HIGH QUALITY PHARMACEUTICALS FOR SUCCESSFUL THERAPY

CONTRACT MANUFACTURING
PHARMA-ZENTRALE was founded as a private company in 1953 by Mr. Hans Proppert. Today, we are a group of successful companies and still family-owned.

The company’s philosophy is based on the knowledge of pharmaceutical tradition, combined with professional competence and future-oriented ideas. High standards of quality assurance, continuous pre-clinical and clinical research and up-to-date manufacturing technologies guarantee the constantly high quality of production, research and development.

The main activities of PHARMA-ZENTRALE are:
- Manufacturing of traditional pharmaceuticals and bio-pharmaceuticals
- Contract manufacturing
- Drug registration procedures
- Supply of pharmaceutical bulkware (liquid, semi-solid and solid forms) and cosmetic substances

As our speciality we offer biotechnological production of probiotics (both as food supplements and as pharmaceuticals) according to GMP standards.

We offer full service starting from API production by fermentation (according to part II EC-GMP guideline) followed by manufacturing the finished product, from mixing the excipients with API up to encapsulation and packaging.
ASSURANCE

A particularly important aspect in the production of high quality medicinal products: To achieve this high quality, our group of companies has developed its own standards for all steps of the production process. Standards which go considerably beyond the statutory norms.

High quality of the final product also depends on the careful selection of starting materials.

Standardized conditions of production and up-to-date technology ensure consistently high product quality.

Our Technical Department, Production, Laboratory and R & D as well as our Medical and Clinical Research Departments are continuously occupied with further improving quality, efficacy and safety of our products.

PHARMA-ZENTRALE, ARDEYPHARM and DR. POEHLMANN are located in the picturesque city of Herdecke, a traditional trading center in the western part of Germany, about 70 kilometres (45 miles) north-east of Cologne and about 20 km south of Dortmund.

PHARMA-ZENTRALE has three internationally acting subsidiaries:

- Ardeypharm
- Dr. Poehlmann & Co.
- BBT Biotech
COMPANY PROFILE

ARDEYPHARM is a leading company of research on the gut microflora and is specialised in probiotic drugs for the gastrointestinal tract.

Our principal microbial product is the probiotic drug Mutaflo® containing a unique bacterial strain (non-pathogenic Escherichia coli strain Nissle 1917) as the active component.

It is a microbial drug, evidence-based by confirmatory clinical studies for the treatment of intestinal diseases caused – at least in part – by a disturbed gut microflora.

We are continuously in search for new therapeutic indications for Mutaflo®.

Mutaflo® meets all biosafety requirements for modern probiotic drugs!

MUTAFLOR®

*Escherichia coli* strain Nissle 1917

**Indications**

Current indications according to German registration supported by numerous controlled clinical trials performed according to the latest GCP standards:

- Ulcerative colitis in the phase of remission
- Chronic constipation
- Diarrhoea in infants, toddlers and children (Mutaflo® suspension)

Further indications as indicated by clinical trials:

- Irritable bowel syndrome (IBS)
- Chronic recurrent diarrhoea
- Antibiotic-associated colitis/pseudomembranous colitis
- Crohn's disease
- Pouchitis
- Collagenous colitis
- Diverticular disease of the colon
- Food intolerances
- Polymorphous photodermatoses
- Enhancement of postnatal immune competence in pre- and fullterm infants (Mutaflo® suspension)
- Infection prophylaxis (Mutaflo® suspension)

**Posology**

Two enteric-coated hard gelatine capsules daily. The capsules will open to release the bacteria not before the terminal ileum. Mutaflo® suspension to be dropped directly into the mouth.

**Commercial forms**

- Mutaflo® capsules (2.5 to 25 x 10⁹ viable cells)
- Mutaflo® mite capsules (0.5 to 5 x 10⁹ viable cells)
- Mutaflo® suspension (10⁸ viable cells)

MUTAFLOR® – THE PROBIOTIC DRUG FOR LIFE
In addition to Mutaflo® the following probiotic drugs complete our microbial product line:

PAIDOFLOR®

*Lactobacillus acidophilus*

**Indication**
To be used against diarrhoea originating in the small bowel.

**Posology**
Three tablets three times a day.

**Commercial forms**
Available in blister packs of 20, 50 and 100 chewable tablets.

YOMOGI®

*Saccharomyces boulardii*

**Indication**
The yeast preparation is effective against acute diarrhoea and travelers’ diarrhoea.

**Posology**
one capsule two times a day.

**Commercial forms**
Available in blister packs of 10, 20, 50 and 100 capsules.
Besides probiotic drugs for the gastrointestinal tract, the ARDEYPHARM product line also comprises chemically defined drugs and herbal remedies.

The following table gives an overview of our total product line and selected main indications:

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Commercial forms</th>
<th>Packsize</th>
<th>Posology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutaflor® E. coli strain Nissle 1917</td>
<td>Inflammatory bowel disease, chronic constipation</td>
<td>Mutaflor® capsules</td>
<td>20, 50 and 100 caps.</td>
<td>2 capsules once a day 1 capsule a day</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea in infants, toddlers and children</td>
<td>Mutaflor® mite capsules</td>
<td>20 capsules</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Mutaflor® suspension</td>
<td>5 and 25 x 1 ml</td>
<td>1–3 x 1 ml a day</td>
</tr>
<tr>
<td>Paidoflor® Lactobacillus acidophilus</td>
<td>Diarrhoea originating in the small bowel</td>
<td>Chewable tablets</td>
<td>20, 50 and 100</td>
<td>Three tablets three times a day</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>chewable tablets</td>
<td></td>
</tr>
<tr>
<td>Yomogi® Saccharomyces boulardii</td>
<td>Acute diarrhoea Travelers’ diarrhoea</td>
<td>Capsules</td>
<td>10, 20, 50 and 100 capsules</td>
<td>One capsule two times a day</td>
</tr>
<tr>
<td>Adiclair® Nystatin</td>
<td>Fungal infections</td>
<td>Tablets</td>
<td>20, 50 and 100 tabl.</td>
<td>2 tabl. three times/d 1 ml 6 times a day</td>
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<tr>
<td></td>
<td></td>
<td>Suspension</td>
<td>24 and 48 ml</td>
<td>Three times a day</td>
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<td></td>
<td></td>
<td>Ointment</td>
<td>20, 50 and 100 g</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Cream</td>
<td>20 and 50 g</td>
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<tr>
<td></td>
<td></td>
<td>Vaginal tablets</td>
<td>12 tablets</td>
<td>Two tablets a day</td>
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<tr>
<td></td>
<td></td>
<td>Mouthgel</td>
<td>25 and 50 g</td>
<td>1 g four times a day</td>
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<tr>
<td>Mykotin® Micronazole</td>
<td>Oral candidiasis</td>
<td>Mouthgel</td>
<td>20 and 40 g</td>
<td>1 g four times a day</td>
</tr>
<tr>
<td>Surfont® Mebendazole</td>
<td>Infection with Intestinal and systemic nematodes</td>
<td>Tablets</td>
<td>6 tablets</td>
<td>One tablet a day for three days</td>
</tr>
<tr>
<td>Ardeyhepan® Milk thistle fruit extract</td>
<td>Liver diseases</td>
<td>Coated tablets</td>
<td>20, 60 and 100 coated tablets</td>
<td>Two coated tablets two times a day</td>
</tr>
<tr>
<td>Ardeycholan® Artichoke leaf extract</td>
<td>Dyspeptic disorders</td>
<td>Capsules</td>
<td>20, 50 and 100 capsules</td>
<td>One capsule three times a day</td>
</tr>
<tr>
<td>Ardeynephron® Java tea leaves</td>
<td>Purging with bacterial and inflammatory disease of the urinary tract, preventing renal gravel</td>
<td>Capsules</td>
<td>20 and 50 capsules</td>
<td>Two capsules three to four times a day</td>
</tr>
<tr>
<td>Product</td>
<td>Indication</td>
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<tr>
<td>Ardeycordal®</td>
<td>Mild to moderate cardiac insufficiency and nervous heart complaints</td>
<td>Coated tablets</td>
<td>20, 50 and 100 coated tablets</td>
<td>Three coated tablets a day</td>
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<tr>
<td>Ardeycordal®</td>
<td>Hawthorn leaf and flower extract</td>
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<tr>
<td>Plissamur®</td>
<td>Symptoms of peripheral chronic venous insufficiency</td>
<td>Coated tablets</td>
<td>20, 50 and 100 coated tablets</td>
<td>Three tablets three times a day</td>
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<tr>
<td>Plissamur®</td>
<td>Horse chestnut seed extract</td>
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<tr>
<td>Doloteffin®</td>
<td>Supportive therapy of degenerative illnesses of the musculoskeletal system</td>
<td>Tablets</td>
<td>10, 20, 50 and 100 tablets</td>
<td>Two tablets three times a day</td>
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<tr>
<td>Doloteffin®</td>
<td>Devil’s claw root extract</td>
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<tr>
<td>Ardeysedon®</td>
<td>Anxiety</td>
<td>Coated tablets</td>
<td>20, 50 and 100 coated tablets</td>
<td>Two coated tablets three times a day</td>
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<tr>
<td>Ardeysedon®</td>
<td>Valerian and Hop extract</td>
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<tr>
<td>Ardeysedon® night</td>
<td>Insomnia (chronic)</td>
<td>Coated tablets</td>
<td>50 and 100 coated tablets</td>
<td>One coated tablet three times a day</td>
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<tr>
<td>Ardeysedon® night</td>
<td>Valerian and Hop extract „extra strong“</td>
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<tr>
<td>Orgaplasma®</td>
<td>Feeling of weakness; lack of concentration and during convalescence</td>
<td>Coated tablets</td>
<td>20, 50 and 100 coated tablets</td>
<td>Two coated tablets two times a day</td>
</tr>
<tr>
<td>Orgaplasma®</td>
<td>Ginseng root extract</td>
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<tr>
<td>Ardeytropin®</td>
<td>Serotonin precursor for chronic insomnia</td>
<td>Tablets</td>
<td>20, 50 and 100 tablets</td>
<td>Two tablets three times a day</td>
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<tr>
<td>Ardeytropin®</td>
<td>Tryptophan</td>
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<tr>
<td>Castufemin®</td>
<td>Premenstrual syndrome and mastodynia</td>
<td>Bottles</td>
<td>20, 50 and 100 ml capsules</td>
<td>30 drops in the morning One capsule once a day</td>
</tr>
<tr>
<td>Castufemin®</td>
<td>Chaste tree fruit</td>
<td>Capsules</td>
<td>30, 60 and 100 capsules</td>
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<tr>
<td>Passidon®</td>
<td>Nervousness Restlessness</td>
<td>Capsules</td>
<td>50 and 100 capsules</td>
<td>Two capsules two times a day</td>
</tr>
<tr>
<td>Passidon®</td>
<td>Passion flower foliage dry extract</td>
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</tbody>
</table>
DR. POEHLMANN & Co. is one of the leading companies offering OTC drugs and tonics of natural origin in Germany.

Preventive medicines become more important alongside curative medicine. In addition, herbal remedies are becoming more popular with customers.

The products of DR. POEHLMANN & Co. are well-known due to their high quality as announced in newspaper and magazine advertisements.

All of these well-known trademarks like Tai Ginseng®, Voltax®, Cevitect®, and Solaguttae®, are sold at pharmacies and drugstores:

**TAI GINSENG®**
An invigorating natural product which boosts energy levels stimulating both mind and body.
Available in bottles of 20 and 500 ml as well as in blister packs with 60 and 120 coated tablets or 20 pastilles.

**VOLTAZ®**
A natural lecithin product which helps to increase permeability of neural membranes. For the improvement of conditions of fatigue and to strengthen the nerves.
Available in blister packs of 40 and 120 capsules.

**CEVITECT®**
Thyme pastilles.
Herbal remedy for colds and the flu.
Available in blister packs of 30 pastilles.
Another example of OTC products from DR. POEHLMANN & Co. is the Solaguttæ® line of natural products:

**Valerian-Hop „extra strong“ coated tablets**
Active substances:
200 mg Valerian and 68 mg Hop extract
Indication: Insomnia
Available in blister packs of 40 coated tablets.

**Valerian-Hop coated tablets**
Active substances:
100 mg Valerian and 24 mg Hop extract
Indication: Restlessness and Anxiety
Available in blister packs of 60 coated tablets.

**Vitamin E 600 mg Capsules**
Active substance: Vitamin E 600 mg
Indication: Ergotropic
Available in blister packs of 40 capsules.

**Pepsin Wine**
Active substance: Pepsin 300 mg
Indication: Improves stomach function
Available in bottles of 700 ml.
COMPANY PROFILE

BBT BIOTECH is specialized in the development, manufacturing and international sales of **pharmaceutically active compounds of biological origin**.

Our key technologies encompass sophisticated manufacturing facilities of therapeutically relevant, healthy bacteria and yeasts (probiotics) as well as special protein purification and separation methods, developed in-house.

Manufacture of our products follows strictest regulatory requirements (GMP), using state-of-the-art technical procedures. This results in products of highest quality.

Our product line includes **active substances** for the international pharmaceutical industry as well as for the healthcare and food industry.

We offer multi-stage production facilities:

**Fermentation – Purification – Finished Products**

As a highly specialized manufacturer, we have strictly separated areas dedicated to the **protein purification** department and the **fermentation** department to prevent any cross-contamination.

Clean-room handling is standard.

We are inspected and regularly controlled and audited by the German health authorities and other bodies supervising the manufacturing of pharmaceutically active compounds.

**Viable microorganisms** and their metabolites are offered not only in **bulk** but also in **finished dosage forms** to the pharmaceutical and health-care industry. The combination of several production steps, which we offer, combined with perfect process technology and state-of-the-art control systems, ensures custom-tailored, high-standard products.

Our reactor capacity ranges from 8l, via 250l, up to 18,000l. The downstream process is based on various separators, filtration systems and freeze-dryers.

BBT supplies a wide range of living bacteria and yeasts, in batch sizes up to 50 kg, e.g.:

- Bacteroides
- Bifidobacteria
- Clostridia
- Enterobacteria
- Lactobacilli
- Saccharomyces
Pharmaceutically active enzymes, hormones and proteins are isolated to highest purity and quality.

State-of-the-art chromatography and ultrafiltration equipment, handled by well-educated, experienced employees, make it possible to achieve batch sizes ranging from a few grams up to 5 kg of final purified product.

While our products are purified from human, animal and fermentative sources, validated production procedures ensure highest quality standards.

Depending on your individual needs we offer the following active bio-pharmaceuticals (API or finished forms, e. g. our brand Diclair®):

- **Thrombolytics**
  - Streptokinase
  - Urokinase

- **Fertility hormones**
  - HCG (Human Chorionic Gonadotropin)
  - HMG (Human Menopausal Gonadotropin)
  - FSH (Follicle-Stimulating Hormone; Urofollitropin)

- **Highly purified fertility hormones**
  - HCG (Human Chorionic Gonadotropin)
  - HMG (Human Menopausal Gonadotropin)
  - FSH (Follicle-Stimulating Hormone; Urofollitropin)

- **Inhibitors**
  - Aprotinin

- **Others**
  - Hyaluronidase

Each of our products passes rigorous tests according to GMP and international pharmacopeia standards, to confirm its identity, purity and activity with respect to its pharmaceutical grade. Certificates of analysis are delivered accordingly.

We have the knowledge and flexibility to follow changing requirements of a dynamic market. BBT recognizes the importance of meeting special product specifications, and listens attentively to each customer’s wishes.

Please ask us to offer solutions to your individual needs for custom manufacturing, or for new product developments.

If you intend to register pharmaceuticals based on BBT’s active substances, of course, we are able to provide you with the corresponding drug master files (DMFs).

The BBT (Baesweiler BioTech) offices, laboratories and manufacturing facilities are located in Baesweiler, a small city close to the Dutch border, 25 km north of Aachen, 60 km west of Cologne and Düsseldorf. Here we benefit from synergy between a healthy and clean environment and the scientific resources of German, Dutch, Belgian and French universities.