Digitalisation in the Quality Infrastructure – Perspectives from Novo Nordisk

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Novo Nordisk at a **glance**

Novo Nordisk is a leading global healthcare company, founded in 1923 and headquartered in Denmark.

Our purpose is to drive change to defeat serious chronic diseases, built upon our heritage in diabetes.

We do so by pioneering scientific breakthroughs, expanding access to our medicines, and working to prevent and ultimately cure disease.

1. https://companiesmarketcap.com/pharmaceuticals/largest-pharmaceutical-companies-by-market-cap/ (As of 25 January 2024).

Supplier of nearly
50%
of the world's insulin

Net sales
232.3
billion DKK

Affiliates in
80
countries

About
64,319
employees

Total tax contribution
51
billion DKK

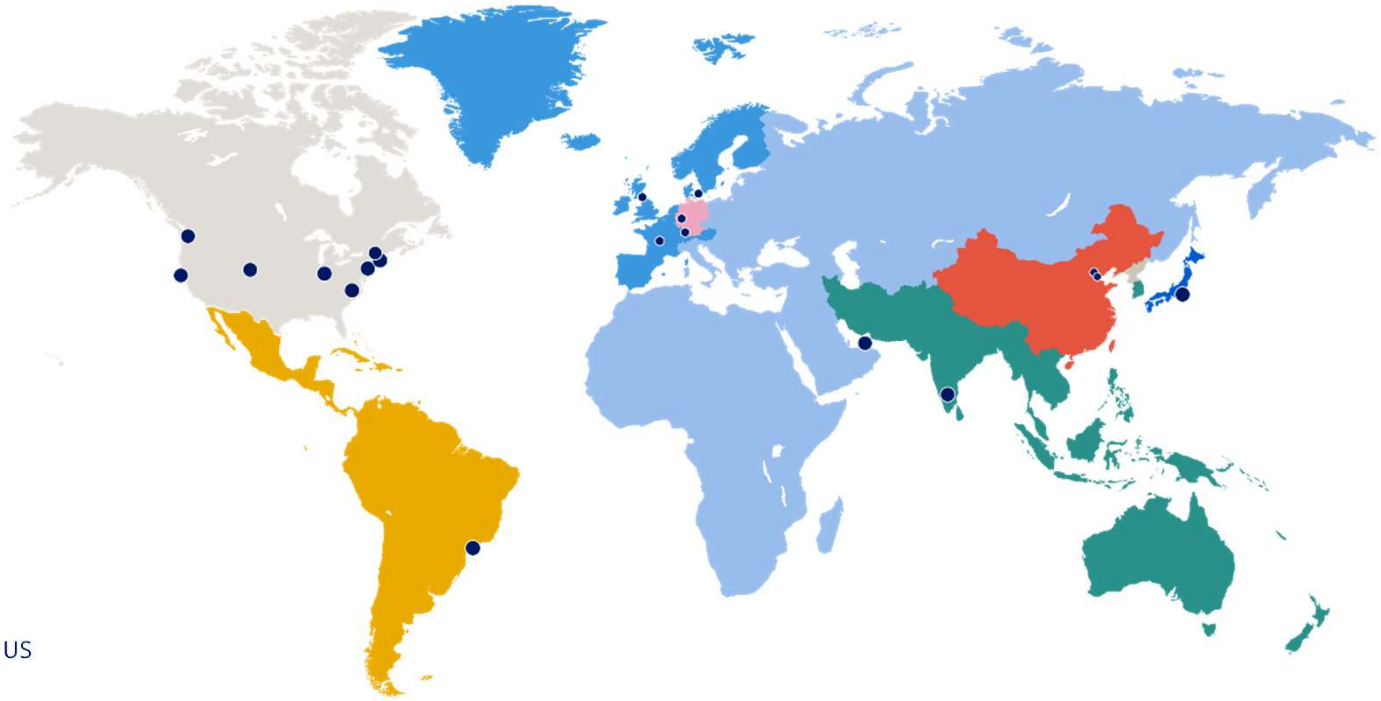
R&D centres in China, Denmark, India, UK and US

Strategic production sites in Denmark, Brazil, China, France and US

Globally, serving
41.6
million people living with diabetes and obesity

A top five
pharma company measured by market value[1]

Our **global** presence



Corporate headquarters
Bagsværd, Denmark

North America Operations HQ
Plainsboro, NJ, US

International Operations HQ
Zurich, Switzerland

Strategic production sites
Brazil, China, Denmark, France, US

R&D centres
China, Denmark, India, UK, US

Regional offices
- Beijing (China)
- São Paolo (Latin America)
- Tokyo (Japan)
- Copenhagen (North West Europe)
- Mainz (Germany)
- Zurich (South East Europe, Middle East & Africa
- Dubai (Asia & Pacific)

64,319 employees worldwide

80 countries with affiliates

Novo Nordisk Calibration Programme

High level

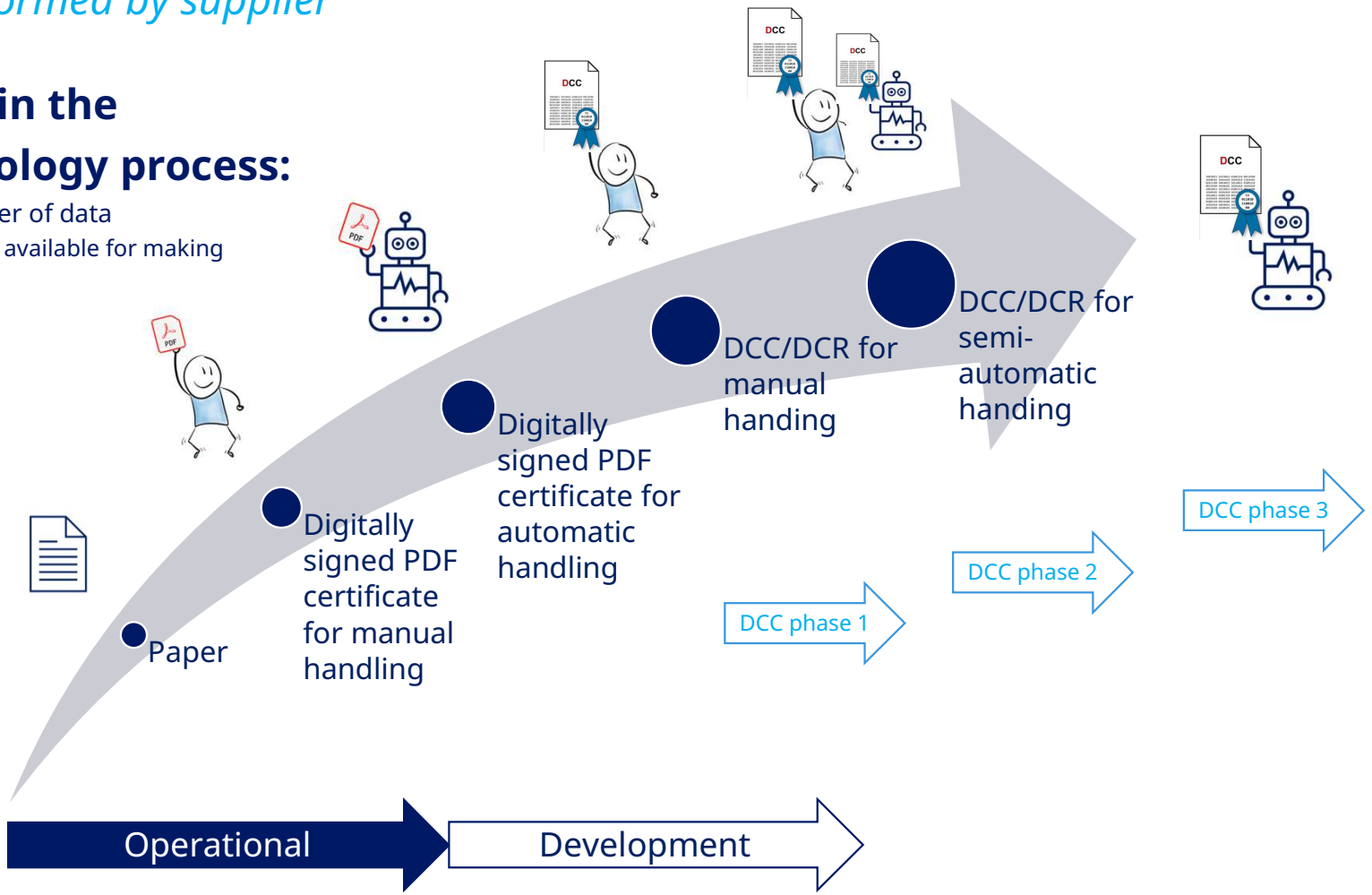
- Define what to measure
- Identify the requirements for the measurand
- Calibration requirements for the measuring equipment is based on the requirements for the measurand
- Calibration intervals are specified based on a risk assessment assessing impact, probability and mitigation
- IT system evaluates if a calibration is pass or fail
- If measuring equipment does not comply with requirements – Deviations are created to evaluate the use in the entire period back to the last passed calibration
- No supplier conformity statements – evaluation and release of measuring equipment for use is a Novo Nordisk responsibility
- Certificates are delivered to Novo Nordisk

Digitalisation and Automation Journey

- Calibration performed by supplier

Strategic goals in the corporate metrology process:

- Remove manual transfer of data
- FAIR and relevant data is available for making decisions

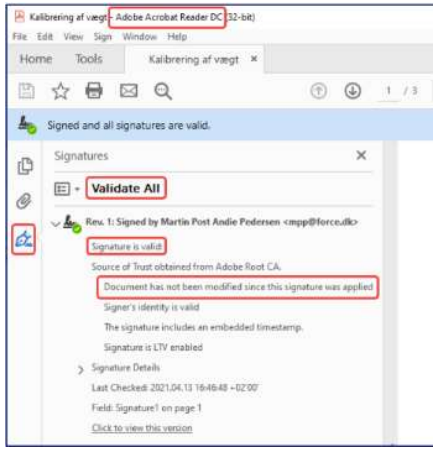


Digitalisation and Automation Journey

Operational – digitally signed PDF calibration certificates

- Corporate procedure for *Requirements for exchanging digitally signed PDF documents with external partners* is established.

- Guidance on how to receive, integrity test and archive digitally signed PDF calibration are established.



Current state:

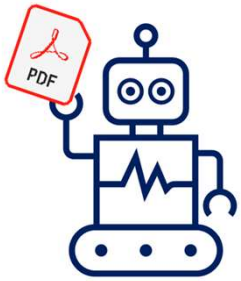
- Agreement with 9 Danish suppliers and 3 Chinese suppliers are established
- Certificates are manually uploaded to IT system for archiving, and data integrity of the calibration certificates are manually verified

Challenges:

- Not a simple task for the end-user
- Robustness in some suppliers' use of root certificates is lacking

Digitalisation and Automation Journey

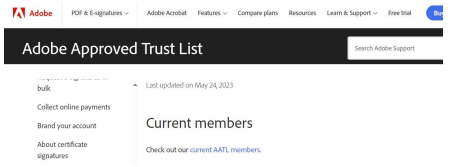
Development – RPA solution for digitally signed PDF calibration certificates



- RPA solution with automatic handling:
  - data integrity verification of the calibration certificate
  - upload of the calibration certificate to IT system for archiving
  - end-user notification.

Supplier performs the calibration → Supplier sends calibration certificate to BOT → BOT handles the certificate → BOT notifies the NN user

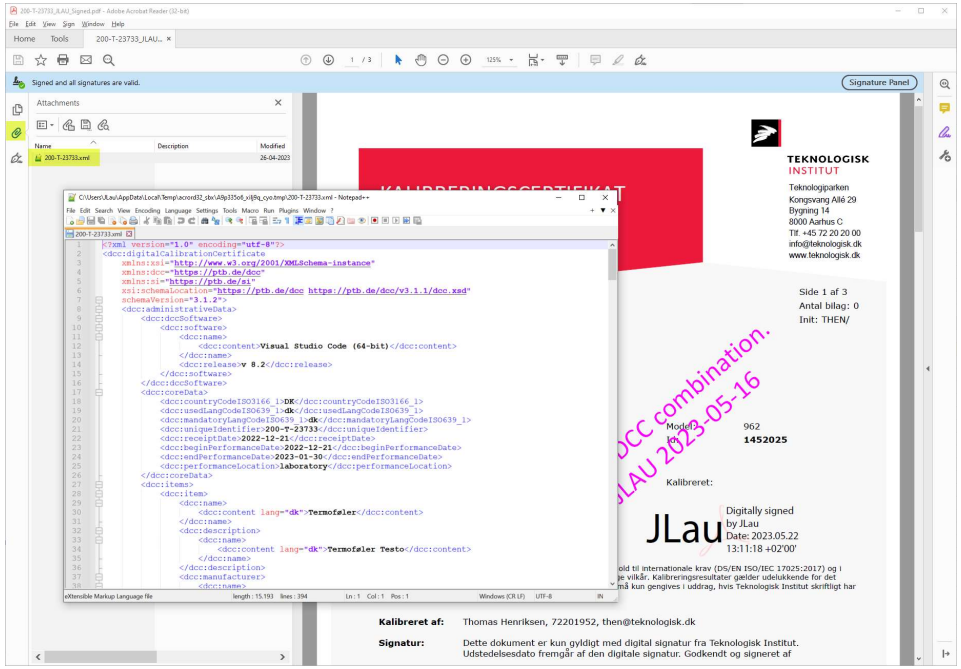
- Preconditions:
  - Agreement with supplier – BOT only accepts e-mail from these
  - Mail body requirements – the PDF certificate is not machine readable but certificate metadata is needed for the archiving process
  - Signature root certificate is available in AATL (Adobe Approved Trust List)



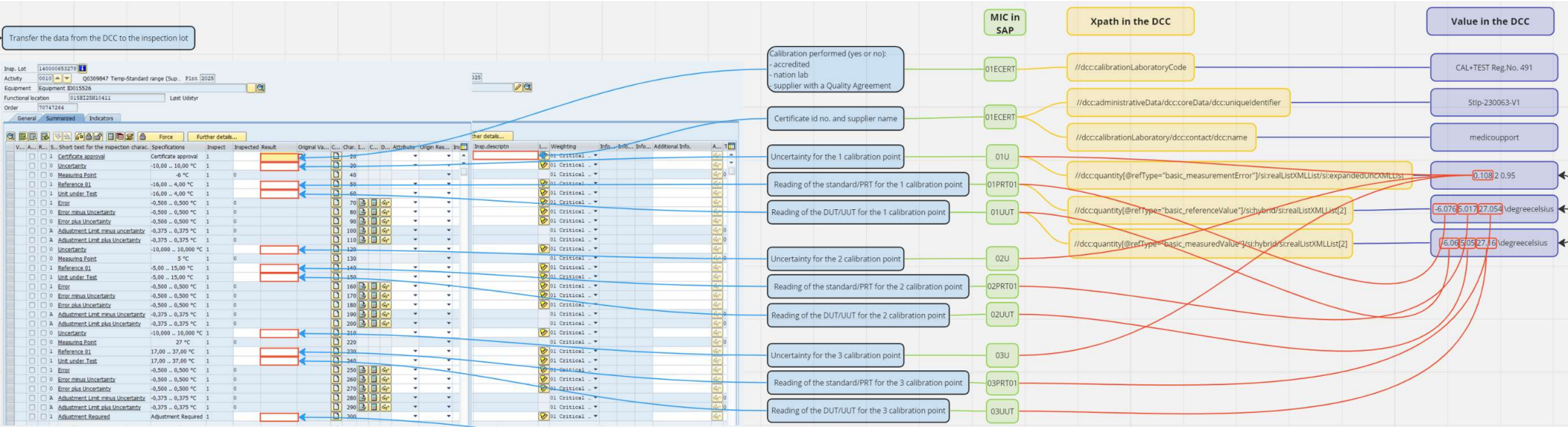
Digitalisation and Automation Journey

Development – Phase 1 DCC/DCR for manual handling (pilot phase)

- Apply experience from work with digitally signed PDF calibration certificates
- Start by having suppliers embed XML files to the PDF as an attachment
- Retain the ability to present the PDF (human readable) during inspection and audit
- Running pilots with DFM, TI and Force (DK suppliers) for implementation of DCC and DCR



Mapping of Dataflow from DCC to NN IT System



Mapping of Dataflow from DCC to NN IT System

Xpaths need to be consistent, well defined and objective

- One Xpath for the administrative data: //dcc:calibrationLaboratoryCode
- More Xpaths for the calibration results:
  - //dcc:quantity[@refType="basic_referenceValue"]/si:hybrid/si:realListXMLList
  - //dcc:quantity[@refType="basic_referenceValue"]/si:hybrid/si:realListXMLList[2]


```
<dcc:data>
    <dcc:list refType="gp_table1">
        <dcc:quantity refType="basic_referenceValue">
            <dcc:name>
                <dcc:content lang="de">Bezugswert</dcc:content>
                <dcc:content lang="en">Reference value</dcc:content>
            </dcc:name>
            <si:hybrid>
                <si:realListXMLList>
                    <si:valueXMLList>267.074 278.167 300.204</si:valueXMLList>
                    <si:unitXMLList>\kelvin</si:unitXMLList>
                </si:realListXMLList>
                <si:realListXMLList>
                    <si:valueXMLList>-6.076 5.017 27.054</si:valueXMLList>
                    <si:unitXMLList>\degreecelsius</si:unitXMLList>
                </si:realListXMLList>
            </si:hybrid>
            <dcc:measurementMetaData>
```

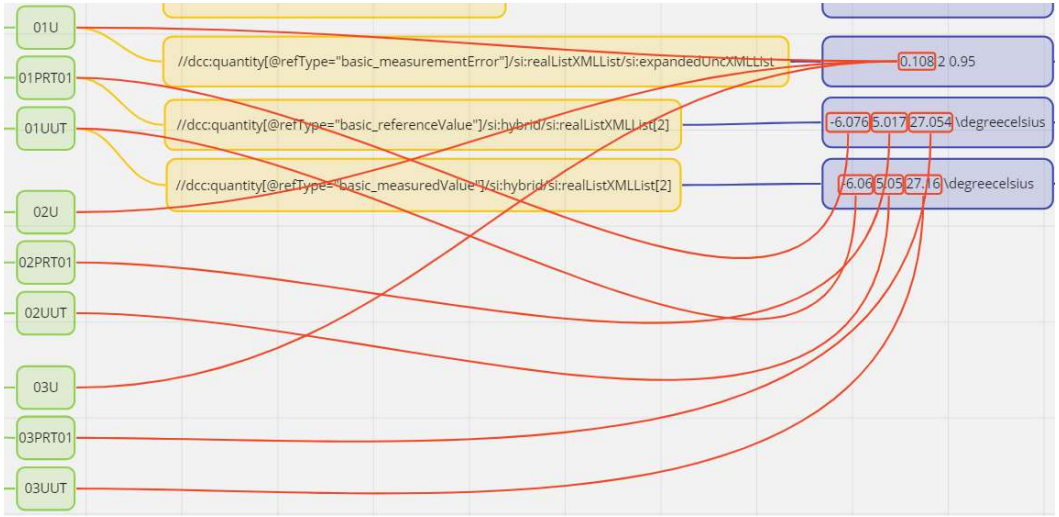
Challenges

DCC feedback from NN IT experts

"How do we know that:

- *the first calibration point is actually the first point?*
- *a calibration point is not missing?*
- *the calibration points are in the correct order?"*

Requirements in the IT process originate from the NN Corporate Quality Processes *Good Documentation Practise* and *Records Management*



List of some of the Requirements NN must comply with related to Healthcare-regulated Records

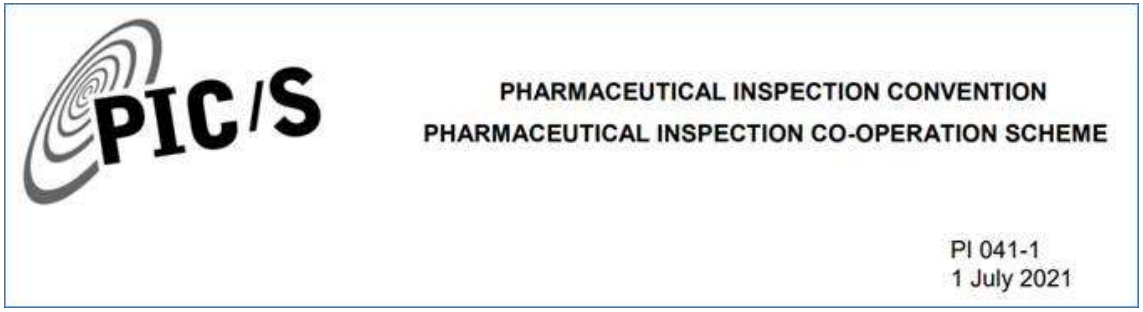
- ANVISA - GMP Computerized Systems REGULATORY DIRECTIVE - IN NO. 43
- China - Guidance - Drug Data Management
- DK - Part 1245 - Good laboratory practice for drugs
- DK - Part 1358 - Producing and importing drugs and intermediates
- EMA - Guideline GMP / GDP compliance Questions and answers: GMP - Data integrity
- EU - Regulation 2017/745 on Medical Devices
- EU GMP - Annex 1 - Sterile Medicinal Products
- EU GMP - Annex 11 - Computerised Systems
- EU GMP - Part I - Chapter 2 Personnel
- EU GMP - Part I - Chapter 4 Documentation
- EU GMP - Part I - Chapter 7 Outsourced Activities
- EU GMP - Part III - Q10 Pharmaceutical Quality System
- FDA - 21 CFR Part 11 - Electronic Records
- FDA - 21 CFR Part 211 - cGMP for finished pharmaceuticals
- FDA - 21 CFR part 820 - Medical devices
- FDA - Guidance - Data Integrity and Compliance With CGMP
- ISO - 13485 - Medical devices, Requirements for regulatory purposes
- MHRA - GMP Data Integrity Definitions and Guidance for Industry
- OECD - no 1 - GLP and Compliance Monitoring
- OECD - no 15 - Establishment and Control of Archives within GLP
- OECD - no 17 - Application of GLP Principles to Computerised Systems
- OECD - no 22 - Advisory Document of the Working Party on Good Laboratory Practice on GLP Data Integrity
- US – Pharmacopeia
- WHO - Guidance - Good Data and Record Management Practices

By following the ALCOA+ PRINCIPALS we are covered

Regulatory Requirements that NN needs to fulfil

- Requirements to records including calibration records

- Novo Nordisk advanced QMS Expert in Records Management referred to *PIC/S GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS (PI 041-1)* *link*



  - Describing the ALCOA+ principles

ALCOA+ Attributable

Attributable	It should be possible to identify the individual or computerised system that performed a recorded task and when the task was performed. This also applies to any changes made to records, such as corrections, deletions, and changes where it is important to know who made a change, when, and why.

- Identification of the individual performing the task is OK
- Date for when the task was performed is OK
- We expect the calibration certificate to be locked for editing with a **trusted signature** and in a way so it can be verified that the document has **not been altered after the last signature** was applied

ALCOA+ Legible

Legible	All records should be legible – the information should be readable and unambiguous in order for it to be understandable and of use. This applies to all information that would be required to be considered Complete, including all Original records or entries. Where the 'dynamic' nature of electronic data (the ability to search, query, trend, etc.) is important to the content and meaning of the record, the ability to interact with the data using a suitable application is important to the 'availability' of the record.

```
<dcc:quantity refType="basic_measuredValue">
    <dcc:name>
        <dcc:content lang="de">Angezeigter Messwert Kalibriergegenstand</dcc:content>
        <dcc:content lang="en">Indicated measured value probe</dcc:content>
    </dcc:name>
    <si:hybrid>
        <si:realListXMLList>
            <si:valueXMLList>267.09 278.20 300.31</si:valueXMLList>
            <si:unitXMLList>\kelvin</si:unitXMLList>
        </si:realListXMLList>
        <si:realListXMLList>
            <si:valueXMLList>-6.06 5.05 27.16</si:valueXMLList>
            <si:unitXMLList>\degreecelsius</si:unitXMLList>
        </si:realListXMLList>
    </si:hybrid>
</dcc:quantity>
```

- The calibration results presented as numbers in a row are not **unambiguous**. We will be challenged during audits and inspections with questions such as:
  - *How do you know that:*
    - *the first calibration point is actually the first point?*
    - *a calibration point is not missing?*
    - *the calibration points are in the correct order?*

ALCOA+ Contemporaneous

Contemporaneous	The evidence of actions, events or decisions should be recorded as they take place. This documentation should serve as an accurate attestation of what was done, or what was decided and why, i.e. what influenced the decision at that time.

```
<dcc:calibrationLaboratory>
  <dcc:calibrationLaboratoryCode>CAL+TEST Reg.No. 491</dcc:calibrationLaboratoryCode>
    <dcc:contact>
        <dcc:name>
            <dcc:content>medicoupport</dcc:content>
        </dcc:name>
        <dcc:location>
            <dcc:city>Herlev</dcc:city>
            <dcc:countryCode>DK</dcc:countryCode>
            <dcc:postCode>2730</dcc:postCode>
            <dcc:street>Marielundvej</dcc:street>
            <dcc:streetNo>46C</dcc:streetNo>
            <dcc:further>
                <dcc:content>2th</dcc:content>
            </dcc:further>
        </dcc:location>
    </dcc:contact>
</dcc:calibrationLaboratory>
```

- Covered by requirements in ISO 17025 section 7.8.1.2

7.8.1.2 The results shall be provided accurately, clearly, unambiguously and objectively, usually in a report (e.g. a test report or a calibration certificate or report of sampling), and shall include all the information agreed with the customer and necessary for the interpretation of the results and all information required by the method used. All issued reports shall be retained as technical records.

ALCOA+ Original

Original	The original record can be described as the first-capture of information, whether recorded on paper (static) or electronically (usually dynamic, depending on the complexity of the system). Information that is originally captured in a dynamic state should remain available in that state.

- Covered by requirements in ISO 17025 section 7.8.1.2

```
<dcc:calibrationLaboratory>
    <dcc:calibrationLaboratoryCode>CAL+TEST Reg.No. 491</dcc:calibrationLaboratoryCode>
    <dcc:contact>
        <dcc:name>
            <dcc:content>medicoupport</dcc:content>
        </dcc:name>
        <dcc:location>
            <dcc:city>Herlev</dcc:city>
            <dcc:countryCode>DK</dcc:countryCode>
            <dcc:postCode>2730</dcc:postCode>
            <dcc:street>Marielundvej</dcc:street>
            <dcc:streetNo>46C</dcc:streetNo>
            <dcc:further>
                <dcc:content>2th</dcc:content>
            </dcc:further>
        </dcc:location>
    </dcc:contact>
</dcc:calibrationLaboratory>
```

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ALCOA+ Accurate

Accurate	Records need to be a truthful representation of facts to be accurate. Ensuring records are accurate is achieved through many elements of a robust Pharmaceutical Quality System. This can be comprised of: • equipment related factors such as qualification, calibration, maintenance and computer validation. • policies and procedures to control actions and behaviours, including data review procedures to verify adherence to procedural requirements • deviation management including root cause analysis, impact assessments and CAPA
	• trained and qualified personnel who understand the importance of following established procedures and documenting their actions and decisions. Together, these elements aim to ensure the accuracy of information, including scientific data that is used to make critical decisions about the quality of products.

- ISO 17025 ✓

```
<dcc:calibrationLaboratory>
    <dcc:calibrationLaboratoryCode>CAL+TEST Reg.No. 491</dcc:calibrationLaboratoryCode>
    <dcc:contact>
        <dcc:name>
            <dcc:content>medicoupport</dcc:content>
        </dcc:name>
        <dcc:location>
            <dcc:city>Herlev</dcc:city>
            <dcc:countryCode>DK</dcc:countryCode>
            <dcc:postCode>2730</dcc:postCode>
            <dcc:street>Marielundvej</dcc:street>
            <dcc:streetNo>46C</dcc:streetNo>
            <dcc:further>
                <dcc:content>2th</dcc:content>
            </dcc:further>
        </dcc:location>
    </dcc:contact>
</dcc:calibrationLaboratory>
```

ALCOA+ Complete

Complete	All information that would be critical to recreating an event is important when trying to understand the event. It is important that information is not lost or deleted. The level of detail required for an information set to be considered complete would depend on the criticality of the information (see section 5.4 Data criticality). A complete record of data generated electronically includes relevant metadata (see section 9).

- The calibration results presented as numbers in a row are lacking metadata information about which number relates to which calibration point

- DCC

```
<dcc:quantity refType="basic_measuredValue">
    <dcc:name>
        <dcc:content lang="de">Angezeigter Messwert Kalibriergegenstand</dcc:content>
        <dcc:content lang="en">Indicated measured value probe</dcc:content>
    </dcc:name>
    <si:hybrid>
        <si:realListXMLList>
            <si:valueXMLList>267.09 278.20 300.31</si:valueXMLList>
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        </si:realListXMLList>
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            <si:valueXMLList>-6.06 5.05 27.16</si:valueXMLList>
            <si:unitXMLList>\degreecelsius</si:unitXMLList>
        </si:realListXMLList>
    </si:hybrid>
</dcc:quantity>
```
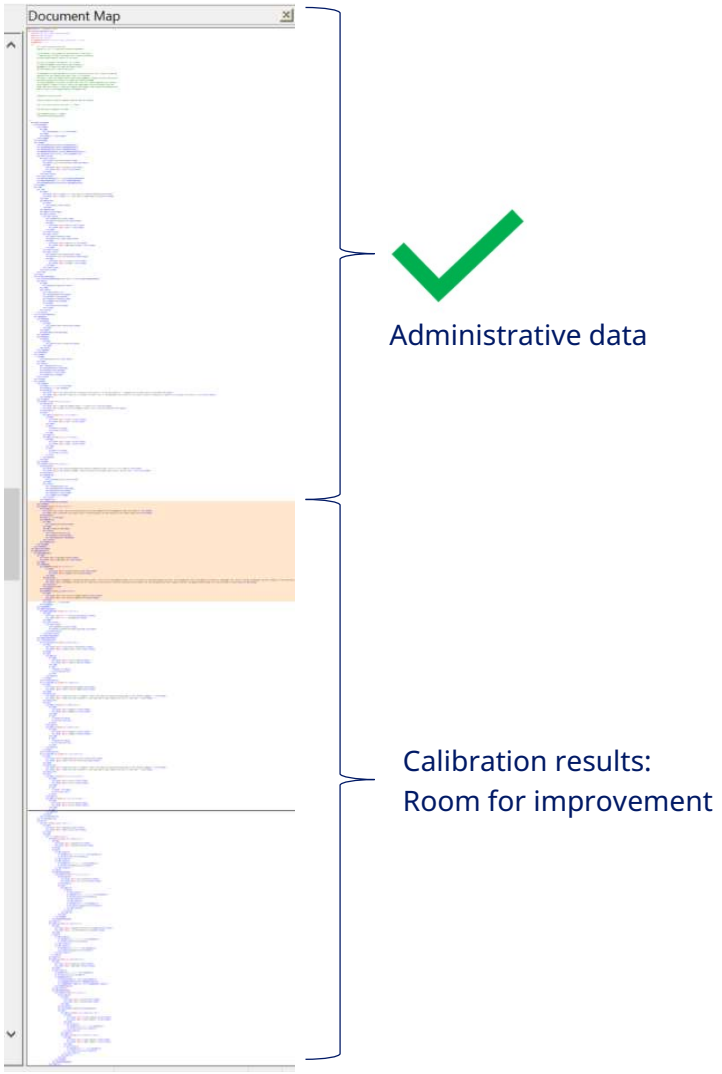

9.1.5.2 In dealing with metadata, some metadata is critical in reconstruction of events, (e.g. user identification, times, critical process parameters, units of measure), and would be considered as 'relevant metadata' that should be fully captured and managed. However, non-critical meta-data such as system error logs or non-critical system checks may not require full capture and management where justified using risk management.

ALCOA+ Consistent

Consistent	Information should be created, processed, and stored in a logical manner that has a defined consistency. This includes policies or procedures that help control or standardize data (e.g. chronological sequencing, date formats, units of measurement, approaches to rounding, significant digits, etc.).

- We need an international procedure/standard for a DCC to support this requirement
  - Metadata for the administrative data in the DCC is good



ALCOA+ Enduring

Enduring	Records should be kept in a manner such that they exist for the entire period during which they might be needed. This means they need to remain intact and accessible as an indelible/durable record throughout the record retention period.

- Info: the retention period for a calibration certificate at Novo Nordisk is 10 years
- Novo Nordisk plans to upload the DCC to a database to archive and protect the records

ALCOA+ Available

Available	Records should be available for review at any time during the required retention period, accessible in a readable format to all applicable personnel who are responsible for their review whether for routine release decisions, investigations, trending, annual reports, audits or inspections.

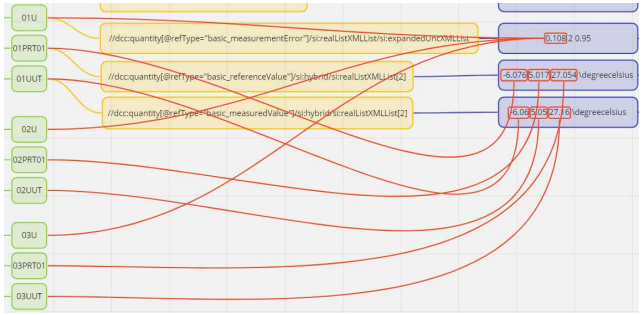
- Novo Nordisk plans to upload the DCC to a database to archive and protect the records
- This requirement relates to Novo Nordisk capability of reading the record in the retention period

PI 041-1 Section 9.4

9.4 Data Transfer

Item:	Data transfer and migration
1.	**Expectation** Interfaces should be assessed and addressed during validation to ensure the correct and complete transfer of data. Interfaces should include appropriate built-in checks for the correct and secure entry and processing of data, in order to minimise data integrity risks. Verification methods may include the use of: ○ Secure transfer ○ Encryption ○ Checksums Where applicable, interfaces between systems should be designed and qualified to include an automated transfer of GMP/GDP data. **Potential risk of not meeting expectations/items to be checked** • Interfaces between computerised systems present a risk whereby data may be inadvertently lost, amended or transcribed incorrectly during the transfer process. • Ensure data is transferred directly to the secure location/database and not simply copied from the local drive (where it may have the potential to be altered).

- The Novo Nordisk project team is concerned about meeting this requirements in the current structure of the calibration points in the DCC



PI 041-1 –Section 5.5.3 Risk (Good Guidance)

5.5.3 Examples of factors which can increase risk of data failure include processes that are complex, or inconsistent, with open ended and subjective outcomes. Simple processes with tasks which are consistent, well defined and objective lead to reduced risk.

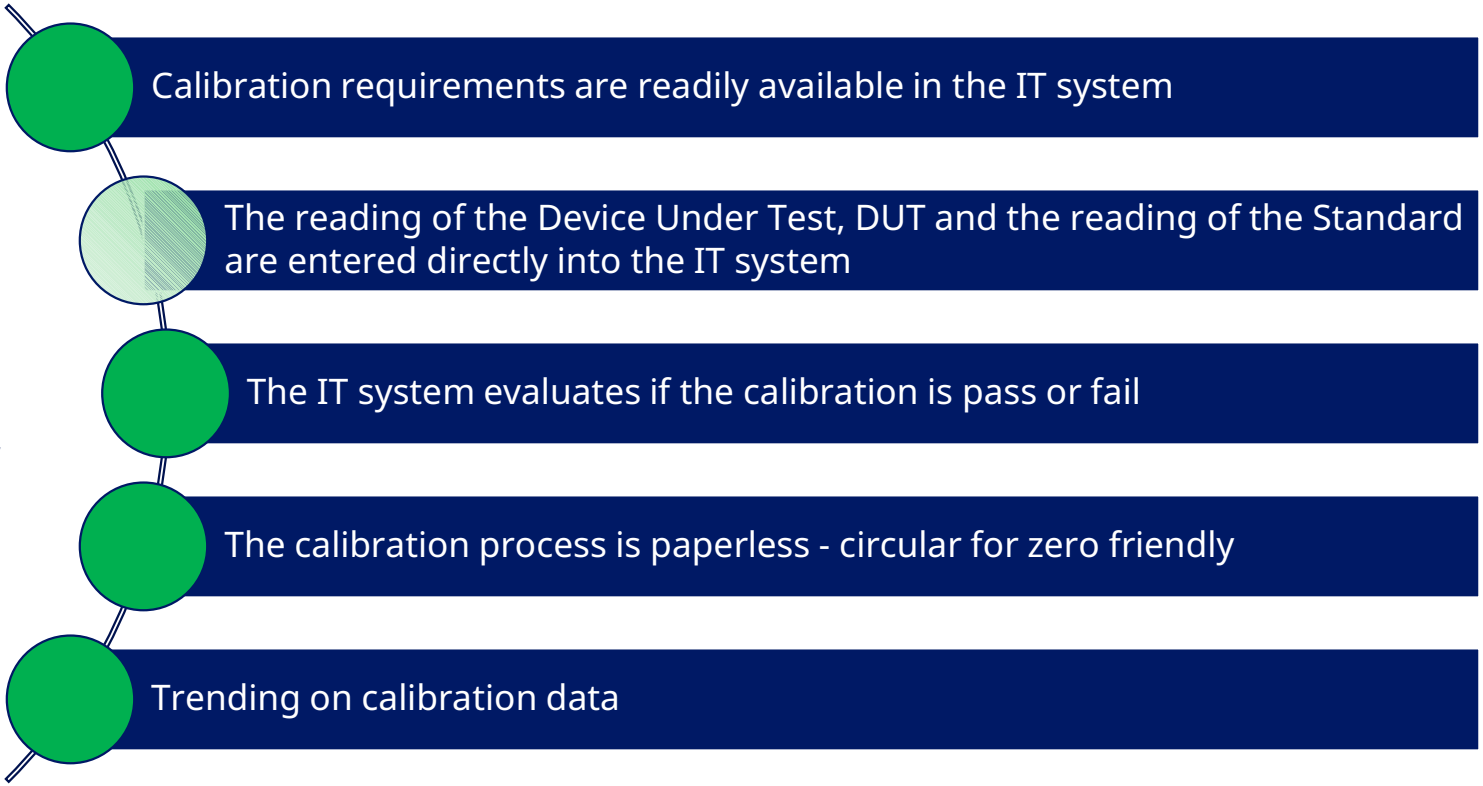
At Novo Nordisk we prefer simplicity

Calibration Performed by Novo Nordisk Employee

- most measuring equipment is calibrated in-situ

Strategic goals in the corporate metrology process:

- Remove manual transfer of data
- FAIR and relevant data is available for making decisions

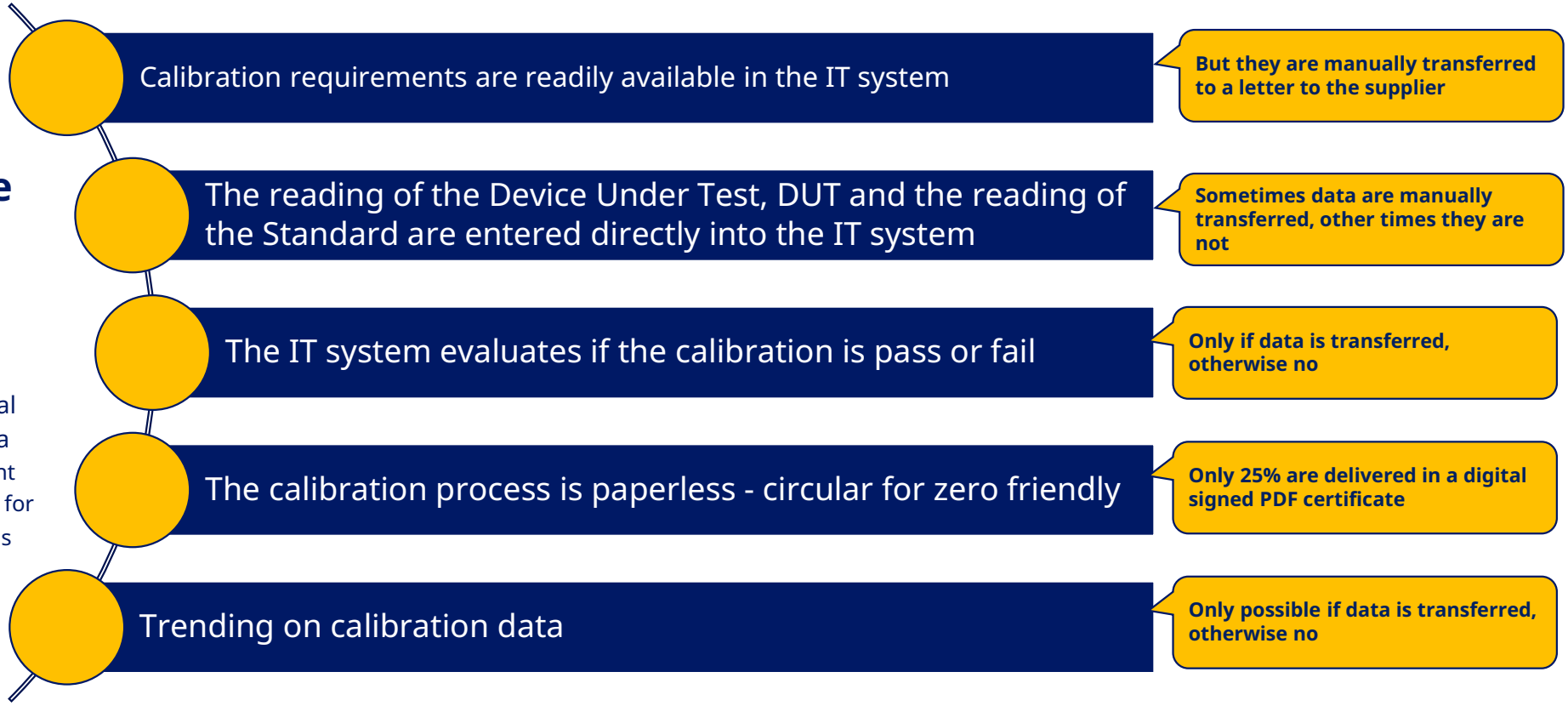


Calibration Performed by Supplier

- 20.000 calibrations a year

Strategic goals in the corporate metrology process:

- Remove manual transfer of data
- FAIR and relevant data is available for making decisions



WHY

- 20.000 supplier calibrations a year

Current status:

- Calibration certificates are analogue and not machine readable or interoperable
  - In average it takes 20 minutes to transfer data from the calibration certificate to the IT system including second person review
- Communication from Novo Nordisk to supplier is manual
  - In average it takes 25 minutes to transfer data from IT system to a letter
  - 5% of all revised calibration certificates are revised due to errors in NN calibration request

- Trending on calibration data
  - Transparent data insight via the dashboard above
  - Machine Learning under development to trend on data including metadata, and classify between equipment exhibiting systematic drift or not

Summery

- Digitalization and automation creates more stable and robust processes
- Implementation of DCR and DCC is a huge project with a long timeline but by applying agile prototyping the goal is reached with realizations of the project as it matures over time