コンピュータ外科における役割と期待

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1. 承認審査の問題点、ガイドラインの必要性

従来、薬事審査について開発サイドでは承認に必要な要件は、断片情報を基にこうあるであろうと推察されていた。したがって、情報の共有化が行われず知の情報は暗黙知のまま伝達されてきた。また、開発サイドと審査サイドが同じ言葉を話しているという大いなる誤解が存在していた。本来は、断片情報を統合して全体像を把握することが必要であったが、それがなされないまま過ぎていたのが現状だった。群盲象をなでるが如く全体像を完全に把握されること無く、目指すべきゴールが違うことも気づかずに過ぎてきた。その間に競争力は失われたのであった。失われた10年いやもっと永いかもしれない。薬事審査の問題は、開発サイド、審査サイドお互いに不満を持ちながらシステムの問題に起因することが解っていながら、ヒューマンファクターをも問題にするという、ここ数年の医療安全で議論され、問われていることが延々となされてきたのである。

日本のロボットは、産業用と基礎研究で世界一だが手術ロボットの製品化が出遅れたことは、異論の無いことだと思う。未だに薬事承認を受けたものもないことも事実である。特に問題なのは臨床研究が進まずユーザーたる医師や医療機関のノウハウが一向に向上しないことである。ロボット関連のガイドラインができれば、医療関係者が待ち望んだインパクトのある応用が待っていることは間違いない。

2. 期待するガイドライン内容

ガイドラインには開発するサイドも承認するサイドも前例が無い要件をクリアするために最低限必要な事項を明示するマトリックスを明瞭で且つ透明性を持って提示することを期待する。手術ロボットなどの処置具では、それを使う医師の技量が治療結果を決定的に左右することを肝に銘じるべきである。そのような機器の有効性を機器のみで担保しようとすることは意味を成さない。よって、ユーザー層が普通に期待するレベルの安全を担保することで割り切るべきと考える。どんな技量の医師がユーザー層になるかについては慎重な検討が必要だろう。その普及は市場が判断する。

3. あるべきガイドライン検討体制

開発と審査のガイドラインが同じマトリックスの上で、議論されることが必須である。最低限必要な要件とクリアすべき最低限の基準が、同じ土俵上で開発サイドの視点と審査サイドの視点で議論されなければ意味が無い。一物一価であり、二価であってはならない。

4. 革新的な処置具・治療器具における有効性とリスク

一度投与したら、回収不能な条件にある薬物と、不調なら即座に回収でき従来の医療システムに代替できる機器・システムが同じ土俵で論じられるべきでは無い。リスク評価に際して、コンバージョンを有効なリスクコントロールの方法の一つと認めるべきである。また、多くの場合において革新的な医療機器が最初から全ての医師をユーザーとしないことも留意すべきである。革新的医療機器・システムの初期の有効性は、それを使いこなせる技量のある医師が使った場合に従来のものとおおむね同等以上であればよいという基準で十分である。医療は、一握りの開拓者が機器も含めて革新的な試みを少しずつ前進させることで進歩してきた。そのような医師が最新の医療機器を使ってより良い治療結果を挙げようとすることを制度が阻んではならない。最後に、革新的医療機器・システムの有効性は機器・システムの進展とユーザー層の技量水準向上により、時々刻々と変化することは必定である。それに応じて改良型が使えるようにするための努力やインセンティブの付与に行政、業界、学界が一丸になって取り組まないと中古品市場が増えるだけである。

組織工学における役割と期待

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再生医療に供する組織工学製品は、治験申請の前に独立行政法人医薬品医療機器総合機構（以下機構）の確認申請を必要としている。厚生労働省の承認を受けている組織工学製品が1点もない日本の現状では、他家由来細胞を用いた製品の認可はきわめて難しいと考えられており、これまでにこれらの申請をおこなった技術はすべて自己細胞を用いるものである。

しかし、患者自己細胞を材料として、これを培養して最終製品を製造することは、有機合成を用いて最終製品としての薬を製造する場合とは大きく異なる点が少なくないため、従来の薬事法では十分に対処できないのではとの疑問の声も聞こえている。たとえば、有機合成に供する原材料は現在の分析化学の水準をもってすれば容易に基準化でき、受け入れ基準に満たない原材料を拒否することには何の問題もない。しかし、遺伝的背景や年齢、病歴等にもとづく個々の患者の違いを十分に許容しうるかたちで受け入れ基準をもうけることは容易ではない。また万が一この受け入れ基準に満たない場合、患者を拒否するという発想がどこまで正しいのかにも議論の余地がある。

たとえ一例であっても組織工学技術を用いた再生医療をヒト患者に施す際には必ずFDAの承認が必要な欧米とは異なり、日本では薬事法の外にあるという解釈のもとに少数例であればIRBの承認により臨床研究として施行が可能となっている。このため厚労省や機構は、組織工学製品の申請に対し、臨床研究データが存在するという前提で議論を進める傾向がありうることを否定できるであろうか。この日本特有の枠組みの是非については、近く厚生科学審議会科学技術部会から提出される「ヒト幹細胞治療臨床研究指針」[1]でも議論されているようである。欧米の動向も合わせ、組織工学製品を取り巻く環境は、この数年で大きく変化していくものと推測される。

このような背景のもと、組織工学技術を用いた安心かつ有効な再生医療を広く患者に届け、再生医療社会を本格化させ現実のものとするためには、産業化に際し十分な拠り所となるガイドラインが必要であることは明らかである。

現状では、包括的なガイドラインは存在しないため、申請する企業側がすべての根拠を示さねばならない。事前有料相談などで機構側のコメントを求めることが可能だが、ここ

でその根拠が有効でないと指摘され、再度データをとる必要が出ることも少なくない。このような状況を打開すべく、科学的根拠を有し、パブリックなガイドライン作製のための研究がぜひとも必要である。GLP レベルの試験となるべきだと考えられ、容易な作業ではないが、たとえば経産省の支援のもと、このような研究を誰かがおこなう必要があると考えられる。

1) たとえば下記の URL を参照。
http://www.mhlw.go.jp/shingi/kousei.html#kagaku-hito
http://www.mhlw.go.jp/shingi/kousei.html#kagaku-hito2

医機連・ＭＥＴＩＳとガイドライン

日本医療機器産業連合会
産業戦略委員長　齊藤　清人

日本医療機器産業連合会（医機連）[注1]の委員会のひとつ産業戦略委員会は、医療技術産業戦略コンソーシアム（METIS）[注2]の支援を大事なミッションと位置づけています。

その、METISでは、これから日本がしっかり取り組むべき、重点開発促進７テーマを定め産業の育成を目指して取り組んでいます。しかしながら、新聞紙上で大きく取り扱われている、日本発の先進的な医療機器についての記事に目を通すと、最近は先ずヨーロッパで次いで米国で承認を受けビジネスをはじめると書かれており、日本が後回しになるという非常に憂慮すべき状況を招いていると思います。

そのような折、今回の様に５テーマについてガイドラインを策定し、早く先端的な医療機器を世の中に送り出そうという動きは誠に重要で、METIS・医機連としても非常に期待したいところです。

異業種あるいはベンチャーの医療機器への参入を促進するなど、我が国の医療機器産業の育成と国際競争力の強化の為に、ガイドラインの策定が有効ではないかとの考えをかねて経済産業省から聞いていましたが、その後の進捗を経て昨年11月、医療機器開発ガイドライン評価検討委員会のもとに設けられた開発WGとMETISの連携をはかる為に、METIS推薦委員としてWGに加わる人が決まり現在に至っています。しかしながら、設置されたWGのミッションが何なのか、明確に理解できておらず、医機連・METISとしてガイドラインの策定に向けて議論を深めることが出来ずにいます。

開発の迅速化、薬事法審査の円滑化に資する為のガイドラインであり、評価指標であるとの事であれば、親委員会を含め主体である産側がどうして参画していないのかという素朴な疑問を産側は抱いています。今回の５分野は産業として、まだ、未熟な先端分野なので、学側の役割が重要であることは充分認識していますが、産側が産の立場で意見を述べるのは非常に重要なはずであると思います。規制される側である産が主体であることに問題ありとの考えがひょっとしてあるのかもしれませんが、そうではなく、立場の異なる委員が対等の立場で意見を述べ合い、議論を深め、より良い結論を導く事こそが大切であると考えます。

国民の為という視点があれば意見の対立に終わるということは生じない筈だと信じたいものです。

ガイドライン策定に向けての現状を良く把握できないでいる事を承知の上で敢えて申し上げる事を許していただくならば、親委員会はガイドライン策定分野の選定もさることながら、前例のない新しい分野についての策定にあたり、ガイドラインの理念・位置づけを

示すことが重要かと思います。その意味で分野の専門家だけでなく、法の専門家の意見も聞いてみたいものです。

示された理念のもと、ガイドラインを医療現場での使われ方や、技術の成熟度など夫々の分野の実態に合わせてWGで個別に定めることについては妥当かと思います。

只、分野毎に個別的であればあるほど、現在予見できない技術の進歩に対する適応性に留意する必要があります。適応性に対しての解が得られない様なら、策定したガイドラインの修正、変更の容易性を確保しておく必要があると思います。

それにしても、一旦策定されたガイドラインは、産業に大きな影響を与えることも起り得るでしょう。

物事に結論を早く出すのが重要な案件と、よく議論をつくし、正しい結論を導き出すのが重要な案件があるとすれば、ガイドライン策定は後者にあてはまるのではないでしょうか。

METISテーマ別委員会のガイドライン策定に寄せる期待とガイドラインについての政策提言の意欲が大きいだけに、これから METIS･医機連として積極的にかかわって行きたいと願っています。

METISでは現在､産学の委員からなる７つのテーマ別委員会を設け活動をしていますが、いずれの委員会からも産業育成の為の環境整備という観点からの課題、問題として薬事法にかかわるものが指摘されています。

そこで、産学の委員からなる重点テーマ共通課題検討委員会を立ち上げ、臨床研究、臨床試験、治療、機器と薬剤の整合のとれた承認、適用症例の拡大などにかかわる問題に取り組み始めたところです。この委員会活動もガイドラインと深いつながりがあると考えています。

以上

（医機連）[注1]：　日本医療機器産業連合会。
保健・医療用の用具・機器・器材・用品等の開発、生産・流通に携わる 20 の事業者団体（約 4800 社）で構成されており、それら団体の連合会として医療機器産業界の総意を形成して活動。

（METIS）[注2]：医療技術産業戦略コンソーシアム。
日本発の新しい医療機器開発による医療機器産業の国際競争力強化を目指し、産官学が連携して研究開発から実用化までの戦略を検討し、インフラの整備等を推進しようとするもの。現在、産学の委員からなる７つのテーマ別委員会を設け、開発目標や内容の絞込みを行う一方、産業育成の為の環境の整備という観点から課題、問題点の抽出にも取り組んでいる。

事務局：医機連。　オブザーバー：厚生労働省、経済産業省、文部科学省 他。

ベンチャー企業からの期待

株式会社ビーシーエス
代表取締役　　稲見 雅晴

再生医療の研究・開発は、欧米はもとよりアジア諸国においても国策として支援がなされ、大きな成果が生まれようとしている。これは、再生医療が全く新しいカテゴリーに区分される医療であり、患者への福音と共に産業化への期待が大きいからである。

一方、我国では再生医療の産業化について目に見えた成果は全くないのが現状である。再生医療材料は培養皮膚(表皮)、培養軟骨等の臨床使用例があるものからES細胞研究のような基礎研究レベルにあるものまで様々である。

医療という特殊なカテゴリーの範疇にあることは事実であるから、その審査には慎重を期すことは当然であるが、再生医療材料とはいえ、諸外国で多くの臨床使用例や産業化例があるものでも基礎研究レベルと同様の審査をする事は使用を欲する患者や国民医療にとってメリットがあるとは言い難い。

弊社は、国内唯一の国産製造特許による自家培養皮膚の産業化に取り組んでおり、約10年が経過するが未だ産業化の目処が立っていない。本稿では、ベンチャービジネスの1社としてこれまでの経験から、望むべきガイドラインのあり方について提案する。

GUIDELINES: PREPARATION & CONTENTS OF APPLICATION FOR VENTRICULAR ASSIST DEVICES AND TOTAL ARTIFICIAL HEARTS PP: 33.

FDA NO.: F89-33838
DEVICE CLASSIFICATION: ARTIFICIAL HEART.
SOURCE: FOI SERVICES FULL TEXT (FT).
PUBLICATION DATE: December 4, 1987 (19871204)
RECORD TYPE: Fulltext
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Freedom of Information Act Request
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PRELIMINARY DRAFT

GUIDELINE FOR THE PREPARATION AND CONTENT OF APPLICATIONS TO THE FOOD AND DRUG ADMINISTRATION FOR VENTRICULAR ASSIST DEVICES AND TOTAL ARTIFICIAL HEARTS

Division of Cardiovascular Devices (HFZ-450)
Center for Devices and Radiological health
Food and Drug Administration
8757 Georgia Avenue
Silver Spring, MD 20910
(301) 427-7594

Patient Management
Definition of Adverse Events
Pathology Studies and Device Analysis
Deviations from the Protocol
Follow - up Plan
Training
Participants
Content
Continuing Education
Investigators Manual
Monitoring
Reports

1.0 PURPOSE

This guidance is intended to address the specific information that must be collected to support the safety and effectiveness of a ventricular assist device (VAD) or total artificial heart (TAH). This guidance was written to cover both temporary and permanent use including partial support, biventricular support, and total replacement devices. Because of the broad scope intended for this document, there may be instances where the information requested may not be applicable or alternative information may be more suitable. Some of these instances are discussed in this document, but any questions will be addressed by the Division of Cardiovascular Devices (DCD) at (301) 427-7594.

This guidance is intended to complement, but not replace, the general information necessary for an investigational device exemption application (DE) or a premarket approval application (PMA). These and additional requirements such as the Good Laboratory Practice Regulation, Current Good Manufacturing Practice Regulations, etc., are referenced in Appendix I. For your convenience, a glossary of terms is provided in Appendix II.

To evaluate the safety of a device in an IDE application, information describing the device, the manufacturing process, and performance data from in - vitro, in - vivo, and clinical tests are required. Some of the requirements have been explicitly stated, but many requirements have not. Instead, some general considerations, particularly in the clinical investigation section, are presented that must be addressed.

At this time, this document is still in draft and under revision. A copy of this guidance, as well as other guidance documents, is available on an electronic bulletin board. Through this electronic bulletin board, you can download copies of the guidance documents, and enter your comments, suggestions, or questions. The electronic bulletin board can be accessed on (301) 443-7496. If you do not have access to a computer and communication equipment, please contact DCD.

2.0 SYSTEM DESCRIPTION

2.1 DETAILED DESCRIPTION

Provide a detailed description of the system (pump and controller) including design, dimensions, and materials. Diagrams, engineering drawings, and photos can be used to clarify details of the system and each component of the system.

2.1.1 Pump Placement

Describe the placement of the pump in the body (internal or external) and how it is connected to the circulatory system. How is fit determined? Is implantation limited to patients of certain anatomical dimensions?

2.1.2 Design Features

Describe features of the device designed to modify or lessen the incidence of clinical complications generally attributed to heart pump devices, i.e., thromboembolism, hemolysis, bleeding, infection, calcification, device failure, immune deficiency, neurological

deficiencies, etc.

2.1.3 Operation

Describe the algorithm or modes of operation. Indicate whether VAD operation will be synchronous or asynchronous with the natural heart, and whether adjustment of beat rate and flow is automatic or manual.

2.1.4 Safety Factors

Describe anticipated loads, transvalvular pressures, power requirements, and design safety factors. Discuss the worst case conditions under which the pump can operate and compare to physiological conditions expected.

2.1.5 Alarm Systems

Describe alarm systems. What physiological conditions or control system states is the software designed to detect?

2.1.6 Materials

Provide a complete listing of all materials used in the fabrication of the pump and leads that are implanted in the body. Include the chemical generic name or biological source. Indicate the thermal/mechanical/chemical condition of all constituent materials in both the raw material and finished product form (e.g., for metals - cast, solution annealed, percent cold - worked, etc.; for polymers - degree of crystallinity, molecular weight distribution, etc.).

Provide information on the relevant properties of all materials in the condition of the finished product. Test samples shall have undergone sterilization by the process described in Section 3.3, subjected to the recommended maximum number of resterilization cycles using the worst case method and/or conditions specified. Include the effects of the service environment, as appropriate.

2.1.7 Environmental Assessment

Provide an environmental assessment as described by 21 CFR 25.31(a), or claim a categorical exclusion from this requirement by stating that approval of this IDE or PMA will not result in release of substances that, at the expected levels of exposure, may be toxic to organisms in the environment as provided in 21 CFR 25.24(e).

2.2 SYSTEM DESIGN

Provide a description of the engineering considerations that went in to the design specifications for the device. Include a description of the loads applied to all critical structural members throughout the entire cardiac cycle. Consideration of worst - case, within - tolerance conditions for geometry, material properties, configuration of placement, power system, etc., should be included, as well as an evaluation of the effects of all forming, joining, and other manufacturing processes of each component on the design life of the device.

2.2.1 Design Qualifications

Provide the design qualification for the console including mechanical tests, electrical tests, component tests, pressure tests, and environmental tests. If the console will be used to transport patients, the entire system must be qualified for this purpose.

2.2.2 Performance Specifications

Provide performance specifications including tolerance of error. This information must be included in the labeling. See Appendix II for the definition of labeling.

2.2.3 Accuracy

Document the accuracy and range of the console in estimating blood flow and other control parameters. Provide a description of the methods used to verify the accuracy of the controller including assurance that the test equipment has been accurately calibrated or standardized. Describe potential causes of controller failure and the intended response of backup systems.

2.2.4 Limits of Operation

Describe conditions under which the pump or pump components will fail and compare this with worst case physiological conditions expected in order to calculate a safety margin.

2.2.5 Software Validation

Describe the validation of your system software including:

o the numerical input boundaries of the software.

o an overview of the software algorithm and the methods used to verify its performance.

o a description of safety features and an analysis of possible errors and failures (i.e., a failure mode and effects analysis) for both the software alone and the total system. This analysis should indicate the conditions that may lead to erroneous information and/or cause patient injury, the steps taken to minimize these occurrences, and the steps the user should take in the event of failure. The results of this analysis should be consistent with indications, warnings, and precautions in the labeling.

2.2.6 Heat Generation

If the pump is implanted, quantify the amount of heat generated that will be transferred to body tissues. Discuss the physiologic heat absorption capacity in the area in which the device will be implanted comparing heat generation to dissipation capacity. Under worst case conditions (i.e., maximum heat generation), what is the safety factor of heat output to heat absorption capacity?

3.0 MANUFACTURING

3.1 PROCESS DESCRIPTION

Identify the critical components of the system, describe the steps involved in manufacture of the device including components, subassemblies, system integration, key equipment, testing, packaging, and the layout and location of your manufacturing facility.

3.2 PROCESS VALIDATION

Provide documentary evidence that establishes a high degree of assurance in the processing and quality assessment procedures used in the manufacture of the device. Guidance in the establishment of the documentation of process validation as outlined below is provided in the 'Principles of Manufacturing Process Validation' in Appendix III.

3.2.1 Quality Control

Specify acceptance/rejection criteria for critical quality control tests. Explain the rationale behind the test and why the criteria were chosen. Specify the schedule of quality control tests (e.g., 100% test, lot testing, periodic, etc.). If an automated inspection or test system is used, information demonstrating validation of the system must be provided.

3.2.2 Specification Tolerance

Demonstrate that the window of specification tolerances and test acceptance criteria is adequate to consistently produce a device of life supporting quality. See Appendix III for a general discussion of process validation.

3.2.3 Records (PMA Applications)

The manufacturer must certify that adequate records are maintained to comply with Current Good Manufacturing Practices.

3.3 STERILIZATION

For any implanted device, a sterilization assurance level of 10(SUP -6) must be accomplished. See Appendix IV for references.

3.3.1 Procedure

Specify in detail the sterilization procedure including cycle parameters, corrective action levels, and indicator use and placement. Specify residue levels after aerating (when a gas sterilant such as

ethylene oxide (ETO) is used) or rinsing (when a liquid sterilant is used) as specified in the labeling, the worst case size and configuration of the device. Appendix IV contains a copy of the Federal Register notice that specifies the allowable limits of ETO residuals. Include procedures and sampling requirements for sterility testing done for lot release.

3.3.2 Resterilization

Discuss provisions for resterilizing returned or failed goods, if applicable. Provide results of physical and performance testing that show resterilization does not affect the properties of the device. If resterilization or disinfection by the user will be recommended, specific instructions must be given in the labeling including maximum number of times the device may be resterilized. If resterilization is not recommended, a contraindication must appear in the labeling.

3.3.3 Validation

Supply data used to validate the sterilization process, including the sterility assurance level achieved, chemical or biological indicators used, product functionality tests performed, and results of testing. Specify any standards followed to validate the sterilizer and cycle.

3.4 SHELF LIFE

Provide results of testing or a protocol describing testing to be performed to establish a sterile shelf life date which is to appear in the labeling. Testing must include exposure of an adequate sample size of may be subjected
during shipment, handling, and storage. Testing should include, but is not limited to, exposure to dropping, vibration, humidity, atmospheric pressure changes, temperature extremes, and shock. Provide a rationale for all parameters chosen. After stress, aging, and exposure, testing must demonstrate the package and product integrity. FDA recommends that a protocol be submitted prior to testing and aging.

4.0 TESTING

4.1 IN VITRO TESTING

The following is needed to document bench testing done before clinical trials are initiated. All final testing must be done with final design devices, using devices sterilized by the method described in Section 3.3.

4.1.1 Preliminary Studies

Report the results from any performance characterization studies done with prototypes claimed to simulate the final design. Discuss changes made to the prototype device that have lead to the current configuration.

4.1.2 System Characterization

Operation of the device/system must be demonstrated to characterize the operating domain and limits of performance. Demonstrate the device performance on a mock circulatory system in all modes of operation under a full range of steady state conditions under which the device is expected to clinically operate. Demonstrate the full range of cardiac outputs that the device will provide under varying operating conditions such as fill pressure, drive pressure, cycle rate, stroke volume, and any other applicable parameters that affect device output. Characterize the device's response under transient conditions that include rapid changes in systemic pressure and flow, beat rate, and when applicable, changes in stroke volume and switching between synchronous and asynchronous modes. Demonstrate system response to simulated cardiogenic shock, i.e., AOP (LESS THAN) 20 mmHg, fill pressure (GREATER THAN) 20 mmHg, CO (LESS THAN) 2-3 L/min. For a VAD, with the jock ventricle in a passive state, characterize the VAD response to simulated ventricular fibrillation.

4.1.2.1 Test conditions

Describe the mock loop, test fluid, operating temperature range, measurement instrumentation, and calibration equipment. Define a range of

beat rates and cardiac outputs including the upper and lower limits of expected physiological conditions of operation as described above. Explain the rationale for these limits.

4.1.2.2 Test results

Provide output flow data for the device as a function of all loop and control parameters that determine this flow and for the modes of operation described above including the norms and extremes of steady state flow, simulated cardiogenic shock, and ventricular fibrillation where applicable. Report peak pressure gradients (dP/dt) across each valve and peak outlet pressure for the range of flows and modes described above.

For battery operated devices, report the electrical power consumption per unit time for the device in operation in each mode.

4.1.3 Durability and Reliability Testing

Describe the experimental protocol for durability and reliability testing of the final clinical model of the pump and console.

4.1.3.1 Test apparatus

Provide a detailed description of the durability test loop and its ability to simulate physiological pressures and flows. Describe the instrumentation used to test the system. Specify the actual flow conditions during the tests, the role of the mock ventricle, if one is used, and the duty cycle for each operating mode.

Where applicable, describe the number and duration of each internal battery run and the pressure/flow conditions during each run.

Describe the environmental conditions under which the test was conducted and the instrumentation used to monitor inlet/outlet and drive pressures, flows, pressure gradients, temperature, viscosity, run time, (electrical) power consumption, and other relevant parameters.

At this time, it is expected that durability testing be done in real time. At some point in the future, however, testing done at an accelerated rate may be accepted if it can be shown that equivalent wear will occur.

4.1.3.2 Failure criteria

Define the failure criteria used to evaluate reliable performance of the system over a specified short or long term (permanent) duration. These criteria should not be limited to simple component failure but should extend to circumstances when, for any reason, the system is unable to meet specified clinical pressure and flow requirements. When applicable, failure criteria must also be specified for an implantable battery in terms of the system's ability to provide minimum periods of operation, at specified clinical pressures and flows, without an external power source.

4.1.3.3 Reliability objectives

Depending on the proposed indications for use, the device must meet the following objective:

Short term: At least ---- devices must be run under the specified test conditions with no more than ---- failures over a period of at least twice the intended clinical implant duration.

Long term: At least ---- devices must be run under the specified test conditions with no more than ---- failures over a period of at least ---- years.

4.1.3.4 Results and documentation

Provide a tabular description of the overall test results including run times, down times, operational conditions, duty cycles, cycle rates, input/output flows, pressures, pressure gradients, and for battery operated devices, electrical power consumption. If a failure occurred, identify the failure and indicate the time of occurrence.

For those devices that did not fail, compare the results of functional performance tests over the full range of system operating parameters, with similar results obtained before durability testing. Provide the results

from a detailed examination of all components for wear and fatigue using SEM, thermal imaging, or other high resolution examination methods with emphasis on the blood sac or diaphragm and valves, and where application, the energy converter. Discuss the performance of the controller/console used in the durability testing, noting all failures.

4.1.4 Biocompatibility/Toxicity

Describe testing and results to ensure the biocompatibility, non - pyrogenicity and non - toxicity of the implantable components of the system.

4.2 IN VIVO TESTING

4.2.1 Summary of Literature

Summarize the results of animal studies published in scientific journals using the device proposed for this study or similar devices. Discuss definitive findings from these studies and questions posed by the results that require further investigation.

4.2.2 Summary of Prototype Studies

Describe the animal tests that were done to develop your prototype model and subsequent studies leading to your final design for clinical evaluation. Include all evaluations of the device in animal failure models such as artery ligation or induced fibrillation.

4.2.3 Protocol

A scientific study of the final clinical design is expected to accompany the application for the investigational device exemption (IDE). In - vivo testing is expected to demonstrate both durability and performance of the system as a complement to in - vitro testing. The device must be tested in animals for at least twice the expected duration of implantation for intended for permanent implant
must demonstrate operation in - vivo for a minimum of five months. The following are minimum protocol expectations for this study:

A. Provide standardized procedures and data collection techniques.

B. Discuss the rationale for the choice of animal(s) selected in the study.

C. Provide the rationale for the number of animals to be studied and the duration of the studies (a minimum of eight animals for each model is expected).

D. Describe the implant techniques and the post operative care procedures.

E. Submit a complete evaluation of system effects including all of the following:

1. a discussion of the anticoagulation regimen(s) tested and a coagulation profile for the study;

2. a discussion of hemolysis in the animal model accompanied by a profile of relevant studies (hematocrit, hemoglobin, plasma hemoglobin, reticulocytes, LDH); and

3. blood chemistry profiles including blood gases, electrolytes, SGPT, bilirubin, creatinine, and BUN.

The test data requested above are suggested as the minimum test data needed to evaluate the system effects.

F. Provide an evaluation of the safety of the weaning protocol.

G. Describe and evaluate all of the device - related and non - device - related adverse events.

H. Submit all of the pathology studies for all animals that expire on the device or are sacrificed. The information that is submitted must include:

1. a description and photos of the device in situ;

2. a gross necropsy examination with conventional histologic studies of major organs; and

3. histological evaluation of all areas of grossly evident pathology.

I. Provide an evaluation of the explanted device including:

1. a description and pictures of the total explanted device and its individual parts;

2. a detailed examination for wear and fatigue at susceptible areas; and

3. a gross and microscopic evaluation of any tissue attached to the device or any damaged material.

4.2.4 Data Analysis

Data analyzed should be presented in a systematic way to facilitate assimilation of the results. Laboratory data should include normal values for the type of animal in that laboratory, and data points on charts should indicate the number of animals represented by each data point. Device analysis results should be presented in a manner that compares the results for animals by date and should include other relevant information such as anticoagulation and adverse events.

4.2.5 Relationship To Clinical Studies

The results of this study must be discussed in relationship to the proposed clinical study. Discuss the purpose of animal studies using your device including your hypotheses for use of the intervention.

5.0 CADAVER STUDIES

Provide a summary of the cadaver studies that were performed to arrive at the optimum configuration for the device. Discuss the variables that were studied, the basis for your conclusions, the specific limitations on the size of the patient, and the specific recommendation for insertion.

6.0 CLINICAL INVESTIGATION

to
call or write the Division of Cardiovascular
Devices (DCD), and to discuss
their plans and ideas before submitting an IDE or PMA application.

6.1 PROTOCOL DEVELOPMENT FOR THE CLINICAL TRIAL

The accrual of a sufficient number of subjects into a heart pump study requires the inclusion of more centers than are ordinarily required in a clinical trial. This section of the guidance includes minimum requirements to facilitate a scientific study of a complicated device within a limited patient population in a large number of institutions. For scientifically valid conclusions to be drawn from the study, the study must have clear objectives with a fully developed protocol that is developed by both the investigators involved in the study and the sponsors of the study. From the experience of past clinical investigations, if the clinical investigators have participated in development, or agree to adhere to the protocol, conduct of the investigation will be uniform.

Note: FDA encourages the sponsor of a multi - center investigation to establish an investigation steering committee composed of the investigators involved in the investigation.

6.1.1 Objectives

The purpose of the study including the specific objectives and the specific study design are the first considerations. Based on the study objectives, discuss the following:

A. How you intend to demonstrate success or failure to meet the objectives of the investigation, and

B. How the data collected during the investigation will be used to determine whether the criteria for success have been met.

6.1.2 Study Size

A proposal for the size of the study with a rationale for the number of patients and institutions required to draw statistically valid conclusions about the safety and efficacy of the device and its indications for use should be submitted. If you anticipate evaluating several patient groups (i.e., post - cardiotomy, post acute myocardial infarction, chronic

degenerative heart disease), the proposal should reflect the effect of multiple patient subgroups in study size. The time frame should be outlined taking into consideration planning time, center recruitment, patient entry, data analysis and the preparation of a final report.

6.1.3 Preliminary Investigations

It may be beneficial to do a preliminary IDE study of five to ten patients at one or two centers to test the device, study design, procedures (implant, patient management, weaning, follow - up, etc.), to determine the feasibility of extending the study to multiple centers. In order to get meaningful data from such a study, characteristics discussed below should be incorporated. Based on the results of this study, the design may be modified for the final study design.

Note: If a preliminary investigation is conducted, the investigation should be designed to reduce as many variables and confounding factors as possible, e.g., a single system configuration, strict limits on patient selection, etc.

6.2 CHARACTERISTICS OF INVESTIGATIONAL CENTERS

6.2.1 Investigational Center

Special attention should be given to the characteristics of an investigational center to assure that the center is a viable study participant. For instance, what is the annual cardiovascular caseload and does it support the projected annual rate of patient entry into the study? Are the surgeons, the surgical team, and the hospital sufficiently experienced in cardiac transplant procedures and the management of transplantation patients? Are the facilities adequate? Can the laboratory perform the required testing and can the pathology department carry out the autopsy and device evaluation protocols? How committed is the center to participation in this multicenter study? Are there sufficient qualified people that can be assigned to the study for data management, operation and maintenance of the equipment, and patient care? Include this information in the IDE application. The wholehearted commitment of the investigator and the center will facilitate your progress. A monitoring plan which addresses all of these issues should be included with the clinical protocol. For bridge to transplant studies, the investigational center must be an established heart transplant center (Section 6.2.3).

6.2.2 Principal Investigator

IDE submissions should include pertinent information on the principal investigator's background and characteristics of the center that make them an appropriate combination for inclusion in the investigation.

6.2.3 Established Heart Transplant Center

An established center is one that has performed a minimum of 12 heart transplants in the 12 months prior to submission with an overall success rate (survival) of 70 percent or better at the time of the submission. All submissions must include:

A. the number of heart transplants at an institution in the last 12 months and the number of patients alive in that group,

B. the total number of heart transplants performed at the center to date and the overall success rate at 12 months, 2 years, etc.,

C. whether the heart transplant surgeon is the same person as the investigator for the proposed study, and

D. the experience of the heart transplant surgeon.

6.2.4 Institutional Review Board

Heart pumps are complex devices that have stimulated considerable public debate concerning their use in humans. FDA therefore requires that an institutional review board (IRB) considering that institution's participation in a TAH/VAD study must have at least:

A. one member or consultant who is knowledgeable about the engineering -

related aspects of the device development and who is not directly associated with the study; and

B. one member who is considered to be an expert in regard to the moral and ethical issues concerning artificial implantations, organ transplants, etc.

6.2.5 Permanent Dependence

FDA also requires that the IRB of each study center certify its understanding that patients implanted for temporary use may become permanently dependent upon the device and that the center is prepared, should such dependence occur, to provide for the needs of such patients. Based on experience with the permanent implant study, the needs of these patients would include full time availability of cardiac surgeons and TAH/VAD technicians, additional backup equipment, adaptation of the hospital environment to patient's needs, transportation, housing for the patient's family, social and psychiatric services for patients and their families, nutritional, physical and occupational therapy services, on - going medical consultations, and continued staff training.

6.2.6 Cost and Reimbursement

A study center policy must also make clear who will pay for the care associated with continued implantation of the device.

6.2.7 Backup System

Each center must have at least one complete backup system that is available and ready to be used in the event of a failure of the system in use.

6.3 STANDARDIZATION OF PROCEDURES

A critical element in a manufacturer - sponsored clinical trial is the elimination of conflicting issues that might arise during the progress of the study. Obtaining agreement early in protocol development among centers on the conduct of the study (i.e., methodologies, judgments, and data collection procedures) facilitates an unbiased multi - center study. When planning a multi - center study, it is useful to have a steering group that includes several investigators plus investigator committees to develop different aspects of the protocol. In any case, procedures must be standardized for use at each study center. This requires a written description of procedures, specific data collection formats, with instructions for use. Study personnel at each center must be trained in the use of methods and form completion and must be monitored on a regular basis. The following are areas in which study management agreement must be reached.

6.3.1 Data Collection Forms

Uniform assessment criteria and data collection forms for pertinent pre - op, on study, and post - op information should be in place, (i.e., past history, operative assessments, post - op procedures). As the study population increases, this information will foster an insightful analysis.

6.3.2 Patient Selection

Patient selection criteria and patient exclusion criteria should be sufficiently specific to allow for a valid analysis of who may and who may not benefit from the intervention. Particular attention should be given to the development of TAH/VAD implant criteria for bridge to transplant patients that can be implemented at each center and are also consistent with each center's heart transplant criteria. A theoretical or empirical rationale for each criterion must be given.

6.3.3 Control Group(s)

There must be a control group(s) for the study. The ideal group would be subjects similar to the study group in all ways except that they do not receive the intervention. Prospective or retrospective patient groups as well as morbidity and/or mortality statistics may be appropriate. A

rationale for the choice of control group must be included in the submission.

6.3.4 Consent Form

In addition to the requirements of 21 CFR part 50, the following items must be added when appropriate for your protocol:

A. a statement of the center's experience in obtaining a donor heart (i.e., longest wait, average wait, and recent experience for patients in the most urgent category);

B. situations that might cause the waiting period to be extended;

C. complications arising from use of the device that could preclude transplantation;

D. that the study center is prepared to care for the needs of patients shouldthey become permanently dependent upon the device; and

E. whether the study center, the manufacturer, the patients or other will bear the cost of the patient's extended care as a permanent implantee.

6.3.5 Operative Procedures

In order to decrease potential bias in study results, variations in operative technique must be kept to a minimum. The operative procedures should be described in detail in the investigator manual and training manual, and should be fully reported on the appropriate patient forms.

6.3.6 Laboratory Procedures

Reliability of the data depends on standardization of results across study sites. A methodology should be specified for standardizing results among centers in order that data between centers can be compared and combined. The selection, assessment, and schedule of testing should be standard among centers.

6.3.7 Patient Management

Based upon experience to date, specific areas that warrant systematic evaluation in studies of these devices include infection control, hemodynamic control, management of bleeding, the anticoagulation regimen, renal, hepatic, pulmonary, neurological, metabolic, nutritional, and immune system function. Procedures for the assessment of these issues must be included in the submission.

6.3.8 Definitions of Adverse Events

Standard definitions of adverse events must be developed for use at each study site. Consideration should be given and criteria developed for use in the evaluation of each adverse event in terms of its severity, its significance, its relationship to the device being tested, the outcome of the event, and whether the subsequent death of the patient was related to the event. For instance, in the event that a transplanted patient develops an acute episode of rejection or infection, it should be evaluate as to whether implantation of the bridging device caused or contributed to the occurrence. Procedures should be developed for following up on the occurrence of all adverse events.

6.3.9 Pathology Studies

Submit all of the pathology studies on all patients who expire. Precise procedures including location of samples, number of samples, type of photographs, number of photographs, etc., must be included in protocols for use at each study site. The information that is submitted must include:

A. a description and photos of the device in situ;

B. a gross necropsy examination with conventional histological studies of major organs; and

C. histological evaluation of all areas of grossly evident pathology.

6.3.10 Device Analysis

Provide an evaluation of the explanted device including:

A. a description and pictures of the total explanted device and its individual parts;

I. pertinent information on other centers participating in the study (names, addresses, telephone numbers).

6.6 MONITORING

Frequent and close monitoring of subject recruitment, adherence to protocols, the quality of data collection and processing, and the quality of laboratory procedures is required. Monitoring concerns when preparing for a multicentered trial are: the number of monitors, the qualifications of the monitors, types of monitoring (telephone, site visit), frequency of site visits, monitoring report forms, and resolving problems.

IDE submissions for TAH/VAD multicenter trials should include a proposed monitoring plan that takes all areas mentioned above into consideration. Site visits must be scheduled prior to start - up and as soon as possible following the first implant. A schedule should be proposed for subsequent visits.

6.7 REPORTS

6.7.1 Adverse Events

A complete description of all adverse events must be reported.

6.7.2 Investigator List

A list of each investigator and clinical center participating in the investigation must be provided every 6 months from the date of the original approval of the IDE application.

6.7.3 Annual Report

The annual progress report must provide a comprehensive picture of what has occurred in each center and in the study as a whole at the time of the report. A summary is required for each new case entered into the study in the current report year, accompanied by a presentation of the data for all patients entered in to the study to date. It should be formatted in such a way that the information is readily assimilated by the reader, readily updated at regular intervals, and readily developed into a final report or PMA application.

6.7.3.1 Content

The annual report must address experience as discussed in section 6.3.7 with the patients entered into the study, with the performance of the entire system and components (number of failure/error free operations, description of failures or problems, etc.), and with the investigators and investigational team (evaluation of the training program, etc.). Documentation such as patient case report forms (CRFs) and raw data must be submitted unless specifically exempted by FDA.

6.7.3.2 Analysis

In addition to the CRFs on all patients, raw data must be provided on specific analyses. An analysis for each individual center and aggregated multicenter data should include, but need not be limited to, the following:

A. descriptive statistics on demographic data and summary data on patient characteristics (i.e., age, sex, etiology, device size, NYHA, hematology studies, blood chemistries, device evaluation, autopsy results, complement activation, etc.);

B. survival analysis (comparison of control and study groups and/or subgroups of interest);

and nondevice related

adverse events;

D. examination of the similarities and differences among patients in the control and study groups; and

E. analysis of additional hypotheses (relationships of disease etiology versus outcomes of interest, complication rate profiles versus outcomes, waiting times versus outcomes, etc.).

6.7.3.3 Summary and conclusions

The report generated as a result of this aggregation and analysis should

B. detailed examination of the device for wear and fatigue; and

C. a gross and microscopic evaluation of any tissue attached to the device or any damaged material.

6.3.11 Deviations from the Protocol

Any deviations from established clinical plan must be noted on the appropriate patient record and all reasons for the deviations provided.

6.3.12 Follow - up Plan

This plan should include standardized assessments, e.g., at one month, six months, and one year. A rationale must be included for timing of assessments and the type of data to be collected at each assessment. Patients should be seen at follow - up by the principal investigator or other members of the investigational team. Followup exam by a non - study physician is not recommended unless the physician has been oriented to the study test and data protocols.

6.4 TRAINING

Training is an essential element in promoting standardization and quality in a multi - center study. IDE submissions must include a detailed training protocol that assures the proper training and retraining of study participants.

6.4.1 Participants

The principal investigator and all staff associated with the investigation should receive training appropriate to their level of involvement. Trainees should include the following types of participants: physicians (surgeons, cardiologists, anesthesiologists), biomedical engineers, perfusionists, OR nurses, ICU nurses, laboratory personnel, data managers, etc.

6.4.2 Content

The content of the training and the location of the training should be appropriate to the needs of the trainees. Some items that have been included are: theory and practice (lecture); practical experience (implanting and explanting animals; setup, running, and trouble shooting; overview of clinical protocol; data collection and management; inservice education; dry run; etc.). All trainees should receive adequate instruction regarding the clinical protocol, standardization of procedures, and data collection methods.

6.4.3 Continuing Education

The use of periodic evaluation and the retraining of study participants should be considered in the overall plan for assuring safety and quality. This issue should probably be addressed by the steering committee of participating physicians or another committee of center participants.

6.5 INVESTIGATOR'S MANUAL

A manual that contains all information about the clinical trial must be site. Some of the items that should be included are:

A. a description of the study;

B. the investigator's responsibilities (21 CFR, 812.100);

C. the protocol (information on control groups, patient selection criteria, preoperative history/assessments, operative procedures, laboratory procedures, patient management procedure, adverse event reporting, autopsies and device analysis, deviations from the protocol, and follow - up procedures);

D. data management (data collection forms and instructions for use);

E. maintenance/repair of equipment (routine procedures, contacts);

F. procedures for updating/maintaining the skills of participants (physicians, nurses, lab technicians, etc.);

G. approved consent form;

H. emergency guidelines; and