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Conceptual Proposal of a Facility Design for Accommodating Minipigs for Pharmaceutical and Radiopharmaceutical Research

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Abstract: The use of Animal House Facilities of IPEN-CNEN/SP (Nuclear and Energetic Research Institute—National Nuclear Energy Commission/SP, Brazil) has provided rats and mice with controlled sanitary quality for research and quality control in the production of radiopharmaceuticals lots, produced at IPEN, following rules of CONCEA—Brazilian National Council for Animal Experimentation Control and approved in CEUA (Ethics Committee on the Use of Animals), before they are sent to hospitals and clinics spread out in Brazil, for use in nuclear medicine. The production and the supply of high quality laboratory animals have fundamental importance for the accomplishment of vanguard scientific research, with reproducibility and universality. The quality of those animals depends, largely, on the available facilities for their production and lodging, to assure the demanded sanitary control and animal's welfare, in agreement with the ethical principles that control the activity. Therefore, the facilities design is of vital importance so that the mentioned requirements can be reached. Nevertheless, pigs and miniature pigs have gained importance as large animal models in medicine. With their size, organ capacity, and physiology resembling in several aspects that of humans, pigs are well suited for preclinical experiments and long-term safety studies. Minipigs will be used for preclinical testing of radiopharmaceuticals and assays radioactive materials for cardiac tests. This paper describes the premises and preliminary activities that have been performed at IPEN for the design of new Animal House Facilities dedicated to keeping minipigs taking into account fundamental aspects such as: animal's welfare, sanitation, genetic, in agreement with the ethical principles that control the activity and environmental concerns.

Key words: Research animals, minipigs, housing, facility, design, conceptual proposal.

1. Introduction

Animal experimentation has played a central role in biomedical research throughout history. The use of animals in biomedical research has given important contributions to the medical progress and important medical advances (for both humans and animals) have been made through the use of animals in research laboratories. For centuries, different species of animals have been used in experimental investigation. Specially bred laboratory animals, such as mice, rats, dogs, monkeys, pigs, rabbits, cats and birds are a fundamental part of biomedical research. Animal species are used in every step of the research and development, such as safety testing, clinical trials and manufacture of medicine due to their biological systems, genetic structures, and immunological responses, in various ways, similar to ours.

For centuries, the pig has been considered a suitable animal model in medical research due to its many similarities with human anatomy. Early assumptions about human anatomy were possible due to parallels drawn between human and pig anatomy. There are anatomical and physiological differences between pigs and humans. Nevertheless, dissected pigs were of fundamental importance for a basic understanding of

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human anatomy. Many similarities make pigs a very important model for the study of human diseases and treatment.

Besides the use of pigs, miniature pigs (also known as minipigs) have been developed for research purposes. Smaller pigs require less space and diet, are easier to handle and require a lesser amount of the compound being tested [1].

IPEN (Nuclear and Energy Research Institute) has a long tradition as supplier of quality animals for biomedical research. The project of the present IPEN Animal House Facilities was accomplished in the year of 1964. The facility was planned with the objective of being a production unit and a local for keeping of defined animals from sanitary, genetic and environmental point of view. The Animal House Facilities occupy an area of 840 m^2, with one pavement, where the production areas and the stock of original animal models of its own institution are distributed, as well as the maintenance of animals from other national or foreigner institutions. It supplies rats and mice for biological tests of radiopharmaceutical lots, produced in IPEN, before they are sent to hospitals and clinics spread out in Brazil, for use in nuclear medicine. It also supplies rats and mice for tests of materials for odontology, for tests with growth hormones and for researches of new pharmaceuticals and radiopharmaceuticals, among others applications. Recently, the laboratory has been fully refurbished. In Fig. 1, it shows pictures of the IPEN's Animal House Facilities and one of its refurbished laboratories.

Nowadays, it is being prepared the design of a new facility to be built at IPEN with the main goal of keeping minipigs for biomedical research. The facility will have all characteristics to assure research animals with the best qualities from sanitary, genetic and environmental point of views and respecting all the ethics principles involved in the use of animals for research. Then, the main focus of this work is the design of the facility from an architectonic point of view, with special emphasis in the wellbeing of the animals and the respect to the ethical recommendations, besides the functionality, safety, animal quality assurance and welfare of operators.

2. Minipigs and Their Importance for Biomedical Research

For the selection of non-rodent animals for safety evaluations, dogs and primates are the most frequent used models. Nevertheless, minipigs are becoming a more established research model and seem suitable to be used as "most human like" model for the identification and prediction of undesirable effects and risks for humans due to a number of anatomical similarities like structure and function of the skin, cardiovascular system, gastrointestinal tract, renal and

(a) (b)

Fig. 1 IPEN's: (a) Animal House Facilities; (b) refurbished laboratory.

urinary and possibly immune system [2]. Swine are considered to be one of the major animal species used in translational research, surgical models, and procedural training and are increasingly being used as an alternative to the dog or monkey as the choice of non-rodent species in preclinical toxicological testing of pharmaceuticals.

There are unique advantages to the use of swine in this setting given that they share with humans similar anatomic and physiologic characteristics. There are areas of pharmacological research where pigs and minipigs are established research models mainly because of anatomical and/or functional similarities to humans and/or because of availability of disease models. Because of its anatomical features, pigs and minipigs have eminent advantages in testing medical devices and surgical methods. It is likely that pigs and minipigs will become an increasingly important animal model for research and pharmaceutical development applications [3].

A miniature pig is a breed of pig developed and used for medical research or for use as a pet. "The differences between domestic farm breeds and miniature breeds are related to their growth rate and size at sexual maturity rather than actual anatomic differences in organs and structures. Thus, when different breeds are age matched, the organ sizes will reflect the increased size of domestic breeds compared with miniature breeds; however, the physiologic function should be the same. Conversely, when animals are weight matched, the sizes will be similar for organs and structures; however, the physiologic function will be related to the relative maturity of the animals. As an example, most domestic breeds would be expected to grow from 1~2 kg at birth to more than 100 kg at 4 months of age. The minipig strains that are used today in research were developed out of a need for a smaller and thus more manageable version of the domestic pig. These minipigs are derived by selective breeding and are in no way to be regarded as transgenic or genetically modified animals" [3].

Reasons for choosing the minipig as the non-rodent of choice included: lack of tolerance of administered compounds to dogs, hereby vomiting was a jeopardizing reaction, also high counter reaction of the cardiovascular system by dogs with compounds of blood pressure lowering potential; there were major differences in metabolism in those species selected first for testing and accordingly search for higher similarity to humans, further there were special applications like dermal administrations [2].

Minipigs have been selectively bred for small size, light skin pigmentation and docility. Minipigs are easier to house and carry fewer zoonotic diseases than nonhuman primates; they share more physiological and metabolic similarities to humans than other large mammals, and their large litter sizes and quick development time make them easier to breed. These animals are bred under controlled conditions and are raised specifically to be laboratory animals. The quality of the animals varies from the conventional to specific pathogen—free types. Minipigs are larger and grow faster than dogs. Minipigs also become sexually mature earlier. There are various strains available, each with its own characteristics. There is a wide variation in size and weight, which of course has an influence on amounts of drug needed for testing. Furthermore, other characteristic differences can influence choice of strain. In Fig. 2, it shows an example of minipig.

Fig. 2 Example of minipig [2].

Fig. 3 Examples of devices used for minipigs environmental enrichment [6].[1]

3. Ethic Principles and Welfare of Minipigs as Premises for Facility Design[1]

The use of animals in biomedical research has a lengthy history. Early Greek writings (circa 500 B.C.), for example, describe the dissection of living animals by physician-scientists interested in physiological processes. Later, Roman physicians, including perhaps the single most influential figure in the emergence of the medical sciences, the physician Galen, began to perform what we would now regard as the first genuine experiments involving animals. These early physician-researchers were among the first advocates of the idea that the use of animals in research was morally justifiable in light of the potential health benefits associated with those experiments. Throughout the history, philosophical or moral objections were voiced regarding the use of animals in biomedical studies. Several decades of experience with current regulations regarding the use of animals in biomedical research have produced a strong moral consensus for such practices. Researchers who fail to comply with those regulations should expect to be judged by their peers as unprofessional, to be subject to various institutional sanctions and to face significant moral disapproval [4].

Like all pigs, minipigs are social animals. It is assumed that the motivations and consequent behavioral needs have remained little changed from their wild ancestors. When possible, minipigs are housed in groups in the laboratory. It is recommended that all minipigs, with the exception of mature boars, are kept in groups when housed for biomedical research purposes. It is important that each minipig has visual, auditivy, and olfactory contact with other pigs. In the wild, the pig is an animal of prey and until trust has been established, pigs may seem cautious of caretakers. Pigs are very curious of their surroundings and a variety of toys and enrichment devices are used with laboratory pigs to encourage their sense of play and their desire to explore and learn [2]. Fig. 3 shows a picture of examples of devices used for minipigs environmental enrichment.

4. Design Drivers for the IPEN's Minipigs Housing Facility

An animal housing facility, or animal research facility also known as vivarium, is critical to the biomedical research. Proper housing and management of animal facilities are essential to animal well-being, to the quality of research data and teaching or testing programs in which animals are used, and to the health and safety of personnel. A good management program

[1]http://minipigs.dk/fileadmin/filer/Newsletters/Newsletter_40.pdf, http://www.ottoenvironmental.com/rubber-toys?pagenumber=9, and http://animalspecialties.biz/product-category/pig/pig-ne/.

provides the environment, housing, and care that permit animals to grow, mature, reproduce, and maintain good health; provides for their well-being; and minimizes variations that can affect research results [5].

The design of a new facility for animals housing, taking into account the ethical principles and welfare involved, must be directed by the comprehension of the animal's behavior and needs. Many factors should be considered in planning for adequate and appropriate physical and social environment, housing, space, and management. The animal research facility is a specially designed building type, which accommodates selected controlled environments for the care and maintenance of experimental animals. Animal research facilities are different from research laboratories. The facilities arecomplex, and expensive to build and to operate, but they are vital to the support of a proper, safe, and humane research effort. Through the capabilities of their particular architecture and building systems, they maintain tight environmental control over the facility to avoid the introduction of contaminants or pathogens, and prevent the possibility of infectious outbreaks, and avoid the transmission of odors [7].

These facilities are fundamentally dedicated to the care and maintenance of quality research animals. Then, it is very important that the operator keeps the environmental control of the facility to avoid contaminants or infections. This is achieved by the controlled flows of people, animals, material, supplies and wastes.

The main components of an animal housing facility are: animal housing rooms, procedure rooms, barrier elements, cage systems, containment facilities, corridors, necropsy room, quarantine rooms, staff support areas and spaces for mechanical/electrical equipment. AHRs (animal housing rooms) accommodate caging, bedding change stations, and sinks. AHRs are organized as individual rooms accessed from a corridor system or multiple rooms could be organized into self-contained suites. Procedure rooms are located near to AHRs and are a primary setting for research activity within the unit. The method of allowing researcher access under controlled conditions is a critical issue to be solved.

Barrier elements provide the primary barrier and access control that separates the controlled animal care environment from external influences. These operate under positive pressure to keep contaminants out. As in containment facilities, control and monitoring systems and equipment are utilized in barrier facilities to maintain the required pressures and flows. Wastes and effluents are separately contained and decontaminated. Sophisticated control and monitoring systems and equipment are employed to achieve closely controlled and regulated air pressurizations and flows. Cage sizing and cage systems are species-dependent and are governed by the standards. Since cleaning, sanitizing, and husbandry are frequent and indispensable activities, there are many other equipments included such as pass-through rack washers, tunnel washers, pass-through autoclaves, bedding dispensers and dump stations, and bottle washing and filling stations. Necropsy room is used for post mortem procedures on sacrificed animals and it is a "dirty" environment that should not be proximate to "clean" areas. Quarantine rooms are isolated AHRs for suspect and incoming animals that could be a source of infection.

The movements inside the facility and the connection between the several environments are done by corridors. These should be wide enough to accommodate animal rack, cart, and material traffic flow and should have a clear width to permit the traffic of the facility's components, and done with finishes so that they are easy to clean and maintain. Protective components should be employed to protect walls and doors from heavy traffic, avoiding damages. It is a necessary space for storage of food and equipment used in the facility's operational procedures. A specific area dedicated to receiving animals is required.

Besides all these facility components, staff support areas are also necessary. They include: break area,

cafeterias, workstation, lockers, and rest-room facilities. All are intended to support veterinary and research staff during their duty. Mechanical and electrical equipment rooms, rooms for devices such as dampers, coils, humidifiers and controls and distribution shafts are also indispensable. A desirable goal is to locate the spaces and devices in a manner that allows the separation of maintenance functions from animal care functions.

Some architectural drivers and recommendations have been adopted in the design of the new facility. Floor will be monolithic, with concrete and a resinous coating. The clear height from floor to ceiling will be at least 3 m and the clear height above the ceiling will be approximately 2 m to accommodate infrastructure support system distribution. Since walls should have an impervious, easily cleanable finish, it will be adopted epoxy based coatings and paints that have the capability of withstanding different aggressive agents and washing procedures.

The doors are very important components to control flows and contamination of environments. They will be constructed with absence of voids in the top and bottom rails of the door and made of easily cleanable and maintainable surfaces like epoxy painted steel or stainless steel to avoid the growth of vermin or bacteria. The door dimensions will be large enough to accommodate the free movement of cages and rack systems in use. The doors will be protected by electronic latches and locks with passwords to control the access of individuals to restricted areas.

Dirty areas such as necropsy and quarantine will be located near the dock. Cage washing area will be divided between a clean, which is an incoming or supply side, and a dirty, an outgoing or return side.

Air filters and the ventilation systems are one of the most important items to control the animal health and spread out any contamination or pathologic agent. Depending on the availability of suitable systems, the facility will have a centralized and automatic control of temperature, humidity, air pressure and air flow, since they are very important components for the production of quality research animals.

5. Conclusions

It is likely that minipigs will become an increasingly important animal model for research and pharmaceutical development applications. The production and the supply of high quality laboratory animals have fundamental importance for the accomplishment of vanguard scientific research, with reproducibility and universality. The quality of those animals depends, largely, of the available facilities for their production and lodging, to assure the demanded sanitary control and animals' welfare, in agreement with the ethical principles that control the activity.

An animal housing facility is a specially designed building type, which accommodates selected controlled environments for the care and maintenance of experimental animals. It is a complex and expensive facility to build and operate, but they are vital importance for the biomedical research with animals.

Nowadays, the design of a new facility is being prepared to be built at IPEN with the main goal of keeping minipigs for biomedical research. Many factors should be considered in planning for adequate and appropriate physical and social environment, housing, space, and management. The facility will have all characteristics to assure research animals with the best qualities from sanitary, genetic and environmental point of views and respecting all the ethics principles involved in the use of animals for research. Then, the main focus of this work is the design of the facility from an architectonic point of view, aiming to reach functionality, safety, animal quality assurance and welfare of operators. Many characteristics of the new facility at IPEN will be unique and it will be incorporated in the design of the installation the state of the art in terms of systems and concepts, with special emphasis in the welfare of the animals and the respect to the ethical recommendations.

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