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Implantable Electrical Stimulator for Parkinson's Tremor

Final Report

By

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1. Overview

The device that will be evaluated is the Implanted Electrical Stimulator for Parkinsonian Tremor (IESPT). This device consists of components as follows:

- Electrode and stimulating leads which are implanted in the target area that injects electrical impulses to regulate abnormal brain impulses.
- Pulse generator implanted near the clavicle which generates electrical impulses and is connected to the electrode through extension leads.
- Handheld remote used by the patient for minor adjustments of the pulse generator programming or activity.
- Charger which periodically replenishes the battery of the pulse generator through radio frequency charging.
- Trademark software which allows clinicians to program the settings of the pulse generator through efficacy analysis and input/feedback by the patient.

This device is intended to be used in alleviating symptoms of moderate to advance levodopa-responsive Parkinson's disease by means of bilateral stimulation of the subthalamic nucleus for patients that do not find adequate treatment of their symptoms through medications. For this device to achieve market

authorization in China, the NMPA will act as the notified body. The following report will address the Technical Documentation required for this process.

2. Risk Assessment

Medical devices inherently carry residual risk which will always be present despite the extent of risk control performed. Provided the potential benefits can outweigh any remaining risk, the device will have a net positive impact on the health of the public. A risk assessment will be conducted for the IESPT with a brief section evaluating possible risk control actions for risks that are deemed unacceptable through the assessment. Prior to completing the risk assessment, ISO/TR 24971:2020 chapter 5 indicates that it is crucial that the intended use including patient population and device characteristics are acknowledged, and that foreseeable misuse of the medical device within sensible reason is recognized. The characteristics of the device and the patient population are as follows:

- The device is intended to reduce moderate to advanced levodopa-responsive Parkinson's disease for patients with symptoms that are not adequately treated with medication.
- Patient-device interaction: permanent contact with subcutaneous tissue and brain tissue.
- Operating principle: stimulates the subthalamic nucleus through electrical impulses.
- Use environment: at home and daily use.
- Patient population: Parkinson's patients around the age of 60 with possible dementia [1].

Several potential misuses that can be recognized are as follows:

- Lack of patient commitment to the long-term programming of the electrical impulse settings.
- Mishandling of the remote control and its settings for the pulse generator.

Based on this information, foreseeable hazards that may be associated with the IESPT can be derived and can be seen in the table below, considering both normal and faulty conditions:

Risk No.	**Hazard**	**Foreseeable sequence of events**	**Hazardous situations**	**Harm**
R_1	Mechanical Failure (Leads fracturing) [2,9,13]	1. Inadequate lead placement and fixation 2. Rotation of lead causes deformation beyond material capability	Non-functioning medical device	Symptoms progression
R_2	Bacteria (infection)	1. Inadequate sterilization of components/tools prior to operation 1. Lack of perioperative antibiotics given to patient	Bacteria introduced around the impacted area	Organ damage Removal of leads and pulse generators
R_3	Implant Repositioning (Lead Migration) [3,9]	1. Inadequate lead fixation on the brain 2. Jerk/tugging of lead cables due to head movement 1. Brain movement post-surgery due to swelling	Optimal position not satisfied	Symptoms progression
R_4	Abrasion (friction on tissue) [4]	1. Inadequate fixation of the lead cord under the skin during surgery 2. Frequent movement around the lead cords	Lead cord rubbing against tissue	Subcutaneous Bleeding and erosion of epidermis
R_5	Electric/Magnetic Fields (Electromagnetic interference) [5,12]	1. MRI performed irrespective of the manufacturer's criteria 1. Patient close in proximity to high electromagnetic fields density	Electromagnetic induction/heating	Sensation of heat or shock Involuntary movement
R_6	Functionality (Ineffective Programming)	1. Inaccurate adjustment to the programming due to inaccurate verbal input of patient 1. Patient does not commit to the periodic visit to the clinician to adjust programming	Speech, gait, and balance complications	Fall injuries [6]
R_7	Depleted energy source	1. Patient forgot to conduct periodical recharge of pulse generator	Inactive medical device	Temporary symptoms progression

Table 1. foreseeable hazard and its foreseeable sequence of events resulting in hazardous situations and potential harm based on Annex C.2 of ISO14971:2019 for hazard identification

It can be argued that the intrinsic aspect of applying electrical impulses to the subthalamic nucleus itself is a hazardous situation. But for this case, it can be assumed that this electric stimulation can and will

be consistently done in a controlled manner which only results in the appropriate response, thus electric shock to the patient will not be considered as a hazard.

For risk estimation of the potential risks above, semi-quantifiable risk estimations can be done through evaluation of available data such as clinical studies, research and case reports. For those that cannot be sufficiently quantifiably estimated such as the severity of these risks, a qualitative method based on expert opinions can be used as a conservative estimate that may give appropriate indication of the risks involved.

Descriptor of occurrence	Probability range (% of conducted study)
Frequent	> 6%
Probable	<= 6%
Occasional	<= 4%
Remote	<= 2%
Improbable	<= 0.1%

Descriptor of severity	Severity description
Critical	Result in patient death
Urgent	Result in life threatening injury urgently requiring professional medical intervention
Moderate	Result in injury requiring professional medical intervention or permanent disablement of a body function
Minor	Result in temporary injury not requiring professional medical intervention or quality of life/function reduction
Negligible	Result in minor inconvenience or reduced efficacy

Table 2. semi-quantitative probability occurrence [2,7,10] and qualitative severity level

For risks such as R_6, the probability of occurrence is hard to determine since it is a case-to-case basis and is highly dependent on the qualification of the technician reprogramming the pulse generator. For this purpose, its risk may be evaluated based on the severity of harm alone based on ISO/TR 24971:2020. In this case, considering the patient population of the elderly, falling related injuries can be considered moderate.

	Negligible	Minor	Moderate	Urgent	Critical
Frequent				R_2	
Probable		R_1, R_3			
Occasional			R_4		
Remote	R_7		R_5		
Improbable					

	Area 1: Unacceptable risk
	Area 2: Investigate risk reduction
	Area 3: Acceptable risk

Table 3. Risk evaluation matrix

The risk acceptability matrix is based on the estimated risk-benefit comparison from the perspective of the patient. Research shows that the most frequent death post-DBS surgery is due to Parkinson's induced pneumonia and worsening of the disease [8]. Since the number of deaths through this inherent risk is significantly smaller than the deaths through the medical condition, this decreases the region of unacceptable risk to the more-frequent moderate to critical severities. The remaining risks outside of the unacceptable region should be investigated for further mitigations until reduction to an acceptable residual risk amount, which would be in the low occurrence probability with very minor severity levels.

Additionally, although the frequency and severity would put R_2 (infection) in an unacceptable risk category, this risk is inherently present in all implantable medical devices due to the nature of the installment procedure. Surgical operation based risks such as infection will be disregarded in the

mitigation as it is a standard operational procedure to conduct sterilization on surgery tools and equipment. For the risks that require further investigation of risk control, a brief technical (irrespective of cost) risk control measures are shown below:

Hazard	Inherent Safe Design	Protective Measure	Information for Safety
R_1 – Mechanical Failure	Ductile and flexible lead cable material	Indications for implanting the connectors posterior and superior to the ear [9]	Warning against the activity/motion that may cause lead fracture
R_3 – Implant Repositioning	Anchors integrated in the leads and electrode tips	Fixation of lead cables to biological structures (bones and muscles) [11]	Inform patient of potential lead migration and recommend follow up brain imaging to ensure accurate position
R_4 – Abrasion	Smooth and low resistance lead cable casing	Buffering the skin-device interface with surgical flap or acellular dermal matrix [4]	Warning against activity/motion that may increase likelihood of abrasion
R_5 – Electric / Magnetic fields	Use of a fiber optic-based lead cable [13]	Filter out frequency bands of MRI [12]	Precaution against being around sources of electromagnetic fields
R_6 – Ineffective Programming	Minimal adjustments in software with presets available	Training provided to clinician regarding operation of the trademark software	Inform clinician regarding the influence of mis-programming to the efficacy of the device

Table 4. Risk mitigation for risks in area 2 of the risk evaluation matrix, including inherent safe designs, protective measures, and information for safety

3. Quality Systems

An appropriate Quality System must be in place to maintain NMPA approval. China's GMP provides relevant standards which must be implemented [14, 19]. These requirements are similar to ISO13485, though there are some major differences [17].

ISO 13485 provides standards for the quality management system, management responsibility, resource management, product realisation and measurement, analysis and improvement, and will be used as a reference for this section. Notable updates to the NMPA Quality Systems guide in 2020 echoed these areas by providing guidelines for internal staff, work environment and equipment, documents and records controls, design and development, procurement, production and quality control.

ISO 13485 mandates clearly defined roles and responsibilities and appropriate training, qualifications and skills for each of these roles. These should be well-established and recorded. There should also be sufficient authority and independence within the organization for each role to fulfil their intended responsibilities appropriately [22, 23]. Some roles to consider would include authorised representatives, distributors and manufacturers [21]. China's QMS was updated in 2023 to include strengthened responsibilities for personnel in key positions in quality or safety roles for device production or operating enterprises, and to detail their expected responsibilities and qualifications (including degree and experience level) [20]. Guarantee mechanisms should also be provided to ensure performance of duties including mandatory quality and management scheduling and a risk consultation system, formulation of quality job descriptions, training and continued education and a due diligence exemption system as well as a reward/sanction system for relevant personnel [20].

Controlled processes should be implemented throughout all stages of product realization including the determination of requirements, the design and development process and production [23]. Design control is a key area addressed in ISO 13485 and mandates the use of the V-model: design inputs, derived from user needs, are used to verify design outputs; and final medical devices resulting from design outputs are validated against user needs [22, 23]. Additionally, reviews should be performed at every stage [21, 23]. A design and development file (Technical Documentation) should demonstrate conformity of the design with any requirements or plans and should record any changes [22, 23]. Product and Process Controls must be implemented to ensure the manufacturing process is capable of consistently making products which meet the needs and requirements outlined in the product specification. This can be achieved either through verification, where inspection is completed for all specifications, or a Process Validation Study. A hybrid system may also be implemented. A Process Validation Study should first use a process failure mode and effects analysis to identify the critical process parameter settings. Following this, the IQ, OQ and PQ protocols should be implemented [22].

The NMPA requires a one-time on-site QMS audit for both foreign and domestic manufacturers for registration certification and a second GMP audit prior to obtaining a manufacturing license. Local manufacturers must complete this audit annually. The audits require an on-site audit checklist and company meetings [19]. An important aspect of the QMS is the implementation of measurement, analysis and improvement systems. China has strong Post Market Surveillance requirements which cannot be substituted with other international approvals such as the CE mark. In 2018, China's Decree No. 1 increased strictness and timeline requirements for PMS and implemented more severe penalties for violations.

As a part of China's PMS mandates, the Periodic Risk Evaluation Report (PRER) is a key requirement. The PRER is comparable to the EU PSUR and is based on ISO 14971 [17]. Risk Analysis is generally a strict requirement of a QMS system across all jurisdictions [14]. The key purpose of this report is to describe the likelihood, consequences and tolerances of possible risks of using the device [15]. It includes documentation of passive vigilance and active post market surveillance [16]. For a Class III device, the PRER should be submitted online via a Chinese agent to the NMPA annually for the first five years, dating from the product certificate approval date, within 60 days of the expiry period of the previous PRER submission (1 year) [15, 16]. After five years, when the product certificate is renewed, the PRER should be filed as a record on the renewal date (i.e., once per five years). Overseas registrants may submit the report in English, but a Chinese translation is required [16, 17].

The NMPA outlines the required content of the PRER. Key inclusions are the global marketing history, vigilance summary, literature evaluation and risk analysis related to adverse effects, adverse events (local and global) and recalls (local and global) [15, 16, 17]. Additionally, risk control measures, changes, revisions or re-evaluations due to AEs or other safety concerns and relevant literature and risk information relating to risks examined in similar products should be included [15, 16]. As- for this product, the multiple components which may have been certified individually work cohesively as a system, a single report for the multiple product certificates is viable [16].

Adverse events (AEs) are harmful events which have occurred during normal use of approved medical devices and have caused or may cause human injury [14]. Global and local AEs- in particular, serious Global AEs (SAEs) should be reported [17]. Global AEs should be submitted by a legal representative within China. The NMPA outlines strict deadlines and requirements for reporting AEs and ensuing actions (such as recalls). These requirements vary for overseas manufacturers and depending on the severity and extent of the event [16, 17, 18]. For implantable devices the registration holder should keep any AE records permanently, regardless of other countries' requirements [17]. Similar to the FDA's Maude Database, there is a database (confidential to the manufacturer) for AE reporting to the NMPA. A site master file should be maintained by manufacturers and should include information on QMS, personnel, manufacturing, facility and process, equipment, document control, material and storage, quality control, sales, distribution, defects and recalls, internal audits and R and D, and Document authenticity statements [17].

Inspections form a critical part of QMS regulation to ensure compliance with Chinese regulations, details of which are outlined in various decrees and will vary for overseas based manufacturers [14, 17]. Inspections are conducted by the NMPA in the first quarter of the year and include risk evaluation and random selection of medical devices, R&D sites and manufacturing sites [14, 18, 19]. An auditing interval is not specified, though high-risk (e.g., implantable) and questionable quality devices have a higher chance of selection [17]. A local representative in China should be designated by any foreign manufacturers to co-operate with the Chinese health authorities for these random inspections [19]. The General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ) also carries out safety, certification, and inspection of certain medical devices to ensure adherence to quality standards in addition to the NMPA [19]. China does not currently have an MDSAP program in place [17].

4. Standards

The NMPA announced in 2018 that a revision of its standards would include standards for manufacture, performance testing, biological evaluation, non-clinical standards and quality systems of medical

devices. Where national standards do not exist then China's Decree 680 mandates that industry recommended standards be met. While China does provide some of its own standards, the below table outlines the relevant International Standards for this device.

ISO 13485	Medical devices — Quality management systems — Requirements for regulatory purposes
ISO 14971	Medical devices — Application of risk management to medical devices
ISO/TR 24971	Medical devices — Guidance on the application of ISO 14971
ISO 62366-1	Medical devices - Part 1: Application of usability engineering to medical devices
IEC 62304	Medical device software — Software life cycle processes
ISO 11135	Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices
ISO 14155	Clinical investigation of medical devices for human subjects — Good clinical practice
ISO 20916	In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice
IEC 80001-1	Safety, effectiveness and security in the implementation and use for connected medical devices or connected health software — Part 1: Application of risk management
ISO 10-993	Biological evaluation of medical devices
ISO 14708-1	Implants for surgery — Active implantable medical devices — Part 1: General requirements for safety, marking and for information to be provided by the manufacturer
ISO 14708-3	Implants for surgery - Active implantable medical devices - Part 3: Implantable neurostimulators
ISO 15194	In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Requirements for certified reference materials and the content of supporting documentation
ISO 16142	Medical devices — Recognized essential principles of safety and performance of medical devices
ISO 17664-1	Processing of health care products — Information to be provided by the medical device manufacturer for the processing of medical devices — Part 1: Critical and semi-critical medical devices
ISO 20417	Medical devices — Information to be supplied by the manufacturer
ISO 22442-1	Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management
IEC 60601-1	Medical electrical equipment – Part 1: General requirements for basic safety and essential performance
IEC 60601-2-10	Medical electrical equipment – Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators

Table 5. Table of Standards

5. Biocompatibility Approach

Biocompatibility involves the interaction between the materials and the system for which, prior to market release, a device must be assessed for two components: the material response and the host response. The material response is reflected by how the material components of the device interact with the living system, whilst the host response refers to how the living system reacts to the biomaterial.

To ensure safety, the device is to be constructed with biocompatible materials ensuring that no adverse reactions can occur such as the effects listed in Table 6.

Material response	**Host response**
• Swelling (adsorption of fluid) • Leaching (Fine material particles leaching into surrounding fluid) • Degradation • Corrosion • Wear & Tear	• Haemolysis/coagulation • Inflammation • Wound healing • Tissue remodelling • Hypersensitivity • Rejection • Carcinogenesis • Genotoxicity

Table 6. Host and material responses assessed during biocompatibility tests

For this device, materials that are used in the IESPT follow those used in currently marketed DBS systems as well as medically used electrodes, consisting of titanium, silicone, and various polymers. Despite the materials having known examples existing in currently graded medical devices in China, biocompatibility tests are still required to ensure the device meets ISO 10993 biocompatibility standards [30]. The electrodes in the implantable electrical stimulator are a major component of the device and deliver degrees of electrical stimulation to the brain. They are thus critical to the safety and effectiveness of the device. Consequently, aside from assessment of the material used, the electrodes' shape and size are also essential factors that require biocompatibility assessment. This is to conclude whether the inherent design of the electrical components will harm any surrounding tissue and hence incur strategies to minimise or eliminate such adverse effects on the human body. To conduct these examinations, tests must be conducted in vitro and in vivo. In vitro tests are critical to assess primarily cytotoxicity and how the cells of the living system will react when interacting with the implanted material. These tests

are conducted in a controlled laboratory environment and can determine factors such as device toxicity, assessment of cell damage, interaction between material and immune response and review for harmful by-products of the device and their effects to the system [312 32].

Additionally, in-vivo tests can create further evaluation on biocompatibility to the host system by performing tests on animal subjects [33]. These tests provide a more intricate and realistic environment to allow for assessment of the physiological effects the implanted electrode may have on the host system as well as any other biocompatibility measures as animals have comparable responses to humans. To ensure the implantable electrical stimulator successfully reduces potential harm to the host system, the following biocompatibility approach is followed.

Test Type	Test	Description
In Vitro	Cytotoxicity/ ISO 10993-5	Incubation of cultured cells that contact the device and/or extracts of a device to assess potential cell death/damage
	Hemocompatibility/ ISO 10993-4	General interactions of the device with blood, assessing factors such as platelet adhesion, thrombin generation, and haemolysis assays performed using blood or blood components.
In Vivo	Sensitisation/ ISO 10993-10	Procedure to assessment if the material or material constituents influence skin irritation or sensitisation. Test examples are the Guinea Pig Maximization Test (GPMT) and Local Lymph Node Assay (LLNA) to determine allergic reaction of the electrode after implantation.
	Irritation/ ISO 10993-10	Tests performed, usually in conjunction with sensitisation tests to assess irritation to the skin. Special irritation tests can be performed to assess irritation in areas other than the skin. Intracutaneous tests, such as the rabbit skin irritation test, are an example of a test that can be used to assess irritation or inflammation of an implanted electrode.
	Implantation/ ISO 10993-6	Assesses the local effects of implantation of the electrode in which it is surgically implanted into an animal and the effects are measured over a time period.
	Chronic toxicity tests/ ISO 10993-3	Tests that review the potential irreversible biological effects that arise from exposure of the electrode components to the host system such as genotoxicity, carcinogenicity, and reproductive toxicity. These tests are performed on animals over an extended period of time to review long term effects.

Table 7. Biocompatibility approach of an implanted electrical stimulator for Parkinson's disease

6. Clinical Trials

To ensure safety and effectiveness of the IESPT, rigorous testing must be conducted through the form of clinical trials. As aforementioned, the device is classified as a Class III device in China, meaning clinical trial data is mandatory and thus the device must be evaluated for safety, efficacy, and tolerability through 3 trial phases. The trials must be conducted in compliance with ISO 14155 Good Clinical Practice (GCP) [29] to ensure the tests can be recognised as well as ensure safety practices throughout the completed trials. Clinical trials are regulated by the NMPA, for which the NMPA require that the device undergo extensive clinical trials to ensure safety and efficacy before marketing in China, through which Phase I identifies the devices maximum tolerability or dosage, Phase II determines optimal dose, and Phase III demonstrating efficacy within a larger cohort of patients [31].

Before the clinical trial can begin, the safety and effectiveness of the IESPT must be established prior to any applications for testing through systemic analysis of preclinical research on existing data and/or predicate devices. Once this process is conducted and submitted for review by a committee at the NMPA, an application for clinical trial approval is submitted by the sponsor including a dossier containing the preclinical data, device components and specifications, manufacturing processes and a completed clinical trial protocol [32, 33]. Once the prospected documentation is assessed, there are a few steps that are required before clinical trial protocol approval. The steps that are necessary to advance the application are a conducted trial site evaluation and selection, protocol discussion meeting with the NMPA, and consequent review and approval by the Institutional Review Board (IRB) and Human Genetic Resources Administration of China (HGRAC) [32].

It is advised that agencies such as China Med Devices help select the designated facilities to conduct the clinical trial protocol from a catalogue of pre-approved locations [34] to increase efficiency and reduce the trial application process. This step is then followed by a discussion meeting organised by the

NMPA in which the dossier containing the clinical trial protocol is reviewed to ensure that the protocol design strictly follows the Medical Device Clinical Trial Design Guidelines as well as the Clinical Trials Guideline for In Vitro Diagnostic Reagents [35]. Once the dossier is reviewed and approved by the IRB, the device must then be registered with the HGRAC otherwise will be at risk of having the clinical trial protocol rejected. During these steps, the NMPA may ask for further information or continual revisions of the submitted documents until approval is given by the respective parties [32].

After the clinical trial protocol is approved and signed, it is permitted to be conducted after site initiation and patient recruitment within three phases, with a fourth phase being designated towards post market surveillance. The phases of the clinical trial process are conducted as with respect to Good Clinical Practices (GCP) as follows [30]:

Phases:
Phase I: typically involve testing within a small population of patients (10-30 patients) in which evaluations on the safety and tolerability of the IESPT are made. To assess these factors, the trial is conducted to monitor adverse effects or complications that are caused by the implantation process as well as a primary goal of identifying the highest tolerated dosage of the device that doesn't result in adverse events to the subjected patients.
Phase II: the primary focus of these tests is to determine the optimal stimulation parameters of electrical stimulation required for this device and to be tested on a larger population of several hundred patients. The concept of determination of optimal dosage relates to the level of electrical stimulation that provides the most effective feedback with minimal adverse event drawbacks.
Phase III: final phase of the clinical trial focuses on establishing safety of the device. Patients are monitored for any adverse effects with respect to the device, such as infections, device malfunctions, and complications with respect to the implantation procedure. This is then compared to existing treatments to compare the efficacy of the new device and can involve several hundred to thousands of patients.

Table 8. Phases of the Clinical Trials

Throughout the clinical trial protocol, data is to be collected, analysed, and managed in compliance with correct protocols identified by the NMPA [36], with incorrect data recording potentially leading to a request for further clinical evidence, increasing the time to market, or rejection of the submitted data. The data can be, at any point in the clinical trial stage, audited by a selected professional. Once all the trials are completed, the sponsor of the device is to submit a comprehensive report to the NMPA for review and for determination on whether the device meets safety and efficacy requirements to be marketed against the existing methods of Parkinson's disease treatment.

If the IESPT is to be approved and successfully marketed, the clinical trial protocol is to be extended into a phase IV that involves post-market surveillance in which the NMPA requires the sponsor to conduct further ongoing monitoring and reporting of the safety and efficacy of the device during post-market release. These technical documents are outlined in section 7 and involve collection of real-world data and adverse event reporting to which the data can be audited at any point in time [36x. Consequently, the combined process of the clinical trials can last up to 3-5 years to conduct, varying depending on trial design and regulatory requirements, surmounting several million in costs to run the effective procedures. Despite the extensive time and costs required to perform these clinical trials, for an implantable electrical stimulator for Parkinson's disease, these clinical trial processes are fundamental and required to ensure safety and efficacy of the device prior to product approval in China for market release.

7. Technical Documentation

The technical documents submission required by the NMPA for the electrical stimulator for Parkinson's contains multiple chapters - Regional Administrative, Submission Context, Non-Clinical Evidence, Clinical Evidence, Labelling and Promotional Material, Quality Management System Procedures and Quality Management System Device Specific Information. The following section briefly outlines the contents and noteworthy considerations of each chapter.

Chapter 1: Regional Administrative

In this section, medical device manufacturers are required to introduce their device. The NMPA requires that the attached documents should be signed by applicants and their authorised representative. This section should also include an application form consisting of administrative information, which should

be filled out and submitted online. Next, a table listing each variant, mode, configuration or component that is to be included in the device for submission should be included in a tabular format and should state a description of these components. The next component of this section includes a summary of the Quality Management System and Other Regulatory Certificates. The NMPA requires imported medical device applicants to provide supporting documents of marketing authorisation, or a certificate of the product issued by the applicant's home country or where the manufacturing headquarters are located- a Certificate of Free Sales (CFS). A document describing Pre-Submission Correspondence and Previous Regulator Interactions is also required. This document must list prior submissions where regulator feedback was provided OR affirmatively state that there have been no prior submissions interactions for the specific device. For the NMPA, this includes an innovative medical device communication record.

The NMPA also requires a Truthful and Accurate Statement. This document must declare the authenticity of submitted data and is issued by the corresponding agent. This is followed by the Declaration of Conformity. The NMPA requires that for registration of a medical device, a declaration that the product complies with the classification requirements of the Medical Device Classification Rules, current national standards, industrial standards, and an up-to-standard list. In addition, a Letter of Authorisation providing evidence of power of attorney of the foreign applicant for designation in China is required. Copies of a letter of commitment and business license or a copy of the organisation registration certificate of the agent is also required by the NMPA.

Chapter 2: Submission Context

Here, a general summary of the submission including device type, submission type, general purpose, high-level summary of key supporting evidence, high level background information and unusual details are presented. For the NMPA specifically, the applicant is required to describe the management category and criteria for determining the classification code. The General Description of the device includes the previously mentioned components as well as many more. These include details on where it is to be used and how it works, product specifications, a list of accessories intended to be used in combination with the device, indication of any other medical devices or general product to be used in combination with the device and components or accessories that can be sold separately.

This section should include a description of the features/operating modes that enable the device to be used for its intended use and a brief description of the underlying science/technology, design and theoretical principles supporting the device function. Since the IESPT is a device with many components, the NMPA requires a description of how the components relate and function together. An identification of software and firmware and their role are also to be described. The product specification section should detail the physical characteristics of the device, its features and operating modes, input specifications (electrical power requirements, settings, voltage limits etc.), output (range and type of energy delivered), performance characteristics and a summary of the differences in specifications of the variants (if applicable). Engineering diagrams including prints and schematics of the device must be provided as a separate file within the submission.

As part of this section, the NMPA also requires a description of the device packaging, history of development, references and comparisons to similar and/or previous generations of the device, indications for use, purpose and contradictions, intended environment and settings for use. Finally, any other submission context information that may be important to the submission but doesn't fit in any other headings of this chapter may be provided.

Chapter 3: Non-Clinical Evidence

This chapter should include a risk management, essential principles checklist, list of standards and guidance documents and a declaration or certification of conformity. The NMPA specifically requires a declaration that the device complies with the current national standards and industrial standards. The risk management should summarise the identified risks during the risk analysis process and how

these risks have been contained to an acceptable level. The results should provide a conclusion with evidence that remaining risks are acceptable when compared to the benefits.

The risk management should also include details on a variety of electrical and mechanical systems and environmental protection as well as biocompatibility and toxicology evaluations among other tests. The list of standard and guidance documents should include all the NMPA registration standards that have been referred to. For the non-clinical studies performed, a summary of the non-clinical evidence that falls within this category, a discussion of the non-clinical testing considered and support for their selection of verification and validation studies conducted must be submitted. A discussion to support why the evidence presented is enough to support the application should also be submitted. In addition, a summary of the studies performed and a full report of each of them should be submitted.

Chapter 4: Clinical Evidence

For Class III devices such as the IESPT, the NMPA requires that the devices should be submitted with clinical evaluation data. This section is also to include a full Clinical Evaluation Report (CER) which includes device-specific clinical trials, trial description protocol number and date of initiation, clinical trial report and a clinical literature review. The NMPA specifically requires that the clinical trial report should align with the Medical Device Registration Regulations, the Medical Device Clinical Trial Quality Management Specifications and other relevant clinical guidelines. It should also include elements such as the investigational study protocol, protocol changes, description of patients, data quality assurance and an analysis of results.

Chapter 5: Labelling and Promotional Material

In this section the product/package labels must be provided. The NMPA specifically requires the applicant to provide label samples of minimum sales unit that conform to the Provision on the Management of Instruction and Labels of Medical devices. As part of the labelling and packaging, Instructions for Use (IFU) must be included in the package. The NMPA requires the provided IFU to conform to Provisions on the Management of Instructions and Labels of Medical Devices. The applicant is also required to provide details on the best case of e - labelling for medical devices with standalone software and details of this in the risk management. Also, a description of the procedure and operations on providing IFUs when requested. In addition, labelling directed at physicians (surgical manual) and patients should be included – that is, informational material written to be comprehended by a patient or a caregiver. A technical/operator manual should also be included, focusing on the proper use and maintenance of the device.

Chapter 6A: Quality Management System (QMS) Procedures

This section should include general manufacturing information which includes address and contact information for all sites where the device and its components are manufactured. The NMPA requires that, for a change registration, if the manufacturing site of the imported medical device changes, a comparison table and description is provided. Quality management system procedures that document the management commitment to the establishment and maintenance of the QMS must be included. In addition, procedures that document the adequate provision of resources to implement and maintain the QMS including human resources, infrastructure and work environment should also be included – this can be summarised in the resource management procedures. More requirements include documentation on product realisation procedures, design and development procedures, purchasing procedures, production and service control procedures, control of monitoring and measuring devices procedures and QMS measurement analysis and improvement procedures.

Chapter 6B: Quality Management System Device Specific Information

This section should include documentation specific to the IESPT that results from the high level QMS procedures for establishing and maintaining the quality manual, quality policy, quality objects and control of documents. Other information to be included is resource management information, device

specific quality plan, product realisation information, QMS measurement analysis and improvement information. Any other device specific QMS information can also be included here.

The technical documentation required by the NMPA for the electrical stimulator for Parkinson's is rigorous and extensive, however it ensures a transparent and secure process to safely allow a medical device into the market.

8. References

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