BioChem
Labor für biologische und chemische Analytik GmbH

LIST OF SERVICES

VALID FROM JULY 1, 2023

BioChem Labor für biologische und chemische Analytik GmbH
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OUR EXPERIENCE - YOUR ADVANTAGE

For almost 50 years now, **BioChem Labor für biologische und chemische Analytik GmbH**, has been an independent, family-owned, analytical, **contract laboratory** based in Karlsruhe, Germany, offering high quality laboratory services and expertise in all areas of

- microbiological
- physicochemical and
- molecular biological

contract analysis for the pharmaceutical, chemical, medical, diagnostic and cosmetic industries.

Our scientific and practical experience, combined with the professional expertise of more than 100 well-trained specialists at our side, guarantees maximum quality, safety and efficiency. We attach great importance to a reliable, trustful and long-term collaboration with our clients.

As an internationally oriented, modern full-service provider, BioChem always finds individually adapted and innovative solutions within client projects and issues. We embrace the challenges our clients face and constantly align our range of services to them.

Our expertise includes, for example, analytical analyses of raw materials, intermediate or finished products of any dosage form in the context of quality control or pharmaceutical development, EU re-analysis or ICH stability studies.

BioChem's quality management (QM) and quality assurance (QA) are based on the many years of experience of our motivated employees and our will to continuously improve our processes. We always work in compliance with the relevant laws, regulations, guidelines, current pharmacopoeia specifications and client-specific requirements in order to guarantee the safe handling of products and data integrity.

BioChem holds a **Manufacturer's Authorisation,** is **GMP- and GLP*-certified** as well as **FDA-registered** and repeatedly **successfully inspected**. For decades we have been working together with the responsible authorities in Germany and abroad on a trustful basis. In regular client audits we also prove our compliance with all necessary requirements in the pharmaceutical environment.

We have the authorisation for handling of narcotics and narcotic precursors and to operate a genetic engineering facility of security level 1 and 2 (project-bound, according to arrangement). In addition, we have reported the handling of pathogenic organisms and epizootic disease germs to the authorities.

Below you will find an overview of our services including indicative basic costs. All prices listed are net prices plus German VAT (where applicable). With the publication of this list of services as on 1 July 2023 previous versions become invalid. Prices, errors and technical changes are reserved.

We would be pleased to prepare a product- and project-specific offer, which of course takes quantity-specific synergy effects within the scope of combination or graduated prices into account.

OUR EXPERIENCE - YOUR ADVANTAGE

*If you are interested in analyses according to **GLP** (Good Laboratory Practice), please contact us, we would be pleased to prepare an individual offer

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1. MICROBIOLOGY

1.1 MICROBIOLOGICAL TESTING OF NONSTERILE PRODUCTS

1.1.1 MICROBIAL ENUMERATION TESTS

According to current versions of Ph. Eur., Chapter 2.6.12 plus USP, Chapter <61>

Basic prices

Pour plate, spread plate or spiral plate method:
TAMC (total aerobic microbial count) with max. 2 product dilutions .....
TYMC (total yeasts/moulds count) with max. 2 product dilutions .....
Combination of TAMC and TYMC .....
Any further product dilution within the same testing .....
Required sample volume: at least 10 g or ml

Membrane filtration method without additional rinsing of membrane filter:
TAMC (total aerobic microbial count) with max. 1 product dilution .....
TYMC (total yeasts/moulds count) with max. 1 product dilution .....
Combination of TAMC and TYMC .....
Any further product dilution within the same testing .....
Required sample volume: at least 10 g or ml

Membrane filtration method for CMR substances without additional rinsing of membrane filter:
TAMC (total aerobic microbial count) with max. 1 product dilution .....
TYMC (total yeasts/moulds count) with max. 1 product dilution .....
Combination of TAMC and TYMC .....
Any further product dilution within the same testing .....
Required sample volume: at least 10 g or ml

Additional charges

Membrane filtration method including rinsing of membrane filter
with 100 ml rinsing volume per membrane .....
Membrane filtration method including rinsing of membrane filter
with 3 x 100 ml rinsing volume per membrane .....
Quantitative detection of obligatory anaerobic microorganisms .....
Testing for the detection of obligatory anaerobic microorganisms is performed before and after heat treatment (80 °C, 10 min.) of a test solution or product dilution.

1.1.2 TEST FOR SPECIFIED MICROORGANISMS

According to current versions of Ph. Eur., Chapter 2.6.13 and USP, Chapter <62>

Basic prices

Detection of *P. aeruginosa, Staphylococcus aureus, Salmonella species* and
E. coli as well as other gram-negative bile tolerant Enterobacteriaceae
in 1 g/ml or 10 g/ml
together .....

Combined Prices

Microbial enumeration test (TAMC and TYMC) as well as qualitative detection of specified microorganisms (according to section 2.1.1 and 2.1.2) ..... [1]

..... [2]

Required sample volume: at least 30 g or ml

Combined prices include all testing parameters for the respective dosage forms and areas of application in accordance with the acceptance criteria of Ph. Eur., Chapter 5.1.4.

1.1.3 TESTING IN ACCORDANCE WITH ACCEPTANCE CRITERIA OF PH. EUR., CHAPTER 5.1.4

Basic prices

Preparations for rectal use (required sample volume: at least 10 g or ml)
Microbial enumeration test (TAMC and TYMC)

..... [1]

..... [2]

Preparations for oromucosal, gingival, cutaneous, nasal and auricular use
(required sample volume: at least 10 g or ml)
Microbial enumeration test (TAMC and TYMC)
and detection of *P. aeruginosa* and *S. aureus* in 1 g/ml

..... [1]

..... [2]

Aqueous and non-aqueous preparations for oral use (required sample volume: at least 10 g or ml)
Microbial enumeration test (TAMC and TYMC) and detection of *E. coli* in 1 g/ml

..... [1]

..... [2]

Oralia with raw materials of natural origin (required sample volume: at least 30 g or ml)
Microbial enumeration test (TAMC and TYMC) and qualitative determination of salmonellae in 10 g/ml plus *E. coli*, *S. aureus* und quantitative determination of gram-negative bile tolerant bacteria in 1 g/ml

..... [1]

..... [2]

Preparations for vaginal use (required sample volume: at least 10 g or ml)
Microbial enumeration test (TAMC and TYMC)
and determination of *P. aeruginosa*, *S. aureus* and *C. albicans* in 1 g/ml

..... [1]

..... [2]

Inhalables (required sample volume: at least 20 g or ml)
Microbial enumeration test (TAMC and TYMC) and determination of
P. aeruginosa, *S. aureus* and gram-negative bile tolerant bacteria in 1 g/ml

..... [1]

..... [2]

Transdermal patches (required sample volume: at least 10 patches)
Microbial enumeration test (TAMC and TYMC) by membrane filtration
and qualitative determination of *P. aeruginosa* and *S. aureus* in 1 g/ml .....
Sample preparation for transdermal patches (per 10 pieces) .....

1 Microbial enumeration test (TAMC and TYMC) by means of surface spread, pour plate or spiral plate method
2 Microbial enumeration test by means of membrane filtration method incl. rinsing of membrane filter with at least 1 x 100 ml rinsing volume

Qualitative determination of obligatory anaerobic microorganisms in 1 g/ml

Testing for the detection of obligatory anaerobic microorganisms is performed before and after heat treatment (80 °C, 10 min.) of a test solution or product dilution by means of enrichment process

Additional testing or other combinations of specified microorganisms

With simultaneous testing of the above-mentioned combinations, per specified germ

For individual testing without bacterial count, per specified germ

1.1.4 TESTING OF HERBAL PHARMACEUTICALS FOR ORAL USE IN ACCORDANCE WITH PH. EUR., CHAPTER 2.6.12 AND 2.6.31 AND ACCEPTANCE CRITERIA OF CHAPTER 5.1.8

Category A-Products (required sample volume: at least 35 g or ml)
Microbial enumeration test (TAMC and TYMC) and quantitative detection of
E. coli in 1 g/ml and qualitative detection of salmonellae in 25 g/ml

[1]

[2]

Category B- and C-Products (required sample volume: at least 45 g or ml)
Microbial enumeration test (TAMC and TYMC) and qualitative detection of
E. coli in 1 g/ml, Salmonella in 25 g/ml and quantitative detection of
gram-negative, bile tolerant bacteria in 1 g/ml

[1]

[2]

The above prices do not include the identification of grown colonies. All microorganisms detected during enrichment procedures are identified according to state-of-the-art methods (see section 1.2 Identification of microorganisms) in order to provide clients a comprehensive, GMP-compliant view of the microbial status. At client's request, we also carry out identifications of microorganisms from enumeration tests. The above prices refer to tests according to methods defined in the pharmacopoeias.
Product-specific suitability tests (validation) are not included in the prices and will be invoiced separately according to offer. The suitability tests are a prerequisite for the proof of a valid test procedure and are required in the pharmacopoeia.

1.1.5 ADDITIONAL CHARGES FOR MICROBIOLOGICAL TESTS

Special sample preparations
e.g. emulsification in Tween® 80, sonication, Ultra-Thurrax®, Stomacher®, tablet mill, etc.
per each weighed sample

pH value adjustment of stock solutions
for each product dilution or stock solution

Buffer and culture medium volumes other than specified by pharmacopoeia (e.g. 500 ml up to a maximum of 1,000 ml) after method modification following validation
per container

Additional weighing, per weighing

1 Microbial enumeration test (TAMC and TYMC) by means of surface spread, pour plate or spiral plate method
2 Microbial enumeration test by means of membrane filtration method incl. rinsing of membrane filter with at least 1 x 100 ml rinsing volume

Working with highly effective and/or toxic substances e.g. narcotics, cytostatic drugs, hormones, antibiotics and CMR substances (carcinogenic, mutagenic, reproductive toxicity)
per test .....

1.1.6 PRODUCT-SPECIFIC VALIDATION OF TEST METHODS

depending on test methods, acceptance criteria and product .....
We would be pleased to give personal advice and prepare an individual offer for your specific questions.

1.2 IDENTIFICATION OF MICROORGANISMS

Colony morphological identification up to family or genus level
within microbial purity testing in accordance with Ph. Eur., Chapter 2.6.13
.....
additionally: Gram-colouring .....
additionally: catalase test, oxidase test, aminopeptidase .....

Identification of microorganism isolates on sent-in agar media up to the species
(also within microbial purity testing in accordance with Ph. Eur., Chapter 2.6.13)
by means of MALDI TOF by means of
- extended direct transfer method .....
- formic acid extraction method (following extended direct transfer method, if necessary) in addition .....
- formic acid extraction method (depending on microorganism spectrum) .....
- additional cultivation in liquid growth media and special sample preparation for the identification of moulds, in addition .....

The above prices for microorganism identification include the inoculation of a maximum of two subcultures for the production of pure cultures and purity controls at the common incubation temperatures of 20-25 °C, 30 °C or 30-35 °C.

Further subcultures, if necessary, in the case of non-growth, to verify the purity control or to verify coloniemorphologically not clearly identical microorganism isolates prior to identification
per subculture .....

Subcultivation of mould cultures in the context of plausibility checks on three different growth media (e.g. DG18, malt extract and Sabouraud agar), macroscopic and microscopic evaluation as well as literature research
per microorganism .....

Identification of moulds via coloniemorphological and microscopic characteristics
on different growth media .....

Storage of vegetative mircoorganisms after identification by BioChem:
Isolation of microorganism isolates with different colony morphologies, preservation of pure cultures as master cultures (10 containers with 1 to 2 ml microorganism suspension) and storage at -75 °C to -80 °C as well as client-specific documentation of the measures carried out.
per microorganism .....

Molecular biological methods for the identification of microorganisms possible, please refer to:
MOLECULAR BIOLOGY/BIOANALYTICS, PAGE 25, CHAPTER 3.8

Storage of aerobic aerobic spore-forming microorganisms after identification by BioChem:
In the case of aerobic spore-forming microorganismsl, preparation of a spore suspension after prior identification, preparation of spores on sporulation agar, cultivation, washing off of the spores after sporulation, washing of the spores and heat treatment to kill vegetative cell forms, storage/preservation of the spores in absolute ethanol, preservation of the pure cultures as master cultures (10 containers with 1 to 2 ml suspension) and storage at -75 °C to -80 °C, determination of the microorganism count of the spore suspension as well as client-specific documentation of the measures carried out.
per microorganism .....

1.3 STERILITY TESTING

Testing in accordance with Ph. Eur., Chapter 2.6.1 and USP, Chapter <71> in the current version. Tests are carried out in sterility test isolators.

1.3.1 MEMBRANE FILTRATION METHOD

By means of cellulose mixed ester membrane

Testing of 1 to max. 20 individual containers, without rinsing the membrane filters
2 growth media, incubation time 14 days, per test .....
additionally, from 21 to max. 40 individual containers, per test .....

By means of PVDF (polyvinylidene difluoride) membrane

Testing of 1 to max. 20 individual containers, without rinsing the membrane filters
2 growth media, incubation time 14 days, per test .....
additionally, from 21 to max. 40 individual containers, per test .....

1.3.2 DIRECT INOCULATION METHOD

Growth media volume 200 ml, sample to growth media ratio 1:10 for liquid formulations,
1:100 for solid, insoluble preparations
2 growth media, incubation time 14 days .....
Multiple tests to be compliant with minimum sample volumes per culture medium
each additional culture with 2 culture media within the same test .....

1.3.3 ADDITIONAL CHARGES FOR STERILITY TESTING

Rinsing both membrane filters to remove inhibiting substances
with 3 x 50 ml each (3 x 100 ml per test), per test .....
with 3 x 100 ml each (3 x 200 ml per test), per test .....
with 5 x 100 ml each (5 x 200 ml per test), per test .....

Dissolving of lyophilizates, powders, etc. (up to 20 containers)
depending on volume, per test .....
for each additional container .....

Penicillinase treatment .....

Preparation of mixed samples for creams and eye ointments
from a maximum of 10 tubes .....

Larger volumes of culture media (> 200 ml up to a maximum of 2,000 ml)
for 2 growth media .....

Detection of microbial growth with substantial turbidity at the end of the sterility test
by transferring aliquots from the nutrient bouillons into fresh bouillons
per test .....

Subcultures from growth media at the end of sterility testing
by means of inoculation loops if bacterial growth is suspected on 5 to 6 different growth media with aerobic and anaerobic incubation
per test .....

Identification of microorganism isolates in case of a positive sterility test
.....

Working with highly effective and/or toxic substances e.g. narcotics, cytostatic drugs, hormones, antibiotics and CMR substances (carcinogenic, mutagenic, reproductive toxicity)
per test .....

Tests in accordance with validated methods with increased effort .....

Testing for air tightness of primary container during
hydrogen peroxide sterilization in the isolator .....

Notes on sterility testing

Prices include batch-specific testing and documentation of sterility and growth properties of culture media and solutions used; in addition, microbiological environmental monitoring using settle plates, contact agar plates and active air sampling is conducted for every test.
The above prices refer to tests performed in accordance with the methods defined in the pharmacopoeias. Product specific suitability tests (validation) of sterility testing are not included in the prices and will be invoiced separately according to offer. The suitability tests are a prerequisite for the proof of a valid test procedure and are required in the pharmacopoeia.

1.3.4 PRODUCT-SPECIFIC VALIDATION OF TEST METHODS

Depending on test method and product .....
We would be pleased to give personal advice and prepare an individual offer for your specific questions.

1.4 BIOLOGICAL INDICATOR TESTING

Sterility testing (e.g. for checking the efficacy of sterilization processes)
one biological indicator + positive control .....

Each additional biological indicator at the time of result presentation
in one combined report .....

Quantitative determination of population of spores on spore strips, discs and in spore suspensions.
Individual testing of 4 units

following USP

Preparation and testing of **one** dilution series in decimal order
each unit .....

in accordance with USP

Preparation and testing of **two** dilution series in decimal order
each unit .....

1.5 BACTERIAL ENDOTOXIN TESTING BY LAL-METHODS

Performance in accordance with Ph. Eur., Chapter 2.6.14 and USP, Chapter <85> in the current version

1.5.1 GEL CLOT AND KINETIC-TURBIDIMETRIC METHODS

One sample or prepared test dilution of the preparations to be tested
up to the maximum valid dilution (MVD)
as single sample or as mixed sample beginning/middle/end .....

Any further dilution within the same test series on the same plate
or against the same standard series .....

1.5.2 KINETIC-CHROMOGENIC METHOD

One sample or prepared test solution of the preparations to be tested
up to the maximum valid dilution (MVD)
as single sample or as mixed sample beginning/middle/end .....

Any further dilution within the same test series on the same plate .....

All tests in accordance with the requirements of the current pharmacopoeias including standard series, negative controls with water-LAL/buffer in duplicate, positive controls with water-LAL/buffer in duplicate, positive controls for each measured test solution in duplicate.

1.5.3 ADDITIONAL CHARGES FOR LAL-TESTING

Each additional test solution or dilution with a new standard series or after new plate loading
.....

pH value adjustment of the test solution .....

Use of endotoxin-free Tris buffer for adjustment of pH value
or as dilution medium for the test solution
each test dilution .....

Test of pH value of non-product-specific validated samples .....

Sample processing (e.g. for medical devices) .....

Working with highly effective and/or toxic substances e.g. narcotics, cytostatic drugs, hormones, antibiotics and CMR substances (carcinogenic, mutagenic, reproductive toxicity)
per test .....

1.5.4 PRODUCT-SPECIFIC VALIDATION OF TEST PROCEDURES

Depending on test procedure and product .....
We would be pleased to give personal advice and prepare an individual offer for your specific questions.

1.6 MICROBIOLOGICAL ASSAYS OF ANTIBIOTICS

According to Ph. Eur., Chapter 2.7.2 in the current version, agar diffusion method

Determination of potency of active substances and drug products with official pharmacopoeia or client's working standards including variance analysis
single test .....

Multiple determination in parallel preparation
each further determination .....

Combined drug products against mixing standards, per antibiotic .....

Working with highly effective and/or toxic substances e.g. narcotics, cytostatic drugs, hormones, antibiotics and CMR substances (carcinogenic, mutagenic, reproductive toxicity)
per test .....

Determination of potency in combined drug products .....

Additional charges

Extraction of antibiotics from ointments and
further elaborately sample preparation .....

Calculation of weighted mean values for multiple determinations .....

Non aliquotable reference standard substances (declared in IU/container or µg/container)
per standard substance and container .....

Product-specific validation of test procedures following ICH guidelines

According to client requirements and depending on product .....

1.7 EFFICACY OF ANTIMICROBIAL PRESERVATION (ANTIMICROBIAL EFFECTIVENESS TEST)

1.7.1 ACCORDING TO USP, CHAPTER <51> IN THE CURRENT VERSION

5 test organisms
for category 1 products .....
for category 2 to 4 products .....

1.7.2 ACCORDING TO PH. EUR, CHAPTER 5.1.3. IN THE CURRENT VERSION

At the relevant times of reisolation (see below) depending on product type
parenteral and ophthalmic preparations (4 test organisms) .....
oral preparations (5 test organisms) .....
topical preparations (4 test organisms) .....

Indicated prices refer to the following times of reisolation:

Parenteral and ophthalmic preparations:

bacteria: t_0, 6 hours, 24 hours, 7 and 28 days

yeasts: t_0, 7, 14 and 28 days (according to requirements of criteria A and B)

Oral preparations:

bacteria and yeasts: t_0, 14 and 28 days

Topical preparations:

bacteria: t_0, 48 hours, 7, 14 and 28 days

yeasts: t_0, 7, 14 and 28 days (according to requirements of criteria A and B)

1.7.3 ACCORDING TO DIN ISO EN 11930

on request according to offer

1.7.4 ADDITIONAL CHARGES FOR ANTIMICROBIAL EFFECTIVENESS TEST

Per additional test organism .....

Each additional point of time of reisolation in addition to the required times of reisolation, per test strain .....

Complex sample preparations e.g. emulsification of ointments with Tween® 80 each reference organism and point of time .....

Modified tests varying from pharmacopoeial requirements .....

Working with highly effective and/or toxic substances e.g. narcotics, cytostatic drugs, hormones, antibiotics and CMR substances (carcinogenic, mutagenic, reproductive toxicity) per test .....

1.7.5 PRODUCT-SPECIFIC VALIDATION OF TEST METHODS

Product-specific validation of test methods depending on the test procedure, product and product category .....

We would be pleased to give personal advice and prepare an individual offer for your specific questions.

Please note:

The basic prices for microbiological tests shown under section 1.1 to 1.7 apply on the basis of the test methods specified in the pharmacopoeias, for which the testing costs can be estimated. Depending on the respective test sample, there may be an increase in additional work involved in sample preparation and test performance.

If this additional expenditure should be known in advance or becomes obvious on the basis of validation studies, the client will be informed in advance of any additional charges incurred. This also applies to tests of additional specification parameters that are not shown in our service specifications.

Please contact us, we would be pleased to advise you and send you an individual offer for any questions.

1.8 ON SITE ENVIRONMENTAL MONITORING

Active air sampling is performed using a RCS®Plus microbial air sampler or semiquantitative by settle plates. Surface monitoring is performed using Rodac® plates as well as swab tests including supply of the media by BioChem.

Round trip
at an hourly rate of .....
per km travelled .....

Sampling on site
at an hourly rate of .....

Incubation and evaluation of air sampling strips, settle plates, Rodac® plates
per air sampling strip or plate .....
per swab test .....

Additional charges
Identification of microorganism isolates .....

Rental of an air sampler including days of dispatch and return
per day .....

Supply of culture media for environmental monitoring .....

1.9 FURTHER MICROBIOLOGICAL SERVICES

Incubation and evaluation of tests within the scope of hygiene inspections of ventilation and air conditioning systems according to VDI 6022 .....

Drinking water testing in accordance with German Drinking Water Regulation (TrinkwV)
Determination of the total bacterial count at 22 °C ± 2 °C and at 36 °C ± 2 °C.
Testing for absence of *E. coli*, coliform germs, faecal enterococci in 100 ml, per sample .....

Testing for absence of *P. aeruginosa*, *C. perfringens* and *Legionella spp.* .....

Determination of minimum inhibitory concentration .....

Bactericidal and fungicidal testing .....

Microbiological qualification of sterilisation processes,
e.g. by use of bio indicators and endotoxin reduction .....

Disinfectant tests under simulated practical conditions .....

Simulated microbiological in use stability tests .....

Microbiological container closure integrity tests .....

Growth controls of culture media with test organisms according to pharmacopoeia
depending on test organisms, number of test organisms and simultaneously ordered tests
per test organism .....

Media Fills: storage, incubation, evaluation, checking of growth characteristics, depending on
the number of sample containers to be stored and evaluated .....

Testing of medical products

Bioburden, sterility, bacterial endotoxins and further tests with microbiological background can be offered. Testing depending on the product geometry, test methods and number of items

Further services

Shipment of culture media or sample container

Shipment of microorganism cultures on culture media

The microbiological tests listed in this service specification represent the majority of tests required for pharmaceutical quality control in accordance with the current pharmacopoeias and other guidelines. Further microbiological tests that we offer in our laboratory with a wide variety of microbiological questions are not listed in this service specification. All prices quoted relate to validated test methods. Additional charges need to be invoiced for non-validated test methods.

We would be pleased to give personal advice and prepare an individual offer for your specific microbiological questions. Please do not hesitate to contact us.

2. ANALYTICS

2.1 CHEMICAL AND PHYSICAL ANALYSES

2.1.1 SAMPLE PREPARATION

The following sample preparation techniques are established as standard at BioChem:

- Preparation of sample, standard or reference solutions
- Mechanical sample preparation, e.g. crushing, washing, homogenization, recrystallization
- Concentration of solutions by means of rotary evaporators
- Distillation
- Extraction
- Solid-phase extraction
- Filtration
- Ashing
- Drying
- Digestion, e.g. closed digestion, open digestion, microwave digestion
- Column chromatographic processing
- Sample preparation for chromatography
- Derivatization
- Preparation of mixed samples etc.

Prices will be calculated on a time and material basis. We would be pleased to give personal advice and prepare an individual offer for your specific questions.

2.1.2 CHROMATOGRAPHY

2.1.2.1 Thin layer chromatography (TLC)

Including photographic documentation

TLC identity testing .....

TLC purity testing (semi-quantitative), limit testing .....

Application of special spray reagents .....

TLC content determination ..... [1]

2.1.2.2 High performance liquid chromatography (HPLC)

Detection: UV-VIS, diode array detector (DAD), refractive index (RI),
fluorescence detector und light scattering detector (ELSD), mass spectrometry (MS)[1]

(U)HPLC identity testing .....

(U)HPLC identity/content testing .....

(U)HPLC purity testing /related substances .....

2.1.2.3 Ion chromatography (IC)

Conductivity detection; anions/cations with/without suppressor technology, amperometric detection

IC identity testing .....

IC identity/content testing .....

IC purity testing .....

2.1.2.4 Capillary gas chromatography (GC)

Detection: flame ionization detection (FID), electron capture detection (ECD), phosphorus nitrogen detection (PND), thermal conductivity detection (WLD or TCD), mass spectrometry (MS)[1]

Carrier gases: helium, hydrogen. Make-up gases: helium, nitrogen

Sample feeding systems: liquid: autosampler or manual; gaseous: headspace

1 Tests are carried out at a qualified partner laboratory

GC content testing
GC limit testing
GC testing for related substances
GC testing for residual solvents
GC fatty acid composition
GC ethylene oxide (EO)/dioxane determination
GC residual oxygen determination
GC ethylene oxide (EO)/ethylene chlorohydrin (ECH)/ethylene glycol (EG) determination

2.1.2.5 Special chromatographic methods

Chromatographic enantiomer separation

2.1.3 SPECTROSCOPY/SPECTROMETRY

2.1.3.1 UV/VIS spectroscopy/photometry

UV/VIS identity testing
UV/VIS content testing

2.1.3.2 Infrared spectroscopy (FT-IR)

Measurement: liquid or solid/ KBr pellet or via ATR
FT-IR identity testing: KBr pellet
Film
Measurement by attenuated total reflection ATR
FT-IR quantitative

2.1.3.3 Atomic absorption spectroscopy (AAS)

AAS flame, graphite furnace or cold steam/hydride technology
Additional special techniques and reprocessing steps
in case of interferences caused by sample matrix

2.1.3.4 Inductive coupled plasma mass spectrometry (ICP-MS)

qualitative and quantitative determination/
identity, content, purity and residue testing
Additional reprocessing steps
in case of interferences caused by sample matrix

2.1.4 ELECTROCHEMICAL ANALYSES AND TITRATION

pH value (potentiometric)
Ions with selective electrode
Conductometry (conductivity)
Titration (visual endpoint determination)
Titration (potentiometric)
Water content according to Karl Fischer (volumetric)

2.1.5 PHYSICAL ANALYSES

Polarimetry, specific rotation at 589 nm
Refractometry, refractive index at 20 °C

1 Tests are carried out at a qualified partner laboratory

Gravimetry to constant weight (e.g. loss on drying)
Density by densimeter (oscillation measurement)
Density by pycnometer - liquids
Melting point/solidification range
Boiling point
Viscosity according to Ubbelohde
Viscosity by rotational viscometer (spindle)
Surface tension
Osmolality (by freezing point reduction)
Osmolality (by vapour pressure osmometer)
Consistency (micro-penetrometer)

2.1.6 TOTAL ORGANIC CARBON (TOC)

Total organic carbon (TOC)
Additional processing steps
Cleaning validation

2.1.7 TOTAL NITROGEN (TN)

Total nitrogen (TN)
Combined with TOC

2.1.8 VISUAL TESTS

Clarity and opalescence of solutions
Colouring of solutions

2.1.9 PARTICLE TESTING

Testing for visible particles
Testing for non-visible particles:
Measurement by light blockage (method 1)
Microscopic determination (method 2)

2.1.10 ADDITIONAL ANALYSES ON REQUEST, E.G.

Elemental analyses, per element [1]
Nuclear magnetic resonance spectroscopy (NMR) [1]
Mass spectrometry (MS) [1]

2.2 SPECIAL PHARMACEUTICAL ANALYSES

2.2.1 IN-PROCESS CONTROL, RELEASE AND STABILITY TESTING FOR PHARMACEUTICAL QUALITY CONTROL AND DEVELOPMENT

We accompany you with our analyses through all phases of the life cycle management of your raw materials and pharmaceutical products: from the first pharmaceutical developments within clinical studies phase I, II, III and IV, or comparative studies of generic drug development to registration and routine quality control up to launch and market release. The prices for Individual testing of characteristics, identity, purity and content correspond to the indicative basic prices of the chemical, physical and instrumental analyses listed above. We would be pleased to prepare a project-based individual offer that take into account the desired procedure, matrix and deadline. Please do not hesitate to contact us.

1 Tests are carried out at a qualified partner laboratory

2.2.1.1 Testing according to a monograph

full analyses according to specification of the respective current pharmacopoeia or client's test instruction

2.2.1.2 Method development, validation and transfer

Method development/optimization

Validation/verification of procedures/product-specific validation according to ICH guidelines including test plan and report in agreement with the client (test scope)

Method transfer including test plan and report

2.2.1.3 Technological characteristics of solid dosage forms

Dimensions (n = 10)

Abrasion/friability

Resistance to crushing of tablets (n = 10)

Disintegration of tablets or capsules (n = 6)

2.2.1.4 Uniformity of mass/content

Uniformity of mass (n = 20)

Tablets, film-coated tablets

Divided tablets

Hard gelatine capsules

Uniformity of content, depending on analytical method

Photometry, HPLC, titration, etc. (n = 10)

2.2.1.5 Release of active substances

Paddle or rotating basket (n = 6), depending on analytical method

Photometry, HPLC, etc.

comparative dissolution profiles (f_2 test)

2.2.1.6 Water for pharmaceutical purposes

Physico-chemical tests according to current Ph. Eur.

Aluminium

Ammonium

Calcium, Magnesium

Chloride

Conductivity

Non-visible particles

Nitrate

oxidable substances

Acidic or alkaline reacting substances

Sulphate

Heavy metals

TOC

Evaporation residues

2.2.2 STABILITY STUDIES (STORAGE AND ANALYSES)

BioChem is your experienced partner for all issues regarding stability studies of pharmaceutical products (stress and photostability testing, short-term and long-term stability studies, on-going studies according to ICH guidelines).

Computer-monitored and alarm-secured climate rooms and climate chambers are available for the storage of samples. Beside storage conditions according to ICH guidelines (- 20 °C, 5 °C, 25 °C/60 % r.h., 30 °C/65 % r.h., 40 °C/75 % r.h.), further climatic settings can be offered on request. In addition, the storage of narcotics is possible. Costs for storage, logistics and analysis result from the specifications of the test material, the quantities to be stored and the stored study protocols. Please specify the number of batches, the volume of test samples, storage conditions needed and, if already determined, the test parameters and testing schedule, so we can prepare an offer for you. We would be happy to advise you.

Basic prices for storage and testing:

Initial storage (receipt etc.) of samples and preparation of stability test plans .....
Storage per batch, storage condition and month .....
Preparation of stability reports per test time .....
Return of test samples .....
Stability tests depending on scope .....

2.2.3 PHOTOSTABILITY TESTING/STRESS TESTS

Irradiation according to ICH Q 1B .....
Stress tests according to ICH Q 1A .....

2.2.4 PHARMACEUTICAL DEVELOPMENT

Within pharmaceutical development, BioChem supports you in any analytical issues: starting from the selection of suitable raw material batches, through the analyses of the first product formulations and testing for their suitability, to the first short-term stability studies and testing of pilot batches based on your preliminary release and runtime specifications, right up to testing first approval batches including preparation of the analytical documentation for registration.

This includes a screening of raw materials for impurities, the set-up of comparative release profiles and evaluation by means of f_2 tests or packaging material tests to optimize the duration as well as further tests according to client specifications.

For complex and long-term pharmaceutical developments, a BioChem project member is appointed to provide capable and consulting support in all project phases to ensure the success of your project: the approval.

2.2.5 PHARMACEUTICAL APPROVAL

We would be pleased to support you in planning and implementation of analytical questions in the context of your approval projects. Please ask for an offer related to your current project.

3. MOLECULAR BIOLOGY/BIOANALYTICS

MISCELLANEOUS

We would be pleased to offer you further molecular biological analyses on request. We also offer method validations and transfers on request. We will be happy to advise you in this regard and prepare an offer individually tailored to your requirements.

Prices listed refer to first samples, scale prices for samples in parallel analysis (follow-up samples) are possible.

Surcharges for working with highly effective and/or toxic samples and reagents such as narcotics, cytostatic drugs, hormones, antibiotics and CMR substances (carcinogenic, mutagenic, reproductive toxic) may be incurred.

3.1 DETECTION OF MYCOPLASMA

Testing according to current versions of Ph. Eur. and USP
by means of real-time PCR

Routine according to verified method, per sample .....

Each additional sample for parallel testing .....

3.2 DETECTION OF BIOLOGICAL CONTAMINANTS

IN CONSUMABLES (E.G. PIPETTE TIPS, REACTION TUBES, ETC.), REAGENTS ETC.

Detection of DNase .....

Detection of human DNA .....

Detection of bacterial DNA .....

Detection of human and bacterial DNA .....

Detection of RNase .....

Detection of human RNA .....

Detection of bacterial RNA .....

Detection of protease .....

Detection of PCR inhibitors .....

Detection of ATP .....

On request we offer further PCR and real-time PCR based detections. We would be pleased to prepare you a project-based individual offer. Please do not hesitate to contact us.
Prices listed refer to first samples, scale prices for samples in parallel analysis (follow-up samples) are possible.

3.3 DETERMINATION OF CONTENT AND IDENTITY OF NUCLEIC ACIDS

Fluorometric determination of DNA .....

Determination of UV/VIS DNA .....

Determination of nucleic acid size .....

Determination of nucleic acid identity .....

3.4 DETERMINATION OF BIOLOGICAL ACTIVITY

Determination of streptokinase activity ..... *

Determination of trypsin activity
testing according to USP in the current version ..... *

Determination of Heparin Anti-Factor Xa- or Anti-Factor IIa-activity
testing according to Ph. Eur. in the current version ..... *

Determination of Heparin Anti-Factor Xa- or Anti-Factor IIa-activity
testing according to USP in the current version ..... *

Further determinations of activity are available on request. Please ask for an offer related to your current question.

3.5 PROTEIN ANALYSES

Determination of identity and purity by means of SDS-PAGE (reducing and non-reducing)
testing according to current versions of Ph. Eur. and USP .....

Determination of content

Testing according to current versions of Ph. Eur. and USP
OD280 .....
according to Bradford .....
according to Lowry .....
BCA .....
Biuret .....
ELISA .....

Capillary electrophoresis

Testing according to Ph. Eur. in the current version
Testing for glutathione related substances ..... *
Testing for enantiomeric purity of ropivacaine hydrochloride monohydrate ..... *

Testing according to USP in the current version
Testing for the degree of substitution of Betadex Sulfobutyl Ether Sodium ..... *

Determination of identity and purity by means of capillary gel electrophoresis
.....

Further capillary electrophoresis tests are available on request. Please ask for an offer related to your current question.

Amino acid analyses

Testing according to Ph. Eur. in the current version

Testing for ninhydrin positive substances .....

Testing for ammonium .....

Testing for ninhydrin positive substances and ammonium .....

Determination of the amino acid profile of peptides/proteins .....

Further amino acid analyses are available on request. Please ask for an offer related to your current question.

* plus material costs and surcharges if applicable (please also see section "miscellaneous", page 22)

3.6 DETECTION OF HOST CELL PROTEINS OR RESIDUAL DNA CONTENT

Determination by quantitative real-time PCR
Determination by ELISA

3.7 DETERMINATION OF SMALL MOLECULES

Chiral Purity
Determination by capillary electrophoresis
Determination by ELISA

3.8 IDENTIFICATION OF MICROORGANISMS BY MEANS OF MOLECULAR BIOLOGICAL METHODS (PCR/SEQUENCING)

Identification of bacterial and fungal isolates (up to species level) by PCR amplification of the 16S rRNA gene (1,500 bp) or the ITS regions with sequencing and phylogenetic classification by means of *ID by tree* database
Identification of microorganisms (up to species level) based on transmitted DNA sequences per isolate

Microbiological methods for the identification of microorganisms possible, please refer to:
MICROBIOLOGY, PAGE 8, CHAPTER 1.2

3.9 DNA-FINGERPRINTS

DNA-fingerprints for intra-species-relationship analyses (molecular phylogenetics)

3.10 *NEW*: BACTERIAL ENDOTOXINS TESTING BY MEANS OF RFC TEST (RECOMBINANT FACTOR C ASSAY)

Testing according to Ph. Eur., chapter 2.6.32 in the current version
Product-specific suitability test of the test method

3.11 CELL-BASED ASSAYS

Potency assay (calcitonin salmon) testing according to USP in the current version
Metabolic activity assay

4. GENERAL ADDITIONAL CHARGES

Project meeting

first project meeting .....

each additional project meeting (incl. travel expenses, excl. hotel expenses)

- daily rate for expert .....
- daily rate for senior expert .....

Audits/Inspections

first audit (one day) .....

each further audit

- remote audit ½ day .....
- remote audit 1 day .....
- on site audit 1 day .....

unannounced inspection from notified bodies .....

Materials

special materials like chromatography columns, reference substances,
special reagents etc., unless provided by the client

.....

Working with highly effective and/or toxic samples or reagents e.g.
narcotics, cytostatic drugs, hormones, antibiotics and CMR substances (carcinogenic, mutagenic, reproduction-toxic) or substances with high or unknown hazard potential
incl. inactivation and disposal; per sample and test .....

Documentation

shipping of certificate of analysis (CoA) by post, per shipment .....

copies of raw data (including control and authorization)

.....

preparation of a validation plan or report (if not included)

- in German or English language .....

interim certificates and new issues of certificates of analysis

- one page/multiple pages .....

translation of documents in German or English language .....

OOS procedures

processing of OOS procedures in case of a non-obvious laboratory error

- for sterility testing, estimated time approx. 2.5 hours, flat .....
- other analysis, estimated time approx. 1.5 h, flat .....
- increased time expenditure.....

Failure investigation

performing of failure investigation and preparing a report

- for OOE/OOT results .....

Changes

Processing of customer-initiated changes

- estimated time approx. 2.5 hours, flat .....
- increased time expenditure .....

Client specific documentation

preparation of customer-specific test specifications/working procedures .....

updating and storage of customer-specific work instructions/SOPs (standard operating procedures) .....

Miscellaneous

independent test certificates by a drug law cross-check expert for pharmacies
in accordance with section 65, paragraph 4 AMG (German Medicines Act)
each test report .....

confirmation of quality control by a Qualified Person .....

authentication of documents
without apostille .....
with apostille .....

service fee for the handling of data loggers .....

disposal of materials with increased volume/effort .....

return of raw data after expiry of the archiving period .....

disposal of raw data after expiry of the archiving period .....

compilation of data for Product Quality Review (PQR) .....

processing of contracts, Self-disclosure forms, confirmations, customer-specific documents .....

processing of administrative request
for the handling of narcotics .....

storage of retention samples .....

Working on weekends (Saturday/Sunday) or holidays

Evaluation of results by an employee on a Saturday
with an average workload of up to max. 3 hours .....

Evaluation of results by an employee on a Sunday or on a holiday
with an average workload of up to max. 3 hours .....

Performance of tests by two employees on a Saturday
with an average workload of up to max. 3 hours, together .....

Performance of tests by two employees on a Sunday or on a holiday
with an average workload of up to max. 3 hours, together .....

5. GENERAL TERMS AND CONDITIONS

1. Scope

The following Terms and Conditions of Order (Terms and Conditions) apply to all business dealings between BioChem Labor für biologische und chemische Analytik GmbH, Daimlerstrasse 5b, 76185 Karlsruhe, Germany – referred to hereinafter as BioChem - and the Client, even if reference is not made hereto in subsequent contracts. By placing an order, the Client acknowledges these Terms and Conditions as legally binding. The general terms and conditions of the Client are hereby revoked in full, unless it has been agreed separately and in writing that they are to apply. These General Terms and Conditions also apply if BioChem performs services for the Client without reservation, in full knowledge of its contradictory, supplementary or deviating terms.

Terms and Conditions that supplement or deviate from these General Terms and Conditions that are concluded between BioChem and the Client in execution of a contract must be set forth in written in the contract. This also applies to the waiver of this written form requirement.

Rights going over and above these General Terms and Conditions to which BioChem is entitled under the statutory provisions or under other agreements remain unaffected.

2. Conclusion, Scope and Performance of the Order

Unless otherwise agreed, all offers issued by BioChem are non-binding. Information concerning the services and other specifications set forth in the information and documentation that form part of the offer do not constitute any form of binding agreement or guarantee, unless such characteristics are explicitly designated binding. BioChem reserves all ownership, copyright, proprietary and other rights in all offer documentation. Such documentation is not permitted to be made available to third parties.

As a rule, the Client must place all orders in writing. In the case of orders placed by other means, the Client bears the transmission risk. The contract is concluded upon written order confirmation by BioChem. Verbal declarations, confirmations or commitments issued by employees of BioChem are subject to written confirmation. BioChem has the right to determine the method and type of inspection or tests at its reasonable discretion, unless otherwise agreed, in writing. Amendments or additions to the order placed must be made in writing and are deemed agreed only once they have been confirmed by BioChem in writing. If through no fault of its own BioChem is not able to perform the order, BioChem is entitled vis-à-vis the Client to withdraw from the contract, in whole or in part. In this case, the Client will be notified without delay.

If the Client applies for the initiation of insolvency proceedings or comparable proceedings concerning its assets or if a legitimate application by a third party for the initiation of insolvency or comparable proceedings concerning the assets of the Client is rejected due to lack of assets, BioChem is entitled to withdraw from the contract, in whole or in part.

3. Client Obligations

The Client shall to the best of its ability provide comprehensive support to BioChem in the performance of its services. In particular, the Client will immediately provide BioChem with all documentation and information necessary and expedient to the performance of the service. The nature and scope of further cooperation duties of the Client arise out of the offer or the order.

If fixed time periods are agreed between BioChem and the Client, these commence only once the Client has provided BioChem with all necessary documentation and all applicable preconditions (e.g. approvals, test samples, reference products) have been fulfilled by the Client. Where reasonable, the Client will grant BioChem an appropriate additional deadline within which to perform the order, even if BioChem is responsible for any failure on its part to meet agreed deadlines.

4. Prices

The price is always that stated in written in the offer or in the order confirmation. The most recent service specification is always to be taken as the basis for the price for standardised services, in particular inspections or tests. The prices stated therein are basic prices for such services. BioChem will charge additional fees or deduct discounts based on the actual effort for the individual case. For all other services not listed in the service specification, the price is agreed on a project-specific basis. On request, BioChem will issue project-specific written offers. The price is in Euros, plus VAT at the statutory rate. Prices quoted by telephone are not binding.

5. Terms of Delivery and Payment

For samples sent from Clients within the EU, including Germany, INCOTERMS 2020 DPU Karlsruhe, sample receipt at BioChem's site, is deemed to be agreed. For sample sent from Clients outside the EU, INCOTERMS 2020 DDP Karlsruhe, sample receipt at BioChem's site is deemed to be agreed; consequently, in deviation from INCOTERMS 2020 DDP, the Client also owes the unloading of the samples from the incoming means of transport.

All invoices are payable net upon receipt without deduction to the account stated in the invoice in each case. Based on the order volume, BioChem reserves the right to invoice a partial amount as advance payment upon placement of the order, upon return of the test plan, or upon attainment of certain testing phases.

6. Liability

The coverage amount under existing liability insurance is Euro 6,000,000 for personal injury and damage to property (maximum coverage amount Euro 6,000,000 for each individual), and Euro 100,000 for financial loss. The Client has expressly acknowledged the foregoing. BioChem is liable without limitation for losses relating to the breach of a guarantee or relating to damage to life, limb or health. The same applies to intentionally caused damage and gross negligence. BioChem is liable for slight negligence only in the event of the breach of material duties that are inherent to the nature of the contract and of material importance to the attainment of the contractual purpose (cardinal obligations). In the event of the breach of such duties, as well as in instances of default and frustration of contract, BioChem's liability is limited to typically foreseeable damage for this type of contract.

If and as far as BioChem's liability is excluded or limited, this also applies to the personal liability of BioChem executives, employees, staff, representatives and agents.

7. Usability of Work Results /Copyright

The results of the services performed as contractually agreed apply only for the test samples submitted and used as contractually agreed. Statements going above and beyond this based on the results are not permissible.

All data used or provided by BioChem in performance of its services are and remain the property of BioChem. BioChem without limitation reserves all rights in the method development and validation processes. All results, in particular the test results, reports, recommendations and information provided by BioChem in connection with the order are, and remain, the property of BioChem. BioChem thus reserves all rights herein without restriction. BioChem grants the Client, without temporal or geographical restriction and without the right to grant sub-licenses, a simple, non-transferable right in the results for all known types of use. The duplication and publication of test results, reports, recommendations or information for purposes other than the contractually agreed purpose is subject to BioChem's written consent.

8. Confidentiality

The parties are mutually obliged to maintain strict confidentiality with respect to all information that becomes accessible to them and that is marked confidential, or which, based on other circumstances, can be identified as business secrets, for a period of five years beginning with the disclosure of the confidential information and, unless required for the business relationship, not to record, disclose or utilise such information.

The obligation of secrecy does not apply if

(a) the information has been proven to already be known to the receiving party before the commencement of the business relationship or was generally known or generally accessible before the commencement of the business relationship; or
b) become generally known or accessible without fault of the receiving party; or
c) the receiving party is obliged by law, by administrative or other legal act or by court order to disclose the confidential information; in this case, the party requested to disclose shall immediately inform the party whose confidential information is affected of the request in writing; disclosure shall be limited to the respective judicial or administrative proceedings.

The receiving party shall bear the burden of proof.

The parties will ensure by means of appropriate contractual agreements with their employees and contractors that they, too, refrain from any own exploitation, reproduction or unauthorised recording of such business secrets for a period of five years beginning with the disclosure of the confidential information.

BioChem undertakes in particular to make available all results attained in connection with the order to the Client and without its consent not to publish or disclose the same to third parties. The Client is indefinitely not permitted without BioChem's written consent to pass on method developments and validation processes to third parties.

9. Claims Based on Defects and Statute of Limitation

The Client is required within twelve days of notification of the work result to accept it, or in the event of evident serious defects, to submit a written objection. In the case of such defects in the inspections, tests or other services rendered (advice, information) the Client is entitled to subsequent performance. If a second attempt to render subsequent performance is unsuccessful, the Client has the right to reduce the remuneration or to withdraw from the contract. The Client's right to withdrawal is excluded if it is unable to return the service received and this is not attributable to the fact that the return is impossible on account of the nature of the service received or is within the responsibility of the Contractor.

The claim to the rectification of defects (subsequent performance) must be asserted by the Client without delay and in writing.

Claims to the rectification of defects are statute barred on expiry of one year, calculated from the date of notification of the work results by BioChem. Obvious errors in the work results, e.g. spelling errors or formal defects, may be rectified by BioChem at any time.

10. Storage of Samples and Documents

Unless otherwise agreed, in writing, residual material from the samples provided for inspection – where the characteristics allow – are to be stored for up to two weeks from the inspection date. Documents will be stored in accordance with the test specifications used (e.g. GMP, GLP). After expiry of the storage period they will be disposed or destroyed at the expense of the Client at the discretion of BioChem. If a return of residual material or documents is desired, this must be agreed in writing when the contract is concluded. The costs of return shipment shall be borne by the Client.

If the test specification requires the storage of a sample or a retained sample, the stored sample or the retained sample will be disposed or destroyed at the expense of the client at the end of the storage period at the discretion of BioChem. Sentence 3 and sentence 4 of this number 10 apply accordingly.

11. Applicable Law, Place of Performance and Place of Jurisdiction

The legal relationship between BioChem and the Client is governed exclusively by the laws of the Federal Republic of Germany. The place of performance for all services of the Client and BioChem is Karlsruhe. The exclusive place of jurisdiction for all disputes arising under and in connection with the business relationship between BioChem and the Client is Karlsruhe. BioChem is also entitled to file suit at the Client's seat and at any other permissible place of jurisdiction.

12. Final Provisions

Counterclaims of the Client entitle it to set-off only if these have been conclusively legally determined or are uncontested. The Client may assert a retention right only if its counterclaim is based on the same contractual relationship. This is without prejudice to the Client's claims based on defects.

Should any provision of these General Terms and Conditions be or become invalid or unenforceable, in whole or in part, or should these General Terms and Conditions contain a gap, this shall not affect the validity of the remaining provisions. In place of the invalid or unenforceable provision the valid or enforceable provision is deemed agreed that comes as close as possible to attaining the purpose of the invalid or unenforceable provision. In the event of a gap, the provision is deemed agreed that corresponds to what the parties would have agreed, in view of the purpose of these General Terms and Conditions, had they considered the matter from the outset.