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Foreign Body Detection in Lyophilization Products

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AFFIDAVIT

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Juni, 2015 .....

DI Johannes Gursch

"not because they are easy, but because they are hard"

John F. Kennedy

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Abstract

Matter in injectables is a hot topic in pharmaceutical manufacturing. Even though the dangers posed to patient health are rather well known, guidelines are but vague, specifying products for injection to be "essentially or practically free from ptcl.". Recent product recalls by the Food and Drug Administration (FDA) have shown that there is still a significant lack of adequate inline monitoring equipment. This thesis strives to close the gap, providing in-depth analyses of promising methods to be incorporated in an in-line system for 100% control.

A special focus is given on lyophilized products contained in casings. The manufacturing process for lyophilized products is analyzed in detail, providing a structured approach to identify type, and nature of possible ptcl. substances. A survey is shown to highlight existing methods and possible issues concerning the equipment to be developed. Promising methods are addressed in a detailed technology survey comprising basic working principles, SWOT, and market analyses.

Experimental results of e.g., short wave, using samples containing lyophilized product with representative substances, are presented. The suitability of each technology is assed and critical parameters such as, detection limits, etc., are reviewed. For the most promising method, strategies for implementation, and best practice operation of a final setup are presented.

Kurzfassung

Verunreinigung in Injektionsmittel sind ein aktuelles Thema in der pharmazeutischen Fertigung. Obwohl deren Gefahr für die Patientengesundheit seit langem bekannt ist, verbleiben Vorschriften und Regulatorien vage in der Beschreibung von Injektionsmittel als „essentiell oder praktisch frei von ptcl.". Aktuelle Produktrückrufe seitens der Food and Drug Administration (FDA) weisen auf einen signifikanten Mangel an in-line Equipment hin. Um diese Lücke zu schließen, zeigt diese Arbeit fundierte Analysen potenzieller Methoden zur Integration in ein Prüfsystem zur 100% Kontrolle.

Der Fokus dieser Arbeit liegt bei Lyophilisationsprodukten in Behältnissen. Detailierte Analysen des Herstellungsprozesses für Lyophilisate werden präsentiert und stellen eine strukturierte Basis zur Identifikation möglicher ptcl.-typen zur Verfügung. Eine Recherche zeigt bereits existierende Methoden und soll möglichen Problemen vorbeugen. Geeignete Methoden werden im Zuge einer Technologierecherche aufgezeigt. Funktionsprinzipien, SWOT-Analysen sowie Marktanalysen werden präsentiert.

Die Eignung von z.B.: Kurzwellen, wird experimentell evaluiert. Mittels lyophilisierter Proben mit repräsentativen Substanzen werden kritische Prozessparameter bestimmt. Für die am besten geeignete Methode werden Implementierungsstrategien und optimierte Betriebsstrategien erarbeitet.

Contents

"and he how seeks finds"

Matthew 7:8

1. Introduction

1.1 Lyophilization basics

Lyophilization, also known as freeze drying, is a drying process where removal of water is achieved via sublimation. Products to be treated are frozen and subjected to vacuum atmosphere, where phase transition of the frozen water is achieved directly from the solid state in one single step to the gas phase. The energy necessary for sublimation is usually provided via radiation from hot surfaces or by direct contact with a hot surface. Alternatively, also microwaves are used for heating. Freeze drying usually is a two stage process. In the first stage, sublimation drying, most of the water is removed via sublimation. In the second stage, desorption drying, water absorbed on the solid matrix is removed. Usual final moisture contents are between 1-3%.[1]

Freeze drying equipment, as shown in Figure 1 consists of a lyophilization chamber with twaves, shelves, charts, etc. to hold the product to be lyophilized, heating and cooling systems, condensers to separate the sublimated water from the air, a vacuum system and process control and instrumentation.[2]

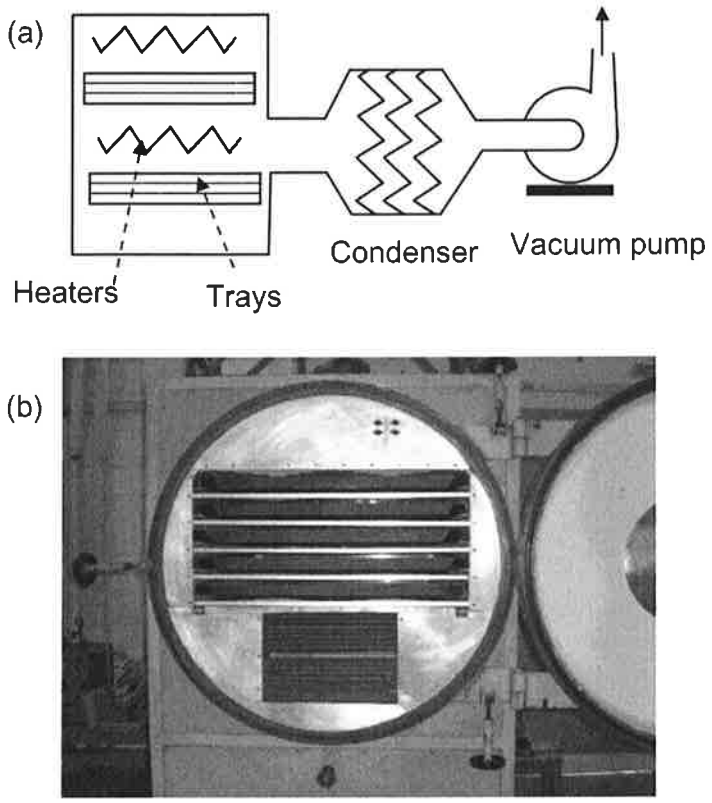

Figure 1: Main elements of a freeze dryer (upper image) and image of a batch freeze dryer (part image) [1]

The greatest user of freeze drying equipment is the pharmaceutical industry. As freeze drying is a very expensive method for drying, it is only economically feasible for products with a high added value.[1] Many pharmaceutics and biopharmaceutics are unstable as aqueous solutions and furthermore often are prone to degradation reactions at elevated temperatures. For such products freeze drying is an effective method for solvent removal to promote long-term stability.[2] Due to the low temperatures during the lyophilization process following benefits can be achieved [1]:

- Preservation of colour
- Preservation of flavour
- Preservation of appearance
- Avoidance of thermal damage to heat sensitive products

Additionally benefits due to direct sublimation from the solid state can be attained [1]:

- Avoidance of shrinkage
- Avoidance of structural changes (e.g. in proteins)

Usually products to be lyophilized are filled into small containers. Containers have to withstand vacuum and need to allow heat transfer from the environment to the product. Even though a large variety of materials and standardized forms exist, substance C ampoules and round-part flasks are the most commonly used containers.[3]

1.2 Motivation

Freeze drying processes in pharmaceutical manufacturing are usually carried out under specified clean room conditions. Even though good manufacturing practice (GMP) guidelines have to be followed [4]–[7], a large number of cases are known where substances were found in the final lyophilization product, as e.g. published in US food and drug administration (FDA) warning letters.[8]–[10]

Lyophilisation products are, after re-suspension, often directly injected intravenously. Those parc. substances, even in the ent. range, [11] pose a high risk to the patient, causing e.g. damage of organs such as lung, kidney, liver and spleen.[12]–[14]

Up to now solid lyophilization products are inspected manually, using screens to show enlarged images of final product casings to operators. Thus only ptcl.s large enough to be seen by the naked eye can be identified (assuming a typical distance to the object to be analyzed of 200 ent. and 0.0175 rad resolution of the eye, objects sizing around 55 ent. can still be detected).[15] Also substances within the lyophilized product or hidden by casing stoppers or sealing cot. be detected.

With the evolution of process analytical technology (PAT) also GMP restrictions will become more stringent. To meet future restrictions and reduce patient risk adequate tools have to be thought of to allow advanced IT. of lyophilization products. That is, new tools for detection of substances below the detection limit of the naked eye, and

also allowing detection of substances hidden within the lyophilized product will be needed.

1.3 Aim of this work

The overall goal of this work is to identify PAT tools apt to identify relevant substances (larger than 50 ent.) in lyophilization products contained in typical vessels. As typical vessels substance C casings according to DIN EN ISO-1 from borosilicate substance C size 3R are chosen. Substance C casings are a very common vessel type and their absorption and stt. behavior can be expected to have a higher influence on measurement equipment as e.g. substance N casings.

A thorough process analyses is to be performed to specify typical relevant substances. Qualtiy by Design (QbD) principles are applied in the process, providing tools and regulatory guidance and assuring an efficient structured approach to develop product and process understanding.[16]–[18]

Additionally a ptt. research is conducted, not only to avoid propt. issues in later project stages but also to generate a wide basis of ideas and concepts to improve detection concepts and processing solutions throughout the design phase of the measurement concept to be developed.

Samples containing typical lyopilization products and identified typical relevant substances are prepared. These samples are used to quantify applicability and detection performance of promising technologies for substance detection.

Promising technologies are evaluated concerning detections limits as well as ability of integration into pharmaceutical production. Influences of equipment parameters, as well as of sample attributes, such as type and size of substance, casing orientation and so on, are analyzed.

Strategies and methods for implementation of suitable PAT technologies in the existing production process are prepared. Thus a set of recommendations as basis for implementation in an industrial IT. setup is provided.

The influence of the measurement system on the lyophilization product was analyzed but will not be presented in this work.

1.4 Thesis content

This thesis deals with the identification of parc. substances in lyophilization products presented in substance C casings.

Chapter 1 gives a short introduction to the subject of lyophilization. Furthermore a problem description is given and project goals and non goals are addressed.

Chapter 2 encompasses a detailed description of the production process including process steps such as casing and stopper preparation, sterile filtration, casing filling, stoppering, lyophilization and sealing. Process flow charts, input-output (IPOP) diagrams, Ishikawa diagrams, as well as a process FMEA will be presented. As a result typical relevant substances are identified. The results are subsequently incorporated in a cause-and-effect diagram concerning possible influences on the measurement concept to be developed.

Chapter 3 comprises results of a ptt. survey and illuminates the market situation, showing existing IT. methods and control mechanisms already implemented in production. Furthermore, restrictions arising from propt. issues concerning technologies used for the new IT. concept will be addressed.

Chapter 4 introduces PAT technologies predestined to handle the IT. task at hand. Requirements for IT. will be detailed and basic information on promising technologies is given. Additional for each technology a strength-weakness-opportunity-threats (SWOT) analysis is performed.

Chapter 5 the most important findings of trials conducted with selected IT. technologies. Spectral analyses -, short wave (Sw)-, and Wave test results will be presented and evaluated.

Chapter 6 provides a summary of the major findings as well as an outlook, giving insight to further steps necessary to enable industrial application of the developed IT. concept.

2. Process assessment

This chapter provides a detailed description of the lyophilization process. Profound knowledge of the production process is needed as a basis for further analyzes in order to:

- Identify critical process steps for substances to occur
- Identify possible substances (material type, form, size, etc.)
- Evaluate probability of occurrence as well as severity of identified substances
- Derive requirements and specifications for the IT. technology to be implemented (including strategies for technology validation)
- Specify optimal points of integration to the manufacturing process for the IT. technology to be implemented

In order to provide a structured approach, as used during risk assessment [17], [19]–[24], process mapping, Ishikawa diagrams and Input-output diagrams (IPOP) were used. Subsequently the generated data was used to conduct a thorough failure mode and effects analysis (FMEA) of the lyophilization process.

2.1 Literature research

As a starting point for the process assessment procedure a literature research was performed in order to identify known srce.s of substances and typical substance materials, -sizes and shapes. Substances known to be found in lyophilized products are:

- Substance C ptcl.s [13], [25]
- Substance L ptcl.s [26]–[28]
- Substance A ptcl.s [29], [30]
- Substance Hs /Bristles [29], [31]

- Substance M [29], [31]
- Substance H [32]
- Substance N ptcl.s [33]
- Substance Q [34]
- Substance P[35]
- Substance Os [29]
- Detergents [29], [36]

2.2 Process mapping

Figure 2 shows a flow chart of a lyophilization process, including solution-, casing- and stopper preparation.

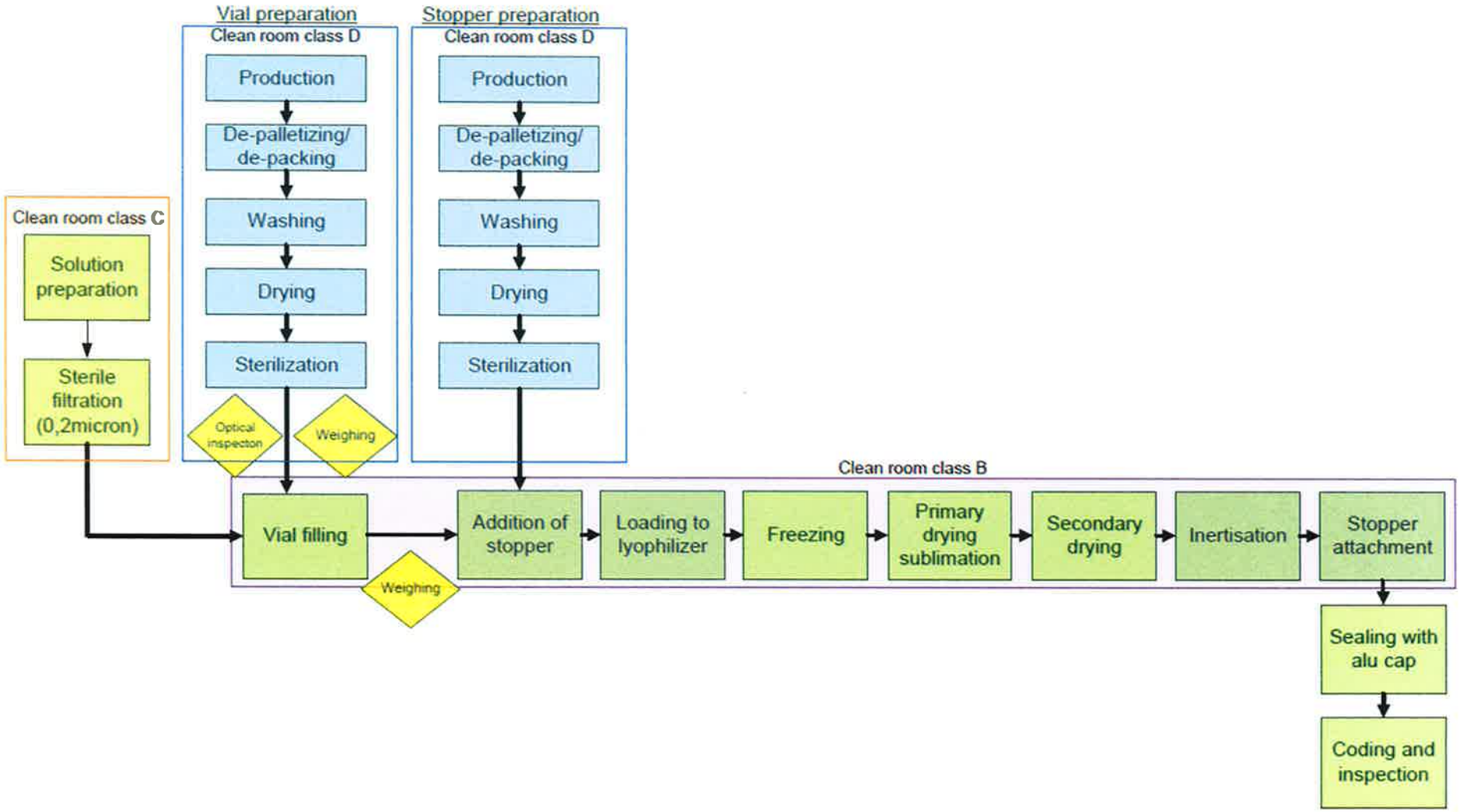

Figure 2: Process flow chart of a typical freeze drying process including designated clean room classes

The main process steps as specified in Figure 2 were further analyzed using IPOP diagrams.

An IPOP diagram has been made for each main process step. It shows main- and auxiliary materials treated in the step as input and the product of the step as output. Additionally all relevant sub-process-steps are listed and measurements already implemented. Furthermore, first preliminary ideas concerning potentially critical parameters and material attributes are listed. Thus a starting point for a processes FMEA is provided.

In the following the main process steps and associated sub-process-steps are listed:

1. Casing preparation (tunnel/ rotary casing washing) [37], [38]
   - Transporting the casings to the washing machine
   - Ultrasonic cleaning
   - Rinsing and spwaveing of the casings interior and exterior
   - Blow drying
   - Spwaveing with water for injection (WFI); dried air (blow dry)
   - Sterilization
     - UV
     - Radiation
     - Autoclaving
     - Sterile air

2. Stopper preparation (stopper washing)
   - Washing (with or without detergent)
   - Rinsing
   - Substance Dizing (with substance De oil or emulsion)
   - Hot air drying
   - Cooling
   - Sterilization
     - Hot air
     - Radiation
     - Autoclaving

3. Sterile filtration
   - Feeding the solution to sterile filter (pumping system)
   - Pumping of solution through filter

4. Casing filling
   - Supply and positioning of casing to the filling station
   - Weighing of empty casing
   - Positioning of injection device
   - Injection of filtered solution
   - Removal of injection device
   - Weighing of filled casing
   - Movement of filled casing to next process step

5. Addition of stopper
   - Unpacking
   - Blow Cleaning
   - Transport into feeder
   - Feeding (usually vibratory bowl)
   - Positioning of stopper
   - Partial stoppering (different methods)

6. Loading to lyophilizer
   - Transport to lyophilizer by substance A twaves
   - Transport to lyophilizer on twaves by operator
   - Removal of the part of the twave (usually)

7. Lyophilization [2], [39]–[41]
   - Freezing
     - Product conversion into ice
     - Ice-Nucleation
     - Supercooling
     - Low temperature drying
   - Primary drying sublimation
     - Application of vacuum by lowering of chamber pressure
     - Sublimation
     - Increase of shelf temperatures
   - Secondary drying
     - Removal of unfrozen water by desorption
     - Removal residual moisture content
     - Isothermal desorption
     - Raising shelf temperature
     - Decrease of chamber pressure
   - Purging with nitrogen (Inertisation)
   - Stopper attachment (Stoppering)
   - Unloading from lyophilizer

8. Sealing with alu cap
   - Transport to the crimping machine
   - Crimping
   - Unloading from the machine

2.3 Cause and effect analyses

Ishikawa or fishbone diagrams are structured brainstorming tools. They are used to link possible direct or indirect causes and effects to quality attributes. Causes and effects are shown as branches of the diagram, affected quality attributes are shown in the head of the fishbone diagram. Referring to the 6M-method (main branches: methods, machine, material, measurement, men and milieu) equipment, environment, op-

erator, materials and process were defined as main branches. The minor branches then narrow down the related causes.[42], [43]

2.4 Failure mode and effects analysis (FMEA)

FMEA is a risk assessment tool widely used in pharmaceutical quality systems. Since its introduction a variety of approaches and standards have been published.[19], [20], [44], [45] In a process FMEA each manufacturing step is analyzed in detail to identify possible failure modes. Causes and effects get linked to the failure mode and together with the likelihood of occurrence a risk priority number (RPN) is generated. The RPN allows classification of failures according to their criticality. Thus, a need for corrective actions can be deduced. Corrective actions include e.g. adaptations in process layout, or as in our case, implementation of additional IT. devices. Thus the FMEA can be used to deduce requirements for the system to be developed. That is, the criticality of a failure (e.g. caused by a substance) should be significantly lowered by implementation of the IT. device.

The FMEA was conducted in a multidisciplinary team, including all information generated during previously mentioned process assessment steps. Special efforts have been made to include firsthand knowledge and experience of experts from the industrial field. Hence, valuable process insight and information based on year long experience in manufacturing of lyophilized products for the pharmaceutical industry could be included.

To calculate the RPN, assigned values for severity, occurrence and detectability are multiplied.

Severity describes the impact of a failure on product quality or patient safety. The higher the negative consequences the higher the numerical value assigned as shown in Table 1. [21], [45]

Table 1: Modified severity assessment catalog (based on risk management standards ISO/IEC 31000 and ISO/IEC 31010)

Severity		
Ranking	Description	Definition
1	low	error is not noticed, severity of potential failure mode indistinguishable, potentially critical quality is not affected, no impact on product quality
2	negligable	error is noticed, potentially critical quality is not affected, no impact on product quality
3	low to moderate	error can be fixed constructionally, no time loss; low impact on product quality
5	moderate	disturbing, patient compliance, leads to increased corrective measures in the documentation, low impact on product quality
7	moderate to high	disturbing, patient compliance, leads to increased corrective measures in the documentation, failure mode causing moderately severe impact to product quality,
8	high	critical, hazard with warning, high impact on product quality, efficacy and patient safety, significant impact to product quality
9	high and possible allergic reaction	critical, hazard with warning, high impact on product quality, efficacy and patient hazard (microbiological infections, hypersensitivity, immune response), significant impact to product quality
10	high and UNKNOWN effects	batch lock, failure mode causing extremely severe impact on product quality and patient safety; patient hazard UNKNOWN;

Occurrence considers the frequency of appearance of a failure. Three classes were defined to allow a basic differentiation between rare/ uncommon, moderate and high possibility of occurrence, as shown in Table 2. [21], [45]

Table 2: Modified occurence assessment catalog (based on risk management standards ISO/IEC 31000 and ISO/IEC 31010)

Occurrence		
Ranking	Description	Definition
1	rare / uncommon	unlikely, never occurs; no likelihood
5	moderate	hardly any, very low probability of occurrence;
9	high	frequent moderate probability

Detectability describes the likelihood of detection of a failure. The higher the risk, that a failure will remain unnoticed, the higher the numerical value assigned, as shown in Table 3. [21], [45]

Table 3: Modified detectability assessment catalog (based on risk management standards ISO/IEC 31000 and ISO/IEC 31010)

Detectability		
Ranking	Description	Definition
1	failure will always be detected (offline, online, inline measurement)	error is obvious, permanent technical monitoring and alarm system exist; monitored by at least one or more sensors; high probability of detection of failure
3	detection highly likely (offline measurement)	error is obvious, regular but not permanent supervision, moderate probability of detection
5	occasionally not detected - failure may be missed sometimes	low probability of detection of failure, manual IT. necessary
7	probably not detected - failure may be missed often	unrepresentative sampling, very low detectability of failure
8	impossible to detect (no equipment/method)	failure cot. be checked because of technical and economic reasons, random testing; possibility of discovering unlikely; nature of error prohibits detection in some cases;
9	totally impossible to detect (no equipment/method)	failure cot. be checked because of technical and economic reasons, testing does not occur or is not possible; possibility of discovering just by chance; nature of error prohibits detection regularly;

Following columns were included in the FMEA excel table structure: process phase, process parameter or material attribute, potential failure mode, potential effect of failure, severity, potential cause or mechanism of failure, occurrence, cut. design control prevention, cut. design control detection, detect ability, RPN and actions. Detailed results and analyses of the FMEA were provided to the project partners.

2.5 Specifications for the measurement concept

Based on the findings of the FMEA detailed specifications for the measurement concept to be developed were derived.

To allow practical assessment of promising measurement concepts, test samples were produced. During the process, all bold market factors were varied in accordance with the expected ranges identified during the process assessment procedure. Considering variances expected from the production process allows validation of promising measurement technologies with a small set of samples only.

3. Ptt. survey

This chapter shall summarize the information gained about the cut. ptt. situation on the market concerning IT. of casings. Even though the main focus of this survey is on IT. of powder filled casings, a broad spectrum of ptt.s is analyzed. The report shall serve as a srce. of ideas as well as to detect possible restrictions resulting from protected intellectual property.

3.1 Survey procedure

The survey was conducted following the guidelines issued by the Austrian ptt. office.[46] Three databases were utilized

1. DEPATISnet (http://depatisnet.dpma.de/)
   Provides information available on the German ptt. information system DEPATIS.
   This database has a main focus on ptt.s drafted in German language.
2. Espacenet (http://worldwide.espacenet.com/)
   Provides information available on the European ptt. information system.
   National as well as international ptt.s are comprised in this database.
3. Google Ptt.s (https://www.google.com/ptt.s)
   Provides information on ptt.s originating from the United States Ptt. and Trademark Office (USPTO), the European Ptt. Office (EPO), and the World Intellectual Property Organization (WIPO).

Following keywords were used for the survey: foreign matter; powder casing; substance detection powder; casing IT.; vibration IT.; casing powder imp.; powder container IT.; IT. powder casing; container IT.; WI; SI;

3.2 Survey results

In the course of this survey three ptt. types could be identified:

1. IT. in general
2. IT. of liquid filled casings
3. IT. of powder filled casings

3.2.1 IT. in general

In this chapter all ptt.s are summarized, concerning general optical IT. of casings (un-filled) or apparatus concerning final IT. of filled casings, without especially addressing the topic of substance detection in lyophilized cakes, e.g. headspace analyses for leak testing.

IT. of casings only

A large number of ptt.s could be identified concerning equipment to transport casings and present them to some kind of optical detection unit or camera. Failures such as scratches in the substance C, chipped casing rims, or out-of-roundness are detected,[47]–[60] e.g., as shown in Figure 3.

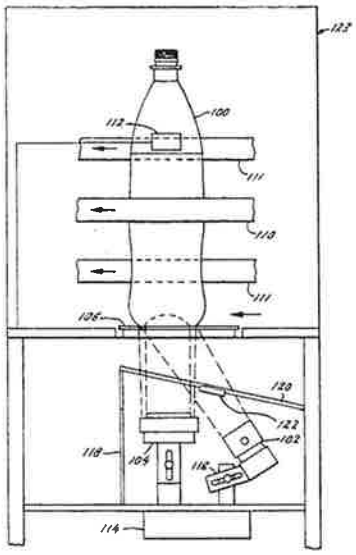

Figure 3: Schematic of a casing IT. unit using a light srce. to illuminate certain areas of a moving bottle and camera systems (e.g. mounted below the moving bottle) to detect defects as presented in [60]

SI Masch. GmbH holds a ptt. [61] offering a means to distinguish between scratches and cracks in a casing using high vtg.. Therefore the casings are presented between two electrodes. In the case of a crack in the casing, a disruptive discharge can be detected once high vtg. is applied to the electrodes.

Final IT. of filled casing

WI AG also holds a set of ptt.s concerning leakage detection for filled casings [62]–[70]; applied principles range from measurement of a biasing force, pressure measurement to detect penetration of gas into the casing, mass spectroscopy analyses to detect leakage of tracer gas or analyses of transmitted laser light.

3.2.2 IT. of liquid filled casings

In the following section ptt.s concerning the IT. of casings filled with a liquid phase are addressed.

Optical analysis

A set of ptt.s were issued applying optical analyses to liquid filled containers [71]–[74] with some cases applying agitation of the casing contents. Deviations in movement are in consequence detected by a camera system. Such a system is shown in Figure 4. Ptt. [75] uses pulsated laser photometry to determine product concentrations in liquid filled bottles with sedimentation residues.

Optical analysis by operators

Also mechanisms or apparatus for improved casing handling to present casings in enhanced functional ways for optical IT. by operators are found [76].

Vibrational analysis

Other ptt.s apply piezoelectric crystals to detect variations in vibration patterns caused by impt..[77], [78]

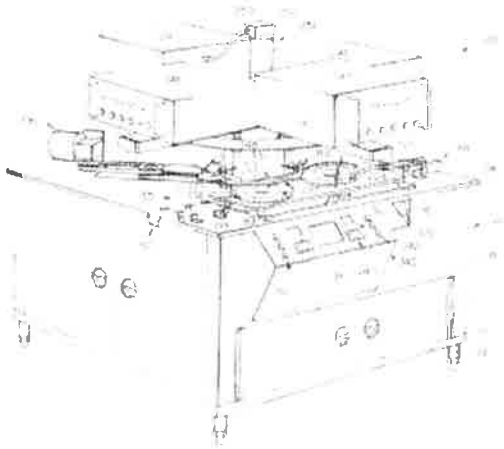

Figure 4: Schematic of a casing IT. unit using cameras to detect motion of ptcl.s inside liquid filled casings as presented in [71]

3.2.3 IT. of powder filled casings

This chapter comprises all ptt.s found concerning IT. of powder filled casings, with the target to detect substances within the contained powder.

Optical analysis

Even though visual IT. can't penetrate into a powder bed, a large number of ptt.s were issued dealing with optical IT. of powder filled casings. In this ptt. class cameras together with suitable presentation mechanisms are used to identify impt. and other irregularities like cracks in the surface areas of the powder bed.[79]–[84]

Optical analysis using electrostatic charging

A ptt. using optical IT. coupled with electrostatic charging of the powder content is [85]. The electrostatic charge is used to spread the powder as a thin layer on a transparent substance C wall. The so formed thin and even powder layer is subsequently optically inspected.

Optical analysis using vibration

Another category of ptt.s combine vibrations and optical IT.. That is, vibration is applied to the powder filled casing and according to the nature of the substance it is forced to float to the top or segregate to the casing bottle. The surfaced substance is then detected via visual IT. using optical detectors [86]–[90].

Sound analysis using vibration

Also under application of vibration, the changes in sound patterns caused by impt. is analyzed as described in [91].

Infrared analysis

In ptt. [92] infrared radiation is used to determine water content of the casing content.

Magnetization analysis

One ptt. was found using magnetization to identify magnetic foreign matter. During the scanning process substance Alic impt. are magnetized and the whole sample is stirred. A superconducting quantum interference device (SQUID) is used to detect the magnetized substance.

Eddy cut. analysis

Eddy cut. induction can also be used to detect substance Alic impt. as described in [93]. Therefore, an eddy cut. is induced in substance Alic impt. by magnetic flux. Infrared cameras are used to detect emitted infrared waves from the agitated substance Alic substance.

Wave analysis

Three ptt.s were found using Wave technology to detect impt.. One describes a specially designed scintillator constituted by substance C beads and fluorescent bodies. The scintillator is used to amplify the signal usually resulting from penetrating Wave beams only. In the described method, after penetrating the probe, Wave beams hit the scintillator. In consequence, the scintillator emits light that hits a photoelectric converting element, which generates an electrical signal [94].

The second ptt. using Wave technology was issued by WI AG. As described in [95] it is an improvement to [96]–[98] due to improved positioning of the Wave srce. and presentation of the casing on the transport test path (using a set of container supports or holders). The ptt. comprises the use of a single Wave srce. and a plurality of detectors (semiconductor-type direct wave detectors as well as scintillator plates). The method presented in [95] also claims to result in improved image quality compared to [99] where Wave beams have to pass through a conveyor belt prior to hitting the probe.

Systems using Wave computer tomography scanners to create dynamically-computed images are described in [100], [101], and also shown in Figure 5.

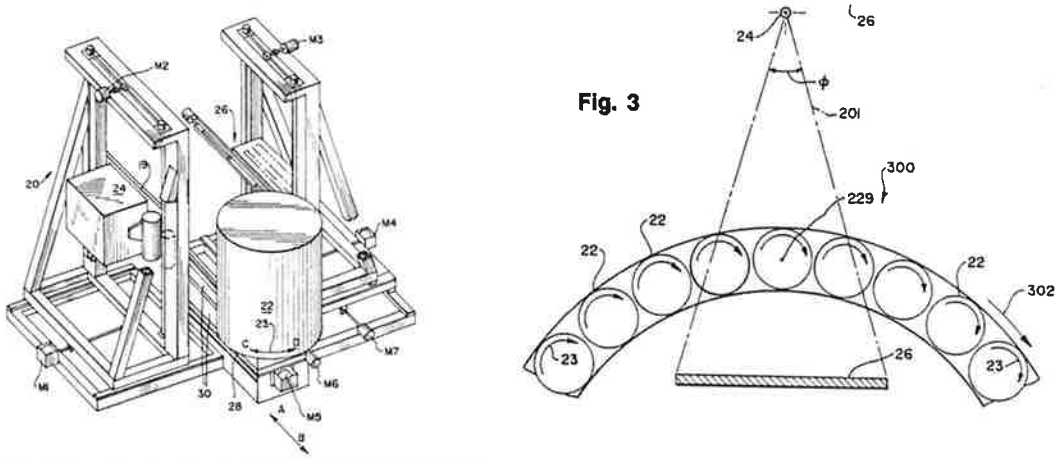

Figure 5: Schematic of an apparatus using wave computer tomography scanner for substance detection as presented in [100]

A third ptt. was issued by SI Masch. GmbH. The mentioned setup is based on the use of one wave tube and two or more detectors. The samples are rotated from one IT. position to the next to obtain images taken from different locations.[102]

3.3 Summary and conclusion

A plentitude of ptt.s exists on the market to address the task of inspecting casings. For detection of impt. in vessels filled with lyophilized powder, especially ptt.s listed in chapter 3.2.3 are of interest. However, ptt.s relying sole on optical IT. can only be used to detect impt. on the surface of a lyo-cake. Other methods like the vibration based methods or methods using electrostatic charging risk the destruction of the cake. However, all methods including the destruction of the lyo-cake structure should not be applied during final testing. Magnetization, eddy cut., and wave analysis are interesting approaches. Ptt.s are hold by WI GmbH as wells SI Masch. GmbH, on the wave sector concerning methods for scanning and ways of transporting and presenting the casings to be inspected. Propt. issues have to be considered during design phase of the IT. system to be developed.

4. Technology survey

This chapter contains information gained about methodologies, technologies apt to the task of identifying impt. in casings filled with lyophilized powders. The chapter comprises a broad technology survey with short descriptions of the working principles of each method. Furthermore a SWOT analysis was performed for each measurement technology as a sum up for further investigations.

4.1 Restrictions

Foremost, restrictions and limits for the technology survey are listed.

Penetration of lyophilized powder cake

Due to the nature of this project impt. need to be detected not only on the surface of lyophilized powder cakes but also inside the cake. Therefore, technologies not capable of penetrating the surface of a lyophilized cake, e.g. optical methods, are to be excluded in this study.

Penetration of containing vessel

The planned system shall be used for final quality IT., subsequent or in parallel to the lyophilisation process. Consequentially, the lyophilized product will be presented in a closed casing. Therefore the IT. method needs to be capable to detect impt. unaffected by the container material, be it substance C or substance N containers. Effects, as the geometry of the vessel, sight blocking by the crimping seal, etc. have to be considered.

Applicability for in-line IT.

The measurement method needs to be integrated in a continuous manufacturing production process. A 100% check of all products is intended. Hence product disrupting measurements as well as very time consuming measurements are to be excluded in this study. However, parallelization of the IT. system is considered.

4.2 Technology overview

According to their frequency a basic classification of methods can be done:

- Penetration of material via high-frequency electromagnetic radiation
  (γ-waves, waves, Short wave, Microwaves)
- Penetration of material via low-frequency or static electric and magnetic fields
  (EKP -, ERSI -, ipd. measurement, magnetic resonance imaging)
- Penetration of material via sound waves
  (Ultrasound)
- Penetration of material via ptcl.s
  (electron -, neutron – scanning, β-radiation)

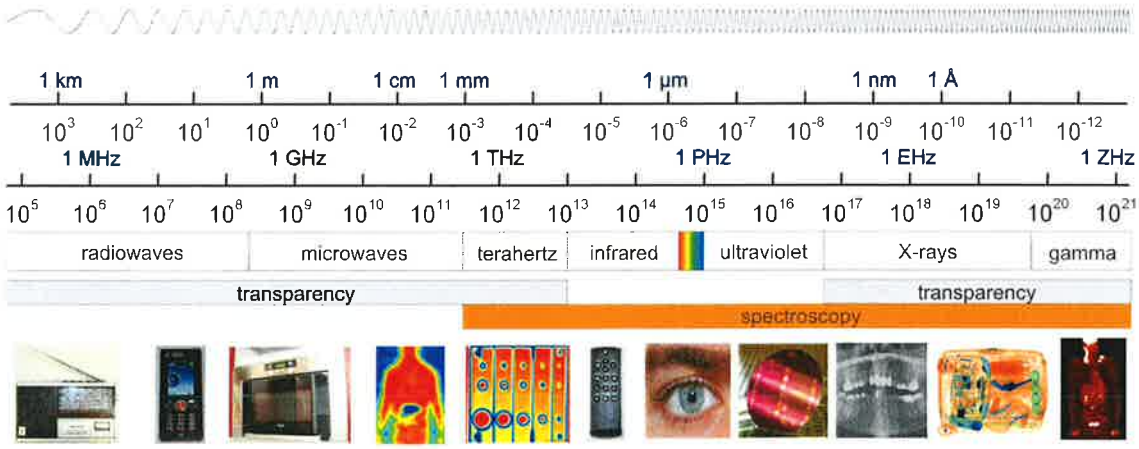

Figure 6: Overview of electromagnetic spectrum, and typical diagnostic applications. Note the lack of transparency in the center of the graph [103]

As shown in Figure 6 analytical methods based on ultraviolet- (UV), visible- (VIS) infrared- (IR) as well as near infrared (NIR) spectra cot. be used in the course of this project due to the demanded in-depth analyses of the lyophilized powder cake.

The same is true for methods depending on secondary emissions in the above mentioned emission ranges such as wave fluorescence or thermal imaging. Even though these technologies are successfully implemented in substance detection in the food processing industry, they are not considered for this survey. As impt. could be in the middle of the inspected cake, radiation would be emitted, however the emitted secondary radiation would not be able to penetrate encompassing material layers.

Hence, the following methods are not applicable here, although found in industrial applications, especially in food processing.

- β-radiation, because substance C cot. be sufficiently penetrated.
- Thermal imaging, because substance C cot. be penetrated at all.

4.3 Feasible methods and technologies

A short overview of the different methods is given in Table 4; a detailed discussion of the various methods follows subsequently.

Table 4: Summary of possible IT. technologies

Principle	Resolution	Application	Comments
Wave			
Attenuation by material dnty. and atomic number	High-Resolution: 40 ent. Regular: 100 ent.	Foreign ptcl. IT.	- no organic impt.
Wave Tomography			
Tomography of waves	0.5 ent.	Materials with high difference in dnty.;	- mtme depends on the resolution to be achieved
Ultrasonic			
Echoes when encountering variations in acoustic ipd.	0.6 ent.	Dnty. measurements; Interfaces between materials; Substance C in substance C;	
Microwaves			
Foreign body in microwave field changes electromagnetic permittivity	ent. range	Detection of substance A, substance C, stone, wood splinters, fruit stones, substance L, seeds;	
Short wave Imaging			

Attenuation of Sw-waves on transit	150–250 ent.	Detection of polar substances, substance Q, substance Ns; Water is opaque to Sw.	- cot. pass through substance A layers
EPDA Tomography			
Measurement of vtg. on object surface	ent. range	Medical applications for imaging breast, skin, brain;	- requires galvanic coupling
EKP Tomography (ECT)			
Measurement of the dielectric permittivity distribution	ent. range	Distribution of solids in fluid; Measurement of flow in pipes;	
ERSI Tomography / Imaging			
Measuring the potential between electrodes		Scanning for ground and oil reservoirs	
Magnetic Induction Tomography and Friends			
Exploiting the eddy cut. effect.	ent. range		- low spatial resolution
Magnetic Resonance (Tomography / Imaging)			
Detecting resonance frequency of excited atomic nuclei, usually hydrogen.	ent. to ent. range	Foreign body substance; Fruit moisture, ripeness, sugar content, etc.	- scanning time of at least several minutes

The resolutions given in the table are valid for imaging applications. For the detection of a substance, it may not be necessary to resolve the substance, but a distinct change in the received signal may be sufficient (e.g. for microwave detection).

4.4 Wave and wave tomography

4.4.1 Wave basics

Wave technology uses electromagnetic waves of the wavelengths in between 0.005 to 10 nm. While passing through matter they are differentially absorbed depending on varying composition (dnty. and the atomic number) and thickness of the material passed.[104]

An wave system consists of an wave srce. and detector elements. For the controlled generation of waves, usually wave tubes are used. To generate waves, electrons provided in the cathode of the wave tube, are accelerated under a potential difference. While the accelerated electrons hit the anode of the wave tube, their kinetic energy is converted into electromagnetic radiation, as a result of collisional and radiative interactions. The potential difference, regulated by the applied electrical vtg., controls the "hardness" of the wave radiation. Tube vtg. (usually ~20-100 ent. for "soft matter" or more for substance A analysis), tube cut. (usually several 100 ent. for analytical, or up to 10 ent. for imaging applications) and exposure duration are adjustable parameters determining the measurement. The emanated wave beams are shaped and controlled by collimator shutters in order to direct them to the points of interest in the material to be analysed.[105]

When passing through a probe wave beams can cause 4 different types of interactions [107]:

a. Photoelectric absorption
   The probability of photoelectric absorption is directly proportional to the atomic number of the probe and inversely proportional to the transmitted wave energy. During this process, the wave photon is absorbed, and an excited electron is emitted.
b. Waveleigh stt.
   The probability of Waveleigh stt. increases for higher atomic numbers. The wave photons are scattered at the atoms without energy loss.

c. Compton stt.

   The probability of Compton stt. is proportional to the electron dnty. of the probe. In Compton stt., the wave photon loses energy and changes direction, the excess energy and impulse is transferred to the bulk.

d. Pair production

   The probability of pair production increases at high photon energy levels (>1.02Ent.). Only then the energy of the wave photon is sufficient to produce an electron-positron pair. This effect is of no concern in the cut. application.

These modified wave beams are subsequently detected and mapped, e.g. into a two-dimensional image. Thus the absorption is usually the property of interest, whereas the other factors are negligible (like pair production in our case), or reduce the signal-to-noise ratio by the detection of scattered photons.

Scintillators can be used to detect incoming wave beams and convert them into an amplified signal proportional to the detected wave flux, e.g. phosphorescent material which emits visible light as result of wave absorption. This secondary signal can be optical photons or electrons. Photomultiplier tubes, photodiodes or other light-sensitive sensors are subsequently implemented to record the secondary signal.[107]

Direct wave detection can be conducted using semiconductors. In this case incoming wave energy leads to generation of electrical charges within the semiconductor via creation of electron-hole pairs. The direct method offers a higher quantum efficiency and better spatial and energy resolution.

Wave tomography is based on the same methods as standard wave analyses, the only difference being that a plurality of images are taken at various locations and subsequently used to reconstruct a 3D-image.

4.4.2 Wave advantages and challenges

As wave attenuation results from wave interactions, detectable variations depend on dnty., atomic number and thickness properties of the probe. Low atomic number substances as well as object thickness and enlarged field size can increase stt. and thus reduce obtainable subject contrast by adding background signals.[107]

Consequently, wave technologies are suitable to detect materials of high dnty. or high atomic number such as substance A, substance C, stone, bones (Ca), etc., whereas impt. such as substance Hs, substance Q, paper, etc., are difficult to detect. This is especially true if similarity of wave interaction (attenuation coefficients) is given with the surrounding lyophilized powder material.

Usually resolution goes down to 100 ent. (high resolution: 40 ent.). Higher resolutions can be achieved using wave tomography (down to 0.5 ent.). However, mtme increases exponentially.[108] Typical measurement frequencies for an wave image are in the order of several Hz. Micro-CT images can take up to several minutes (with basically the same frequency for single images, but capturing several hundred images for the subsequent reconstruction).[109]

4.4.3 Wave SWOT analysis

Based on the measurement principle, market research as well as discussions with vendors and technology suppliers a SWOT analyses has been performed. The results are not presented here. An additional SWOT analysis was performed concerning Wave tomography (not presented here).

4.4.4 Wave dark field imaging

Wave dark field imaging (also known under phase-contrast imaging) does not exploit the absorbance of waves when transecting matter, but the phase shift of the radiation. Experimental set-ups to realize a measurable shift in phase vary. Those usable with a

conventional wave srce. are usually based on comparing the interference pattern of (Talbot-) grids for an undisturbed beam and when a sample is present.

The greater sensitivity of the phase to matter (as compared to absorbance) makes it an upcoming technique for clinical tissue monitoring. However, for the application intended here, it would also be advantageous because of the higher contrast between similar materials.[110]–[113]

Despite its success, but due to its elaborate set-up, dark field imaging has not reached the commercial market yet.[114]

4.5 Ultrasonic

4.5.1 Ultrasonic basics

Ultrasonic is similar to vibration analysis, where the noise generated during the IT. is analysed. Ultrasonic techniques use acoustic waves in the range of 20 to 100 ent. (wavelength > 1 m). The probe to be tested is impinged with an ultrasonic signal. Based on varying acoustic ipd. ratios (sound pressure to associated acoustic ptcl. velocity [115]) the signal is partially reflected, scattered or absorbed at interfaces (e.g. substance B-air, powder-air, etc), as exemplarily shown in Figure 7.[116] The acoustic ipd. can also be understood as a measure of collective resistances against wave propagation in a specific environment.

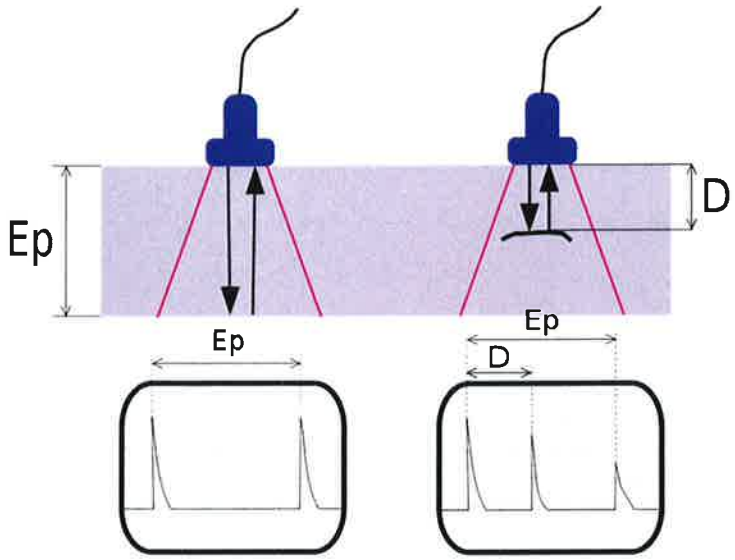

Figure 7: Detection of an interface, e.g. an air inclusion in substance B, using ultrasonic [117]

Dynamic (piezoelectric) or electrostatic (capacitive or magnetostrictive) ultrasonic transducers are used to generate and detect ultrasound waves.[118] Especially piezoelectric ceramic or substance N membranes are often implemented. A schematic of a piezoelectric substance N film membrane is shown in Figure 8.[119] In contact mode the ultrasound srce. directly touches the probe surface but also non-contact senders exist as mentioned further below (Air coupled ultrasonic). Measurements are conducted in the rms. configuration as well as in echo mode (reflection configuration), as shown in Figure 10.

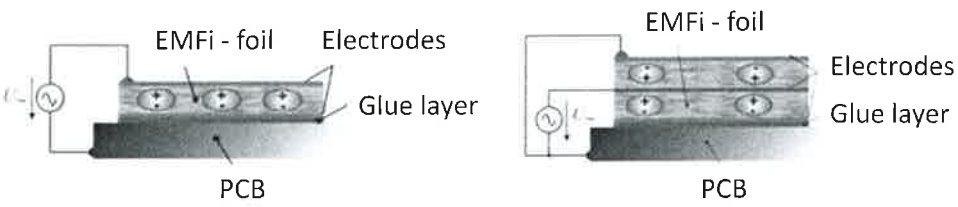

Figure 8: Schematic of a broadband ultrasound srce. implementing electro mechanical film technology (EMFi) [119]

The usual limit for resolution, in an ultrasound imaging application, is around 0.6 ent.. [120]

4.5.2 Ultrasonic advantages and challenges

As this analytic method depends on acoustic ipd. analysis, only impt. with a significant ipd. difference compared to the lyophilized powder can be detected. Furthermore powder offers a high number of interface changes (powder ptcl. and air), causing a high amount of noise for the measurement. In addition, the amount of air included in the probe has a strong influence on the measurement, given the mediocre propagation of ultrasonic waves in air. That means, variances in the bulk dnty. of the probe would cause large variances in the analyzed signal. Surface impt. will also be difficult to detect as boundary layers cause a large disturbance for the signal per se. The measurement itself is more or less instantaneous; however, the correct placement of the vessel is the time limiting step. Irregular areas, e.g. rnd. casing parts or areas with changing diameter, create dead spots, which cot. be analysed using ultrasonic. This also prevents the investigation of the topmost layer of the cake, due to its uneven surface.

4.5.3 Ultrasonic SWOT analysis

Based on the measurement principle, market research as well as discussions with vendors and technology suppliers a SWOT analyses has been performed. The results are not presented here.

4.5.4 Air coupled ultrasonic

Regularly water is used as a coupling medium in between ultrasound transducers and the specimen in question. Advantages in the construction of ultrasound srce.s however have enabled to use air-coupling for ultrasound measurements, despite the large dampening factor at air-solid interfaces. Air coupled ultrasonic always works with more than one probe, to achieve adequate transducer and amplifier isolations. The number and arrangement of probes can vary greatly, and is adapted to the problem [122]–[124], as is also shown in Figure 9. Air coupled ultrasonic is often already an option offered by the vendors of ultrasonic analyzers.

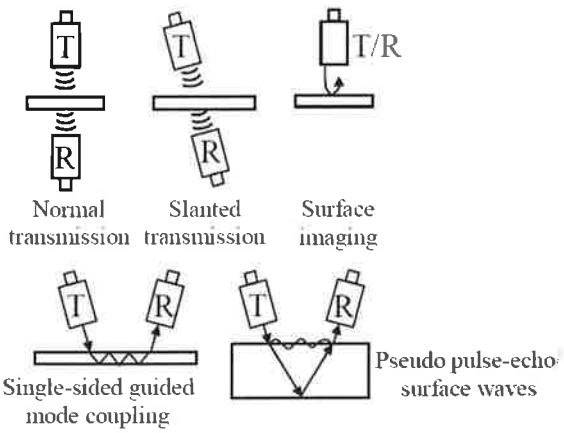

Figure 9: Different set-ups for air coupled ultrasonic [123]

4.6 Microwaves

4.6.1 Microwave basics

The wavelength of microwaves ranges from 1 ent. to 1 ent. Microwaves can be used for imaging applications to investigate dielectrics like substance N, clothes, ceramics, etc. Yet due to the long wavelength, achievable resolutions are very low.[103] Recent applications mostly focus on moisture detection. Non-conductive materials are transparent for microwaves. In materials with bipolar structure, like water, the electric field of microwaves induces oscillations.[125] That is, strong attenuation occurs. Conductive materials reflect microwaves. Reflection and stt. also occur at the boundary layers of isolator materials with varying dielectric constant.[126]

Two principle setups are known based on rms. or reflection analysis, as shown in Figure 10.

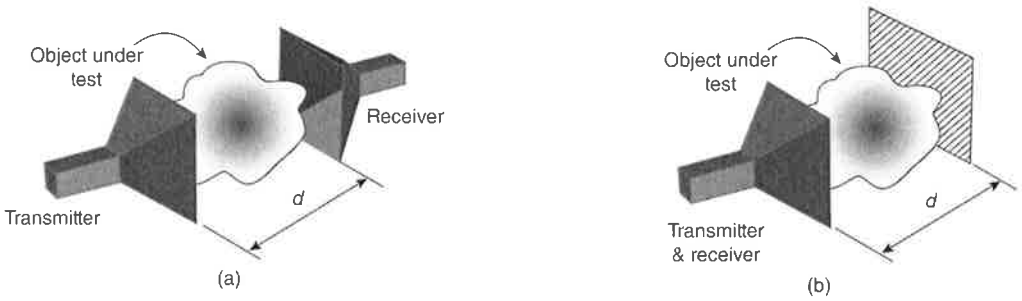

Figure 10: Schematic a) shows a setup based on rms. analysis, b) shows a setup based on flx. analyses, where one antenna is used to send and receive the signal reflected from the probe [127]

In the rms. configuration the amplitude and phase shift of transmitted microwaves are measured, using e.g. horn antennas. In the reflection configuration, commonly used for surface imaging, one antenna emits and detects the signals reflected from the sample. Magnitude and phase of the reflected signal are measured to determine reflection coefficients. As antennas, contacting antennas or non-contacting antennas are used. An example using contacting antennas is the open-ended coaxial rms. line where the antenna is pressed against the probe and operates as a resonator. An example for non-contacting antennas is the broadband microwave horn.[127] As microwave analysis is very similar to eddy-cut. testing (physical principle of the test area, hardware, error patterns) standard eddy-cut. test equipment with adequate adapters could be used.

Due to the long wavelength of microwaves (1 ent. – 1 ent.) achievable resolutions for imaging are very low (cm range). However, microwave detection does not rely on imaging, but on the change of the typical microwave rms. pattern. Existing on-line applications of microwave technology (predominantly moisture measurements) exhibit that the rate of measurement is well below a second.

4.6.2 Microwaves advantages and challenges

Microwaves have a high transparency, however lateral resolution is only around the cm range.[103] Still problematic is the high amount of stt. at boundary layers, as is to be expected for lyophilized cakes constituted of a multitude of ptcl.s and air.

4.6.3 Microwave SWOT analysis

Based on the measurement principle, market research as well as discussions with vendors and technology suppliers a SWOT analyses has been performed. The results are not presented here.

4.6.4 Surface penetrating radar

Similar, but exploiting even longer wavelengths than microwaves, surface penetrating radar is used. The amplitude and phase change of micro(radio-)waves is measured. This enables to find substance Ns, substance L, etc. in contained vessels (although substance A cot. be penetrated).[129]–[131]

However, contact to the manufacturer and ptt. holder revealed, that at the moment powders and dry matters cot. be analyzed and that ptcl.s smaller than 1 ent. are problematic.

4.7 Short wave imaging

4.7.1 Short wave basics

Short wave (Sw) waves comprise electromagnetic radiation in the wavelength between 30 ent. and 3 ent.. Sw radiation offers high transparency in dielectrics along with spectral selectivity.[103] Sw spectroscopy can be used to generate individual 'fingerprint' spectra for crystalline materials inducing specific lattice phonon modes. That is, distinct frequencies are absorbed by the crystalline material. As amorphous materials are too disordered to sustain phonon modes, most pharmaceutical amorphous materials are semitransparent to Sw radiation. Therefore, internal structures can be mapped.[132] Substance As do strongly reflect Sw radiation. Water and some substance C types are strongly absorbent to Sw radiation. Changes in penetrating Sw radiation amplitude correspond to absorption, porosity, homogeneity and thickness.

Observed signal delays depend on the refractive index as well as thickness of the material.[103]

Sw radiation can be generated using electronic srce.s, e.g. electron beams, solid-state srce.s, frequency multipliers, or photonic srce.s, e.g. Sw semiconductors, gas lasers, optoelectronic srce.s (e.g. Sw photoconductive antennas,).[133]

Commonly applied detectors are either homodyne or heterodyne. Homodyne detectors measure a physical property of a detecting element, which changes with absorbed incident Sw signals. Such properties can be volume, electric and dielectric properties, etc. Examples for such detectors are bolometers, plasma wave oscillation field effect transistors, Golay cells, pyroelectric detectors, etc.

Heterodyne detectors blend the incoming Sw signal with an additional signal from a local oscillator, resulting in an intermediate frequency signal, which can be processed further.

Alternatively optoelectronic detectors can be used such as optically gated Sw photoconductive antennas or nonlinear electro-optic crystals. Both systems can incorporate short pulsed lasers or pairs of CS lasers. In the photoconductive antenna system the photocut. produced in the antenna is proportional to the amplitude of the incident Sw electric field. In electro-optic crystal systems the polarization state of a co-propagated gating laser is detected via photodiode detectors. The amplitude of the incoming short wave electric field is proportional to the vtg. output of the photodiode. For both optoelectronic detection systems phase information can be detected via controlling the arrival time of the gating laser beam with respect to the incident short wave signal.

Detection limits for parc.s can be as low as 150 – 250 ent.. In principle, a sample is screened point for point, however a single measurement can be done very fast, and images can be gained with several Hz frequencies. However, for higher resolution the necessary mtme rises accordingly.[135], [136]

4.7.2 Short wave advantages and challenges

Sw photon energy (single ent. [137]) is a million times smaller than that of waves and therefore non-ionizing. Thus damage of pharmaceutical samples is unlikely.[132] Substance C containers can cause difficulties for this technology due to their strong absorbance behaviour (exception: silica substance C). Furthermore, usual resolution limits are high, but are strongly dependent on the difference of absorption and refraction index of the substance in contrast to the sample material.

4.7.3 Short wave SWOT analysis

Based on the measurement principle, market research as well as discussions with vendors and technology suppliers a SWOT analyses has been performed. The results are not presented here.

4.8 EPDA tomography (EPDA)

EPDA tomography comprises measurement systems used to determine the admittivity (i.e. reciprocal specific ipd.) distribution in materials. Admittivity of materials varies according to their variation in electrical properties. In ipd. tomography an alternating electric cut. and induced vtg.s on the boundary of the object are simultaneously measured. The derived admittivity is a complex valued function. It consists of an imaginary part (frequency of the electrical cut. multiplied with the permittivity of the object) and a real part (electrical conductivity).[138] Two of the most rapidly developing areas based on ipd. imaging are EKP tomography (ET) and ERSI tomography (ERT).[139] Both techniques are further explained in the following sections.

4.8.1 EKP tomography (ET)

4.8.1.1 EKP tomography basics

In ET the capacitance between mtp. electrodes located around the area of interest is measured. The measured capacitance depends on the permittivity of the material in

the analysed area. That means, materials with different dielectric properties can be distinguished as to their varying influence on the electric field. To obtain a spatially resolved image the inter-electrode capacitances are measured as shown in Figure 11. Suitable algorithms are applied to calculate the permittivity distribution inside the analyzed area, usually implementing linear relationships between capacitance and permittivity. Yet, in reality the relationship between capacitance and permittivity is strongly nonlinear. Therefore intensive research is done on nonlinear reconstruction techniques.[140]

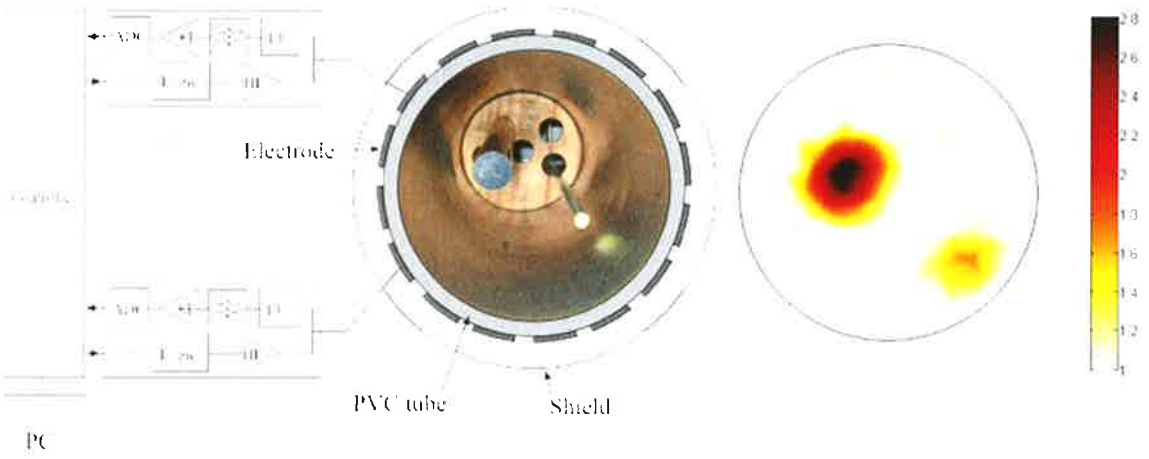

Figure 11: Schematic of a ET measurement system and example reconstruction result. The system utilizes 16 electrodes in circular arrangement around a SUBSTANCE F pipe. [140]

Usual applications for this technique are, e.g. surveillance of binary mixtures and mixing processes, due to the high temporal resolution.[141] Possible image resolutions are in the ent. range. Image resolution increases with increasing number of electrodes used. However the larger the electrode number, the smaller the surface area of each single electrode. Thus the magnitude of inter-electrode capacitance is reduced and in consequence the obtainable signal-to-noise ratio is lower.[139] In ET the electrical field lines are influenced ('bend') by analysed materials/ impt.. Thus ET is a soft-field sensor technology. As a result blurred images are obtained and computational efforts have to be made to overcome this problem.

4.8.1.2 EKP tomography advantages and challenges

A big challenge is the large resolution limit in the ent. range. Furthermore significant differences in dielectric constant between substance and measured medium have to be given.

4.8.1.3 EKP tomography SWOT analysis

Based on the measurement principle, market research as well as discussions with vendors and technology suppliers a SWOT analyses has been performed. The results are not presented here.

4.8.2 ERSI tomography/ - imaging (ERT/ERI)

4.8.2.1 ERSI tomography basics

ERT systems are used to measure the variation of electrical conductivity of an area of interest. The electrical conductivity is a measure of how well a material conducts electric cut., also defined as the reciprocal value of the ERSI (measure of opposition to flow of electric cut.). A multitude of electrodes are installed invasively but non-intrusively into, e.g. a pipeline wall. Low AC cut. is injected (tens of milliamperes) at a pair of electrodes and the resulting vtg. at the remaining electrode pairs is measured. The inserted cut. doesn't flow in straight lines but follows the path of least resistance (also depending on the measurement configuration).

As the sensing field of an ERT system is altered according to sample properties, the ERT technology belongs to the so called soft-field sensor technologies. This results in limited resolution compared to hard field sensing. An increased number of sensor elements would help improve resolution, yet a too large number of sensors poses high computational efforts, reducing real time capabilities of the analytical system.[21]

In contrast for using a single frequency as for ERT, in spectral analyses (also known as ipd. spectroscopy) a broad frequency band is used. This can be exploited to activate and measure the relaxation of dipoles, thus gaining information on the physical state of the specimen. Recent applications in this field deal with "through-casing ipd. spectroscopy". For that purpose casings are electrically conducted and macroscopic electrical properties can give insights into the behavior of the lyophilisate throughout the freeze-drying process, e.g., formation of cracks or crystallization. For this applications non-invasive coupling of the electrodes at the outside of the vessels is sufficient.[142]–[145]

4.8.2.2 ERSI tomography advantages and challenges

As the electrodes need to be directly in touch with the sample to be analyzed, common single frequency ERT seems not adequate to test lyophilised powders in closed vessels (without damaging the vessel and contaminating sterile conditions of the product). However spectral analyses methods as reported in [142]–[145] can be used applying non-invasive electrodes. Expected resolutions are low, due to the fact that ipd. tomography in general is a soft-field technology.

4.8.2.3 Spectral analyses SWOT analysis

Based on the measurement principle, market research as well as discussions with technology suppliers a SWOT analyses has been performed. The results are not presented here.

4.9 Magnetic induction tomography (MIT)

Magnetic induction tomography (MIT) is also known as electromagnetic tomography (EMT), or mutual inductance tomography (MIT).

4.9.1 Magnetic induction tomography basics

The basic principle behind this technology is the detection of eddy cut.s induced by a magnetic field. The magnetic field is created by an excitation coil. The eddy cut.s subsequently induce a magnetic cut. in sensing coils. All three passive electromagnetic properties of materials can be analysed using MIT: [146]

- Conductivity

  Is a measure of the ability of a material to conduct electrical cut.. It is also defined as the reciprocal value of the electrical resistivity.
- Permittivity

  Is a measure of how a dielectric medium influences an electric field or how well a material transmits or permits an electrical field. It describes the resistance encountered when forming an electric field in a material.
- Permeability

  Is a measure of the degree of magnetization of a material in response to a magnetic field.

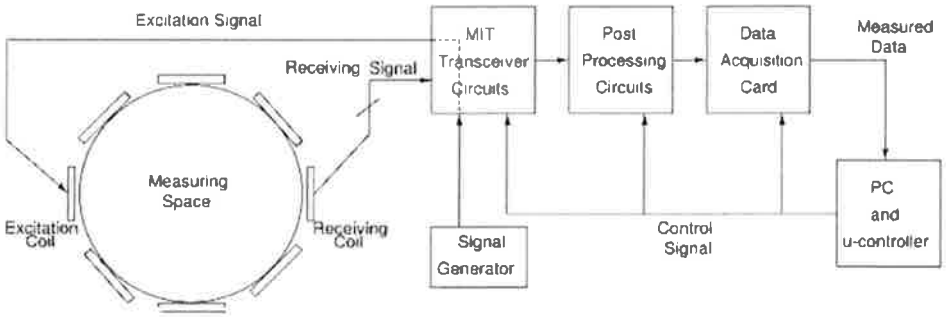

Figure 12: Block diagram of an MIT system [147]

Achievable spatial resolutions strongly depend on the number of independent transmitter and sensing coil combinations.[146] Schematically, the set-up is shown in Figure 12. Due to the disperse nature of the electromagnetic field, the transmitting field

doesn't follow a straight pace through the tested area; hence this technology belongs to the soft-field tomography techniques. Therefore, changing material parameters are more difficult to localize. Also computation of the acquired signals is more complicated than in EPDA tomography.[147]

4.9.2 Magnetic induction tomography advantages and challenges

As of now, there are no commercially available systems on the market. Development is strongly advancing in this sector. First cost effective systems were already presented, e.g. in [148].

4.9.3 Magnetic induction tomography SWOT analysis

Based on the measurement principle, market research as well as discussions with vendors and technology suppliers a SWOT analyses has been performed. The results are not presented here.

4.10 Magnetic resonance tomography

Magnetic resonance tomography and magnetic resonance imaging are used as synonyms, as a cross sectional image is a result of a tomographic procedure.

4.10.1 Magnetic resonance tomography basics

For MRT a strong external magnetic field leads to a preferred orientation of the atomic nuclei in the sample based on their spin orientation. A secondary oscillating external magnetic field leads to a tilting of the atomic spin. The resulting precession behaviour around the main magnetic axes induces cut. in an external detection circuit, which can be detected. The schematic set-up is shown in Figure 13.

The relaxation time of the atomic nuclei is the important attribute determining the finally received image. Secondary, the different content of hydrogen atoms in the specimen leads to image contrast.

To initiate resonance behaviour in only certain cross sections of the sample, and hence to allow a localisation of the received signal, spatially dependent magnetic fields are used.[149], [150]

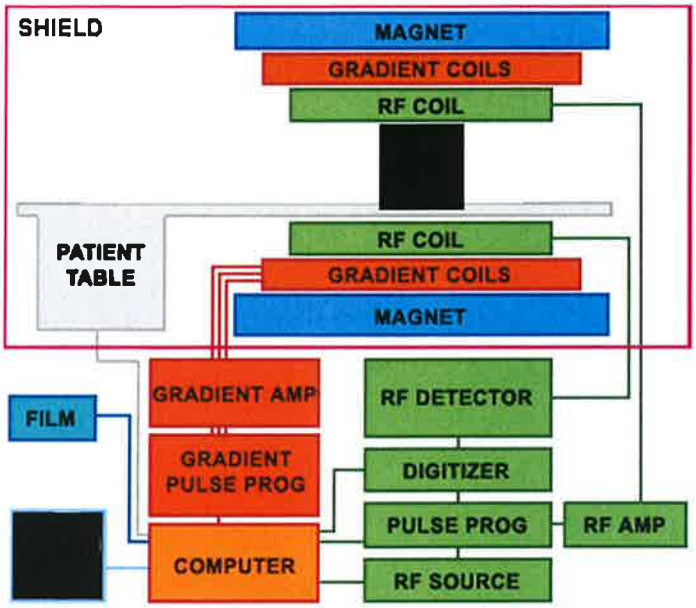

Figure 13: Scheme of magnetic resonance tomography application [151]

4.10.2 Magnetic resonance tomography advantages and challenges

A huge advantage of MRI is the ability to distinguish between similar materials (e.g. different tissues in the human body). With real-time MRT fast image capturing is possible.

The resolution of the system is basically dependent on the magnetic field strength, which can be used.

The mtme is still longer than for comparable imaging methods in the order of minutes or even longer. The higher the resolution to be obtained, the longer is the necessary mtme.

Furthermore, the method is cost intensive, because of the necessary infrastructure, especially cooling can be exertive. Also surrounding equipment must be compatible to the strong magnetic fields.[152], [153]

4.10.3 Magnetic induction tomography SWOT analysis

Based on the measurement principle, market research as well as discussions with vendors and technology suppliers a SWOT analyses has been performed. The results are not presented here.

4.11 Summary and conclusion

As a result of an extensive literature and market research seven major technologies apt to address the task of substance detection in lyophilized powder filled casings could be identified.

The SWOT analyses give a good overview of advantages and disadvantages of each technology and were used as decision basis for identification of favorable technologies. Ultrasonic, Microwave, ET as well as MRT were not further investigated. Wave, short wave and spectral analyses (DES) were chosen for further analyses.

All analytical technologies in question base the substance detection on differences in physical properties (e.g. permittivity, dnty., etc). The quality of the measurement (resolution, measurement speed) strongly depends on the difference in the measured physical property. That is, a large difference between substance and lyophilized powder allows for detection of a finer substance. The smaller the difference, the larger the substance has to be for the analytical technology in question to be able to assure detection. Therefore, the physical properties of the substances as well as the physical properties of our chosen lyophilized powder substances need to be evaluated.

However, a definitive decision based on sound understanding of detection limits and mtmes can only be taken after the influence of the casings, and the needed difference of physical properties between substance and lyophilized powder have been experimentally analyzed.

5. Experimental results

In this chapter a short overview of the conducted experiments at equipment suppliers will be presented. Based on theoretical considerations, as presented in chapter 4, experiments were conducted using spectral analyses, short wave and wave equipment. The experiments were conducted using samples containing model lyophilization products and substances accounting for both: typical substances as well as possible influences on the measurement methods in question, as identified during process assessment, presented in chapter 2.

5.1 Spectral analyses

This chapter summarizes the information gained during trials conducted using the ipd. measurement setup available at the Institute of Electrical Measurement and Measurement Signal Processing, Graz University of Technology. It comprises information on the test setup and exemplary results including interpretations of the latter. The tests were performed and evaluated by Markus Neumayer and Johannes Gursch.

5.1.1 Test setup and procedure

Tests were performed using a custom made casing holder made from substance F and 2 measurement electrodes. The blind hole in the middle of the casing holder had the same diameter as the casings.

A 2x2 scatter matrix measurement (evaluation of Z12: ipd. between electrodes) was performed with a frequency range between 9 ent. to 50 Ent.. Measurement data below 5 Ent. contained a large amount of noise and will not be used for further analyzes.

The test casings contained unpolluted substance J-substance I-lyo. Each casing was measured twice before adding a substance. The repeated measurement of the empty casing was conducted to account for variances originating from casing positioning in the casing holder. Also cake structure slightly varies in the lyophilisate, thus ipd. measurement between the electrodes can vary with variations in casing positioning.

5.1.2 Results and discussion

In the following section an exemplary test result is presented and discussed. All data lines labelled as "Reference" refer to the empty casing holder. Casings without contaminants are marked "empty" for the first measurement and "empty2" for the second measurement. In the following figures the S stt. parameter is shown over the tested frequency range. It can be referred to as the reciprocal value of the insertion loss (with opposite signs) which describes the loss of signal power resulting from inserting an object in a rms. line. A negative sign for the S value indicates signal attenuation.[154] It can be used to subsequently calculate rms. ipd..[155] Ipd. is a measure of the opposition of an alternating cut. circuit to electrical cut. if vtg. is applied. The vtg. to cut. ratio is frequency dependent and ipd. describes the ratio of vtg. to cut. amplitude but also the phase shift between the latter.[156] In all plots only every 30th data point is plotted with a marker. An overview of the conducted trials and their outcome is presented in Table 5.

Table 5: Conducted ipd. measurement trials and results

Substance type	**Sample**	**Results**
Substance B	AMS7	Not detectable
Substance C	AGS7	Not detectable
Substance D	ASiS7	Not detectable
Substance E	AVS7	Not detectable
SUBSTANCE F	AHS7	Not detectable
Substance G	ASubstance GS	Not detectable

As example the measurements of a sample containing a substance B substance (AMS7, size >800 ent.) was chosen, as substance B is expected to have the largest influence on the S value. No influence of the substance can be seen. Regarding the deviations between first and second measurement of the unpolluted casing (1empty and 1empty2) it can be concluded that a large variance is caused in dependence of casing positioning.

5.1.3 Summary and conclusion

As stated in Table 5 all substances cdnt. be detected even in a size range of over 800 ent.. Even substance B, which should have a strong influence on ipd. didn't affect the measurement significantly. It was shown that the volume of a substance in comparison to the sampled volume (whole casing) is too small to cause significant influence on the ipd. or S value.

Larger differences in volume and or humidity level of substance to lyophilisate would improve detectability. The deviations of the reference measurement line observed around 25 Ent. can result from irregularities caused by the cabling to and from the electrodes. Deviations were observed in consequence to differences in casing positioning. However, the deviations were rather small and deviations seen during measurement of a contaminated casing were even smaller. To improve the situation the measurement electrodes could be pressed against the casing with a constant force (e.g., via springs) instead of a more or less tight fit in the blind hole (depending on the casing diameter).

However, based on the results obtained, this technology must be excluded from any further considerations.

5.2 Short wave

In the following chapter information gained during trials conducted using the Sw equipment at RECENDT GmbH, Linz is presented. It comprises information on the test setup and exemplary results including interpretations of the latter based on a report filed by Dr. Stefan Katletz and Harald Pühringer (RECENDT GmbH, Linz).

5.2.1 Test setup and procedure

Two different test setups were used, as described in the following sections.

5.2.1.1 Flx. mode

Sw radiation is generated using photoconductive antennas stimulated via a femto-second-laser. For flx. measurements, a beam splitter is used and the beam is directed to the sample via adaptable mirrors. Focusing is accomplished using a Teflon scan-lense. The reflected pulses are collected and detected time-resolved after passing the beam splitter. Flx.s originating from different sample depths exhibit a time delay, therefore changes in runtime correspond with optical thickness (=geometric thick-ness · refraction index).

5.2.1.2 Rms. mode

Sw radiation is generated using photoconductive antennas stimulated via a femto-second-laser. After rms. of the sample the Sw pulse is detected time-resolved via a detector antenna.

Analysing runtime changes and attenuation of the signal, optical properties (refrac-tion and absorption coefficient) can be deduced using a reference measurement without sample. Fourier transformation of the signal also allows analyses in the fre-quency domain. The analysed frequency domain is 0.1 – 2 Sw, equaling a wavelength of 3 ent. to 150 ent.. For imaging, the sample is moved in two directions relative to the focus point.

5.2.2 Results and discussion

In Table 6 a summary of the conducted experiments and their outcome is given.

Table 6: Conducted ipd. measurement trials and results

Test setup mode	Substance type	Sample	Results
Flx. - casing part	Substance B	AMS7	Not detectable
Flx. - otherwise positioned casing	Substance B	AMS7	Not detectable
Flx. –otherwise positioned casing (no lyophilizate)	Substance B	AMS7	Not detectable
Rms.	Substance B	AMS7	Not detectable
Rms.	Substance C	AGS7	Not detectable
Rms.	Substance G	Substance GS	Not detectable

5.2.2.1 Flx. mode

Substance A contaminants are expected to generate a strong signal variation (reflection of Sw radiation by substance A). Primary tests were conducted with substance A contaminants (size >800 ent.) to assure ease of detection. To identify optimal scan conditions casing positioning was varied. Scans were conducted through the casing part, with the casing lying in a horizontal position and through the casing wall, with otherwise positioned casings.

Scan through casing part - substance A contaminant (>800 ent.) in product filled casing

The inner and the outer substance C surface can be distinguished. Deduced refraction index is 1.65 (optical thickness 1.65 ent.; geometrical thickness 1 ent.).

Due the bend casing part an inhomogeneous amplitude distribution was generated. Despite the expected high contrast between substance A and substance C or lyophilisate, only noise was generated when scanning deeper into the casing. The substance A substance cdnt. be identified.

Scan of otherwise positioned casing - substance A contaminant (>800 ent.) in otherwise positioned product filled casing

To eliminate the influence of the bend casing part a scan of the otherwise positioned casing was conducted. Stt. at the outer region of the round casing was expected, therefore the casing was positioned as to present the substance in a central position where stt. is minimized.

The reflected Sw signal taken at three different heights in the casing:

- Blue: in the lyophilisation product (substance C / cake interface)
- Green: at the substance position (substance C / substance A interface)
- Red: over the lyophilisation product (substance C / air interface)

No significant variation of the signal over the casing height was encountered, that is, the substance A substance cdnt. be detected. Also the influence of the lyophilisate seems to be minimal as no variation of the signal was encountered comparing the substance C / lyophilisate and the substance C / air interface.

5.2.2.2 Rms. mode

For rms. mode the casings were scanned in an otherwise positioned position. The casings were turned to ensure substance position close to the central symmetry line. Time domain, as well as the frequency domain of the signal were analyzed. Tests were conducted with substance A as well as with other contaminants with expected smaller interactions with Sw radiation (substance G and substance C substance).

Scan of otherwise positioned casing

The bandwidth of the Sw radiation was reduced from 3.5 Sw to 1 Sw and the Amplitude of the time signal was reduced to ~15% of the reference signal. The substance A substance cdnt. be detected.

A distinction of lyophilisate and air can be made. However, the substance cdnt. be found.

5.2.3 Summary and conclusion

Throughout the conducted trials the detection of small contaminants using Sw radiation was not possible. The casing geometry, as well as the material properties of substance C, are sub-optimal for the detection of small contaminants using radiation in the Sw domain. The influence of the lyophilisate is minimal as it is almost transparent to Sw radiation (only minimal signal attenuation encountered).

For the flx. measurements the used scanning system has a small signal to noise ratio (~100 or 40 ent.) and a small resolution of approximately 2 ent.. With adaptations of the Sw system, such as scanning in the axial direction and rotation of the sample or better optical resolution via diminution of the scanning area, at least detection of samples with high contrast (substance A, SUBSTANCE F) should be possible.

As a result of optical properties in rms. mode at 0.5 Sw an optical resolution of 1.5 ent. and 6 ent. focus depth can be achieved. However, even for the substance A substance the Sw beam was not sufficiently blocked to lead to a shadow on the rms. image.

Better results are expected when using another system (CS). A CS system would allow higher energy levels and therefore the influence of the substance C casing (strong attenuation) could be minimized, resulting in a better signal to noise ratio (~100 times better). RECENDT expects to acquire such a system in spring 2015. Further tests with the CS system are planned. However, it seems unlikely to be able to detect very small substances. Especially non-substance A contaminants with low Sw interaction will remain difficult to detect.

5.3 Wave

This chapter presents information gained during trials conducted using the Wave equipment at our industrial partner's site. It comprises information on the test setup and results including interpretations of the latter based on image files processed by MATLAB.

5.3.1 Test setup and procedure

The setup consists of a wave srce. VB and a RE large area wave detector with 48 ent. pel. size. The casings to be inspected were positioned in tweezers (held at the casing neck) 118 ent. from the focal spot of the srce. and 283 ent. from the detector. This results in magnification of approximately 2.4 times. That means an object of 100 ent. length will be depicted on the detector with 240 ent.. Wave images were taken of the otherwise positioned casings as well as of casings at a otherwise location. In some cases the analysed sample was rotated around the central casing axes to facilitate differentiation of artefacts generated by image treatment, stt. effects, etc. from the sample impt.. That is, when rotating the sample, a substance depicted on the Wave image has to move in accordance with the applied sample rotation. Center of analyses was the lower half of the casing. For headspace analyses or analyses of the stopper, etc. it is advisable to use a second detector module for the upper part of the casing (to ensure minimal detection limits/ maximal magnification with one detector module).

5.3.1.1 Optimization of srce. settings

Three srce. parameters can be adapted in order to optimize the obtained images: anode cut., etme as well as anode vtg.. Anode cut. and etme can be adapted to optimize noise and incoming tnsi. levels. Anode cut. was set to the Wave srce. miu. of 800 ent. and etme was adapted to avoid oversaturation of relevant detector areas (where the casing was posed). That is, etme was adapted until a high overall tnsi. level was achieved without oversaturation in all relevant detector areas (750 ms). In order to

decrease etme and therefore to speed up IT. time for industrial application, anode cut. can be increased (with equivalent image quality). As third parameter the anode vtg. can be adapted, in order to generate harder or softer Wave radiation (higher or lower radiation-energy). Contaminants with low atomic number or dnty. (such as Substance E) are easier to detect with soft Wave radiation as hard radiation just passes through them. On the other hand, high dnty. material, such as substance A, strongly attenuates all radiation regimes. Therefore, the anode vtg. was adapted to optimum detection of soft tissue, in our case: Substance E (30 ent.). As a consequence all trials were conducted at following srce. settings: 750 ms; 30 ent.; 300 ent.. Only during the analyses of substance C contaminated samples and the sample containing a substance G, anode vtg. was adapted to 40 ent. as the quality of obtained images seemed to be slightly better.

5.3.1.2 Optimization of casing positioning

Images were taken of an otherwise positioned casing (right) as well as of a otherwise positioned casing.

The outer regions (bent casing walls) are prone to exhibit strong stt. effects. In these areas the tnsi. level of the transcending Wave beams is low (dark areas). Such areas are very difficult to analyse as attenuation of Wave beams by impt. might not be detectable due to the overlay of stt. effects. Both images, the otherwise positioned as well as the image of the otherwise positioned casing show dark areas around the casing side walls. Regarding the part areas it was suspected, that the positioned casing part might be easier to analyse for impt. (smaller dark areas). Therefore, most trials were conducted with otherwise positioned casings. However, regarding the obtained MATLAB treated image casings (for this procedure see section 5.3.1.3), it can be seen that the casing part of the positioned image is also difficult to analyse due to stt. effects of the inward bent and rnd. casing part. As a result attenuation effects of substance C impt. cot. be seen as they are covered by stt. effects around the casing part.

5.3.1.3 Image processing and analyses

All sample images presented in the following were generated using calibrated images (calibrated at the defined set point of 750 ms, 30 ent., 300 ent.) in order to compensate for detector defects such as damaged pel.s on the detector, darker or lighter areas, gaps between detector panels.

A total of three separately taken images are used to calculate a mean tnsi. value for each pel.. The same procedure has been applied to generate a reference image of an unpolluted empty sample casing. The tnsi. values of the reference image are subsequently subtracted from the generated sample image. In a next step, the generated subtraction image is normalized. That is, the lst. tnsi. value is subtracted from all values and the result is divided by the miu. value. Thus, an image based on 0 to 1 tnsi. scale is generated with the highest tnsi. pel.s being colored in white and the lst. tnsi. being colored in black. A predefined area in the middle region of the casing, is then analyzed in order to identify the spot with the lst. tnsi. value. The lst. tnsi. value corresponds to a substance in the sample, given that the substance in question has a higher absorption characteristic as the surrounding lyophilisate.

The lst. tnsi. value is obtained by comparing the lst. mean value of 5x5 pel.s of the whole region of interest. The definition of a predefined area in the middle of the casing is necessary in order to allow for an automated image analyses. Otherwise stt. effects close to the substance C casing walls (image areas of low tnsi.) distract the applied very basic substance identification procedure. All calculations were performed in MATLAB.

5.3.2 Results and discussion

In the following section exemplary test results will be presented and discussed. For improved clarity only the most significant test images are shown. However, all generated images have been analyzed and screened.

Table 7: Summary of Wave test results per substance type

Substance type	Sample	Wave srce. settings
Substance E	AVS7	750 ent.; 30 ent.; 300 ent.
	AVS5	750 ent.; 30 ent.; 300 ent.
	AVS4	750 ent.; 30 ent.; 300 ent.
	AVS3	750 ent.; 30 ent.; 300 ent.
	AVS2	750 ent.; 30 ent.; 300 ent.
Substance D	ASiS4	750 ent.; 30 ent.; 300 ent.
	ASiS3	750 ent.; 30 ent.; 300 ent.
	ASiS2	750 ent.; 30 ent.; 300 ent.
Substance C	AGS6	750 ent.; 30/40 ent.; 300 ent.
	AGS4	750 ent.; 30/40 ent.; 300 ent.
	AGS3	750 ent.; 30/40 ent.; 300 ent.
SUBSTANCE F	AHS3	750 ent.; 30 ent.; 300 ent.
	AHS2	750 ent.; 30 ent.; 300 ent.
Substance G	ASub-stance GS	750 ent.; 30/40 ent.; 300 ent.
Substance H	ASub-stance HS	750 ent.; 30 ent.; 300 ent.
Substance A	DMS7	750 ent.; 30 ent.; 300 ent.
	DML7	750 ent.; 30 ent.; 300 ent.
	AMS1	750 ent.; 30 ent.; 300 ent.

As single ptcl. administration was not feasible for ptcl.s below 160 ent., application in bulk was conducted. In consequence bow shaped structures, as exemplarily shown in However, the bow shaped structures can also be artefacts generated in the course of image treatment. In order to differentiate between image artefacts and "substance clouds" the samples in question were rotated around their central axes. In the case of a real substance, the substance position on the subsequently taken image would change according to the casings rotation. An image artefact, however, doesn't change in accordance to the casing rotation. In the following images of samples from mtp. rotation locations are shown for clarification (only if needed).

Scan of positioned casing -substance E contaminant (250-400 ent.)

The substance can easily be identified as long as the substance position is close to the central casing axis. However, once the substance position is further to the outer casing region, stt. effects due to the round casing form, substance C irregularities and other errors in image treatment prevent clear distinction (Test_19_2).

Scan of positioned casing -substance C contaminant (90-150 ent.)

Using MATLAB treated images the substance cot. be identified at the casing part. The substance position is outside of the defined, easy to analyze, area.

In an untreated single image only contrast (from 0 to 100) and gamma-correction (from 1 to 0.1) have been (digitally) adapted. In this image the substance C substances are clearly to be seen. Clear substance identification is possible, as there are a multitude of ptcl.s present (bulk application). Automated detection of a single substance C ptcl. will be challenging (low differentiation to noise and surrounding irregularities). It can be observed that the substance position changes according to the casing rotation. Thus, a clear distinction from noise or other artifacts caused by the rim of the casing part is possible

Scan of positioned casing -fruit substance G contaminant (90-150 ent.)

The substance can be clearly seen with both Wave srce. settings. However, as shown in the right image (Test_30_3) the position of the substance is crucial, as overlapping

with areas of high stt. levels (e.g., round casing part) could prevent successful detection. Detectability of insect parts of smaller thickness (legs, wings, etc.) is questionable.

Scan of positioned casing -substance K substance I as lyophilisate no contaminantion

Substance K-substance I lyophilisate exhibits abnormalities leading to dark rims in the Wave image. Crystalline structures cause stt. and attenuation. Hence crystallized material can be distinguished from amorphous lyophilisate.

5.3.3 Summary and conclusion

Table 8: Summary of Wave test results per substance type

Substance type	Sample	Detect-ability	Comments
Substance E	AVS7	Single article found	
	AVS5	Single ptcl. found	
	AVS4	Single ptcl. found	
	AVS3	Single ptcl. found	
	AVS2	Not detectable	
Substance D	ASiS4	Single ptcl. found	
	ASiS3	Agglomeration found	
	ASiS2	Not detectable	
Substance C	AGS6	Single ptcl. found	
	AGS4	Agglomeration found	Manual detection
	AGS3	Agglomeration found	Manual detection
u. SUBSTANCE F	AHS3	Single ptcl. found	
	AHS2	Not detectable	
Substance G	ASub-stance GS	Single ptcl. found	
Substance H	ASub-stance HS	Not detectable	
Substance A	DMS7	Single ptcl. found	Slight prodinf.

DML7	Single ptcl. found	Slight prodinf.
AMS1	Single ptcl. found	

Substances could be identified as listed in Table 4 using a static large area detector and the Wave srce. as described in section Appendix. Following topics arose in the course of the test campaign:

- Anode vtg.

  During the trials it seemed that measurements at higher anode vtg. (40 ent.) lead to higher image quality and subsequently lower detection limits for substance C impt.. The MATLAB treated images don't support this personal perception. However, the uncalibrated images taken at 40 ent. contain a high amount of noise originating from detector defects. Further tests are planned to evaluate, whether calibrated images taken at 40 ent. lead to better results.
- Anode cut. and mtme

  During our experiments anode cut. was limited by the miu. srce. value of 300 ent.. Thus a mtme of 750 ms was needed for IT. of one casing. To allow 100% IT. of all casings produced by the continuous lyophilzation line (2-3 casings per second), IT. time needs to be reduced significantly. Therefore in the final setup another wave srce. with higher anode cut. should be used. An increase of anode cut. to 1 mA could reduce mtme to 225 ms. Thus, jamming or the need for paralyzed IT. stations could be avoided.
- Focal spot size

  The focal spot size of the wave srce. used was 30-55 ent.. Small focal spot sizes help reduce shadow areas (blurring) around substances. Implementation of a wave srce. with even smaller focal spot size is expected to allow a further reduction of the detection limit.
- Casing presentation

  It can be seen that automated analyses of the positioned casing might be difficult due to large tnsi. deviations caused by the rnd. casing part. Further tests are planned to evaluate whether analyses of the casing part using an otherwise

positioned casing presentation mode leads to better results. Especially in the case of substance C substances lower detection limits are expected.

- Substance presentation

  As single ptcl. application of substances below 160-250 ent. is not possible, bulk application was conducted. Contaminants applicated in bulks often tend to agglomerate. Agglomerates are much easier to detect then single ptcl.s. Furthermore, in some cases distinction of impt. and noise is often difficult, as the exact substance position in the casing is unknown. Therefore, to allow clear identification of substances (as such) and to avoid facilitated detect-ability in bulk, application of contaminants in form of wires or filaments is planned.

  Another aspect concerning the substance presentation is, that the lyophilisate exhibits no significant attenuation behavior. Therefore, the complex process of sample generation (embedding a substance in the lyphilisate) could be avoided. It is suggested to conduct further trials using empty casings and contaminants only. This implies that the substance is always present at the casing part or at the casing walls. However, these two positions represent worst case scenarios. If a substance can be detected at these positions, it can be detected in or on the lyophilised product as well.

- Prodinf.

  In contrast to the substance J-substance I samples, dextran-substance I probes showed slight attenuation behavior at the top of the lyophilisate cake. This results from abnormalities of the lyophilisate. However, most lyophilisation products are amorphous, with crystalline phases representing an error in the lyphilisation process.

- IT. process

  Due to the bent casing walls regions far from the casings' axis of rotation are difficult to analyze. Therefore IT. of the casing from different locations is advisable. A similar setup might be necessary for IT. of the casing part, to keep "dark zones" to a minimum. Furthermore, in a multi point analyses system, dif-

ferentiation of noise and substances could be simplified, as only substances are seen on all systems, at the same time and at the same position.

6. Summary and Outlook

6.1 Summary of major findings

Chapters 1 to 3 address the topic of lyophilization in the field of pharmaceutical manufacturing.

Providing a sound basis for subsequent development of an IT. system, chapter 2 presents the findings of a through process analysis. Process flow charts, IPOP as well as Ishikawa diagrams were compiled in order to provide a structured basis for a process FMEA. The results are:

- Identification of critical process steps for substances to occur.
- Identification and specification of possible contaminants.
- Identification of optimal integration position of the IT. system to be developed in the manufacturing line.
- Deduction and specification of requirements on test samples to adequately account for factors influencing the measurement methods to be used in the IT. system.

Chapter 3 illustrates the cut. ptt. situation in the field of IT. systems for lyophilized products. The findings are:

- A large variety of IT. systems for monitor product quality, besides identification of substances within the lyo cake, could be identified.
- A ptt. issued by WI AG concerning wave based identification of substances within lyophilized products contained in vessels, could be identified. Ptt. protection is still valid. Details concerning scanning method as well as methods for casing transport and presentation at the IT. site are listed in the ptt..

- WI AG [95] as well as SI Masch. GmbH [157] offer wave based IT. systems for lyophilized products. Infringement issues have to be considered during the design of the IT. system to be developed.

Chapter 4 encompasses basic information on promising PAT tools suitable for detection of substances in lyophilized products. Summaries of extensive SWOT analyses are given as well as possible equipment vendors identified during a market research. The findings are:

- Through evaluation of suitable measurement technologies.
- Identification of the three most promising measurement technologies for further experimental evaluation.
- Development of supplier basis to enable comparison of mtp. measurement setups and allow incorporation of expert know-how to literature data.
- Establishment of a knowledge base to allow adaptation of test runs to account for threats and weaknesses as identified during the SWOT analyses.

Chapter 5 shows the results of the conducted experiments to evaluate performance of spectral analyses-, short wave- and wave IT. methods. Relevant parameters such as detection limit, mtme influence of substance or casing were assessed. The findings are:

- Spectral analyses is not suitable for the IT. task at hand. Volumetric ratio of sample- to substance size is too low to cause significant ipd. differences.
- Short wave measurement is not suitable for the IT. task at hand. The influence of the substance C casing containing the lyophilized product masks potential influences on the short wave signal by substances of relevant size classes.
- Wave IT. of lyophilized products in substance C containers is feasible with detection limits as well as mtmes being within acceptable ranges.

- Optimized parameters for wave IT. could be identified.
- Potential points of improvement to further reduce detection limits and mtme have been highlighted.

6.2 Outlook

Adverse effects of parc. substance administered via intravenous administration are known since the 19th century. Parc.s ranging from 10-12 ent. can clog pulmonary capillaries, 3-6 ent. can cause troubles in the spleen and hepatic lymph nodes, even smaller ptcl.s are known to damage the liver.[11] At present, IT. guidance documents specify a need for lyophilized products, dedicated for intravenous injection, to be „essentially or practically free from ptcl.s".[158] As companies, such as WI AG or SI Masch. GmbH, already offer equipment apt to allow 100% IT., it is but a matter of time until such IT. systems will become standard in pharmaceutical manufacturing.

The performed experiments using wave equipment showed the outstanding potential of wave IT. systems for the detection of contaminants even in the ent. range. Primary trials have been performed using the equipment available at our industrial partners site. Wave detector and srce. for the final machine setup remain to be chosen (detector: e.g., SoB HS by TD; srce.: e.g., YX – tube). To verify effective detection limits additional experiments are necessary using the selected detector combined with the selected srce.. Reproducibility, that is, ability to find substances in images taken from varying locations, was tested. However, additional trials will be needed using the final setup.

Depending on the achievable detection limits, one set of srce.-detector transition line could be sufficient. However use of two or three detectors at the same time is expected to enable detection of even smaller size classes, as areas prone to stt. effects (casing part, outer areas of the casing), for one transition line, can be covered by the second or third. Also differentiation of noise and substances will be achievable.

During design of the final machine layout additional challenges will be posed to fast casing handling. Fast feed of casings to the measurement position and subsequently

fast expulsion from it will be needed. Final mtmes are expected to be below 250 ms and therefore will not represent a limiting factor. A plentitude of concepts for casing handling is mentioned in a ptt. hold by WI AG.[95] Therefore, during development of the machine setup care has to be taken to avoid propt. issues.

Furthermore, machinery directives have to be considered and safety concepts need to be implemented to allow integration of the IT. machine into production environment.

7. Appendix

7.1 References

[1] Z. Berk, *Food Process Engineering and Technology*. Elsevier, 2013.

[2] H. R. Costantina and M. J. Pikal, Eds., *Lyophilization of Biopharmaceuticals*. 2004.

[3] J. Everse and F. E. Stolzenbach, *Enzyme purification and related techniques*, vol. 22. Elsevier, 1971.

[4] A. Maas, B. Peither, and T. Peither, "12.F Gefriertrocknung (Lyophilisation)," in *GMP Berater - Nachschlagewerk für Pharmaindustrie und Lieferanten*, Maas & Peither AG GMP Verlag, 2012.

[5] FDA, "Guide to IT.s - Lyophilization of Parenterals," 2010.

[6] U.S Pharmacopeial Convention, "U.S. Pharmacopeia <788> Parc. matter in injections," 2012.

[7] A. Maas, B. Peither, and T. Peither, "12.G Visuelle Kontrolle in Parenteralia," in *GMP Berater - Nachschlagewerk für Pharmaindustrie und Lieferanten*, Maas & Peither AG GMP Verlag, 2012.

[8] FDA, "Warning letter Bristol-Meyers Squipp," 2010.

[9] FDA, "Warning letter Bachem California," 2002.

[10] FDA, "Warning letter Bell More Laboratories," 2007.

[11] Ball PA, "Intravenous in-line filters: filtering the evidence.," *Curr Opin Clin Nutr Metab Care*, vol. 6, no. 3, pp. 19–25, 2003.

[12] J W Puntis, K M Wilkins, P. A. Ball, D I Rushton, and I. W. Booth, "Hazards of parenteral treatment: do ptcl.s count?," *Arch. Dis. Child.*, vol. 67, no. 12, pp. 1475–1477, 1992.

[13] Braun Melsungen AG, "Parc. Substance," *Hospital Care*, Melsungen, 2011.

[14] H. Lehr, J. Brunner, R. Rangoonwala, and C. J. Kirkpatrick, "Parc. Matter Substance of Intravenous Antibiotics Aggravates Loss of Functional Capillary Dnty. in Postischemic Striated Muscle," *Am J Respir Crit Care Med*, vol. 165, pp. 514–520, 2002.

[15] P. I. Murwave and A. K. O. Dennistion, "Oxford Handbook of Ophthalmology," *J. Neuro-Ophthalmology*, vol. 30, no. 2, p. 207, 2010.

[16] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonised Tripartite Guideline, Final Concept Paper Q10 : Pharmaceutical Quality Systems." pp. 1–4, 2005.

[17] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonised Tripartite Guideline, Quality Risk Management Q9." 2005.

[18] European Medicines Agency, "Pharmaceutical Development Q8(R2)." 2009.

[19] International Organization for Standardization, "ISO Guide 73 Risk management — Vocabulary," 2009.

[20] H.-C. Liu, L. Liu, and N. Liu, "Risk evaluation approaches in failure mode and effects analysis: A literature review," *Expert Syst. Appl.*, vol. 40, no. 2, pp. 828–838, Feb. 2013.

[21] International Organization for Standardization, "ISO/FDIS 31010:2009 Risk management - Risk assessment techniques," ISO/IEC, 2009.

[22] ICH, "ICH E10 - Q9_Guideline.pdf," *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*, 2005. [Online]. Available: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf. [Accessed: 20-Mar-2015].

[23] CMC, "A-Mab: a Case Study in Bioprocess Development," 2009.

[24] N. a Charoo, A. a a Shamsher, A. S. Zidan, and Z. Rahman, "Quality by design approach for formulation development: a case study of dispersible tablets.," *Int. J. Pharm.*, vol. 423, no. 2, pp. 167–78, Feb. 2012.

[25] "Pharmacy Filtration: Critical protection for providers and patients," *Pall Medical - clinical update*, 1999. .

[26] F. Pavanetto, B. Conti, I. Genta, and T. Modena, "Parc. substance from substance Dized substance L stoppers," *Int. J. Pharamceutics*, vol. 74, no. 190 1, pp. 175–181, 1991.

[27] A. Colas, J. Sinag, and K. Ulman, "Substance Des in Pharmaceutical Applications," in *Substance Dization of Parenteral packaging Components*, DowCorning, 2006, pp. 1–5.

[28] C. E. Wells, E. C. Juenge, and K. Wolnik, "Contaminants leached from substance L stoppers into a water soluble vitamin E intravenous injectable product," *J. Pharm. Sci.*, vol. 75, no. 7, pp. 724–725, Jul. 1986.

[29] S. L. Prabu, "Article Cleaning Validation and its importance in Pharmaceutical Industry," vol. 42, no. 07, pp. 21–25, 2010.

[30] B. M. Stellmack and K. Rhodes, "Substance A Substance in Bio- pharmaceutical Drugs Solving a puzzle without all the pieces," pp. 1–4, 2014.

[31] M. Butchers, M. Littlewood, and S. Baty, "UK sensing technologies for substance in food," *The Knowledge Transfer Network: Food Sensing Report.*.

[32] William Reed Business Media SAS, "Human substance H in heparin casing prompts Hospira recall," *in-Pharma Technology.com*, Sep-2014..

[33] Gretchen L. Shearer, "Contaminant Identification in Pharmaceutical Products," *Microsc.*, vol. 5, pp. 3–10, 2003.

[34] FDA, "Warning letter APP Pharmaceuticals," no. 4, 2012.

[35] FDA, "Warning letter Escalon Medical Corp," pp. 5–9, 2007.

[36] A. Maas, B. Peither, and T. Peither, "4 H Reinigung von Anlagen," in *GMP Berater - Nachschlagewerk für Pharmaindustrie und Lieferanten*, Schopfheim: Maas & Peither AG GMP Verlag, 2012.

[37] Biopharma process systems, "Introduction to casing washing," 2010.

[38] L. Pereira, T. Edge, L. Shick, and M. Slade, "How clean are your casings and clusres." 2010.

[39] G. R. Nireesha, L. Divya, C. Sowmya, N. Venkateshan, M. N. Babu, and V. Lavakumar, "Lyophilization / Freeze Drying - An Review," vol. 3, no. 4, pp. 87–98, 2013.

[40] S. L. Nail and L. A. Gatlin, "Freeze-drying : principles and practice," in *Pharmaceutical Dosage Forms: Parenteral Medications*, 3rd ed., 2010.

[41] S. L. Nail, S. Jiang, S. Chongprasert, and S. A. Knopp, "Fundamentals of freeze-drying.," *Pharm. Biotechnol.*, vol. 14, pp. 281–360, Jan. 2002.

[42] D. C. Lighter, Donald E. Fair, *Quality Management in Health Care Principles and Methods*, 2nd ed. Michael Brown, 2004.

[43] Kaoru Ishikawa translated by David J. Liu, *What is Total Quality Control? The Japanese Way*. 1985.

[44] International Electrotechnical Commission, "IEC 60812:2006 Analysis Techniques for System Reliability- Procedures for Failure Mode and Effects Analysis (FMEA)," 2006.

[45] D. H. Stamatis, *Failure Mode Effects Analysis: FMEA from Theory to Execution*, 2nd ed. Milwaukee: William A. Tony, 2003.

[46] "Wie recherchiere ich? - Ein Leitfaden für Einsteiger und Fortgeschrittene." Österreichisches Ptt.amt.

[47] "Automatic appearance inspecting device for freeze dry casing bottle," JPH01152347 (A)1989.

[48] "Apparatus for inspecting casing automatically," KR20070093648 (A)2007.

[49] "Method and apparatus for IT. of casings," EP0701117A21996.

[50] "Medicine casing IT. device," JPH07159348 (A)1995.

[51] "Method and apparatus for inspecting casing bottle," JPH0875671 (A)1996.

[52] "Transparent/translucent hollow object e.g. casing, defect inspecting method, involves adjusting exposure of sensors based on tnsi. of infrared radiation to standardize response of sensor irrespective of origin of objects," FR2854460 (A1)2004.

[53] "Detection of surface defects in substance C containers," GB2185101 (A)1987.

[54] "Detection of surface defects in substance C containers," GB1508035 (A)1978.

[55] "Device for testing substance C containers," DE3524943 (A1)1987.

[56] "Apparatus for inspecting flaw of transparent container," JPS63109352 (A)1988.

[57] "Vorrichtung zur Überprüfung der Oberfläche einer Mehrzahl kleiner Gegenstände," DE29620128 (U1)1997.

[58] R. SI, "Vorrichtung zur optischen Prüfung und Kontrolle von Flaschen und Ampullen," DE2913541 (A1)1980.

[59] MBM, "Process and device for inspecting the surface of a plurality of small objects," EP0632888 (A1)1995.

[60] "System and method for seeking and presenting an area for reading with a vision system," 5,405,0151995.

[61] "Vorrichtung zur Prüfung von Erzeugnissen," DE202009010781 (U1)2010.

[62] M. Lehmann, "Method and apparatus for leak testing colosed containers," DK2040054 (T3)2014.

[63] M. Lehmann, "Methods for manufacturing unleaky closed containers and leak testing apparatus," EP2642269 (A2)2013.

[64] A. Wertli, "Method for leak testing closed, at least partially gas filled containers," SI2449356 (T1)2013.

[65] M. Lehmann, "Method and apparatus for leak testing containers," MX2013001608 (A)2013.

[66] M. Lehmann, "Method for leak testing and leak testing apparatus," US2010251805 (A1)2010.

[67] M. Lehmann, "Method and apparatus for leak testing containers," WO2011012730 (A2)2011.

[68] L. Emmenegger and J. Jagerska, "Method of detecting a propellant gas," WO2012107597 (A2)2012.

[69] M. Lehmann, "Verfahren und vorrichtung zur leckprüfung," EP1021697 B127-Oct-2004.

[70] M. Lehmann, "Verfahren und Vorrichtung zur Dichtheitsprüfung geschlossener Behälter," EP2040054 B119-Mar-2014.

[71] "IT. system," US4172524 (A)1979.

[72] "Casing IT. machine," 4,417,6621983.

[73] "Casing IT. system," JP2005017003 (A)2005.

[74] "INSPECTING APPARATUS OF AMPOULE AND CASING," JPS55138641 (A)1980.

[75] "Vorrichtung zur Prüfung von mit Insulin gefüllten Behältnissen," DE202007001444 (U1)2008.

[76] "Vorrichung zum visuellen prüfen des Inhaltes von Flaschen," DE7418360 (U)1975.

[77] "IT. device for inspecting foreing matter," US2013233437 (A1)2013.

[78] "IT. device for inspecting foreign matter," US2013248321 (A1)2013.

[79] "Foreign substance IT. apparatus," US2004085531 (A1)2004.

[80] "Method for inspecting foreign matter on solid body," JPH06138056 (A)1994.

[81] "Method of inspecting solid body for foreign matter," EP 0 595 261 B11993.

[82] "Powder material IT. apparatus," US5239358 (A)1993.

[83] "Surface foreign matter IT. apparatus," JP2012189351 (A)2012.

[84] "Method and apparatus for inspecting a rotating medicine casing with cameras," 5,719,6791995.

[85] "IT. apparatus for foreign matter," JPH11218501 (A)1999.

[86] "Automatic inspecting apparatus for sealed transparent container of powder," JPH0351748 (A)1991.

[87] "Device for inspecting foreign matter in powder in trasparent container," JPH02150752 (A)1990.

[88] "Foreign matter detection device," JP2012220453 (A)2012.

[89] "Method and device for inspecting foreign matter in powder in transparent vessel," JP2010008339 (A)2010.

[90] "Method of inspecting foreign matter in powder packed into sealed transparent container," JPH02187646 (A)1990.

[91] "Foreign body IT. in filled containers," US2014216142 (A1)2014.

[92] "Method and apparatus for inspecting casing filled with powdered agent," JPH04110641 (A)1992.

[93] "Detector and detection method for substance Alic foreign matter," JP2005083889 (A)2005.

[94] "Wave utilizing IT. instrument, wave line sensor used for the instrument, and its manufacture," JPH03158711 (A)1991.

[95] M. Lehmann, "Wave detection of flaws in containers and/or in their contents," WO2013185816 (A1)2013.

[96] "Method and apparatus for analysis of moving objects by radiography," EP 0 604 302 B11998.

[97] "Non-destructive IT. of material in container," US 7,164,750 B22007.

[98] "Non-destructive Wave IT. apparatus for food industry," US60059121999.

[99] "Device for examining filled containers by means of Wave and use of this device," US 7,106,827 B22006.

[100] "Cat scanner with simultaneous translation and rotation of objects," US49892251991.

[101] "Ultra-high resolution computed tomography imaging," WO2001057795A22001.

[102] Schindel, "Monitoring system for use in e.g. food industry for monitoring presence of foreign ptcl.s in products, has detectors arranged opposite to each other for receiving IT. radiation, where goods are moved along curved path," DE 10 2012 019 851 A1Apr-2014.

[103] "Short wave Waves." [Online]. Available: http://www.physik.uni-kl.de/en/beigang/forschungsprojekte/. [Accessed: 08-Oct-2014].

[104] P. Russo, *Comprehensive Biomedical Physics*. Elsevier, 2014.

[105] J. A. Seibert, "Wave Imaging Physics for Nuclear Medicine Technologists. Part 1: Basic Principles of Wave Production," *J. Nucl. Med. Technol.*, vol. 32, no. 3, pp. 139–147, Sep. 2004.

[106] L. Scicron Technology Co., "Cone beam computed tomography." [Online]. Available: http://www.scicron.co.th/phonixMain.html. [Accessed: 10-Oct-2014].

[107] J. A. Seibert and J. M. Boone, "Wave imaging physics for nuclear medicine technologists. Part 2: Wave interactions and image formation.," *J. Nucl. Med. Technol.*, vol. 33, no. 1, pp. 3–18, Mar. 2005.

[108] S. Sleutel, V. Cnudde, B. Masschaele, J. Vlassenbroek, M. Dierick, L. Van Hoorebeke, P. Jacobs, and S. De Neve, "Comparison of different nano- and micro-focus Wave computed tomography set-ups for the visualization of the soil microstructure and soil organic matter," *Comput. Geosci.*, vol. 34, no. 8, pp. 931–938, Aug. 2008.

[109] R. a. Ketcham and W. D. Carlson, "Acquisition, optimization and interpretation of Wave computed tomographic imagery: applications to the geosciences," *Comput. Geosci.*, vol. 27, no. 4, pp. 381–400, May 2001.

[110] M. S. Nielsen, T. Lauridsen, L. B. Christensen, and R. Feidenhans'l, "Wave dark-field imaging for detection of foreign bodies in food," *Food Control*, vol. 30, no. 2, pp. 531–535, Apr. 2013.

[111] R. Liu, X. Yin, H. Li, Q. Shao, P. York, Y. He, T. Xiao, and J. Zhang, "Visualization and quantitative profiling of mixing and segregation of granules using synchrotron radiation Wave microtomography and three dimensional reconstruction.," *Int. J. Pharm.*, vol. 445, no. 1–2, pp. 125–33, Mar. 2013.

[112] M. Ando, K. Yamasaki, F. Toyofuku, H. Sugiyama, C. Ohbayashi, G. Li, L. Pan, X. Jiang, W. Pattanasiriwisawa, D. Shimao, E. Hashimoto, T. Kimura, M. Tsuneyoshi, E. Ueno, K. Tokumori, A. Maksimenko, Y. Higashida, and M. Hirano, "Attempt at Visualizing Breast Cancer with Wave Dark Field Imaging," *Jpn. J. Appl. Phys.*, vol. 44, no. No. 17, pp. L528–L531, Apr. 2005.

[113] M. Bech, T. H. Jensen, O. Bunk, T. Donath, C. David, T. Weitkamp, G. Le Duc, A. Bravin, P. Cloetens, and F. Pfeiffer, "Advanced contrast modalities for Wave radiology: Phase-contrast and dark-field imaging using a grating interferometer.," *Z. Med. Phys.*, vol. 20, no. 1, pp. 7–16, Jan. 2010.

[114] A. Olivo and I. Robinson, "'Taking Wave phase contrast imaging into mainstream applications' and its satellite workshop 'Real and reciprocal space Wave imaging,'" *Philos. Trans. R. Soc. A*, no. 372, 2014.

[115] M. Long, *Architectural Acoustics*. Elsevier, 2014.

[116] R. K. Mobley, *An Introduction to Predictive Maintenance*. Elsevier, 2002.

[117] Wikipedia, "Ultrasound." [Online]. Available: http://en.wikipedia.org/wiki/Ultrasound. [Accessed: 13-Oct-2014].

[118] R. Stark, "Kleiner Preis und hohe Effizienz Ultraschall zum Eigenbau," Universität Bielefeld, 2011.

[119] R. Lerch, G. M. Sessler, and D. Wolf, "Erzeugung , Detektion und Anwendung," in *Technische Akustik Grundlagen und Anwendungen*, Springer Berlin Heidelberg New York, 2009.

[120] R. G. Maev, *Acoustric Microscopy: Fundamentals and Applications*. John Wiley & Sons Ltd., 2008.

[121] DIN, *Injektionsbehälter und Zubehör - Teil 4: Injektionsflaschen aus Hüttenglas (ISO 8362-4:2011)*. Deutsche Norm, 2011.

[122] R. E. Green, "Non-contact ultrasonic techniques.," *Ultrasonics*, vol. 42, no. 1–9, pp. 9–16, Apr. 2004.

[123] S. J. S. Martín, "Air-coupled ultrasound propagation and novel non-destructive bonding quality assessment of timber composites," ETH Zürich, 2012.

[124] E. Hæggström and M. Luukkala, "Ultrasound detection and identification of foreign bodies in food products," *Food Control*, vol. 12, no. 1, pp. 37–45, Jan. 2001.

[125] "Microwave moisture measurement / principles." [Online]. Available: http://www.rgi-ms.com/html/moisture_principles.html. [Accessed: 13-Oct-2014].

[126] T. Beller, J. Hinken, M. Voigt, and I. F. C. Composite, "Hochauflösende Mikrowellen-Defektoskopie," 2007.

[127] M. Q. Feng, G. Roqueta, and L. Jofre, *Non-Destructive Evaluation (NDE) of Polymer Matrix Composites*. Elsevier, 2013.

[128] J. H. Hinken, "Einführung in die Mikrowellenbasierte Zerstörungsfreie Prüfung."

[129] M. Edwards, Ed., *Detecting foreign bodies in food*. Abington Hall: Woodhead Publishing Limited, 2004.

[130] F. Radar, "A New Unique Detection Technology for 'Invisible' Foreign Bodies," *Food Saf. Mag.*, no. June, 2014.

[131] M. Edwards, "Foreign body complaints in the food and drink industry," *new food*, no. 2, 2013.

[132] Y.-C. Shen and B. B. Jin, *Handbook of Short wave Technology for Imaging, Sensing and Communications*. Elsevier, 2013.

[133] D. Saeedkia, *Handbook of Short wave Technology for Imaging, Sensing and Communications*. Elsevier, 2013.

[134] C. Jördens, F. Rutz, and M. Koch, "Quality Assurance of Chocolate Products with Short wave Imaging." European conference of non-destructive testing, pp. 1–8, 2006.

[135] M. Theuer, G. Torosyan, F. Ellrich, J. Jonuscheit, and R. Beigang, "Short wave-Bildgebung in industriellen Anwendungen (Short wave Imaging in Industrial Applications)," *tm - Tech. Mess.*, vol. 75, no. 1, pp. 64–70, Jan. 2008.

[136] G. Ok, H. J. Kim, H. S. Chun, and S.-W. Choi, "Foreign-body detection in dry food using continuous sub-Short wave wave imaging," *Food Control*, vol. 42, pp. 284–289, Aug. 2014.

[137] Zomega, "What Is Sw?," *Homepage*. [Online]. Available: http://www.zomega-Short wave.com/index.php?option=com_content&view=article&id=48&Itemid=55. [Accessed: 18-May-2015].

[138] M. A. Heravi, L. Marin, and C. Sebu, "The method of fundamental solutions for complex EPDA tomography," *Eng. Anal. Bound. Elem.*, vol. 46, pp. 126–139, Sep. 2014.

[139] M. Z. Abdullah, *Computer Vision Technology in the Food and Beverage Industries*. Elsevier, 2012.

[140] M. Neumayer, "About ECT." [Online]. Available: http://www.emt.tugraz.at/sensors/aboutect. [Accessed: 14-Oct-2014].

[141] B. S. Kim, A. K. Khambampati, Y. J. Jang, K. Y. Kim, and S. Kim, "Image reconstruction using vtg.–cut. system in EPDA tomography," *Nucl. Eng. Des.*, vol. 278, pp. 134–140, Oct. 2014.

[142] G. Smith, E. Polygalov, M. S. Arshad, T. Page, J. Taylor, and I. Ermolina, "An ipd.-based process analytical technology for monitoring the lyophilisation process.," *Int. J. Pharm.*, vol. 449, no. 1–2, pp. 72–83, Jun. 2013.

[143] G. Smith, M. S. Arshad, E. Polygalov, and I. Ermolina, "An application for ipd. spectroscopy in the characterisation of the substance C transition during the lyophilization cycle: the example of a 10% w/v maltodextrin solution.," *Eur. J. Pharm. Biopharm.*, vol. 85, no. 3 Pt B, pp. 1130–40, Nov. 2013.

[144] G. Smith, T. Page, M. S. Arshad, E. Polygalov, K. Nazari, J. Taylor, and I. Ermolina, "Through-Casing Ipd. Spectroscopy: A New In-Line Process Analytical Technology for Freeze Drying." Advanstar, 02-Apr-2014.

[145] M. S. Arshad, G. Smith, E. Polygalov, and I. Ermolina, "Through-casing ipd. spectroscopy of critical events during the freezing stage of the lyophilization cycle: the example of the impact of sucrose on the crystallization of substance I.," *Eur. J. Pharm. Biopharm.*, vol. 87, no. 3, pp. 598–605, Aug. 2014.

[146] H. Griffiths, "Magnetic induction tomography," *Meas. Sci. Technol.*, vol. 12, pp. 1126–1131, 2001.

[147] H. Wei and M. Soleimani, "Electromagnetic Tomography for Medical and Industrial Applications: Challenges and Opportunities [Point of View]," *Proc. IEEE*, vol. 101, no. 3, pp. 559–565, Mar. 2013.

[148] H.-Y. Wei and M. Soleimani, "A Magnetic Induction Tomography System for Prospective Industrial Processing Applications," *Chinese J. Chem. Eng.*, vol. 20, no. 2, pp. 406–410, Apr. 2012.

[149] L. F. Gladden and P. Alexander, "Applications of nuclear magnetic resonance imaging in process engineering," *Meas. Sci. Technol.*, vol. 7, no. 3, pp. 423–435, Mar. 1996.

[150] J. R. Mathiassen, E. Misimi, M. Bondø, E. Veliyulin, and S. O. Østvik, "Trends in application of imaging technologies to IT. of fish and fish products," *Trends Food Sci. Technol.*, vol. 22, no. 6, pp. 257–275, Jun. 2011.

[151] DYNAPAR, "Dynapar Industry Solutions - Incremental Encoders for Medical/Life Sciences - Homepage." [Online]. Available: http://www.dynapar.com/Products/Industry_Solutions/Medical_/_Life_Sciences/. [Accessed: 05-May-2015].

[152] A. Melado-Herreros, N. Hernandez-sanchez, T. Jimenez-, B. Verlinden, J. Val, and P. Barreiro, "On-line MRI sequences for the evaluation of Apple internal quality," in *Inside Food Symposium*, 2013, vol. c, no. April, pp. 9–12.

[153] C.-J. Du and D.-W. Sun, "Recent developments in the applications of image processing techniques for food quality evaluation," *Trends Food Sci. Technol.*, vol. 15, no. 5, pp. 230–249, May 2004.

[154] Y. Fujishiro, "Taking Advantage of S-Parameter," *Guidbook TDK EMC Technology*. [Online]. Available: http://product.tdk.com/en/products/emc/guidebook/eemc_basic_03.pdf. [Accessed: 02-Mar-2015].

[155] "How can the S to rms. ipd. (Zt) conversion equation on the 4395A Operation Manual be derived?," *Keysight technologies*. [Online]. Available: http://www.keysight.com/main/editorial.jspx?ckey=1536926&id=1536926&nid=-11143.0.00&lc=eng&cc=CA. [Accessed: 02-Mar-2015].

[156] S. Grassini, *Corrosion and Conservation of Cultural Heritage Substance Alic Artefacts*. Elsevier, 2013.

[157] SI, "Wave IT. System by SI," *Homepage*. [Online]. Available: http://www.SI.de/uploads/tx_kmpproduct/Wave_EN.pdf. [Accessed: 05-May-2015].

[158] *// 788 // Parc. matter in injections*. The United States Pharmacopeial Convention, 2011.

7.2 List of figures

7.3 List of tables