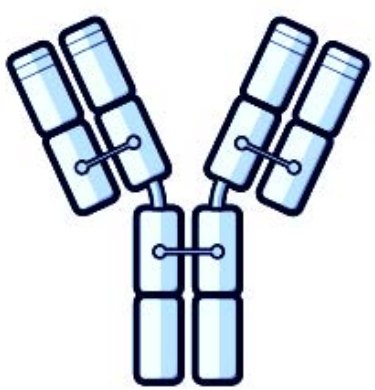
documentation

Laboratory Records
Documentation

Certificate of Analysis

Certificates / Licenses

- „Good Laboratory Practice“ acc. to „Chemikaliengesetz“ (German Chemicals Act)
- „Good Manufacturing Practice “ acc. to „Arzneimittelgesetz“ (German Pharmaceuticals Act)
- Working acc. to „Tierschutzgesetz“ (German Animal Welfare Act)
- Working acc. to „Gentechnikgesetz“ S1 (German Genetic Engineering Act)
- Working acc. to „Infektionsschutzgesetz“ S2 (Ger. Law on the Prevention and Control of Infectious Diseases)
- Working acc. to „Strahlenschutzverordnung“ (German Radiation Protection Ordinance)
- Approved training provider for biology laboratory assistants



* Chemikaliengesetz (German Chemicals Act) ** Arzneimittelgesetz (German Pharmaceuticals Act)

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Thanks for your attention!