1. Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the risk management process for medical devices or combination products that have a device constituent part at Outlook Therapeutics, Inc. (OTLK), in accordance with ISO 14971 requirements.

1. **Scope**

This SOP is applicable to medical devices or combination products that have a device constituent part that are developed by Outlook Therapeutics or under the supervision of OTLK.

This SOP is not applicable to drug substance manufacturing, drug product manufacturing, or supplier, financial, and business risks.

1. **Responsibilities**

## Technical Operations is responsible for:

### Ensuring that personnel are trained on and comply with this procedure.

### Ensuring that device risk management documentation is updated as applicable.

## Quality Assurance is responsible for review and approval of device risk management documentation.

## Regulatory Affairs is responsible for review and approval of device risk management documentation when appropriate.

1. **References**

| **Document number/ID** | **Document Name** |
| --- | --- |
| N/A | ISO 14971: Medical Devices – Application of Risk Management to Medical Devices |
| SOP-0275 | Design Control for Medical Devices and Combination Products |

1. **Definitions and Abbreviations**

| **Phrase, item, word** | **Definition** |
| --- | --- |
| **Accompanying Documentation** | Materials accompanying a product and containing information for the user or those accountable for the installation, use, maintenance, decommissioning, and disposal of the product, particularly regarding safe use. |
| **Benefit** | Positive impact or desirable outcome of the use of a product on the health of an individual, or a positive impact on patient management or public health. |
| **Harm** | Injury or damage to the health of people, or damage to property or the environment. |
| **Hazard** | Potential source of harm. |
| **Hazardous Situation** | Circumstance in which people, property, or the environment is/are exposed to one or more hazards. |
| **Intended Use** | Use for which a product, process, or service is intended according to the specifications, instructions, and information provided by the manufacturer. |
| **Manufacturer** | Natural or legal person with responsibility for the design and/or manufacture of a product with the intention of making the product available for use, under their name, whether or not such a product is designed and/or manufactured by that person themself or on their behalf by another person(s). |
|  |  |
| **Reasonably Foreseeable Misuse** | Use of a product or system in a way not intended by the manufacturer, but which can result from readily predictable human behavior. |
| **Residual Risk** | Risk remaining after risk control measures have been implemented. |
| **Risk** | Combination of the probability of occurrence of harm and the severity of that harm. |
| **Risk Analysis** | Systematic use of available information to identify hazards and to estimate 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. |
| **Risk Evaluation** | Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk. |
|  |  |
| **Safety** | Freedom from unacceptable risk. |
| **Severity** | Measure of the possible consequences of a hazard. |
| **Use Error** | User action or lack of user action while using the product that leads to a different result than that intended by the manufacturer or expected by the user. |

# **Procedure**

## Outlook Therapeutics (OTLK) risk management process includes Planning, Risk Analysis, Risk Evaluation, Risk Control, Evaluation of Overall Residual Risk, Risk Review, and Production and Post-Production Surveillance as shown in the flowchart below, see Figure 1.

## **Figure 1: Device Risk Management Flowchart**

## **A diagram of a risk management process Description automatically generated**

## Product specific project team is responsible for risk management activities.

## Risk management activities performed by vendors may follow vendors’ internal processes. OTLK may accept vendors’ risk management outputs as-is, leverage and reference vendor’s risk management outputs for internal use(s) or perform risk management activities independently from vendors’ risk management activities. Evaluation of vendors’ risk management outputs shall be performed by functional subject matter expert(s) and the acceptance of vendor’s risk management outputs shall be approved by subject matter expert(s) and Quality Assurance.

## Risk Management File

### A risk management file shall be created and maintained for each product or product family.

### Risk management file shall contain all documents generated per this SOP and product specific risk management plan.

### The risk management file shall provide traceability for each identified hazard to:

#### Risk analysis

#### Risk evaluation

#### Implementation and verification of the risk control measures

#### Results of the evaluation of the residual risks

## Planning

### Risk management activities shall be planned.

### A risk management plan shall be created for each product or product family and be part of the risk management file.

### The risk management plan shall include the following at minimum:

#### Scope of the planned risk management activities, identifying and describing the product and life cycle phases for which each element of the plan is applicable.

#### Assignment of responsibilities and authorities, including risk management activities performed by external partners.

#### Requirements for review of risk management activities. Risk management review shall be performed at appropriate phases as part of Design Review per SOP-0275 Design Control for Medical Devices and Combination Products

#### Criteria for risk acceptability.

#### A method to evaluate the overall residual risk, and criteria for acceptability of the overall residual risk.

#### Activities for verification of the implementation and effectiveness of risk control measures.

#### Activities related to the collection and review of relevant production and post-production information.

## Risk Analysis

### Outputs of risk analysis shall be part of the risk management file.

### Documentation of the conduct and results of risk analysis shall include :

#### Identification and description of the product that was analyzed.

#### Identification of the person(s) and organization who carried out the risk analysis.

#### Scope and date of the risk analysis.

### The intended use and reasonably foreseeable misuse of the product shall be considered and documented. The Intended Use Specification shall be created per SOP-0275: Design Control for Medical Devices and Combination Products and summarized or referenced by the risk analysis documentation.

### Product characteristics that could impact safety shall be identified.

### Hazards and hazardous situations associated with the product shall be identified based on the intended use as well as reasonably foreseeable misuse in both normal and fault conditions and documented in a Hazard Analysis.

### OTLK shall generate the risk analysis for the finished combination product. Additional risk analyses may be performed at the subassembly or subsystem level as appropriate. The combination product risk analysis shall incorporate information from risk management activities performed by external partners as appropriate.

### For each identified hazard situation, risk(s) shall be estimated using available information or data. Information for estimating risks may be obtained from:

#### Published standards

#### Scientific or technical investigations

#### Field data from similar products already in use, including publicly available reports of incidents

#### Usability testing

#### Clinical evidence

#### Results of relevant investigations or simulations

#### Expert opinion

### Risks shall be estimated based on severity of harm and probability of occurrence of harm and documented using Failure Modes and Effects Analysis (FMEA) or other appropriate methodology.

### Risks associated with the device design, usability, and manufacturing shall be evaluated (e.g., Design FMEA, Use FMEA, Process FMEA).

#### For products subject to review by FDA, usability risks shall be provided in Use-Related Risk Analysis (URRA) format per current FDA guidance.

### Harm severity shall be estimated based on the following scoring system, refer to Table 1. Severity rankings shall be approved by persons with appropriate medical expertise.

### **Table 1: Harm Severity Score**

| **Score** | **Severity Description** | **Harm Description** |
| --- | --- | --- |
| 1 | Negligible | Results in inconvenience or temporary discomfort. |
| 2 | Minor | Results in temporary injury or impairment not requiring medical or surgical intervention. |
| 3 | Major | Results in injury or impairment requiring medical or surgical intevertion. |
| 4 | Critical | Results in permanent impairment or irreversible injury. |
| 5 | Catastrophic | Results in death. |

### Product not meeting its intended use shall receive a harm severity score of 3 or higher depending on the indication(s) of the product.

### Probability of occurrence of harm shall be estimated based on the following scoring system, refer to Table 2:

### **Table 2: Probability of Occurrence of Harm Score**

| **Score** | **Qualitative Description** | **Qualitative Reference** | **Quantitative Reference1** |
| --- | --- | --- | --- |
| 1 | Improbable | Not expected to occur | Less than 1 in 1,000,000 |
| 2 | Remote | Has not occurred often | Between 1 in 100,000 to 1,000,000 |
| 3 | Occasional | Occurs occasionally | Between 1 in 10,000 to 100,000 |
| 4 | Probable | Likely to occur routinely | Between 1 in 1,000 to 10,000 |
| 5 | Frequent | Certain to occur routinely | More than 1 in 1,000 |

## ISO 14971



### Risk analyses shall be reviewed and updated when new information becomes available.

## Risk Evaluation

### Outputs of risk evaluation shall be documented in the applicable FMEA or other risk analysis document.

### Risks shall be evaluated based on their severity of harm and probability of occurrence of harm per the following risk evaluation matrix, refer to Table 4:

### **Table 4: Risk Evaluation Matrix**

|  | |  | | | | |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

|  | | **Severity** | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 |
| Occurrence of Harm | 5 |  |  |  |  |  |
| 4 |  |  |  |  |  |
| 3 |  |  |  |  |  |
| 2 |  |  |  |  |  |
| 1 |  |  |  |  |  |

#### Low (green) risks are not considered significant and are considered acceptable.

#### Moderate (yellow) risks require investigation of further risk controls. Justification shall be provided if risk control measure(s) is not High (red) risks are unacceptable and require mitigation.

|  | |  | | | | |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

## Risk Control

### Outputs of risk control shall be documented in the applicable FMEA or other risk analysis document.

### Risk control measures shall be investigated for all high and moderate risks. Risk control measures shall be considered and implemented in the priority order listed below:

#### Inherently safe design and manufacture

#### Protective measures in the product itself or in the manufacturing process

#### Information for safety and where appropriate, training to users

### Relevant standards should be applied as part of the risk control option analysis.

### The effects of risk control measures shall be reviewed with regard to whether:

#### New hazards or hazardous situations are introduced.

#### The estimated risks for previously identified hazardous situations are affected.

### Any new or increased risks shall be managed.

### After risk control measures are implemented and effectiveness is verified, risks can be re-evaluated per Section 6.7.

### Risk controls shall be implemented until risks are reduced as far as possible based on the current state of the art. Risks that cannot be reduced further are residual risks.

### If a residual risk is considered significant and further risk control is not practicable, benefit-risk analysis shall be performed to determine whether or not the benefits of intended use of the product outweigh this residual risk based on the current state of the art.

#### If the evidence does not support the conclusion that the benefits outweigh the residual risk, then product shall be modified, or the intended use of the product shall be modified. Otherwise, the risk is considered unacceptable.

### Completeness of risk control activities shall be reviewed to ensure that risks from all identified hazardous situations have been considered and all risk control activities are completed.

## Evaluation of Overall Residual Risk

### After risk control activities are complete, an evaluation of overall residual risk shall be performed, taking into account the contributions of all residual risks, in relation to the benefits of the intended use, using the method and acceptance criteria outlined in Section 6.7.

#### If the overall residual risk is judged acceptable, any significant residual risks shall be included in the accompanying documentation of the product.

#### If the overall residual risk is not judged acceptable in relation to the benefits of the intended use, additional risk control measures, modification of the product and/or the intended use of the product may be considered.

### A Risk Management Report shall document or reference the evaluation of the overall residual risk.

## Risk Management Review and Report

### Prior to clinical or commercial distribution of the product, the execution of risk management activities per this SOP and the product specific risk management plan shall be reviewed and documented in a Risk Management Report. The review shall ensure that:

#### This SOP and risk management plan have been appropriately followed and executed.

#### The overall residual risk is acceptable.

#### Appropriate methods are in place to collect and review information in the production and post-production phases.

### At a minimum, Senior Management (or designee), the Head of Quality Assurance, and Clincal representative with appropriate medical expertise shall approve the risk management report.

## Production and Post-Production Activities

### The following information shall be actively collected and reviewed:

#### Information generated during the production and monitoring of the production process.

#### Information generated by the user.

#### Information generated by the supply chain.

#### Publicly available information.

#### Information related to the generally acknowledged state of the art.

### At least once per year, the information collected from section 6.11.1 shall be reviewed for possible relevance to safety, especially whether:

#### Previously unrecognized hazards or hazardous situations are present.

#### An estimated risk arising from a hazardous situation is no longer acceptable.

#### The overall residual risk is no longer acceptable in relation to the benefits of the intended use.

#### The generally acknowledged state of the art has changed.

### The results of the review shall be recorded in the risk management file.

### If the collected information is determined to be relevant to safety, the following actions shall be taken:

#### Concerning the particular product:

##### Risk management file shall be reviewed to determine if reassessment of risks and/or assessment of new risks is necessary.

##### If a residual risk is no longer acceptable, the impact on previously implemented risk control measures shall be evaluated and should be considered as an input for modification of the product.

##### Any needed actions regarding the product on the market should be considered.

##### Any decisions and actions shall be recorded in the risk management file.

#### Concerning the risk management process:

##### The impact on previous risk management activities shall be evaluated.

##### The results of the evaluation shall be considered as an input for the review of the suitability of the risk management process by senior management.

## Risk Communication

### Risk communication is the sharing of information about risk and risk management to relevant parties and is an integrated part of the risk management process. Product-specific risk communication may be performed throughout the risk management process.

1. **Attachments and Associated Forms**

|  |  |  |
| --- | --- | --- |
| **Attachment Number** | **Document Number** | **Description or Document Name/Title** |
| N/A | N/A | N/A |

1. **Change History**

|  |  |
| --- | --- |
| **Revision** | **Change Description(s)** |
| 00 | Per CC-24-011:  Initial Issuance of Document. |
| **Author** |
| E. Chan |

**REQUIRED APPROVAL SIGNATURES**

|  |
| --- |
| **AUTHOR** |
| Edwin Chan, Director, Drug Product Operations |
| **OWNER** |
| Chris Yonan, Senior Vice President, Technical Operations |
| **REGULATORY** |
| Pam Monterola, Senior Director, Regulatory Affairs |
| **QUALITY ASSURANCE APPROVAL** |
| George Bitar, Vice President, Quality Assurance |