Master's Thesis

Development and implementation of a UDI system for the identification and traceability of in vitro diagnostics

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Abbreviations

AI	Application Identifier
AIDC	Automatic Identification and Data Capture
CFR	Code of Federal Regulations
DIN	Deutsches Institut für Normung
DNA	Deoxyribonucleic acid
EC	European Commission
EN	Europäische Norm
EU	European Union
EUDAMED	European database on medical devices
FDA	Food and Drug Administration
GTIN	Global Trade Item Number
GMN	Global Model Number
GUDID	Global Unique Device Identification Database
HIBCC	Health Industry Business Communications Council
HRI	Human Readable Interpretation
ICCBBA	International Council for Commonality in Blood Banking Automation
IFA	Informationsstelle für Arzneispezialitäten
IFU	Instruction for use
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
IVD	In vitro diagnostic

IVDD	In vitro Diagnostics Directive
IVDR	In vitro Diagnostics Regulation
LIC	Labeler Identification Code
MDCG	Medical Device Coordination Group
MPHO	Medical Products of Human Origin
PCR	Polymerase chain reaction
PPN	Pharmacy Product Number
RFID	Radio Frequency Identification
SRN	Single Registration Number
tbd	to be done
UDI	Unique Device Identification
UDI-DI	UDI – Device Identifier
UDI-PI	UDI – Production Identifier
USA	United States of America
WHO	World Health Organization

1 Introduction

The area of medical devices is advancing rapidly at a scientific and technical level becoming increasingly effective and innovative. In particular, in vitro diagnostics (IVDs) are an important medical device segment. Rising expectations for early and precise disease diagnosis and recurrent infectious diseases are increasing the demand for IVDs. The term *in vitro* describes a process which occurs outside a living organism. It usually involves isolated tissue structures, organs or cells [1]. The In vitro Diagnostics Regulation (IVDR) defines the term *in vitro diagnostic medical device* in the second paragraph of article 2. This section describes that this is a medical device designed for in vitro examination of samples taken from the human body. With the help of an IVD, information on the course of therapy, physiological and pathological processes or congenital anomalies can be obtained [2].

The IVDR officially came into force on 25th May 2017 and replaced the In vitro Diagnostic Directive (IVDD), which had been in effect until then [3]. The difference between a directive and a regulation is that a regulation is directly enforced by law in all Member States. In contrast, a directive has to be transposed into national law in order to achieve the objectives defined in the directive [4].

The aim of the IVDR is to ensure the quality of devices and reliability of supply in the field of medical devices throughout Europe [3]. By changing the directive into a regulation, manufactures have to adopt to new requirements. The number of articles has increased from 24 to 113.
Reasons for revising the directive were to ensure a high level of health and safety protection, but also to encourage innovation. The regulation sets high standards for the quality and safety of IVDs, thereby resolving general safety concerns. Furthermore, the regulation intends to assure a well-functioning internal market for IVDs [2].

By introducing the IVDR, previously applicable requirements have been considerably reinforced and new requirements have been added. One of the new requirements in the regulation is the Unique Device Identification (UDI) system. The purpose of this system is to ensure the traceability of medical devices and IVDs. It enables the identification of individual devices and is created using international coding standards. The UDI consists of a sequence of numeric and alphanumeric characters [2].

The IVDD did not contain specific provisions on traceability and therefore this aspect should be taken into account in the regulation. Traceability of medical devices including IVDs throughout the supply chain is intended to enhance patient safety. The meaning of patient safety is to prevent and minimize the negative consequences of a health service or the injuries caused by it [5].

In order to achieve traceability within the entire European Union (EU), the IVDR provides for a harmonized UDI system. In case Member States have already developed a traceability system, it has to be compatible with the UDI system defined by the EU [5].

On the one hand, the main objectives of improved patient safety and the optimization of their treatment will be achieved by the introduction of the UDI system, and on the other hand, the system will contribute to the attainment of further objectives. These objectives can be also considered as positive effects of the UDI system [5].
One possible benefit is considered to be an improvement in warehouse management. Healthcare providers can share their stock information with their vendors and manufacturers, which helps manufacturers prevent overproduction. Since the medical devices including the IVDs contain a machine-readable UDI, which means it is displayed in form of a bar code, the inventory will be made easier and not prone to human error. The bar codes enable more accurate data capture, minimizing errors that can occur when manually entering data into the system [6].
As another benefit, more efficient recalls are expected. This aspect is more related to medical devices, such as implants. The allocation of a UDI to a specific device and its worldwide use throughout the entire distribution chain allows the device to be clearly identified. With the UDI system, the recall process is less time-consuming because scanning the bar code identifies whether the device is affected or not [6].
Moreover, it is anticipated that medical errors will be diminished through the use of a consistent identification mechanism. Due to the unique identification, confusion or incorrect selection of device can be prevented. Since the information about the device has to be stored in a database, this also facilitates the reliable identification of the product and thus confusion with similar devices can be avoided [5, 7].

A further important aspect of the IVDR is transparency and adequate access to information. This requires the establishment of the European database on medical devices (EUDAMED). This database includes various systems, including the UDI database. In this database, information on manufacturers and devices is entered and made available to the public [2].

In the field of IVDs, altona Diagnostics GmbH based in Hamburg is specialized. The company develops and commercializes real-time PCR-based tests with a focus on infectious diseases. Polymerase chain reaction (PCR) is a method by which deoxyribonucleic acid (DNA) sections are amplified. It enables small amounts of DNA to be replicated within a very short time, so that a DNA analysis is possible [8].

The objective of this Master's thesis is to meet the requirements of the UDI system for the IVDs of altona Diagnostics GmbH. Therefore, the requirements for the UDI have to be specified and the UDI

carrier has to be printed on the label. The generated labels have to be compared with the specifications using a test protocol.

In chapter 2 the UDI system and its individual components are introduced. Besides the UDI there is a Basic UDI-DI, which is required by the IVDR and which is also explained here. Unlike the EU, the UDI was introduced earlier in the United Stated of America (USA). This chapter will also highlight the differences between the UDI system in the EU and USA.

Chapter 3 deals with the implementation of the UDI system. One of the aims is to have the UDI carrier printed on the label of the IVDs. To achieve this, the requirements of the regulation has to be taken in account and a design input has to be developed, which is presented in section 3.1.
In order to integrate the UDI system into an overall system, the necessary documents such as Standard Operating Procedure and Work Instruction have to be created to provide the employees of altona Diagnostics GmbH an understanding of it. Section 3.3 deals with the verification of the created labels. For this purpose, a form sheet should be created. The last section covers the transfer and release of the labels containing the UDI carrier.

The outcome of the implementation of the UDI system and the resulting difficulties are discussed in chapter 4. To verify the applicability of the Work Instruction, an internal test was performed, which results are also presented in this chapter. Furthermore, it is explained why certain phases could not be implemented in the time frame.

The Master's thesis is concluded with the fifth chapter. In the annex the created documents are presented.

2 Background

In this chapter, the theoretical basics are considered which are necessary for understanding as well as for implementation. The focus is on how a UDI system is structured and what has to be considered. This chapter also compares EU and US requirements.

2.1 UDI system

The UDI system is composed of three elements as shown in figure 1. The first component is the UDI, which is classified into UDI-DI and UDI-PI. The UDI-DI is static data that is used to uniquely identify the device. The dynamic data is represented under the UDI-PI [9].
Another element is the UDI carrier. It displays the device data in a machine-readable part, however, it also contains a plain-text part that is easily readable by the human eye [9].
As the final element, the UDI database completes the whole system, where only static data is stored [10].

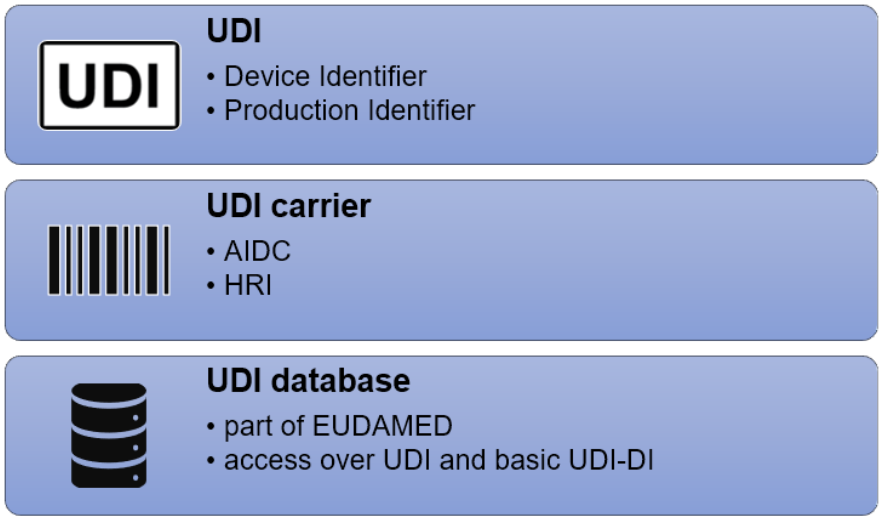


Fig. 1*: The UDI system is a new requirement in the IVDR. It consists of the three elements UDI, UDI carrier and UDI database (Own development)*

In July 2019, the European Commission (EC) published an implementing decision naming four issuing entities that are allowed to issue UDIs in accordance with the IVDR. The following four companies were selected by the EC [11]:

- GS1 AISBL
- Health Industry Business Communications Council (HIBCC)
- International Council for Commonality in Blood Banking Automation (ICCBBA)
- Informationsstelle für Arzneispezialitäten (IFA) GmbH.

GS1 is a global organization for supply chain standards, which is the most widely used and applied by all stakeholders in healthcare supply chains worldwide. In order to comply with the UDI requirements of the IVDR, the GS1 standards can be taken into consideration. In fact, for all three elements of the UDI system there are solutions based on GS1 standards [12].

HIBCC is an internationally accredited, industry-supported nonprofit organization with global reach. Standards are developed to address the unique needs of global healthcare providers. These includes also bar code labeling and UDI compliance to location identifiers [13].

Another international non-governmental and non-profit organization is ICCBBA, established in official relations with the World Health Organization (WHO). Their purpose is to improve patient safety by standardizing the procedures for indicating critical information on labels of medical devices of human origin [14]

The last issuing entity designated by the EC is IFA GmbH, which is an information service provider for the pharmaceutical market. IFA GmbH provides specifications for machine reading and automated processing of the data elements. UDI data elements for the labeling of medical devices can be generated using IFA coding system [15].

Moreover, the FDA has also accredited the first three mentioned as issuing agencies for assigning UDIs [16].

2.1.1 Structure of a UDI

The UDI is comprised of the following two parts:

- UDI Device Identifier (UDI-DI)
- UDI Production Identifier (UDI-PI)

The UDI-DI is a numeric or alphanumeric code specific to a manufacturer and unique at all levels of device packaging. It is assigned by the above-mentioned organizations designated by the European Commission. The manufacturer contacts such an organization and can purchase the UDI-DIs there. Eventually, the assigned number is registered in its database to confirm that the number and the device belong to this manufacturer [10].

One of the known identification number is the Global Trade Identification Number (GTIN), which is issued by GS1. If the manufacturer is already using GTINs in his company then this can be taken as the UDI-DI. Part of this GTIN is a global localization number, which is unique to the manufacturer and thus prevents the likelihood of confusion between companies [17].

According to the HIBCC standard, the Device Identifier consists of several parts. First part is the Labeler Identification Code (LIC) assigned by HIBCC after an application is submitted. This identifies a registered company. A device or catalog number is the second component of the UDI-DI and the unit of measure identifier is the third. The final part of the Device Identifier is one check character, which can be alpha-numeric [18].

When considering ICCBBA, the Processor Product Identification Code allocated by ICCBBA can be regarded as a UDI-DI. This data structure includes a Facility Registration Number identifying the manufacturer [19].

The Pharmacy Product Number (PPN) is issued by IFA GmbH and is unique for each manufacturer. It is characterized by the fact that it always starts with 11. This number can be used as the UDI-DI, if the manufacturer decides to work with the IFA standards [20].

Second part of the UDI code is the production identifier, which concerns variable data. Similar to the UDI-DI, numeric or alphanumeric characters are used here to represent the unit of device production. The variable data can include:

- Expiry date
- Lot number
- Serial number.

Generally, the date of manufacture is not part of the UDI-PI. But in case the above-mentioned data is not available, then it becomes part of the production identifier [10].

With a change in the device data, a new UDI-DI has to be generated. The following data elements are regarded as triggers to produce a new UDI-DI [2]:

- Name or trade name
- Device version or model
- Labeled as single use
- Packaged sterile
- Need for sterilization before use
- Quantity of devices provided in a package
- Critical warnings or contra-indications.

The generated UDI is affixed to the device itself or its packaging. Considered as discrete commodities, each defined packaging layer has its own UDI-DI. Exception to this are shipping containers since they are not classified as packaging layers and therefore do not include UDI [2]. Figure 2 clarifies the individual packaging layers.

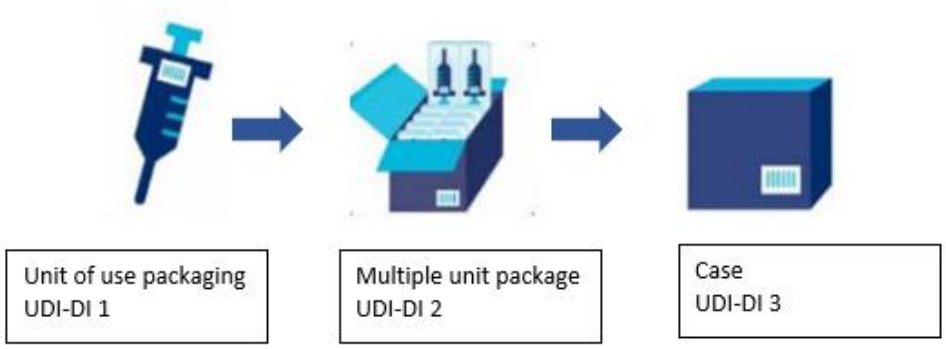


Fig. 2: *Three different packaging levels with their respective UDI-DIs (Own development modified according to [21])*

2.1.2 UDI carrier

According to the IVDR, the UDI carrier has to be both machine-readable and in plain-text. For the machine-readable form, the Automatic Identification and Data Capture (AIDC) technology is used, which enables automatic data acquisition. This comprises linear and 2D bar codes, smart cards, biometrics and Radio Frequency Identification (RFID) [2].
The issuing entities mentioned above offer different possibilities to display the UDI code in the AIDC and Human Readable Interpretation (HRI) format.

GS1 enables UDI-DI and UDI-PI information to be encoded in a linear bar code, 2D bar code and QR code. The GS1-128 bar code can be applied for the linear bar code and the GS1 DataMatrix for the 2D bar code. In addition, the GS1 standards can be used to create a QR code [12]. All three machine-readable form are exemplified in the figure below. If the plain-text begins with numbers in brackets, it is an indication for a GS1 standard.

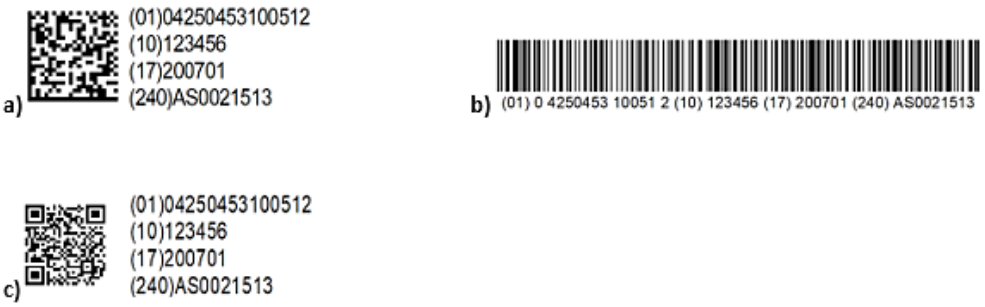


Fig. 3: *Three different UDI carriers of GS1, a) GS1-128 bar code, b) DataMatrix, c) QR code (Own development)*

Besides the AIDC, it is additionally required to have a HRI, which provides the information in plain-text, making it readable by the human eye. The plain-text should be placed near the machine-readable form.

Figure 3 shows that certain digits are in brackets. These indicate an Application Identifier (AI) prefix code, which assigns a meaning to the encoded date. The AIs are attributed their meanings by GS1 [12]. Some commonly used AIs are listed in table 1.

Application Identifier	Meaning
(01)	GTIN
(10)	Lot number
(11)	Production date
(17)	Expiration date
(21)	Serial number
(240)	Additional product identification assigned by the manufacturer
(8200)	Extended Packaging URL

Tab. 1: *Application Identifiers with the corresponding meanings provided by GS1* [22]

With HIBCC it is also possible to create the same bar codes as with GS1. While GS1 bar codes are identified by numbers in brackets at the beginning, HIBCC bar codes start with a *+* sign. To concatenate the Device Identifier with the Production Identifier a */* sign is used. But this sign is also used to distinguish the individual data, such as expiration date or serial number [23]. In figure 4 the linear bar code, Data Matrix and QR code are visualized.

a)

+A99912349/$1ØX3/16D2Ø111231/14D2Ø2ØØ131/Q5ØØZ

b)

+A123PROD789Ø5/$$81Ø494121523SN654C

c)

+A123PROD789Ø5/$$81Ø494121523SN654C

Fig. 4: *HIBCC UDI carriers, a) Linear bar code, b) Data Matrix and c) QR code [24]*

Besides the / character, HIBCC has also defined identifiers to differentiate the individual data in plain-text, which are shown in table 2.

Identifier	Meaning
+	UDI-DI
$	Lot Number only
$$3	Expiration Date (YYMMDD) followed by Lot Number
$$4	Expiration Date (YYMMDDHH) followed by Lot Number
/16D	Manufacturing Date (YYYYMMDD) (supplemental to secondary bar code)
/14D	Expiration Date (YYYYMMDD) (supplemental to secondary bar code)
$+	Serial number only
/S	Supplemental Serial Number, where lot number also required and included in main secondary data string

Tab. 2: *HIBCC specific identifiers with the respective meanings [18]*

Another issuing entity is IFA GmbH. According to the IFA Coding System the use of the Data Matrix is preferred [15]. Similar to GS1 the HRI form begins with brackets, but GS1 only has numeric characters in brackets, whereas IFA GmbH can combine alphanumeric or alphabetic characters in brackets [15]. In order to separate the different data, Data Identifiers are used, which are listed in table 3.

Data Identifier	Meaning
(9N)	UDI-DI
(1T)	Lot Number
(D)	Expiration Date [YYMMDDHH] or [YYYY-MM]
(16D)	Manufacturing Date [YYMMDDHH] or [YYYY-MM]
(S)	Serial number

Tab. 3: *Data Identifiers provided by IFA GmbH* [20]

Figure 5 shows two different versions of the same UDI carrier. In the first Data Matrix, depicted in figure 5a), the UDI-PI data includes the lot number and the expiration date. The second UDI carrier has the lot number, serial number and expiration date encoded.

Fig. 5: *Two Data Matrix codes with different UDI-PI information [25]*

The last entity designated by the EU and FDA is the ICCBBA. Figure 6 shows a linear bar code as well as a Data Matrix with ICCBBA standards.

Fig. 6*: ICCBBA UDI carriers, a) linear bar code, b) Data Matrix [26]*

In figure 6a) the UDI code is broken down into its various components. The first linear bar code is the UDI-DI. The second bar code is part of the UDI-PI and is the Donation ID code. This is followed by the serial number and finally the expiration date [19]. Figure 6b) shows the Data Matrix with the same data.

Similar to other issuing entities, ICCBBA has its own identifiers to distinguish the individual data, listed in the table below.

Identifier	Meaning
=+	Compound message
=/	UDI-DI
&,1	Medical Products of Human Origin (MPHO) Lot number
=}	Manufacturing date
=>	Expiration date
=,	Serial number
=	Distinct ID code Donation ID number

Tab. 4: *The identifiers provided by ICCBBA contain only special or numeric characters and no alphabetic characters [26]*

Furthermore, RFID technologies can be used in addition to the bar codes. In the IVDR it is stated that if the manufacturer uses the RFID technology, a linear bar code or a 2D bar code will be required on the label [2]. It is possible to implement RFID technology with GS1, HIBCC and IFA GmbH, however that is not applicable to ICCBBA.

With this technology, the data is stored on a transponder. Since the data is transmitted by electromagnetic waves, there does not have to be any visual contact between transponder and reader, as it would normally be the case with bar codes. This can be seen as one of the main advantages of the RFID technology. Apart from that, they are not sensitive to dust and cover [27].
But the RFID technology is only an additional option and not a requirement.

The UDI carrier has to be placed on all levels of the device packaging. However, if there are significant space limitations on the unit of use packaging, the UDI carrier can be located at the next higher level. In case the carrier is easy to read or if the AIDC can be scanned through the device packaging, the carrier does not need to be affixed to the device packaging. For labels that do not allow the combination of AIDC and HRI, only the AIDC format has to be printed on the label [2].

2.1.3 UDI database

The European Commission has set up the EUDAMED, which contains different electronic systems and collects and processes information on medical devices that are placed on the market [2]. Figure 7 shows the seven electronic systems of the EUDAMED, where the UDI database is also part of.

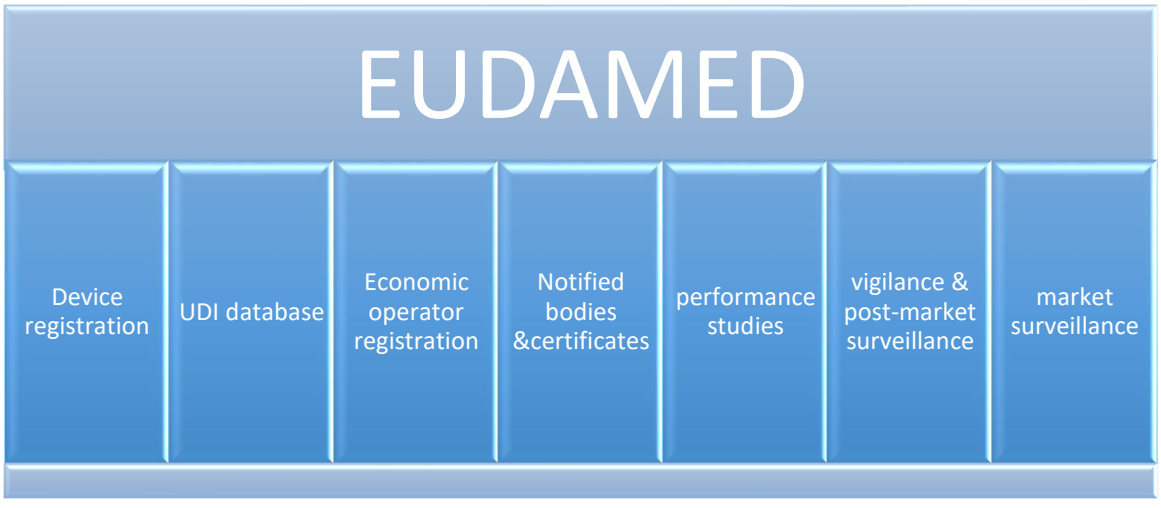


Fig. 7*: Structure of the EUDAMED. It contains seven electronic systems and one of them is the UDI database (Own development)*

This European database is intended to be accessible not only to the authorities but also to economic operators and the public. Information on the device and economic operators will be entered into the database [28].

The UDI database is a database with static data. For instance, the database stores that the device has an expiration date, but the exact date is not registered. An important element of the UDI database is the UDI-DI. Furthermore, information about the device such as trade name, risk class but also whether the device is sterile or not is stored, which are part of the 21 core data elements of the UDI database [10].

It is the manufacturer's responsibility to enter and update the core data elements. In case a core data element changes, it has to be ensured that the database is updated within 30 days. Devices that are no longer on the market remain available in the database [2].

2.1.4 Basic UDI-DI

Besides the device-specific UDI, there is also a Basic UDI-DI which is required by the IVDR. The Basic UDI-DI identifies devices of a manufacturer that have the same properties. These properties include the same intended use, risk class, design and manufacturing characteristics [29].

Even if the devices can be clustered, each device has its own UDI-DI. This is clarified in the figure 8, using a stethoscope as a reference.

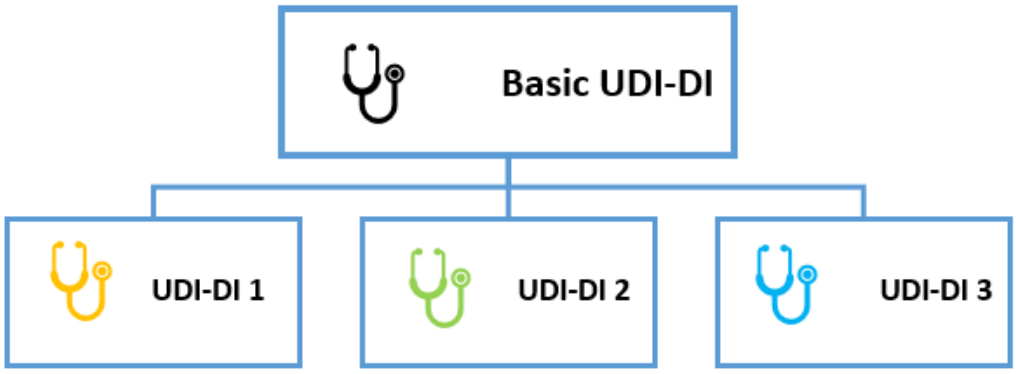


Fig. 8*: Basic UDI-DI illustrated with a stethoscope as an example. As illustrated, the Basic UDI-DI can contain numerous UDI-DIs, but a UDI-DI is connected to only one Basic UDI-DI (Own development)*

As shown in the figure above each color represents a different version of the stethoscope. But since they have the same characteristics, such as the intended use, they can be grouped together under the category stethoscope with one Basic UDI-DI. Each device in this group has its own UDI-DI implying that a Basic UDI-DI can contain several UDI-DIs, but a UDI-DI can only belong to one Basic UDI-DI.

Unlike the UDI, the Basic UDI-DI does not appear on the device label, neither in plain-text nor encoded in a bar code. It features in the UDI database and all relevant documents such as technical documentation, summary of safety and performance, EU declaration of conformity and certificate of free sale [29].

The Basic UDI-DI can be realized with one of the four accredited issuing agencies.
When implementing the Basic UDI DI, the Global Model Number (GMN) of GS1 can be taken into account. The GMN is used to specify device models or device families. Devices varying in color, size or version but technically identical are aggregated. This corresponds to the concept of the Basic UDI-DI [30].

The Basic UDI-DI is made up of three parts as visualized in figure 9. First part is a company prefix, which is unique to each company and is assigned by GS1. Then follows the model reference, which is allocated by the manufacturer. While the company prefix is numeric, the model reference can be alphanumeric. The final part is formed by two mandatory check characters, which are generated by the GS1 check character calculator. The maximum length of this Basic UDI-DI is 25 characters [30].

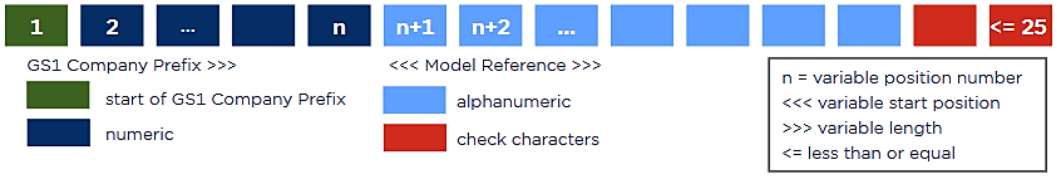


Fig. 9: *Composition of the Basic UDI-DI according to GS1. It is divided into three parts with a maximum length of 25 characters [30]*

HIBCC provides a HIBC Basic UDI-DI that corresponds to the Basic UDI-DI requirements of the IVDR. Here, the code is made up of four components as shown in figure 10. The Basic UDI-DI starts with a *++* character, which indicates the HIBCC Basic UDI-DI Flag. After this the LIC follows, which is assigned by HIBCC and is comprised of four alphanumeric characters. However, the first character of the LIC is always alphabetic. The third part is the model identifier which is given by the manufacturer. Two check characters form the final part of the Basic UDI-DI that are calculated using algorithms available from HIBCC [31].

Fig. 10: *Generating the Basic UDI-DI with HIBCC which is split into four parts [31]*

Both GS1 and HIBCC allow some components of the Basic UDI-DI to have a variable length, so that the maximum length of 25 characters can be reached. But ICCBBA sets the total length for the code to 18 characters [26]. The Basic UDI-DI is divided into four sections as illustrated in figure 11.

Fig. 11: *Four different components of the ICCBBA Basic UDI-DI (Own development)*

The first section of the Basic UDI-DI is the Facility Identification Number, assigned by ICCBBA. It consists of alphanumeric characters and has a fixed length of five characters. For the next part of the code, the manufacturer provides a Facility-defined Product Code, which can be a catalogue number identifying the device type within the system. Third part is the Production Description Code. The final part of the Basic UDI-DI are two check characters, calculated with an algorithm provided by the ICCBBA [26].

With IFA standards the Basic UDI-DI is generated using the four components shown in figure 12.

Fig. 12: *IFA GmbH Basic UDI-DI (Own development)*

The first two components are allocated by IFA GmbH and have a fixed length. As the Issuing Agency Code two alphabetical characters PP have to be taken. The Manufacturer Code contains five numeric characters. Part three of the Basic UDI-DI is defined by the manufacturer. Similar to the other issuing agencies, two check characters constitute the end. The algorithm for the calculation of these characters is provided by IFA GmbH [32].

2.2 Comparison of the UDI system in EU and USA

The requirements for the UDI system in the EU as well as in the USA are based on the UDI Guidance document provided by the International Medical Device Regulators Forum (IMDRF) [9]. Despite this, there are some differences in the IVDR and 21 CFR Part 830 regarding the implementation of the two systems. The comparison is contrasted in the table 5.

According the IVDR, the manufacturer is responsible for the UDI system, from assignment to placement on the device [2]. In the CFR it is said that the labeler is accountable for this. This does not mean essentially the unit that applies the label to the device. Labeler is the person who is legally responsible for the labeling information. In most cases it is the manufacturer of the device. But it is also possible that a specification developer or a kit assembler is the labeler [33].

Requirements	EU	USA
UDI database	✓	✓
Basic UDI-DI	✓	✗
Date of manufacturer	✗	✓
Standardized date format (YYYY-MM-DD)	✗	✓
UDI on next higher package level in case of significant label space constraints	✓	✗
RFID	✓ But an additional linear or 2D bar code is required	✗
Trigger for new UDI-DI	✓	✓
Responsibility	Manufacturer	Labeler
AIDC and HRI on the label	In case of limited of space the AIDC shall be used	AIDC and HRI required
Direct marking	AIDC and HRI required	Choose between AIDC or HRI

Tab. 5: *Comparison of the requirements regarding the UDI system in EU and USA (Own development)*

In the EU the date of manufacture does not mandatorily have to be included in the UDI-PI. Only if information on the lot number or expiry date is missing, the date of manufacture has to be included. However, in the USA, all variable data on the label has to be encoded in the UDI-PI as well. Therefore, the date of manufacture has to be included in the UDI-PI when it appears on the label [33].

The FDA as well as the EC has designated issuing agencies. GS1, HIBCC and ICCBBA have been approved by the FDA, which have also been authorized by the EC. In addition, the EC selected IFA GmbH as the fourth issuing agency [11] [16].

In the IVDR and the CFR a UDI database is mentioned in which core data elements are stored for each device. In the EU the UDI database is part of EUDAMED and in USA it is the GUDID. The number of data elements to be entered varies in both databases. In EUDAMED around 20 data elements have to be entered and GUDID these are around 50. These data elements include information about the manufacturer or labeler, risk class of the device, production and packaging [34].

Another difference is the Basic UDI-DI. This is an additional requirement in the IVDR, but does not exist in the USA [35].

The FDA has decided that the UDI carrier has to be both machine-readable and easily readable plain-text. In principle, this also applies in the EU, but there is the exception that only the AIDC format is sufficient due to lack of space [33].

Regarding direct marking, the IVDR states that the AIDC and HRI format have to be available. In 21 CFR Part 830 it is possible to choose between the AIDC or HRI format [36].

3 Implementation of the UDI system

This chapter explains the procedure for implementing the UDI system. The UDI system has to be integrated into an overall system, affecting several phases in the development. The present steps of the design and development process at altona Diagnostics GmbH are outlined in figure 13. While the blue-marked fields indicate the design stages, the grey fields mark the design review. For the implementation of the UDI system, the fields in green were developed in the Master's thesis.

In the following, the individual phases for the implementation of the UDI system are described in more detail.

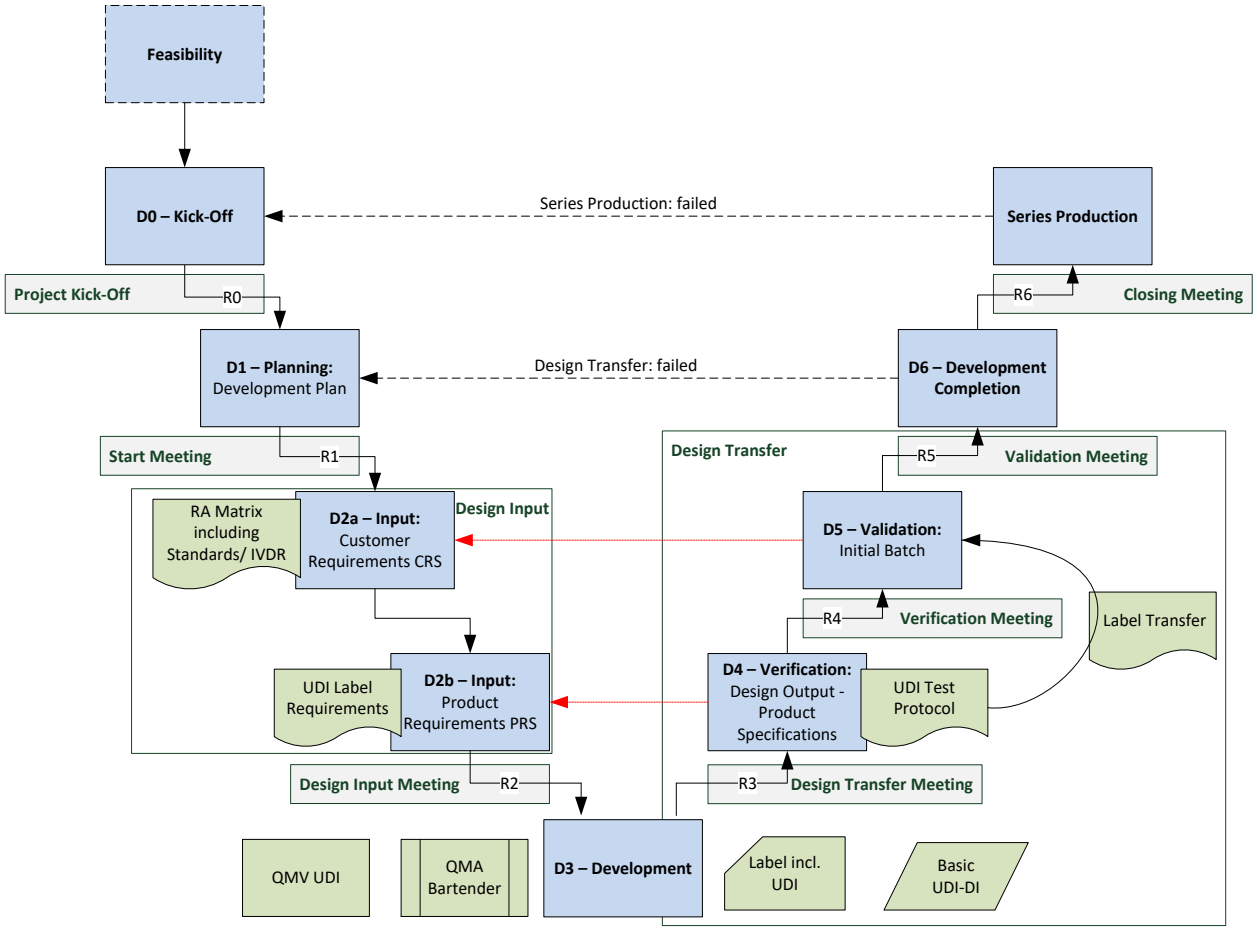


Fig. 13: *Design and Development Process Overview including the UDI. The green fields were created as part of this Master's thesis (Own development modified according to [37])*

3.1 Design Input

In order to generate the labels with the UDI, the requirements have to be specified. Before the UDI can be printed on the label, it has to be determined to which extent the requirements of the IVDD differ from the IVDR. Until now, the labels have been created on the basis of the IVDD and three standards. However, this must be adapted to the IVDR. In chapter III of Annex I the regulation defines the information which has to be on the label.

Up until now, the standards DIN EN ISO 18113-1:2011, DIN EN ISO 18113-2:2011 and DIN EN ISO 15223-1:2016 have been used for the creation of labels, as they are harmonized with the IVDD. Harmonized standards are developed on behalf of the EC. The application of the harmonized standards is mostly voluntary, but compliance with them gives a presumption of conformity with the essential requirements of the EU legislations [38].
In June 2020, a draft standard DIN EN ISO 20417:2019 was published for the new regulation, specifying the requirements for the general information to be provided by the manufacturer. According to the above-mentioned regulation and standards, specifications for the label have to be established.

As a first step, chapter III of Annex I from the IVDR has to be compared with section 8 of Annex I of the IVDD. These two Annexes describe the requirements for the information supplied with the product. This information includes both the requirements for a label and for an instruction for use (IFU). The requirements for the IFU were excluded and the focus was only on the labels.

A Regulatory Matrix (RA Matrix) created in Excel should be used to compare and contrast the requirements. The aim was to perform a gap analysis to determine which requirements are the same or resembling and which are new to the IVDR. Then it was checked whether the requirements were applicable. For example, altona Diagnostics GmbH does not distribute devices that are intended for single use or supplied sterile. Consequently, these requirements do not need to be applied.
The next step was to take a closer look at the three harmonized standards of the IVDD. A separate worksheet was created in Excel for these standards. For the standards DIN EN ISO 18113-1:2011 and DIN EN ISO 18113-2:2011 specifications were developed based on the requirements. To these specifications the symbols from DIN EN ISO 15223-1:2016 were included. IDs were assigned to those specifications depending on the category. The categories were classified into general (GEN), outer container label (OCL) and immediate container label (ICL). The outer container is the kit box and the immediate container are the tubes that are inside the kit box.
Afterwards, it was necessary to establish a correlation between the directive and regulation and the three standards, as shown in figure 14.

LR-EU-ID	Requirement 98/79/EC	Requirement EU 2017/746	Applicable	ISO 18113-1	ISO 18113-2	ISO 15223-1	ISO 20417
Category: Label and IFU - General							
20.1.	Each device must be accompanished by the information needed to use it safely and properly, taking account of the training and knownledge of the potential users, and to identify the manufacturer. This information comprises the data on the label and in the instructions for use. [Annex I, B, 8.1]	Each device shall be accompanied by the information needed to identify the device manufacturer, and by any safety and performance information relevant to the user or any other person, as appropriate. Such information may appear on the device itself, on the packaging or in the instructions for use, and shall, if the manufacturer has a website, be made available and kept up to date on the website.	yes	4.1. 4.2.1. 4.6.	5. 6. 7.	—	tbd tbd tbd
20.1a	Each device must be accompanished by the information needed to use it safely and properly, taking account of the training and knownledge of the potential users, and to identify the manufacturer. [Annex I, B, 8.1]	The medium, format, content, legibility, and location of the label and instructions for use shall be appropriate to the particular device, its intended purpose and the technical knowledge, experience, education or training of the intended user(s). In particular, instructions for use shall be written in terms readily understood by the intended user and, where appropriate, supplemented with drawings and diagrams.	yes	4.1. 4.2.1. 4.6.	5. 6. 7.	—	tbd tbd tbd
20.1b	As far as practicable and appropriate, the information needed to use the device safely and properly must be set out on the device itself and/or, where appropriate, on the sales packaging. If individual full labelling of each unit is not practicable, the information must be set out on the packaging and/or in the instructions for use supplied with one or more devices. [Annex I, B, 8.1]	The information required on the label shall be provided on the device itself. If this is not practicable or appropriate, some or all of the information may appear on the packaging for each unit. If individual full labelling of each unit is not practicable, the information shall be set out on the packaging of multiple devices.	yes	4.1. 4.2.1. 4.6.	5. 6. 7.	—	tbd tbd tbd
20.1c	—	Labels shall be provided in a human-readable format and may be supplemented by machine-readable information, such as radio-frequency identification or bar codes.	yes	—	—	—	tbd
20.1d	Instructions for use must accompany or be included in the packaging of one or more devices. In duly justified and exceptional cases no such instructions for use are needed for a device if it can be used properly and safely without them. [Annex I, B, 8.1]	Instructions for use shall be provided together with devices. However, in duly justified and exceptional cases instructions for use shall not be required or may be abbreviated if the device can be used safely and as intended by the manufacturer without any such instructions for use.	yes	4.1. 4.2.1. 4.6.	5. 6. 7.	—	tbd tbd tbd
20.1e	—	Where multiple devices, with the exception of devices intended for self-testing or near-patient testing, are supplied to a single user and/or location, a single copy of the instructions for use may be provided if so agreed by the purchaser who in any case may request further copies to be provided free of charge.	yes	—	—	—	tbd
20.1f	—	When the device is intended for professional use only, instructions for use may be provided to the user in non-paper format (e.g. electronic), except when the device is intended for near-patient testing.	no	—	—	—	—

Fig. 14: *Section of the gap analysis between the IVDD and IVDR. The three harmonized standards of the IVDD and the draft DIN EN ISO 20417:2019 were considered as well (Own development)*

As shown in figure 14, the first column indicates the reference ID of the requirement in the IVDR. In the next column the IVDD requirements are presented, where each requirement is allocated its own row. The third column contains the IVDR requirement associated with reference ID. The fourth column verifies if the requirements are applicable or not. The following three columns represent the three harmonized standards. Here, the link between the described requirement in the directive and regulation and the corresponding requirements in the standard is established. In the last column the connection to the standard DIN EN ISO 20417:2019 has to be created, which has not yet been made, as it is currently still available as a draft version. Therefore, the abbreviation 'tbd' is used for 'to be done'. The entire gap analysis can be viewed in annex 1.

For the draft of DIN EN ISO 20417:2019 another worksheet was created in Excel. Firstly, it was checked which requirements in the draft coincide with the requirements of the standards DIN EN ISO 18113-1:2011 and DIN EN ISO 18113-2:2011. In case of a match, the specification with the ID was transferred to the draft. For new requirements, new specifications were created, and a new ID was tried to be assigned. A new category in the DIN EN ISO 20417:2019 is the UDI.
Requirements that did not apply to devices at altona Diagnostics GmbH were marked grey. In addition, the reference to DIN EN ISO 20417:2019 was noted in DIN EN ISO 18113-1:2011 and DIN EN ISO 18113-2:2011.

A section of the RA Matrix is provided in figure 15, which lists the specifications of the UDI system. On the left the requirement from the DIN EN ISO 20417:2019 can be seen. The next column shows the IDs. These are marked orange as a new category with IDs had to be assigned for the UDI system.

Chapter		Description	LS-ID	Specification
Anforderungen an Verpackung				
	7.1.a) 5)	falls von der zuständigen Behörde für das Medizinprodukt oder Zubehör gefordert, ein eindeutiger Identifikator eines Medizinprodukts (UDI) nach 6.6; ANMERKUNG Es wird erwogen, ein Symbol für diese Anwendung in eine zukünftige Ausgabe von ISO 15223-1 aufzunehmen. i) Der UDI muss auf allen Verpackungsebenen des Medizinprodukts oder Zubehörs vorhanden sein.	LS-UDI-01.1	The outer container (kit box) shall contain on the box label "Etikett Oberseite" a UDI carrier, both in machine-readable and in plain text.
			LS-UDI-01.2	The UDI carrier shall be represented by a GS1 DataMatrix.
			LS-UDI-01.3	The following data shall be encoded in the DataMatrix: - (01) GTIN xxxxxxxxxxxx - (10) LOT xxxxxx - (17) Expiry date xxxxxx - (240) REF xxxxxxxxx - (8200) website of altona Diagnostics Gmbh http://altona-diagnostics.com
			LS-UDI-01.4	The plain text including the Application Identifiers shall be positioned to the right of the DataMatrix as shown below. (01) GTIN (10) LOT (17) Expiry date (240) REF (8200) website of altona Diagnostics GmbH The X-dimension of the DataMatrix shall be 0.36 mm.
			LS-UDI-01.5	After each Application Identifier a line break shall follow.
			LS-UDI-01.6	The font size of the plain text shall be set to 6.
			LS-UDI-01.7	The basic UDI-DI shall consist the following parts: - company prefix, given by GS1 42504531 - model reference, given by altona Diagnostics GmbH xxxxxxxxx - two check characters, calculated with the GS1 check character calculator xx

Fig. 15*: In the RA Matrix defined specifications of the UDI system including the information to be encoded in UDI carrier, the dimension of the carrier and the structure of the Basic UDI-DI. In red the placeholders are marked. The standard requirements are in German, as this was only available in German. However, the specifications are generally prepared in English (Own development)*

In chapter 2 the four different issuing authorities were described. GS1 was chosen for the creation of the UDI code, as altona Diagnostics GmbH already works with the GTINs of GS1.

To display the UDI carrier in the AIDC format, the GS1 DataMatrix was chosen. One major benefit of the DataMatrix compared to other representations is that it takes only little space and is therefore suitable for smallest areas [39].

Following data was specified to be encoded in the DataMatrix with the GS1 AIs:

- (01) GTIN
- (10) Lot number (LOT)
- (17) Expiry date
- (240) Reference number (REF)
- (8200) Website of altona Diagnostics GmbH.

Placeholders have been specified for the data so that it is clear how many characters are required for the respective data. Furthermore, the size of the UDI carrier and the font size for the plain-text were defined in the RA Matrix.

The specifications for the construction of the Basic UDI-DI were also determined. As with the UDI carrier, the GS1 standards should also be considered here. The Basic UDI-DI has to contain the three parts described in section 2.1.4. The company prefix for altona Diagnostics GmbH is 42504531, which remains unchanged.

The complete RA Matrix can be found in annexes 1, with the gap analysis and the other four respective standards.

Once the RA Matrix for the labeling requirements has been created, a document with labeling specifications for a particular product from altona Diagnostics GmbH can be derived from the matrix. These specifications are intended as actual design input for the development of the labels. As an example, the product AltoStar® CMV PCR Kit 1.5 was regarded, for which these specifications were created.

The UDI specifications for AltoStar® CMV PCR Kit 1.5 are represented in figure 16. On the left side the ID is given, which is taken from the RA Matrix. Here, *LS* denotes Labeling Specification. In the next column the ID for product specification or risk management is given. These still have to be done (tbd), as this is not part of this thesis. The next column reflects the category, which in this case is the UDI. Finally, the specification for the example product is noted.

As seen in the figure below, some placeholders have been replaced by concrete data. The GTIN or the company prefix are static data that do not change for a specific product. It is different for the lot number or the expiration date, which are only entered when the labels are printed. Hence, these variable data are not specified more precisely.

The document with the labeling specifications can be seen in annex 2.

LS-ID	PS-ID/RM-ID	Category	Requirement
LS-UDI-01.1	tbd	UDI	The outer container (kit box) shall contain on the box label "Etikett Oberseite" a UDI carrier, both in machine-readable and in plain text.
LS-UDI-01.2	tbd	UDI	The UDI carrier shall be represented by a GS1 DataMatrix.
LS-UDI-01.3	tbd	UDI	The following data shall be encoded in the DataMatrix: GTIN (01)04250453100512 LOT (10)xxxxxx Expiry date (17)YYMMDD REF (240)AS0021513 Website (8200)http://altona-diagnostics.com
LS-UDI-01.4	tbd	UDI	The plain text including the Application Identifiers shall be positioned to the right of the DataMatrix as shown below. (01) GTIN (10) LOT (17) Expiry date (240) REF (8200) website of altona Diagnostics GmbH The X-dimension of the DataMatrix shall be 0.36 mm.
LS-UDI-01.5	tbd	UDI	After each Application Identifier a line break shall follow.
LS-UDI-01.6	tbd	UDI	The font size of the plain text shall be set to 6.
LS-UDI-01.7	tbd	UDI	The basic UDI-DI shall consist the following parts: - company prefix, given by GS1 42504531 - model reference, given by altona Diagnostics GmbH xxxxxxxxxx - two check characters, calculated with the GS1 check character calculator xx

Fig. 16: *Extract from the labeling specifications document derived from the RA Matrix. Shown here are the UDI specifications for the AltoStar® CMV PCR Kit 1.5 (Own development)*

3.2 Development

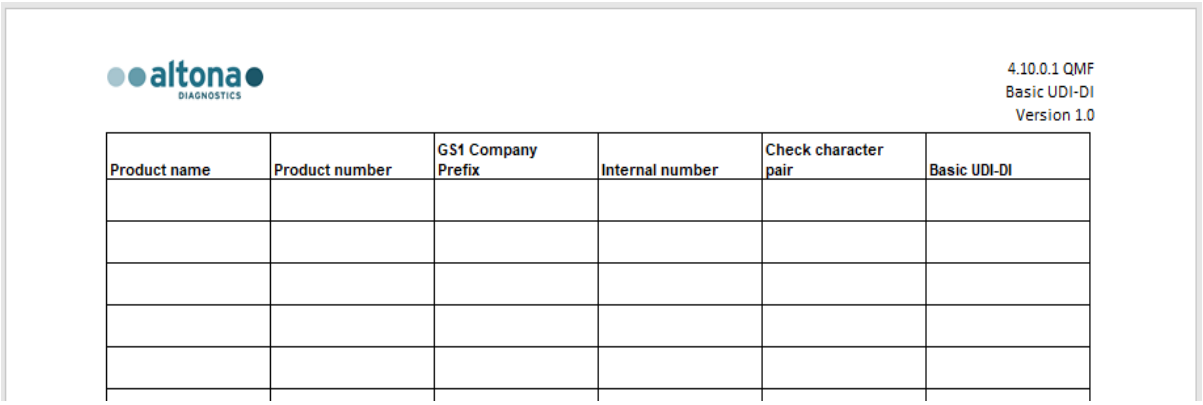
After the design input has been determined, the development phase is entered where the actual development outputs are generated. The outputs aim to satisfy the requirements of the design inputs. With the specifications developed in section 3.1, the labels can be created with the UDI carrier. Before starting to produce the labels, a Standard Operating Procedure (QMV) and a Work Instruction (QMA) have to be prepared.

The Standard Operating Procedure and Work Instruction are part of the quality management system. The Standard Operating Procedure is a high-level document that provides an overview of a process or activity to be carried out in the company. Thus, the employees gain an understanding for a process.

Part of the development phase was to write a Standard Operating Procedure for the UDI system. This should cover the requirements of the IVDR. This document describes the purpose as well as the scope of the UDI and also takes a closer look at the individual components of the UDI system. In addition, responsibilities assigned to the process were defined in this document.
Besides, the Standard Operating Procedure also explains how the Basic UDI-DI is created and maintained. The developed specifications only reflect how the Basic UDI-DI is structured but a detailed

description is provided in the Standard Operating Procedure. It also indicates in which documents the Basic UDI-DI has to appear. In order to maintain the assigned Basic UDI-DIs, a form sheet (QMF) has been created that is to be maintained by the department Product Management at altona Diagnostics GmbH. As shown in figure 17 not only the Basic UDI-DIs are entered into the form sheet, but additionally the product name, product number and the individual components of the Basic UDI-DIs are listed.

The complete Standard Operating Procedure can be found in annex 3 and the QMF in annex 4.


altona DIAGNOSTICS

4.10.0.1 QMF
Basic UDI-DI
Version 1.0

Product name	Product number	GS1 Company Prefix	Internal number	Check character pair	Basic UDI-DI

Fig. 17: *Section of the developed form sheet to maintain the allocated Basic UDI-DIs. The department Product Management is responsible for maintaining this list (Own development)*

The UDI requirements in the labeling specification document indicate which data has to be encoded in the UDI carrier but the Work Instruction (see annex 5) explains step by step how to generate a UDI carrier with the information in a software.

The labels are generated with the software BarTender at altona Diagnostics GmbH. With the same software the UDI carrier is created, both in machine-readable format and in plain-text.
BarTender is a labeling software enabling the creation and automation of labels, bar codes and RFID tags, among other things and is considered as standard in the manufacture of medical devices. For the construction of the UDI, it also offers GS1 and HIBCC standards as an auto format [40].

As mentioned above, the GS1 DataMatrix was selected for generating the UDI. However, BarTender additionally offers the GS1 QR code and GS1-128 as options for the UDI carrier.
At altona Diagnostics GmbH, there are three different box labels for marking the device packaging:

- “Components”
- “Etikett Oberseite”
- “Symbole”.

The box label “Components” contains information about which tubes are in the kit. Both the name of the component and the quantity with the volume are shown on that label. However, this label is not considered further for the purposes of constructing the UDI.

For the creation of the UDI carrier only the box labels “Symbole” and “Etikett Oberseite” are considered. In figure 18 the box label “Etikett Oberseite” is shown in the upper left corner. This includes the device name and a short description of its purpose. The label also makes clear that this is an IVD which is CE certificated. On this box label the UDI carrier has to be placed.
Next to this label there is the box label “Symbole”. This comprises the actual data that is referenced in the UDI carrier. The relevant data is marked in color. Furthermore, the label displays information about storage of the device, the total number of IVD reactions and the address of the manufacturer.

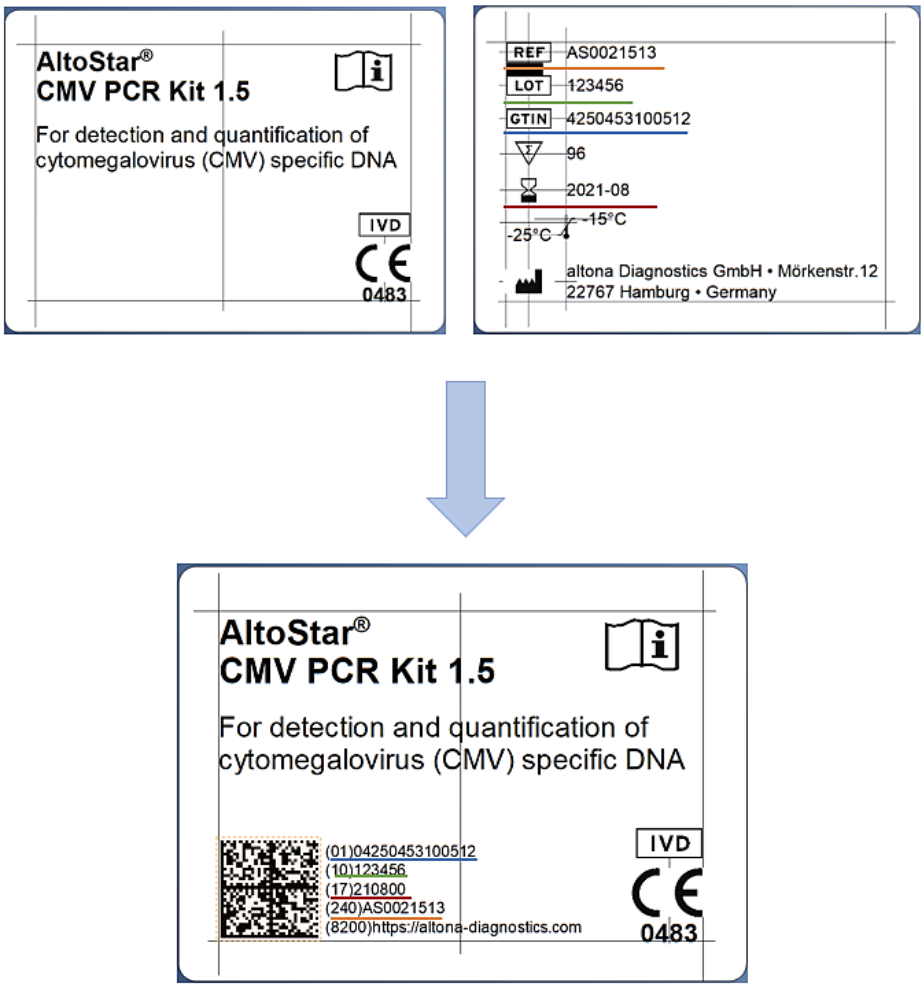


Fig. 18: *The UDI carrier shall be placed on the box label “Etikett Oberseite”. To create the DataMatrix, the information from the box label “Symbole” (top right) is utilized. At the bottom is the completed label with the UDI carrier, which is both machine-readable and in plain-text (Own development)*

If the steps described in the Work Instruction are followed, the output appears as depicted in figure 18 below. With the information from the box label “Symbole” the DataMatrix is represented in both machine-readable and plain-text.

In figure 18, fictitious data was entered for the lot number and the expiration date since this data is only entered by the department Operations when the labels are printed in serial production. The BarTender print file containing the generated UDI and the two relevant box labels for the CMV PCR Kit 1.5 can be viewed in annex 6.

As described in section 2.1.4, a Basic UDI-DI is assigned to a group of devices with the same characteristics. For altona Diagnostics GmbH devices, it is conceivable to group the devices based on pathogens and to assign a Basic UDI-DI accordingly.

3.3 Verification

The next phase in the design and development process is verification. The purpose of verification is to confirm that certain requirements have been satisfied by providing objective evidence. This means that it has to be checked whether the output meets the input requirements. This is done using a verification protocol that examines the UDI requirements.

The developed specifications are defined as acceptance criteria. It is then queried whether these criteria are met or not. With regard to the UDI, it has to be ensured that there is a machine-readable format, but also a plain-text format. Furthermore, the data encoded in the UDI carrier has to be consulted individually. One of the criteria is the size of the DataMatrix. Moreover, the representation of the DataMatrix with the plain-text, where the plain-text is displayed right of the UDI carrier with line break, must be verified.

For a successful verification all criteria have to be fulfilled. In case a criterion is not fulfilled, the verification has failed. At first sight, this means that the output does not satisfy the defined criterion. In this case, it is necessary to consider how to proceed further.

One possible approach would be to check whether the input can be changed to match the obtained output. Thereby it is important to make sure that the regulatory requirements are complied with. Another possibility is that the design input remains unchanged, but the output is adjusted to correspond to the defined criteria [41].

The labeling verification can be seen in annex 7.

3.4 Label Transfer

After the successful verification, the last step is the transfer of the labels with the UDI. For this purpose, there is a form sheet in which the product information is first entered. This includes the product number and the product name [42].

The next section in the form sheet refers to the box label templates. As mentioned before, there are three box labels, each with different information on it. In this section, all three labels are printed out and pasted into the space provided in the form sheet. The name of the box label as well as the file name is noted. The file name reflects the name of the BarTender file in which the labels were designed [42].

This is followed by the release confirmation. This lists all the information that has to be included in a correctly displayed label. At the end it is approved and signed by the four departments Research & Development, Product Management, Quality Management and Regulatory Affairs [42].

Once the release is confirmed by the above-mentioned departments, the form sheet is then handed over to the department Operations, which is the final step. As part of this transfer, the BarTender files containing the labels will be made available by Product Management for a proof print by Operations. The printed labels are affixed in the space provided [42].
If the labels printed for the sample match the released labels, then the head of Operations confirms this with a signature. Therewith, the label transfer is completed and the labels may be used for serial production.

4 Discussion

As part of the implementation of the UDI system a Standard Operating Procedure and Work Instruction were created. The purpose of the Standard Operating Procedure is to provide an overview of the entire UDI process on a high-level basis. The aim of the Work Instruction is to describe in detail the steps for the creation of the UDI carrier. In principle, the document should be written in such a way that any employee can create a UDI carrier using the Work Instruction only. To verify this applicability, a two-step review was conducted.

In the first step, the created Work Instruction was checked by one employee each from Quality Management and Product Management. Since they both are proficient with the software BarTender, the document was reviewed for comprehensibility and structure. Both succeeded in creating the UDI carrier based on the Work Instruction.

The second step was to carry out an internal test, which three employees of Quality Management agreed to participate in. It should be noted that none of them are familiar with the software BarTender, which allows an objective evaluation. For the test, a printed version of the Work Instruction and the corresponding BarTender file were provided. The test was conducted individually and an approximate time window of 60 to 90 minutes was defined.

All three employees succeeded in creating the UDI carrier on the label. The processing time for creating the UDI carrier varied, as shown in table 6. The participants also made suggestions for improvement, which are discussed in the following.

Participant	Required time in minutes
1	60
2	60
3	30

Tab. 6: *The time required by each participant to create the UDI carrier using the Work Instruction (Own development)*

One aspect that was mentioned by all three participants is that the information was missing to manually enter the number when adjusting the font size. To select the font size, a drop-down list is displayed in BarTender. According to the Work Instruction, the font size should be set to five. However, the smallest output font size in the list is eight. All three participants tried to find the corresponding number in the list and could only continue processing after a hint that it is also possible to enter the number manually. For this reason, it was added in the Work Instruction that the font size is entered manually.

The final step in the Work Instruction is to place the UDI carrier in the correct position. In order to modify the position, coordinates for X and Y have to be entered. After entering the values, the window should be closed so that the UDI carrier is brought into the correct position. A suggestion was made to add a sentence at the end that after entering of the values “Schließen” button has to be pressed and thus the window is closed. This has been adapted accordingly in the Work Instruction.

It was also noticeable that two employees aligned themselves more with the images in the Work Instruction than with the text. The images were only intended to serve as illustrations and not to show any work steps. In some figures, data had been selected, but it was only explained step by step in the text which data should be selected and how to proceed. Since both employees chose the data based on the figures, they were confused when they read the following section. However, this is a user error because the Work Instruction was not followed.

As a whole, the second step of the review confirmed that it is possible to create the UDI carrier with the Work Instruction, even if the software was not previously used. Therefore, it can be concluded that with the exception of minor shortcomings, the Work Instruction was overall positively received, being user-friendly for both laypersons and experts.

The developed Work Instruction describes how the UDI carrier has to be created. But which information and how it should be displayed in the carrier is defined in the labeling specifications. The labeling specifications were developed for the labels, the IFU part is still missing, which was not part of this thesis. Furthermore, the link to the design input specifications is not yet established as shown in figure 19.

The IDs in the second column are not yet covered in this document. This column shows the connection to design input specifications or risk management. As it can be seen in the fourth column, the kit components are given with their volumes. Furthermore, the total number of reactions that can be performed with the IVD is stated (see red box in the fourth column). This information is derived from the design input specifications and used for the labels.

LS-ID	PS-ID/RM-ID	Category	Requirement
LS-OCL-01.4	tbd	Outer Container Label	The outer container (kit box) shall contain the Box Label "Components" with the product name, the contained component names, the quantity and content of these and the which cap colour indicates which component. The information shall be illustrated by the following symbols: CAP cap colour COMP component name NUM x CONT quantity and content Cap colour / component name / quantity x content in µl Blue / Master A / 8 x 60 µl Purple / Master B / 8 x 180 µl White / NTC / 2 x 250 µl Red / QS1-4 / 8 x 250 µl The outer container (kit box) shall contain the following symbol to indicate the total number of IVD reactions that can be performed with the IVD. The number shall be displayed next to the symbol on the right side. It shall be stated on the Box Label "Symbole". Σ 96

Fig. 19: *Extract from the labeling specifications. In this document the IDs in the second column are not present, which are related to the product specifications and risk management. As shown here, the information regarding the kit components comes from the design input (Own development)*

Despite this, the RA Matrix could not be completed in its entirety. A reason for this is that only a draft of the standard DIN EN ISO 20417:2019 was published and the final version of the standard is expected to be released in the near future. With the help of the draft, it was only checked which requirements are similar to the standards DIN EN ISO 18113-1:2011 and DIN EN ISO 18113-2:2011. However, the final version of the DIN EN ISO 20417:2019 may contain changes to the draft, which is why the focus was not placed on it. It can be assumed that with the final version no explicit new requirements for the UDI part will be added, but rather general requirements.
Apart from that, the RA Matrix was created using the standards that were harmonized under the IVDD. In May 2020, the European Commission submitted a standardization application for the IVDR, which included the standards DIN EN ISO 15233-1:2016 and the draft of DIN EN ISO 20417:2019. This application was rejected in June [43]. The previously valid harmonized standards can still be applied, as they correspond to the state of the art. However, it can be assumed that probably 2020 and 2021 there will be no harmonized standards for the IVDR [44].

In section 3.4 the label transfer was described. The actual transfer has not yet taken place as a change in the labels entails a product change. For a product change, a product change number has to be requested from Product Management. Afterwards, Product Management invites representatives from the departments Quality Management, Regulatory Affairs and if necessary, Research and Development, Operations and Sales/Customer Care to a product change meeting.

In the meeting, a form sheet for the product change will be filled out, stating the cause and type of the change. This form sheet includes an evaluation of the product change. In the case of the UDI system, the change will have an impact on the label, as a UDI carrier is added to the label. This means that

certain actions have to be followed. For instance, the manufacturing instructions and the labels have to be changed for all products. According to the IVDD, the notified body must be informed for products on lists A and B [45]. This makes it clear that the label transfer is a process of several months.

When creating the labels, it was noticed that for the AltoStar® products, the year and month are specified as the expiry date. According to the IVDR, the year and month are mandatory and, if applicable, the day is indicated [2]. This is how it is displayed on the label "Symbole". But the format of the date in the UDI carrier depends on the issuing entities. Since altona Diagnostics GmbH already works with the GTINs of GS1, the UDI code was created using GS1 standards. It is defined by GS1 how the UDI is to be implemented.

As for the AltoStar® products only the year and the month are entered for the expiry date, the format YYMM was initially assumed for the UDI carrier. However, in the document "GS1 General Specifications" the requirements are clearly stated. In case of the date format, YYMMDD must be given and may not differ as show in the figure below. If there is no indication of the day, the digits are filled with two zeros. The two zeros are considered as the last day of the respective month [46].

Expiration date: AI (17)

The GS1 Application Identifier (17) indicates that the GS1 Application Identifier data fields contain an expiration date. The expiration date is the date that determines the limit of consumption or use of a product/coupon. Its meaning is determined based on the trade item context (e.g., for food, the date will indicate the possibility of a direct health risk resulting from use of the product after the date, for pharmaceutical products, it will indicate the possibility of an indirect health risk resulting from the ineffectiveness of the product after the date). It is often referred to as "use by date" or "maximum durability date."

The structure is:

- Year: the tens and units of the year (e.g., 2003 = 03), which is mandatory.
- Month: the number of the month (e.g., January = 01), which is mandatory.
- Day: the number of the day of the relevant month (e.g., second day = 02); if it is not necessary to specify the day, the field must be filled with two zeros.

Note: When it is not necessary to specify the day (the day field is filled with two zeros), the resultant data string SHALL be interpreted as the last day of the noted month including any adjustment for leap years (e.g., "130200" is "2013 February 28", "160200" is "2016 February 29", etc.).

Note: This element string can only specify dates ranging from 49 years in the past to 50 years in the future. Determination of the correct century is explained in section 7.12.

Fig. 20: *Extract from the GS1 document. This part defines the format for the UDI carrier with the regard to the expiration date. It describes that the format YYMMDD must be followed. If the day is not exactly defined, two zeros must be entered for the position [46].*

How the realization is done on the label "Symbole" and in the UDI carrier can be seen in figure 21.

Fig. 21*: On the left, the label "Symbole" where the date is only given with month and year. On the right, the date is displayed in the format YYMMDD in the UDI carrier. Two zeros are entered for the day, since no exact day is specified (Own development)*

In the case that the products are to be approved both in the USA and in Europe, it is recommendable to use a standardized date format in order to be less prone to errors. The format YYMMDD is specified by the FDA. This means that the format is used both on the label and in the UDI carrier. Up to now, only the month and year have been indicated on the box labels, but the day has been included on the tubes. It is therefore advisable to change the date format of the products in order to cover the American market and avoid problems.

For the assignment of the Basic UDI-DI, the guidance document of the Medical Device Coordination Group (MDCG) was also consulted in addition to the IVDR. In the regulation itself the Basic UDI-DI is only defined as a “primary identifier of a device model” [2]. But with the guidance document the criteria for grouping devices were described in subchapter 2.1.4 of this thesis. Concerning the grouping, the manufacturer has to decide how many devices should be covered under a Basic UDI-DI. If a Basic UDI-DI contains many devices, it is possible that in case of a recall of a device in the group, all devices within the group will be under general suspicion [47].
For this reason, it makes sense for altona Diagnostics GmbH devices to categorize them according to the pathogens and assign the Basic UDI-DI respectively.
Furthermore, the Basic UDI has to be mentioned in all relevant documents such as technical documentation, EU declaration of conformity, summary of safety and performance and certificate of free sales. These documents are not yet finalized for the following reasons:
When it comes to technical documentation, it is a file that contains several documents. It serves as proof that the general safety and performance requirements are fulfilled and supports the EU declaration of conformity. The technical documentation provides information about the design, manufacture and operation of the device. It also contains the document with the labeling specifications. Only

when all device information is attached, the technical document is completed. This document is also required to affix the CE marking to the device [48].
The EU declaration of conformity confirms that the device complies with the EU requirements. This is only issued when product development is complete. In the declaration it is also included which harmonized standards were used for the device [48].

The Basic UDI-DI is also entered into the UDI database by the manufacturer. One aspect that was not considered any further in this Master's thesis was the UDI database. The requirements for the database were described in the developed Standard Operating Procedure but were left out during the implementation. Initially, the EC published in October 2019 that the fully functional EUDAMED will be available for May 2022. However, then in March 2020 it was decided that the Commission would progressively make the individual systems in EUDAMED available to the Member States as soon as they were ready for use. Thus, the system for registration of the economic operators is to be launched at first in December 2020. This will also make it possible to obtain the Single Registration Number (SRN) which is one of the 21 core elements of the UDI database [49]. The SRN is intended to identify the manufacturer and is assigned to the manufacturer by the competent authority. The manufacturer uses the SRN to apply access to EUDAMED [2].
The electronic system for the UDI database is expected to be functional by May 2021 [50].

The GS1 DataMatrix was selected to create the UDI carrier. As described in subchapter 3.2, the UDI carrier was constructed with the corresponding data. It is important to check whether the resulting 2D bar code also provides the correct information when the carrier is scanned. To test this, the bar code was scanned with different apps on the mobile phone and with a scanner in the department Logistics. The data that could be seen in the plain-text was also output after scanning. It is to note that only in plain-text the AIs are set in brackets. During scanning, the brackets are not output as the brackets are only used for readability in plain-text and are not encoded in the bar code [51].
Since the labels are created with the software BarTender at altona Diagnostics GmbH, no new software had to be acquired to produce the UDI carrier. The printer was also able to print the carrier without any problems and display it correctly. Therefore, no new investments were necessary for the company.

The UDI system is intended to establish a worldwide standardized system to improve the traceability of medical devices including IVDs. However, there are differences between the UDI system in the USA and EU, as explained in subchapter 2.2. Both the USA and EU use their own UDI database. This also involves the entry of different data elements, which does not result in a worldwide standardized system. EUDAMED allows a single UDI database, which makes a harmonized system possible within the European Union.

Another difference is the date format. While the USA specifies a consistent date format for both the label and the UDI carrier, in the EU the date format on the label may differ from the UDI carrier. To cover the American market, the date format specified by the FDA should be adopted.
This raises the question of what the implementation in other countries will look like. If each additional country introduces its own database and requirements for the UDI format, then it is no longer possible to speak of a worldwide system.

In chapter 1 some benefits of the UDI system were outlined. There it was also briefly mentioned that some of the advantages apply more to medical devices, but not necessarily to IVDs.
An interesting aspect for altona Diagnostics GmbH is certainly the improvement of warehouse management with the UDI system. As already mentioned, the DataMatrix was also scanned in the department Logistics with the currently used scanner. Since the department is already working automated and no new equipment is necessary to scan the UDI carrier, it is possible to manage the stock with the UDI.
At present, QR codes are used to regulate the arrival of products. As soon as the kits are picked up from the packing department, they have to be stored in appropriate drawers of the freezers. Therefore, the kits as well as the drawers are provided with QR codes. The kits are scanned individually and then the corresponding QR code of the drawer is scanned. This has the consequence that the scanned kits are assigned to that drawer. If the QR code of the drawer is scanned, the information about which and how many kits are contained is displayed. Furthermore, the reference number and lot number are displayed. With the introduction of the UDI system the currently used QR Codes can be replaced by the UDI carrier.
If the customers also share information about their stock with manufacturer or distributor, production can be carried out accordingly. This emphasizes that the benefits of the UDI system can only be used if an appropriate IT infrastructure exists [52].

It is not only essential to focus on the IT infrastructure but also to make sure that the appropriate equipment is available. To ensure the traceability of medical devices throughout the entire supply chain, it has to be determined whether the bar code is readable by all participants in the supply chain. On the one hand, it is about the quality of the bar code where it has to be tested if the plain-text is readable. On the other hand, when scanning the DataMatrix, the correct information must be output. In this regard, it has to be clarified in advance whether all participants in the supply chain have a suitable scanner for reading [53].

Overall, there were no major difficulties in the development and implementation of the UDI system. The implementation could not be finished completely, but the preliminary work was accomplished in the scope of this thesis.

5 Conclusion

The UDI system is a new requirement of the IVDR. It enables the unambiguous identification of a device on the market and thus ensures the traceability of devices using bar code technology.
The objective of this Master's thesis was to develop and implement a UDI system for the IVDs manufactured and distributed by altona Diagnostics GmbH, which was partially achieved.
In order to integrate the UDI system into the company several steps had to be taken. The beginning was to determine what the regulatory frame was. Based on this, the RA Matrix for labeling requirements was developed, from which the labeling specifications were derived. These documents serve as design input for the design and development process.
To give an overview of the UDI system to the employees of altona Diagnostics GmbH, a Standard Operating Procedure was written. It also includes a description of how the Basic UDI-DI is created and in which relevant documents it must appear. The adaption of these documents is still pending.

The creation of the UDI carrier is based on the developed Work Instruction. It should be noted that the Work Instruction was prepared for AltoStar® products and must be adapted accordingly for other products. For the machine-readable part of the UDI carrier the DataMatrix was chosen. Especially the size of the DataMatrix, which fits on the smallest areas, favored the decision. An interesting aspect for the future is certainly the RFID technology. With regard to reading ranges, mass detection or insensitivity, the bar codes or the DataMatrix reach their limits. At this point RFID offers clear advantages. For example, a pallet of products can be scanned in one go instead of scanning each product individually.

For this work, the label with the UDI was created exemplary for AltoStar® CMV PCR Kit 1.5. However, the labels have to be changed for all products, which will require more time. With the change of the labels, documents must be adapted and approvals have to be made, which requires the cooperation of several departments at altona Diagnostics GmbH.
The final step in the design and development process is the label transfer and subsequent series production. This step could be achieved for one AltoStar® product within this thesis. However, it requires more time to realize it for all products.

USA has taken the first step with the introduction of the UDI system. A few years later the EU introduced the UDI system with the IVDR. Although the intention of the system is similar, there are differences in the implementation. For manufacturers, such as altona Diagnostics GmbH, who market their devices worldwide, this means that both regulations must be followed. This includes also the maintenance of two different UDI databases.
Other countries such as Australia, India or South Korea are also working on the introduction of the UDI

system [54]. Certainly, there will be some differences. For the manufacturer, however, it is easier the more standardized the regulations are. Since the USA and the EU have recognized the same issuing entities, it is conceivable that the other countries will follow this.

To conclude, the thesis has created a basis and there are still cross-departmental tasks that are necessary for a successful implementation of the UDI system at altona Diagnostics GmbH.

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Declaration

I declare that I have written the present Master's thesis by myself without any help from others and that I have only used the sources and aids indicated. Literal passages or passages taken from other works are in all cases marked as the source.

Hamburg, 28th October 2020 _____

Mithila Thavayogarajah

Annex

The enclosed CD-ROM contains the following documents:

Annex 1 – RA Matrix

Annex 2 – Labeling Specification

Annex 3 – QMV UDI

Annex 4 – QMF Basic UDI-DI

Annex 5 – QMA Creating a UDI Carrier with BarTender

Annex 6 – BarTender file with UDI

Annex 7 – Labeling Verification