Microsynth

# *Guide to GxP-compliant Analytical Testing of Novel Biological Drugs*

**What are the critical considerations when developing and validating advanced nucleic acid-based assays, to support biological drug development and manufacturing activities worldwide?**

## General Introduction

Drug development follows a general process that includes early drug discovery, the pre-clinical phase, the clinical phase, and eventually the approval of the drug/therapy by the relevant authorities. Typically, the development of a new drug takes around 10 years. It is a costly process that is full of uncertainty. Furthermore, the possibility of failure cannot be ruled out.

In addition to the complex drug development process and the manufacturing of the drug product, the analytics for quality control must be established to ensure that everything is in the right place at the right time to enable a successful production. Finally, the drug developer needs to define the deadlines by which its contract manufacturer and/or analytical laboratories must complete the important steps in the manufacturing or analytical life cycles, in other words when a validation of an analytical procedure has to be completed. In an ideal scenario, the drug developer will share a document with its manufacturers and testing labs that aligns timelines for the many regulatory, manufacturing, and analytical milestones.

The manufacturing and analytics follow their own life cycles (see Figure 1). Good Manufacturing Practice (GMP) guidance applies whenever a drug is intended for human use, which means that GMP manufacturing applies to investigational drugs that are still undergoing clinical trials. This is regardless of whether or not they are being manufactured in large-scale or small-scale environments. In addition, the manufacturing process must include qualified personnel, rooms , and equipment to ensure the drugs are being produced consistently in line with strict quality controls.

The FDA requests that the analytical methods used in the "IND stage" are qualified. In other words, the analytical procedure must be shown to be suitable for the specific purpose. Formal validation of the analytical procedure should then occur once sufficient knowledge has been acquired and it is generally speaking considered advisable to run the validation as early as possible in the drug development process. Moreover, the analytical procedures must be validated before the process validation for commercial production has been initiated.

This white paper focuses on the development of analytical procedures with references to the drug development and manufacturing cycles. As an analytical company, Microsynth runs GMP DNA/RNA-based analytics throughout the drug development process and for therapies on the market. Microsynth supports its customers in developing and managing the analytical procedures that are required for the quality testing of the drug/drug candidates.

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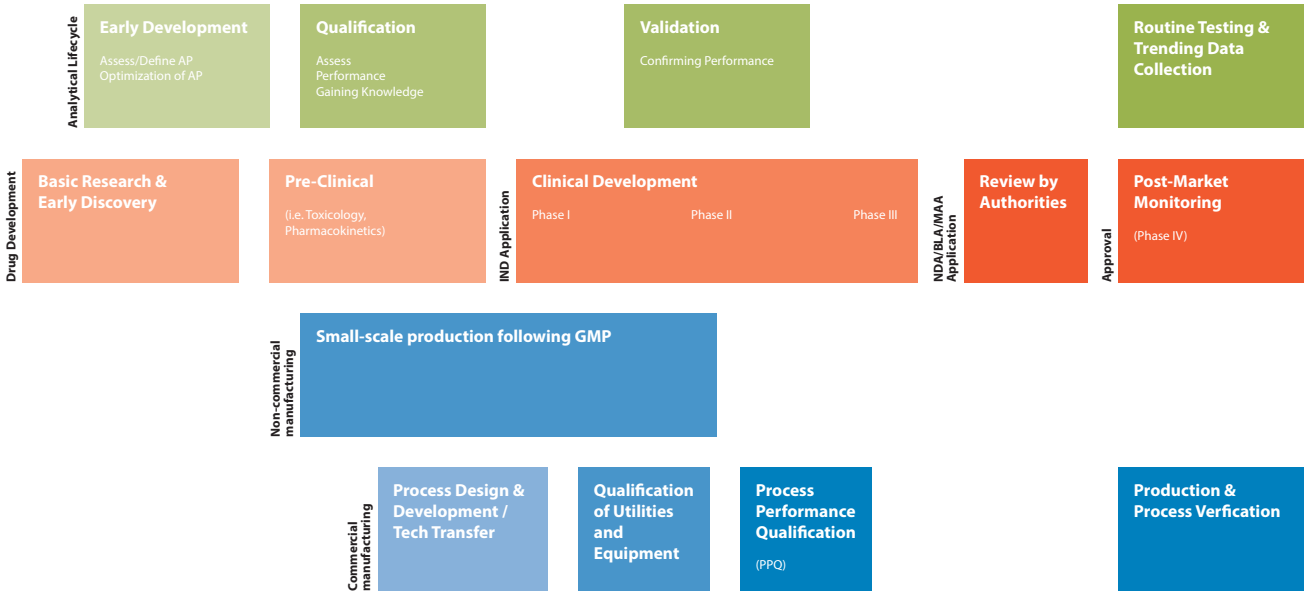



***Figure 1.*** *Interplay of the life cycle of the analytical procedure (AP) with the drug development pathway and the manufacturing process. The figure is a simplified representation .*

## Analytical Life Cycle and Assay Classes

### Analytical Life Cycle

Each analytical procedure follows a specific life cycle. While the different guidelines are similar in many areas, the wording can sometimes tend to be rather confusing between the guidelines. The first step in early development involves defining the test method and analytical platform that shall be used based on the analytical demands of the sponsor (Figure 2). This assessment relies on the available knowledge of the different analytical platforms by the sponsor and Microsynth. Expected accuracy and precision in the case of quantitative assays can be assessed based on similar analytical procedures that are already run at Microsynth and this can be compared against product specifications (analytical target profile (ATP)) for the testing as defined by the sponsor. Once the testing strategy and analytical platform have been defined, the assay is developed, and its functionality is tested. This completes the early development phase.

This is subsequently followed by the qualification of the analytical procedure. While pre-set acceptance criteria can be defined, this is not mandatory as the focus of the qualification is to assess (i) the performance of the analytical procedure, (ii) the capability of the assay to analyze the specifications of the test item, and (iii) to define the analytical strategy (i.e. replicates to analyze for the test item) and control strategy (system suitability testing criteria). Moreover, the qualification helps define the acceptance criteria for the validation and final specifications for the test article. These two steps are summarized as Analytical Procedure Development in ICH Q14 and USP 1220 (Figure 2). The FDA does not request a formal qualification protocol and report for the IND filing. However, Microsynth's policy is to document the qualification in a protocol and report that is approved by the sponsor. This means that the results of the qualification are well documented. Moreover, the analytical procedure is also documented in sponsor-specific SOPs following the qualification. The SOP describes the analytical procedure with reference to Microsynth's internal SOPs for specific methods (i.e. droplet digital PCR and ddPCR) and includes information on system suitability testing criteria (SST) and acceptance criteria for the controls.

The validation is a formal study designed to demonstrate the ability of the analytical procedure to meet the pre-defined acceptance criteria that are specified in the validation protocol. Besides the criteria, the protocol defines details of the work that will be performed: controls, details on the experimental layout and the analytical procedure, as well as the statistical analysis that will be used. The cri

teria are based on the analytical target profile (ATP) and the knowledge of the analytical procedure from the routine testing as well as the qualification. If the criteria are not met, the validation fails. However, the performance of the analytical procedure is often well-understood at the start of validation, which means that the possibility of a failure is unlikely. However, if the validation fails, the action required includes the analytical procedure needing to be optimized, the ATP having to be adapted, or, possibly even the analysis strategy having to be changed (see Figure 2).

On occasions, the analytical procedures are developed in the analytical department of the sponsor and the protocol is subsequently transferred to Microsynth (see Figure 3). Independent of the status of the analytical procedure, the first test runs on control samples (the familiarization run) are carried out at Microsynth to show that the assay performs as expected. In this step, slight modifications (i.e. the number of PCR cycles and/or annealing temperatures in PCR) can be made. If the analytical procedure has already been qualified/validated by the sponsor, the familiarization run is then completed by a protocol transfer. This involves a protocol that describes the experiments to be performed and the acceptance criteria are defined by the sponsor. Following the execution of the protocol, the results are summarized in a protocol transfer report and if all the acceptance criteria have been met, the analytical procedure can be used by Microsynth for GMP testing.

Based on its experience with transferred assays, Microsynth recommends that it is involved in the early development the assay in order to benefit from its significant experience. An early collaboration with the contract laboratory could prevent the need for any unexpected optimization work during the protocol transfer that will inevitably impact the timelines to start GMP testing and hence the overall timelines in the drug development process.

A special experiment is performed to address the robustness of the analytical procedure. Robustness is a significant parameter that confirms the analytical procedure remains unaffected by small but deliberate variations in method parameters. Whereas guidelines advise that the robustness is run during the development phase/early development phase, it is also possible to run a robustness study in a later stage when more knowledge has been gained from the routine testing during the clinical studies. A risk-based approach is used to identify possible critical parameters as not all factors can be studied. In a DNA-based quantitative assay, there can be, for example, some degree of variation in the DNA input, the effect of primer/probe lots, slight changes in PCR volumes, etc.

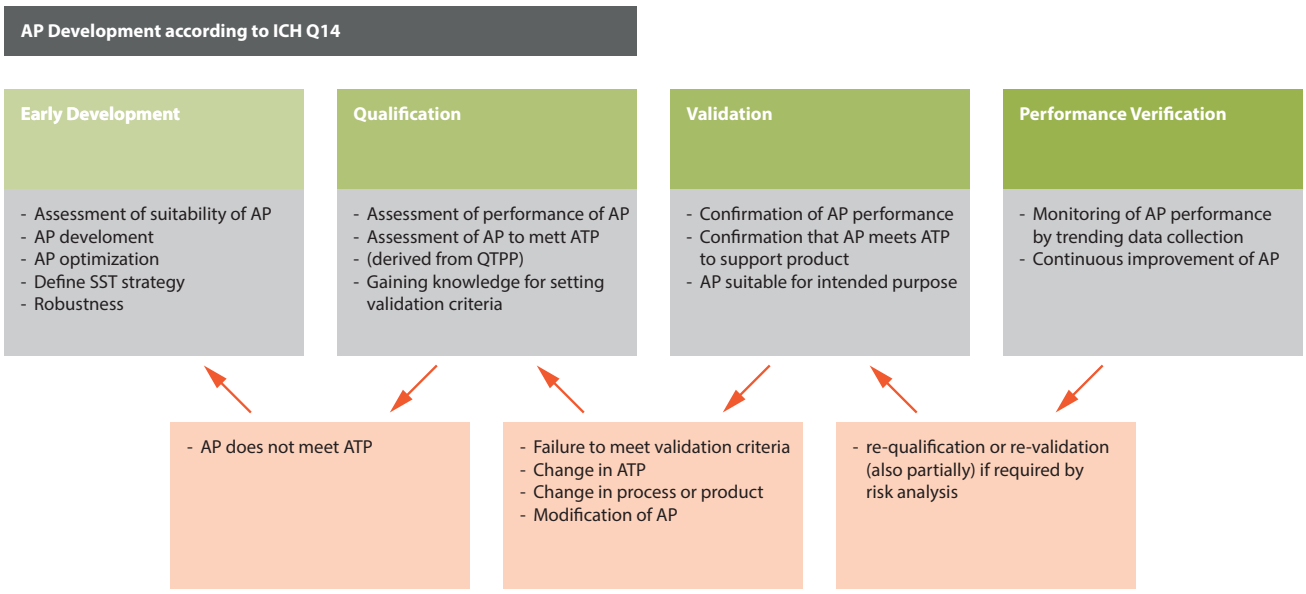



***Figure 2.*** *Life cycle of analytical procedure and specific questions addressed in the different steps. Depending on the source describing the analytical life cycle the early development and qualification are grouped as development as for example in ICH Q14.*

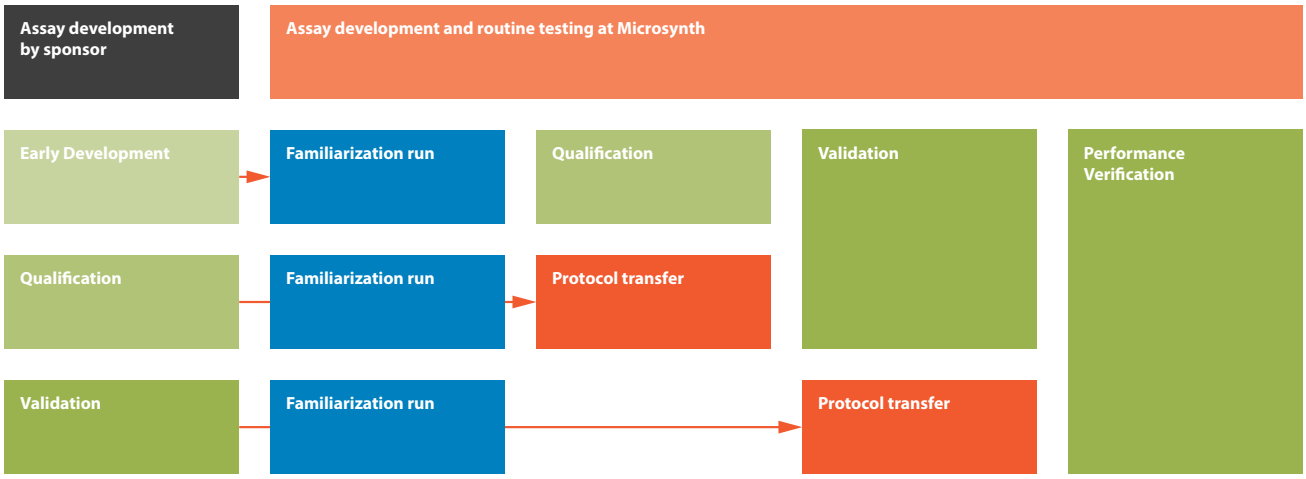



***Figure 3.*** *Transfer of analytical procedures developed at the premises of the customer.*

## Qualification and Validation of Analytical Procedures

The extent of qualification/validation depends on the ICH assay class and the application of the assay for characterization or release testing. The ICH Q2 guideline includes four assay classes (see **Table 1**) and the criteria to address during the qualification/validation depends on the assay class (see **Table 2**). A schematic representation of quantitative assays grouped in class II and class IV is shown in **Figure 4**.

A typical **Class I** assay at Microsynth is the identity testing of the sequence of the drug substance/drug product against the expected sequence by Sanger sequencing. The results are reported either as "identity confirmed" or "identity not confirmed." Based on the ICH Q2 guidelines, it is only the criteria **specificity** that must be addressed. As Sanger sequencing is by definition specific, in other words, Sanger sequencing results in a sequence and is not comparable with an HPLC peak that could represent different substances, no qualification is required. Instead, a validation can be directly performed. In the validation, the aim is to show that a sample provided by the sponsor shows 100% identity with the reference sequence. Moreover, in the validation, a set of sequencing primers is defined that enables a fast routine testing. In the case of the identity testing of a plasmid sample, Sanger sequencing can be performed directly on the plasmid DNA template, whereas for other applications the region of interest must first be PCR amplified before sequencing. Besides Sanger sequencing, next-generation sequencing can also be used for identity testing. A next generation sequencing (NGS) approach is significantly more sensitive and it can also detect low frequency mutations (<5%) present in a DNA population or the sample.

Quantitative assays as grouped in ICH **classes II** and **IV** (see **Table 1**) are regularly run at Microsynth. More often than not, these assays are based on droplet digital PCR (ddPCR) or next-generation sequencing. The criteria to investigate during the qualification/validation of both classes are very similar, except for the "limit of quantification" that is only addressed in class II assays. A qualification/validation study includes at least three analytical runs that have been performed by two operators on a defined number of samples covering the range of the assay including some "safety margin." The accuracy is then measured by comparing the expectation value (theoretical accepted value) against the measurements (the fit between expected and measured). In the case of DNA-based and RNA-based assays, it is often more complex to calculate the theoretical expected value than it is for other assay types. For example, if a plasmid representing the transgene is spiked in the host DNA, the plasmid DNA must be highly diluted compared to the host genomic DNA. The precision can then be separated in the repeatability (within run variation) and intermediate precision (the variation caused by the analytical run and the operator) using, for example, an Analysis of Variance (ANOVA) approach.

A typical **class II** assay is the measurement of CRISPR off-target editing rates at a specific locus using an amplicon deep-sequencing strategy. Class II assays are normally quite ambitious as very small quantities (i.e. editing rates) must be quantified. The experimental layout and statistical analysis for a qualification/validation is very similar

to that of class IV assays.
The testing of residual DNA of the production host is a typical **class III** assay, i.e. the analysis of E. coli DNA in recombinant therapeutic products such as antibodies. In a class III assay, it is only the criteria specificity and limit of detection that is addressed during a qualification/validation. In contrast to quantitative assays, the result of the testing is recorded in binary mode (0 and 1) and the LOD is determined using serial dilutions and probit regression analysis. However, class III assays are often replaced by class II assays, which results in the quantification of the impurities. Moreover, ICH guidelines also define analytical platforms that can be generically validated, which reduces the need for product-specific validations. According to ICH Q2 guidelines, a platform analytical procedure is defined by ICH as "… a multi-product method suitable to test quality attributes of **different products without significant changes to its operational conditions, system suitability**, and **reporting structure**. This type of method would apply to molecules that are sufficiently alike with respect to the attributes that the platform method is intended to measure." In the case of a platform analytical procedure, it can be validated, which reduces the effort required for further product-specific validations.

***Table 1**. Assay classes as defined in the ICH Q2 guidelines.*

| ICH Q2 assay class | Description |
|---|---|
| Class I | Identification test |
| Class II | Quantitation of Impurities |
| Class III | Qualitative limit test for impurities |
| Class IV (4 + 5) | Quantification of active ingredients; the Class IV assays can be further divided whether a target +/- a specific range must be measured, or the measured value should be no lower than (≥) a specific acceptance criteria; see below) |

***Table 2.** Assay classes and criteria that must be addressed for the different assay classes.*

| | Assay Class | | | |
|---|---|---|---|---|
| Criteria | I (1) | II (2) | III (3) | IV (4 + 5) |
| Specificity | X | X | X | X |
| Accuracy | - | X | - | X |
| Precision – Repeatability | - | X | - | X |
| Precision – Intermediate Precision | - | X | - | X |
| Linearity | - | X | - | X |
| Range | - | X | - | X |
| Limit of Detection (LOD) | - | - | X | - |
| Limit of Quantification (LOQ) | - | X | - | - |

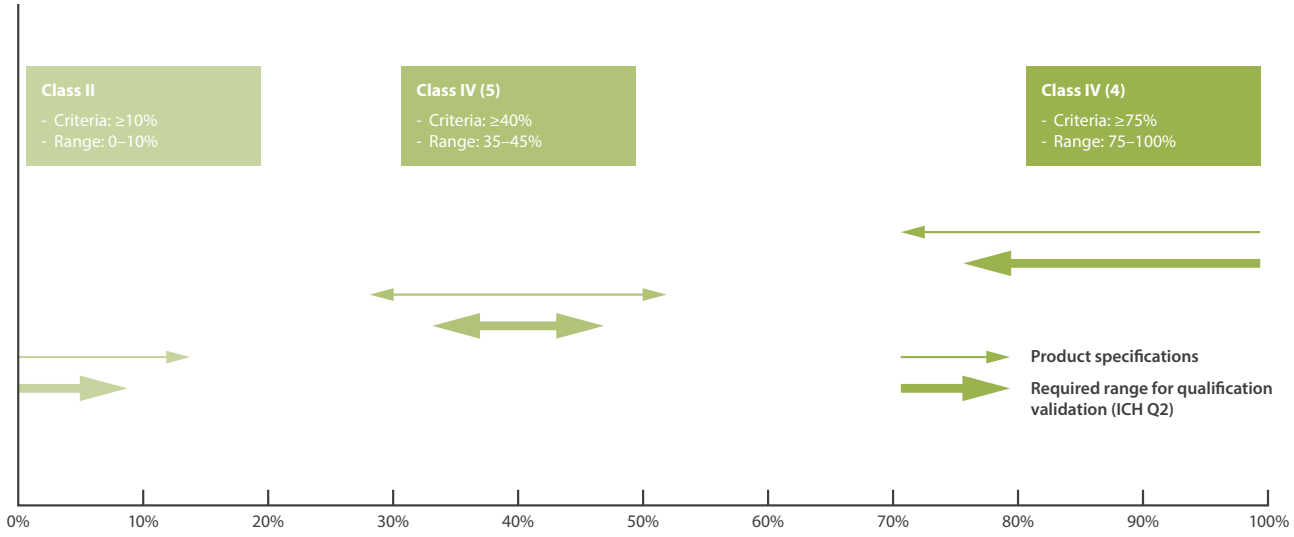



***Figure 4.*** *Schematic representation for Class II and Class IV assays. Class IV assays can be further classified based on the product-specific criteria that must be analyzed. The range of the analytical procedure to be qualified/validated exceeds the requested range of the assay. Specific wording is often used to describe the acceptance criteria for the samples in these assays, i.e. non-lower than (NLT) or no more than (NMT), which can simply be described using universal mathematical notifications.*

## Setting System Suitability Testing Criteria (SST) and Criteria for Qualifications and Validations

System suitability testing (SST) is used to show that an analytical run has resulted in trustworthy results. In other words, it demonstrates that the platform on which the analyses were run was suitable for its intended use. Purely technical SST criteria are frequently used to evaluate a measurement during qualification/validation (i.e. minimal read depth in amplicon deep-sequencing or accepted droplets in ddPCR). Besides these platform-specific SSTs, positive and negative controls are included depending on the test class and/or assay layout, and, especially in routine testing, controls are crucial. Based on the knowledge it has gained regarding the performance of the different analytical platforms, Microsynth can help the customer in terms of meaningful SSTs for each platform/analytical assay.

The difference between qualification and validation is that qualification uses either relaxed acceptance criteria or some criteria are not defined, as the qualification is used to assess the performance of the analytical procedure and helps to define the acceptance criteria for the later validation. Setting acceptance criteria for qualification/validation is the responsibility of the sponsor and this depends on the Analytical Target Profile (ATP) of the drug product defined by the sponsor. The ATP is derived from the Quality Target Product Profile (QTPP), which is also defined by the sponsor. The role of Microsynth is to assess how realistically these criteria can be met based on the performance of similar analytical procedures that are already run at Microsynth. Moreover, Microsynth draws attention to possible pitfalls and difficulties it might expect and helps to define the experimental layout and analysis strategy.

## Analytical Platforms at Microsynth

Microsynth focuses on the DNA-based and RNA-based analytics and each analytical platform has a focus on some of the ICH assay classes (see **Table 3**).

***Table 3.*** *Typical usage of the different analytical platform available at Microsynth for the different ICH assay classes.*

| Assay Class | Analytical Platform | | | | |
|---|---|---|---|---|---|
| | Sanger Sequencing | Fragment Analysis | ddPCR (qPCR) | NGS Amplicon | NGS WGS |
| Class I | X | X | (X) | - | X |
| Class II | - | - | X | X | - |
| Class III | - | X | - | - | - |
| Class IV | (X) | - | X | X | - |

## Sanger Sequencing

Sanger sequencing is a comparable mature platform and it plays a key role in the first sequencing of the human genome. Depending on the analytical procedure, either the DNA sample (i.e. plasmid DNA) can be sequenced directly, or some PCR/RT-PCR steps are needed. Relatively high concentrations of a PCR product or plasmid DNA are combined with a single sequencing primer, the polymerase, nucleotides, as well as labelled chain terminator nucleotides. The cycle sequencing PCR reaction will result in a pool of DNA fragments of different lengths that are labelled by the chain terminator nucleotides. The pool of DNA fragments is then separated by capillary electrophoresis and the fluorescence is readout (Applied Biosystems 3730xl Genetic Analyzer). Microsynth considers Sanger sequencing to be one of the best examples of an analytical platform that meets the criteria for platform validation. This is because (i) the Sanger sequencing always starts with purified dsDNA (or occasionally ssDNA) although the sequence may differ between test articles, (ii) Sanger sequencing is performed under identical operational conditions, (iii) system suitability criteria applied for results reporting are highly similar in their structure (coverage and the quality of each base in the sequences; see below), and (iv) the reporting will either confirm or not confirm identity with the theoretical expected sequence (reference sequence). A platform validation was performed at Microsynth for the Sanger sequencing. Sanger sequencing is almost exclusively used to demonstrate the identity of a test article (ICH Q2 class I assay). According to the ICH Q2 guidelines, the **specificity** criteria must be addressed for class I assays. Sanger sequencing is **inherently specific** as the outcome of Sanger sequencing is the sequence of bases present in the test article (template DNA). For Sanger sequencing to be successful (i) a primer matching the sequence of the template DNA and (ii) the template DNA itself must be present in the Sanger sequencing reaction. If a primer is present in the Sanger sequencing reaction that does not bind to the template DNA, then this means either no or poor Sanger sequencing results will occur. Furthermore, if the template DNA is missing, either no or poor Sanger sequencing results will occur. Sanger sequencing is best used for identity testing for sequences up to a few kilobases. For longer sequences, the next-generation sequencing platform is preferred. Moreover, an advantage of Sanger sequencing is that low-frequency mutations in the DNA population will not affect the testing results (frequencies of around <15%).

## Fragment Analysis

Fragment analysis (FLA) can be used as an alternative to PCR and gel electrophoresis. When using fragment analysis, the PCR is run with a labelled primer and the PCR product is separated on the same platform as the Sanger sequencing reactions (Applied Biosystems 3730xl Genetic Analyzer). By adding an internal size standard to each reaction following the PCR amplification, the product length can be estimated very accurately (a few base pairs) for PCR products in the range of 100-600 bp. The advantage of FLA is that it is highly sensitive and multiple loci can be analyzed in parallel. Paternity analysis used in forensics or cell line authentication is a typical application that is based on FLA (identity testing). Moreover, the amplification can be used as a qualitative limit test such as analyzing the presence of Mycoplasma species in cell culture supernatant.

## Digital Droplet PCR (ddPCR)

Digital droplet PCR (ddPCR) is a relatively new PCR-based technology combining real-time qPCR with microfluidics. ddPCR allows the absolute quantification of specific DNA molecules in a sample. In contrast to qPCR, ddPCR is an endpoint PCR. Rather than running a single PCR, the PCR reaction is performed in thousands of oil droplets. This step is called droplet generation, where microfluidics are used to encapsulate the PCR reaction mix into small oil droplets. The PCR reaction is then run on a standard PCR cycler. However, after PCR, the oil droplets are analyzed for fluorescence, which results in a digital read-out of positive and negative droplets. This readout is then used to calculate the copy numbers of the respective molecule per microliter. As the latest platforms enable the readout of several different fluorophores, it is possible to run complex multiplex assays.
ddPCR is the method of choice for copy number determination or quantification of translocation frequencies in CRISPR-edited samples. In these cases, a duplex ddPCR assay is run that measures the frequency of the genome copies compared to the event (i.e. transgene or translocation).

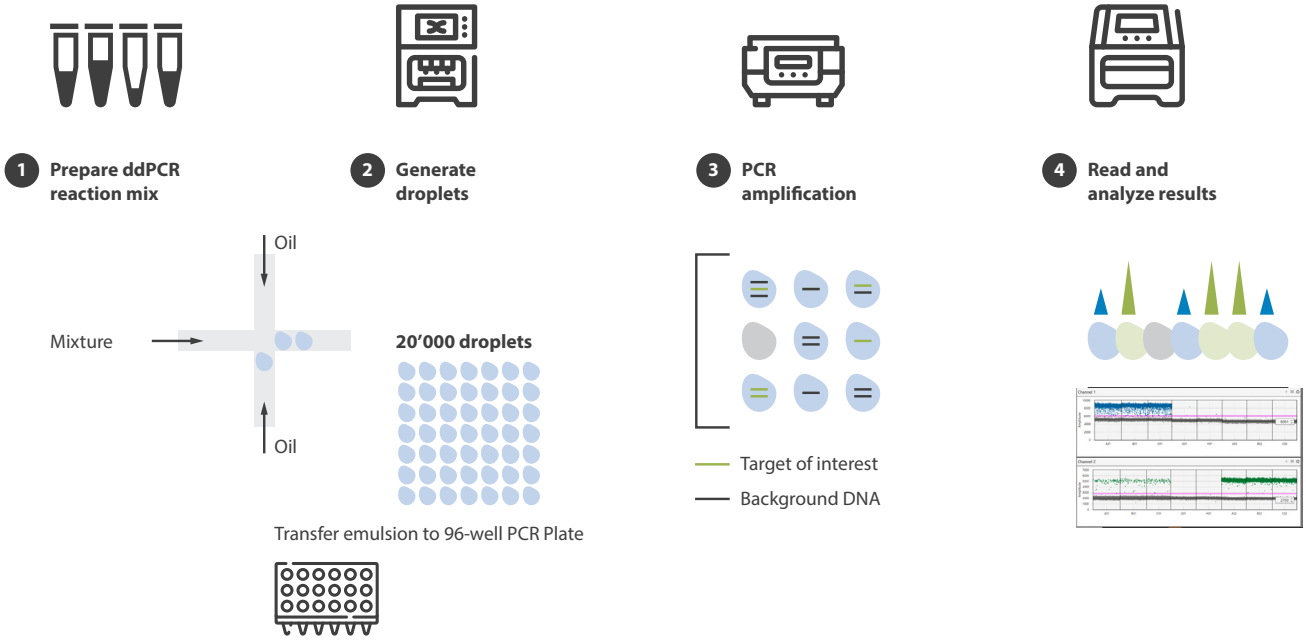



***Figure 5.*** *Workflow for ddPCR analysis. The PCR amplification is performed in thousands of small reaction droplets which are generated before the PCR cycling. After PCR amplification, individual droplets are analyzed for amplification of the target (fluorescence).*

### Next Generation Sequencing

Next generation sequencing includes a wide variety of platforms that differ in terms of the length of the sequences generated and the throughput. Whereas the most dominant short sequencing platform is Illumina with sequences of 2*50 to 2*300 and millions to billions of reads generated per run, long-read technology platforms from Pacific Biosciences and Oxford Nanopore Technologies are well renowned Long-read platforms can generate reads of many kilobases, although the read quality can be lower than it is for short-reads.

The selection of the platform depends on the analytics that are being run. A typical analysis that is addressed with the short-read technology is the measurement of the editing frequency on CRISPR-edited cell pools, either on-target or off-target. Moreover, NGS can also be used for identity testing of long regions of interest for which a Sanger sequencing approach is not practicable. However, in the case of identity testing, the advantage of NGS, specifically the detection of low frequency mutations in the population of molecules, can complicate the identity testing. In contrast to Sanger sequencing, NGS can quite easily detect mutations with frequencies <5% and, therefore, criteria must be set with regard to what mutation frequencies are relevant for the identity testing. Mutations with frequencies <10% are often not considered.

Sanger sequencing, as well as short-read NGS technologies, will have difficulties if long repetitive elements are present in the region of interest that is included in the identity testing. In such cases, an NGS long-read technology can help to overcome the technical limitations of the other two technologies. At Microsynth, there are two available long-read technology platforms: PacBio and Oxford Nanopore.

## Regulatory Requirements to be Considered

### Contractual Agreements

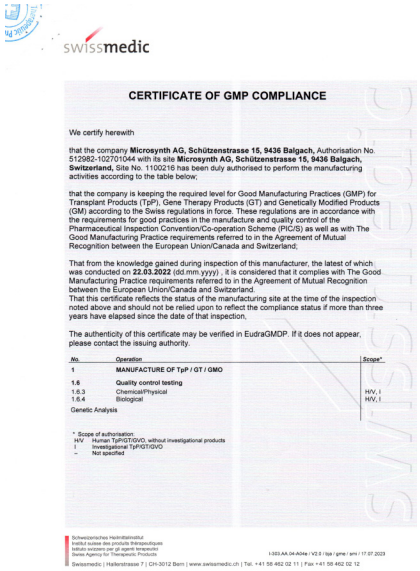
Before establishing a business relationship, certain regulatory documents should be in place. To facilitate discussions between the sponsor and Microsynth, a Confidentiality Disclosure Agreement (CDA) must be signed by both parties. The CDA allows for the sharing of confidential information between the parties and is useful for any discussions, even before commencing any laboratory work at the testing facility. Typically, the CDA is followed by a Master Service Agreement (MSA) and/or a Quality Agreement (QA). While an MSA is a basic contract that outlines the scope of the relationship between the two parties and contains terms for current and future activities and responsibilities, a QA defines specific quality parameters for a project and specifies which party is responsible for meeting those parameters. The QA should cover all aspects of the project related to the identity, quality, safety, efficacy, and purity of a product or service.

### Sponsor Audits

Sponsor audits that follow GMP guidelines are conducted in Microsynth's analytical testing laboratories. Once the analytical tests have been qualified, validated, and approved by the sponsor, the responsibility towards regulatory authorities remains with the sponsor. In the pharmaceutical sector, maintaining a lasting relationship with sponsors requires adherence to GMP quality standards and mutual trust. According to GMP guidelines, sponsors are obligated, along with regulatory authorities, to ensure that laboratories comply with good manufacturing practice specifications through audits. These sponsor audits are highly appreciated as they provide sponsors with the opportunity to thoroughly familiarize themselves with the laboratory and establish the necessary trust in Microsynth as a high-quality service partner. They also enable the exchange of information and quality requirements, allowing companies to learn from each other's interpretations and implementations of GMP guidelines.

## Accreditation / Certification / Authorities / Notified Bodies @Microsynth

Our quality management system undergoes regular audits by independent authorities and is accredited or certified according to various standards and guidelines, as illustrated in **Figure 6**.


swissmedic

CERTIFICATE OF GMP COMPLIANCE

We certify herewith

that the company **Microsynth AG, Schützenstrasse 15, 9436 Balgach,** Authorisation No. 512982-102701044 with its site **Microsynth AG, Schützenstrasse 15, 9436 Balgach, Switzerland,** Site No. 1100216 has been duly authorised to perform the manufacturing activities according to the table below;

that the company is keeping the required level for Good Manufacturing Practices (GMP) for Transplant Products (TxP), Gene Therapy Products (GT) and Genetically Modified Products (GM) according to the Swiss regulations in force. These regulations are in accordance with the requirements for good practices in the manufacture and quality control of the Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S) as well as with The Good Manufacturing Practice requirements referred to in the Agreement of Mutual Recognition between the European Union/Canada and Switzerland;

That from the knowledge gained during inspection of this manufacturer, the latest of which was conducted on **22.03.2022** (dd.mm.yyyy) , it is considered that it complies with The Good Manufacturing Practice requirements referred to in the Agreement of Mutual Recognition between the European Union/Canada and Switzerland.
That this certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection.

The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

| No. | Operation | Scope* |
|---|---|---|
| 1 | MANUFACTURE OF TxP / GT / GMO | |
| 1.6 | Quality control testing | |
| 1.6.3 | Chemical/Physical | H/V, I |
| 1.6.4 | Biological | H/V, I |
| Genetic Analysis | | |

* Scope of authorisation:
H/V Human TxP/GT/GVO, without investigational products
I Investigational TxP/GT/GVO
– Not specified

Schweizerisches Heilmittelinstitut
Institut suisse des produits thérapeutiques
Istituto svizzero per gli agenti terapeutici
Swiss Agency for Therapeutic Products

I-303.AA.04-A04e / V2.0 / lpa / gme / smi / 17.07.2023

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**GMP Certification**
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Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Federal Department of Economic Affairs, Education and Research EAER
**State Secretariat for Economic Affairs SECO**
Swiss Accreditation Service SAS

Swiss Confederation

Based on the Accreditation and Designation Ordinance dated 17 June 1996 and on the advice of the Federal Accreditation Commission, the Swiss Accreditation Service (SAS) grants to

**Microsynth AG**
**Schützenstrasse 15**
**9436 Balgach**

SWISS ACCREDITATION sas.admin.ch SR 946.512

**Period of accreditation:**
**15.03.2020 until 14.03.2025**
(1st accreditation: 15.03.2005)

the accreditation as

**Testing laboratory for nucleic acid sequencing and establishing of DNA profile**

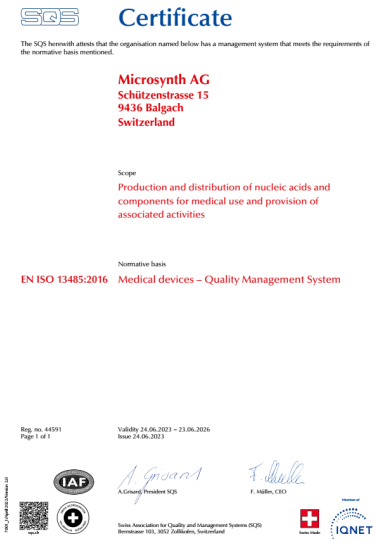
International standard: ISO/IEC 17025:2017
Swiss standard: SN EN ISO/IEC 17025:2018

3003 Berne, 03.03.2020
Swiss Accreditation Service SAS

Head of SAS
Konrad Flück

SAS is a signatory of the multilateral agreements of the European co-operation for Accreditation (EA) for the fields of testing, calibration, inspection and certification of management systems, certification of personnel and certification of products, processes and services, of the International Accreditation Forum (IAF) for the fields of certification of management systems and certification of products, processes and services and of the International Laboratory Accreditation Cooperation (ILAC) for the fields of testing and calibration.

**ISO/IEC 17025:2017 Accreditation**
Swiss Accreditation Services (SAS)


SQS Certificate

The SQS herewith attests that the organisation named below has a management system that meets the requirements of the normative basis mentioned.

**Microsynth AG**
**Schützenstrasse 15**
**9436 Balgach**
**Switzerland**

Scope
Production and distribution of nucleic acids and components for medical use and provision of associated activities

Normative basis
EN ISO 13485:2016 Medical devices – Quality Management System

Reg. no. 44591
Page 1 of 1

Validity 24.06.2023 – 23.06.2026
Issue 24.06.2023

IAF

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Bernstrasse 103, 3052 Zollikofen, Switzerland

Member of IQNet

**ISO/IEC 17025:2016 Certification**
Swiss Association for Quality and Management Systems (SQS)

**Figure 6.** *Authorities, certifications and accreditations @ Microsynth ( ISO 9001:2015 not shown).*

The **ISO/IEC 17025:2017** re-accreditation is performed every 5 years by the Swiss Accreditation Service (SAS), with surveillance audits taking place every 2 years or at shorter intervals, if necessary. The identification of risks takes place on an ongoing basis. Both the risk of providing invalid results, including invalid statements of conformity, and risks regarding impartiality are considered once a year through internal audits.

As part of the accreditation of testing laboratories in accordance with the ISO/IEC 17025:2017 standard, participation in interlaboratory testing is mandatory. This proves the quality of the work performed.

The **ISO 9001:2015 / EN ISO 13485:2016** re-certification takes place every 3 years and is performed by the Swiss Association for Quality and Management Systems (SQS). Meanwhile, maintenance audits take place annually. The fulfilment of requirements and the identification of risks regarding product quality are checked by annual internal audits. The DNA/RNA synthesis with the components for medical use and provision of related activities used for medical analytics are produced carefully and with strict quality requirements in place to ensure patient safety.

Our GMP status is verified every two years through a basic inspection by the government agency Swissmedic, as well as via regular internal quality assurance audits and sponsor audits.

Third-party reviews of Microsynth's actions help it overcome "operational blindness," enabling critical examination of the processes and continuous improvement in place within the Microsynth quality management system (QMS).

# Glossary

## Relevant Abbreviations

| Abbreviation | Description |
|---|---|
| AP | Analytical Procedure |
| ATP | Analytical Target Profile |
| BLA | The Biologics licensing application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce. |
| CDA | Confidentiality Agreement (Non-disclosure agreement) |
| CoA | Certificate of Analysis |
| CTA | Clinical Trial Appication |
| EMA | European Medicines Agency |
| FDA | U.S. Food and Drug Administration |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| MAA | Marketing Authorization Application |
| MSA | Master Service Agreement |
| NDA | New Drug Application |
| OOS | Out of Specification |
| OOT | Out of Trending |
| QA | Quality Agreement |
| QM | Quality Management |
| QTPP | Quality Target Product Profile |
| SST | System Suitability Testing; used to verify that an analytical method was suitable for its intended purpose |

## Important Guidelines and Regulations

| Abbreviation | Description |
|---|---|
| ICH Q14 (R2) | ICH guidelines Analytical Procedure Development |
| ICH Q2 (R2) | ICH guidelines Validation of Analytical Procedures |
| FDA-2015-N-0007 | Analytical Procedures and Methods Validation for Drugs and Biologics – Guidance for Industry |
| USP | United States Pharmacopeia |
| Ph.Helv. | Pharmacopoea Helvetica |
| Ph.Eur. | Pharmacopoea Europaea |
| USP 1220 | Analytical Life Cycle |
| USP 1033 | Biological assay validation |

## Further Readings

1. *Krause, SO (2002)* ***Good Analytical Method Validation Practice: Setting Up for Compliance and Efficiency: Part I****. Journal of Validation Technology, 9:31-47.*

2. *Krause, SO (2002)* ***Good Analytical Method Validation Practice: Deriving Acceptance Criteria for the AMV Protocol: Part II.*** *Journal of Validation Technology 9:48-57.*

3. *Little, TA (2016).* ***Establishing Acceptance Criteria for Analytical Methods****, BioPharm International 29:10.*

4. *Orchard, T (2006)* ***Specification Setting: Setting Acceptance Criteria from Statistics of the Data****. Biopharm International 19:11.*

5. *Seely, RJ, Munyakazi, L, Haury, J (2001)* ***Statistical tools for setting in-process acceptance criteria****, BioPharm International. 14:10.*

6. *Walfish, S (2006) Analytical Methods:* ***A Statistical Perspective on the ICH Q2A and Q2B Guidelines for Validation of Analytical Methods****. BioPharm International 19:12.*