

# Considerations in the Construction of a New Preclinical Facility

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## *Summary*

Many aspects need to be considered in details before construction of a new preclinical facility. These aspects include requirements in relation to international guidelines for preclinical studies, Good Laboratory Practice, barriers, animal welfare legislation, occupational health and customer expectations. This article describes some of the most important elements that should be considered in this respect, seen in the light of drug development.

It should be remembered that detailed individual plans are always required for each specific facility for the following reasons. Legislative discrepancies between countries may influence the final design of a facility from one country to another. In addition, different types of work may be undertaken by each individual laboratory, leading to various needs for each site. Furthermore, as working routines to some extent are usually site-specific, this may also influence the optimal construction between laboratories. This article should therefore be seen as a guide to thoughts that should be made before construction of a new facility. It is not the intention that it should be used as a detailed check-list.

## *Guideline requirements*

Internationally accepted guidelines, issued by authorities in Europe, the USA and Japan and by organisations like the ICH and the OECD, are important documents to study. These guidelines gives details such as the total number of animals to be included in each study, which elements of the investigation that need to be included in each particular study, thereby leading to requirements for a variety of service laboratories, and details concerning environmental conditions that generally should be followed during the conduct of a study.

The total number of animals per study is of importance as this will have an impact on the optimal size of each room. Also, the number of animals per group and the fact that both genders should be included needs to be considered when designing the size and the detailed arrangement

of the animal rooms. For example, the number of non-rodents required as a minimum is usually 3 animals of each sex per group when dosing for up to 4 weeks and 4 animals per sex per group when dosing beyond that period. This gives a total number of 24 and 32 animals per study, respectively, when using three dose levels and a control. To this number potential recovery animals may be added.

Regarding the various elements of the investigation that should be included during the course of a study, some service laboratories will be needed in addition to the animal rooms. This is the case in relation to a pharmacy for storage and handling of test items, dosing rooms for carrying out the different dosing procedures, rooms for blood sampling and handling of these samples, and rooms for urine collection in metabolism cages. When planning rooms for conducting ophthalmoscopy procedures and electrocardiographic recordings, issues like darkness and quiet surroundings are important elements to remember. Laboratories for analysis of blood and urine samples, and bioanalysis, should also be considered. In case specialised dosing routes are to be used, like intravenous infusion, it will

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also become relevant to include a surgical facility. Finally, a necropsy laboratory must also be present. Guidelines also describe environmental conditions under which preclinical studies should be conducted, stating limits for temperature, relative humidity, number of air changes and light-darkness periods. Therefore technical installations ensuring these conditions must be evaluated during the planning process.

#### *Legislative perspectives, housing conditions*

Specifications of housing conditions for laboratory animals are given in The European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS 123), Appendix A (housing conditions of laboratory animals) and in the Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes, currently undergoing revision.

In relation to construction of new preclinical facilities, important information in these regulatory documents includes the minimum pen/cage area that should be allowed for per animal. This is relevant when planning the size of the animal rooms, allowing for sufficient space for the required number of animals, both for non-rodents housed in floor pens and for rodents housed in cages of a certain size. Whenever possible, group housing in harmonised groups should be allowed for most species, and therefore this should be thought into the plans as well. However, for some studies it may be relevant still to have the possibility for individual housing at least during some parts of the day, for instance during feeding, when dermal dosing of the animals is used as the route of dose administration or when the animals have externalised catheters implanted. Hence, a flexible approach is optimal.

Also, requirements for the environmental conditions are specified in the above mentioned documents and, for each animal species used, limits for temperature, humidity and the number of air changes per hour is given. Furthermore, light-darkness cycles are described and for some species also dim light at

night time. Again, technical equipment allowing for these conditions must be included into the planning of the facility.

Finally, environmental enrichment is also described for each animal species. Things like toys for dogs and shelters for rodents are among other things mentioned. These are not items that per se have impacts on the construction of a new facility. However, it is important to think of where to store these items while not in use and also how and where to clean them.

#### *Good Laboratory Practice*

Besides a number of many other different issues, Good Laboratory Practice (GLP) should also be included in the considerations for constructing a new preclinical facility. GLP is a quality assurance concept that applies to preclinical regulatory studies and is in most countries regulated by law. It states plenty of details that must be fulfilled for undertaking and conducting such studies, including details of relevance in relation to the facilities.

Concerning these details, GLP specifies that the facility must be of an appropriate size for the activities undertaken. Furthermore, the activities must be separated, which may be interpreted as separate rooms should be available for each study. The test system must be free of any disease, isolated from biologically harmful substances and all supplied materials must be free of any contaminants. These are all demands that should give some sort of guarantee that potential effects seen during the course of a study can be linked to the test item and not to any other external factor. Hence, some barriers must be established protecting the test systems. Furthermore, there must be dedicated rooms for diagnosis and treatment of disease available, as well as separate storage rooms for diet and utensils. The handling and preparation of test substances must be performed in separate areas and therefore a pharmacy department must be present. There should be clear procedures for handling and disposal of waste, and therefore these working processes should also be thought into the project. Once again,

environmental conditions should be controlled. Furthermore, all procedures carried out in relation to a GLP compliant study should be documented. In case documentation is performed in paper format, it is thus relevant to consider space for storage of your raw data files. In case documentation is performed electronically, it will be relevant to consider wiring of your animal facilities and also storage areas for the computer terminals.

Finally, there are GLP requirements relating to the staff working within the environment that indirectly could have an impact on the construction of your facility. The organisation must be clearly structured and roles and responsibilities should be defined. In this respect it may be worthwhile to consider the number of offices that should be included as well as other staff facilities like meeting rooms. Another point in relation to staff is training. GLP specifies that every member of staff should be properly trained for the activities performed. In relation to this aspect it may be valuable to consider dedicated areas for training purposes.

#### *Legislative perspectives of occupational health and working conditions*

Working with substances of unknown toxicity puts some special demands on safety issues, regulated by law. The arrangement of the facility should ensure that safe working routines can be followed and all necessary safety equipment has to be available. Things like ergonomics must also be considered: It could be relevant to include equipment that eases working procedures. This would for instance be equipment like robots for cage handling and cleaning, where the space requirements and installations for such equipment should be investigated during the planning phase.

Another important issue in relation to a new facility is that special attention must be paid to noise reducing arrangements within the working environment. Ventilation should be sufficient to protect the staff from test substances and allergens, and should be considered in relation to the different working procedures and working routines. Staff

facilities, like changing areas and canteen, are often also regulated by occupation health laws as may be the access to daylight for staff, at least in some countries.

#### *Barriers*

As mentioned under the relevant issues to consider in relation to GLP, barriers protecting the test systems should be in place. This is also for scientific reasons, as it is important to keep a high health status of the animals used ensuring a minimum of interference with the test performance and the test results.

It is therefore important first of all to discuss and define what the health status of the animals housed within the facility should ideally be and what sort of barrier is then needed to maintain this status.

In relation to establishment of barriers it is worthwhile to consider which procedures should be implemented for admittance into the animal facility. Passage into the facility could for instance be through vet-showers or airshowers, with change of clothing. Therefore, arrangements of the changing areas become important and in this respect also the expected number of daily users. In case visitors are expected to enter the facility, a separate changing area may be necessary. Also, the procedures for passage of all generally used materials like diet, bedding materials and utensils must be defined and adequate barriers arranged allowing for carrying out these procedures in the most practical way. This is also valid for bringing in new equipment, cage materials and test items.

Storage areas within the facility for equipment when not on use is often overlooked. However, especially in rodent units it should not be underestimated. It is beneficial to keep such storage areas inside the barrier in order to limit the extent of transportation of such equipment over the established barrier for external storage.

In case multiple animal species are being used at the same facility, it is worth considering what should be the separation between the species and what impact that will have on the staff access facilities and storage facilities. It may also be that animals of

the same species but of different health standards are to be used within the same facility. Again, clear procedures should be made for the isolation of the various parts of the facility, which needs to be integrated into the drawings of the new building.

The most important aspect once your barrier has been defined is to think workflow. This will help with designing the facility in the most appropriate way. Various staff groups should be included in these considerations, as the coming daily users might see something that others overlook.

#### *Customer expectations*

Finally, your customers will also have some expectations of a new preclinical facility. And with customers, both external and internal (your staff) should be remembered. As a default, all relevant legislation should of course be followed. But furthermore it is a plus if the facility is to be ranked as “state of the art”. It should be clean and tidy, spacious and light and invite practical working routines. Noise should be kept under control and finally animal welfare should be given a high priority.

#### **Conclusion**

Planning and construction of a new preclinical facility is a challenging and time consuming task. It should not be underestimated how much effort such projects will take. The first thing is to define what task the new facility should fulfil. And to study relevant legislation and to identify which permissions are needed.

The budget for the construction of the new facility is important to have in place before start of the planning process. As many different wishes will develop during the construction process, as well as unforeseen events occur, it is important to keep the budget under control constantly and reserve some part of the budget for additional wishes and unforeseen events. Furthermore, it must be defined who is in charge of the project, so that the necessary priorities and final decisions can be made.

The facilities must be properly planned in due time.

And during the planning phase it is very important to think in terms of workflow. In order to get as many important inputs as possible, it is highly recommended to establish a project group with all necessary skills and knowledge represented. Also, you should know your own limitations, and use external professionals wherever required. Preferably someone you have worked with before who knows the business and your needs. Finally, you should consider potential future changes of work type and work flow and think that into the project, if possible.

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