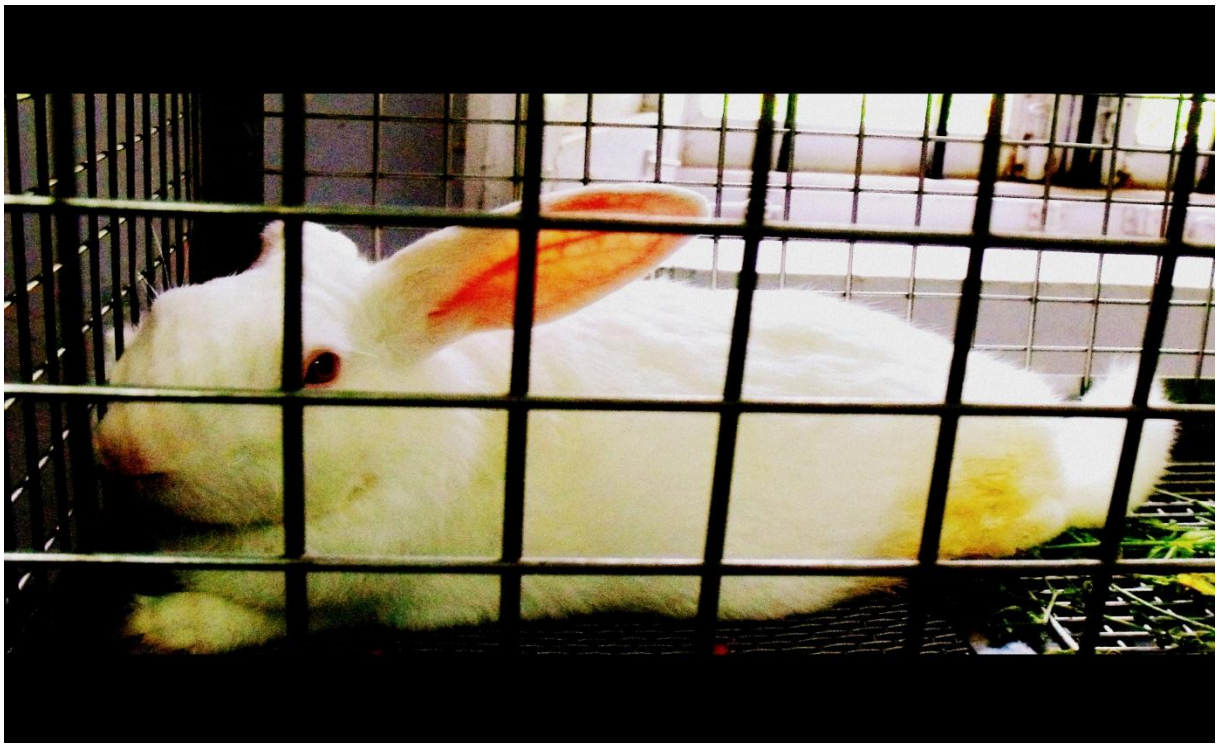
TOXICITY TESTING IN INDIA

An Animal Welfare Perspective



FIAPO
Federation of Indian Animal Protection Organisations

HUMANE SOCIETY INTERNATIONAL

Suggested citation:

Sengupta, Alokparna (2012) Toxicity testing in India: An animal welfare perspective. Federation of Indian Animal Protection Organisations and Humane Society International April 2012

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I. Introduction

Toxicity testing or safety testing is defined as the study of the adverse effects of chemical and physical agents on biological systems. Toxicity testing can be of various kinds - *In vitro, In vivo* or *In silico*.[1] Modern regulatory systems contain extensive requirements for safety testing of new chemical products before they enter the stream of commerce.[2] Animals have been used extensively in the evaluation of new chemicals, as well as substances intended for use as food additives, pesticides, pharmaceuticals and cosmetics. The animals range from rats, mice, guinea pigs to rabbits, dogs and monkeys.

The idea of and need for this research emerged from HSUS/HSI's efforts to leverage the 2007 National Academy of Sciences Report, Toxicity Testing in the 21st Century: A Vision and a Strategy[3]. The National Research Council (of the NAS) published this report which described limitations of animal-based toxicology tests and proposed a new focus on non-animal methods that may present potential advantages over animal tests. This document supported the concept that replacement of animal-based methods in toxicology promises practical benefits, aside from humane advances.[4]

The Humane Society of the United States, from the initiative offered by the 2007 NAS report, proposed a 'big biology' project known as "The Human Toxicology Project" to help and guide the transformation of toxicity testing.[5] It formed affiliations with Humane Society International and Humane Society Legislative Fund to campaign globally to promote greater reliance on proven non-animal testing methods. HSI is currently actively working to implement a landmark vision of the "21st century toxicology"[6]. Its implementation in India starts with the understanding of the Indian safety regulatory system, which is the main motive of this paper.

In late 2010, HSI and FIAPO entered into an agreement to develop a research project that would serve the following objectives:

a. Identify private companies, contract research organizations, government and academic institutions in India that do toxicity testing work.

b. Identify toxicity testing requirements for regulatory approval in India of Biologicals, Drugs, Foods, Pesticides, Cosmetics and Industrial Chemicals in the country.

c. Identify key individuals and agencies involved in chemical safety regulation and in toxicity testing.

e. Identify progressive Indian scientists who are considered to be visionaries as regards the development and application of new technologies (e.g. genomics, proteomics, metabonomics, bioinformatics, in silico studies) and who are at the forefront of promoting alternate methods to animal testing, particularly in toxicology.

This research is thus expected to shed light on the toxicity testing scenario in India. It will particularly look at the use of animals in regulatory safety testing. It will also delve into the growing arena of contract research where toxicity testing may be performed by private companies for domestic as well as international clients. Such toxicity testing would enable the client to meet the regulatory requirements of the country where they propose to introduce a new product.

Of particular interest to FIAPO and HSI is the question of the mandatory regulatory requirements that require the use of animals for certain safety tests. This research exercise has gone into detail to investigate the specific laws, government orders and guidelines that require animal testing to be performed for regulatory purposes.

Such regulatory safety testing presents the frontier from where reduction or phasing out of animals can take place. Hence our particular interest in understanding the regulatory provisions and the space available for reducing numbers of animals tested upon as well as complete phase out, where possible.

We have also developed a road map for the future which includes working with progressive scientists to promote toxicity testing methods that require less or no animals, capacity building of agencies involved with regulating the use of animals for research and refinement of particular regulatory provisions that require the use of animals and floating the idea of an Indian centre for the validation of alternatives.

Limitations

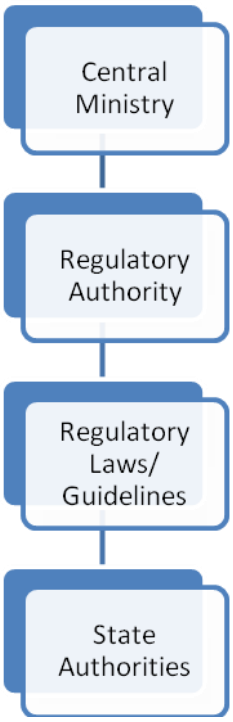
- The single largest hindrance we faced through the course of research is the lack of clearly codified regulations across different product categories. The specific regulatory provisions have had to be derived through extensive interviews with various players involved in testing as well as regulation;
- Often the factual solution has been arrived at through triangulation of different views.
- The understanding of specific regulations, their provisions and the regulatory bodies has been limited among the practitioners of toxicology. This slowed our research down as we had to resort to a large number of interviews to arrive at sources of regulatory provisions.

II. The Regulatory Framework

This chapter summarizes the procedure involved in the safety evaluation of a product for presence of toxic nature and the administrative framework in India.

(i) A Conceptual Understanding of the regulatory framework in India

A specific ministry of the central government is responsible for each product category listed below. Further, there exists a regulatory body (under the operational control of the concerned ministry of the central government) that specifies the safety testing requirements for new products specifying safety testing guidelines, procedures and protocols – including the use of animals for specific tests. Examples of such agencies are Genetic Engineering Approval Committee, Central Drugs Standard Control Organization, Central Insecticides Board, Food Safety and Standard Authority, the Central Committee for Food Standards and so on.



(ii) Legal and other instruments that specify the mandatory standards

The specific instruments through which safety testing is mandated for various product categories is variable. In some cases the mandate derives from a specific act and the rules framed within it (such as for drugs, pharmaceuticals and cosmetics). In other cases such mandating is accomplished by executive government orders either in the form of circulars or gazette notifications. For instance in case of Drugs and Pharmaceuticals, the protocols are specified in the Drugs and Cosmetics Act, 1940 & Rules, 1945 (Amendment 2005) by its regulatory body, Central Drug Control Standard Organization whereas for food products the regulatory body has chosen to adopt pre existing guidelines (the CODEX standards) and has made such guidelines mandatory in the country by adopting them through an executive order.

In the text below, the precise instruments that specify safety testing mechanisms for different product categories are detailed.

In summary, it emerges that the regulatory framework in India that governs the safety testing of new product categories (including the use of animals for such tests) is not uniform – either in terms of the government agencies involved or in terms of the administrative instruments (acts and rules, gazette notifications, circulars) that lend formal mandate to safety testing mechanisms.

(iii) The role of international standards in toxicity testing in India[7]

Indian laws and regulations only satisfy the marketing needs in India. Most companies, in order for their product to be eligible to be marketed everywhere in the world, integrate a number of guidelines and regulations required by other countries. It was found that the most common guidelines, beyond the Indian regulatory structure, used by safety testing players in India are:

1. The U.S Food and Drug administration (USFDA) guidelines for pre-clinical testing.
2. Organization for Economic Co-operation and Development (OECD) guidelines. OECD guidelines for evaluating toxicological effects of chemicals for risk assessment purposes are generally practiced by most companies producing chemicals.
3. The International Conference on Harmonisation
4. ISO standards are another set of standard guidelines which are used extensively by Indian pharmaceutical and other chemical companies to standardize their products internationally.

   This is not an exhaustive list, merely an indicative one listing the most commonly used international guideline that we came across during this research.

(iv) The Indian regulatory framework for toxicity testing

The table below summarizes the

Serial no:	Product	Regulating Act	Regulatory Authority	Regulatory Ministry
1.	Drugs & Pharmaceuticals	Drugs & Cosmetics Act, 1940 Schedule Y	Central Drugs Standard Control Organization	Ministry of Health & Family Welfare
2.	Cosmetics	Drugs & Cosmetics Act, 1940 Schedule S	Central Drugs Standard Control Organization	Ministry of Health & Family Welfare
3.	a) Vaccines b) Biologicals & Biosimilars	Drugs & Cosmetics Act, 1940 DBT Guidelines	Central Drugs Standard Control Organization Department of Biotechnology Genetic Engineering Appraisal Committee	Ministry of Science and Technology Ministry of Environment & Forests
4.	Food and Food Products	Food standard & Safety Act, 2006	Food standard and Safety Authority of India	Ministry of Health & Family Welfare
5.	Genetically Modified Crops	Revised Guidelines for Research in	Department of Biotechnology, Genetic Engineering	Ministry of Science & Technology Ministry of

		Transgenic Plants, 1998, 1989 Rule	Appraisal Committee	Environment & Forests
6.	Pesticide and Agricultural Chemicals	Central Insecticides Act, 1968	Central Insecticides Boards and Registration Committee	Ministry of Agriculture
7.	Medical Devices	Drugs & Cosmetics Act, 1940	Central Drugs Standard Control Organization	Ministry of Health & Family Welfare
8.	Household chemicals, detergents and other surface active agents	Chemical Council Division Committee (Voluntary)	Bureau of Indian Standards (Voluntary)	

Based on the extensive research and communication with Dr. Dinesh Kumar Bharadwaj, General Secretary, Indian Pharmacological Society and Dr. P. Balakrishna Murthy, Director, IIBAT, we have deduced the following categories for which regulatory toxicity testing is carried out:

1. Drugs and Pharmaceuticals
2. Cosmetics
3. Vaccines, Biologicals and Biosimilars
4. Food and Food products
5. Genetically modified crops
6. Pesticides and Agricultural Chemicals
7. Medical devices
8. Soaps, Detergents and Surface active agents

The sections below describe the specific regulatory provisions for safety testing of each of these product categories.

1. Drugs &Pharmaceuticals

"Drug" includes[8]—

(i) all medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes;

(ii) (ii) such substances (other than food) intended to affect the structure or any function of human body or intended to be used for the destruction of 6(vermin) or insects which cause disease in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette;]

(iii) [(iii) all substances intended for use as components of a drug including empty gelatin capsules; and

(iv) (iv) such devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, as may be specified from

time to time by the Central Government by notification in the Official Gazette, after consultation with the Board ;]

The drug discovery process covers a range of therapeutic areas and treatment regimens. The very purpose is to develop a new product with preventive and therapeutics benefits as well as safety margin. The drugs development process starts at the technologist's bench for new molecules. This is followed by evaluations using in vitro and in vivo models. Once the proof of concept is developed, the preclinical safety is evaluated following the non regulatory – regulatory guidelines. The purpose of preclinical safety testing is to understand adverse effects of the candidate drug during clinical trials. Clinical safety, pharmacokinetic, and pharmacodynamic studies are initiated based on the acceptance of efficacy and safety of the pharmacology and initial toxicology profiles.[9]

In India, the Ministry that oversees the regulation related to the pre clinical toxicity of drugs and pharmaceuticals is the Ministry of Health and Family Welfare. Under the jurisdiction of the Ministry is the Directorate General of Health Services (DGHS). Under the aegis of the DGHS is the Central Drug Standard Control Organization which is in turn is reported to by the Drug Controller General of India (DCGI). [10]

The CDSCO lays down standards of drugs, cosmetics, diagnostics and devices along with coordinating the activities of the State Drugs Control Organizations to achieve a uniform administration of the Drugs and Cosmetics Act, 1940.[11] The manufacture, regulation of manufacture and sale of drugs is looked after by the State Drugs Control Authorities appointed by the State Governments while approval of new drugs, clinical trials, standard and quality of drugs, imports, market authorization and new drugs are the responsibility of the Central Government.[12] [13]

Any new drug that needs to be approved for sale in India needs to go through a process consisting of meeting requirements first at the CDSCO headquarters which then passes it on to the new drug division for examination. The Investigational New Drug (IND) committee then reviews the examination and application completely and sends its recommendation to the Drug Controller General of India (DCGI) who, then, according to the review and recommendations, either approves or rejects the proposal of the new drug.[14]

The CDSCO administers the Drugs and Cosmetics Act, 1940[15] which prescribes, in detail, the requirements that a new drug needs to fulfill under the Schedule Y of the **Drugs and Cosmetics Rule, 2005**[16]**.** This **Schedule Y**[17] includes rules and protocols related to pre-clinical and clinical testing for import and manufacture of a drug. Appendix III of schedule Y of the Drugs and Cosmetics Rules, 2005, specifies the type of test to be conducted, timelines, number of animals to be used, etc. These are the guidelines that Indian companies or other drug discoverers have to comply with to manufacture and market their products in this country.

Currently Schedule Y prescribes the following tests as Preclinical animal toxicology for approval to Phase I clinical trials:

- Single-dose toxicity studies – Minimum lethal dose (MLD) and Maximum tolerated dose (MTD)
- Repeated dose systemic toxicity studies
- Male fertility study
- Female reproduction and development study
    - Teratogenic study

- Perinatal study
- Local toxicity

- Genotoxicity
- Carcinogenicity

2. Cosmetics

In the year 1940, a Drugs Bill that was passed by the Central legislative assembly was then sent to the Governor General for assent. This assent was accorded on April 10, 1942 and following this, the Drugs Bill became statute and came to be known as the Drugs Act, 1940. In the year 1962, through section 2, Act 23 of the Drugs (Amendment) Act, 1962, its nomenclature was amended and the words "and Cosmetics" was added after the word "Drugs". It is therefore, with effect from 1964 that the Drugs Act, 1940 became the Drugs and Cosmetics Act, 1940 and came into effect.[18]

According to the Indian Drugs and Cosmetics, 1940, cosmetic means "means any article intended to be rubbed, poured, sprinkled or sprayed on, or introduced into, or otherwise applicated to, the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and includes any article intended for use as a component of cosmetic".[19]

Schedule S of the Drugs and Cosmetics Act states that cosmetics in their finished form must conform to the relevant quality parameters as prescribed by the product standards issued by the Bureau of Indian Standards (BIS). [20] Hence the Drugs and Cosmetic Act confers responsibility to the BIS to issue standards and testing protocols for cosmetics. The Cosmetics sectional committee (PCD19)of the BIS prescribes that all cosmetic products that are formulated should conform to the restrictions imposed by IS 4707 (Part 1 and 2) and the lists of CTFA (Cosmetics, Toiletries and Fragrance Association, USA), EEC (European Economic Community) and the guidelines of IFRA (International Fragrance Association). IS 4707 provides classification of cosmetic raw materials and adjuncts. Whereas part 1 provides for dyes, colors and pigments, part 2 lists raw materials generally not recognized as safe for use in cosmetics. Cosmetic products formulated according to the restrictions imposed on the above mentioned guidelines and documents are deemed safe and need not be tested for safety again. **However, if the manufacturer feels it is necessary, they may test for safety. This is entirely up to the manufacturer's discretion and BIS does not have any role in it.** Novel products which do not contain the ingredients mentioned in the above documents do need to be tested for safety. This safety testing is performed according to test protocols given in BIS 4011:1997. This document is the "Method of Test for Safety Evaluation of Cosmetics." [21]

The products that the Drugs and Cosmetic Act mentions under Schedule S are as follows:[22]

1. Skin Powders
2. Skin Powder for infants
3. Tooth Powder
4. Toothpaste
5. Skin Creams
6. Hair Oils
7. Shampoo, Soap-based
8. Shampoo, Synthetic-Detergent based
9. Hair Creams
10. Oxidation hair dyes, Liquid
11. Cologne.]

3[12 Nail Polish (Nail Enamel)
13. After Shave Lotion
14. Pomades and Brilliantines
15. Depliatories chemicals
16. Shaving Creams
17. Cosmetic Pencils
18. Lipstick]
19. Toilet Soap
20. Liquid Toilet Soap
21. Baby Toilet Soap
22. Shaving Soap
23. Transparent Toilet Soap]
2[24. Lipsalve IS:10284
25. Powder Hair Dye IS: 10350
26. Bindi (Liquid) IS: 10998
27. Kum Kum Powde IS: 10999
28. Henna Powder IS: 11142]

The standards of all these products are present and except Bathing bars and toilet soaps, there is no other product that prescribes specific procedure for safety testing on animals.[23] Each of the above mentioned documents specifies that safety testing on animals is to be conducted according to IS4011:1997. **This is only for circumstances where a new raw material (materials other than the ones mentioned in the aforementioned documents) in an old formulation or an entirely new formulation is used.[24]** This forms the crux of ongoing safety testing on cosmetics in India.

For marketing to other countries, Indian companies fulfill their procedural requirements of the concerned country. For international companies wanting to test their products for safety and for marketing their products in India, if they fulfill the criteria required by BIS, they need not perform any separate safety testing. The referral laboratory of the Ministry of Health and Family Welfare, the Central Drugs Laboratory usually performs some random sampling to check for safety. Currently there is no registration for import of cosmetics, however, it is understood that certain guidelines may be imposed shortly. These new guidelines may accept country of origin safety guidelines which may further reduce the scope of animal use in safety testing of cosmetics. [25]

For products not tested for safety on animals, a sentence in the original 1997 document stated; "any formulation not tested on animals may bear the label – "The product has not been tested on animals for safety". This has been deleted according to the first amendment made in 2002.[26]

In standard IS4011:1997, whereas Draize tests in the form of skin irritation tests and eye irritancy test in rabbits were banned and removed and is are no longer permitted by the government of India (according to the second amendment of 2007), skin sensitization tests in guinea pigs and oral toxicity tests in rats are still continued.

According to a document enlisting the program of work published by the Petroleum, Coal and related products department (PCD) of the Bureau of Indian Standards, a draft of a third amendment of the IS4011:1997 is under finalization and is yet to come into action.[27]

3. Vaccines, Biologicals and Biosimilars

Vaccines and various other products were included in the Schedule C of the Drugs and Cosmetics Act through an amended notification by the government of India in 1950.[28] According to the 1988 Amendment of the above mentioned act, all vaccines are to be considered new drugs and the safety testing has to be performed according to Schedule Y of the Drugs and Cosmetics Act. Therefore, for new, vaccines, safety testing is required to be carried out through toxicity tests prescribed in Schedule Y.[29] For new batches of old vaccines, only "undue toxicity" is tested. This is done according to the Indian Pharmacopeia where specific tests for specific vaccines is mentioned.[30]

Genetically engineered medicines also known as **biologic drugs, biologics, biopharmaceuticals or recombinant therapeutics** have revolutionized the treatment of many life threatening diseases. These products refer broadly to substances produced by living cells used in the treatment, diagnosis or prevention of diseases**.** [31]The Department of Biotechnology, under the Ministry of Science and Technology has prescribed guidelines for the safety evaluation (preclinical and clinical) of recombinant DNA vaccines, diagnostics and other biologicals. It prescribes the kinds of tests to be performed and the need for such tests.[32]

A **Biosimilar** is defined as "A biological product/ drug produced by genetic engineering techniques and claimed to be "similar" in terms of quality, safety and efficacy to a reference innovator product, which has been granted a marketing authorization in India by a competent authority on the basis of a complete dossier, and with a history of safe use in India." Whereas the market of biopharmaceuticals is increasing constantly, the patents of the first generation of these products have either expired or are likely to expire shortly. This has provided opportunities to different manufacturers to introduce follow on substitutes to original biologics, which are also known as **biosimilars** in different countries. Various agencies viz. World Health Organization (WHO), European Medicines Agency (EMA), Health Canada, Korean Food and Drug Administration (KFDA), Ministry of Health, Malaysia etc. have developed guidelines for dealing with these products. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has also provided useful guidance for biological therapeutics, though not specific to biosimilars. Other national regulatory bodies worldwide including US Food and Drug Administration (FDA) are in the process of developing separate set of regulations for such products.[33]

Currently safety testing of biosimilars follows the same guidelines as those for biologicals. However, the Department of Biotechnology is in the process of drafting "Guidelines for Preclinical Evaluation of Similar Biologics" to provide guidance to applicants for generating data for approval of similar biologics and regulations for evaluating the submissions in India.[34]

Other regulatory bodies that are involved in the approval process of recombinant pharmaceutical products include Institutional Biosafety Committee (IBSC), RCGM, GEAC apex bodies formed under the "Rules for the Manufacture, Use, Import, Export and Storage of Hazardous Microorganisms/Genetically Engineered Organisms or Cells, 1989 (Rules1989)" under the Environment (Protection) Act, 1986. The rules mentioned above cover the area of research as well as large scale applications of Genetically Modified Organisms (GMOs) and products thereof. The recombinant biological products are regulated under these rules from the research and product development stage up to its release into the environment.[35]

Tests prescribed in the Guidelines for generating Preclinical and Clinical data for r-DNA vaccines, diagnostics and other biologicals, 1999[36]

- Single dose toxicity tests
- Immunotoxicity
- Reproductive performance and Developmental toxicity
- Genotoxicity
- Carcinogenicity Studies

4. Food and Food products

According to the Food Safety and Standards Act of 2006[37], the definition of Food and Food products is as follows:

- ""food" means any substance, whether processed, partially processed or unprocessed, which is intended for human consumption and includes primary food, to the extent defined in clause (ZK) genetically modified or engineered food or food containing such ingredients, infant food, packaged drinking water, alcoholic drink, chewing gum, and any substance, including water used into the food during its manufacture, preparation or treatment but does not include any animal feed, live animals unless they are prepared or processed for placing on the market for human consumption, plants prior to harvesting, drugs and medicinal products, cosmetics, narcotic or psychotropic substances."
- ""food additive" means any substance not normally consumed as a food by itself or used as a typical ingredient of the food, whether or not it has nutritive value, the intentional addition of which to food for a technological (including organoleptic) purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food results, or may be reasonably expected to result (directly or indirectly), in it or its by-products becoming a component of or otherwise affecting the characteristics of such food but does not include "contaminants" or substances added to food for maintaining or improving nutritional qualities;"

Every study, test or examination related to Food or food additives is regulated under the **Food Safety and Standard Act, 2006**.[38] The Food Safety and Standard Authority was formed through the Food Safety Act, 2006 which has provisioned it to take over the function of laying down standards and regulation for food and food products, their manufacture, storage, distribution, sale and import. It will repeal various other acts like Prevention of Food Adulteration Act, 1954, Fruit Products Act, 1955, Meat Food Products Order, 1973, Vegetable Oil (Control) Products, 1947, and various others.[39] The Food Safety Act is currently completely harmonized with the Codex Alimentarius Commission through the WTO-TBT agreement.[40] [41] "Codex India" the National Codex Contact Point (NCCP) for India is the Food Safety and Standard Authority of India (FSSAI)[42] and located at the Directorate General of Health Services, Ministry of Health and Family Welfare (MOH&FW), Government of India. Codex activities in India are facilitated through the National Codex Committee which mediates India's input to the work of Codex through an established consultation process by the FSSAI. [43]

In addition to the Food Safety and Standard Authority, the Central Committee for Food Standards [CCFS] also plays an important role in the regulation of food additives [to be replaced by the Food Safety and Standard Authority scientific panel]. Any company or institution wanting to introduce a food additive into the market would have to write to the CCFS and subsequently give a presentation, depending on which, the committee would either approve or reject the proposal. If the proposal is approved, a field study is required to be done by State Agricultural Universities. These universities are deputed to then perform various tests including safety and efficacy tests with the help of CODEX guidelines. [44]

5. Genetically Modified Crops

The application of biotechnology in agriculture is currently being dealt with by three different Ministries/Departments:[45]

(1) Ministry of Agriculture;
(2) Ministry of Environment and Forests; and
(3) Department of Biotechnology, Ministry of Science and Technology.

Concerns about the safety of genetically engineered plants have increased as more of these are being developed for commercial release.[46]

In India, the manufacture, import, use, research and release of genetically modified organisms (GMOs) as well as products made by the use of such organisms, as mentioned previously in the chapter, are governed by the rules notified by the MoEF on December 5, 1989 under the Environmental (Protection) Act 1986. These rules and regulations commonly referred to as Rules 1989, cover the areas of research as well as large-scale applications of GMOs and products made throughout India (MoEF 1989).[47]

The regulatory agencies responsible for implementation of the Rules 1989 are MoEF and the Department of Biotechnology (DBT), Government of India, through six competent authorities:[48]

- Recombinant DNA Advisory Committee (RDAC);
- Review Committee on Genetic Manipulation (RCGM);
- Genetic Engineering Approval Committee (GEAC);
- Institutional Biosafety Committees (IBSC);
- State Biotechnology Coordination Committees (SBCC);
- District Level Committees (DLC).

Prior to seeking approval for the Genetic Engineering Appraisal Committee, the Biosafety data of genetically modified crops is required to be generated by applicants as per "Rules for the manufacture, use, import, export & storage of hazardous micro organisms, genetically engineered organisms or cells, 1989" and "Revised Guidelines for Research in Transgenic Plants & Guidelines for Toxicity and Allergenicity Evaluation of Transgenic Seeds, Plants and Plant parts - 1998." The IBSC is empowered to give approval to recombinant experiments or seek permission of the RCGM in case of experiments with higher risk potential. This data is then submitted to the GEAC for environmental clearance.[49]

Till Date, the Department of Biotechnology has prepared five protocols. Each of these is based on international best practices, including guidance and peer reviewed publications available from the Codex Alimentarius Commission, The Food and Agriculture Organization, the World Health Organization, the Organization for Economic Cooperation and Development, and the International Life Sciences Institute.[50]

In 2005, the Department of Biotechnology published a draft National Biotechnology Development Strategy which elaborated a ten year vision for the future of Biotechnology in India. It was approved by the Government after consultations with various experts including stakeholders such as ministries, universities, private sector, nongovernmental, voluntary and international organizations. The Department of Biotechnology was given the entire responsibility of setting up a National Biotechnology Regulatory Authority, a body that would be responsible for regulating the safe development and deployment of biotechnology products and processes. It also wants to promulgate, through the National Biotechnology Regulatory Act (NBR Act), which would ensure that all biotechnology products and processes are subject to regulation regarding their safety. [51] The National Biotechnology Regulatory Authority has now transformed into the Biotechnology Regulatory Authority of India (BRAI). In August, 2010, the union cabinet passed the bill for the formation for the Biotechnology Regulatory Authority of India. However, this is yet to be passed by the parliament. The BRAI is said to replace the GEAC if the proposed bill is passed.[52] There has been considerable opposition to the setting up of the BRAI with many states and nongovernmental organizations

opposing it on grounds that it will take away powers from both the farmers and the consumers.[53]Therefore it is expected that preclinical, safety testing of all genetically modified organisms and their application will be regulated by a single regulatory body i.e. the Biotechnology Regulatory Authority of India.[54]

6. Pesticides and plant protection chemicals

The realization for the need for regulation of Pesticides and other plant protection chemicals in India came after an incident in 1958 after a number of deaths were reported in Kerala and Tamil Nadu when pesticide contaminated wheat was shipped with food grains. The government of India appointed a commission of enquiry. The Indian Council of Agricultural Research then formed an expert executive committee. This committee looked into pesticide use and provided recommendations for the Central Insecticides Act.[55]

The Department of Agriculture in the Ministry then framed the Central Insecticides Act. Under this act, rules and regulations were framed for the manufacture, sale, formulation and import of pesticides. It is also responsible for regulating the safety testing of pesticides. The act also makes it compulsory for every pesticide to be registered.[56]

For the registration of the pesticides and implementation of the above mentioned rules and regulations, the Central Insecticide Board (CIB) and Registration Committee (RC) was formed in 1971 under the Central Insecticides Act.[57]

The structure of the Central Insecticide Board and Registration Committee is common excepting the Chairman, where there is a separate chairman for the Central Insecticide Board and a separate one for the Registration Committee. [58]

While the Central Insecticide Board or the CIB is responsible to advise the central government on technical matters regarding the act[59], the RC's function is to register each pesticide in the country after scrutinizing the formulae and claims made by the applicant as regards to both its efficacy and safety to human beings and animals. It also formulates guidelines and laws for safety testing of the pesticides.[60]

For successful registration of a pesticide, the applicant who wants to either manufacture or import a pesticide files an application. This Registration committee, after an inquiry (if required) and checking that the application conforms to the regulations including that of efficacy and safety to humans and animals, issues a certificate of registration and allots a registration number for an initial period of 2 years (for new pesticides). If the pesticide is seen to cause risk to human beings or animals, the registration committee has the power to refuse or reject the registration of the same.[61]

The procedure for safety testing of pesticides is given in the guidelines specified by Gaitonde Committee Report (GCR) of 1977. This Gaitonde Committee Report was formed after the Registration Committee had called for a special meeting to discuss the progress and problems faced by the pesticide industry in generating the toxicological data requirement. Under the chairmanship of Dr B.B. Gaitonde, three industry associations namely Pesticide Association of India (PAI), Pesticide Formulation Association of India (PFAI) and National Alliance of Youth Entrepreneurs (NAYE) participated in this specially convened meeting to recommend toxicological and residue data for registration of pesticides.[62]

Approximately 42 years after the GCR, a new committee, under the chairmanship of Dr D.Kanungo formulated a new set of guidelines. This revision of current toxicological data requirements present under the Gaitonde Committee report is an effort to harmonize India's legislation with international guidelines, especially those of the OECD (Organisation for Economic Cooperation and Development).[63]

The Kanungo committee has already submitted its report and has been given a period of three months as of February 2012 to come up with detailed study wise protocols by the Registration committee. A special subcommittee has also been formed for this purpose.[64]

While the effort of the registration committee to come up with revised guidelines is a laudable one, it has to be kept in mind that since India recently joined the OECD agreement on "Mutual Acceptance of Data" in 2011, it is understood that India, for safety assessment of chemicals, can follow what the OECD guidelines already state. With acceptance of OECD data, it will help India hasten the process of preventing unnecessary 40 year old tests that are being performed till this day.[65]

The need for India is to move not only towards reduction of animals in safety assessment tests but also use of alternatives as given in various international guidelines. This, not only promotes good science but also animal welfare.

Risk assessment needs have changed over time and a 40 year old testing guideline will be far from the current state of science. Not only has the number and type of animals required changed, but also techniques. The need of the hour is globally harmonized data which will help, not only in reducing and replacement of animals in safety testing of pesticides but also advanced science in the form of alternatives.

7. Medical devices:

In India import, manufacturing, sale and distribution of Medical devices is regulated under Drugs and Cosmetics Act and Rules. At present, Medical Devices notified by Central Government are regulated under the said Act.[66] [67] [68]

The Ministry of Health and Family Welfare, Govt. of India under several Gazette notifications has notified various medicals to be considered as drugs under Section 3, Clause (b). Sub clause (iv) of the Drugs and Cosmetics Act. Since Medical devices and various products like condoms, sera, blood component bags, intra uterine devices, etc are considered 'drugs' under the Act[69], their safety testing is governed and regulated by Schedule Y. (Personal Communication with Dr. P. Balakrishna Murthy)

The Design Analysis for a medical device comprises of analyzing its physical and metrological standardization and comparing it to the previously approved device of the similar type. The Design Analysis of a medical device in India is carried out in accordance with the established International standards for the device (e.g. ISO standards).[70]

Device performance for its actions including mechanical, electrical, thermal, radiation, etc. and safety data in healthy and with pathology animal model (intended to be treated by such medical device) demonstrating absolute tissue reaction to active and basic parts of the devices, on local tissue and on whole organism are also to be tested. If the active component of device is defined as drug, data for its animal studies also as per schedule Y should be submitted.[71]

The labeling of Medical Devices shall conform to the Indian Standards Specifications laid down from time to time by the Bureau of Indian Standards in addition to any other requirement prescribed under the said rules.[72]

Currently, the Department of Science and Technology has proposed a new Medical Devices Safety Bill, 2008, an updated version of its earlier proposed bill was rejected. But debates between the Ministry of Health and Family Welfare and Department of Science and Technology go on and there is nothing concrete yet.[73]

8. Household chemicals, detergents and other surface active agents

Household chemicals, as such, are not defined anywhere in any document.

There exists, however, guidelines for standards on chemicals used for household purposes. These guidelines are issued by the Bureau of Indian Standards (BIS).

The BIS has a number of divisions, one of them being the Chemical Council Division (CHD). The central CHD committee, in turn has about thirty four sectional committees, each mandated with setting standards for various products such as ceramic material, glassware, explosives, nuclear material, paints and varnishes, etc.[74]

Sectional committee CHD 25 currently has two safety testing guidelines namely IS13424:2001 i.e. Safety evaluation of bathing bars and toilet soaps and IS 11601:2002 i.e. Methods of safety evaluation of synthetic detergents.

While bathing bars and toilet soaps are covered under cosmetics, synthetic detergents come under chemicals other than cosmetics, for which, safety testing guidelines have been prescribed in IS 11601:2002. This is the only document in the CHD 25 sectional committee which has a safety testing guideline on animals. This guideline mentions skin sensitization tests that are performed on guinea pigs.[75] These tests are mainly Buehler tests, Magnusson and Kligman test.[76]

Authorities say that there are no other tests which talk of safety testing other than the ones mentioned above.[77]

The safety tests make use of human volunteers for the skin irritation test while for skin sensitization test, guinea pigs are still used.

Other standards under the CHD 25 committee consist of those for Disinfectants, de-odorizing cum disinfectant fluids, toilet cleaners other cleaning chemicals.

Other than CHD 25, there is no other committee in the CHD division which prescribes or talks of animal tests.[78]

(v) The Regulation of Animal Experimentation in India

Experiments on animals in research and education are regulated by Appendix IV of the Prevention of Cruelty to Animals Act, 1960 (PCA Act) and associated Breeding of and Experiments on Animals (Control and Supervision) Rules, 1998 (as amended in 2001 and 2006). The PCA act empowers the Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), a statutory body formed under the PCA Act, to enforce the law with regard to the regulation of animal experimentation in India and the use of animals in education.

Through the provisions of the PCA Act as well as through stipulations that the CPCSEA issues from time to time, the following provisions exist in India for the regulation of the use of animals in experimentation, including toxicity testing:

1. Any institution that uses animals for research, safety testing or education must register itself with the CPCSEA.
2. Each such institution has to form an Institutional Animal Ethics Committee (IAEC).
3. This body is responsible for inspecting the concerned institution's animal house and approving or rejecting animal research projects.
4. The IAEC, by an amendment brought about to the Breeding of and Experiments on Animals Rules in 2006, was given power to permit only experiments on small animals.
5. Only the central committee of the CPCSEA has the power to approve large animal experiments.[79]
6. The CPCSEA has the power to prohibit any kind of experiment upon receiving a complaint against an institution and upon the establishment of malafide on part of the institution.[80]

Since the IAEC is the first line of defense in the regulation of the use of animals in experimentation, it is instructive to examine the constitution of the IAEC and its designated roles. The IAEC is required to have 8 members, as follows:[81]

- A biological scientist
- Two scientists from different biological disciplines
- A veterinarian involved in the care of animal
- Scientist in charge of the animal facility of the establishment concerned
- A scientist from outside the institute
- A non scientific socially aware member and
- A nominee of CPCSEA

This composition of members forming the IAEC is required to perform the following functions:[8283]

- To review all types of animal research proposals involving small animal experimentation before the start of the study. In case of large animals, it is required to forward the proposals to CPCSEA
- To ensure experiments are performed with due care and humanity and under the influence of anesthesia (where possible) to prevent the animals from feeling pain
- To ensure experiments are avoided where it is possible to do so
- To ensure large animal experiments are avoided if the same results can be achieved by small animals

- IAEC is required to monitor the research throughout the project and after completion of it through periodic reports
- It is required to visit the animal house and laboratories where the experiments are conducted to ensure compliance with all regulatory requirements, guidelines and laws.

While the above mentioned are the general roles of the IAEC and the CPCSEA, with particular regard to toxicity testing, the manner in which the CPCSEA and IAECs participate in the regulatory process is the following:

- Institutions or companies seeking approval for performing regulatory tests submit their proposals to the IAEC or the CPCSEA, depending on the type of animals proposed to be used in the tests.
- They are required to submit information of the product that is being tested and the regulation that governs the testing.
- If the number of animals varies from the ones specified in the Indian regulatory guidelines and laws, the experimenting organization or company is required to justify the reason for such a variation.
- The CPCSEA nominee has to ensure that animals greater than the minimum number specified in the legislation and/or guideline are not used.
- The CPCSEA nominee ensures that the rules regarding animal housing, care and good laboratory practices are followed by the institution.

Hence with regard to toxicity testing (as well as animal experimentation in general), the CPCSEA and its representatives on Institutional Animal Ethics Committees is a key mechanism, legitimized through legislation, for regulating the use of animals in experimentation. There are limitations in these institutions fulfilling their designated role. This is discussed in the last chapter as well as interventions possible to strengthen and support these bodies.

III. Role of the Private sector in Regulatory toxicology

Background and Structure of the Sector

The Indian private sector is basically divided into two parts:[84]

1) Product Discovery Companies who discover or develop new formulae and compositions for various products. They are the discoverers and innovators.
2) Contract Research Organizations (CRO) who work on those projects which are contracted out to them by discovery or innovator companies. (Personal communication, Dr.Uday Kumar, Incogen)

Key characteristics of the sector in India are outlined below. These have been gleaned through interviews with experts in the private discovery arena as well as CROs: [85]

1. The Product discovery company may choose to perform their Preclinical toxicity either in-house or may outsource its work to a Contract research organization.
2. Earlier discovery work in India was very limited. The safety testing for this limited discovery work was mainly monopolized by government institutes.
3. About 15 years back (in the mid 1990s), the floodgates of contracting opened both in the pre clinical as well as clinical arena - riding mainly on drug discovery companies in the west outsourcing their work to India. This also, incidentally, coincided with the boom in the biotechnology sector in India.
4. At this point several Indian (discovery) companies saw business opportunity in pre clinical and clinical work and diversified their businesses to include contract divisions. This experiment attempted by companies failed as a result of intellectual property rights issues i.e. the contract division did not attract adequate business as rivals /innovators were apprehensive of giving them business.
5. As a result of this, there emerged a clear demarcation between private discovery research companies and contract research organizations (CROs). A number of companies that started out as drug discovery companies, subsequently ventured into contracting, ultimately either quit the contracting arena or the discovery one. Hence in the current scenario in India, there is nearly a watertight compartmentalization of discovery companies and contract testing ones.

Scale of the CRO Sector and Major Players

India ranks fourteenth in the Global market for Pharmaceuticals with sales going up to US $ 19 billion. Estimates are that it will rise to US $ 50 billion by 2020.[86] India's domestic market was at about US $ 11 billion in 2009 and is expected to rise to US $ 30 billion by 2020. The domestic market is huge with around 10,000 firms collectively controlling about 70% of the market. Along with a high number of generic firms (of which many are in collaboration with global pharma companies), India has a strong market for Contract manufacturing units. Because of low costs, high number of trained experts, India has been a suitable place to set up some contract research organizations. [87]With the Indian CRO expected to reach US $ 916 million from around US $ 605 million in 2008, India still has much potential to rise up to the quality expectations.[88] Even though figures have continuously improved, India hasn't done as well as China whose figures are at around 10% of the global market reaching US $10-20 billion.[89] Preclinical toxicology, as a standalone sector is expected to reach US $ 150 million by 2015 accounting to about 15% of the total CRO business.[90]

Leading players in the pre clinical CRO arena include:[91]

- Advinus Therapeutics Private Limited – This is the leader in regulatory animal toxicology landscape in India.
- Jai Research Foundation,
- Aurigene Discovery Technologies,
- RCC Limited India,
- Syngene International Ltd,
- Intox Limited, etc.
- GVK Bio
- Reliance Life Sciences
- Chembiotek
- Clintox Bioservices
- Aurobindo

According to research, India's presence in the preclinical development domain has been historically limited to medicinal/ discovery chemistry. As of 2009, the total Indian export of preclinical services (discovery + development) was dominated by discovery chemistry (at 78% of the total), followed by discovery biology (at 15% of the total) and toxicology services trailing with a mere 8% contribution. However, with expanding global requirement for low-cost and world-class toxicology services, preclinical toxicology services are projected to account for as much as 15% of total preclinical service exports from India by 2015, with preclinical toxicology projected to grow ~ > 30% p.a. during this period. Indian companies providing pre-IND toxicology services can be divided into three broad segments. First, there are over 10 CROs that provide non-GLP toxicity studies to aid lead optimization/candidate selection as part of the overall discovery process. Second, there are 5-6 CROs that are capable of providing selected GLP toxicity services that enable an Investigational New Drug (IND) submission. Lastly, there are CROs that provide end-to-end services required to deliver an IND package.[92]

An aspect that we investigated was the presence of global contract testing players in the Indian arena. Of the 1100 odd CROs worldwide, the majority of them (approximately 70 percent) offer only clinical trials and the remaining 30 percent offer preclinical safety testing to various extents. Covance, PPD Inc, MPI Research, Harlan and Huntingdon Lifesciences provides the majority of the preclinical services. None of them have preclinical toxicology representation in India at this time. The business style in Indian market differs considerably from those in western countries. The key players in the preclinical market in India (listed above) offer stiff competition to western CROs both in terms of quality of work and price.[93]

The Current Status of the CRO Sector

The major growth in activity of Contract Research Organizations (CROs) for safety testing, both clinical and pre-clinical, is about 15 years old in India.[94] This section presents some salient features of the Indian CRO sector, particularly as it pertains to the safety testing arena:

- CROs were initially developed as outsourcing service companies but in recent times, they have expanded their scope to provide comprehensive management of the drug/chemical development processes for their client companies especially in the case of pre clinical toxicology, safety pharmacology and in vitro technologies.[95]

- It emerges that till about 2007-08, the bulk of the safety testing portfolio of Indian contract research organizations comprised of agrochemicals (including pesticides); however following 2009-10, there is an increased testing of drugs as well.[96]
- On the subject of client profile of Indian CROs, the proportion of international clients to national ones was approximately 10 (international):90 (domestic) till 2008. Subsequently, the proportion of international clientele has risen and is estimated approximately at 30 (international):70 (domestic). This shift has followed various GLP accreditations received by Indian CROs, including those that are valid in EU countries. [97]
- Interestingly, this industry has evolved from providing limited clinical trial services in the 1970s, to a full-service industry that today encompasses the entire drug development process, including preclinical safety evaluations, study design, clinical trial management, data collection, biostatistical analysis, and completing product regulatory requirements.
- Another facet that has emerged with regard to Indian CROs is that small to mid-sized preclinical CROs in India run their laboratories to near full capacity. This suggests that the demand for preclinical testing is not being fulfilled and that business opportunities continue to persist for CROs.
- Industry watchers have been predicting a bright horizon for the CRO sector – with regard to toxicity services as well as larger discovery and development services. It is useful to look at some of the projected drivers of this growth:
    - Within the drug development process, preclinical services are the fastest growing outsourced segment. This is associated with a constant shortage of preclinical CRO capacity worldwide. The shortage for preclinical testing is getting translated into long delays in starting the studies. Companies are being forced to reserve toxicology testing slots up to six months in advance, a long lead time for acute toxicology testing. Estimates suggest that there is a gap of approximately 20-30 percent between demand and preclinical capacity, globally. [98]
    - A substantial growth in the preclinical outsourcing market is predicted from 2011 onwards, due to the implementation of Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) legislation and ever tightening controls on chemical, fertilizers, cosmetics and food safety – especially in western countries.[99]
    - Further, the expectation that organization for economic cooperation and development (OECD) will soon approve the Indian GLP program, should provide the necessary impetus to preclinical services from India. [100]
    - Several pharma companies have made significant reduction in their pre clinical work force driven by recession. The CRO sector is expected to benefit from this as a result of outsourcing when the economy turns around.
    - In the non drugs sphere, the cosmetics and tobacco industries in the west are being subjected to tightening regulations and will have to do safety testing, predominantly using in vitro systems.[101]
    - Considering the pending expiration of patents of various drugs in the years 2010-2011 and the haste around bringing new drugs into the market, a rebound growth is expected thereafter. For pharmaceutical companies coming out of recession, cost effectiveness is a factor that is highly emphasized on. They may use CROs to fill the preclinical gaps in their own organizations. This makes Asia approachable for systematic and timely work, without sacrifice in quality of work. All these factors point to India having an excellent potential for preclinical CRO growth starting from 2010-11.[102]

- The pharmaceutical industry has been undergoing a significant change right from drug development, tightening of regulations, to restructuring, in the midst of the economic downturn. The drop in the R&D spending in the last few financial years has taken a toll on the CRO industry in the west. This has also provided a unique situation to the industry in developing countries. The increasing costs and falling productivity, have driven pharmaceutical companies to outsource an increasing range of functions to CROs, in search of time and cost savings. This had produced a strong double-digit growth in the CRO sector between 2003 and 2008.

Performance of CROs in India: Competition with China and associated issues

In this section we examine the constraints in performance of Indian CROs against the growth that had been predicted.

The rate at which CROs were predicted to grow a couple of years back failed to succeed because of various factors such as recession, stricter regulations in India, bureaucracy of the Indian legal system and stiff competition from China.[103]

Additionally, GLP certification has also limited the expansion of the contract research sector. While a few select CROs are Good Laboratory Practices (GLP) certified, a large number of CROs are non GLP certified.[104] This limits the quantum of business they are able to attract. India is currently an observer to the OECD's working group on GLP and a provisional member. GLP certificates are voluntary in nature and the national GLP program functions through an apex body which consists of secretaries of concerned Ministries, Departments, Director- General, CSIR (Council of Science and Industrial Research) and Drugs Controller General of India as its members with the Secretary of Department of Science and Technology as its Chairman.[105] Only approximately 20 Indian institutions and laboratories are GLP certified[106]. The non-GLP certified CROs mostly cater to national clients with standards not matching international ones reducing chances moving up along with the international standards and of increasing the competition for the Indian market with China.[107]

Though the predictions of growth of Indian CROs were higher or at par with China, China has far exceeded India in terms of investment for preclinical studies in CROs. A prohibition on the import of large animals to India, relatively strong animal welfare legislation as well as animal welfare sentiments have resulted in fewer companies coming to India and diverting instead to China.[108]

The view about the future of CROs in India is mixed. Whereas those working within CROs feel that there is very high potential for CROs to grow and that the need of the hour is for more preclinical CROs, others say that the business climate is severely blighted due to lack of standardized animal facilities and bureaucratic red tape present in India. Such constraints will necessarily mean that Indian preclinical CROs will lose out to competition from China. Such opinion holders predict a further dampening of business in the coming years. It has also been felt that due to immense irregularities in clinical trials, preclinical trials are also affected in India due to huge public and regulatory pressure. Therefore predictions of step compound annual growth rates remain paper exercises in light of several variables that introduce unpredictability in the equation. The experience so far suggests that the growth trajectory of pre clinical CROs may not follow a linear path as several twists persist in the business climate. [109]

IV. The Way forward

Based on secondary research, interviews with regulators, toxicity scientists, others who are involved with the use of animals for research and education, interactions with members of the body that regulates animal experimentation in India, animal welfare workers who have campaigned for the development and enforcement of legislation for the protection of animals used in laboratories, we have developed a road map to advance the toxicity testing paradigm in India as well as catalyze a systematic approach to the promotion of alternatives in basic research and education. This road map has the following components:

1. Advocacy for the refinement of safety regulations :

After detailed research into all products that are tested for safety on animals, it is apparent that the current state of the respective legislations is in somewhere in between two extremes. While the legislation for safety testing of pesticides dates from the late 1970s and should be obsolete, in case of drugs the regulation is relatively advanced and more in line with OECD and ICH. The priority areas of intervention as far as safety regulations are concerned are described below:

a) Pesticide Safety evaluation: The safety testing guidelines for pesticides are currently being harmonized to OECD and EU guidelines. This has been in process for quite some time now and is due in June 2012. This process started ever since India became an adherent to OECD's "Mutual Acceptance of Data" policy in 2011. India is the third non member country to do so. Since then, the Central Insecticides Board has since initiated a process to harmonize the test guidelines contained in the Gaitonde Committee Report with OECD. The new guidelines are to be referred to as the Kanungo Committee Report. However, this harmonization does not include revising the toxicity data requirements, which is where the major progress in animal welfare can be expected. In this light, the following actions are proposed by FIAPO:

   i. Review each of test protocol and compare it with the best available, animal friendly tests prevalent in the world and recommend them to the Central Insecticides Board.

   ii. We also propose to recommend refined data requirements for toxicity tests done on animals. This will complement the harmonization of the Indian guidelines to OECD and EU guidelines, without which, the very purpose of harmonization remains under fulfilled.

b) Cosmetic Testing: The guidelines for safety testing of cosmetics are governed by the Drugs and Cosmetic Act of 1940. Schedule S within this act refers to the standards set by Bureau of Indian Standards (BIS) as the means to be followed for safety testing of cosmetics. The BIS has progressed and made amendments in the past year removing the Draize test and has also introduced human patch tests. However, BIS documents: IS 4011:1997 (Method of tests for Safety testing for Cosmetics) and IS 13424:2001 (Safety evaluation of bathing bars and toilet soaps) still consist of tests for which validated alternatives exist. These include non animal methods for some tests and relatively welfare friendly tests for others. FIAPO intends to submit formal proposals to both PCD19 and CHD25 (BIS

committees concerned with cosmetics) to bring about the requisite refinements in the tests.

c) Household chemicals: Safety tests on animals for household chemicals are contained in one document i.e. IS 11061: 2002. FIAPO plans to intervene and propose amendments to replace these tests either with the most animal friendly option or with validated non animal testing methods.

For all the above three arenas, the regulators have been identified, animal welfare issues have been discussed in detail and the proposals for amendments are being drafted.

2. Creating a support system of progressive Indian scientists:

Through the course of this research, progressive scientists keen on advancing knowledge in a manner that also promotes animal welfare have been identified. The identification of such progressive scientists is an ongoing process.It is proposed to bring together such scientists in the form of a network to promote alternative methods, particularly in refining India's regulatory toxicity testing framework.

The broad contours of such a network are elucidated below:

i. Organize periodic meetings among the identified progressive scientists to debate and exchange ideas on alternative methods; keep up with international trends on alternatives to animal testing, with a particular focus on toxicity testing. Initially it is proposed that at least one such meeting be held each year.
ii. The first meeting to initiate such a process was held on the sidelines of the Indian Science Congress in Bhubaneswar in January 2012. During this meeting the possibility of an Indian network of scientists who work on alternatives, or are otherwise interested in it; and also those scientists who are interested in welfare of animals and progress in all spheres of animal experimentation, was broached. Initially this would function as an informal network with the possibility of formalization once a critical mass is built..
iii. A number of possible objectives for the network were discussed in the meeting including liaising with national and international bodies to promote alternatives and welfare of animals, conducting training sessions, assisting and collaborating with government bodies such as the CPCSEA and other scientific associations such as Laboratory Animal Scientist's Association (LASA) and Laboratory Animal Science Association of India (LASAI). HSI would be an important liaison with its world wide experience in the promotion of alternatives. With particular regard to toxicity testing, HSI/HSUS's vast experience would be useful to enable this group to develop a progressive vision for the evolution of the toxicity testing paradigm in India.
iv. It is proposed that this network (or its individual members) will be drawn on to advance proposals that promote alternatives, particularly within the toxicity testing sphere. Hence the promotion of revisions of BIS standards and the Gaitonde Guidelines will be undertaken through the network of progressive scientists.

3. An Indian centre for the 3R's:

FIAPO wants to initiate thinking towards setting up India's very own Centre for 3R's along the lines of a similar agency in United Kingdom. This can then become the focal point for the promotion of alternatives in the country. Naturally, as with other scientific agencies, this will also be a forum for scientists to put forward their progressive, animal reducing and replacing

discoveries to an agency which can validate their tests which can in turn be used by various regulatory bodies. The presence of such a body will be particularly crucial for the phasing out of animals in toxicity testing. It will also hasten the adoption of alternatives in teaching and in basic research.

It is conceivable that the proposed Indian network of scientists on alternatives will form the initial core group that advances the concept of an Indian centre for 3R's. HSI and CAAT will have an important role in supporting the drive towards an Indian Centre for the 3R's by bringing to the table the experience of centers for alternatives to animal testing in other countries, suggesting the pathways for the evolution of such a centre and providing associated support and guidance.

4. Representing Animal Welfare and Alternatives at Scientific fora:

In order to further the dialogue on alternatives within the larger Indian scientific community, FIAPO proposes to engage regularly with scientists in conferences and seminars. This will make an animal welfare presence felt at such fora and present an opportunity to share news about progress on alternatives. Participating in various national and international scientific conferences and workshops will not only help build contacts, particularly with progressive scientists that can become advocates for alternatives, it will also build momentum for the movement towards the use of alternatives. Currently there is nearly no engagement of animal welfare workers with scientists. This is a key lacuna and the FIAPO proposes to addresses this by putting forth an animal welfare perspective at scientific events.

5. Recruiting members for Institutional Animal Ethics Committees (IAEC) and their capacity building:

According to CPCSEA regulations, each institution that uses animals for research or education is required to set up an institutional animal ethics committee. The functions of IAECs are to oversee and ensure the following:

(a) That experiments on animals are avoided wherever it is possible to do so; as for example; in medical schools, hospitals, colleges and the like, if other teaching devices such as books, models, films and the like, may equally suffice;
(b) That experiments on larger animals are avoided when it is possible to achieve the same results by experiments upon small laboratory animals like guinea-'pigs, rabbits, mice, rats etc;
(c) That experiments shall be performed in every case by or under the supervision of a person duly qualified in that behalf, that is, Degree or Diploma holders in Veterinary Science or Medicine or Laboratory Animal Science of a University or an Institution recognised by the Government for the purpose and under the responsibility of the person performing the experiment;
(d) That experiments are performed with due care and humanity and that as far as possible experiments involving operations are performed under the influence of some anaesthetic of sufficient power to prevent the animals feeling pain;
(e) That animals which, in the course of experiments under the influence of anaesthetics, are so injured that their recovery would involve serious suffering, are ordinarily destroyed while still insensible;
(f) That, as far as possible, experiments are not performed merely for the purpose of acquiring manual skill;
(g) That animals intended for the performance of experiments are properly looked after both before and after experiments;
(h) That suitable records are maintained with respect to experiments performed on animals.

In fulfilment of these roles, the IAEC are meant to review and approve all types of research proposals involving small animal experimentation before the start of the study. For experimentation on large animals, the case is required to be forwarded to CPCSEA with a recommendation from the IAEC.

IAEC is required to monitor the research throughout the study and after completion of study through periodic reports and visit to animal house and laboratory where the experiments are conducted. The committee has to ensure compliance with all regulatory requirements, applicable rules, guidelines and laws.

The composition of an IAEC has to be along the following lines: [110]
1. A biological scientist (from within the institute),
2. Two scientists from different biological disciplines (from within the institute),
3. A veterinarian involved in the care of animal (from within the institute),
4. Scientist in charge of animal facility of the establishment concerned,
5. A scientist from, outside the institute,
6. A non scientific socially aware member (to be approved by the CPCSEA) and
7. A nominee of CPCSEA

The IAEC therefore can be a key mechanism for ensuring animal welfare at the grassroots level i.e. at the level of institutions that use animals. However for this to happen, it has to be ensured that the committee is playing the role it is mandated to do. Since the constitution of the committee is skewed in favor of representatives from within the institution that is performing the experiments and using animals, it is essentially the last 2 positions on the IAEC (that are to be nominated by the CPCSEA) that are critical to the IAEC effectively dispensing its duties.

The constraints with regard to CPCSEA representatives on IAECs have been the following:

1. It has been singularly difficult to identify appropriate persons who can serve as CPCSEA nominees. Most animal welfare personnel are already overburdened with existing responsibilities for them to assume additional responsibility that the IAEC membership brings. The CPCSEA itself has no mechanism to identify and recruit IAEC nominees.
2. Even where the CPCSEA has been able to nominate representatives on IAEC's, the capacity of such nominees limits their ability to effectively play a role in the functioning of the committee. The nature of proposals that are presented at IAECs require a basic minimum grasp of technical research and education related issues as well as the regulatory and legal framework. Often such capacity is limited in CPCSEA nominees, thereby limiting the contribution that they can make.

In order to fill these gaps and to better utilize the opportunity that IAECs present, FIAPO proposes to undertake the following:

1. Through our extensive network, FIAPO would identify appropriate candidates that the CPCSEA can nominate on IAECs throughout the country. These candidates will be proposed to the CPCSEA through FIAPO board members, who are also members of the CPCSEA.
2. FIAPO would create short training modules that would equip CPCSEA nominees on IAECs with the requisite knowledge and information to effectively play their role. Such trainings will be held at 4 different locations, thus making it convenient for IAEC representatives to attend.

Clearly, this road map is a dynamic process that will evolve overtime. Our effort will be to collaborate with different stakeholders and build momentum towards a science driven alternatives paradigm. India has the potential to be at the forefront of this global revolution. As animal advocates, FIAPO, HSI and their partners look forward to enabling Indian scientists' surge towards 21st century science that is humane and benefits society at large.

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