

Practical consideration of 3Rs' reduction principle in a private sector CRO on Taiwan

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Abstract

Greenseasons Biotech Company, Ltd. (GBC), a private contract research organization (CRO), founded recently, along with a semi-governmental-run CRO on this island handles most of commercial biosafety testing business for 'healthy-food development' regulatory purpose in Taiwan. The company has operated with limited resources and thus, utilized the 'Reduction principle of the 3Rs' as one way to not only enhance animal welfare, but also to conserve these limited resources without compromising the quality of the scientific data. One of the efforts has been to reducing animal number in rodents for testing. The basic premise is to share the control group between studies having similar nature of test articles and similar procedures, such as route of administration and length of study. Another effort is applying in pyrogenic/fever study with New Zealand white rabbits such that the rabbits were repeatedly to use for 3 to 5 testing with 3 weeks apart between tests as long as the welfare of the animals is not compromised, as evaluated by the animal displaying no adverse reaction or abnormality. The effort approved by our Institutional Animal Care and Use Committee (IACUC) was supported by the team of Experimental Animal Ethics Committee appointed by the gubernatorial Council of Agriculture upon inspection. We welcome comments from abroad and international society on this issue and we would appreciate it for any input on this endeavored effort that we could try and perform for more.

Keywords: Taiwan, CRO, 3Rs' reduction principle

Introduction

Taiwan (Fig. 1), a nearly developed country that has been super in many areas of modern growth of developed country but has never been well advanced in research and development of drug, agricultural and industrial chemicals. It has been insufficient policy, guidance, and efforts that enable Taiwan lead to tangible outcomes in medicinal and industrial chemistry. In safety assessment aspect for further research and development of new drug and chemical discovery, only a semi-gubernatorial run CRO, the Development Center for Biotech (DCB), established for research and development in the past two decades. Recently, due to a trend of investigation for herbal medicine/ phytochemical extract and health-food, demanding animal experimentation for safety assessment purposes increased in the past decade. In 2000, a second one, the Greenseason Biotech Company (GBC), but private sector CRO

was founded by a group of investors. This added to the first CRO on this island. The DCB that had been supported under the guidance and financial support by the Ministry of Economic Affairs for the prior first past 11 years and GBC since then are major institutions for the purpose in Taiwan today.

We, the GBC, the second but a private sector CRO founded and thus had created the business service sector less than seven years but had performed already numerous studies. Nevertheless, running a CRO in private sector for non-clinical or preclinical research on safety assessment issue is difficult as this is costly and labor intensive with small returns and narrow in profit margins, that demands academic and professional skill. Other concerns are standard operation procedures (SOP), good laboratory practice (GLP), and lab animal accreditation (Association of Assessment and Accreditation of Laboratory Animal Care International (AAALAC) that made it difficult

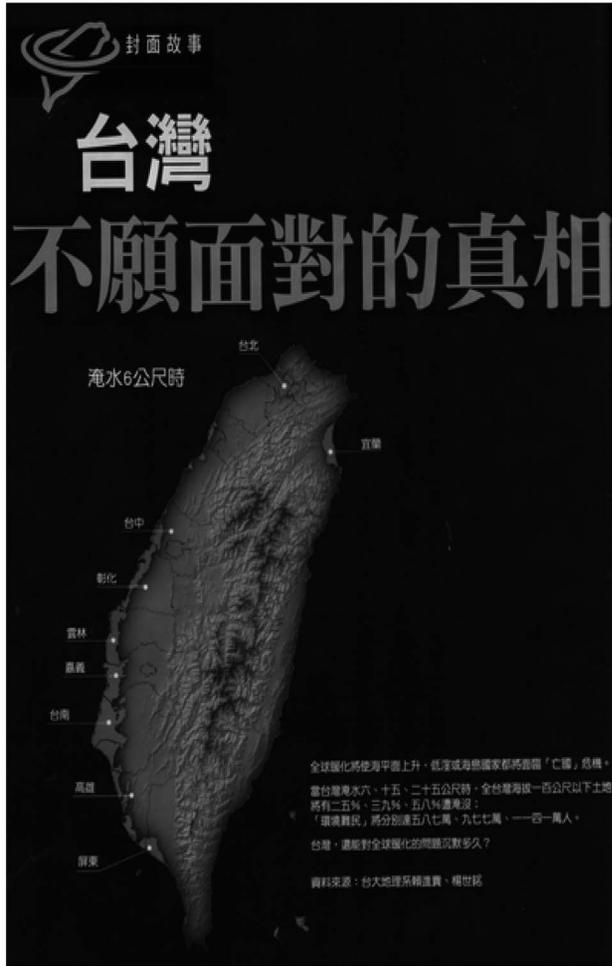


Fig. 1. Taiwan, a nearly developed country on an island across the Taiwan Strait from China, may get land loss to ocean (red color) once the sea level raised 6m under the global warm effect.

for a newly founded CRO to survive and advance. That is especially critical to a CRO in private sector in Taiwan that is a democratic country running businesses as free enterprise. Here is a description of how the "Reduction principle of 3Rs" was applied at GBC in recent years.

General view of GBC

GBC and Employees

Originally the GBC was a biotechnical product-oriented company for several years before it was then transformed to the present service-oriented company in June 2000 when it moved to new location and built new laboratory (Fig. 2). This company transformed to service oriented for safety assessment purposes, i.e., performing nonclinical / preclinical toxicology study for drugs, food, medical devices, environmental chemicals, and also doing functional study for healthy food in Taiwan. The company employed 8 technical persons in June 2000 that increased to 12 in January 2001 when the animal facility and testing lab were ready to operate. The 12 personnel lab included one director, 2 associates, and 9 assistants in 2001 expanded to close to 50 in 2005 when it was at peak.

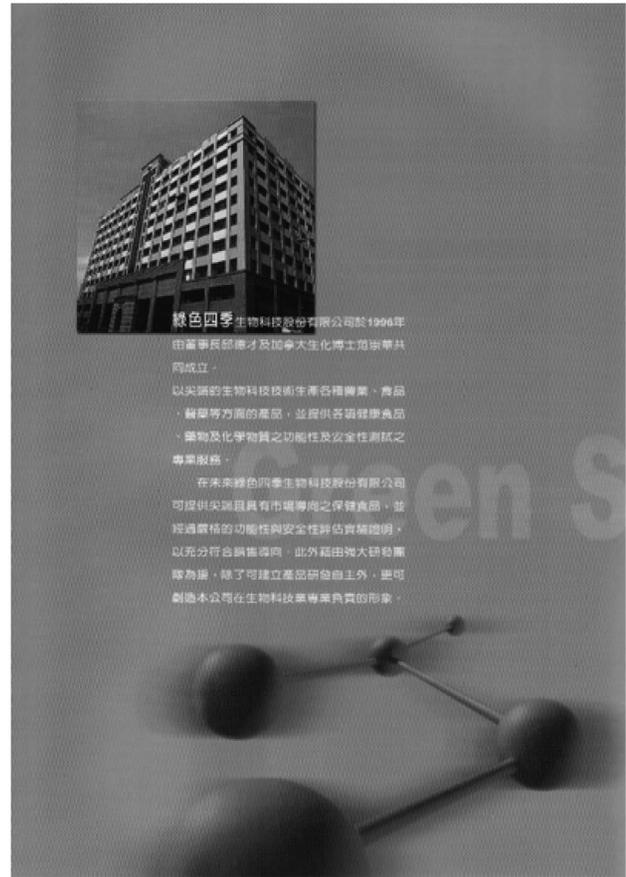


Fig. 2. The site of newly transformed Greenseasons Biotech Company in 2000 added as the second but a private sector contract research organization in Taiwan for biomedical safety assessment service.

Animal Facility

The animal facility includes barrier system for safety assessment study and cleans conventional system for functional study (Fig. 3). The lab provides 3 rooms each sized at 3 x 4.5 m2 for SPF rodents, and 5 rooms sized each at 3 x 4 m2 for clean conventional rodents and rabbits.

Laboratory Facility

The lab was built and operated to met the standard demanding and necessity for animal care and management under the guidance of "A Guidebook for the Care and Use of Laboratory Animals" published by Chinese (Taiwanese) Society of Lab Animal and Use of Lab animals".

Study Projects and Protocols

The laboratory was organized under one director and staffed with 11 associates including 2 study directors, 1 veterinarian, and 8 lab assistants around July 2001 when the lab initiated the first subchronic oral toxicity study with drug business came in. One of the 2 study directors was also a licensed veterinarian with advanced degree in toxicology and pathology.

The study project and protocol was first reviewed by the company's IACUC that was organized under 3 personnel including the one of the two study directors, the licensed veterinarian addition to the

Table 1. Animals Used in Experimentation, 2001-2006

Year	2001	2002	2003	2004	2005	2006
No. of Studies	3	15	58	141	224	149
No. of Animals Used	72	811	3903	4615	7285	5089
Rats	40	425	2704	3058	4168	3176
Mice	32	72	974	614	2080	1227
Hamster	0	188	125	255	600	200
Guinea pigs	0	106	53	508	286	263
Rabbits	0	20	47	172	149	176
Beagles	0	0	0	8	2	47

Table 2. Reduction in Testing Animals Used, 2001-2006

Year	2001	2002	2003	2004	2005	2006
No. of Studies	3	15	58	141	224	149
No. of Animals Used	72	811	3903	4615	7285	5089
No. of Animals in Reduction	0	0	10	10	65	103
Rats	0	0	0	0	0	0
Mice (Genetic toxicity)	0	0	10	10	25	30
Hamster	0	0	0	0	0	0
Guinea pigs (Dermal study)	0	0	0	0	40	25
Rabbits (Pyrogenic study)	0	0	0	0	0	48
Beagles	0	0	0	0	0	0



Fig. 3. The company lab includes barrier system for safety assessment study and cleans conventional system for functional study.

laboratory director or other representative at the early days operation.

Fig. 4. Biosafety assessment service lists and categories.

Performance and discussions

Studies Conducted

The study in the past five years conducted at the GBC is listed in Table 1. The number of animal used to meet the reduction principle in 3Rs is present in Table 2. The origins and sources of animal procured are summarized in Table 3.

Table 3. Animal Sources Procured, 2001-2006

Year	2001	2002	2003	2004	2005	2006
No. of Animals Used	72	811	3903	4615	7285	5089
Rats, domestic	40	380	1877	2488	4168	3176
imported	0	45	827	570	0	0
Mice, domestic	32	72	873	599	1965	1227
imported	0	0	101	15	115	0
Hamster, domestic	0	188	125	255	600	200
imported	0	0	0	0	0	0
Guinea pigs, domestic	0	56	53	508	286	263
imported	0	50	53	0	0	0
Rabbits, domestic	0	20	47	172	149	176
imported	0	0	0	0	0	0
Beagles, domestic	0	0	0	8	2	47
imported	0	0	0	0	0	0

From the data, a total of 188 including 0 rats, 75 mice, 65 guinea pigs, 48 New Zealand white rabbits and 0 Beagles have been reduced to a total of 590 studies conducted for animal experimentation in years of 2001 to 2006. The numbers are not tremendous but are substantial to meet reduction principle in 3Rs for the consideration of animal welfares under the present condition of GBC, regarding its' laboratory animal facility size, manpower available, and studies claimed by the sponsors on this island.

Whether these are reasonable, rationality enough, or more about effectiveness to the testing results and technical issue needed to be scrutinized and discussed. Further inputs and evaluation are expected. We welcome and appreciate for your comments and suggestion at the WC6 conference on animal use in the life sciences, especially under the consideration of animal research on international harmonization of animal care and use guidance. We as a newly founded CRO describe herewith how our effort to operate with limited resources has utilized the "Reduction principle of the 3Rs" to continue operating in recent years. The senior author (HC) had experienced with numerous toxicity studies (oral, inhalation, dermal, i.v., i.p., aquatic) and life span survivability studies in the past with variety of animal species (rats, mice, guinea pigs, hamsters, rabbits, Beagles, cattle, fishes), and exposure duration (acute, subacute, subchronic, chronic) but would not be too much convinced on 3Rs replacement principle, and even transgenic mouse model or hepatectomized model on toxicity and carcinogenicity study, favors much effort on reduction and refinement principles as a veterinarian and toxicologic pathologist. Many issues and themes of replacements remain for our further efforts.

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