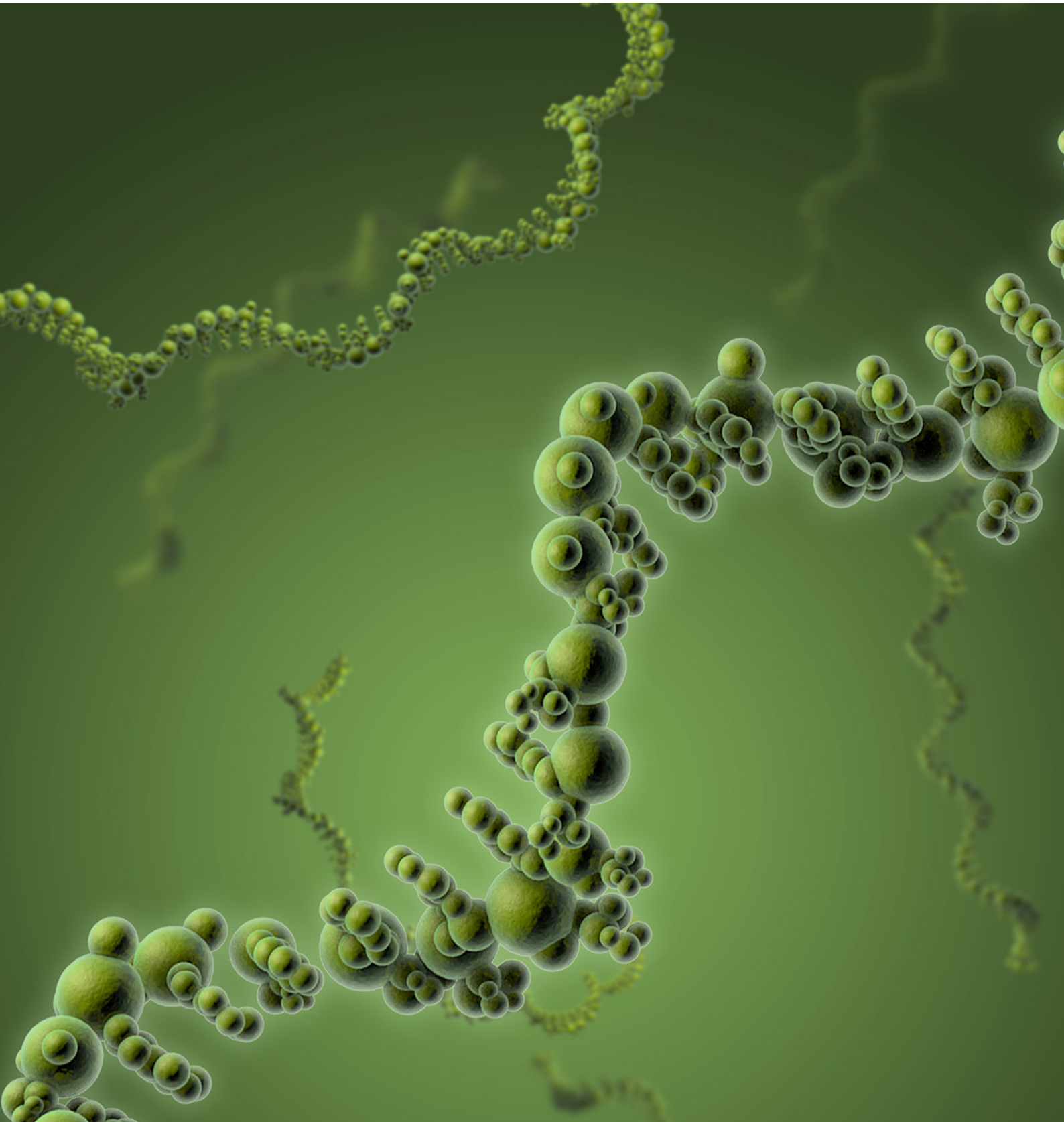


Microsynth



CATALOG 2022/2023

Oligonucleotide Synthesis • DNA/RNA Analysis • Sanger Sequencing
NGS • Isolation and Assaying • Contract Research

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Microsynth – At a Glance

Microsynth AG is a privately held, leading European biotech company in the area of nucleic acid synthesis and analysis. Our headquarters is in Switzerland and we have subsidiaries in Austria, France, Germany and Switzerland. In total Microsynth has over 100 employees.

Our History

Microsynth is a leading European company in the field of nucleic acid synthesis and analysis, and we are currently active in the following three business areas:

1. DNA/RNA synthesis
2. DNA/RNA analysis and sequencing
3. Contract research/outsourcing

Microsynth was founded in 1989 by Dr. Tobias Schmidheini as a spin-off of ETH Zurich. When Dr. Schmidheini started producing DNA oligonucleotides on behalf of Swiss academic institutes, he was one of the pioneers in this field. We now offer our numerous customers a broad spectrum of high-quality DNA/RNA oligonucleotides for research, drug discovery and molecular diagnostics.

In 1992, Microsynth decided to enter the field of DNA sequencing. Almost thirty years on, we are very well positioned in this field and are able to offer our customers both traditional Sanger sequencing services as well as state-of-the-art next generation sequencing services. And through establishing additional Sanger sequencing laboratories in Austria (Microsynth Austria GmbH in 2012), Germany (Microsynth SeqLab GmbH in 2013) and France (Microsynth France SAS in 2021) Microsynth has secured better access to key European markets. In the last two decades, sequencing has been complemented by various other specialized DNA/RNA-related areas such as nucleic acid isolation, PCR & qPCR & digital PCR, genotyping and bioinformatics. Following the acquisition of ecogenics GmbH (which specialized in microsatellite marker development and related genotyping services) in 2011, we were able to expand our methodological repertoire and gain access to new customer segments

- 1989 — The company is founded in Zurich as an ETH spin-off

- 1992 — Entry into the Sanger DNA sequencing business

- 1994 — Relocation to Balgach into own Microsynth building

- 1998 — Establishment of qPCR & genotyping labs

- 2004 — Headquarters extended by 2'000 m2 lab & office space, launch of RNA synthesis

- 2007 — Entry into the NGS sequencing business

- 2010 — Own DNA/RNA isolation department is built up

- 2011 — Takeover of the genotyping services from ecogenics GmbH, Switzerland **Microsynth**
ECOGENICS

- 2012 — Foundation of Microsynth Austria GmbH **Microsynth**
AUSTRIA

- 2013 — Merger with SeqLab GmbH in Germany **Microsynth**
SEQLAB

- 2014 — Handover of the executive management to Markus Schmid and Christof Wunderlin

- 2015 — Official launch of CR/Outsourcing department

- 2016 — Clinical research studies according to ICH guidelines

- 2017 — Contract manufacturing of oligos for IVD and drug discovery

- 2018 — Digital PCR technology is established

- 2019 — 30th anniversary is celebrated
Headquarters extended by two floors

- 2021 — Merger with Biofidal SARL in France **Microsynth**
FRANCE

(e.g. ecologists, breeders, botanists and zoologists).

The third and most recent department that Microsynth has created (which is known as Contract Research/Outsourcing) combines the companies state-of-the-art portfolio in nucleic acid synthesis, sequenc-

ing and analysis to establish tailor-made analysis pipelines for customer projects. Following the successful execution of various projects with customers in the clinical or regulated environment in the recent past, decisive regulatory and project-related competencies have been developed.

Consequently, Microsynth is nowadays a proven CRO offering GLP/GMP-compliant assay development, validation and sampling to support the development and production of drugs worldwide.

Our Mission

It is Microsynth's mission to continue to be a leading service and solution provider for molecular biologists who require either

high-quality DNA/RNA oligonucleotides, robust DNA/RNA sequencing and analysis solutions, or want to outsource project

work. Microsynth recognizes our responsibility to the environment by working in a comprehensive, sustainable manner.

Our Management

Our two Co-CEOs, Christof Wunderlin (right) and Dr. Markus Schmid (left). Christof Wunderlin is responsible for Sales, Finance and Human Resources, while Dr. Markus Schmid is responsible for Operations and Quality Systems.

The members of the management team together determine Microsynth's strategy and have committed themselves to drive forward the internationalization and further growth of the company, while always acting in a sustainable and socially responsible manner.



Our Brand Promise

As a pioneer in our field, we have gained extensive critical expertise and experience related to DNA/RNA services since our incorporation in 1989. This expertise is our most valuable asset and we attach great importance to continuously enhancing our expertise through our commitment to technical competence, diligence and reliability. For more than three decades, our objective has been to serve our customers



by delivering products and services of the highest quality, on time, and with an outstanding service – and all this at competitive prices.

Last but not least, we are committed to sustainable development and to the protection of the natural resources of our planet.

Our Locations

Microsynth
THE SWISS DNA COMPANY

The **Microsynth AG** headquarters in Balgach, Switzerland, where the company owns and occupies a 5-floor building with an oligo production facility, analytic laboratories and offices.



Microsynth
ECOGENICS

ecogenics is also located at the headquarters.

Microsynth
AUSTRIA

The industrial building at Leberstrasse 20 in Vienna. **Microsynth Austria** is housed on the 4th floor.



Microsynth
SEQLAB

The industrial building at Maschmühlenweg 36 in Göttingen. **Microsynth SeqLab** is housed on the 2nd floor, where it occupies state-of-the-art lab and office facilities.



Microsynth
FRANCE

Microsynth France is housed in a building at 170 Av. Gabriel Péri in Vaulx-en-Velin near Lyon.



Quality System

Quality awareness is of critical importance to us. This includes the quality of all Microsynth products and services, as well as the quality of all processes and procedures at Microsynth AG and our subsidiaries. And our continuously improving quality system is flexible enough to respond to the needs of different customers in different markets.

Microsynth AG is certified according to **ISO 9001:2015** and accredited according to **ISO/IEC 17025:2017** (STS 0429) for Sanger Sequencing, Next Generation Sequencing and Fragment length analysis. Microsynth's oligonucleotide synthesis facility is certified according to **EN ISO 13485:2016**, which is formal recognition of our competencies in the area of production and distribution of nucleic acids and components for IVD manufacturers and the provision of associated activities. The company participates in proficiency tests, which are an important part of on-going qualification/validation.

Our Sanger sequencing laboratory holds the **GMP Compliance** certification issued by Swissmedic for manufacturing medical products including quality control (chemical, physical, biochemical and biological) of medical products as a contract laboratory.

The **Qualified Person** (QP) is in direct contact with relevant production coordinators on GxP issues and cooperates with production to ensure continuous improvement in all our processes. The QP provides details on corrective actions required for batch deviations and assists in the implementation of quality systems within production to ensure compliance with GxP.

In addition, we are working according to the

EU Guidelines for Good Manufacturing Practice (EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines / Arzneimittel-Bewilligungsverordnung (AMBV) and the ICH / PIC/S Guidance in GxP-projects (Contract Research)).

Our **company structure** in terms of processes, interfaces, and responsibility of resources is described in the **Quality Manual**. Process performance is monitored via **Key Performance Indicators (KPIs)** and it is enhanced via quality objectives and continuous improvement (KV). QMS relevant documentation and the associated records are managed in a controlled manner. This includes approval and release, identification, creation date and versioning. **Change management**, which is a **continuous improvement process** and **risk management** are implemented. Non-conformities / OOS are linked to a **CAPA process**. Customer complaints and deviations are recorded and brought up at team meetings so that they can be incorporated into our training programs.

Processes are described in Standard Operating Procedures (SOPs) and they are reviewed periodically. We always maintain a clean and hygienic manufacturing area and our processes are clearly defined, **validated**, and controlled. Furthermore, instruments are **qualified** and the requalification period is defined. Instrument-related

test documents are archived, and changes that affect the quality are validated if necessary. In cases where the quality cannot be covered by verification, the production process is validated. Records demonstrate that all the steps required by the defined procedures and instructions have in fact been taken. Any deviations are investigated and documented. Records of manufacture that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.

Our **operators** receive training on a regular basis in practical work and documentation procedures. In addition, all new personnel are trained according to a clearly defined introductory plan, which is documented in a dedicated dossier. If new functions are taken over by our employees, the pre-defined training/introduction must be completed.

Audits are performed not only to confirm that activities within the different processes correspond to internal and external demands but also, to investigate the efficiency and suitability of the quality management system. By conducting internal audits we are able to verify that the company policy is being implemented throughout the entire organization. Furthermore, supplier qualification is performed on a regular basis.

Certification	Authority
ISO 9001:2015	SQS (Swiss Association for Quality and Management Systems)
EN ISO 13485:2016	SQS (Swiss Association for Quality and Management Systems)
ISO/IEC 17025:2017	SAS (Swiss Accreditation Service)
GMP	Swissmedic

Ecological Commitment

Microsynth and our subsidiaries are committed to sustainable development¹ and the responsible use of finite resources. We are convinced that the sustainable way of working will be the foundation of our success in the future.

At Microsynth, we are committed to acting in an ecologically responsible way. The following examples illustrate the ecological commitment of Microsynth AG and our subsidiaries:

- Our headquarters in Balgach, Switzerland, is a compact, well-insulated, and airtight building according to the Swiss Minergie standard. On the roof of the old Microsynth building, we operate a photovoltaic power system featuring an annual power output of approximately 18,000 kWh. The remaining electricity supply is 100% from renewable energy sources (Naturstrom basic business).
- The immediate environment has been shaped and ecologically enhanced by various structural elements (including groups of trees and woody plants, still-water areas, boxes for birds and bats, and gaps in the roof) to match the needs and natural habitat of the animals. These niches have already been populated by birds and bats.
- Wherever possible, we sort waste material for recycling and we then use the recycled products. Organic solvents needed for synthesis and analytic requirements are collected and eventually disposed of in a safe and environmentally compliant manner
- Our printed materials are predominantly made from recycled fiber-based paper or FSC-certified paper. All of our marketing materials printed at external printing shops are printed in a climate-neutral way.
- Business travel (e.g. customer visits, congresses etc.) is largely done via train (within Switzerland and Austria we travel almost 100% by train). Business trips via airplanes are extremely rare and many of our employees travel to their respective workplaces by bicycle.
- Sequencing samples in Austria, France, Germany, and Switzerland (where we operate sequencing facilities) are predominantly delivered via environmentally friendly transport vehicles (e.g. train, bicycle) to our labs. Only samples originating from outside of our core markets are operated via (aircraft-managed) express courier services such as DHL or UPS.
- The provision of common home office capabilities for business managers beyond the Coronavirus pandemic will lead to a considerable reduction in the daily distances our employees travel by car to their respective Microsynth workplaces.
- For company-owned cars, our aim is to soon switch to electric cars.

Microsynth and our subsidiaries are constantly striving to achieve further improvements and optimizations in order to produce and analyze as sustainably as possible.

Our goal is to minimize resources and waste in our processes and workflows.

1) Sustainable development meets the needs of the present without compromising the ability of future generations to meet their own needs.

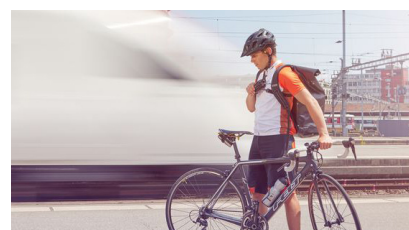
This is the most frequently quoted definition for sustainable development. It is from "Our Common Future", which is also known as the Brundtland Report.



Native plants were planted on the flat roof of the new part of our headquarters in 2020 with the aim of providing an appealing habitat for animals and plants. In a few years, it will be fully grown and offer a beautiful environment for our native insects to thrive.



The electric charging station, which is fed by the photovoltaic system installed on our roof.



Microsynth operates decentralized sequencing facilities. This approach enables the company to rely on much more environmentally friendly courier systems with trains and bicycles being the predominant mode of transport.

Customer Support – We Are Here to Help

Microsynth and its subsidiaries stand behind each and every product and service offered, and take pride in offering the highest level of customer and technical support. We have a staff of highly-trained molecular biologists/ biochemists as well as administrative personnel ready to assist with any questions that you may have. If you have any question, please do not hesitate to call us!

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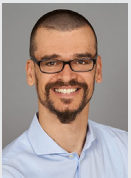
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DNA/RNA Synthesis

Microsynth is a pioneer in the area of oligonucleotide synthesis and is proud to look back on more than 30 years of experience. This valuable know-how combined with the application of state-of-the-art synthesizer technologies, purification as well as analytical systems allow us to produce a broad range of DNA/RNA oligonucleotides meeting the highest quality standards and requirements.

Microsynth's highly automated production systems ensure that you receive your oligonucleotides as needed. Further, an easy ordering system and our competent customer support will help to make your life easier.

General Features and Benefits:

- **Stringent quality control** (online trityl monitoring and MALDI-TOF MS or analytical PAGE)
- **Rapid turnaround time:** Synthesis scales up to 1 μmol of unmodified

DNA oligonucleotides are shipped the next day

- **Standard modified oligos are shipped within 3 days**
- **Large range of synthesis scales** (yields from nmol to μmol are available)
- **Broad range of 5', 3' and internal modifications**
- **4 different purity levels**
- **Very competitive pricing** for large quantity and/or prepaid orders
- **High guaranteed yields**

- **Trained scientists** with molecular biology background are happy **to support you** (from 8 am to 5 pm)!
- **Easy-to-use online portal** with a series of helpful tools (e.g. order tracking & history, convenient search and re-order option)
- **EN ISO 13485:2016** certified

E.1 Standard Synthesis Services

E.1.1 Unmodified DNA Oligonucleotides

Microsynth uses proprietary synthesizer technologies to offer oligonucleotides of highest quality. Our state-of-the-art production facilities and processes enable fast synthesis of unmodified DNA oligonucleotides in 4 different purity levels.

Desalted Oligonucleotides

Synthesis Scale ¹	Length [nt]	Guaranteed Yield		Production Time [wd]
		[OD260] ²	[nmol] ³	
Genomics	13–60	2	10	1
0.04 μmol	13–80	3	15	1
0.2 μmol	6–150 ⁴	8	50	1
1.0 μmol	6–80	50	250	1
15 μmol	13–60	700	3'500	2

HPLC Purified Oligonucleotides

Synthesis Scale ¹	Length [nt]	Guaranteed Yield		Production Time [wd]
		[OD260] ²	[nmol] ³	
Genomics		not available		
0.04 µmol	13–50	1	5	2
0.2 µmol	6–50 ⁵	3	15	2
1.0 µmol	6–50 ⁵	15	75	2
15 µmol	6–50	300	1'500	3

HPLC Purified & Dialysed Oligonucleotides

Synthesis Scale ¹	Length [nt]	Guaranteed Yield		Production Time [wd]
		[OD260] ²	[nmol] ³	
Genomics		not available		
0.04 µmol		not available		
0.2 µmol	8–50 ⁵	3	15	3
1.0 µmol	8–50 ⁵	15	75	3
15 µmol	8–50	200	1'000	4

PAGE Purified Oligonucleotides

Synthesis Scale ¹	Length [nt]	Guaranteed Yield		Production Time [wd]
		[OD260] ²	[nmol] ³	
Genomics		not available		
0.04 µmol	13–80	0.5	2.5	2
0.2 µmol	8–80	2	10	3
	81 – 150 ⁴	0.5	2.5	
1.0 µmol	8–80	7	35	3
15 µmol		not available		

1) The synthesis scale represents the initial amount of 3' nucleotides (starting material).

2) Guaranteed yields in OD are valid for unmodified oligonucleotides >20mer only.

3) Yields indicated in nmol represent an example calculation for a 20mer. For this calculation the following rule of thumb equation was applied: $\text{nmol of oligonucleotide} = \text{OD} \times 100 / \text{length of oligonucleotide}$. Please note that this calculation is based on sequences with virtually homogenous distribution of the 4 DNA nucleobases; it may vary for sequences with high GC contents >70% etc.

4) Oligos longer than 150 nt on request (we would like to discuss the proposed experiment/application with you beforehand in order to guarantee the best possible outcome).

5) On request up to 80 nt.

E.1.2 Modified DNA Oligonucleotides

Microsynth offers a wide variety of modifications (5', 3' and internal) for DNA oligonucleotides. The following 6 tables represent the most common modifications our customers usually ask for. If your desired modification or synthesis scale is not listed here, please contact us for availability.

Dyes

Type of Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int. ¹	0.04 ²	0.2	1.0	Des	HPLC	PAGE
AlexaFluor 350	X	X			X	X		X	X
AlexaFluor 430	X	X	X		X	X		X	X
ATTO 425/488/532/565/590/620	X	X		X	X	X		X	X
ATTO 550/647N	X	X	X		X	X		X	X
Cy3/Cy5	X	X	X		X	X		X	
Cy5.5/Cy7	X	X		X	X	X		X	
Methylene Blue (ATTO MB2)	X	X			X	X		X	X
Dyomics 510XL/530	X	X	X		X	X		X	X
Dyomics 630/681/781	X	X		X	X	X		X	X
FAM	X	X	X	X	X	X		X	X
HEX	X			X	X	X		X	X
JOE	X	X	X		X	X		X	X
ROX	X	X			X	X		X	X
TAMRA	X	X	X		X	X		X	X
TET	X			X	X	X		X	X
Texas Red	X				X	X		X	X
Yakima Yellow	X				X	X		X	X
California Red	X				X	X		X	X

1) Internal modifications are offered as dT compounds (e.g. ATTO550-dT). 2) 0.04 μmol synthesis scale is available for 5' dyes only..

Quenchers

Type of Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int.	0.04	0.2	1.0	Des	HPLC	PAGE
BHQ-1/BHQ-2		X	X ¹		X	X		X	X
Dabcyl		X			X	X		X	X
IQ-500			X		X	X		X	X
MGB-Q500		X			X	X		X	
MGB-Q530		X			X	X		X	

1) Internal BHQ-1/BHQ-2 are available as dT-compounds on request.

Bioactive Labels

Type of Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int. ¹	0.04	0.2	1.0	Des	HPLC	PAGE
Biotin	X	X	X	X	X	X		X	X
Digoxigenin	X	X	X		X	X		X	X
Cholesterol		X			X	X		X	X
(GalNAc)3-Spacer		X		X	X	X		X	X

1) Internal modifications are offered as dT-compounds (e.g. Biotin-dT).

Functional Groups

Type of Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int. ²	0.04 ¹	0.2	1.0	Des	HPLC	PAGE
Alkyne (mod. for cycloaddition)		X			X	X		X	X
Amino	X	X	X ²	X	X	X	X	X	X
Azide	X	X	X ²		X	X		X	X
DBCO (Cu-free cycloaddition)	X	X	X ²		X	X		X	X
Hexynyl (cycloaddition)	X				X	X		X	X
Phosphate	X	X		X	X	X	X	X	X
Phosphorothioate (PTO)	X	X	X	X	X	X	X	X	X
Thiol	X	X			X	X		X	X

1) 0.04 μmol synthesis scale is available for 5' functional groups only. 2) Internal modifications are offered as dT compounds (e.g. Amino-dT).

Spacers

Type of Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int.	0.04	0.2	1.0	Des	HPLC	PAGE
C3 Spacer		X	X		X	X		X	X
Spacer 18			X		X	X		X	X
Spacer C12			X		X	X		X	X
dSpacer (abasic site)			X		X	X		X	X

Modified Nucleobases

Type of Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int.	0.04	0.2	1.0	Des	HPLC	PAGE
2'-Deoxyinosine (INO)		X	X		X	X		X	X
2-Aminopurine			X	X	X	X	X	X	X
5-Me-dC			X		X	X		X	X
Deoxyuridine			X		X	X		X	X
Mixed Bases			X	X	X	X	X	X	X
Propynyl-dC			X		X	X		X	X
Propynyl-dU			X	X	X	X	X	X	X
2'-O-Methyl-RNA			X	X	X	X	X	X	X
2'-Methoxyethyl-RNA (MOE)			X	X	X	X	X	X	X
2'-Fluoro-RNA			X	X	X	X	X	X	X
LNA			X	X	X	X	X	X	X
S-cEt ¹			X	X	X	X	X	X	X
2'-Deoxy-dA, dC, dG and dT ¹		X	X		X	X		X	X
Inverted dA, dC, dG and dT			X		X	X		X	X

1) 3'-Deoxy-dA, dC, dG and dT is equivalent to 2'3' dideoxyA/C/G/T.

E.1.3 Custom qPCR and Digital PCR Probes

Probe-based qPCR or digital PCR relies on the sequence-specific detection of a desired PCR product. Unlike dye-based methods that detect all double-stranded DNA, probe-based approaches utilize a fluorescent-labeled target-specific probe resulting in increased specificity and sensitivity. Therefore, use high-quality probes from Microsynth to improve the sensitivity and specificity of your qPCR or dPCR assay.

Advantages:

- **Possibility to adjust binding affinity via MGB, LNA and other Tm enhancers** or even combine different Tm enhancers to tailor your assay
- **Fast turnaround times:** 3-5 business days
- Wide variety of fluorophore-quencher combinations
- **ISO 13485 certified production process**
- qPCR & digital PCR assay development,

validation, manufacturing and testing can be outsourced to Microsynth.

Dual-labeled Probes

5' Label	3' Label	0.04 µmol Scale ¹	0.2 µmol Scale ¹	1.0 µmol Scale ¹
		Minimum Yield ²	Minimum Yield ²	Minimum Yield ^{2,3}
FAM	TAMRA BHQ-1	1 OD / 5 nmol	2 OD / 10 nmol	10 OD / 50 nmol 8 OD / 40 nmol
HEX, TET	TAMRA	n/a	2 OD / 10 nmol	10 OD / 5 nmol
FAM, HEX, TET, AlexaFluor 350	Dabcyl	n/a	2 OD / 10 nmol	10 OD / 50 nmol
HEX, JOE, TET ATTO 425/532, AlexaFluor 350 Yakima Yellow (equivalent to VIC)	BHQ-1	n/a	1.5 OD / 10 nmol	8 OD / 40 nmol
ATTO 550 (equivalent to NED) ATTO 620, 647N, TAMRA, California Red Cy3/Cy5 Dyomics 681, ROX	BHQ-2	n/a	1.5 OD 7.5 nmol	8 OD 40 nmol

MGB Probes

5' Label	3' Label	0.04 µmol Scale ¹	0.2 µmol Scale ¹	1.0 µmol Scale ¹
		Minimum Yield ²	Minimum Yield ²	Minimum Yield ²
FAM	MGB-Q500 MGB-Q530	1 OD / 5 nmol	2 OD / 10 nmol	10 OD / 30 nmol
JOE	MGB-Q530			
Yakima Yellow	MGB-Q530			
HEX	MGB-Q530			

1) The synthesis scale represents the initial amount of 3' nucleotides (starting material).

2) Yields indicated in OD260 apply to a probe consisting of 20 nucleotides; Calculation: 1 OD = 5 nmol (please note that this calculation is based on sequences with virtually homogenous distribution of the 4 DNA nucleobases; it may vary for sequences with high GC contents >70% etc.)

3) For PAGE purified Probes in the 1.0 µmol synthesis scale, guaranteed yield is 5 OD

Other Probes

If you are interested in molecular beacons, double-quenched probes or lightcycler probes, please see our website or get in contact with us.

E.1.4 Large Volume Orders

DNA Oligonucleotides - Large Volume Orders

Do you need large amounts of standard DNA oligonucleotides (≥ 100 oligonucleotides) per one single order or larger amounts of oligonucleotides with a certain modification? Depending on the number of oligonucleotides or modifications to be ordered, you will benefit from volume-dependent discounts.

Unmodified DNA Oligonucleotides — Large-Volume Orders¹

# of DNA Oligonucleotides	Production Time [weeks]	Other Specifications	Price per Nucleotide
100–200	1	<ul style="list-style-type: none"> • synthesis scale: genomics or 0.04 μmol • length: 13–60 nt² • guaranteed yield³: 3 OD • purification: desalted • QC: MALDI-TOF or PAGE • delivery: in 96-/384-well plates or in single tubes; either dry or in solution (100 μM) 	Want the best price possible? Then please contact us (info@microsynth.ch) and request your offer!
201–500	1–2		
501–1'000	1–2		
1'001–2'000	2		
2'001–5'000	2–4		
>5'001	>5		

1) Large-volume order means ≥ 100 oligonucleotides per one single order.

2) For oligonucleotides >60 nt please contact us.

3) Applies to unmodified oligonucleotides >20 nt.

Modified DNA Oligonucleotides — Large-Volume Orders

Significant discounts are possible if you need ≥ 10 modifications (e.g. NH_2 , FAM or 5-Me-dC) of the same type per one single order or within a short time span. To profit from the best price possible, please contact us at Microsynth and request your offer!

Unmodified DNA Oligonucleotides — 1-Year Subscription Orders

In order to benefit from special conditions related to unmodified DNA oligonucleotides at low synthesis scales (genomics and 0.04 μmol scale), in general you have to fulfill two conditions:

1. Your annual volume/need is ≥ 100 oligonucleotides
2. You are prepared to purchase a certain amount of oligonucleotides within a 1-year period

Procedure: You estimate your annual need of oligonucleotides to your best knowledge \rightarrow we make you an offer \rightarrow you profit from the offered price upon your first order \rightarrow should you be significantly below or above your estimate following 1 year, we would make you a new proposal.

E.1.5 Unmodified RNA Oligonucleotides

We utilize state-of-the-art synthesizer and chemistry technologies in combination with various purification methods to offer you unmodified RNA oligonucleotides with 4 different purity levels:

Desalted Oligonucleotides

Synthesis Scale ¹	Length [nt]	Guaranteed Yield		Production Time [wd]
		[OD260] ²	[nmol] ³	
Genomics		not available		
0.04 µmol	10–30	4	21	2
0.2 µmol	10–50 ⁴	8	35	2
1.0 µmol	10–50 ⁴	18	80	2
15 µmol	10–40	400	1'800	3

HPLC Purified Oligonucleotides

Synthesis Scale ¹	Length [nt]	Guaranteed Yield		Production Time [wd]
		[OD260] ²	[nmol] ³	
Genomics		not available		
0.04 µmol	10–30	1	5	2
0.2 µmol	10–80	3	15	2
1.0 µmol	10–80	13	65	2
15 µmol	10–40	300	1'500	4

HPLC Purified & Dialysed Oligonucleotides

Synthesis Scale ¹	Length [nt]	Guaranteed Yield		Production Time [wd]
		[OD260] ²	[nmol] ³	
Genomics		not available		
0.04 µmol		not available		
0.2 µmol	10–80	2	10	4
1.0 µmol	10–80	9	45	4
15 µmol	10–40	200	1'000	4

PAGE Purified Oligonucleotides

Synthesis Scale ¹	Length [nt]	Guaranteed Yield		Production Time [wd]
		[OD260] ²	[nmol] ³	
Genomics		not available		
0.04 µmol		not available		
0.2 µmol	10–50 ⁴	1	5	2
1.0 µmol	10–50 ⁴	6	30	2
15 µmol		not available		

1) The synthesis scale represents the initial amount of 3' nucleotides (starting material).

2) Guaranteed and average yields in OD are valid for unmodified oligonucleotides >20 and <40 nucleotides only.

3) Yields indicated in nmol represent an example calculation for a 20mer. For this calculation the following rule of thumb equation was applied: nmol of oligonucleotide = OD × 100/length of oligonucleotide (calculation is based on sequences with virtually homogenous distribution of the 4 RNA nucleobases).

4) Oligos longer than 50 RNA nucleotides can be produced in combination with HPLC purification.

E.1.6 Modified RNA Oligonucleotides

Microsynth offers a wide variety of modifications (5', 3' and internal) for RNA oligonucleotides. If your desired modification is not listed in the following tables, please contact us for availability.

Dyes

Type of Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int.	0.04	0.2	1.0	DES	HPLC	PAGE
FAM ¹	X	X			X	X		X	X
Cy 3	X	X			X	X		X	
TAMRA ¹	X	X			X	X		X	X
Cy 5	X	X			X	X		X	
Cy 5.5	X	X			X	X		X	
Dyomics 681	X	X			X	X		X	
Cy 7	X	X			X	X		X	
Dyomics 781	X	X			X	X		X	

1) 5' modification also available in 0.04 μmol scale.

Quenchers

Type of Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int.	0.04	0.2	1.0	DES	HPLC	PAGE
BHQ-1/BHQ-2		X			X	X		X	X

Functional Groups

Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int.	0.04	0.2	1.0	DES	HPLC	PAGE
Amino	X	X	X	X	X	X	X	X	X
Phosphate	X	X		X	X	X	X	X	X
Phosphorothioate (PTO)			X	X	X	X	X	X	X

Bioactive Labels

Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int.	0.04	0.2	1.0	DES	HPLC	PAGE
Biotin	X	X			X	X		X	X
Digoxigenin	X	X			X	X		X	X
Cholesterol	X	X			X	X		X	X

Modified Nucleobases

Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int.	0.04	0.2	1.0	DES	HPLC	PAGE
RNA-Inosine (INO)		X	X		X	X		X	X
Deoxyuridine			X		X	X		X	X
Mixed Bases ¹			X		X	X		X	X
2'-O-Methyl-RNA			X	X	X	X	X	X	X
2'-Methoxyethyl-RNA (MOE)			X	X	X	X	X	X	X
2'-Fluoro-RNA			X	X	X	X	X	X	X
Inverted dA, dC, dG and dT			X		X	X		X	X

1) Available on request only.

Spacers

Modification	Position			Synthesis Scale [μmol]			Purification		
	5'	3'	Int.	0.04	0.2	1.0	DES	HPLC	PAGE
C3 Spacer		X	X		X	X		X	X
dSpacer (abasic site)			X		X	X		X	X

E.1.7 siRNA

siRNA, or small interfering ribonucleic acid, is a type of RNA that is involved in a number of biological processes, most notably RNA interference. RNA interference is a regulatory process that is used to control and limit the expression of specific genes. Regulatory active siRNA consists of annealed, complementary RNA sequences, usually 21-25 nucleotide in length and with symmetric 2 nucleotide 3' overhangs.

Chemical synthesis enables the incorporation of DNA nucleotides as overhangs thereby rendering the siRNA-duplex more stable against nuclease degradation.

Microsynth supplies siRNA duplexes from standard (2x21-mers) to extended length (2x27-mers) at different levels of purity and scales, depending on the intended application.

Advantages

- **Ready to use:** unmodified siRNA is manufactured as ready to use aqueous solution (40 μ M siRNA duplex, 10 mM NaCl, 10 mM TrisHCl, pH 7.5)
- **Easy-to-use siRNA design tool** for customized siRNAs*
- **Modified siRNAs** on request (e.g. 2'F, 3'GalNAc)

Synthesis Scale	Desalted		HPLC		PAGE	
	OD260	nmol	OD260	nmol	OD260	nmol
0.04 μ mol	9	21	4	8	not available	
0.2 μ mol	16	35	7	16	2	5
1.0 μ mol	36	84	16	45	5	11
Larger Scales	on request					

Classical siRNA duplexes (2x21-mers) have unit prices; if you need longer duplexes, each additional RNA base will be priced accordingly. Modified siRNAs are available upon request.

**To help you designing the most appropriate siRNA, targeting your gene of interest, Microsynth has developed a proprietary software, and made it available on its webshop. Microsynth's siRNA design tool is making use of the set of guidelines initially provided by Boese et al. The output of a design are various siRNAs ranked according to the Reynolds scores. The siRNA sequences with the highest scores can be selected and directly be ordered online. A link to NCBI BLAST is incorporated so you can properly manage the risk of potential off-target effects of the predicted siRNA.*

E.2 Special Synthesis Services

E.2.1 Antisense Oligonucleotides

Oligonucleotides to be used in antisense experiments must be modified to increase their resistance against nucleases. There are several possibilities to stabilize oligos and to avoid enzymatic degradation during *in vitro* or *in vivo* applications. Microsynth can offer you the following types of modifications:

- **PTO (phosphorothioates) modifications:** PTOs contain one sulfur atom in place of an oxygen atom in the internucleotide linkage of DNA or RNA. This modification of the normal phosphodiester backbone is characterized by an increased cell uptake, high nuclease resistance and elicitation of RNase H activity.
- **2'-O-Me-RNA modifications:** The incorporation of 2'-O-Methyl RNA nucleotides induces a resistance to a wide variety of nucleases, in particular RNase. Furthermore, 2'-OMe oligonucleotides show slightly increased affinity towards their complementary mRNA target sequence, thereby forming more stable hybrid duplexes compared to their non-modified DNA or RNA counterparts. This enables the formation of more stable hybrids with complementary RNA strands than would be the case for non-modified DNA and RNA sequences.
- **2'-MOE-RNA modifications:** Oligonucleotides incorporating 2'-O-methoxyethyl (MOE)-modified nucleotides can support most, if not all antisense mechanisms of action. Further key distinctive characteristics are nuclease resistance, lower toxicity, superior target binding specificity, as well as increased affinity towards complementary RNA. For more detailed information about 2'-MOE antisense oligonucleotides from Microsynth, please see the flyer on our website.
- **LNA modifications:** LNA containing oligonucleotides offer substantially increased affinity for its complementary strand, compared to traditional DNA or RNA oligonucleotides. This and the concomitant high nuclease resistance of LNAs results in unprecedented sensitivity and specificity and makes LNA oligonucleotides ideal for use in antisense applications.
- **S-cEt modifications:** cEt oligonucleotides (constrained ethyl nucleotides) are an advancement of LNA oligonucleotides. They have been developed for antisense applications and are mainly used in gapmers. Such ASOs show superior stability towards nuclease degradation compared to LNA without compromising binding selectivity or hybridization stability.
- **N-acetylgalactosamine (GalNAc):** Conjugation of N-acetylgalactosamine (GalNAc) has become a major clinical strategy for delivery of oligonucleotides to hepatocytes (liver cells). Such conjugates are efficiently internalized by binding to the asialoglycoprotein receptor (ASGR), which exhibits high affinity for N-acetyl galactosamine terminated oligosaccharides.

Modifications	Position			Synthesis Scale [μmol]				Purification ¹
	5'	3'	Int.	0.04	0.2	1.0	15	HPLC + Dialysis
PTO			X	X	X	X	X	X
2'-O-Me-RNA	X	X	X	X	X	X	X	X
2'-MOE-RNA	X	X	X	X	X	X	X	X
S-cEt ²	X	X	X	X	X	X	X	X
LNA	X	X	X	X	X	X	X	X
(GalNAc)3-Spacer ²		X			X	X	X	X

1) In case of *in vitro* experiments we strongly recommend selecting HPLC followed by dialysis as purification in order to achieve physiological condition. Desalted, HPLC and PAGE are also possible purifications (see page 25).

2) Available on request

Desalted ASOs¹

Synthesis Scale	Length [nt]	Guaranteed Yield		Production Time [wd]
		[OD260]	[nmol]	
0.04 µmol	13–30	3	15	2-3
0.2 µmol		10	50	2-3
1.0 µmol		30	150	2-3
15 µmol		600	3000	3-5

HPLC Purified ASOs

Synthesis Scale	Length [nt]	Guaranteed Yield ²		Production Time [wd]
		[OD260]	[nmol]	
0.04 µmol	13–30	1	5	3-4
0.2 µmol		3	15	3-4
1.0 µmol		10	50	3-4
15 µmol		300	1500	4-6

HPLC and Dialysis Purified ASOs

Synthesis Scale	Length [nt]	Guaranteed Yield ²		Production Time [wd]
		[OD260]	[nmol]	
0.04 µmol	13–30	-	-	
0.2 µmol		3	15	3-5
1.0 µmol		10	50	3-5
15 µmol		250	1250	5-7

PAGE Purified ASOs

Synthesis Scale	Length [nt]	Guaranteed Yield ²		Production Time [wd]
		[OD260]	[nmol]	
0.04 µmol	13–30	0.5	2.5	3-4
0.2 µmol		2	10	3-4
1.0 µmol		7	35	3-4
15 µmol		-	-	-

1) Desalted ASOs available for full MOE and full 2' OMe oligos (desalted not available for gapmers).

2) Guaranteed yields are shown for full MOE or full 2' OMe ASOs. For gapmers (MOE, LNA, 2' OMe) values might be different and are shown on the website.

E.2.2 DNA Oligonucleotides for NGS Applications

Do you need NGS adaptors, fusion, UDI or any other specific primers for your next generation sequencing project? Due to our vast experience in the area of oligonucleotide synthesis (>30 years) as well as next generation sequencing (>10 years), Microsynth has a thorough understanding of the stringent quality requirements for oligonucleotides to be used in the NGS field. Therefore, you will be in good hands at Microsynth when requesting NGS oligonucleotides only, or equally when outsourcing your entire NGS project.

Main Product Features and Benefits:

- **High purity:** specific HPLC purification approaches for minimizing the risk of cross-contamination.
- **Cost Effective:** Competitive pricing for volume as well as repetitive orders for oligonucleotides up to 80 nt.
- **Fast production:** down to 2-3 working days
- Availability of popular modifications (5'-Phosphate, PTO, 5-Me-dC etc.).
- **Broad applicability:** recommended for any kind of NGS application and tech-

nology (e.g. Illumina)

- Various delivery formats possible (dried, liquid, tubes, 96-well plates etc.)

Complementary Services:

- Analytical HPLC
- Certificate of Analysis
- Possibility to outsource the entire NGS project (from isolation to bioinformatics)

E.2.3 Click Chemistry

Click chemistry describes a thermodynamically favored reaction which enables quantitative and selective linkage of two different biomolecules. More precisely, the click reaction is a cycloaddition between an azide and an alkyne moiety either under copper-catalyzed or copper-free reaction conditions. The technology is reliable and stable which makes it an ideal oligonucleotide labeling method.

Characteristics of Click Chemistry:

- Reaction occurs in aqueous solution and at room temperature
- Stability toward H₂O, O₂, and most organic synthesis conditions
- Robust catalytic process
- No side reactions and lack of functional group interference
- Remarkable level of specificity for syntheses which require covalent linkage between two biochemical moieties.

Click Chemistry Modifications

Modifications	Position			Synthesis Scale [nmol]			Purification		
	5'	3'	Int.	0.04	0.2	1.0	Desalted	HPLC	PAGE
Azide-dT			X		X	X		X	X
3' Alkyne		X			X	X		X	X
5' Azide	X				X	X		X	X
3' Azide		X			X	X		X	X
5' DBCO	X				X	X		X	X
5' Hexynyl	X				X	X		X	X

E.3 Optional Services

E.3.1 Purification

Desalted

All our oligos are at least desalted to largely remove residual low molecular by-products arising and accumulating from the frequent chemical reactions during synthesis. Such purification is sufficient for oligonucleotides shorter than 30 and/or oligonucleotides used for non-critical applications

such as PCR, sequencing, probing, mobility shift or hybridization. However, desalted oligos are not recommended for use in molecular cloning projects.

Potential Applications:

- 1) PCR
- 2) DNA Sequencing
- 3) Probing
- 4) Mobility shift of hybridization

HPLC Purification

Oligos up to 80 bases in length can be well purified via reverse phase or anion exchange HPLC. Through this purification approach, preferably residual, n-x truncated oligos (lacking the hydrophobic DMT protection group at the 5' end) are

removed. This results in a $\geq 85\%$ purity of the targeted oligonucleotide. RP-HPLC is useful for a higher level of purity required for more demanding applications such as cloning, DNA fingerprinting, real-time PCR, FISH, etc.

Potential Applications:

- 1) Molecular cloning
- 2) DNA fingerprinting
- 3) Real-Time PCR
- 4) FISH

HPLC Purification & Dialysis

Dialysis as an add-on to HPLC is recommended if oligos need to be present in a physiological state. When performing

in vivo experiments (e.g. in mice) this purity level is strongly recommended.

Potential Applications:

- 1) Antisense experiments
- 2) Cell culture studies
- 3) Physical chemistry and structure analysis

PAGE Purification

Polyacrylamide gel electrophoresis (PAGE) purification is generally necessary for long oligos (>50 bases) and for all those primers with critical 5' sequences (restriction endonuclease sites, RNA promoters). It is the best method to differentiate full-length oligos from aborted sequences (n-1 oligos), based on size, conformation and charge. PAGE purification has an excellent resolution and yields a product that

is, on average, $\geq 95\%$ pure. In this context, it is important to note that the purity level declines with increasing length of the oligonucleotide, and this is particularly true for oligos >120 bases. PAGE purification is highly recommended for sensitive experiments such as cloning, mutagenesis, DNA fingerprinting, *in situ* hybridization, gene synthesis, etc.

Potential Applications:

- 1) Molecular cloning
- 2) Mutagenesis
- 3) DNA fingerprinting
- 4) *In situ* hybridization
- 5) Gene synthesis

E.3.2 Hydration

DNA/RNA Oligos are usually shipped in dry form. The dried DNA pellet becomes dislodged from the bottom of the tube during shipping and it can easily fly out of the tube when first opened, particularly as electrostatic attraction is present. For this reason: Always briefly centrifuge your oligos before opening for the first time, if you order oligos in dried format. If you

want your oligos already delivered in liquid format¹ at the commonly used 100 μM concentration (100 nmol/ml), you can easily select this option at our online shop for a small surcharge. Should you prefer to receive your oligos solubilized at a specific concentration and/or in a specific buffer, let us know and we will deliver according to your specifications.

siRNAs are usually delivered ready-to-use: fully deprotected, sense and antisense strand already annealed and in liquid format² at 40 μM concentration. Should you prefer to receive your siRNA in dried format or solubilized with a specific concentration/buffer, let us know.

¹ DNA and RNA oligos are dissolved in water, ² siRNA is annealed in 10 mM Tris, pH 7.5, 20 mM NaCl

E.3.3 Certificate of Analysis

In case the technical datasheet does not meet your requested level of documentation, Microsynth offers various types of CoAs for an extra charge. The standard CoA (Type 1) contains the following information:

- Appearance test by means of visual inspection
- Solubility test by means of solubilization in buffer prior to lyophilization
- Information about re-suspension of your oligo and the stability (shelf life at different storage conditions)
- Identity check by MALDI-TOF mass analysis including the mass spectrum
- Purity test by means of analytical HPLC including the chromatogram (if secondary structure is too strong, or oligo is >50 mer, we do not perform this analysis)
- Proof checked and signed by our head of oligonucleotide department or the delegated representative

In addition to the standard datasheet the following Certificate of Analysis (CoA) can be requested while ordering oligonucleotides:

Type	Description
1	Certificate of Analysis (complete)
2	CoA without declaration of oligonucleotide stability
3	CoA without MALDI TOF
4	CoA without analytical HPLC
5	Only MALDI TOF spectra
6	Only HPLC
7	CoA for ASO or PTO oligos (complete)

E.3.4 Customized Labels

Microsynth standard oligos are usually delivered in 2.0 ml tubes bearing a label with the oligo name, nucleotide sequence, order number, purification and production date.

Should you wish a customized label in order to identify, sort and manage your tubes more conveniently, please let us know. Microsynth is quite flexible in

designing labels that will meet your needs and are available for a small surcharge.

E.3.5 Mixing and Pooling

Preparing oligo mixes at the bench is usually a laborious and error-prone process due to manual handling. Whether you want to order a mixture of forward and reverse PCR primers or need a pool of hundreds

or even thousands of oligos, Microsynth can help. Our automated liquid handling systems can handle the most complex mixing and pooling projects.

Contact your sales manager with your needs, and he will consult you regarding the various possibilities and pricing.

E.3.6 Delivery in 2D Storage Tubes

When working with higher numbers of oligos, storage solutions ensuring sample traceability, sample security and optimal performance become increasingly important. Whether you need to securely store

and keep track of hundreds or thousands of oligos, Microsynth can deliver your oligos in 2D barcoded storage tubes.

Contact your sales manager with your ideas of implementing an optimized storage solution for your oligos, and he will consult you regarding the various possibilities and pricing.

E.4 Contract Manufacturing

E.4.1 Oligonucleotides for Use in IVD

Transitioning oligonucleotides from research to in vitro diagnostics (IVD) applications — where reagent quality may have an influence on critical medical decisions — involves a lot more than merely figuring out how to scale up production. With more than three decades of experience in oligonucleotide synthesis and nucleic acid ana-

lytics, we at Microsynth have established our company as a reliable business partner for contract manufacturing of oligo components for in vitro diagnostic suppliers. Our state-of-the-art laboratories, superior quality reagents, stringent quality standards, and fully customizable manufacturing processes make us the ideal partner for

diagnostic test manufacturers. Microsynth is certified according to EN ISO 13485:2016, which is a formal recognition of our competence when it comes to the production and distribution of nucleic acids and components for IVD manufacturers.

Our customers benefit from the following main advantages:

- Cost-effective and customized customer solutions
- Scalability (all phases from product development all the way through to manufacturing are covered)
- Professional project management
- Full process traceability and risk mitigation
- Consistent lot-to-lot reproducibility



E.4.2 Therapeutic Oligonucleotides

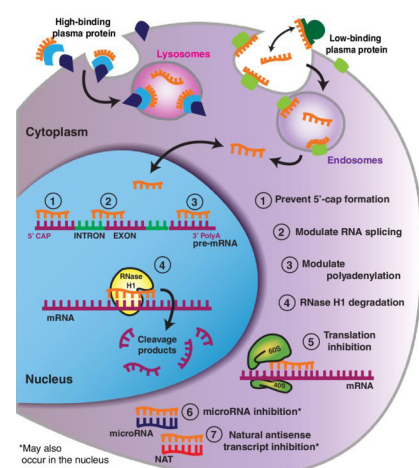
Several oligonucleotide-based drugs have been approved by regulatory agencies (FDA, EMEA) during the past two decades. Antisense and RNAi therapeutics – which are currently amongst the hottest topics in research and development – are forms of treatments that are clearly distinguished from traditional approaches such as small

molecule or antibody-based approaches. Since they can be directed against a broad variety of RNA targets (pre-mRNA, mRNA, lncRNA, miRNA), they open the door to the treatment of a wide range of diseases, as well as diseases that are considered undruggable on the protein level. Microsynth, which has proven to be a well-

renowned oligo supplier for more than three decades, has developed technical capabilities and expertise for offering a portfolio of therapeutic oligonucleotides that are especially suited for leveraging your early drug discovery program in this field.

Our customers benefit from the following main advantages:

- A high level of expertise and experience in the synthesis of oligonucleotides (ASOs, gapmers, siRNAs, anti-microRNAs, aptamers, and CpG oligos) for drug discovery
- The best approach for the chemical synthesis using a broad portfolio of modifications (e.g. MOE, LNA, 2'-O-MetRNA, constrained ethyl, 3' GalNAC, etc.)
- Fast supply available with products delivered at exceptional speed
- A sustainable and cost-efficient setup – from infrastructure to processes and systems
- A fast, flexible, and reliable service from quote to delivery



DNA/RNA Analysis & Sequencing

With more than 30 years of experience in DNA Sanger sequencing, Microsynth has become one of the leading sequencing suppliers in Europe. Since 15 years Microsynth has also been active in next generation sequencing and has gained extensive knowledge in sequencing and bioinformatics. Beyond DNA sequencing, Microsynth has built up critical expertise in related analytical areas such as nucleic acids isolation, PCR (from classical PCR and qPCR to digital PCR) and genotyping (e.g. STR DNA profiling, genotyping by sequencing).

F.1 DNA/RNA Isolation

Microsynth relies on more than 16 years of experience in DNA/RNA isolation from different and difficult matrices like plant material, environmental samples or stool, etc. Our know-how in this area will help you to focus on the data analysis and interpretation rather than expending time and effort on optimizing your DNA/RNA isolation approach.

Each Microsynth nucleic acid isolation protocol includes the following four key factors:

1. Effective pre-isolation handling of the sample to allow high-yield nucleic acid isolation
2. Adequate choice of the isolation procedure specific for the matrix type
3. Validated workflow
4. Quality control of the isolated nucleic acids

The following table gives you an overview of the various matrices where we have solid experience in isolating DNA, RNA or plasmid DNA. We are also able to develop high-throughput isolation protocols for our customers due to our knowledge in laboratory automation.

Sample Matrix	Description
Industry Products	
Organic and inorganic chemical products	Powders, liquids, gels, complex and demanding chemical composition
Biotechnological products	Robust validated methods fit for purpose
Drug products	Raw material and finished products
Biological Fluids, Cells and Solid Tissues	
Cell culture	Animal, supernatants (viral)
Animal soft tissues & cells	Liver, brain, lung, heart, kidney, spleen
Animal hard tissues	Bones, teeth, shells
Animal integumentary system	Feathers, hair, fin, etc.
Body fluids	Blood, lymphocytes, plasma, urine, mucus, cerebrospinal fluid, saliva
Fixed tissues	FFPE and glass-slide samples
Medical samples	Ichor, collections and biobanks
Tough to Lyse	
Plants and seeds	Fresh, dried and herbarium samples
Fungi	Mycelium, fruiting body
Culture	Fungal, bacterial, archeal, supernatants (phage)
Environmental samples	Biofilm, fecal, scat, soil (clay, loam, aquifer, sediments, potting soil, sand, sewer sludge, manure, compost, marine sediments), water
Plasmid DNA Purification	
<i>E. coli</i>	Mini-, Midi-, Maxi-, Gigaprep scales, BAC, YAC, PAC plasmid
Yeast	Miniprep scale

F.2 DNA Sanger Sequencing

With 30 years of experience in DNA Sanger sequencing, Microsynth has become one of the leading sequencing suppliers in Europe. Microsynth is proud to offer its customers a high-quality Sanger sequencing service. By having established labs in Switzerland, Austria, Germany and France, we can offer this service with unmatched speed and environmentally friendly pickup service in those countries. Microsynth's decentralized approach results in shorter shipment distances and consequently the predominant use of bicycle/train-based courier logistics. With the Ecoli NightSeq®, Microsynth has developed an innovative new service for the sequencing of plasmids that does not require plasmid preparation.

General Features and Benefits:

- **Read length** per run: **up to 1100 bases** or more in PHRED20 quality
- **Free sample shipment** via Microsynth drop boxes or prepaid envelopes
- Standard (>90) but also specific **primers** can be **added** to your sample **free of charge**
- Fast **in-house sequencing primer synthesis**
- Possibility to **fine-tune software analysis parameters** to achieve your desired performance
- **Special protocols** for plasmids with severe hairpin structures **free of charge**
- **Storage of primers up to 10 months**
- **Online archive** with 3 months of data access

- **Useful information for initial troubleshooting** is provided automatically for sequencing results that are difficult to sequence
- Direct access to **support by experienced academic staff**
- **Helpful online tools** enabling you to oversee your stock of labels and primers but also to share it among your group members
- **ISO 9001** and, on request, **ISO/IEC 17025 accredited** or **GMP sequencing**

A key feature of the Microsynth Sanger sequencing service is the great flexibility regarding the utilization, handling and storage of sequencing primers. The following table shows and describes the various primer sources you can use. Apart from "Order Now" and "Design at Microsynth", all other services are free of charge.

Name	Description
Premixed Primer	Primer added by customer.
Standard Primer List	Primer added by us (select your sequencing primer from a list of >90 standard primers which are stored at Microsynth).
Enclosed in Separate Tube	Primer added by us. Customer ships primer and DNA in separate tubes to Microsynth.
Stored at Microsynth	Primer added by us. Prerequisite for this option: You have already used the primer in the past. Your primer is stored for 4 months at our site.
Custom Primer List	Primer added by us. This option is an add-on to the option "Stored at Microsynth". If you know that a primer will be used frequently in future orders, send us a larger volume of this primer (at least 200 µl) and add it to your custom primer list. We will then store it for an extended period of time (up to 10 months).
Order Now	Primer added by us. Via this option you can order a new primer already during the order process. Microsynth produces your primer while your DNA is on the way to our sequencing lab.
Design at Microsynth	Primer added by us. This option is similar to "Order Now". In addition to the primer synthesis, we also perform the primer design. You only need to send us an email with a primer target sequence of 50–200 bases.

F.2.1 Single Tube Sequencing

Service-Specific Features for Single Tube Sequencing at a Glance

Service Features	Economy Run	Ecoli NightSeq®	Premium Run
Template source	Isolated plasmids, PCRs (purified/unpurified)	<i>E. coli</i> , gram-negative bacteria, plasmids ¹	Plasmids, BACs, cosmids and fosmids, PCRs
Speed and time saving in the laboratory		1 day compared to Economy Run (<i>E. coli</i>) and Premium Run (<i>E. coli</i>) ²	
Read length per run in PHRED 20 quality	up to 1'100 nt or more	up to 1'100 nt or more	up to 1'100 nt or more
Upfront template prep or purification possible	yes ³	included	yes ³
Sample inspection and concentration adjustment	no	not necessary	yes
Applicability of special sequencing protocols	yes	yes	yes
Sequencing of low sample amounts	no	yes	yes
Multiple sequencing out of one tube	yes	yes	yes
Results delivery following sample receipt	MON-SAT	MON-FRI	MON-FRI
	before 8 AM next day	before 2 PM next day	next day
Data delivery via email	available	available	available
Re-run of failed reactions free of charge ⁴	available	available	available
Technical support & troubleshooting	standard	standard	extended & comprehensive
Storage time of samples	4 days	1 month	3 months
Storage time of specific primers	4-10 months	4-10 months	4-10 months
Payment mode	prepaid & non-prepaid	prepaid & non-prepaid	non-prepaid

1) Traces of plasmid DNA are sufficient to gain high-quality sequencing results.

2) The Ecoli NightSeq® is currently the fastest service for plasmid sequencing on the market, in case you have access to a drop box in Switzerland, Germany or France that is connected to our same-day courier system.

3) Additional charges apply.

4) In general, Microsynth automatically repeats failed sequencing reactions when an improvement potential is detected and the sample meets the sample requirements (concentration range). In addition, it is always possible to ask for specific repetitions of failed reactions (preferably by phone or e-mail).

Economy Run

Best-in-class Sanger sequencing service in 1.5 ml tubes for routine but also most difficult-to-sequence PCR products and plas-

mids. This service is available in a prepaid and non-prepaid version.

Main Service Features and Benefits:
See page 29 as well as table above.

Sample Requirements

General Information

DNA samples and sequencing primers can be sent premixed (within one tube) or separately (different tubes). Each DNA sample should have a volume of 12 µl. In case you wish that Microsynth adds your sequencing primer, please make sure that you send us sufficient amounts of your primer solu-

tion (minimally 20 µl of a 10 µM solution; in case you want to store your primer at our lab, consider that each sequencing reaction consumes about 3 µl). DNA samples and primers for sequencing reactions are preferentially dissolved in pure water. Alternatively, 10 mM Tris-HCl (pH 8) with a maximum of 0.5 mM EDTA can be used for a better long-term DNA stability. Standard

TE-buffer is not suitable, because higher EDTA concentrations inhibit polymerase activity. Your templates will be stored for 4 days whereas your specific sequencing primers will be kept at our sequencing lab for at least 4 months (or for 10 months in case you have added them to your "Custom Primer List").

Sample Amounts and Concentrations

DNA Template	Concentration	Pipetting Scheme for Premixed Option
Plasmid ¹	40–100 ng/μl	12 μl DNA template solution + 3 μl sequencing primer solution (20μM) ³
PCR Products ²	General Rule: 1.5 ng/μl per 100 bp	
Length 100 - 400 bp	2 - 6 ng/μl	
Length 401 - 900 bp	4 - 17 ng/μl	
Length 901 - 2000 bp	12 - 70 ng/μl	
Primer (premixed)	4 pmol/μl = 4 μM	
Primer (separate)	10 pmol/μl = 10 μM	

- 1) Optimal plasmid concentration is 80 ng/μl.
- 2) Regardless of whether the PCR is purified or non-purified.
- 3) The addition of 3 μl of a 20 μM primer solution instead of a 10 μM primer solution to 12 μl DNA template solution (premixed option) usually leads to more robust sequencing results.

Overnight Sequencing

Customers in Switzerland, Germany, Austria and France with direct access to a Microsynth drop box may benefit from our overnight sequencing service. Samples

are processed overnight and results are ready for download before 8 AM in the morning of the next working day (you will be informed by email once your results are available). Please contact us in order to find

out if an overnight service is possible for your location. As a registered customer you will find the information under Options & Preferences, Show Nearest Collection Points on the webshop.

Ecoli NightSeq®

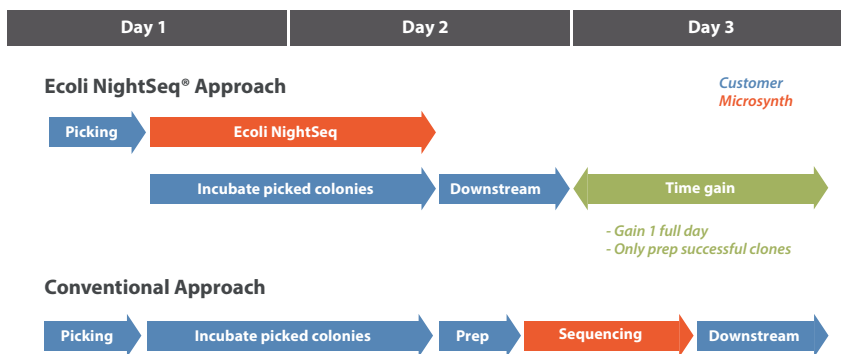
Innovative new Sanger sequencing service in 1.5 ml tubes for plasmids. Drop your *E. coli* colonies into a Microsynth drop box, receive your result the next working day before 2 PM and accelerate your research by one day.

New Standard in *E. coli* Sequencing: Game-changing new service from Microsynth. Save handling time in the lab and significantly reduce your expenditures on plasmid DNA purification kits by only isolating plasmids from clones showing the desired sequencing result. Get results with greater robustness.

Overnight Sequencing Customers in Switzerland, Germany and France with direct access to a Microsynth drop box may benefit from our overnight sequencing service. Please contact us to find out if an overnight service is possible for your location.

Main Service Features and Benefits.

See page 29 as well as table at the top of page 30.



Comparison of the conventional with the new Ecoli NightSeq® approach. Send us your *E. coli* colonies directly. After receiving the sequencing results, isolate only the plasmids from relevant clones and win one extra day.

Sample Requirements

Grow your *E. coli* on agar plates long enough to have a colony diameter of at least 1 mm. This will ensure a high cell density and is a prerequisite for reliable

sequencing. Use a toothpick or something similar to take as much as possible of the *E. coli* colony and inoculate it into our tube. Use the same toothpick to inoculate your masterplate or a liquid culture which

can be used straight away for your downstream process as soon as you get the sequencing results.

Premium Run

Looking for a personalized sequencing service that includes comprehensive customer support and troubleshooting? Need a top-quality sequencing service that is

able to decode even difficult sequences? Then we recommend taking a closer look at our Premium Run Service.

Main Service Features and Benefits:

See page 29 as well as table at the top of page 30.

Sample Requirements

General Information

Each DNA sample and each primer must have a **minimum volume of 20 µl**. DNA samples and primers for sequencing reactions are preferentially dissolved in pure

water. Alternatively, 10 mM Tris-HCl (pH 8) with a maximum of 0.5 mM EDTA can be used for a better long-term DNA stability. Standard TE-buffer is not suitable, because higher EDTA concentrations inhibit sequencing polymerase activity. Your tem-

plates will be stored for 3 months, whereas your specific sequencing primers will be kept at our sequencing lab for at least 4 months (or for 10 months in case you have added them to your "Custom Primer List".)

Sample Amounts per Sequencing Reaction and Concentration

Same as for the Economy Run (see table on page 31).

F.2.2 Plate Sequencing

Service-Specific Features for Plate Sequencing at a Glance

Service Features	Economy Run	Economy Run Plus	Ecoli NightSeq®
Template source	<i>E. coli</i> , plasmids, PCRs	<i>E. coli</i> and unpurified PCRs	<i>E. coli</i> , gram-negative bacteria, plasmids
Speed and time saving in the laboratory			1 day compared to Economy Run (<i>E. coli</i>) and Economy Run Plus (<i>E. coli</i>)
Read length per run in PHRED 20 quality	up to 1'100 nt or more	up to 1'100 nt or more	up to 1'100 nt or more
Upfront template prep or purification possible	yes (non-prepaid service)	included	included
Applicability of special sequencing protocols	yes	yes	yes
Sequencing of low sample amounts	no	no	yes
Multiple sequencing out of one well ¹	yes (all samples)	yes (all samples)	yes (all samples)
Results delivery following sample receipt	MON-SAT	MON-SAT	MON-FRI
	next day ²	day after next	from 3 PM on next day
Data delivery via email	available	available	available
Re-run of failed reactions free of charge ³	on request	on request	on request
Technical support and troubleshooting	standard	standard	standard
Storage time of samples	1 month	1 month	1 month
Storage time of specific primers	4 - 10 months	4 - 10 months	4 - 10 months
Return delivery of isolated plasmids to customer ³	yes	yes	on request
Colony picking from agar plates into high throughput 96-well plates	on project basis	on project basis	
Generation of glycerol stocks	on project basis	on project basis	
Plasmid isolation at larger scales (Midi/Maxi) from selected clones	on project basis	on project basis	
Sequencing of large DNA constructs such as BACs, cosmids and fosmids	on project basis	on project basis	
Payment mode	prepaid & non-prepaid	prepaid only	prepaid & non-prepaid

1) Additional charges apply.

2) Applicable only for purified PCRs and isolated plasmids that arrive at our facility in the early morning (no overnight sequencing possible!).

3) In general, Microsynth automatically repeats failed sequencing reactions when an improvement potential is detected and the sample meets the sample requirements (concentration range). In addition, it is always possible to ask for specific repetitions of failed reactions (preferably by phone or e-mail).

Economy Run

Do you have relatively high numbers (≥ 24) of PCR products or plasmids that can or need to be sequenced in parallel? And furthermore, have you come to the con-

clusion that you want to do the purification yourself? Then we recommend our Economy Run for 96- and, on request, 384-well plates.

Main Service Features and Benefits:
See page 29 as well as the table above.

Sample Requirements

Please provide at least 10 μ l/well in 96-well plates. See the table "Sample Amounts and Concentrations" on page 31 for information on sample and primer concentrations.

Economy Run Plus

Best-in-class Sanger sequencing service in 96-well plates for PCR products and plasmids. The Economy Run Plus includes plasmid isolation from *E. coli* or PCR puri-

fication. This prepaid service (per plate pricing) is very popular due to its excellent price-performance ratio.

Main Service Features and Benefits:

See page 29 as well as the table on page 33.

Sample Requirements

Non-purified PCR Products

PCR reactions can be sent directly after PCR in their reaction buffer at room temperature (RT) in the barcoded 96-well plate. The only requirement is that you check the quality of the sample on an agarose gel (a random subset is sufficient; at least one sample per PCR primer pair) before shipment. To obtain optimal sequencing

results, it is important that all samples are in the recommended concentration range.

E. coli Cells (for Isolation of Plasmids at our Laboratories)

If you send us *E. coli* cells, we recommend that you ship them in the barcoded 96-well plate within Luria Broth (LB) medium (or similar) at RT. Please make sure that your cells are incubated in 50 µl medium (con-

taining the appropriate antibiotics!) for at least 3-4 hours with gentle shaking at 37° C prior to shipping. If no shaker is available at your lab, please let us know. We then perform a longer incubation at our lab.

Ecoli NightSeq®

Innovative new Sanger sequencing service in 96-well plates for plasmids. Drop your *E. coli* colonies into a Microsynth drop box, receive your result the next working day from 3 pm on and accelerate your research by one day.

Overnight Sequencing

Customers in Switzerland and Germany with direct access to a Microsynth or Microsynth Seqlab drop box may benefit from our overnight sequencing service. Please contact us to figure out if an overnight service is possible for your location.

Main Service Features and Benefits:

See page 29 as well as the table on page 33.

Sample Requirements

Grow your *E. coli* on agar plates long enough to have a colony diameter of at least 1 mm. This will ensure a high cell density and is a prerequisite for reliable

sequencing. Use a toothpick or something similar to take as much as possible of the *E. coli* colony and inoculate it into our plates. Use the same toothpick to inoculate your masterplate. Alternatively you can also use

5 µl of a bacterial suspension (e.g. LB liquid culture) or 1 µl of plasmid DNA (if concentrations are extremely low).

Ready-to-Load Run

Convenient and cost-effective Sanger sequencing service in 96-well plates for ready-to-load plates. This service is particularly suitable for customers who have a workflow in their lab for sample preparation, cycling and purification and just want to outsource the actual analysis.

Main Service Features and Benefits:

- Rapid turnaround time: sequencing time in the lab down to 3 h, depending on the amount of samples
- Very cost-effective Sanger sequencing service

Complementary Services:

- 96-well or 386-well plates can be provided upon request.

Sample Requirements:

Sample preparation, cycling and purification according to protocols from Applied Biosystems. Deliver samples dissolved in

water or formamide in 96-well or 384-well reaction plates compatible with Applied Biosystems 3730xl devices.

F.2.3 Advanced Services

GMP-Compliant Sanger Sequencing

Established cGMP Sanger sequencing service¹ for release testing of regulated biological drugs as well as for validation of DNA-based diagnostic tests/devices for market clearance applications. Whether you wish to make a European or FDA-level submissions, Microsynth's quality system has been set up to meet the most stringent quality requirements from regulatory authorities worldwide.

Our GMP DNA sequencing service have been established to support our customers in the following areas:

- **GMP Biologics Lot Release:** Sanger sequencing is applied as QC for final lot release of plasmid DNA and viral products used for biologics manufacturing
- **DNA/RNA identity and stability studies:** Sanger sequencing is used for identity and stability tests of various cell banks, plasmids, viruses and vaccines
- **Genetic testing for preclinical and clinical testing:** Sanger sequencing is utilized as "Gold Standard" method to analyze clinical trial samples (e.g. for SNP detection) or to validate assays to be used in preclinical or clinical trials
- **Validation of in vitro DNA-based diagnostic assays:** Sanger sequencing is used as "Gold Standard" method to validate nucleic acid based diagnostic assays or devices for regulatory clearance.

1) The certificate of GMP compliance has been granted by Swissmedic and is restricted to DNA sequencing by the Sanger method.

Main Service Features and Benefits:

- **2-fold or 4-fold coverage** sequencing service available
- All analyses performed according to **GMP requirements**
- **Extended GMP project reporting**
- Each project is guided by a designated study director
- Fast turnover time due to in-house synthesis of primers
- Guaranteed accuracy of final data >99.999% per base
- Sequence verification against a known reference sequence including mutation detection or de novo sequencing
- Evaluation of each chromatogram
- Assembly of sequence data and detailed sequencing strategy reporting
- Quality assurance statement (ISO/IEC 17025 (STS 429) and GMP Swissmedic 20-0362)
- Archiving of samples and data for 10 years (longer times available on request)

Primer Walking

Fast and comfortable Sanger sequencing service for DNA templates longer than 1'400 bases. By sequencing from both ends, we advance about 1600 base pairs

per day and can help our clients to:

- Confirm the sequence integrity of your clone or PCR products
- Examine failed amplifications and incorrect restriction digest pattern
- Sequence full length AAV plasmids and hard to sequence ITR regions

Main Service Features and Benefits:

- Fast in-house design and synthesis of primers
- Fast sequencing: **up to 1600 base pairs per day** (even faster when a reference sequence is available)
- Option to choose single-stranded (SS) and double-stranded (DS)¹ sequencing
- Editing and accurate assembly of single sequences
- Delivery of electronic files such as project data sheet including sequencing strategy, text files and chromatograms for each single reaction
- **Free verification** of an assembled sequence with the original sequence. Condition: You must send us a reference sequence. In case of PCR products, you must select double-stranded sequencing.

1) In the double-stranded Primer Walking Service both strands of your DNA sample are sequenced and compared. In this way an accuracy of at least 99.99% per base is achieved.

Clone & Sequence

PCR amplification of heterogeneous biological samples results in a heterogeneous mixture of PCR products (e.g. ribosomal 16S PCR generated from stool or soil samples). In order to be able to sequence individual PCR products by DNA Sanger sequencing, it is first necessary to clone them. At Microsynth, we are able to

perform the entire process of cloning and sequencing, no matter how many clones your sequencing project may require.

Beyond Sanger DNA sequencing, we are also able to offer you comprehensive next generation sequencing services. In general, a next generation sequencing

approach allows to circumvent the cloning step and becomes more economical with increasing sample numbers and throughput requirements. Please contact us to figure out which approach best fits your needs.

Exon Sequencing & Mutation Detection

Are you interested in identifying (point) mutations in genes or exons with great accuracy on a nucleotide level? Then we recommend our Exon Sequencing & Mutation Detection Service.

Main Service Features and Benefits:

- Project management and consulting
- PCR amplification of exons
- Double-stranded sequencing of the resulting PCR products
- Mutation reports

F.3 Next Generation Sequencing

F.3.1 Overview and Key Application Areas

Microsynth can offer you a broad spectrum of applications in the area of next generation sequencing.

The image below gives you a rough overview of our NGS core domains. As NGS is still a very dynamic field, please do not hesitate to inquire about additional or customized applications. Focused on but not restricted to Illumina sequencing platforms and with a long-standing experience in SOLiD, 454 and PacBio sequencing, Microsynth is happy to advise you in picking the right strategy and technology for your application. Discussing your project with our NGS experts will help

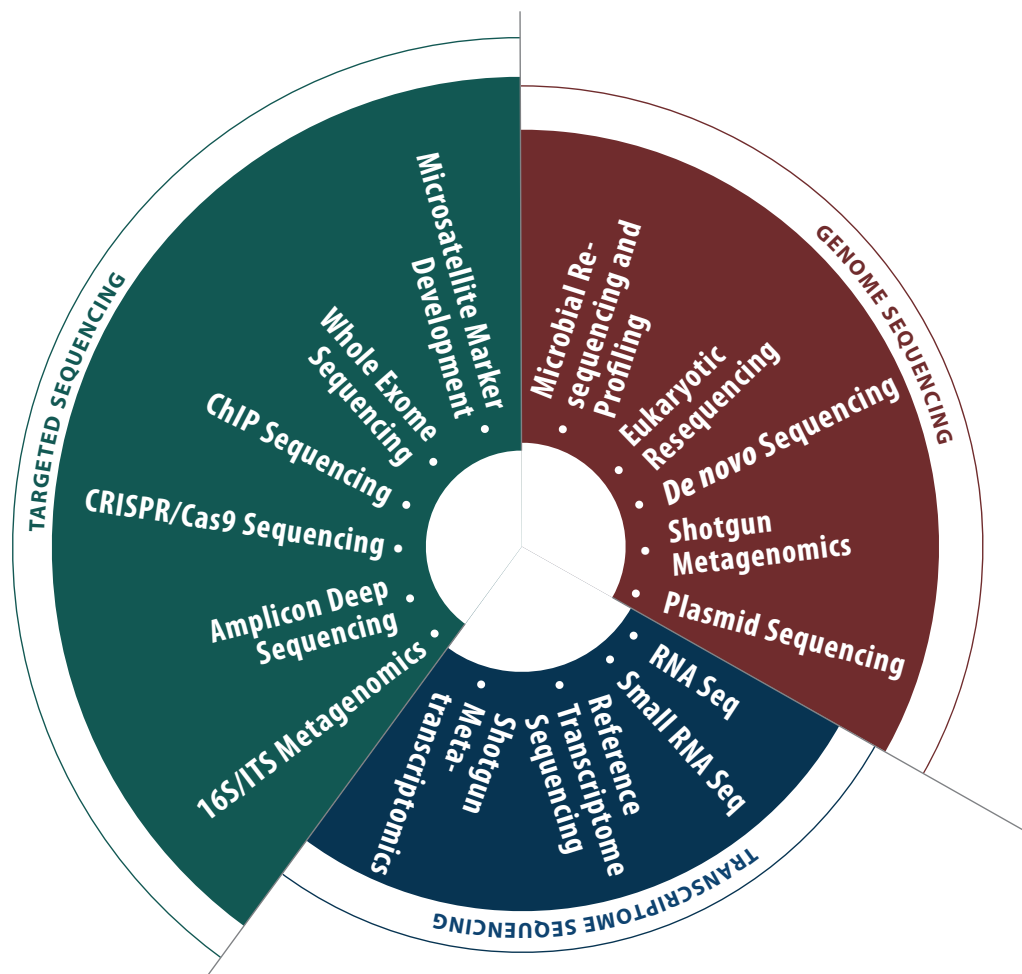
you to find the optimal approach for your project. Next generation sequencing at Microsynth means that you will get much more than the access to state-of-the-art NGS technologies. You can rely on our profound expertise and our more than 30 years of experience in DNA sequencing as well as related molecular biology knowledge such as DNA/RNA isolation, PCR/real-time PCR analysis and/or synthesis of DNA oligonucleotides.

In addition, you can expect extensive consultation during the entire phase of your NGS project. A study manager is interacting with you but also internally with

a team of molecular biology experts and bioinformaticians to ensure that your project is optimally designed and carefully executed.

For analyzing your sequencing data, you can make use of our in-depth bioinformatics know-how and solutions, irrespective of the data source (whether data was generated by Microsynth or not).

Hence, your sequencing project will be in good hands at Microsynth and we do everything possible to deliver you high-quality results as basis for your further ongoing scientific work.



F.3.2 Project Consultation

The result and impact of a study depends on its experimental design. Therefore let our expert teams guide you in choosing the most suitable technological setup

and accompany your experiment with knowhow to make it a success. If your project involves our bioinformatics services, our experts will guide you through

the results and ensure that you get the most out of the data gathered.

F.3.3 Library Preparation and Sequencing

Depending on the requirements of your project, the DNA/RNA input material is prepared with the most suitable protocol and sequencing is performed on one of our Illumina platforms (MiSeq, NextSeq

500/550 or NovaSeq) which support high read throughput and variable read lengths. If very long reads are required to close gaps in bacterial genomes or to sequence full length 16S amplicons for instance then

long read sequencing can also be offered. Check the table on page 40 to learn more about the short turnaround times of Microsynth.

F.3.4 Bioinformatics Analysis

Microsynth bioinformatics services are divided into stand-alone and complementary service modules. The latter offer valuable additional information to the stand-alone services, especially in a given experimental context (e.g. comparative analysis). All our service modules may also be applied on sequencing data obtained elsewhere. Microsynth uses community

accepted, peer-reviewed open source software wherever possible. Standard data formats are utilized to facilitate publication, to enable downstream analysis and further deployment and long-term usability of the data. Essential results are presented as an interactive and user-friendly HTML report to guide you through the data. As a consequence, our bioinformat-

ics services spare you laborious low level data handling, parametrization, necessary computational power and in turn provides you with state-of-the-art bioinformatics expertise to handle NGS projects in a professional manner.

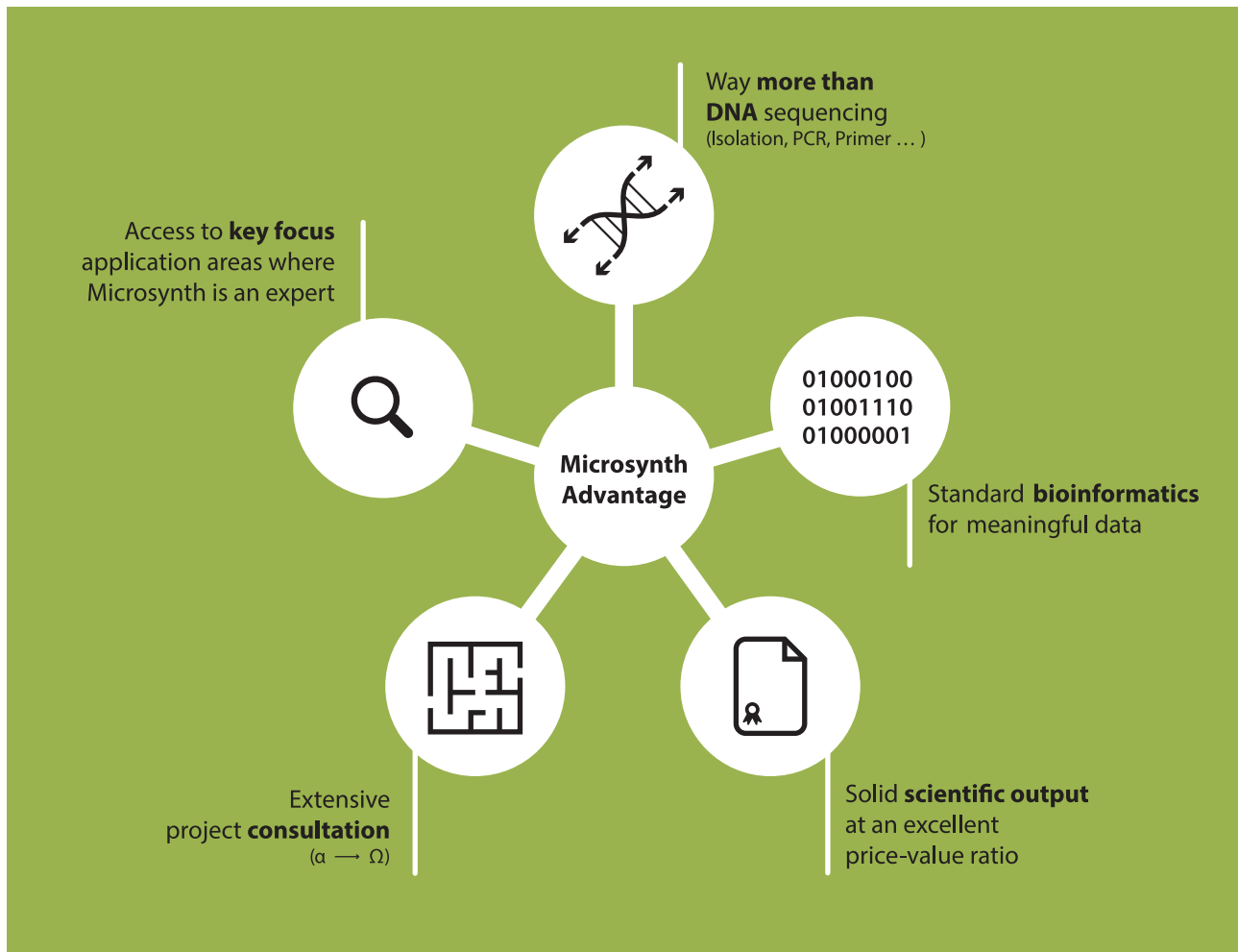
F.3.5 Complementary Services

Make use of the synergy we provide with our profound know-how and diverse technology portfolio. For instance, you may verify Microsynth's NGS results by Microsynth's Sanger sequencing.

Further Complementary Services:

- DNA/RNA isolation
- PCR, digital and qPCR services
- Synthesis of NGS primers

F.3.6 The Microsynth Advantage



F.3.7 Practical Information

Shipping Address

Microsynth AG
Next Generation Sequencing
Schützenstrasse 15
9436 Balgach
Switzerland

Shipment Recommendations

We recommend shipping the samples at ambient temperature/with ice pack (gDNA and PCR products) or frozen on dry ice (RNA). Please use properly sealed 96-well plates for larger sample amounts (more information on our website).

Buffer Recommendations

DNA: 10 mM Tris-HCl buffer (pH 7.5–8.5)
RNA: 10 mM Tris-HCl buffer (pH 7.0)

Sample Amounts Required for Illumina Sequencing

Type of Library	Amount (µg)	Concentration (ng/µl)
DNA for Illumina tagmentation library	>0.075	>2
DNA for TruSeq library	>0.5	>10
DNA for Illumina DNA Library	>0.5	>10
RNA for RNASeq library (poly(A) enriched)	>1	>20
RNA for RNASeq library (ribo depletion)	>3	>20
DNA for amplicon preparation (e.g. 16s rDNA or ITS analysis)	>0.1	>05
1st or 2nd step Nextera PCR product	>0.2	>05
Ready-to-sequence amplicon library *	>0.2	>10
ChIP-Seq libraries (req. ChIP DNA)	>0.05	>05
miRNA/small RNA (req. total RNA)	>3	>200
low input RNA (req. total RNA)	>0.01	>01

* for single samples to be pooled >50 ng and >5 ng/µl per sample

Sample Amounts Required for PacBio Sequencing

Type of Library	Amount (µg)	Concentration (ng/µl)
DNA Library	>10	>300

DNA/RNA Quantification

DNA/RNA quantification is recommended to be done by a fluorometric method, e.g. PicoGreen®, RiboGreen®, Qubit® etc.

DNA Quality Control

On each received sample, Microsynth performs a complete quality control prior to further sequencing steps. However, we do recommend that you also check your DNA on a gel or on the Bioanalyzer to

allow a straightforward approach for your sequencing project. If you do so, please provide us with the gel picture or trace file as well.

Turnaround Times for Different Applications (Illumina Sequencing)

Service	Service Group	Turnaround Times in Weeks ¹ Library Preparation /Sequencing/ Bioinformatics
Microbial Resequencing and Profiling	Genome Sequencing	2/2/1
Eukaryotic Resequencing	Genome Sequencing	2/2/2
De Novo Sequencing	Genome Sequencing	2/2/3
Shotgun Metagenomics	Genome Sequencing	3/2/3
Plasmid Sequencing	Genome Sequencing	2/2/1
RNA Sequencing	Transcriptome Sequencing	3/2/1
Small RNA Sequencing	Transcriptome Sequencing	3/2/2
Reference Transcriptome Sequencing	Transcriptome Sequencing	4/2/2
16S/ITS Metagenomics	Targeted Sequencing	2/2/1
Amplicon Deep Sequencing	Targeted Sequencing	3/2/2
CRISPR/Cas9 Sequencing	Targeted Sequencing	3/2/2
ChIP Sequencing	Targeted Sequencing	3/2/2
Whole Exome Sequencing	Targeted Sequencing	on request

1) Express service possible on request.

F.4 Digital PCR and Real-Time PCR

Microsynth, a leading provider of molecular biology services, offers a broad range of PCR services and products. More than 20 years of experience with customer projects of any size, our in-depth understanding of DNA/RNA quantification and our in-house

production facility for oligonucleotides qualify Microsynth as your partner of choice for the development and validation of qPCR and digital PCR assays. Microsynth is also a competent and reliable partner for the subsequent performance of biological

analyses, regardless of scale.

For further information, see **G5 Contract Research / Outsourcing** (pages 47 - 50).

F.4.1 qPCR/dPCR Assay Development

With Microsynth, you can order your **customized** and **MIQE-compliant qPCR** or **digital PCR assay** at very attractive prices and unbeatable delivery times.

Main Features and Benefits:

- Strong experience in digital PCR and qPCR assay design and validation
- High quality: Real-time and digital PCR assays with proven functionality due to

comprehensive testing using a specific positive control as well as a no template control

- Optimal functionality: we design, synthesize and test your primer set(s) for their PCR performance
- Cost effective
- Easy publishing due to compliance with MIQE guidelines (full transparency with respect to sequence information of used

primer and probes)

- Very fast delivery: You will receive your functional singleplex PCR assay within 1-3 weeks after the order.

Potential Applications:

Applications including absolute quantification, relative quantification, SNP genotyping, and presence/absence tests.

Available Assay Types:

Assay Type	Deliverables
Singleplex TaqMan qPCR Assays	Lyophilized probe & primer pair (>1000 reactions); Positive control; All information regarding sequence, scale, purification and yield
Singleplex SYBR Green qPCR Assays	Primer pair (>1000 reactions); Positive control; All information regarding sequence, scale, purification and yield
Singleplex TaqMan digital PCR Assays	Lyophilized probe & primer pair (>1000 reactions); Positive control; All information regarding sequence, scale, purification and yield
Singleplex EvaGreen digital PCR Assays	Primer pair (>1000 reactions); Positive control; All information regarding sequence, scale, purification and yield
Multiplex Assays	Subject to agreement between customer and Microsynth

F.4.2 Assay Validation

The Microsynth team has more than two decades of experience in validating assays. According to your requirements, we develop reliable, fit-for-purpose methods

in a cost-effective manner to validate your assay. The validation is performed in compliance with appropriate regulations (e.g. ICH Q2(R1)) to assess accuracy, repeatabil-

ity, intermediate precision, assay range, dilutional linearity and specificity.

F.4.3 Analysis Services

Microsynth offers competent project-based analysis services using real-time PCR and droplet digital PCR technology. All data is provided according to MIQE and digital MIQE guidelines.

Potential Applications:

- Absolute and relative quantification of the analyte
- Transgene copy number quantification
- Detection and quantification of the pathogens
- Detection and quantification of rare alleles

- microRNA analysis
- Genome editing detection and quantification
- Transgenic animal genotyping
- GMO testing
- Allergen testing
- Gene expression analysis
- SNP genotyping

F.4.4 qPCR and digital PCR Food Testing Assays

Microsynth offers a wide range of advanced, cost-effective food testing assays. The portfolio includes allergen-, species-, GMO- and microorganism-specific assays for qualitative and quantitative analysis.



Main Product Features and Benefits:

High quality: Ring-trial validated qPCR and digital PCR assays¹ with primer & probes manufactured inhouse by Microsynth

Attractive prices: for 5 x 20 qPCR or 4 x 24 digital PCR reactions

Digital PCR Assays for Species Testing

Product Name	Assay Type
dNoBA	Digital PCR EvaGreen duplex assay for quantitative determination of non-basmati rice content in basmati rice.
dBePo	Digital PCR probe duplex assay allows quantitative determination of beef and porc in meat samples.
dMarzipan	Digital PCR probe duplex assay allows quantitative determination of marzipan and apricot in marzipan products.
dChiTu	Digital PCR probe duplex assay allows quantitative determination of chicken and turkey DNA.
dHoSh	Digital PCR probe duplex assay allows quantitative determination of horse and sheep DNA.
dWheSp	Digital PCR probe duplex assay allows quantitative determination of wheat and spelt DNA.

Multiplex qPCR Assays for Animal Classification and Meat Testing

Product Name	Assay Type	Marker 1	Marker 2	Marker 3	Marker 4	Marker 5
AllMeat	Tetraplex	Chicken	Pork	Beef	Turkey	n.a.
AllHorse	Tetraplex	Sheep	Pork	Beef	Horse	n.a.
AllMilk	Tetraplex	Cow	Goat	Sheep	Water buffalo	n.a.
AllPaté	Pentaplex	Chicken	Duck	Goose	Turkey	Pork
AllWild	Pentaplex	Chamois	Cattle	Roe Deer	Red, Sika Fallow D.	Pig and Wild Boar
AllCheese	Triplex	Sheep	Goat	Cattle		
AllVegi	Triplex	Fish	Myostatin (B/M	Plants		
AssignAnimal	Classification of animal species in combination with Sanger sequencing (cytochrome b)					

Multiplex qPCR Assays for GMO Testing

Product Name	Assay Type	Marker 1	Marker 2	Marker 3	Marker 4	Marker 5
AllGVOScB	Pentaplex	Nos Terminator	35S Promotor	Soy (lectin)	Maize (mhmG)	CaMV
AllGVOScC	Tetraplex	FMV Promotor	Bar gene	CP2/CP4/EPSPS	Pat Gene	n.a.
AllSoyA	Pentaplex	RoundupReady	Mon89788	Soy (Le1)	Soy2704	A5547-127
AllSoyB	Pentaplex	DP305423-1	DP356043-5	Lectin	CV127-9	Mon87701
AllSoyC	Pentaplex	Mon87708	Mon87769	Lectin	FG72	Mon87705
AllMaize C	Pentaplex	Starlink CBH	Mon863	T25	Maize (mhmG)	Mon810
AllMaize D	Pentaplex	Bt11	Nk603	Ly038	Maize (mhmG)	Bt176
AllMaize E	Pentaplex	GA21	DAS-59122-7	Mon89034	Maize (mhmG)	Mon88017
AllMaize F	Pentaplex	Syngenta3272	MIR604	TC1507	Maize (mhmG)	DP-98140
AllMaize G	Pentaplex	Mir162 Maize	DAS-40278-9	Mon87460	Maize (mhmG)	EventBt10

Multiplex qPCR Assays for Allergen Testing

Product Name	Assay Type	Marker 1	Marker 2	Marker 3	Marker 4	Marker 5
AllAll A	Tetraplex	Peanut	Celery	Soybean	Hazelnut	n.a.
AllAll B	Tetraplex	Cow's milk	Almond	Chicken egg	Sesame	n.a.
AllAll G	Tetraplex	Lupine	Almond	Brazil nut	Sesame	n.a.

Multiplex qPCR Assays for Bacteria Testing

Product Name	Assay Type	Marker 1	Marker 2	Marker 3	Marker 4	Marker 5
AllBakA IPC	Pentaplex	E. coli Stx1 Stx2 intimin	Salmonella (incl. bongori)	Listeria monocytogenes	Campylobacter spp	IPC pUC19
AllCamp	Tetraplex	Campylobacter jejuni	Campylobacter lari	Campylobacter coli	IPC pUC19	n.a.
AllColi	Tetraplex	E. coli spp	E. coli eae/intimin	E. coli Stx1	E. coli Stx2	n.a.
AllBaktB	Pentaplex	E.coli	Clostridium perfringens	Staphylococcus aureus	Bacillus cereus	IPC pUC19

1) Each assay has been fully validated and tested in interlaboratory ring trials. Assays are included in the Official Collections of Methods of Analysis of the Federal Office of Consumer Protection and Food Safety of Germany and of Switzerland as well as in the Scientific Opinion on the Evaluation of Allergenic Foods and Food Ingredients of the European Food Safety Authority. Food testing assays are supplied with the certificate of analysis from the federal food testing laboratory of Zurich.

F.5 Genotyping

Since 2003 Microsynth has been offering various routine as well as project-based genotyping services, especially those based on fragment length analysis of short

tandem repeats (STR). Our solid experience in this area, our profound understanding of DNA/RNA isolation and lab automation as well as our in-house production facility

for oligonucleotides qualify Microsynth as your partner of choice for a variety of genotyping questions.

F.5.1 Fragment Length Analysis

Comprehensive service packages for fragment length analyses including data analysis. Whether your application is a plain routine service or more complex R&D, Microsynth can offer you both the knowhow and the necessary lab infrastructure.

Main Product Features and Benefits:

- Trusted reliability due to >20 years of experience
- FLA laboratories are ISO/IEC 17025:2017 (STS 0429) accredited
- Turnaround times down to 2 working days for standard services
- Easy ordering via Microsynth's webshop

- Design and inhouse synthesis of high-quality fluorescent-labeled PCR primers for individual or multiplex strategies
- Dedicated Microsynth application specialists available for project management, data handling and troubleshooting

Available Service Types:

Service	Format
Standard Fragment Length Analysis: Customer performs the PCR reaction and submits an aliquot of diluted, labeled PCR products. Microsynth will add the size standard and separate the fragments by capillary electrophoresis on an ABI 3730 XL system. The resulting data is provided by email as an FSA file.	Flat fee for 1-24 samples, 25-48 samples and for 49-96 samples in plates..
Ready-to-load Fragment Length Analysis: Customer performs the PCR reaction and submits an aliquot of diluted, labeled PCR products in size standard /HiDi formamide. Microsynth separates the fragments by capillary electrophoresis on an ABI 3730 XL system. The resulting data is provided by email as an FSA file.	Flat fee for 1-24 samples, 25-48 samples and for 49-96 samples in plates.
Fragment Length Reporting: includes following information <ul style="list-style-type: none"> • Allele calling (determination of allele name and bp size as EXCEL file) • JPEG exports of allele calling • Additional information such as height, area, ratio and intensity of signals (customized reporting on request) 	Flat fee for 1-24 samples, 25-48 samples and for 49-96 samples.
Customized Fragment Length Analysis: Customized service from DNA isolation over PCR optimization to fragment analysis including reporting is available. Since every project is different, please contact a Microsynth application specialist to discuss your project.	On request

Applications:

- Microsatellite (STR) Analysis
- DNA Fingerprinting
- SNP Genotyping
- Relative Fluorescence Quantitation
- Replacement of manual gel electrophoresis



F.5.2 Cell Line Testing

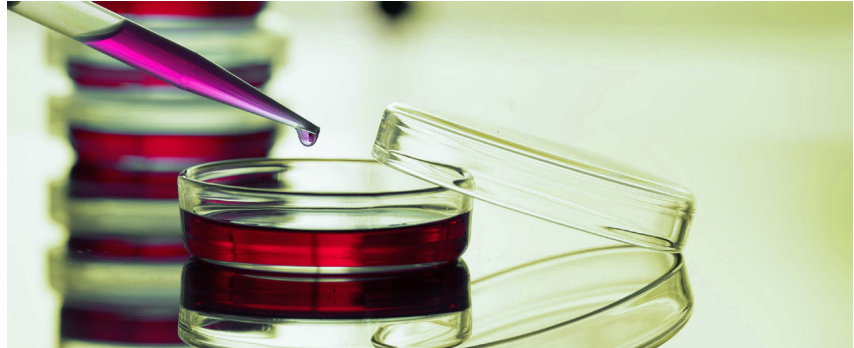
Why Test Cell Lines?

It is a fact that cross-contamination and misidentification of mammalian cell cultures is widespread. An incredible high number of 15-20% of all cell line based biomedical research is affected by misidentified cell lines. Therefore, it has become a necessity for any in vitro cell culture experiments to use unambiguously characterized cell lines to get reliable and reproducible results. Moreover, more and more journals (not only those with a high impact factor!) are requesting the authentication of cell lines as prerequisite for acceptance of manuscripts. Microsynth offers an easy-to-use service for human, mouse, rat, hamster, and dog cell lines.

Microsynth has over 10 years of experience in genotyping. Rely on our experience and make your research reliable!

Main Service Features and Benefits:

- **Easy sample handling:** Just send us your cell line at room temperature.
- **Easy sample shipment:** Just put your cell lines in one of our numerous drop boxes of Microsynth in Europe and benefit from cost-free shipment via a courier service. Alternatively, send the cell lines with your preferred postal service at room temperature.
- **Reliable results within just 1 week:** Microsynth has over 10 years of experi-



ence in genotyping. We will isolate and genotype your cell lines and return a meaningful analysis report including electropherogram within 1 week only.

- **Multiple organisms:** Currently a standard cell line typing service is offered for human, mouse, rat, hamster and dog cell lines. However, we can expand the service to any other organisms on demand. In cooperation with our subsidiary ecogenics GmbH, we are able to develop high-quality microsatellite markers for virtually any organisms. Contact us to discuss your specific needs!

Useful Add-on Services:

- Database comparison of the DNA profile on Cellosaurus
- Mycoplasma contamination testing of cell culture supernatant
- Microsatellite instability testing for continuous cell line monitoring
- Species identification if contamination is unknown

Service	Species
Cell Line Authentication	Human, mouse, rat, hamster, dog
Mycoplasma testing	Cell culture supernatant
Microsatellite instability testing	Human, mouse
Species identification	Unknown

F.6 Ecogenics

ecogenics GmbH is a subsidiary of Microsynth AG and has put its focus on microsatellite marker development and related genotyping services since its incorporation in 2001. Our commitment is to be the partner of choice for ecologists, breeders, botanists and zoologists looking to outsource DNA work.

From research project developments through routine analysis our protocols, based on state-of-the-art technologies, combined with our excellent project management allow rapid and successful accomplishment.

Together with our mother company we will find the best and most cost-effective solution for you. From project design to data analysis you can get everything from one source. Furthermore, after project completion we don't leave you alone, we provide our support with our know-how to make sure the data works for you.

F.6.1 Microsatellite Marker Development

The generation of SSR-enriched data by next generation sequencing allows straight-forward microsatellite development for any species within a short time span. We deliver well-characterized

markers and provide you with all information needed to publish the markers in a primer note or in a public database. It is up to you, until which step of development you plan to involve ecogenics and whether

you want to perform subsequent genotyping projects by yourselves or whether you wish to further collaborate with us.

F.6.2 Genotyping by Microsatellite Markers

For genotyping projects involving larger numbers of samples and markers, it is more cost effective to run multiplex PCR reactions compared to singleplex reactions. We can establish multiplex assays to the needed degree of complexity. We are happy to establish multiplex assays for markers developed by ecogenics or for markers published in scientific journals. If you are not sure if published markers

run on your species or subspecies, we can include further initial tests to ensure that the markers perform stably on your samples. For markers developed and multiplexed by us, we offer free allele calling for further genotyping work done at ecogenics.

In order to ensure highest data quality and to speed up the progress of your research

projects, we offer the full range of genotyping services. Our vast experience with DNA isolations from many sources, combined with our expertise in PCR, ensures optimal results. For fragment length analysis, we use Applied Biosystems 3730xl DNA Analyzer. Whether you wish to receive fluorescent trace files (.fsa) or also an allele table with all identified alleles per marker and sample is up to you to decide.

F.6.3 Genotyping by Sequencing (GBS)

With the rapid progress of next generation sequencing technologies, GBS became available to researchers and breeders for a very attractive price. We do not leave you alone with complex data sets, but can assist you through bioinformatics support. Furthermore, we are happy to support

you with setup of robust library preparation protocols and sequencing strategies for GBS.

In contrast to more traditional genotyping methods, SNP genotyping by next generation sequencing does not require previous

marker development or sequence information, but allows direct SNP genotyping within any population of interest at the desired marker density.

Contract Research/Outsourcing

In today's competitive environment, the pharmaceutical, biotech, and life science industries, as well as academic/public institutions are increasingly being forced to reduce costs and become leaner. In other words, doing more R&D with less – and doing it smartly – has become the overriding strategy!

G.1 Expertise

Microsynth has accumulated comprehensive knowledge to translate the customer demand into a well-defined analytical procedure that takes advantage of a state-of-the-art toolbox in DNA and RNA-based synthesis and analytical platforms, all of which are operated in-house.

The first and most important step in designing an efficient and successful analytical procedure is to fully understand the project both at the scientific level as well as in its regulatory context.

Notwithstanding the idiosyncratic features of a given project, it can usually be handled by a stereotypical approach that is divided into the following distinct phases: (1) the research & development phase, (2) an optional qualification/validation phase, and finally, (3) the analysis of the samples.

After careful evaluation of the customer demand, the analysis strategy is defined as a sequence that is composed of modules from our comprehensive analysis toolbox: Sanger sequencing, digital PCR, real-time PCR, next generation sequencing, and dedicated bioinformatics solutions.

The laboratory work then starts with the research and development phase: different methods and parameters are explored and tested on a small scale in order to identify the successful approach. Depending on customer needs, the successfully developed analytical procedure can then be further qualified or validated – this is mandatory for analytical procedures used in the regulated environment.

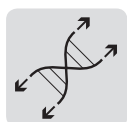
Once the analytical procedure has been established, the customer's samples will be analyzed.

G.2 Working with Microsynth

In today's competitive environment, the pharmaceutical, life-science and biotech industries as well as academic and public institutions are driven to optimize their research and production to become faster and leaner in order to save costs. As a consequence, compared to diverting valuable internal resources to projects outside the

core competence, outsourcing to a competent partner may in fact be a more promising strategy for your success. Outsourcing is also an attractive option in terms of testing an idea for its potential or to carry out routine procedures that are not economically feasible to establish in-house. Microsynth has accumulated vast knowl-

edge in designing and executing outsourcing services in the realm of RNA/DNA analytical procedures for diverse customers ranging from start-up biotechnology firms, large multinational pharmaceutical or nutritional companies, to university hospitals and scientific institutions.



Expertise & Know-how



Solution Driven



Quality

G.3 Technical Portfolio

DNA/RNA is our world. Microsynth provides a broad portfolio for DNA/RNA-based analytics ranging from DNA/RNA isolation to bioinformatics analyses. Moreover,

in-house DNA/RNA synthesis is available to complement the analytical portfolio.



G.4 Regulatory Expertise

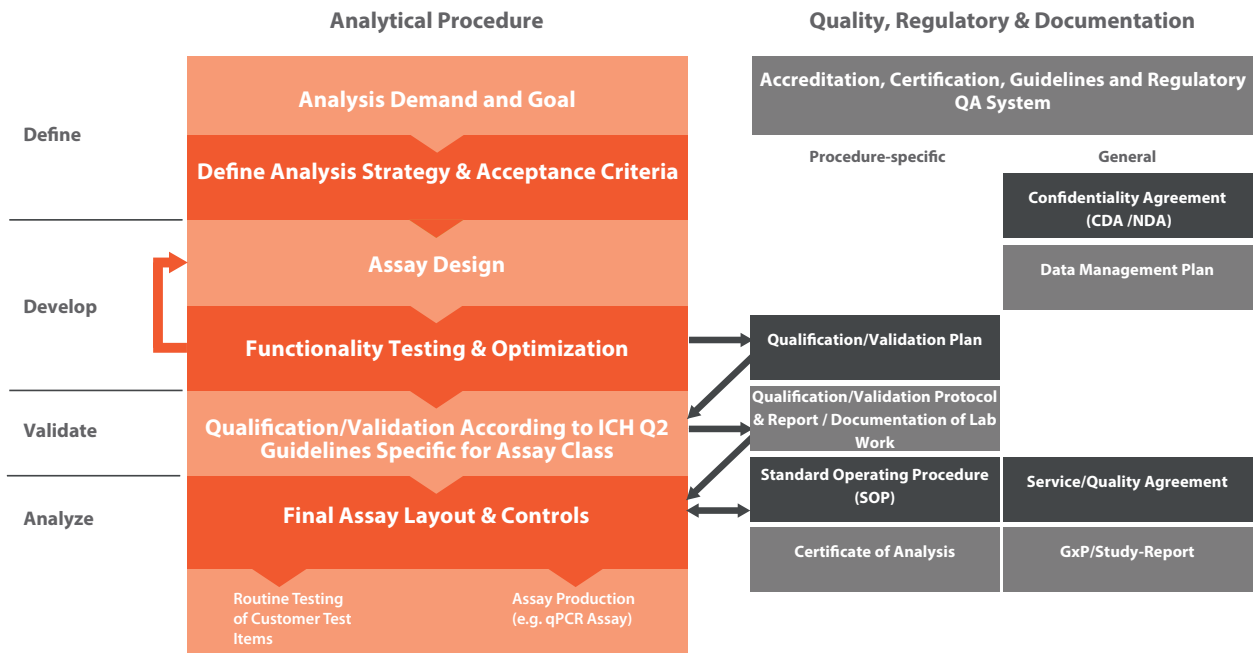
The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has defined the standards for the development and registration of medicines. In VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY (Q2R1), three major types of analytical procedures have been defined: identification tests (for example a Class A assay showing that a particular personalized RNA vaccine has an identical sequence as expected), quantitative tests for specific DNA/RNA species (for example a Class Bq assay to quantify genome edits in CRISPR/CAS9

test items), and limit tests for the control of impurities (for example a Class Bd assay demonstrating the absence of contaminating RNA/DNA species in a test item).

Microsynth has considerable experience in the qualification/validation of all three types of analytical procedures. All validation tests require high-quality reference material, which is either provided by the customer or developed by Microsynth. Identification tests are typically straightforward, while quantitative tests for impurities' content and limit tests for the control of impurities usually require a develop-

ment phase in order to establish the relevant assays.

The qualification/validation will result in a report that describes the final assay, the details of the analytical procedure and the standard operating procedure (SOP) for the specific analysis. In addition, important information about control samples and standards used in each analysis round are also provided. This information is instrumental in terms of evaluating whether the data of each testing round is valid.

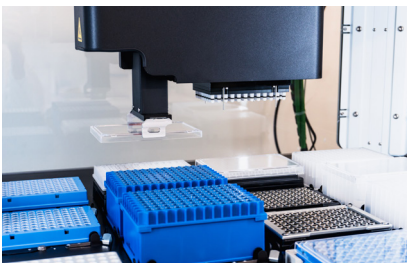


G.5 Possible Applications



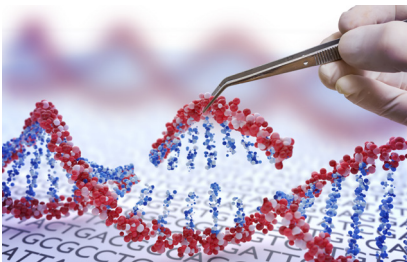
Assay Development

- Development of molecular biology assays (e.g. companion animal diagnostics, IVD, GMO, etc.)
- Qualification and validation of molecular biology assays according to ICH guidelines
- Cross-validation against a reference method



Biologics Testing

- Contamination and impurity testing
- Lot and final drug product release testing
- Cell line characterization



Gene Editing / Gene Therapy

- CRISPR editing analysis
- rAAV characterization
- Off-target analysis

For further information, please visit our website (www.microsynth.com) and use our contact form if you are interested in discussing your contract research project with an expert or to receive an offer.

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