Remote Accessibility to Diabetes Management and Therapy in Operational healthcare Networks.

REACTION (FP7 248590)

D7-5 Safety Issues in REACTION Applications

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1. Executive summary

This document reviews the safety issues that pertain to REACTION devices and applications. It includes reference to and discussion of the standards and guidelines that apply to REAC|TION devices or applications. The document further provides a summary of the standards and guidelines that are applied in the assessment of risk for safety in REACTION devices and applications, with particular reference to the Medical Device Directive (MDD).

The document intends to cover all aspects of safety and conformance and includes; electrical, mechanical, wireless, electromagnetic compatibility, communication protocols, and semantic interoperability. It also includes description of standards and guidelines to be used to assess risk.

This document does not include assessment of risk for REACTION devices or applications. Risk assessment for specific devices and applications is contained in separate documentation for that device or application. Such documentation may be required for ethical approval.

2. Terms and Definitions

2.1 Abbreviations and Acronyms

BT	Blue Tooth
CEN	Committee European Normalisation
EN	European Normalisation – European standard of CEN
HCP	Health Care Profile
HDP	Health Device Profile
HL7	Health Level 7
IEC	International Electrotechnical Commission
IEEE	Institute of Electrical and Electronics Engineers
IHE-PCD01	Integrating the Healthcare Enterprise - Patient Care Devices technical framework version1
ISO	International Organization for Standardisation
JWG	Joint Working Group
MDD	Medical Device Directive
PHD	Personal Health Device
SPP	Serial Port Profile
USB	Universal Serial Bus

3. Overview of Safety Issues

3.1 Safety Issues that Apply to REACTION Applications

Devices and applications that will be used or developed within the REACTION project shall be required to comply with domain and device specific safety standards that shall include; electrical and mechanical safety, reliability, electromagnetic compatibility and conformance, security and privacy. Domain and device specific standards shall be used to ensure semantic interoperability. Standards for risk management of networked devices and interconnection of medical devices shall be applied.

REACTION devices shall comply with the IEC 60601 [B1] base standards and its parts such as IEC 60601-1 [B2] with respect to electrical and mechanical safety and any device specific standard as defined in IEC 60601-2-XX [B3].

REACTION devices attached to networks shall also comply with all network equipment and network infrastructure related standards which includes IEEE 11073-30400:2010 for Ethernet connected devices [B4].

The physical interconnection between devices shall comply with appropriate standards and specifications pertaining to that technology to ensure interoperability:

- For Blue Tooth devices this shall be the version 2.1 Blue Tooth specification [B5] and the Health Device Profile [B6] where used. The Serial Port Profile (SPP) may be used for legacy support and development.
- For Zigbee devices this shall be Zigbee Specification Document 053474r17 [B7] and the Health Care Profile [B8] where used.
- For USB devices this shall be the USB specification revision 2.0 [B9] and the USB Device Class Definition for Personal Healthcare Devices [B10] where used. Serial port (COM) may be used for legacy support and development.
- Devices that conform to social alarms shall comply with EN300-220-2 [B11].

REACTION devices and applications shall comply where appropriate with IEEE 11073-20601a:2010 [B12] for data communication, IEEE 11073-10101 for nomenclature [B13], and IEEE 11073-104xx [B14] for each specific device, to ensure semantic interoperability of data.

REACTION devices and applications that operate within a network environment shall be subject to risk assessment and risk management appropriate to the application and use and should adhere to standards IEC 80001-1 [B15].

Risk assessment of medical devices is specified by ISO 14971:2007 [B16]. Risk assessment for the interconnection of devices shall be undertaken in accordance with the ICE standard and guidelines, currently under development.

4. Electrical and Mechanical Safety

4.1 IEC 60601

4.1.1 IEC 60601-1-Ed 3 (2005) Brief Summary

IEC 60601-1 provides for the electrical and mechanical safety of medical devices. This covers issues such as maximum leakage current for patient connected medical devices, prevention of access to dangerous voltages and bio-compatibility. These aspects of medical devices are deemed specialist, and it is expected that manufacturers of medical devices in the REACTION project will be aware of the ways in which their device must comply with IEC 60601-1. It is outside the scope of this document to consider these issues in detail.

4.1.2 IEC 60601-1-Ed 3 (2005) Compliance

Manufacturers of medical devices being used within the REACTION project shall ensure that devices comply with IEC 60601-1 and that all documentation is available to partners for purposes such as making request for ethical approval.

5. Transmission Protocols and Safety

5.1 IEEE 802.3 and IEEE 11073-30400:2010

5.1.1 Background

IEEE 11073-30400:2010[B4] provides for devices that are connected using IEEE 802.3 cabled Ethernet. It defines the clauses of IEEE 802.3 that apply. It further defines the connection sockets, plugs and cables for medical devices.

There are no specific issues in IEEE 11073-30400:2010 of concern to medical devices in the REACTION project.

5.2 Wireless Protocols

5.2.1 IEEE 802.11

IEEE 802.11, commonly known as WiFi, provides the radio physical layer for high speed local area networks, and is normally seen as the wireless form of IEEE 802.3 cabled Ethernet.

However, unlike IEEE 802.3 cabled Ethernet, IEEE 802.11 suffers from all issues relating to radio communication. Specifically this includes not only issues of correct data transmission; range, interference, error, data throughput; but also issues of the interference to other equipment through electromagnetic compatibility (EMC). This is seen as particularly important for medical equipment. There are also issues relating to security.

The problems of wireless are well known and general guidelines are available for use in the clinical setting. Specific guidelines relating to the issues of the use of wireless communication for medical devices connected to a network are to be addressed within a report in the IEC 80001 family [B15]. The recommendations made in this report will be adopted in REACTION.

5.2.2 Blue Tooth

There is little guidance on the use of Blue Tooth (BT) for medical devices. Recent development of a health care profile for Blue Tooth [B6] that has been adopted by the Continua Alliance will lead to an increase in availability of devices and this will lead to an increase in experience of its use. It is anticipated that at that time, guidelines will become available from appropriate standards bodies. Until that time, medical devices in the REACTION project will require careful risk analysis.

5.2.3 Zigbee

There is little guidance on the use of Zigbee for medical devices. Recent development of a health care profile for Zigbee [B7] that has been adopted by the Continua Alliance will lead to an increase in availability of devices and this will lead to an increase in experience of its use. It is anticipated that at that time, guidelines will become available from appropriate standards bodies. Until that time, medical devices in the REACTION project will require careful risk analysis.

6. Semantic Interoperability and Safety

6.1 Background

In addition to consideration of the electrical, mechanical, electromagnetic compatibility, physical transmission and communication issues, communicating medical devices must further provide assurance of safety with respect to semantic interoperability. Semantic interoperability refers to the ability to convey the meaning and interpretation of data. This is particularly important in pan-European projects where terms may have different meaning, and different units are employed for measures.

Semantic interoperability can be ensured by adoption of standardised nomenclature. There are several standards of specific importance for the REACTION project.

6.1.1 IEEE 11073

IEEE 11073-10101 [B13] provides a standard nomenclature for medical devices. This covers nomenclature for device specific issues, units of measure, body sites, lead positions, types of device, types of measure, etc. This standard has been augmented by further standards that provide nomenclature for specialised areas such as annotation of the ECG and implanted cardiac devices.

The IEEE 11073-10101 nomenclature further describes all aspects of the object oriented approach to modelling medical devices defined in IEEE 11073-10102. By adopting a common approach to modelling all medical devices improves interoperability, and thereby safety.

IEEE 11073-20601 [B12] provides a standard communication protocol that is optimised for use in personal health devices, such as those being developed in the REACTION project. This uses the object oriented modelling of IEEE 11073-10102 and the nomenclature of IEEE 11073-10101.

Additionally, a family of standards has been created to describe standard medical devices as IEEE 11073-104xx [B14]. These, together with IEEE 11073-20601, fully define the object model of specific devices and extend the nomenclature of IEEE 1103-10101[1] where necessary to cover new devices, new concepts and new terms. This approach will increase interoperability and thereby safety.

6.1.2 HL7

HL7 defines a protocol to communicate between medical systems. It is generally considered for use between enterprise systems, but recent work within the IHE has extended the use of HL7 for use by medical devices.

Important work also includes developing a standard representation of the object models of IEEE11073 within the HL7 message, so that data can be conveyed transparently from the medical device as IEEE 11073 and then mapped to the HL7 message without change of representation, only presentation.

Use of such an approach eliminates changes of code, format or nomenclature, thus ensuring increased safety of the device.

Such an approach is recommended for REACTION.

6.1.3 SNOMED-CT

In order to ensure semantic interoperability, medical data within medical systems is generally codified. Several coding schemes exist, including ICD, and SNOMED-CT.

SNOMED CT (Systematized Nomenclature of Medicine-Clinical Terms) is considered to be the most comprehensive, multilingual clinical healthcare terminology in the world.

[1] IEEE 11073-10101 is to be revised on a frequent basis to incorporate all new nomenclature

Each year, avoidable deaths and injuries occur because of poor communication between healthcare practitioners. The delivery of a standard clinical language for use across the world's health information systems can therefore be a significant step towards improving the quality and safety of healthcare.

SNOMED CT aims to improve patient care through the development of systems to accurately record health care encounters. Ultimately, patients will benefit from the use of SNOMED CT, for building and facilitating communication and interoperability in electronic health data exchange.

SNOMED CT intellectual property rights were transferred to the SNOMED SDO® in the formal creation of the IHTSDO.

SNOMED CT was originally created by the College of American Pathologists by combining SNOMED RT and a computer based nomenclature and classification known as Clinical Terms Version 3, formerly known as Read Codes Version 3, which was created on behalf of the UK Department of Health and is Crown copyright. It also includes and maps nomenclature from IEEE 11073-10101.

SNOMED CT is

- a clinical healthcare terminology
- a resource with comprehensive, scientifically-validated content
- essential for electronic health records
- a terminology that can cross-map to other international standards
- already used in more than fifty countries

SNOMED CT provides the core general terminology for the electronic health record (EHR) and contains more than 311,000 active concepts with unique meanings and formal logic-based definitions organized into hierarchies. When implemented in software applications, SNOMED CT can be used to represent clinically relevant information consistently, reliably and comprehensively as an integral part of producing electronic health records.

SNOMED CT is currently used throughout electronic health systems within the NHS in the UK.

6.1.4 LOINC

Loinc is a coding scheme that is employed for reporting laboratory results. It is widely employed.

6.1.5 Proprietary

Proprietary coding schemes and representation exist. These predominate in systems provided by a single manufacturer and where data is rarely communicated outside a single enterprise. They are also prevalent in legacy systems.

The REACTION project will likely need to integrate legacy systems with the REACTION platform. Where this is the case, there needs to be careful consideration of the approach. This can include conversion of data from the legacy format to a standard coding scheme. Alternatively data can remain in the original coding form, with an indicator of the coding scheme being used. There are advantages and disadvantages depending on the number of distinct coding schemes that exist and the likelihood that data will be exported to another system having a different internal coding scheme.

7. Risk Assessment of IT Networks incorporating Medical Devices

7.1 IEC 80001-1: Application of Risk Assessment for IT Networks Incorporating Medical Devices

7.1.1 Scope

This report summarises aspects of IEC80001 that are different from ISO 14971. The IEC 80001-1 standard requires the use of a risk management process that is compliant with ISO 14971 and addresses specifically how medical devices can be connected to IT Networks, including general purpose IT Networks, to achieve interoperability without degrading the delivery of health care in terms of safety, effectiveness, and data and system security. There are a number of potential risks associated with the incorporation of medical devices into IT Networks, including lack of support from manufacturers of medical devices for the incorporation of their products into IT networks, incorrect operation resulting from combining medical device software and other software applications, lack of security controls across many medical devices and the threat of cyber attack.

IEC 80001-1 is addressed to responsible organisations, to manufacturers of medical devices and to providers of other information technology. It is particularly pertinent to the REACTION platform.

7.1.2 Terms and Definitions

Change-release management: process that ensures that all changes to the IT Network are assessed, approved, implemented and reviewed in a controlled manner and that changes are delivered, distributed, and tracked, leading to release of the change in a controlled manner with appropriate input and output with configuration management.

Change permit: an outcome of the risk management process consisting of a document that allows a specified change or type of change without further risk management Activities subject to specified constraints.

Configuration management: a process that ensures that configuration information of components and the IT Network are defined and maintained in an accurate and controlled manner, and provides a mechanism for identifying, controlling and tracking versions of the IT Network. Note: Adapted from ISO/IEC 20000-1:2005, Subclause 9.1.

Data and systems security: an operational state of a medical IT Network in which information assets (data and systems) are reasonably protected from degradation of confidentiality, integrity, and availability.

Event management: a process that ensures that all events that can or might negatively impact the operation of the IT Network are captured, assessed, and managed in a controlled manner; a property permitting diverse systems or components to work together for a specified purpose.

IT Network (information technology network): a system or systems composed of communicating nodes and transmission links to provide physically linked or wireless transmission between two or more specified communication nodes. Note: The scope of the medical a IT Network in this standard is defined by the responsible organization based on where the medical devices in the medical IT Network are located and the defined use of the network. It can contain IT infrastructure, home health and non-clinical contexts.

Key properties: three risk managed characteristics (safety, effectiveness, and data and systems security) of medical IT Network.

Medical device software: software system that has been developed for the purpose of being incorporated into the medical device or that is intended for use as a medical device in its own right.

Medical IT Network: an IT Network that incorporates at least one medical device.

Medical IT Network risk manager: person accountable for risk management of a medical IT Network

Responsibility agreement: one or more documents that together fully define the responsibilities of all relevant stakeholders.

Responsible organization: entity accountable for the use and maintenance of a medical IT Network.

Top management: person or group of people who direct(s) and control(s) the responsible organization accountable for a medical IT Network at the highest level.

7.1.3 Roles and Responsibilities

Responsible organisation shall maintain a medical IT Network risk management file. The responsible organisation shall have overall responsibility for risk management for a medical IT Network, i.e. planning, design, installation, device connection, configuration, use/operation, maintenance, and device decommissioning. Compliance will be assessed by the responsible organisation.

The responsible organization shall obtain the accompanying documents and additional documentary information for a medical device incorporated in an IT Network as necessary to perform risk management for the medical IT Network, including any known hazardous situations that need to be managed by the responsible organization. These documents shall be maintained in the medical IT Network risk management file.

The top management shall be responsible for establishing policies (risk management policy and risk acceptability policy), allocating resources including assignment of qualified personnel, monitoring the risk management process to ensure suitability and effectiveness of the process and review the results.

Different from ISO 14971, IEC 80001-1 defines another role, *medical IT Network risk manager*. The IT Network risk manager shall be appointed by the top management and be responsible for managing the risk management process during design, putting the network into use, managing necessary communication between the internal and external participants of the risk management process (like medical device manufacturers, other suppliers of IT equipment/software/services, clinical users, technical support team like biomedical engineers), change-release management and change management throughout the entire life cycle. Although the risk management tasks may be delegated, the medical IT Network risk manager remains responsible for ensuring their adequate performance. The medical IT Network risk manager is responsible for consolidating all project risk management activities into a single risk management file for the medical IT Network.

Each *medical device manufacturer* shall provide accompanying documents to the responsible organisation that describe the intended use and give instructions necessary for safe and effective use of the medical device. The accompanying document shall include required characteristics and configuration for the IT Network incorporating the medical device, technical specifications of the network connection, intended information flow between device(s) on the medical IT Network and a list of hazardous situations resulting from a failure of the IT Network.

Providers of other information technology (e.g. infrastructure components/services, client devices (non-medical), servers, applications software or middleware) shall provide accompanying documentation with essential information such as technical description or manuals, information for network connectivity, product configuration, operating requirements and cyber security notices.

7.1.4 Life Cycle Risk Management in Medical IT Networks

The policy for risk management for incorporating medical devices in IT Networks shall be defined and documented by the top management. The policy shall include criteria for risk acceptability and a description of processes relevant to IT Networks (e.g. event management, change-release management, configuration management and monitoring).

The risk management process shall be carried out by the medical IT Network risk manager. Compliance is checked by inspection of the medical IT Network risk management file.

The responsible organisation shall plan the risk management by maintaining risk-relevant asset description, i.e. list of assets including hardware, software and data Medical IT Network documentation: this document shall include network configuration (both physical and logical), applied standards, network communication requirements, etc.

The responsible organisation shall determine the need for responsibility agreement(s) defining the responsibilities of all relevant stakeholders. The responsibility agreement may cover project(s) and

maintenance of medical IT Networks, and shall identify responsibilities and activities for all aspects of the medical IT Network life cycle. The responsibility agreement shall contain at least the definition of roles and responsibilities in the risk management process, a list of the medical devices incorporated into the medical IT Network and a list of accompanying documents to be supplied by the device manufacturers together with the names of organisations responsible for the provision of technical information necessary for the completion of the project. The agreement shall also identify the nature of the co-operation required and responsibilities if any co-operation of manufacturers and/or other organisation is required.

The risk management plan for the medical IT Network: the responsible organisation shall establish and maintain a risk management plan for the medical IT Network. The plan shall contain a description of the medical IT Network (including intended use, expected benefit and identified stakeholder), a description of activities, roles and responsibilities for all parties involved with respect to the risk management and criteria for risk acceptability.

IEC 80001-1 applies a risk control management process that is compliant with ISO 14971. The medical IT Network risk manager is responsible for managing the risk management process.

Change-release management and configuration management: For any change to an existing medical IT Network, the responsible organisation shall apply and document a change-release management process. The medical IT Network risk manager shall:

- Ensure that a change-release management process includes the risk management process.
- Assess the results of the risk management process for approval and acceptability.

In order to control the versions of the medical IT Network, the responsible organisation shall document and apply a configuration management process across all risk management processes.

The responsible organisation shall decide whether the change requirements are met by an applicable change permit. If no applicable change permit exists, a medical IT Network project shall be initiated.

A change permit is a way of avoiding unnecessary repetition of risk management for some frequent activities. Based on the results of risk management activities, the responsible organisation may decide that a specified type of routine change (e.g. adding a user) may be performed with acceptable risk, subject to specified constraints (e.g. a limit on the number of users) and may define a change permit which allows such routine changes and specifies the constraints.

Change permits shall be maintained in the medical IT Network risk management file.

Medical IT Network projects: The responsible organisation shall establish and maintain a project plan for change and activity that has the potential to introduce new risk. The project plan shall provide requirements for risk management activities, a description of the project including the parts affected by the project and the scope of the planned changes to the medical IT Network. The scope shall include, but not limited to, specifications of components (both software and hardware) relevant to the project, and physical and logical configuration of the medical IT Network before and after the planned changes.

The project plan shall be kept in the medical IT Network risk management file in accordance with the life cycle processes of event management, change-release management, and configuration management.

Go-live: Before going live, the medical IT Network risk manager shall approve the specified change to the medical IT Network and the responsible organization shall review the medical IT Network residual risk. The approval of the medical IT Network residual risk shall be documented in the medical IT Network risk management file.

7.1.5 Live Network Risk Management

After the medical IT Network is put into use, as a part of the risk management plan, the responsible organisation shall monitor for emerging or increasing risks, effectiveness of risk measures and accuracy of estimated risks (similar to gathering safety-related post production information in ISO 14971).

If potential increase in risk associated with the network or its components is detected, the event management process shall be initiated and significant findings shall be reported to the responsible organisation.

Event Management is used to capture, document and evaluate safety relevant events and, if necessary, propose changes through change-release management.

Document control: The standard uses the Medical IT Network risk management file to provide traceability for each identified hazard across the risk management process.

7.2 Relevance to REACTION

The REACTION platform will, in many instances, include medical devices within an IT Network. Furthermore, the platform will be defined for use in a number of environments, including; in the hospital; in primary care health centres; and in the home. Hospital and primary care are both clinical settings, and would be expected to be subject to the same risk management processes.

REACTION will also have to consider risk management for medical devices in an IT Network in the home of the patient. Although not designed for such a setting, IEC 80001-1 will provide essential guidelines that should be followed in determining risk for operation of REACTION devices in such a manner.

8. Risk Assessment of Medical Devices

8.1 ISO 14971:2007 - Application of Risk Management to Medical Devices

8.1.1 Background

ISO 14971 provides a logical sequence of stages for risk management to ensure safety of medical devices and is addressed to medical device manufacturers. ISO 14971 emphasizes that the risk management process is an ongoing process of review and risk assessment throughout the medical device life cycle, and therefore sees post-market surveillance as a key tool in this process. Different from IEC 80001-1, which applies to medical devices on the same IT Network by a third party, ISO 14971 applies to medical devices that are on a physically isolated IT Network.

8.1.2 Terms and Definitions

Risk management: systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk.

Harm: Physical injury or damage to the health of people, or damage to property or the environment.

Hazard: potential source of harm.

Risk: combination of the likelihood of harm and the severity of that harm.

Intended use/purpose: use for which a product, process or service is intended according to the specifications, instructions and information provided by the manufacturer.

Residual risk: risk remaining after risk control measures have been taken.

Risk analysis: systematic use of available information to identify hazards and to estimate the risk.

Risk evaluation: process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk.

Risk assessment: overall process comprising a risk analysis and a risk evaluation.

Risk control: process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels.

Risk estimation: process used to assign values to the probability of occurrence of harm and the severity of that harm.

Use error: act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

In vitro diagnostic medical device (IVD medical device): medical device intended by the manufacturer for the examination of specimens derived from the human body to provide information for diagnostic, monitoring or compatibility purposes.

Top management: person or group of people who direct(s) and control(s) a manufacturer at the highest level.

Life cycle: all phases in the life of a medical device, from the initial conception to final decommissioning and disposal.

8.1.3 General Requirements for risk management

8.1.3.1 Risk Management Process

The risk management process involves identification of all potential hazards associated with the medical devices, including in-vitro diagnostic (IVD) medical devices, assessment of the associated risks, risk control, i.e. minimisation of risks or reducing them to an acceptable level, evaluation of overall residual risk for acceptability and documentation.

The risk management process needs to be iterative, covering each risk in turn and returning to the earlier steps if the risk control measures introduce new hazards or when new information that could affect the device safety becomes available or if any modifications have been carried out.

8.1.3.2 Management Responsibilities

The top management shall provide an overall guidance on the risk management process. They are responsible for defining the policy for risk acceptability based on applicable national or regional regulations and relevant international standards, establishing a risk management process as a part of the design, carrying out periodic reviews of the risk management activities for their effectiveness and suitability and rectifying weaknesses, and documenting decisions and actions taken.

The top management shall provide adequate resources and assign qualified personnel for risk management.

8.1.3.3 Qualification of personnel

The risk management process should be performed by a multi-disciplinary team, consisting of people with complementary skills, such as people who are knowledgeable of the design/construction/use of the particular device/service or similar devices/services, technologies involved and risk management techniques.

8.1.3.4 Risk Management Plan

The manufacturer shall establish and maintain a risk management plan for each medical device in accordance with the risk management process. The risk management plan shall provide an organised approach for the risk management process and shall include:

a) description of the particular medical device including its intended use and expected benefits

b) mapping of all elements of the risk management process to the manufacturer's defined product life-cycle

c) Assignment of responsibilities and authorities for the execution of specific risk management activities, e.g. reviewers, experts, independent verification specialists, approval authorities

d) Requirements for monitoring the risk management activities

e) Criteria for risk acceptability, based on the manufacturer's policy for determining acceptable risk, including criteria for accepting risks when the probability of occurrence of harm cannot be estimated

f) Risk management report (Details of the verification activities, effectiveness of the risk control measures,etc)

g) Methods of gathering relevant post-production information from various sources such as users, service personnel, training personnel, reports and customer feedbacks (and this information will be fed back to the risk management process)

Note 1: refer to Annex F of ISO 14971 for guidance on developing a risk management plan

Note 2: refer to Annex D.4 ISO 14971 for guidance on risk acceptability and methods used in risk evaluation

8.1.3.5 Risk Management File

The manufacturer shall establish and maintain a risk management file. This file shall provide traceability for each identified hazard to demonstrate that the risk management process has been applied correctly and to assure completeness of the risk management process. Incompleteness at any stage of the risk management process, e.g., unidentified hazard, risks not assessed, unspecified risk control measures, unimplemented or ineffective risk control measures might jeopardize safety. The risk management file, in essence, provides an evidence of conformance to the requirements of the standard. The following are documented in the risk management file:

- Project description and plan

- o Risk management plan
- o Requirements for risk management activities
- o Scope of any planned changes
- o Identified hazards/hazardous situations and their consequences
- o Risk control measures chosen and effectiveness of these measures
- o Any decisions made including the rationale throughout the risk management process
- o Evaluation of the new risks arising from risk control activities, e.g. changing a part of the device, change of medical network or decommissioning of the device

8.1.4 Risk Analysis

The manufacturer should think about and shall identify and document all characteristics affecting safety of the medical device by taking into account the intended users and situations other than those intended/foreseen by the manufacturer.

The manufacturer shall identify known or foreseeable hazards and estimate the associated risks using available information or data. If the likelihood of the hazard cannot be estimated, the possible consequences shall be listed for use in the risk evaluation and risk control.

Intended use and any foreseeable misuse, the implementation of the planned risk analysis activities results of these activities shall be recorded in the risk management file.

Note 1: refer to Annex C ISO 14971 for sample questions that can be used to identify medical device characteristics that could impact on safety

Note 2: refer to Annex D ISO 14971 for guidance on risk analysis

Note 3: refer to Annex G ISO 14971 for some risk analysis techniques

Note 4: refer to Annex I ISO 14971 for risk analysis techniques for toxicological hazards

8.1.5 Risk Evaluation

The manufacturer shall evaluate risk associated with each identified hazard and hazardous situation, and decide whether the estimated risk is acceptable using the risk acceptability criteria defined in the risk management plan. Unacceptable risks shall be passed onto the risk control procedure for risk reduction.

The decision and rationale for each decision shall be documented in the risk management file.

8.1.6 Risk Control

The manufacturer or responsible organisation shall identify appropriate risk control measures and record them for each unacceptable risk until the residual risk is judged to be acceptable. The manufacturer shall use one or more of the following risk control measures listed in priority order:

a) Inherent control by design

b) Protective measures (e.g. including alarms, barriers)

c) Information for safety (e.g. warnings, user documentation, training)

If practicable, the medical device should be designed to be inherently safe. If this is not possible then protective measures such as barriers or alarms are appropriate.

The risk control may trade-off key properties, in priority order of safety, effectiveness and data and system security.

If the manufacturer determines that required risk reduction is not practicable, the manufacturer shall employ a risk/benefit analysis, i.e. determine whether the benefit of the medical device to the patient outweighs the residual risk.

The manufacturer/responsible organisation shall select risk control measures and verify their implementation and effectiveness, and document decisions, rationale for decisions and the results.

After the risk control measures are applied and verified, the manufacturer shall assess both individual risks and combined impact of the individual risks, i.e., overall residual risk, for acceptability using the criteria defined in the risk management plan.

The manufacturer shall review and document the effects of risk control measures to identify any new or increased, and follow all necessary steps of the risk management process for these risks.

8.1.7 Evaluation of overall residual risk acceptability

The manufacturer shall decide if the combined effect of the individual residual risks, i.e. overall residual risk, is acceptable based on the criteria defined in the risk management plan.

For a risk judged unacceptable, the manufacturer may gather and review data and literature to determine whether the benefits of the intended use outweigh the overall risk and decide whether to proceed with the medical device. If the manufacturer decides benefits outweigh the overall residual risk, then the overall residual risk can be judged acceptable.

For residual risks that are identified as acceptable, the manufacturer shall decide which residual risks to disclose, to whom the information is provided, how much detail is needed and how it will be disclosed. Users should be informed of significant residual risk and resulting benefits so that users can make informed decisions or can take appropriate actions to minimise the risk (refer to Annex J of ISO 14971).

8.1.8 Risk Management Report

Prior to release for commercial distribution of the medical device, the manufacturer shall review the risk management process to ensure correct implementation of the risk management process and to confirm that the required objective(s) have been achieved.

The responsibility for review should be assigned in the risk management plan to persons having the appropriate authority.

The results of this review shall be recorded as the risk management report and included in the risk management file.

8.1.9 Production and Post-production information

The manufacturer should monitor post-production information for data that affect risk estimates in order to improve the risk management process. Therefore, the manufacturer shall

- maintain a scheme to gather information about the particular medical device in the production and post-production phases
- evaluate the information for possible relevance to safety and effects on the risk estimates
- determine if new risk(s) appear when the device is in use and/or reassessment of risk is necessary
- review new or revised standards
- review publicly available information about similar medical devices on the market

The results of this review and evaluation shall be recorded in the risk management file.

8.2 Relevance of ISO 14971:2007 to REACTION

ISO 14971 is very specific in its application and intent, and places direct responsibility of risk assessment and management on the device manufacturer, where a device is used in isolation, within an isolated system, and for intended purposes.

ISO 14971 shall apply to medical devices developed within REACTION, and it is the responsibility of the medical device manufacturer to ensure compliance with the standard where the device is used for intended purpose.

Where a medical device is employed within REACTION for a purpose for which is was not designed or intended, then ISO 14971 will not apply to the manufacturer, and the responsibility for risk assessment and management will fall upon the Ethical Committee of the REACTION project. All non intended use of medical devices will be subject to receiving ethical approval from the appropriate national organisation.

The REACTION project will in this case undertake risk assessment and management in accordance with ISO 14971.

8.3 EN / IEC 62304 – Medical Device Software – Software Life-Cycle Processes

8.3.1 Scope

This standard defines the life cycle requirements for safety of medical device software. The set of processes, activities, and tasks described in this standard establishes a common framework for medical device software life cycle processes.

The standard emphasizes the combination of three principles for safety of medical device software, namely risk management, quality management and software engineering, and aims to focus on software engineering aspects.

This standard provides a detailed development and maintenance process for high quality and safe medical device software when software is itself a medical device or when software is an embedded or integral part of the final medical device. EN/IEC 62304 uses a software risk management process compliant with ISO 14971, as a part of medical device risk management process. If a medical device contains software that can lead to a hazard, then EN/IEC 62304 should be taken into account. This is because ISO 14971 does not specifically address the risk control in the software development life cycle. EN/IEC 62304 provides additional requirements for software risk control including software contributing to a hazardous situation or software that is used to control medical device risks.

This standard does not cover validation and final release of the medical device, even when the medical device consists entirely of software.

Plans, procedures and documentation for risk management activities can be a series of separate documents or a single document or they can be integrated with the medical device risk management activities and documentation.

8.3.2 Terms and Definitions

Architecture: organizational structure of a system or component.

Change request: a documented specification of a change to be made to a software product.

Medical device software: software system that has been developed for the purpose of being incorporated into the medical device being developed or that is intended for use as a medical device in its own right.

Regression testing: the testing is required to determine that a change to a system component has not adversely affected functionality, reliability or performance and has not introduced additional defects.

Safety: freedom from unacceptable risk.

Security: protection of information and data so that unauthorized people or systems cannot read or modify them and so that authorized persons or systems are not denied access to them.

Serious injury: injury or illness that directly or indirectly:

a) is life threatening,

b) results in permanent impairment of a body function or permanent damage to a body structure, or

c) necessitates medical or surgical intervention to prevent permanent impairment of a body function

d) or permanent damage to a body structure.

Software development life cycle model: conceptual structure spanning the life of the software from definition of its requirements to its release for manufacturing, which:

– identifies the process, activities and tasks involved in development of a software product,

– describes the sequence of and dependency between activities and tasks, and

– identifies the milestones at which the completeness of specified deliverables is verified.

Software item: any identifiable part of a computer program.

Note 3: terms identify the software decomposition. The top level is the software system. The lowest level that is not further decomposed is the software unit. All levels of composition, including the top and bottom levels, can be called software items. A software system, then, is composed of one or more software items, and each software item is composed of one or more software units or decomposable software items. The responsibility is left to the manufacturer to provide the definition and granularity of the software items and software units.

Software product: set of computer programs, procedures, and possibly associated documentation and data.

Software system: integrated collection of software items organized to accomplish a specific function or set of functions.

Software unit: software item that is not subdivided into other items.

Note 4: Software units can be used for the purpose of software configuration management or testing.

SOUP - software of unknown provenance (acronym): Software item that is already developed and generally available and that has not been developed for the purpose of being incorporated into the medical device (also known as “off-the-shelf software”) or software previously developed for which adequate records of the development processes are not available.

8.3.3 General Requirements

Quality Management System

The manufacturer of the medical device software shall demonstrate the ability to meet the applicable regulatory requirements to ensure reliable software (e.g. compliance with ISO 13485 or a national quality management system standard).

Risk Management

The manufacturer shall use a software risk management process compliant with ISO 14971 standard, as a part of medical device risk management process.

Software Safety Classification

The manufacturer shall assign to each software item a software safety class based on severity and document it into the risk management file. There are three software safety classes; class A: no injury or damage to health is possible, class B: Non-serious injury is possible, class C: death or serious injury is possible. If a software failure leads to a hazard, then the probability of such failure is assumed to be 100%. After a risk reduction process, a new software safety classification should be carried out. When a software system is decomposed into software items, such software items shall inherit the software safety classification of the original software item.

8.3.4 Software Development Process

This part includes all the stages of software development and testing from planning to software release, i.e. software development planning, software requirements analysis including functional specifications and risk control measures, software architectural design, software detailed design, software unit implementation and verification, software integration and integration testing, software system testing and software release.

8.3.5 Software Maintenance Process

This includes establishing software maintenance plan (identify procedures for implementing maintenance activities and tasks), problem and modification analysis and modification implementation.

8.3.6 Software Risk Management Process

This includes analysis of software contributing to hazardous situations, risk control measures, verification of risk control measures implemented in software and risk management of software changes. The process shall be compliant with ISO 14971.

8.3.7 Software Configuration Management Process

This process includes configuration identification (i.e. establishing means to identify configuration items, identifying of software with unknown provenance (SOUP), identifying system configuration documentation), change control (approval of change requests, implementation and verification of changes, means of traceability of change), configuration status monitoring and documentation.

8.3.8 Software Problem Resolution Process

This includes preparation of problem reports, investigation of the problem, advising relevant parties, use of change control process, maintaining records, analysing problems for trends, verification of software problem resolution and inclusion of test documentation.

8.4 Relevance of EN/IEC 62304 to REACTION

The REACTION platform will comprise many software items that will manage patient information and therefore fall under EN/IEC 62304. Although software development may be prototype in form and intended only for research purposes, EN/IEC 62304 should be applied as good practice, and may be necessitated in some countries for compliance with MDD.

8.5 ICE – Integrating the Clinical Environment

There is an initiative to develop methodology to identify and manage risks associated with connecting together multiple medical devices, especially where data from one is being used to control another. The work is currently under auspices of the IEEE 11073 committee and is in early stages of development. The closed loop glucose control of REACTION may be a suitable case study for this work.

9. Medical Devices Directive

9.1 General Summary

The Medical Device Directives harmonise the rules on the free circulation of medical devices in the EU. In order to conduct a clinical investigation of a medical device, manufacturers must prove they meet the applicable safety and administrative requirements detailed in the directives. Within the EU's framework of regulation, the Medical Device Directive is of the most importance with regards to REACTION as it covers many types of medical software. If under the REACTION project clinical investigations are to be carried out, they must be conducted under the rules laid out in the Medical Device Directive. An application would involve several important requirements. The manufacturer must include the required documentation and labels with the device. The manufacture must also provide a statement to the relevant competent authorities indicating how it has complied with the essential requirements of the MDD (except those essential requirements that only apply where a device is being placed on the market after a clinical investigation). If the manufacturer has included all documentation needed to show such compliance, authorisation from the competent authority of the member state in question can be granted.

9.2 Introduction

Prior to the introduction of the EU framework on Medical Devices in the 1990s, the regulation of medical devices was subject to the differing regimes of each member state. This created barriers towards the functioning of the internal market. As a consequence the Commission decided to harmonise regulation in the area of the medical devices so as to remove obstacles to the internal market. The framework on medical devices consists of three directives. These are;

- The Medical Devices Directive (MDD) 93/42/EEC (as amended by Directive 2007/47/EC),
- The Active Implantable Medical Devices Directive (AIMD) 90/385/EEC (as amended by Directive 2007/47/EC)
- The In Vitro Diagnostic Medical Devices Directive (IVDMD 98/79/EEC.

The MDD is applicable to most medical devices, with the AIMD[2] and the IVDMD[3] applying in only more narrowly defined circumstances. The focus of this document is therefore on the MDD as it is likely that it will apply to most RECTION components[4]. In order to be placed on the market all products that fall within the scope of the directive and meet its requirements are required to bear an EC-conformity mark to show compliance with the directive. The aim of this is to allow products that conform to the directive's requirements to be sold freely throughout the EEA without hindrance from national governments. As Callens [B17] points out, the MDD was important for the e-health sector especially with regard to medical software that is used in many applications[5]. The directive is not only of importance however for devices which are ready to be placed on the market. This is because there are, broadly speaking, two regimes for the use of devices under the MDD, one is for clinical evaluation/clinical investigations, the other is for general release on the market with the *CE* stamp. The information below is concerned with the legal requirements for a clinical investigation as perceived in task T7.5 of the REACTION project. The following sections will focus on the provisions of the directive that might have a possible impact on the REACTION project. Devices which are to be

2 This Directive covers all powered medical devices implanted and left in the human body, such as pacemakers, implantable defibrillators, implantable infusion pumps, cochlear implants and implantable neuromuscular stimulators. The Directive also covers implanted passive parts of active devices such as pacemaker leads and adapters, and external parts that are
an essential part of the systems, e.g. pacemaker programmers.

3 This Directive covers any medical device, reagent, reagent product, kit, instrument, apparatus or system which is intended to be used for the in vitro examination of substances derived from the human body, such as blood grouping reagents, pregnancy testing and Hepatitis B test kits.

4 The AIMD might apply however in the case of an insulin pump used in a closed loop glycemic control system. At this stage it is not certain that such a device will be produced by REACTION. If such a device is produced the regulatory position will be outlined in a future document.

5 Callens., Stefaan, 'The EU Legal Framework on E-health' in Mossailos., E, Permanand., G, Baeten., R, Hervey., T ,"Health Systems Governance in Europe" Cambridge University Press

used in clinical investigations under the REACTION project must comply with these requirements in order to be used in such investigations. Evidence of compliance with such requirements must be included in a statement to the relevant authorities before authorisation is granted for clinical investigations (See Section BI below).

Note: The Medical Devices Directive (MDD) has been subsequently amended by four directives and one regulation. In reviewing the Medical Device Directive the following analysis also takes into account the amendments made to it by subsequent directives. These include:

- Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998
- Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000
- Directive 2001/104/EC of the European Parliament and of the Council of 7 December 2001
- Regulation (EC) No 1882/2003 of the European Parliament and of the Council of 29 September 2003
- Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007

9.3 Medical Devices and their Categories

9.3.1 Definition of a 'Medical Device'

In order decide whether a device is subject to the rules of the directive it must be discerned whether it is a 'medical device' or not. The definition of what exactly is a medical device[6] is described as any "instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application".

Such a device should be intended by the manufacturer for one of a number of defined purposes, one of which is, "diagnosis, prevention, monitoring, treatment or alleviation of disease"[7]. Devices not used for this purpose, including software, would therefore not be classed as a 'medical device' and therefore not be governed by the directive[8]. However, software that does not perform one of the above functions itself will still be considered a medical device if it is used in combination with another medical device that does.

9.3.2 The Categorisation of Medical Devices.

Medical devices are split into four different classes, being I, IIa, IIb and III[9]. The properties of a device determine which class it falls into.

Non Invasive Devices

In general all non invasive devices are categorised as Class I devices[10]. There are however certain exceptions to this[11]. These include devices intended for channelling or storing blood (Class IIa), devices intended to modify the biological or chemical composition of blood or other body liquids (Class IIa), certain devices that come into contact with wounds (Class IIa or IIb) or injured skin (Class IIa or IIb) (unless they are merely acting as a mechanical barrier in which case they are still Class I)[12].

6 Article 2 (a)

7 'Investigation, replacement or modification of the anatomy or of a physiological process' and 'control of conception' are also given as valid purposes.

8 This might apply for instance to the software used in medical databases.

9 Article 9

10 Annex IX Rule 1

11 Annex 9 Rules 2 - 4

12 Exceptions are also made for non invasive devices which are connected to invasive devices which may be Class II or higher.

Invasive Devices

These devices are generally classified according to their intended duration of use. Those intended for use in body cavities or openings can be categorised as Class I or IIa depending upon their intended duration of use[13].

Surgically invasive devices which are intended only for 'transient use' are generally categorised as Class IIa devices. The exceptions to this are: a) devices used to control, diagnose or monitor a heart or central circulatory system defect through direct contact (Class III); b) reusable surgical instruments (Class I); c) instruments that are used in direct contact with the central nervous system (Class III); d) devices which supply ionizing radiation (Class IIb), devices intended to have a biological effect or to be wholly or mainly absorbed (Class IIb); and e) those intended to administer medicine in a potentially dangerous manner (Class IIb).

Surgically invasive devices intended for 'short term use' are also generally Class IIa. The exceptions stated above for transient devices of type a), c), d) and e) apply to devices of short term use also[14]. In addition to this, is the category of transient surgical devices which undergo chemical changes in the body (except those planted into the teeth) which are categorised as Class IIb).

All 'long term' implantable and surgically invasive medical devices are presumed to be in Class IIb unless[15]: they are intended to be implanted in the teeth (again Class IIa); those used in direct contact with the heart, the circulatory system or the central nervous system (Class III; those meant to have a biological effect or to be wholly or mainly absorbed in the body (Class III); and those devices intended to undergo a chemical change in the body (unless they are placed in the teeth or are used to administer medicines) (Class III).

Active Medical Devices[16]

All active therapeutic medical devices intended to administer or exchange energy are categorised as Class IIa unless they do so in a potentially hazardous way, in which case they are categorised as Class IIb[17]. Active devices intended to monitor the performance of active therapeutic devices or influence their performances are also in Class IIa.

Active Devices for Diagnosis

These are in Class IIa if they will supply energy to be absorbed by the human body, if they are intended to image in vivo distribution of radiopharmaceuticals or they allow direct diagnosis or monitoring of vital pharmaceutical processes (unless such monitoring is in areas where changes could result in immediate danger to the patient e.g. changes in breathing or CNS activity (Class IIb). Devices intended to emit ionizing radiation for diagnostic and therapeutic purposes however will be categorised as Class IIb. Active devices which are intended to administer/remove medicines are also caught by the general classification of Class IIa unless this involves the administration of a potentially dangerous substance in a manner that could be dangerous, in which case they are classified as Class IIb.

Special Categories of Products.

There are also rules for the categorisation of the following special categories of products;[18]

- Devices incorporating medicinal products as an integral part and which are liable to act upon the human body with ancillary action to that of the Medical Device itself are categorised as Class III;

13 See Annex 9 Rule 5. Devices intended for transient duration are classified as type I, devices intended for long term duration are classified as type IIa and devices intended for long term use are classified as type IIb (except those to be used in the oral cavity as far as the pharynx, in the ear as far as the ear drum, in a nasal cavity and which are not liable to be absorbed by a mucosal membrane, such long-term devices are categorised as IIa).

14 Except those short term devices which supply radiation to the body which are classified as Class III

15 Annex IX Rule 8

16 Active Implantable Devices are covered by the Active Implantable Medical Devices Directive (AIMD) 90/385/EEC

17 Annex IX Section 3.1

18 Annex IX Rules 13-18

- Devices that incorporate human blood or one of its derivatives as an integral part (Class III);
- Devices used for contraceptive purposes or those used to prevent the transmission of STD's are classified as Class IIb, unless they are implantable or long term devices, in which case they are categorised as Class III;
- Devices for cleaning, disinfecting or rinsing, or when appropriate, hydrating contact lenses (Class IIb);
- Devices intended to disinfect medical devices (Class IIa);
- Devices which are intended to disinfect invasive medical devices (Class IIb);
- Devices specifically intended for the recording X-ray diagnostic images (Class IIa);
- Devices which utilize animal tissues or their derivatives (rendered non-viable) are in Class III (unless such devices are intended to come into contact with intact skin only);
- Blood bags are categorised as Class IIa.

9.4 Requirements placed upon Manufacturers when Medical Devices are used for the process of Clinical Investigation[19].

The directive contains special requirements for the manufacturers of Medical Devices intended for use in Clinical investigations[20].

9.4.1 Statement of Purpose

For such devices the manufacturer must produce a statement for the authorities of the relevant member state[21]. Such a statement must contain the following items (if applicable);[22]

- data allowing identification of the device in question;
- the clinical investigation plan;
- the investigator's brochure;[23]
- the confirmation of the subjects' insurance status;[24]
- the documents used to obtain informed consent;[25]
- a statement indicating whether or not the device integrates as an integral part a substance or human blood derivative[26];

19 There are also special requirements for the manufacturers of custom devices to meet. Custom devices are those that are tailor made for certain individuals. See Annex VIII Section 1 of the MDD.

20 Article 15 of the MDD states that manufacturers of devices intended for clinical investigation must adhere to the requirements of Annex VIII of the directive.

21 For Example the Medicines and Health Care Projects Regulatory Agency (MHRA) is the relevant UK authority for applications for clinical investigations.

22 Article 15(1)

23 This was a result of Directive 2007/47/EC which came into force in March 2010 and updated the MDD.

24 Ibid

25 This implies that devices can only be used for clinical investigation on those who are able to give fully informed consent.. This can create problems in certain situations in some states where individuals are unable to give consent themselves and proxy consent is not permitted. See for example Druml., C, Singer., E "The European Directive: a further blow to science in intensive care medicine in Austria" Intensive Care Med (2004) 30:335 which describes problems that have arisen in Austria as a result of the need of patients to give informed consent.

26 Precise details of what can be considered as a blood derivative are provided in Annex I, Section IV.

- A statement indicating whether the device is manufactured utilising tissues of animal origin as referred to in directive 2003/32/EC;
- the opinion of the ethics committee concerned and details of the aspects covered by its opinion;[27]
- the name of the medical practitioner or other authorized person and of the institution responsible for the investigations;
- the place, starting date and scheduled duration for the investigations;
- a statement that the device in question conforms to the essential requirements (See Section 9.5)[28] apart from the aspects covered by the investigations and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

Member states may react differently to statements made by manufacturers depending on the categorisation of the device in question. For Class I devices, the relevant authorities of a member state may allow manufacturers to commence clinical investigations immediately after receiving the manufacturer's statement, presuming the ethics committee issues a favourable opinion on the proposed trial including its review of the clinical investigation plan. For devices of types IIa, IIb, III there is normally a 60 day waiting period after negotiation[29]. Member states however may authorise the manufacturer to commence a clinical investigation if the ethics committee has issued a favourable opinion on the programme of investigation in question, including its review of the clinical investigation plan[30].

9.4.2 Providing the Correct Documentation for Devices used in Clinical Investigations

In addition to producing the statement described above manufacturers must provide documentation for the medical devices that are involved in clinical investigations that meets the following relevant requirements[31]:

- a general description of the product and its intended use;
- design drawings, methods of manufacture envisaged, in particular as regards sterilisation, and diagrams of components, sub-assemblies, circuits, etc.;
- the descriptions and explanations necessary to understand the above mentioned drawings and diagrams and the operation of the product;
- the results of the risk analysis (with a list of the standards of the relevant national standards[32] if relevant, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of the directive if the standards referred to have not been applied. See section 9.5 for further explanation);

27 See Annex X Section 2.2; Clinical Investigations must be carried out in accordance with the 18th World Medical Assembly in Helsinki Finland in 1964 as last amended by the World Medical Assembly.

28 The essential requirements are contained in Annex I of the directive and are described in detail in Section 9.5 of this report. They are the essential requirements that a product must meet before it can be placed on the market. Annex VIII Section 2.2 requires that for clinical investigations the manufacturer's statement must describe how the product specifications meet the essential requirements as laid down in Annex I except for those which can not obviously apply by virtue of the fact that the product is currently at the clinical investigation stage.

29 Article 15.2

30 See for example Guidance For Manufacturers on clinical Investigations to be Carried Out in the UK - Updated July 2010 available at: http://www.mhra.gov.uk/Publications/Regulatoryguidance/Devices/GuidanceontheECMedicalDevicesDirectives/CON007504 Before devices intended for clinical investigation in the UK are made available to a medical practitioner for the purposes of clinical investigation, the manufacturer of the device (or his authorised representatives in the European Union) must give 60 days prior notice to the Secretary of State for Health by writing to the UK Competent Authority. If, within 60 days of formal acceptance of the Notice, the UK Competent Authority has not given written notice of objection, the clinical investigation may proceed. The UK Competent Authority may give such notice of objection on grounds relating to public health or public policy (Medical Devices Regulations 2002 section16(4), section 29(3)).

31 See Annex VIII Section 3.2 There are also requirements for products that contain human blood or animal derivatives, but these are not relevant for the reaction project.

32 Article 5 - Compliance with the Essential Requirements can be presumed if relevant national standards are met – see section CI for further details.

- it must state whether the device incorporates as an integral part or substance human blood or one of its derivatives;
- It must state whether the device is manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC and that the relevant risk management measures have been taken to reduce the risk of cross infection;
- the results of the design calculations, and of the inspections and technical tests carried out, etc.

Copies of the manufacturer's statement and the documentation should be retained for at least 5 years[33]. The product produced by the manufacturer should match the description given in the documentation. The manufacturer is obliged to take all necessary steps to ensure that the manufacturing process meets that which it described in its statement and in the device's documentation. Manufacturers should be meticulous in ensuring that all required documentation is enclosed[34]. If the manufacturer meets these requirements member states are not permitted to create obstacles for the use of a medical device in a clinical investigation[35].

9.4.3 Requirements of the Clinical Investigation

Clinical investigations themselves must be conducted according to certain principles[36]. According to the Directive the clinical investigation must be carried out on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge in such a way as to be able to confirm or refute the claims of the manufacturer[37]. The procedures used must be appropriate for the device in question and the conditions must be similar to the normal conditions of use for the device[38]. All appropriate features including the device's safety, its performance and its effect on the patients must be examined during the investigation[39]. All adverse events must be fully recorded and immediately notified to all competent authorities in the Member State in question. Investigations must be carried out under the supervision of an appropriately qualified practitioner who has access to the technical and clinical data regarding the device and in an appropriate environment. The practitioner's report must be signed and contain a critical evaluation of all the data collected during the investigation[40]. As a result of the recent amendment of this directive, manufacturers are obliged to keep this report 'at the disposal of the competent authorities'[41].

Manufacturers are obliged to notify the authorities of the termination of clinical investigations, with a justification if a trial was terminated early. If such termination was on safety grounds such a termination must be communicated to the relevant authorities of all member states and the Commission[42].

33 Ibid. The requirements are greater for implantable devices, being 15 years. This would presumably apply to any pump used in a closed loop system.

34 The Medicines and Health Care Projects Regulatory Agency in the UK states for example that a significant amount of applications encounter problems because they are missing documentation. See http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm

35 Article 4(2)

36 Article 15(5)

37 Annex X Section 2.3.1

38 Annex X Section 2.3.2

39 Annex X Section 2.3.3

40 Annex X Sections 2.3.5 – 2.37

41 This was a result of Directive 2007/47/EC which came into force in March 2010.. See also Donawa., M "New European Device Clinical Requirement: Part 2" European Medical Device Technology, February 2010.

42 Article 15(7)

9.5 Essential Requirements

9.5.1 General Design Requirements

In order to be placed onto the market devices must meet the 'essential requirements' of the directive[43]. Devices intended for clinical investigation must also meet the directive's essential requirements; however with the obvious exception of those it is not possible to do so because the device in question is still at the investigation stage. The manufacturer of a device must include a description of how the product in question complies with the general requirements in its statement to relevant authorities of a member state when applying for a clinical investigation[44] or to be placed on the market[45]. In addition to meeting the requirements laid down in the 'Essential Requirements of the Medical Device Directive member states must assume that a medical device is compliant with the 'essential requirements' if it meets the relevant national standards adopted pursuant to the harmonized standards, the references of such having been published in the Official Journal of the European Communities[46]. Member States are obliged to publish the references of such national standards.

The primary aim is to ensure that devices are manufactured is such a way as to not compromise the clinical conditions of the patient, in addition to the safety and the health of those using such devices. Any risks that are created by the use of a device (including side affects[47]) must be acceptable when weighed against the benefits to the patient and be compatible with a high level of health and safety[48]. In order to achieve this, risks arising out of the ergonomic nature of the project must be considered in addition to the technical knowledge, experience and education of users and where applicable the physical condition of users. The solutions selected by the manufacturer must conform to recognised safety principles taking account of the state of the art[49]. The following principles should be applied by the manufacture (in the following order) in order to achieve this;

- To eliminate or reduce risks in so far as is possible using an inherently safe design and construction;
- To take protection measures where appropriate including alarms if necessary, in relation to risks that cannot be eliminated;
- Users should be informed of any residual risks that cannot be eliminated by the protection measures adopted.

All devices should achieve the performances intended by the manufacturer and should be designed and packaged in such a manner as to be suitable for one of the functions described in the definition of a 'medical device'[50]. These aspects of a device should be expected even with all the stresses and strains of normal use. Devices should be designed, manufactured and packed so that their performance during their intended use will not be adversely affected during transport (including the products instructions)[51]. The pages below describe the responsibilities of manufacturers with regards to several specific but important aspects of the medical devices.

43 Article 3

44 See Annex VIII Section 2.2 and Fn 16

45 Article 2

46 Article 5 Reference to harmonised standards also includes the monographs of the European Pharmacopoeia on Surgical Sutures and on interaction between medicals products and materials used in devices contained in such medical products, the references of which have been published in the Official Journal of European Communities.

47 Annex I Section 6

48 Annex I Section 1

49 Annex I Section 2

50 Annex I Section III

51 Annex I Section 5

9.5.2 Requirements Linked to Specific Hazards

In addition to the generalised requirements described above the directive contains a number of requirements in order to ensure against more specific hazards.

Chemical, Physical and biological properties

The manufacturer must pay close attention to the choice of materials, with regards to such issues as flammability, the compatibility with biological tissues, and where appropriate the results of biophysical or modelling research. The design, manufacture and packaging must minimize risk of contamination in the transport, storage and use of devices. Particular attention should be paid to such problems that might arise with regards to exposed tissues and should take into account the nature and length of exposure[52]. Design should also take into account all foreseeable interaction with other substances during the normal use of the device. If a device is designed to administer medicinal products it must be designed to be compatible with such products according to the previsions and restrictions governing such products, allowing such products to function normally.

Special requirements exist if a medical device incorporates as an integral part a medicinal product. If the substance acts in an ancillary manner upon the body to a medical device it must meet the requirements laid out in Directive 2001/83/EC, the quality, safety and usefulness of the substance must be verified by analogy with the methods specified in Annex 1 of that directive. The relevant notified body is then obliged to verify the usefulness of the substance, taking into account the purpose of the relevant device, and then seek a scientific opinion from one of the competent authorities designated by the member states or the European Medicines Agency acting through its committee in accordance with regulation (EC) No 726/2004[53] Such an opinion will be based upon the quality and safety of the substance including the benefit/risk profile of the incorporation of the substance into the device as determined by the notified body. If a device incorporates a human blood derivative the notified body must also seek an opinion on a similar basis. The notified body should be notified of any changes made to a medical device. It will then have to consult the medicines authority involved in the initial consultation in order to confirm that the ancillary substance retains the same level of quality and safety. All devices must be designed so as to minimise the risk due to the leakage of substances from them[54]. If the parts of the device are intended for use with the treatment of children, pregnant or nursing women, the manufacturer must provide a specific justification for the use of substances. The manufacturer should also provide information in its documentation on residual risks for these patient groups and if available any precautionary measures that should be taken.

Infection and Microbial Contamination

Devices must be designed to eliminate risks, insofar as is possible to the users of the device and to third parties from infection. The design must however allow easy handling but where needed minimise the risks of contamination of the device by the patient during use or vice versa[55]. Devices should be manufactured and sterilised by an appropriate and validated method and under appropriate conditions[56]. Again there are specific requirements for devices that use tissues of animal origin[57]. Devices which are to be delivered in a sterile state must be designed, manufactured and packaged in a non reusable bag or according to the relevant procedures to ensure that they are sterile when placed on the market and remain so throughout transport and storage and until the protective packaging is opened. If the device is to be sterilised prior to use, the packaging should still aim to keep

52 Annex I Section 7

53 regulation (EC) No 726/2004 lays down community procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary use and establishes a European Medicines Agency.

54 Annex I Section 7.5. Special Attention must be given to substances that are carcinogenic, mutagenic or toxic to reproduction in accordance with Annex I of Council directive 67/548/EEC of 27 June 1967

55 Annex I Rule 8.1

56 Annex I Rule 8.4 and 8.5

57 Annex I Rule 8.1 – The tissues must come from animals that have been subject to veterinary controls and surveillance. Processing of such tissues should be carried out in a manner that would provide optimal security.

microbial contamination to a minimum[58]. Packaging and labelling of devices should clearly distinguish between identical or similar products sold in both sterile and non sterile conditions[59].

Construction and Environmental Properties

A device should be designed in a way that (if intended) it can be used in combination with other devices and not impair its, or their intended function[60]. If such restrictions are unavoidable they should be clearly labelled or included with the device's instructions. All devices must be designed to reduce risk of fire or explosion, particularly those intended for uses where exposure to flammable or combustible substances is possible[61]. Devices should be designed so as to avoid or minimise the following risks;[62]

- risk of injury, taking into account volume/pressure ratio, dimensional and where appropriate ergonomic features;
- risks connected with reasonably foreseeable environmental conditions such as magnetic fields, external electrical influences, electrostatic discharge, pressure, temperature or variations in pressure;
- risk of interference with other devices normally used in similar investigations or treatments as the device in question;
- risks arising where maintenance or calibration is not possible. Care should be taken to avoid risks brought about by the aging of materials or the loss of accuracy any measuring or control mechanism.

Devices with a Measuring Function

Such devices must be designed to provide appropriately sufficient levels of accuracy and stability for the intended use of the device in question. The limits of a device's accuracy should be clearly stated by a manufacturer[63]. Measurement, monitoring and display scales must be designed in line with ergonomic principles taking account of the device's intended use[64]. Measurements made by the device should be expressed in the correct legal units[65].

Protection against Radiation

Devices should be designed and manufactured in such a way to avoid the exposure of patients to radiation, taking into account the intended use of the device. Different rules exist for devices that are intended to expose patients to radiation and those which are not[66]. For devices where such emissions are intended, the user must be able to control the level of such radiation. Instructions should advise users in a detailed manner of such radiation emission[67]. Where such exposure is not intended the manufacture of a device should be carried out so as to reduce such risks as much as is possible. The

58 Annex I Rule 8.6

59 Annex I Rule 8.7

60 Annex I Rule 9.1

61 Annex I Rule 9.3

62 Annex I Rule 9.2

63 Annex I Rule 10.1

64 Annex I Rule 10.2

65 Such units are expressed in Council Directive 80/181/EEC

66 Annex I Rules 11.2.1 and 11.2.2

67 Annex I Rule 11.4

directive also provides requirements for devices intended to emit ionising radiation, for treatment, diagnostic and therapeutic purposes.[68].

Requirements for Medical Devices Connected to or Equipped with an Energy Source

Devices incorporating systems that are electronically programmable must be designed to ensure the repeatability, reliability and performance of their systems according to their intended use[69]. Devices that include software, or are software themselves, must be validated according to the state of the art, taking into account the principles of development lifecycle, risk management, validation and verification. If devices are dependent upon an internal power supply those devices must be equipped with a means of determining the state of such a supply. If the device is dependent upon an external power supply the device should be equipped with an alarm mechanism to indicate disruption to that supply. In addition if the device is meant to monitor clinical parameters of a patient, of which problems could lead to deterioration or death, it should be fitted with alarm systems to alert the patient of such situations. It is important that devices are designed and manufactured in such a way to avoid the creation of electromagnetic fields, which could interfere with the operation of other devices or equipment in the usual environment. The risk of electric shock should also be minimised as much as is possible through the design and manufacture of devices. The directive is also concerned with potential mechanical and thermal risks from such powered devices. The manufacturer should ensure that terminals and connectors to energy sources are designed in such a way to minimise risk. Devices are expected to be designed and manufactured to exclude as much as is possible risks associated with:

- Resistance, stability and moving parts;
- Vibrations;
- Noise;
- Heat from accessible parts of the device.

Devices that intended to supply energy to the patient should be designed in such a way that the flow of energy can be set or maintained at a rate that is safe for the patient. Such devices should also be fitted with a means for detecting problems with the flow rate. Manufacturers should incorporate suitable properties to prevent accidental releases of excessive amounts of energy or substances. Devices that have visual systems or instructions indicating the required parameters for its operation should present such information in a way that is readily understandable to both the user and, if appropriate, the patient.

9.5.3 Information Supplied by the Manufacturer

All devices must be accompanied by the information needed for safe and proper use, taking into account the training and knowledge of potential users[70]. The information available should also allow the manufacturer to be identified. Such information should be composed of a label and also instructions for use. If possible the information should be set out on each unit or packaged with each unit. If this is not practicable a leaflet should be sent with one or more devices. Instructions should be included in the packaging for every device. This is however not required for devices in Classes I or IIa which can be used safely without such instructions. Where symbols are used they must conform to harmonised standards. If no such standards exist the symbols must be clearly described in the documentation supplied with the device.

68 See Annex I Rule 11.5 – Such devices should be designed so that where possible the user is able to control the quantity, geometry and quality of radiation emitted. With regard to devices that emit ionising radiation for treatment, diagnostic and therapeutic purposes, the directive states that such devices should be designed and manufactured in such a way as to achieve appropriate results.

69 Annex I rule 12

70 Annex I Rule 13

Labels

Labels are required to display the following information (if applicable):

- the name or trade name and address of the manufacturer[71];
- the details strictly necessary to identify the device and the contents of the packaging, especially for the users;
- were appropriate, the word 'STERILE';
- where appropriate, the batch code, preceded by the word 'LOT', or the serial number;
- where appropriate, an indication of the date by which the device should be used safely, expressed as the year and month;
- where appropriate, an indication that the device is for single use. A manufacturer's indication of single use must be consistent across the Community;
- if the device is custom-made, the words 'custom-made device';
- if the device is intended for clinical investigations, the words 'exclusively for clinical investigations';
- any special storage and/or handling conditions;
- any special operating instructions;
- any warnings and/or precautions to take;
- year of manufacture for active devices other than those supplied with a use by date[72];
- where applicable, method of sterilization;
- an indication that the device contains a human blood derivative (if that is the case).

If the purpose of the device is not obvious to the user, the manufacturer is obliged to clearly state it on the label and in the instructions for use. The devices and attachable components must be identified, where appropriate in terms of batches to allow all appropriate action to detect and risk posed by such detachable components.

Instructions for Use

Instructions for use are required to contain the following particulars[73]:

- The same date required to be placed on labels except for batch number and use by date (if appropriate);
- The expected performances of the device and any undesirable side effects;
- If the device must be installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe combination;

71 For devices imported into the Community, in view of their distribution in the Community, the label, or the outer packaging, or instructions for use, shall contain in addition the name and address of the authorised representative where the manufacturer does not have a registered place of business in the Community;

72 This indication may be included in the batch or serial number.

73 Annex I rule 13.6

- All the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the device operate properly and safely at all times;

- Where appropriate, information to avoid certain risks in connection with implantation of the device;

- Information regarding the risks of reciprocal interference posed by the presence of the device during specific investigations or treatment;

- The necessary instructions in the event of damage to the sterile packaging and, where appropriate, details of appropriate methods of re-sterilisation;

- If the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of sterilization of the device to be re-sterilised, and any restriction on the number of reuses. Where devices are supplied with the intention that they be sterilized before use, the instructions for cleaning and sterilization must be such that, if correctly followed, the device will still comply with the basic principles of the essential requirements[74].

- If the device bears an indication that the device is for single use, information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device were to be re-used[75].

- Details of any further treatment or handling needed before the device can be used (for example, sterilization, final assembly, etc.);

- In the case of devices emitting radiation for medical purposes, details of the nature, type, intensity and distribution of such radiation.

The instructions for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular:

- Precautions to be taken in the event of changes in the performance of the device;

- Precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources, etc.;

- Adequate information regarding the medicinal product or products which the device in question is designed to administer, including any limitations in the choice of substances to be delivered;

- Precautions to be taken against any special and unusual risks related to the disposal of the device;

- Medicinal substances, or human blood derivatives incorporated into the device as an integral part;

- The degree of accuracy claimed for devices with a measuring function;

- The date of issue or the latest revision of the instructions for use.

74 These are laid out in Annex I Section 1 and described in section CI of this document.

75 If in accordance with Section 13.1 (i.e. Class I and IIa devices) no instructions for use are needed, the information must be made available to the user upon request;

9.6 Conclusion on Application of MDD to REACTION Project

Various components of REACTION fit the definition of a 'medical device'. These include a possible blood sugar measuring patch technology[76] and software and networking technology. For these, regulation will be guided by the principles of the MDD. In order to be legally used in clinical investigations a manufacturer must apply to the relevant competent authorities[77] for the Member State concerned. This application involves several important requirements. The manufacturer must include the required documentation and labels with the device. The manufacture must also provide a statement to the relevant competent authorities indicating how it has complied with the essential requirements of the MDD (except those essential requirements that only apply where a device is being placed on the market after a clinical investigation). If the manufacturer has included all documentation needed to show such compliance, authorisation from the competent authority of the member state in question can be granted.

76 Interestingly it is stated that a medical device should not "achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its function by such means." It would seem that this definition would certainly catch the software, networking and telecommunications strategy used in the reaction platform. It also seems likely that the proposed patch in reaction could be deemed a medical device as although it operates 'on' the body it does not achieve its action by pharmacological, immunological or metabolic means, as rather than influencing the metabolic process itself, the patch would be passively monitoring it.

77 See Section 11 of this document for a list of the relevant competent authorities in each member state.

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[B29] Regulation (EC) No 1882/2003 of the European Parliament and of the Council of 29 September 2003

[B30] Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007

11. List of Contact Points within the National Competent Authorities

This annex contains a list of the relevant contacts within the competent authorities of each member state[78].

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78 Taken from the EU Commission web site see: http://ec.europa.eu/consumers/sectors/medical-devices/files/list-of-contact-points-within-the-national_en.pdf

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