NEUTERSOL® FROM LABORATORY TO MARKET—LESSONS LEARNED

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ABSTRACT

Even though there is worldwide human and pet overpopulation, it is difficult to secure enough research funding to support development of male contraceptive medicines and devices. The reality is that research funding in general is limited and development of a product from laboratory to market is lengthy and expensive. Neutersol®, an injectable solution for sterilization of male dogs, is the first product approved by the Food and Drug Administration (FDA) for animal sterilization and was marketed in the United States in 2003. The Research and Development (R&D) process used for Neutersol® may serve as a typical model for most male contraceptive medicines and devices developed with limited resources in the United States and worldwide. R&D of the product was done at the University of Missouri-Columbia and was sponsored by a small business venture capital company. The Neutersol® experience with the following questions offers lessons that are applicable to R&D of most male contraceptive medicines and devices.

QUESTIONS AND ANSWERS

1. **How long is the R&D process from laboratory to market?**

   The drug development process from laboratory to discovery to regulatory approval and marketing is lengthy, typically taking 10 to 15 years or longer. FDA regulations govern the development, testing, recordkeeping, safety, effectiveness, manufacture, labeling, storage, approval, advertising, and promotion of the proposed drug. In the case of Neutersol®, the first chemical sterilant approved by the FDA for use in 3-10 month old male dogs, the INAD (Investigational New Animal Drug) and NADA (New Animal Drug Application) processes took about twelve years. This did not include the time involved in the pre-INAD discovery and pilot studies on which the INAD was based.

2. **How is the process for the new product started?**

   The process begins with a pharmaceutical sponsor of pre-INAD discovery research that involves discovering a new molecular entity and formulation, securing the intellectual property rights (patents and trademarks), determining marketability and route of administration, and conducting pilot studies. The pilot studies include:

   - **Pharmacologic value,**
   - **In vitro laboratory evaluation,**
   - **Target species in vivo,**
   - **Dose, toxicity, and pharmacokinetics, and**
   - **Market potential and sales.**

   In the case of Neutersol®, the pre-INAD and INAD studies were sponsored by Technology Transfer, Inc., Columbia, Missouri, a small business venture capital company.

3. **What major procedures are required for the product?**

   After the pre-INAD discovery research, the Sponsor applies to the FDA for assignment of an INAD number. The major sections of the INAD include:

   - **Protocols,**
   - **Label indications,**
   - **Safety,**
   - **Efficacy, and**
   - **Manufacturing.**

   As with other proposed drugs, data pertaining to each of these major sections was required for Neutersol®.

4. **What are the claims and liability?**

   The FDA requires substantiation of all claims that are made for the drug. The more claims that are made, the greater is the liability. The only claim for Neutersol® is chemical sterilization. The indications for a drug that claims reproductive effect include the following:

   - **Animal species,**
   - **Age,**
   - **Route of administration,**
   - **Dose and frequency, and**
   - **Duration of effectiveness.**

5. **How is the laboratory data transferred to manufacturing?**

   Not all laboratory data are transferable to the manufacturing process. Laboratory data such as formulation and stability are applicable to the manufacturing or the chemistry, methods, and controls (CMC) section of the INAD and should be transferred early in the INAD process. The formulation and stability data for Neutersol® were transferred in the pre-INAD stage since Good Laboratory Practice (GLP) and many analytical tests are required by the CMC section of FDA regulations.

6. **What is the appropriate procedure for responding to the FDA?**

   As soon as the FDA assigns an INAD number to the new drug, it is advisable for the Sponsor to request a pre-submission conference with the FDA to discuss and agree upon the following:

   - **Product development plan, and**
   - **Protocol for each study or use of a standard protocol.**

   The FDA provides guidance documents for the various types of studies and submissions, and these are helpful in understanding FDA requirements. As the INAD stage is nearing completion, the Sponsor should contact the FDA to discuss and agree upon the labeling components, for example, the package insert, and marketing materials, for example, advertisements and brochures. In the case of Neutersol®, the Sponsor met with FDA technical staff on seven different occasions to discuss and agree upon various aspects of the INAD sections.

7. **How is the labeling technical section finalized?**

   As required by the FDA, the labeling technical section requires information with regard to the following:

   - **Public safety use,**
   - **Target animal safety,**
   - **Environmental safety,**
   - **Effectiveness, and**
   - **Manufacturing chemistry.**

   The package insert for Neutersol® contained all of this information specific to Neutersol®, for example, use of the caliper to measure testicular width in order to determine the proper dose.

8. **How is the exclusivity of the marketed product extended?**

   The FDA generally grants a marketing exclusivity period of five years for a new animal drug. In the interim, a Sponsor can submit a request for patent term extension which recovers the period of time that the INAD and NADA were undergoing FDA review. New patents secured in the interim can also be added to the NADA for further protection of the marketed drug. Neutersol® was granted a patent term extension of five years, the maximum period of time, and a new patent has been added to the NADA for Neutersol® since its approval in 2003.

CONCLUSIONS

- **Valuable laboratory discoveries always have the potential of making it from discovery to marketing even with limited research funding.**
- **Combining scientific and economic strategies is one of the key steps to success.**
- **FDA resources (guidelines, conferences, contact) are critical to the drug approval process and time involved.**