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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT – I – Bioethics Biosafety and IPR – SBB1615

UNIT-1 BIOETHICS IN BIOTECHNOLOGY

Definition of ethics and Bioethics, Ethics in Biotechnology(positive and negative effects with classical examples – Rice with Vitamin A, No-till Agriculture, cotton without insecticide, reduced need for fertilizer, biological pest control , slow ripening fruits and controlled ripening, fast growing trees and fishes.

Bioethics

- Bioethics is the study of the typically controversial ethical issues emerging from new situations and possibilities brought about by advances in biology and medicine.
- It is also moral discernment as it relates to medical policy and practice.
- Bioethicists are concerned with the ethical questions that arise in the relationships among life sciences, biotechnology, medicine, politics, law, and philosophy.
- It also includes the study of the more commonplace questions of values ("the ethics of the ordinary") which arise in primary care and other branches of medicine.

Etymology

- The term *Bioethics* (Greek *bios*, life; *ethos*, behavior) was coined in 1926 by Fritz Jahr, who "anticipated many of the arguments and discussions now current in biological research involving animals" in an article about the "bioethical imperative," as he called it, regarding the scientific use of animals and plants.
- In 1970, the American biochemistVan Rensselaer Potter also used the term with a broader meaning including solidarity towards the biosphere, thus generating a "global ethics," a discipline representing a link between biology, ecology, medicine and human values in order to attain the survival of both human beings and other animal species.

Purpose and scope

- The field of bioethics has addressed a broad swathe of human inquiry, ranging from debates over the boundaries of life (e.g. abortion, euthanasia), surrogacy, the allocation of scarce health care resources (e.g. organ donation, health care rationing) to the right to refuse medical care for religious or cultural reasons.

- Bioethicists often disagree among themselves over the precise limits of their discipline, debating whether the field should concern itself with the ethical evaluation of all questions involving biology and medicine, or only a subset of these questions.[4]
- Some bioethicists would narrow ethical evaluation only to the morality of medical treatments or technological innovations, and the timing of medical treatment of humans. Others would broaden the scope of ethical evaluation to include the morality of all actions that might help or harm organisms capable of feeling fear.

Scope

The scope of bioethics can expand with biotechnology, including cloning, gene therapy, life extension, human genetic engineering, astroethics and life in space,[5] and manipulation of basic biology through altered DNA, XNA and proteins.[6] These developments will affect future evolution, and may require new principles that address life at its core, such as biotic ethics that values life itself at its basic biological processes and structures, and seeks their propagation.

Principles

- One of the first areas addressed by modern bioethicists was that of human experimentation.
- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was initially established in 1974 to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects.
- However, the fundamental principles announced in the Belmont Report (1979)—namely, autonomy, beneficence and justice—have influenced the thinking of bioethicists across a wide range of issues.
- Others have added non-maleficence, human dignity and the sanctity of life to this list of cardinal values.
- Another important principle of bioethics is its placement of value on discussion and presentation.
- Numerous discussion based bioethics groups exist in universities across the United States to champion exactly such goals.

- Examples include the Ohio State Bioethics Society[8] and the Bioethics Society of Cornell.[9]
- Professional level versions of these organizations also exist

Medical ethics

- Medical ethics is the study of moral values and judgments as they apply to medicine.
- As a scholarly discipline, medical ethics encompasses its practical application in clinical settings as well as work on its history, philosophy, theology, and sociology.
- Medical ethics tends to be understood narrowly as an applied professional ethics, whereas bioethics appears to have worked more expansive concerns, touching upon the philosophy of science and issues of biotechnology
- Still, the two fields often overlap and the distinction is more a matter of style than professional consensus.
- Medical ethics shares many principles with other branches of healthcare ethics, such as nursing ethics.
- A bioethicist assists the health care and research community in examining moral issues involved in our understanding of life and death, and resolving ethical dilemmas in medicine and science.

Perspectives and methodology

Bioethicists come from a wide variety of backgrounds and have training in a diverse array of disciplines. The field contains individuals trained in philosophy such as H. Tristram Engelhardt, Jr. of Rice University, Baruch Brody of Rice University, Peter Singer of Princeton University, Daniel Callahan of the Hastings Center, and Daniel Brock of Harvard University, medically trained clinician ethicists such as Mark Siegler of the University of Chicago and Joseph Fins of Cornell University, lawyers such as Nancy Dubler of Albert Einstein College of Medicine or Jerry Menikoff of the federal Office of Human Research Protections, political scientists like Francis Fukuyama, religious studies scholars includingJames Childress, public intellectuals like Amitai Etzioni of The George Washington University, and theologians like Lisa Sowle Cahill and Stanley Hauerwas.

- The field, once dominated by formally trained philosophers, has become increasingly interdisciplinary, with some critics even claiming that the methods

of analytic philosophy have had a negative effect on the field's development. Leading journals in the field include The *Journal of Medicine and Philosophy*, The *Hastings Center Report*, the *American Journal of Bioethics*, the *Journal of Medical Ethics* and the *Cambridge Quarterly of Healthcare Ethics*. Bioethics has also benefited from the process philosophy developed by Alfred North Whitehead.

- Many religious communities have their own histories of inquiry into bioethical issues and have developed rules and guidelines on how to deal with these issues from within the viewpoint of their respective faiths.
- The Jewish, Christian and Muslim faiths have each developed a considerable body of literature on these matters.
- In the case of many non-Western cultures, a strict separation of religion from philosophy does not exist.
- In many Asian cultures, for example, there is a lively discussion on bioethical issues.
- Buddhist bioethics, in general, is characterised by a naturalistic outlook that leads to a rationalistic, pragmatic approach.
- Buddhist bioethicists include Damien Keown.
- In India, Vandana Shiva is a leading bioethicist speaking from the Hindu tradition.
- In Africa, and partly also in Latin America, the debate on bioethics frequently focuses on its practical relevance in the context of underdevelopment and geopolitical power relations.
- Masahiro Morioka argues that in Japan the bioethics movement was first launched by disability activists and feminists in the early 1970s, while academic bioethics began in the mid-1980s.

  During this period, unique philosophical discussions on brain death and disability appeared both in the academy and journalism.
- Bioethics has also had its critics.
- Paul Farmer has pointed out that bioethics tends to focus its attention on problems that arise from "too much care," for patients in industrialized nations, while giving little or no attention to the ethical problem of too little care for the poor.
- Farmer characterizes the bioethics of handling difficult clinical situations, normally in hospitals in industrialized countries, as "quandary ethics."
- And he refers to bioethicists as "endlessly rehashing the perils of too much care."

- He does not regard quandary ethics and clinical bioethics as unimportant; he argues, rather, that bioethics must be balanced and give due weight to the poor.

Issues

- Areas of health sciences that are the subject of published, peer-reviewed bioethical analysis include:

• Abortion • Alternative Medicine • Animal rights • Artificial insemination • Artificial life • Artificial womb • Assisted suicide • Biocentrism • Biological agent • Biological patent • Biopiracy • Biorisk • Biotic ethics • Blood transfusion • Body modification • Brain-computer interface • Chimeras • Circumcision • Cloning • Confidentiality (medical records) • Consent • Contraception (birth control) • Cryonics • Disability • Lobotomy • Medicalization	• Eugenics • Euthanasia (human, non-human animal) • Exorcism • Faith Healing • Feeding tube • Gene theft • Gene therapy • Genetically modified food • Genetically modified organism • Genomics • Great Ape Project • Human cloning • Human enhancement • Human experimentation in the United States • Human genetic engineering • Iatrogenesis • Infertility treatments • Intersex • Life extension • Prescription drug prices in the United States • Life support • Procreative beneficence

• Medical malpractice • Medical research • Medical torture • Mediation • Mitochondrial donation • Moral obligation • Moral status of animals • Nanomedicine • Nazi human experimentation • Ordinary and extraordinary care • Overtreatment • Organ donation • Organ transplant • Pain management • Parthenogenesis • Patients' Bill of Rights • Placebo • Pharmacogenetics • Political abuse of psychiatry • Population control	• Professional ethics • Psychosurgery • Quality of Life (Healthcare) • Quaternary prevention • Recreational drug use • Reproductive rights • Reproductive technology • Reprogenetics • Sex reassignment therapy • Sperm and egg donation • Spiritual drug use • Stem cell research • Suicide • Surrogacy • Transexuality • Transhumanism • Transplant trade • Vaccination controversy • Xenotransfusion • Xenotransplantation

Human embryonic stem cell research and ethics

This text has been taken from the following article, Hug K. Therapeutic perspectives of human embryonic stem cell research versus the moral status of a human embryo – does one have to be compromised for the other? Medicina (Kaunas) 2006; 42 (2): 107-14. The author has made some modifications in this web version of the text.

What is ethically at issue with embryo research where the fertilized egg has to be destroyed?

The moral status of the embryos used to derive stem cell lines is debatable (1). Embryonic stem cell research poses a moral problem, as it brings into tension two fundamental moral principles that we highly value: the duty to prevent or alleviate suffering, and the duty to respect the value of human life. The harvesting of human embryonic stem cells violates this second duty as it results in the destruction of a possible human life. Both principles cannot simultaneously be respected in the case of embryonic stem cell research. The question then is which principle ought to be given precedence in this conflict situation. Should we give more weight to the first, and permit destructive embryonic stem cell research because of its potential benefits? The aim of stem cell research (to cure diseases and relieve suffering) is universally recognized as a good aim (2). Or should we give more weight to the second, and prohibit destructive embryonic research because it violates respect for the value of the embryo as the very beginning of a possible human life (3)?

What moral status does the human embryo have?

The moral status that the human embryo is given varies. Three different main positions with variations can be separated.

1. **Having full moral status after fertilization of the egg**

   This point of view can be divided into two: considering embryos worthy of protection simply because they are human or considering them as potential persons. Philosophers differ on this question. Whereas many philosophers, particularly utilitarians, do not consider a fertilized human egg before implantation to satisfy the criteria of personhood, others take a different view. However, the criteria of personhood are notoriously unclear. The perspective of the same point of view is that fertilized eggs are worthy of protection simply because they are human.

   Arguments: There is no non-arbitrary point, a morally significant dividing line in the continuum of physical growth between an embryo and a developed human. Since a developmental point at which personhood is acquired cannot be pointed out, individuals are counted as human beings at their embryonic stage as well as their fully developed stage (3). If our lives are worthy of respect simply because we are human, it would be a mistake to think that at some younger age or earlier stage of development (e.g. when we began our lives as fertilized eggs) we were not worthy of respect (4). Therefore, if

we do not accept fertilization as a morally decisive moment from which full protection should be guaranteed, there is no other similarly decisive moment. Human embryos differ from other human beings not in what they are, but in their stage of development. A human embryo is a human being in the embryonic stage, just as an infant or an adolescent is a human being in the infant or adolescent stage (5).

Counter-arguments: Even if it is not possible to point to an exact dividing line in human development at which personhood is acquired, it may be argued that whenever the transition occurs, early preimplantation stage embryos do not have the psychological, physiological, emotional or intellectual properties that we associate with personhood (3). It, therefore, follows that if human embryo does not fulfill the criteria for personhood, it does not have any interests to be protected and thus may be used instrumentally for the benefit of those who are persons (6). The fact that every person began life as an embryo does not prove that embryos are persons either. For example, although every oak tree was once an acorn, it does not mean that acorns are oak trees or that we should treat the loss of an acornas the same kind of loss as the death of an oak tree (4). There is an opinion that instead of the end of the process of fertilization of the egg, a human embryo becomes worthy of protection at around day 14 after the fertilization. There are several reasons for this opinion: • It may be argued that it is the implantation of the blastocyst in the uterine wall that is the best landmark for the definition of human life. Indeed, this is the first stage at which the individual is defined because the embryo is past the stage in which it can split to form twins (1). The end of the possibility of twinning is around day 14 after fertilization. Before this time, a researcher in a laboratory could divide a four-cell embryo into four embryos and, on the other hand, fuse four early embryos into one. It is only after twinning is not possible any more, when the life of one individual starts as a recognizable one (7). • It may also be argued that it is the formation of the nervous system that is the landmark for the definition of life, since this is then that the possibility of sensation first exists. Up to embryonic day 14, the blastocyst has no central nervous system and, therefore, cannot be considered sensate. If we can remove organs from patients who have been declared brain dead but are still alive in some sense in order to save the lives of those who are alive, we can use two hundred-cell embryos as cell donors at the same moral status as brain dead individuals (1). Embryological studies now show that fertilization is itself a process (not a “moment”). Therefore, it can be argued that an embryo in the earliest

stages (including the blastocyst stage, when stem cells would be extracted for the purpose of the research) is not sufficiently individualized to have the moral weight of personhood (8).

Arguments: Although embryos do not currently exhibit the properties of personhood, they will, if allowed to develop and fulfill their potential. Since embryos are potential persons, they ought to be accorded the moral respect and dignity that personhood requires. For example, we still treat unconscious individuals as persons even though they are not able to exercise the properties of personhood in their present state. But we know that these people will be able to when they become conscious again (3).

Counter-arguments: The embryo in itself cannot develop into a child without being transferred to a woman's uterus. It needs external aid to enable its development and hence it does not have an active potentiality to develop into a human being without help (9). Even with the external aid provided, the probability that embryos used for in vitro fertilization will develop into full-term successful births is low. This probability is also very much context-dependent: e.g. on the quality of external human intervention, such as transferal to uterus, and on other factors such as whether the embryo will implant and grow to term or even on the conditions of giving birth. Thus something that could potentially become a person should not be morally regarded as if it actually were a person. Contrary to the previous statement, the temporarily unconscious persons already had all the properties of personhood before falling into unconsciousness and will have them again when they come out of it (3).

2. **Having a moral status that begins with deserving protection and increases as the fertilized egg becomes more human-like**

   Arguments: The main point of the gradual view is that the moral status and the protection of the embryo should increase as the fertilized egg becomes more human-like. There are several reasons for such a position: • There are degrees of value of a life depending on the stage of that life. Consequently, there are degrees of respect that ought to be shown to that life at those stages. They can be identified as follows: the implantation after the sixth day, the appearance of the primitive streak at the end of the second week, the viability phase or even birth itself (10). At different stages of the end of life we tend to make different judgments of how great that loss is, depending on the stage of the lost life. Thus a fertilized egg before implantation in the uterus could be

granted a lesser degree of respect than a human fetus or a born baby (3). • There is a natural embryo loss in pregnancy, where more than half of all fertilized eggs either fail to implant or are otherwise lost. Therefore, if natural process entails the loss of some embryos for every successful birth, the loss of embryos that occurs in stem cell research should not worry us either. Those who view embryos as persons might reply that high infant mortality would not justify infanticide. But the way we respond to the natural loss of embryos suggests that we do not regard this event in the same way as the death of an infant (4).

Counter-arguments: However, there are also several reasons why human embryos at the very beginning of their existence should have the same protection as more developed embryos or fetuses: • Whatever moral status does the human embryos have, the life that it lives has a value to the one who lives this life. We protect a person's life and interests not because those interests are valuable from the point of view of the universe, but because they are important to the entity concerned. Therefore, the life of the human embryo should be protected because it has a value to the embryo itself (3). • We should be cautious and refrain from destruction of fertilized eggs even if we are not sure about their dignity, simply because being uncertain as to whether a particular organism is a human being, it would be more reasonable to refrain from destroying it. For example, a hunter refrains from shooting if he is not sure whether the particular object at which he is aiming is a deer or a man (11). • Judging the moral status of the embryo from its age is making arbitrary definitions of who is human. For example, even if we consider that the appearance of the primitive streak at day 14 after the fertilization of the egg is the threshold of when the embryo acquires moral worthiness, we must still acknowledge that patients who have lost part of their cortex from a stroke or Alzheimer's disease are no less human than they were before (12).

3. **Having no moral status at all, regarded as organic material, with a status no different from other body parts**

   Arguments: Fertilized human eggs are merely parts of other people's bodies until they reach a certain autonomous or independent developmental stage. Accordingly, they have no independent moral status at all, and are merely the property of the people from whose body they came. The only respect due to these blastocysts is the respect that should be shown to other people's property (3). The blastocysts before implantation cannot be harmed by being destroyed. To be harmed means to have an interest or

interests defeated. For a being to have an interest, this being must have beliefs, desires, expectations, aims, and purposes. The nervous system of such early embryos is not developed enough for this. Because they are not the subjects of interests, such early embryos cannot be the subjects of basic rights that protect interests (3). A pre-implantation embryo contains potentially all the cells of the human body, and by conducting research one is not destroying it, but merely directing it to become certain cells and not others, since the cells of such an embryo are still totipotent (e.g. they are still capable of multiplying into twins) (13). It can also be argued that a new human organism (at the embryo stage) is only the predecessor of the organism that the human being ultimately born will be (11).

Counter-arguments: By directing an embryo to "become certain cells", the embryo is prevented from developing in its normal complete fashion. It is completely reprogramming an embryo and thus preventing it from becoming what it was programmed to become – a human being (14).

Embryonic stem cell research and religion

The view concerning the moral status of the early human embryo before the time of its implantation in the uterus differs depending on religion.

• **Roman Catholic, Orthodox, conservative Protestant Churches**: Since a human embryo is believed to have a status of a human individual from the moment of the fertilization of the egg, it has the right to its own life, and every intervention not in favor of the embryo is a violation of that right. No end believed to be good (e.g. using stem cells to prepare other differentiated cells to be applied in what look to be promising therapeutic procedures) can justify the destruction of the embryo, which is believed to be a wrong action (15). The Orthodox Christians as well as Roman Catholics and Conservative Protestants affirm the sanctity of human life at all stages of development and believe that the process toward authentic human personhood begins with the zygote, which is committed to a developmental course that will ultimately lead to a human person.

• **Less conservative Protestant Churches** believe that the embryo has a potential human status, reflecting its gradual development from basic cells to a fetus. Thus some embryo research may be permitted. The life of the embryo is weighed against the possible benefit for the society from embryo research. The life of the human embryo is sacred from conception, but there are circumstances under which embryo research might be allowed prior to the

"primitive streak" stage (around 14th day after the fertilization), bearing in mind the seriousness of certain medical conditions that could possibly be treated.

• **Judaism**: The Jewish religious tradition emphasizes the importance of the saving of life and considers the ultimate goal of human embryonic stem cell research to be life saving. Healing in Judaism is not only permitted, it is required to be an active partner in the world's repair and perfection (8). Man is obliged to build and develop the world in every direction favorable to humanity. Therefore, any activity that contributes to advancements in the world cannot be considered as contradicting God's decrees (16). It is also believed that it is God who has given the power to create new technologies (10). Anything, which has no reason to be prohibited is permitted without having to find a reason for its permissibility (16). In Judaism the human fetus less than 40 days old (10) and certainly the pre-implantation embryo does not have a full human status (17). After those first 40 days the embryo in the uterus is considered a part of the woman until birth (9).

• **Islam:** The majority of Muslim thinkers through the ages have accepted the morality of abortion through either the fortieth day or the fourth month of pregnancy (8). It is believed that the soul is "breathed in" to the human embryo on the 40th day after fertilization and this is when life becomes sacred (18). All schools of thought in Islam accept that the fetus is accorded the status of a legal person only at later stages of its development, when perceptible form and voluntary movements appear. The thinkers make a distinction between a biological and a moral person, placing the stage of the moral person after the first trimester of pregnancy (8). However, Muslim jurists differ over whether "breathing-in" of the soul takes place in 40 or 120 days (10). Also, it is believed that there is no disease that does not have a cure, and therefore the cure should be sought. Medical progress is a strong value and stem cell research is acceptable due to its therapeutic benefits. According to the Muslim faith, the supernumerary embryos cannot be donated to other couples, as the lineage of the father must be respected. In this view, conducting research on supernumerary embryos that will no longer be used for in vitro fertilization purposes rather than destroying them is choosing the lesser of two evils (18).

Buddhism and Hinduism: Buddhism prohibits harm to any sentient beings, which presents possible restrictions on embryo and animal research (17). Also, every action (e.g. killing) that treats human beings as non-humans is considered immoral. For Buddhists, however, not all areas of medical biotechnology lead to ethical problems: more advanced medical biotechnology (where research is conducted on molecular level) is likely to be acceptable. Molecular human parts, such as cells, are hardly seen as human beings, thus their destruction

in the process of research is not likely to be seen as morally wrong (19). Regarding the research on human stem cells, the intention is important. If the intention of the research is to help and benefit humankind, such research is considered ethical. On the contrary, if the research is done just for the sake of making money out of it, it is considered as unethical. But since Buddhism places great importance on the principle of non-harming, it has grave reservations about any scientific technique or procedure that involves the destruction of life, whether human or animal. However, the principle of non-harming can be interpreted as prohibiting only the harm on sentient beings that is those who are able to feel. Therefore, Buddhism could accept research on non-sentient embryos before the day 14 of their development (8). Hinduism, like Buddhism prohibits injuring sentient beings. The Hindu tradition rejects both animal research and the destruction of sentient embryos (17). Research on supernumerary embryos that will no longer be used for in vitro fertilization purposes rather than destroying them is choosing the lesser of two evils (18).

Golden rice is a variety of rice (*Oryza sativa*) produced through genetic engineering to biosynthesize beta-carotene, a precursor of vitamin A, in the edible parts of rice.[1][2] It is intended to produce a fortified food to be grown and consumed in areas with a shortage of dietary vitamin A, a deficiency which each year is estimated to kill 670,000 children under the age of 5[3] and cause an additional 500,000 cases of irreversible childhood blindness.[4] Rice is a staple food crop for over half of the world's population, providing 30–72% of the energy intake for people in Asian countries, and becoming an effective crop for targeting vitamin deficiencies.[5]

Golden rice differs from its parental strain by the addition of three beta-carotene biosynthesis genes. The parental strain can naturally produce beta-carotene in its leaves, where it is involved in photosynthesis. However, the plant does not normally produce the pigment in the endosperm, where photosynthesis does not occur. Golden rice has met significant opposition

from environmental and anti-globalization activists. A study in the Philippines is aimed to evaluate the performance of golden rice, whether it can be planted, grown and harvested like other rice varieties, and whether golden rice poses risk to human health.[6] There has been little research on how well the beta-carotene will hold up when stored for long periods between harvest seasons, or when cooked using traditional methods.[7]

In 2005, Golden Rice 2 was announced, which produces up to 23 times as much beta-carotene as the original golden rice.[8] To receive the USDA's Recommended Dietary Allowance (RDA), it is estimated that 144 g/day of the high-yielding strain would have to be eaten. Bioavailability of the carotene from golden rice has been confirmed and found to be an effective source of vitamin A for humans.[9][10][11] Golden Rice was one of the seven winners of the 2015 Patents for Humanity Awards by the United States Patent and Trademark Office.[12][13] In 2018 came the first approvals as food in Australia, New Zealand, Canada and the US.

NO TILLAGE FARMING

What is tillage?

Tillage is an agriculture land preparation through mechanical agitation which includes digging, stirring and overturning.

Zero tillage is the process where the crop seed will be sown through drillers without prior land preparation and disturbing the soil where previous crop stubbles are present. Zero tillage not only reduce the cost of cultivation it also reduces the soil erosion, crop duration and irrigation requirement and weed effect which is better than tillage. Zero Tillage (ZT) also called No Tillage or Nil Tillage.

Zero tillage in India

No Till approach started from 1960s by farmers in India. The zero-tillage system is being followed in the Indo-Gangetic plains where rice-wheat cropping is present. Wheat will be planted after rice harvest without any operation. Hundreds of farmers are following the same system and getting more yields and profits by reducing the cost of cultivation. In South, the outhern districts like Guntur and some parts of West Godavari of Andhra Pradesh state follow the ZT system in rice-maize cropping system.

The green revolution paved the way for the rice-wheat production system in the north-western parts of India. But in due course of time, the yields of rice and wheat become stagnant due to inappropriate soil and water management system and late planting of wheat, as in the hot season

rice is being grown and in the winter wheat follows the rice. In 1990's the zero tillage came to mitigate the problem, by planting the wheat by drilling without any land preparation and tillage. The success of zero tillage depends on the machinery to drill seed in the uncultivated land. In late 1980's, CIMMYT introduced a prototype for drilling the seed. In India, the first localized seed drill was manufactured by GB Pant University with a motor to reduce the cost and make it available and affordable. The drills are tractor drawn and used in rice-wheat cropping system. Zero tillage proves better for direct-seeded rice, maize, soybean, cotton, pigeonpea, mungbean, clusterbean, pearlmillet during kharif season and wheat, barley, chickpea, mustard and lentil during rabi season. Wheat sowing after rice can be advanced by 10-12 days by adopting this technique compared to conventionally tilled wheat, and wheat yield reduction caused by late sowing can be avoided. ZT provides opportunity to escape wheat crop from terminal heat stress. Zero tillage reduces cost of cultivation by nearly Rs 2,500-3,000/ha through reduction in cost of land preparation, and reduces diesel consumption by 50-60 litres per hectare. Zero tillage reduces water requirement of crop and the loss of organic carbon by oxidation. Zero tillage reduces Phalaris minor problem in wheat. The carbon status of soil is significantly enhanced in surface soil (0-5 cm), particularly under crop residue retention with zero tillage *(Ref: Policy paper 31 - Doubling Strategy for Doubling Income of Farmers in India).*

Advantages of zero tillage

1. Reduction in the crop duration and thereby early cropping can be obtained to get higher yields.
2. Reduction in the cost of inputs for land preparation and therefore a saving of around 80%.
3. Residual moisture can be effectively utilized and number of irrigations can be reduced.
4. Dry matter and organic matter get added to the soil.
5. Environmentally safe - Greenhouse effect will get reduced due to carbon sequestration.
6. No tillage reduces the compaction of the soil and reduces the water loss by runoff and prevent soil erosion.
7. As the soil is intact and no disturbance is done, No Till lands have more useful flora and fauna.

Conclusion

The natural resources are precious and therefore demand an effective and sustainable use. Zero tillage is a potential technology in this scenario. Although the drawback of use of non-selective

herbicide is more, it still causes less effect than the conventional method of farming. In zero tillage, more returns can be achieved and timely crop can be grown with higher yields.

Reference:

Madhu Kiran Tumma, PBRD Asia-Pacific Millet India, Pioneer Hibrid Pvt Ltd., Hyderabad 500082

K S V Poorna Chandrika, ICAR-Indian Institute of Oilseeds Research, Rajendranagar, Hyderabad, Telangana 500030

Bt cotton

Strains of the bacterium *Bacillus thuringiensis* produce over 200 different Bt toxins, each harmful to different insects. Most notably, Bt toxins are insecticidal to the larvae of moths and butterflies, beetles, cotton bollworms and flies but are harmless to other forms of life.[1] The gene coding for Bt toxin has been inserted into cotton as a transgene, causing it to produce this natural insecticide in its tissues. In many regions, the main pests in commercial cotton are lepidopteran larvae, which are killed by the Bt protein in the genetically modified cotton they eat. This eliminates the need to use large amounts of broad-spectrum insecticides to kill lepidopteran pests (some of which have developed pyrethroid resistance). This spares natural insect predators in the farm ecology and further contributes to noninsecticide pest management.

Bt cotton is ineffective against many cotton pests such as plant bugs, stink bugs, and aphids; depending on circumstances it may be desirable to use insecticides in prevention. A 2006 study done by Cornell researchers, the Center for Chinese Agricultural Policy and the Chinese Academy of Science on Bt cotton farming in China found that after seven years these secondary pests that were normally controlled by pesticide had increased, necessitating the use of pesticides at similar levels to non-Bt cotton and causing less profit for farmers because of the extra expense of GM seeds.[2]

Biological pest control

From Wikipedia, the free encyclopedia

Syrphus hoverfly larva (below) feed on aphids (above), making them natural biological control agents.

A parasitoid wasp (*Cotesia congregata*) adult with pupal cocoons on its host, a tobacco hornworm (*Manduca sexta*, green background), an example of a hymenopteran biological control agent

Biological control or **biocontrol** is a method of controlling pests such as insects, mites, weeds and plant diseases using other organisms.[1] It relies on predation, parasitism, herbivory, or other natural mechanisms, but typically also involves an active human management role. It can be an important component of integrated pest management (IPM) programs.

There are three basic strategies for biological pest control: classical (importation), where a natural enemy of a pest is introduced in the hope of achieving control; inductive (augmentation), in which a large population of natural enemies are administered for quick pest control; and inoculative (conservation), in which measures are taken to maintain natural enemies through regular reestablishment.[2]

Natural enemies of insect pests, also known as biological control agents, include predators, parasitoids, pathogens, and competitors. Biological control agents of plant diseases are most often referred to as antagonists. Biological control agents of weeds include seed predators, herbivores, and plant pathogens.

Biological control can have side-effects on biodiversity through attacks on non-target species by any of the above mechanisms, especially when a species is introduced without a thorough understanding of the possible consequences.

Genetically modified fish

Genetically modified fish (**GM fish**) are organisms from the taxonomic clade which includes the classes Agnatha (jawless fish), Chondrichthyes (cartilaginous fish) and Osteichthyes (bony fish) whose genetic material (DNA) has been altered using genetic engineering techniques. In most cases, the aim is to introduce a new trait to the fish which does not occur naturally in the species, i.e. transgenesis.

GM fish are used in scientific research and kept as pets. They are being developed as environmental pollutant sentinels and for use in aquaculture food production. In 2015, the AquAdvantage salmon was approved by the US Food and Drug Administration (FDA) for commercial production, sale and consumption,[1] making it the first genetically modified animal to be approved for human consumption. Some GM fish that have been created have promoters driving an over-production of "all fish" growth hormone. This results in dramatic growth enhancement in several species, including salmonids,[2] carps[3] and tilapias.[4][5]

Critics have objected to GM fish on several grounds, including ecological concerns, animal welfare concerns and with respect to whether using them as food is safe and whether GM fish are needed to help address the world's food needs.

Delayed Ripening Technology

Ripening is a normal phase in the maturation process of fruits and vegetables. Upon its onset, it only takes about a few days before the fruit or vegetable is considered inedible. This unavoidable process brings significant losses to both farmers and consumers alike.

Scientists have been working to delay fruit ripening so that farmers will have the flexibility in marketing their goods and ensure consumers of "fresh-from-the-garden" produce.

Advantages of DR Technology

The increased shelf life of products offers several advantages to both producers and consumers:

1. Assurance of top quality fruits and vegetables on the market. Farmers can now wait for the fruits and vegetables to attain full maturity before they are plucked from their vines thereby allowing the fruits to exude full quality. Consumers will get value for their money.
2. Widening of market opportunities for farmers as their produce can now be transported for longer periods of time, some of which would not even require refrigeration.
3. Reduction in postharvest losses. DR fruits do not go soft easily compared to conventional ones and are therefore more resilient to damage during handling and transportation. This ensures a significant percentage of the harvested fruits to end up on the market shelves.
4. Extension in shelf life as fruits or vegetables as they stay fresher and nutritious for longer periods. These fruits will not easily go "over the hill".

Safety Aspects of DR Technology

The first ever GM crop approved for marketing was the Flavr-SavrTM tomato produced by Calgene, Inc. (U.S.) in 1994. After thoroughly studying DR technology and its products, US regulatory agencies concluded that the DR technology is safe, it produces tomatoes that have the same nutritional composition as the conventional ones and that show no difference in levels of allergens or toxins compared to normal fruit. In addition, field trials have shown that the DR tomatoes do not pose any threat to other plants nor to any non-target organisms.

Other DR tomatoes that followed thereafter have also been granted deregulated status by regulatory agencies in several countries including the U.S., Canada, and Mexico. In 1996, the UK's food safety regulators also gave their thumbs up to a DR tomato developed by Zeneca Seeds but it is not currently being sold in supermarkets.

A European First

On February 5, 1996, branches of Safeway and Sainsbury's supermarkets throughout the UK started to sell tomato pureé made from genetically-modified tomatoes. This was the first time that food made from a GM organism had been sold in Europe.

Labels on the cans clearly stated that the product had been made with GM tomatoes. Although there was no legal requirement to label the product, both supermarkets adopted an 'open' information policy from the start. For the inquisitive customer there was no shortage of information: leaflets were available describing the product, its benefits to the environment and consumer, the technology, and the regulatory processes through which the product had to pass.

According to the supermarkets, sales in around 80 stores in which supplies were initially available were brisk. Figures indicated that once they bought the product, shoppers came back

for more. In November 1997, Safeway Stores announced that they had sold three quarters of a million cans of the product, and that average sales per store of the modified tomato purée exceeded those of the conventional equivalent. One reason might have been the price: the new purée cost 29 pence for 170 grams while the traditional form cost slightly more: 29 pence for a mere 142 grams.

Both supermarket chains pledged that the new product would always be offered alongside its old-fashioned counterpart. This move pleased consumer groups, which had no objection to the purée, provided that it was safe to eat and that consumers were always given a choice.

However, commercial pressures generated by public concern about GM foods early in 1999 forced Sainsbury's to announce that it would withdraw the product from sale. Stocks were exhausted by July 1999.

Source: http://www.ncbe.reading.ac.uk/NCBE/GMFOOD/tomato.html

Current Status of DR Technology

Delayed Ripening (DR) Technology has been applied for use in tomatoes, melons, and papaya. An interesting application of DR technology is in floriculture where experiments are underway to apply the technology to delay the withering of flowers.

In Southeast Asia, DR technology is being applied for use in papayas, a popular subsistence food and part of the general diet in the region. This technology could significantly increase the availability of this nutritious fruit to consumers and to small-scale and mostly resource-poor farmers in the region.

Regulatory approval of countries for crops with the DR trait

Crop	**Countries**	**Type of Approval**
Carnation	Australia Norway	Cultivation Cultivation

Melon	USA	Food
Pineapple	USA	Food
Tomato	China Canada Mexico USA	Food, feed, cultivation Food Food Food, feed, cultivation

Source: ISAAA GM Approval Database. http://www.isaaa.org/gmapprovaldatabase.

***ELSI** Research Program Overview*

The National Human Genome Research Institute's (NHGRI) Ethical, Legal and Social Implications (ELSI) Research Program was established in 1990 as an integral part of the Human Genome Project (HGP) to foster basic and applied research on the ethical, legal and social implications of genetic and genomic research for individuals, families and communities. The ELSI Research Program funds and manages studies, and supports workshops, research consortia and policy conferences related to these topics.

ELSI Research Priorities

On February 10, 2011, *Nature* magazine published NHGRI's strategic plan for the future of human genome research, called Charting a course for genomic medicine from base pairs to bedside. This plan includes a section on Genomics and Society that outlines four areas that will need to be addressed as genomic science and medicine move forward. Based on these areas, the NHGRI has developed the following broad research priorities.

- **Genomic Research**. The issues that arise in the design and conduct of genomic research, particularly as it increasingly involves the production, analysis and broad sharing of individual genomic information that is frequently coupled with detailed health information.
- **Genomic Health Care**. How rapid advances in genomic technologies and the availability of increasing amounts of genomic information influence how health care is provided and how it affects the health of individuals, families and communities.

- **Broader Societal Issues**. The normative underpinnings of beliefs, practices and policies regarding genomic information and technologies, as well as the implications of genomics for how we conceptualize and understand such issues as health, disease, and individual responsibility.
- **Legal, Regulatory and Public Policy Issues**. The effects of existing genomic research, health and public policies and regulations and the development of new policies and regulatory approaches.

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Chymosin

Chymosin /ˈkaɪməsɪn/ or **rennin** /ˈrɛnɪn/ is a protease found in rennet. It is an aspartic endopeptidase belongs to MEROPS A1 family. It is produced by newborn ruminant animals in the lining of the fourth stomach to curdle the milk they ingest, allowing a longer residence in the bowels and better absorption. It is widely used in the production of cheese. Bovine chymosin is now producedrecombinantly in *E. coli*, *Aspergillus niger var awamori*, and *K. lactis* as alternative resource.

Recombinant Chymosin

Because of the imperfections and scarcity of microbial and animal rennets, producers sought replacements. With the development of genetic engineering, it became possible to extract rennet-producing genes from animal stomach and insert them into certain bacteria, fungi or yeasts to make them produce chymosin during fermentation. The genetically modified microorganism is killed after fermentation and chymosin is isolated from the fermentation broth, so that the fermentation-produced chymosin (FPC) used by cheese producers does not contain any GM component or ingredient. FPC contains the identical chymosin as the animal source, but produced in a more efficient way. FPC products have been on the market since 1990 and have been considered in the last 20 years the ideal milk-clotting enzyme.

FPC was the first artificially produced enzyme to be registered and allowed by the US Food and Drug Administration. In 1999, about 60% of US hard cheese was made with FPC and it has up to 80% of the global market share for rennet.

By 2008, approximately 80% to 90% of commercially made cheeses in the US and Britain were made using FPC. Today, the most widely used fermentation-produced chymosin is produced either by the fungus *Aspergillus niger* and commercialized under the trademark CHY-MAX® by the Danish company Chr. Hansen, or produced by*Kluyveromyces lactis* and commercialized under the trademark MAXIREN® by the Dutch company DSM.

FPC contains only chymosin B, achieving a high degree of purity compared with animal rennet. FPC can deliver several benefits to the cheese producer compared with animal or microbial rennet, such as higher production yield, better curd texture and reduced bitterness.

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Tryptophan

Tryptophan (abbreviated as Trp or W; encoded by the codon UGG) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $–NH3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $–COO^–$ form under biological conditions), and a side chain indole, classifying it as a non-polar, aromatic amino acid. It is essential in humans, meaning the body cannot synthesize it and thus it must be obtained from the diet.

Eosinophilia–myalgia syndrome

There was a large outbreak of eosinophilia-myalgia syndrome (EMS) in the U.S. in 1989, with more than 1,500 cases reported to the CDC and at least 37 deaths. After preliminary investigation revealed that the outbreak was linked to intake of tryptophan, the U.S. Food and Drug Administration (FDA) banned most tryptophan from sale in the US in 1991, and other countries followed suit.

Subsequent epidemiological studies suggested that EMS was linked to specific batches of L-tryptophan supplied by a single large Japanese manufacturer, Showa Denko.[44][45][46][47] It eventually became clear that recent batches of Showa Denko's L-tryptophan were contaminated by trace impurities, which were subsequently thought to be responsible for the 1989 EMS outbreak.[44][48][49] However, other evidence suggests that tryptophan itself may be a potentially major contributory factor in EMS.

The FDA loosened its restrictions on sales and marketing of tryptophan in February 2001, but continued to limit the importation of tryptophan not intended for an exempted use until 2005.

The fact that the Showa Denko facility used genetically engineered bacteria to produce the contaminated batches of L-tryptophan later found to have caused the outbreak of eosinophilia-myalgia syndrome has been cited as evidence of a need for "close monitoring of the chemical purity of biotechnology-derived products."[51] Those calling for purity monitoring have, in turn, been criticized as anti-GMO activists who overlook possible non-GMO causes of contamination and threaten the development of biotech.

IGF-1

IGF-1, or insulin-like growth factor 1, is a growth hormone produced by the liver, and small amounts are also found in the testes. It is an important hormone, involved in blood cell production and the growth of blood vessels, but a 2008 study done by the Schneider Children's Medical Center of Israel showed that a natural deficiency can actually help to increase the life span, possibly by reducing the risk of certain cancers. People who use HCG as a bodybuilding supplement sometimes use IGF-1 in conjunction, hoping to increase their body's ability to absorb and use the HCg. When IGF-1 is isolated from milk, it resists breakdown by digestion.

General Side Effects

IGF-1 and HCG are steroids, and as such, have the potential to cause many undesirable side effects, regardless of whether they are taken together or separately. They can damage your liver and kidneys and keep your body from producing its own hormones. They can cause acne, aggressive behavior and can trigger baldness in people who are genetically predisposed. Because hormones are heavily involved in gender differentiation, IGF-1 and HCG supplementation can cause the development of male breast tissue and the masculinization of women. The masculinization includes the growth of excess body and facial hair and the deepening of the voice, and the male breast tissue may need to be surgically removed.

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Ice-minus *Pseudomonas syringae*

Ice-minus bacteria is a common name given to a variant of the common bacterium *Pseudomonas syringae* (*P. syringae*). This strain of *P. syringae* lacks the ability to produce a certain surface protein, usually found on wild-type *P. syringae*. The "ice-plus" protein (Ina protein, "Ice nucleation-active" protein) found on the outer bacterial cell wall acts as thenucleating centers for ice crystals.[1] This facilitates ice formation, hence the designation "ice-plus." The ice-minus variant of *P. syringae* is a mutant, lacking the gene responsible for ice-nucleating surface protein production. This lack of surface protein provides a less favorable environment for ice formation. Both strains of *P. syringae* occur naturally, butrecombinant DNA technology has allowed for the synthetic removal or alteration of specific genes, enabling the creation of the ice-minus strain.

The ice nucleating nature of *P. syringae* incites frost development, freezing the buds of the plant and destroying the occurring crop. The introduction of an ice-minus strain of *P. syringae* to the surface of plants would reduce the amount of ice nucleate present, rendering higher crop yields. The recombinant form was developed as a commercial product known as **Frostban**. Field-testing of Frostban was the first release of a genetically modified organism into the environment. The testing was very controversial and drove the formation of US biotechnology policy. Frostban was never marketed.

Controversy

At the time of Lindow's work on ice-minus *P. syringae*, genetic engineering was considered to be very controversial. Jeremy Rifkin and his Foundation on Economic Trends (FET) sued the NIH in federal court to delay the field trials, arguing that NIH had failed to conduct an Environmental Impact Assessment and had failed to explore the possible effects "Ice-minus" bacteria might have on ecosystems and even global weather patterns.[4][7] Once approval was granted, both test fields were attacked by activist groups the night before the tests occurred: "The world's first trial site attracted the world's first field trasher".[5] The BBC quoted Andy Caffrey from Earth First!: "When I first heard that a company in Berkley was planning to release these bacteria Frostban in my community, I literally felt a knife go into me. Here once again, for a buck, science, technology and corporations were going to invade my body with new bacteria that hadn't existed on the planet before. It had already been invaded by smog, by radiation, by toxic chemicals in my food, and I just wasn't going to take it anymore."[5]

Rifkin's successful legal challenge forced the Reagan Administration to more quickly develop an overarching regulatory policy to guide federal decision-making about agricultural biotechnology. In 1986, the Office of Science and Technology Policy issued the Coordinated Framework for Regulation of Biotechnology, which continues to govern US regulatory decisions.[4]

The controversy drove many biotech companies away from use of genetically engineering microorganisms in agriculture.[8]

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rBST

Recombinant Bovine Somatotropin (**rBST**)

recombinant bovine growth hormone (**rBGH**), or **artificial growth hormone**. Four large pharmaceutical companies, Monsanto,American Cyanamid, Eli Lilly, and Upjohn, developed commercial rBST products and submitted them to the US Food and Drug Administration (FDA) for approval.[3][4] Monsanto was the first firm to receive approval. Other countries (Mexico, Brazil, India, Russia, and at least ten others) also approved rBST for

commercial use.[5] Monsanto licensed Genentech's patent,[2] and marketed their product as "Posilac".[6][7] In October 2008, Monsanto sold this business, in full, to Eli Lilly and Company for $300 million plus additional consideration.

rBST has not been allowed on the market in Canada, Australia, New Zealand, Japan, Israel, or the European Union since 2000. Argentina also banned the use of rBST.

The FDA,[9] World Health Organization,[4] and National Institutes of Health[10] have independently stated that dairy products and meat from BST-treated cows are safe for human consumption. In the United States, public opinion led some manufacturers and retailers to market only milk that is rBST-free.

A European Union report on the animal welfare effects of rBST states that its use often results in "severe and unnecessary pain, suffering and distress" for cows, "associated with serious mastitis, foot disorders and some reproductive problems"

rBST is present in milk from both rBST-treated and untreated cows, but it is destroyed in the digestive system and even if directly injected, has not been found to have any direct effect on humans.[29] Researchers have found that "IGF-1 in milk is not denatured by pasteurization and the extent to which intact, active IGF-1 is absorbed through the human digestive tract remains still however uncertain" implicating that an extensive study on the nature of IGF-1 in relation to rBST milk is required.[30]

FDA rBST labeling guidelines state, "FDA is concerned that the term 'rbST free' may imply a compositional difference between milk from treated and untreated cows rather than a difference in the way the milk is produced. Without proper context, such statements could be misleading. Such unqualified statements may imply that milk from untreated cows is safer or of higher quality than milk from treated cows. Such an implication would be false and misleading".[31]

The FDA[9] World Health Organization,[4] and National Institutes of Health[10] have independently stated that dairy products and meat from rBST-treated cows are safe for human consumption. The American Cancer Society issued a report declaring, "The evidence for potential harm to humans [from rBGH milk] is inconclusive. It is not clear that drinking milk produced using rBGH significantly increases IGF-1 levels in humans or adds to the risk of developing cancer. More research is needed to help better address these concerns."[32]

Human health

The effects of rBGH on human health is an ongoing debate, in part due to the lack of conclusive evidence. A few of the most debated issues include:

IGF-1 is a hormone found in humans that is responsible for growth promotion, protein synthesis, and insulin actions over the lifecycle. The hormone has been shown to influence the growth of tumors in some studies and may be linked to the development of prostate,[33] colorectal, breast,[34][35] and other cancers.[36][37][38]

IGF-1 is also found in milk (soy included). Previous research has proposed an increase of IGF-1 in rBST-treated cows, but this claim is currently not substantiated. In addition, no current evidence shows that orally consumed IGF-1 is absorbed in humans and the dietary amount is negligible when compared to what the body produces on its own. “IGF-1 in milk is not denatured (inactivated) by pasteurization. The extent to which intact, active IGF-1 is absorbed through the human digestive tract remains uncertain.

The American Cancer Society has reviewed the evidence concerning IGF-1 in milk from rBST-treated cows, and found that: "While there may be a link between IGF-1 blood levels and cancer, the exact nature of this link remains unclear. Some studies have shown that adults who drink milk have about 10% higher levels of IGF-1 in their blood than those who drink little or no milk. But this same finding has also been reported in people who drink soymilk. This suggests that the increase in IGF-1 may not be specific to cow's milk, and may be caused by protein, minerals, or some other factors in milk unrelated to rBGH. There have been no direct comparisons of IGF-1 levels in people who drink ordinary cow's milk vs. milk stimulated by rBGH. At this time, it is not clear that drinking milk, produced with or without rBGH treatment, increases blood IGF-1 levels into a range that might be of concern regarding cancer risk or other health effects.... IGF-1 concentrations are slightly higher (to variable degrees, depending on the study) in milk from cows treated with rBGH than in untreated milk. This variability is presumed to be much less than the normal range of variation of IGF-1 in cow's milk due to natural factors, but more research is needed."[32]

Research is supportive of milk supplying vital nutrients used in childhood development.[39] At this time, evidence does not link rBST-treated milk with adverse health outcomes for children.[40] Several studies have looked at the relationship between type 1 diabetes and infant feeding. Environmental triggers that may elicit an autoimmune reaction is the mechanism in

which is being studied. Some studies have shown early exposure to bovine milk may predispose an infant to type 1 diabetes, whereas other studies show no causality.[41]

The American Society of Animal Science published an article in 2014 after reviewing health issues arising from the rBST debate. The article indicated "there are no new human health issues related to the use of rbST by the dairy industry. Use of rbST has no effect on the micro- and macrocomposition of milk. Also, no evidence exists that rbST use has increased human exposure to antibiotic residues in milk. Concerns that IGF-I present in milk could have biological effects on humans have been allayed by studies showing that oral consumption of IGF-I by humans has little or no biological activity. Additionally, concentrations of IGF-I in digestive tract fluids of humans far exceed any IGF-I consumed when drinking milk. Furthermore, chronic supplementation of cows with rbST does not increase concentrations of milk IGF-I outside the range typically observed for effects of farm, parity, or stage of lactation. Use of rbST has not affected expression of retroviruses in cattle or posed an increased risk to human health from retroviruses in cattle. Furthermore, risk for development of type 1 or type 2 diabetes has not increased in children or adults consuming milk and dairy products from rbST-supplemented cows. Overall, milk and dairy products provide essential nutrients and related benefits in health maintenance and the prevention of chronic diseases." [42]

Environmental impact

On an industry level, supplementing one million cows with rbST would result in the same amount of milk produced using 157,000 fewer cows.[43] Farmers are, therefore, able to improve milk production with a smaller dairy population.

Some studies show that rBST-treated cows reduce the impact of greenhouse gases in comparison with conventional and organic dairy operations. Furthermore, excretion of nitrogen and phosphorus, two major environmental pollutants arising from animal agriculture, was reduced by 9.1 and 11.8%, respectively.[44] Carbon dioxide is recognized to be the most important anthropogenic greenhouse gas,[45] and livestock metabolism and fossil fuel consumption are the main sources of emissions from animal agriculture.

- Livestock metabolism-use of rBST in lactating cows decreases the quantity of energy and protein needed in comparison to conventional dairy operations along with reducing the total feedstuff used.
- Fossil fuel consumption-targets atmospheric pollution and resource sustainability environmental concerns. With cows treated with rBST, producing a higher milk yield

reduces the feed requirement which in turn decreases with electricity for milk production and the energy required from fossil fuels for cropping. In addition, the global warming potential is reduced equivalent to removing 400,000 family cars from the road.

When conventional, conventional with rBST, and organic dairy operations are compared, 8% fewer cows are needed in an rBST-supplemented population, whereas organic production systems require a 25% increase to meet production targets.[44] This is due to a lower milk yield per cow due to the pasture-based system which is attributed with a greater maintenance energy expenditure associated with grazing behavior

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Human Gene Therapy

Introduction

Gene therapy is the use of genes to treat disease. It represents a quantum leap in our approach to the treatment of human disease and will have a significant effect on medicine over the next ten years. William French Anderson, Michael Biase, and Ken Culver performed the first successful gene therapy on a human in 1990. They developed a protocol for treating Adenosine deaminase (ADA) deficiency, severe combined immune deficiency, also known as the" Boy in the Bubble disease". ADA deficiency is a result of inheriting two copies of the defective ADA gene (in other words it is a recessive disease). Possession of a normal gene leads to the continuous, regular production of ADA in cells throughout the body. Without at least one properly functioning gene, children have no way of converting deoxyadenosine (a waste product) into inosine. This leads to the rapid buildup deoxyadenosine in the system, which becomes phosphoralysed into a toxic triphosphate which kills T-cell. The result is an almost complete failure of the immune system and early death.

Concept of Gene Therapy

The term gene therapy originally referred to proposed treatments of genetic disorders that would involve replacing a defective gene with its normal counterpart Current usage of the term now extends to include all treatments in which there is an introduction of genetic material into body cells to treat a variety of diseases. Gene therapy utilizes two theoretically possible approaches:

1) Somatic gene therapy entails the transfer of a gene or genes into body cells other than germ (egg or sperm) cells with effect only on the patient. The new genetic material cannot be passed on to offspring. Examples of Somatic gene therapy have already proven to be clinically effective. The first successful treatments of adenosine deaminase deficiency took place in 1990 in 1991 with two patients aged 4 and 11. Both are thriving with continuing treatment. The first successful treatment of familial hypercholesterolemia, a genetic condition, which affects the livers regulation of cholestrols in the blood, took place in 1992 of a 29-year-old woman. Her improvement was stable for the 18 months of the study and liver biopsy demonstrated activity of the inserted gene and no discernible abnormalities. Five patients have been treated as of 1994.Current research involving Somatic gene therapy is focusing on a number of areas. Clinical trials are being performed on a treatment for cystic fibrosis, a chronic genetic disorder.

2) Germline gene therapy would involve the genetic modification of germ cells. Such therapy would change the genetic makeup of the egg or sperm of an individual and would be carried on to future generations. This would offer the possibility of removing an inherited disorder from a family line forever. This could be achieved by other methods, such as, at present, diagnosis when there is a known risk before embryo implantation during IVF. Germ line therapy is a remote prospect and general opinion is strongly negative; such therapy is currently illegal in most of Europe. Somatic and Germ line gene therapy raise different issues. Somatic gene therapy offers the prospect of effective treatment and cure for previously fatal disorders. Until now it has only been used experimentally for a small range of genetic disorders; even in these cases treatment is complex, difficult and success uncertain.

Technical Aspects of Gene Therapy

The most fundamental requirement for gene therapy to be successful is that a therapeutic gene can be effectively delivered to a target cell. Once delivered that gene must enter the nucleus of cell wall where it will act as a template for production of protein molecule. The protein then exerts the primary therapeutic effect. This may be, for example, cell killing in the case of tumor therapy or cell preservation in the case of neurodegenerative disease.

There are several ways to get genes into cells. The most efficient of these uses disabled, engineered viruses. These systems are efficient because viruses have evolved over long periods of time to deliver their own genes to cells. Whenever, we get a viral disease, be it a cold or AIDS, the particular virus concerned is placing its genes into our cells in order to

reprogrammed our cells to produce more virus. When we use viruses for gene therapy we disable them so that they are unable to cause disease and we engineer them in such a way that they pick up and deliver the genes of our choice rather than their own genes. These derivatives of viruses that are used for gene delivery are known as viral vectors. The most frequently used viral vectors are of two types. The vectors based on adenovirus are generally used for therapeutic strategies that require the therapeutic gene to be active for only a short time. Gene delivery by adenoviruses is very efficient but because the gene does not become integrated into the chromosomes of the target cell the gene is lost overtime.

This not a disadvantage for some therapeutic strategies such as cell destruction in the treatment of some cancers, restinosis or inflammatory disease. However, it is a disadvantage where sustained gene activity required for many months such as in the treatment of some tumors, neurodegenerative disease and HIV infection.

The second major type of vector is generally used and this is based on the retrovirus, murine leukemia virus (MLV). When genes are delivered by derivatives of MLV they become integrated into the chromosomes of target cell and are maintained for as long as the cell remains alive. Gene activity is easy to control and continues over long periods of time. Many clinical trials have been conducted with these MLV based systems and has been shown to be well tolerated with no adverse side effects.

One of the major difference between adenovirus vectors and MLV vectors is that the former can deliver genes to cells that are not multiplying by cell division whereas the latter cannot. Until recently this has meant gene therapy strategies that demand long term gene activity in cells that are not dividing have been feasible. Examples of important target cells that do not divide are neurons, certain cells of the immune system and certain epithelial cells.

Lentiviruses are a subgroup with in the general family of retroviruses but they are distinct from the MLV like viruses in that they are able to infect non-dividing cells. The best studied of the lentiviruses is HIV and when observation was made, about 10 years ago, that HIV could infect terminally differentiated macrophages, which do not divide, there was a move within the research community to develop gene delivery vectors from HIV. There were number of early technical difficulties and first generation vectors could not be used in the clinic as they had potential to generate infectious HIV. Over past two years we have seen new HIV based vectors emerge that are severely disabled containing only the few HIV components that are required

for efficient gene delivery to non dividing cells. These so called minimal vectors are now candidates for gene delivery vehicles for clinical use in gene therapy.

The technique, called Chimeraplasty, was developed for mammalian gene therapy. It has an advantage over current genetic engineering methods in that it can seek out any specific gene and cause tiny mutations with high precision. Instead of adding a new gene to trick a plant into doing something it would not normally do, Chimeraplasty simply switches on or off function for which the plant already has a gene.

Until now, an entire gene had to hitch a ride into the nucleus on a defused viruses, which has the ability to insert itself into the genome. However, the virus could settle anywhere on the genome, sometimes choosing a location that is less than optimal for the replication of new gene. Technique also eliminates the danger from inserting large sections of genes with potentially undesirable side- effects, such as poisoning beneficial insects.

For Chimeraplasty, researchers start with small chunks of artificial genetic material, called oligonucleotides or "oligos", with about 25 bases each. They mirror one specific plant gene except for a mismatch of a few bases. The chunks are hooked up to tiny gold particles, which are then shot into nucleus of cell with a particle gun. When the oligos attach their counterparts in the cell, the DNA repair machinery tries to "fix" the mismatch, using the new sequence of the bases as blueprint.

Boosting blood cell production does little good for patients, whose blood cells are malformed, such as those of sickle cell anemic. The ultimate goal of gene therapy is not to compensate for genetic diseases but to erase them completely. Preliminary work published in the September 6 issue of science offers a reason to hope that goal may be possible .A team led by Allyson Cole-strauss and Kyonggeum Yoon of Thomas Jefferson University in Philadelphia experimented on cells containing a mutant gene that causes sickle cell anemia .To make their genetic drug they combined DNA for the normal version of this gene with RNA for the same gene. When they injected the drug into the diseased cells, the RNA/DNA particles homed in on the particular stretch of the genome that matched their codes and formed triple stranded DNA that covered the mutation. The cells normal DNA repair machinery then apparently replaced the mutation with the normal code thus permanently curing 10 to 20 percent of cells. The researchers still have to demonstrate that this technique works in human cells and in human bodies.

In about half of lung cancer cases, a gene called p53 has mutated and thus falls to encode a protein that oversees programmed cell death. In the absence of this protein, which helps to curb the growth of damaged or abnormal cells, cancer can gain a foothold. Replacing such defective p53 genes with fresh ones has shown promise against a variety of cancers in animal experiments and studies of a few patients.

Scientists now report further progress in such localized gene therapy. By enlisting a virus to deliver p53 to tumor sites in 28 people with lung cancer, they temporarily stabilized or reversed the course of the cancer in more than half patients. The patients, average age 65, had lung cancer that was either inoperable or was no longer responding to radiation treatment or chemotherapy. The researchers injected the tumors with an adenovirus engineered to contain p53 genes. The virus was modified to prevent it from replicating and thus causing the upper respiratory infection that it might otherwise bring about.

During the 6 months treatment period patients received one to six monthly injections of the modified virus. The researchers delivered a range of doses -from 1 million to 100 billion viral units to gauge any toxicity of the treatment. 3 of the 28 patients died of cancer before doctors could make a 1-month follow up examination. Among the 25 others, tumors shrank in 2 patients, stabilized in 16 and continued to grow in the other 7.

The dose of virus mattered; cancer progressed unabated in three of five patients who received injections of 10 million or fewer viral units. In contrast, only 4 of 20 patients getting larger dose experienced cancer growth.

Argument of Human Gene Therapy

Consider what a nation would gain by permitting parents to genetically enhance their children. By assumption, the genetic enhancement technology increases the ability of children to learn and perform cognitive tasks, and thus to acquire and generate knowledge. Permitting or facilitating genetic enhancement would therefore increase the collective human capital embodied in nations workers .The increasing prevalence of high ability genotypes would also multiply the effects of other national investments in education, training, and scientific or engineering research. Because genetic enhancements are heritable, the effect of these investments on the stock of human capital are cumulative unless enhanced offspring or their descendants emigrate. Finally, permitting genetic enhancement would be a cheap way for a state to increase aggregate human capital, because competition between parents would lead

some parents to pay for it out of their own pockets. If expanding stock of nations human capital brings increasing returns in productivity and economic growth, it means that in economic competitions among nations, small initial differences in the distribution of able people can multiply, over time, to large international differences in the rate of economic growth. Thus nations have an incentive to defect from an international ban on genetic enhancement to get a jump on others in the accumulation of human capital.

It is said that the day is not far of when parents will be able to browse through gene catalogs to special order a hazel eyed, red headed extrovert with perfect pitch. Every new discovery gives shape and bracing focus to a debate we have barely begun. Even skeptics admit it's only matter of time before these issues become real. If you could make your kids smatter, would you? If everyone else did, would it be fair not to?

It's an ethical quandary and an economic one, about fairness and fate, about vanity and values. Which side effects would we tolerate? What if making smarter kids also made them meaner? What if only the rich could afford the advantage? Does god give us both the power to re-create ourselves and moral muscles to resist? Self-improvement forever been an American religion, but norms about what is normal keep changing.

While gene therapy shows a great deal of potential, opponents, biomedical reductionism will undoubtedly have several responses. The way a person experiences a disease involves many social and psychological elements (such as emotional impact of the disease, the stigmatism attached to it, the cost and employment implications, etc). These important aspects of disease are neglected by therapeutic approaches aimed strictly at the genetic level.

Today in many countries governments sets up committees, which included not only scientists and doctors but also religious leaders, lawyers and ethicist, to consider the matter (Nichols 1988). A distinction should be drawn between making genetic changes in somatic cells and in germinal cells. The purpose of somatic gene therapy is to treat an individual patient, e.g. by inserting a properly functioning gene into patients bone marrow cells in vitro and then introducing the cells into patients body. They differ, however, in that gene therapy an inherent and probably permanent change in the body rather than requiring repeated applications of an outside force or substance. An analogy is organ transplantation, which also involves the incorporation into an individual of cells containing DNA of foreign origin. Germinal gene

therapy, in which the changes would be made in germ cells and would be passed on to the offspring, is not allowed.

Reference:

https://www.ndsu.edu/pubweb/~mcclean/plsc431/students99/oberoi.htm

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT – II – Bioethics Biosafety and IPR – SBB1615

UNIT-2 GMO-BIOSAFETY AND CONTAINMENT

Guidelines for research with transgenic organisms. Environmental impact of genetically modified organisms (beneficial and hazardous impact), Field trials with GMO, Containment levels. Biosafety protocol, Cartagena Biosafety protocol, Mechanism of implementation of biosafety guidelines. Biosafety and politics. Biosafety database.

Biosafety

'Biosafety' means the need to protect human and animal health and environment from the possible adverse effects of the products of modern biotechnology

Environmental and Biosafety issues in modern Biotechnology

International Evolution

- Environmentalism emerged as a distinct development in the last forty years.
- Emergence of "pressure groups" in the sixties
- First Earth Day (1970)
- The United Nations Conference on the Human Environment and Development (1972)
- The Brundtland Report: our Common Future (1987)
- The Rio Earth Summit (1992)
- Convention on Biodiversity (CBD) [1992]
- Cartagena Protocol on Biosafety (CPB) [1993]

Convention of Biodiversity (CBD) [1992]

- Focus: conservation and sustainable use of biodiversity
- Recognized the potential of modern biotechnology for human well being
- Took cognizance that modern biotechnology could have serious effects on environment and health
- Article 8(g) emphasized the need to regulate the risks associated with the use of LMOS.
- Article 19(3) set the stage for a legally binding international instrument about biosafety.

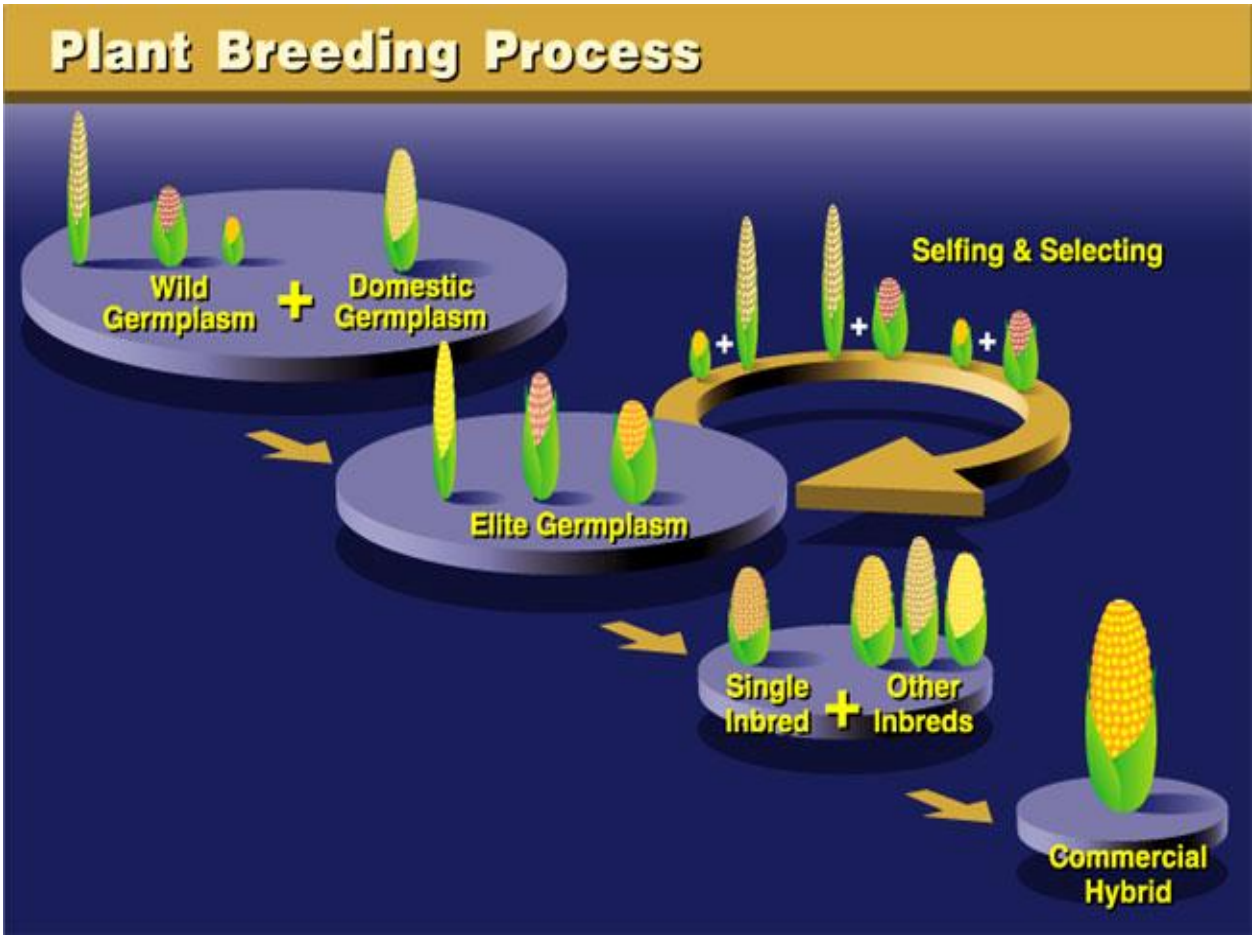
The Cartagena Protocol on Biosafety (CPB)

- Entered into force on 29th December 1993
- Focus on transboundary movement of the LMOS.

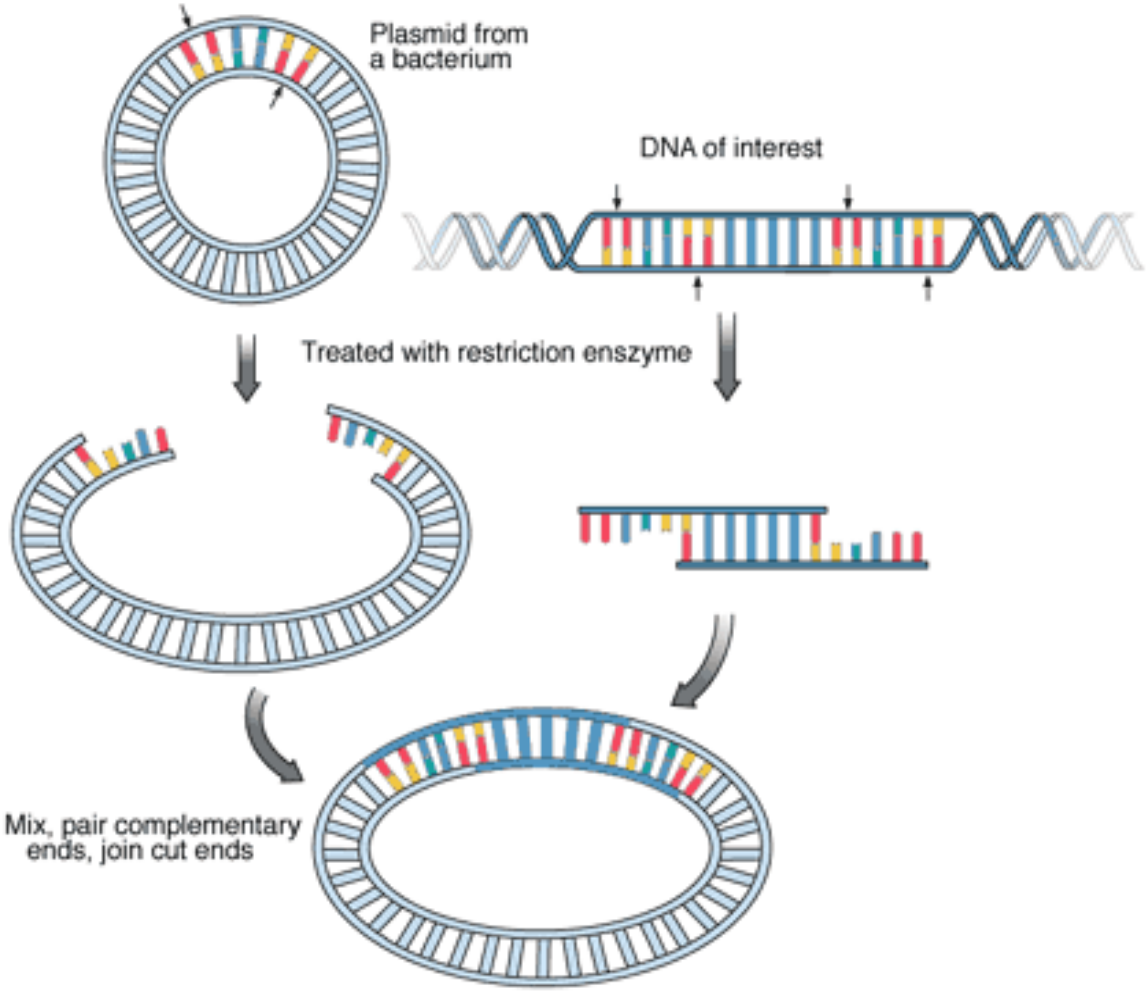
  Seeks to lay down an internationally acceptable framework to provide for an adequate level of protection against the possible adverse effects of LMOS on biodiversity and human health.

How is Genetic Engineering (GE) different from conventional breeding (CB)?

- Combining DNA in new combinations and introducing it into a new organism are the GE tools.
- Main differences between CB and GE
  - Ability to move across sexual barriers
  - Amount of change: a specific gene embodying a particular trait or thousands of genes embodying desirable and undesirable traits
  - Occurrence of change in one or several generations.



Genetic engineering:Recombinant DNA technology



Is GE inherently unsafe?

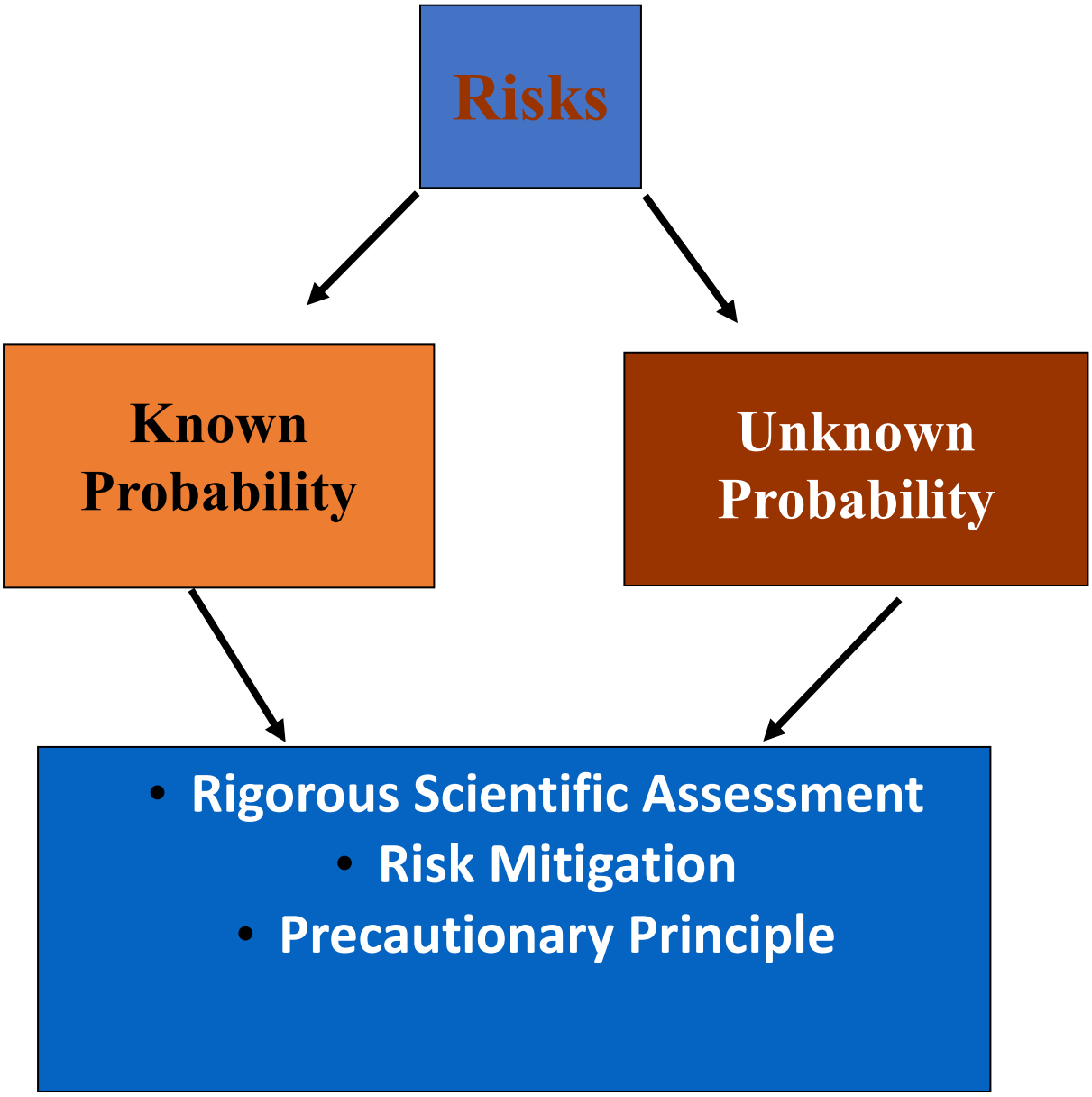
- Two diametrically opposite trends of thought
- US-Canada
  - No new risks associated with GM crops
  - New regulations not considered necessary
  - Safety assessments
    - ‘Product’ rather than ‘process’ based
    - In comparison and contrast to their ‘familiarity’ and ‘substantial’ equivalence to conventional crops
- EU

- GE crops considered new and special
- Existing legislation not considered sufficient

- Safety assessment
  - Process based
  - Principle of 'substantial equivalence' beginning rather than the end
- Adoption of 'Precautionary Principle' as guide
- GE technology carries certain inherent unpredictability
- Some facts
  - Isolation of a gene from its natural environment and integration into entirely different organism
  - Possible transgenic instability due to triggering of the inbuilt defense mechanisms of the host organism leading to inactivation or silencing of foreign genes.
  - Possibilities of integration of foreign gene at a site predisposed to silencing of genes (position effect).
    - Variance in the levels of expression of the transgene in different environmental conditions (heat, humidity, light…..)
    - Possibilities of silencing of genes arising in subsequent generations
- Case by case sound scientific assessment is of utmost significance

Biosafety issues in transgenic crops

- Relate to environmental, human and animal health consequences
- Both can have short and long term implications
- Biosafety risks involve the entire spectrum of biodiversity
- A universal 'true for all' approach may not be applicable



Biosafety concerns arise from:

- Horizontal gene transfer
- Genetic contamination
- Transfer of allergens and toxins from one life form to another and creation of new toxins and allergenic compounds

Main concerns

- Development of **aggressive weeds**/ wild relatives by transfer of transgenic traits
- **Erosion of land races**/wild relatives by genetic pollution in centres of origin/ diversity

- Harm to the **non-target organisms**
- Development of **pest resistance** by prolonged use
- **Monoculture** and limitations to farmers' choice in crop management
- Hazard to human and animal health by transfer of **toxins and allergens** and by creation of new toxins and allergenic compounds

Assessment

- GE venturing into an unknown biological territory
- ASILOMAR Conference (1975): No research till safety guidelines in place
- Initially, focus on laboratory safety procedures
- Wider definition of biosafety with possibilities of commercialization of GM products
- The broad format of biosafety parametres essentially the same in all regulations

Two main stages:

1. Laboratory/green house stage
2. Confined Trial Stage

IMPORTANT

Prevention of the spread of genetically engineered material outside lab/field

Laboratory/green house stage

- Different biosafety levels as per the degree of risk involved
- Two methods of containment
  - *Physical*
  - *Biological*

Confined Trial Stage

A confined trial is a small scale release of a transgenic plant species for research purposes conducted under conditions that prevent spread of the organism and mitigate its impact on the surrounding environment

Objective is to collect data to evaluate the crops' performance

Focus on Risk Mitigation

Risk mitigation – the terms and conditions that are necessary to conduct the trial safely.

- Prevent Gene Flow

- Prevent entry of GMOs into food chain
- Prevent Persistence of GMOs in the field

Bio-pharmaceutical therapeutics

Biosafety risk

- Survival, multiplication and dissemination of GMOs in contained/ open environment
- Interaction of GMOs with biological systems
- Routes of dissemination: physical; biological

Risk depends upon

- Nature of organism invovled
- Extent of use of LMOs
- End product LMO or not?

Risk categorization of micro organisms:

- Determining factors
- Capability to cause disease
- Hazard to laboratory workers
- Risk of spread to community
- Availability of effective treatment

Health risks

- Toxigenicity Pathogenicity
- Allergenicity Antibiotic resistance

Environmental risks

- Outcrossing between GMOs and pathogens

- Negative effects on populations of non target organisms

Risk assessment

- Access
- Expression
- Damage

Risk management and communication

- Physical
- Biological

GM foods: need for safety assessment

- Expressed proteins generally not a part of regular food supply
- Food complex mixtures e.g. nutrients, anti-nutrients and natural toxins
- Directly enter human system
- Assume different forms
- Involve storage, processing, transportation

.. Safety assessment of GM foods comprise

Guidelines by Codex Alimentarius Commission

- Assessment of possible allergenicity
- Assessment of possible toxicity
- Compositional analysis of key components
- Food processing
- Nutritional modification
-

….GM foods: Allergenicity; Toxicity

Allergy

It is a hypersensitive reaction initiated by immunologic mechanisms caused by specific substances called allergens.

Assessment

- Is the gene source allergenic?

- Expression level of introduced gene
- Unintended effect
- Digestibility and heat stability

Toxicity

- New proteins as a result of intended modification
- Unintended new proteins as a result of the modification
- Natural constituents beyond their level of normal variation

<u>….GM foods: nutritional aspects; unintended effects</u>

- Intended and unintended changes in nutrient levels
- Bioavailability of nutrients, stability and processing
- Presence and effect of anti-nutrients
- Impact of individual changes on overall nutritional profile

Unintended effects

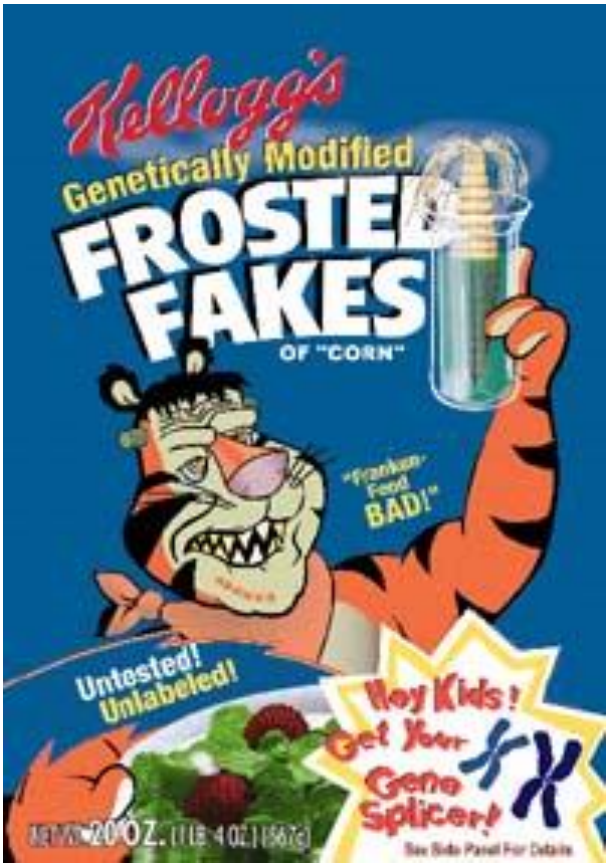
Random integration of transgenes

- Insertional mutagenesis
- Disruption of gene functions
- Production of new proteins
- Changes in
  - Phenotype Metabolites
  - Enzymes Toxins
  - Genotype

- **<u>Concluding Note……</u>**

  - Biosafety is integral to modern biotechnology
  - The adoption of modern biotech products needs to be balanced with adequate biosafety safeguards
  - Case by case scientific risk assessment and cost benefit analysis
  - Greater acceptance of health care applications
  - Need based adoption in GM crops and foods
  - Participation of various stakeholders
  - Dissemination of knowledge and information

Genetically Modified Foods



What are GM's?

- are a result of technology that has altered the DNA of living organisms (animals, plants or bacteria)

Other terms that mean the same thing:

- Genetically engineered
- Transgenic
- Recombinant DNA (rDNA) technology

How does this differ from Mendel and his peas?

GM vs. Selective breading

Selective breading

-slow

-imprecise

-modification of genes that naturally occur in the organism

GM

-very fast

-precise

-can introduce genes into an organism that would not occur naturally!

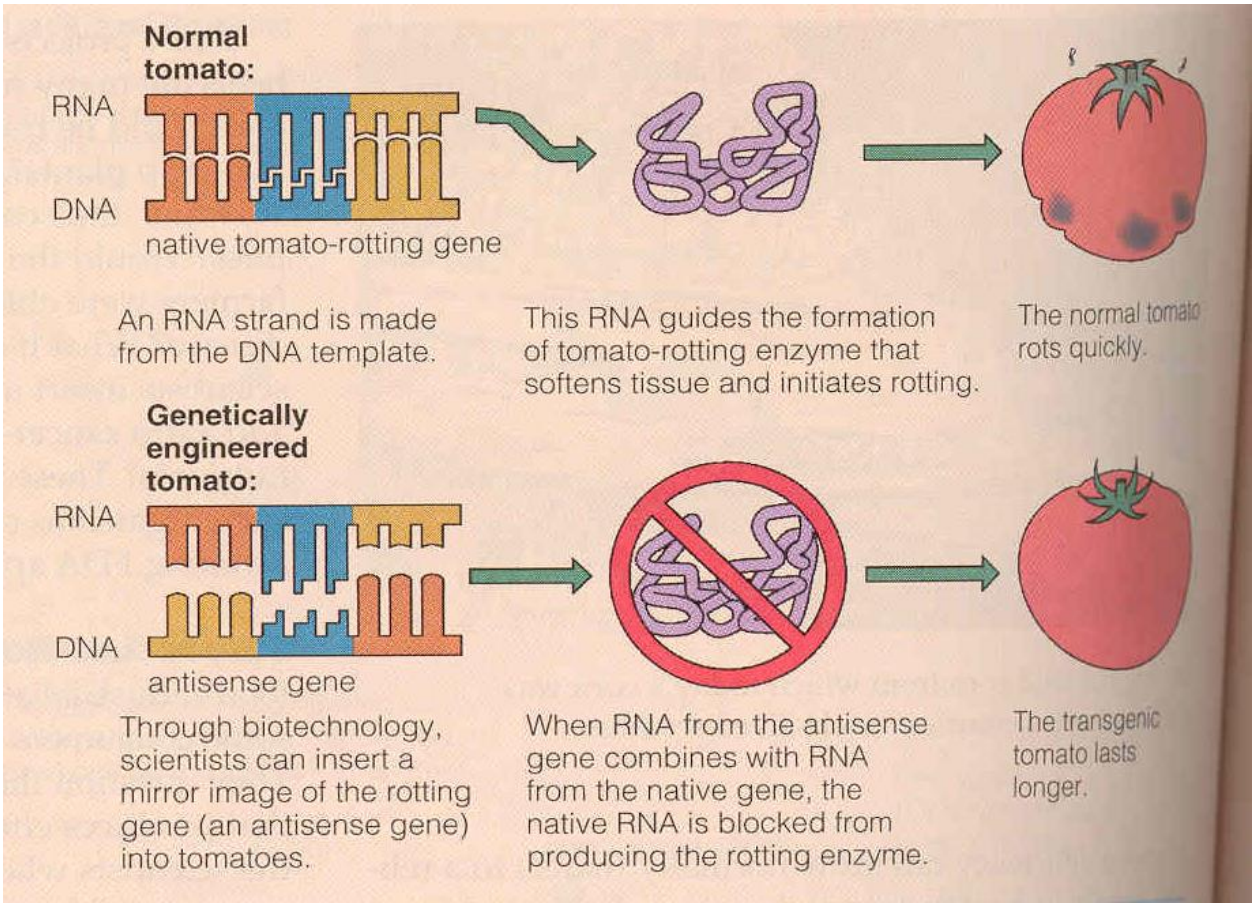
Why do it?

- Rice- not high in essential nutrients

Modification:

- + daffodil genes and a bacterium = beta-carotene content drastically increased
- + genes from a french bean = double the iron content.
- Tomatoes- Introduce genes to increase shelf life.

How is this done?: Transgenic tomatoes



Other applications

- Potato - modified to produce a beetle killing toxin
- Yellow squash – modified to contain to viral genes that resistant the most common viral diseases

- Develop foods that contain vaccines and antibodies that offer valuable protection against diseases such as cholera, hepatitis, and malaria
- Canola – modified to resist one type of herbicide or pesticide

Bayer CropScience

- **Bayer CropScience produces genetically modified canola in Australia for the Canadian market. It is produced to resist the**

Benefits of Genetic Engineering and Modifying

1. Higher yielding crops, more efficient use of land
2. Can save money and promote higher profits
3. Longer shelf life, less waste

   Example: Tomatoes from genetically modified seeds stay fresh longer.
4. Enhanced taste and quality
5. Reduced maturation time
6. Increased and improved nutrients and stress tolerance
   - A single gene genetically engineered into cauliflower can increase production of beta-carotene 100 times.
   - A gene can be implanted into a soybean upgrading the soy protein to a quality equal to that of milk.

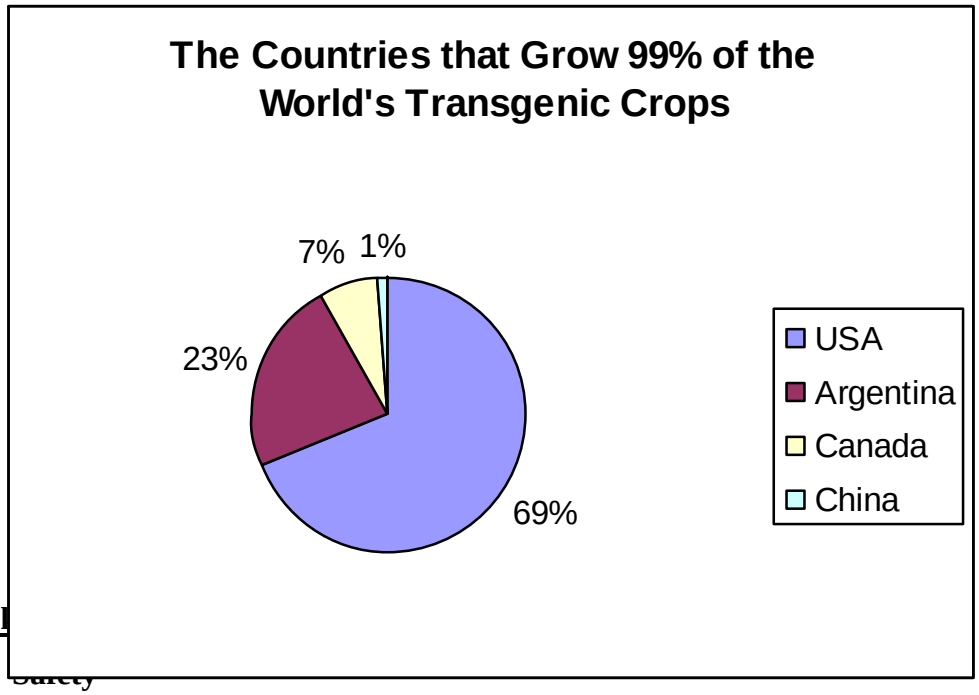
- Corn can be modified to contain its two limiting amino acids, lysine or tryptophan

7. Improved resistance to disease or illness
   - Foods can be enhanced with phytochemicals that help maintain health and reduce the risks of chronic disease.
8. Improved crop resistance to disease, pests, weeds and herbicides
9. New products and growing techniques
   - "Individuals allergic to milk may be able to buy milk that has been treated with the lactase enzyme" (Whiney, 2002).
   - Creating decaffeinated coffee beans are in a process of research.

Society

- Increased food security for growing populations and growth challenges

Who Uses this technology



Risk

1. Safety

- Potential human health implications.
- Potential environmental impact.
  - Out-crossing
    - Inevitable out-crossing of transgenic plants with naturally occurring ones.
    - Creation of super-weeds
- Creation of biological weapons.

2. **Access and Intellectual Property**
    - Domination of world food production by a few companies and developing countries.
3. **Ethics**
    - "Playing God"
    - Tampering with nature by mixing genes among species.
4. **Labeling**
    - Not mandatory in some countries (e.g., Canada and the United States).
    - Mixing GM crops with non-GM confounds labeling attempts.
5. **Society**
    - New advances may be skewed to the interests of rich countries.

(Human Genome Project Information (2003), http://www.ornl.gov/sci/techresources/Human_Genome/elsi/gmfood.shtml)

Biodiversity

- Addition of Bt gene into plants including corn, potatoes and cotton to increase resistance to plants
- Bt gene obtained from *Bacillus thuringiensis (a* soil bacterium that produces a natural insecticide)
- Problem: plants producing Bt toxin are releasing toxin in pollen

(Draper, D. (2002). Our Environment: A Canadian Perspective 2nd Ed. Scarborough: Thompson Canada Limited.)

- Pollen from a Bt plant was dusted on to milkweed:

- only 56% of young monarch butterfly larvae lived
- whereas pollen from organic plants dusted on the milkweed produced a survival rate of 100%.

Approximately half of the monarch butterfly population live in the "corn belt" of the USA = this new gene could have serious repercussions for this organism

Canadian Food Inspection Agency

- Genetically modified foods are currently regulated by the CFIA
- works collaboratively with Environment Canada, Health Canada, and Fisheries and Oceans

- Goal: to ensure that products of biotechnology are considered safe to human and animal health and the environment.
- According to the CFIA, the assessment process for GE foods is very rigorous

- Assessment process
- Criticisms of process

****

Gene Expression Omnibus (GEO)

GEO is a public functional genomics data repository supporting MIAME-compliant data submissions. Array- and sequence-based data are accepted. Tools are provided to help users query and download experiments and curated gene expression profiles.

****

Genetically Modified Organisms (GMO):

When a gene from one organism is purposely moved to improve or change another organism in a laboratory, the result is a genetically modified organism (GMO). It is also sometimes called "transgenic" for transfer of genes.

There are different ways of moving genes to produce desirable traits. For both plants and animals, one of the more traditional ways is through selective breeding. For example, a plant with a desired trait is chosen and bred to produce more plants with the desirable trait. More recently with the advancement of technology is another technique. This technique is applied in the laboratory where genes that express the desired trait is physically moved or added to a new plant to enhance the trait in that plant. Plants produced with this technology are transgenic. Often, this process is performed on crops to produce insect or herbicide resistant plants, they are referred to as Genetically Modified Crops (GM crops).

****

NATIONAL AND INTERNATIONAL LEVEL BIOSAFETY REGULATIONS

In most of developing countries, biosafety regulation is still in its infancy. Appropriate biosafety regulations are one of the prerequisites for a successful transfer of biotechnology to and, among developing countries. Important issues in the debate on biotechnology regulation are the uplifting

of field trials, systematising of regulations, and capacity development in developing countries. The regulation of biosafety is a tool for the safe deployment of biotechnology applications into the environment. It is rather a specialised form of Environmental Impact Assessment (EIA), focussing on the biological consequences of applying Genetically Modified Organisms (GMOs). As a part of EIA, the nature of the organism, the environment in which the organism is to be released, and the interaction of such species, with reference to intraspecific and interspecific are to be analysed. Field trials constitute a major part of the transgenic plants impact assessments, however, biosafety concerns all Genetically Modified Organisms (GMOs).

TRIALS ON–FIELD

Among several industrialized countries, biosafety regulations have been implemented since the mid 1980s; however, there are significant differences among some of these countries. Good experience has been established, both in the regulatory process as well as in analysing the environmental impact of transgenic crops through small demonstration trials. Until December 1992, more than 1,180 small-scale demonstrations with transgenic plants have been conducted in countries having Organisation for Economic Cooperation and Development (OECD). Further, these trials are also conducted to test the expression of the newly-induced trait.

The most commonly tested traits in those demonstration trials are resistant to herbicides, viruses and insects. Herbicide resistance alone accounts to 40 percent of the total number of trials. This high percentage attracts both scientific and commercial interests. In research on transgenic crops, herbicide resistance genes are often used as marker genes for the selection of successfully modified plants. At the same time, commercial interest for herbicide resistance draws from agrochemical companies seeking new markets or safeguarding the existing market shares for their herbicides.

UPSCALING OF FIELD TRIALS

The ecological risks of transgenic crops depend on relatively rare events occasioned by the interaction of particular plants with a particular environment. According to a report of the US Union of Concerned Scientists (UCS), commercial use on a large scale increases the opportunities for the rare harmful conjunctions of factors to occur. Even if a large number of small scale demonstrations are conducted, their outcome does not predict necessarily safety on a commercial scale. The number of plants involved in commercial use is in order of magnitude larger than the number involved in field tests. Most of the field tests involve not more than 4 hectare plots. In contrast, commercial use of major crops such as maize and soya beans could entail cultivation on millions of hectares in the United States alone. Usually field tests are conducted under conditions that severely limit the escape of plants or genes from the test plots. For example, test sites are far removed from other crops or wild relatives with which the transgenic crop can interbreed. Developing countries, however, host many wild relatives of crop plants. Also, sites are monitored to detect transgenic plants that escape. However, no such restrictions apply to commercial use. Once available in the market, engineered plants are free to migrate away from the farm, and their pollen may flow unimpeded to relatives in agricultural and non-agricultural habitats.

Compared to field tests, commercial use will involve crops cultivated in far more diverse environments, in proximity to a broader selection of relatives in different climates, and subject to a greater variety of weather events, such as floods and hurricanes. Floods can expose seeds and plants to many new, potentially congenial environments.

The UCS report offers a framework and guidelines for analyzing the environmental risks of large scale, commercial use of transgenic crops. On discussing the issue of upscaling within the OECD, the OECD has developed a set of scientific principles for the environmental safety of the large scale use of transgenic plants. These guidelines contend that experience and

knowledge gained by traditional plant breeding is essential. The more that is known about a given plant, its traits, its environment and their likely interactions, the easier risk/safety analysis and subsequent risk management will be harmonization.

Many non-governmental organizations, bilateral and multilateral agencies are presently involved in providing direction and assistance in developing appropriate regulations and technical expertise for implementing them. One of the major issues in these international initiatives is harmonization of regulation. Harmonization means that regulatory requirements are made compatible and that reviews are made consistent with each other. However, it does not mean that all countries should have identical policies, priorities or strategies. The aim is uniformity in requirements for data collection and testing procedures, and the exchange of information. Eventually, the outcome of national regulations depends on public perceptions, and public acceptance, as well as on cultural and institutional processes.

Harmonization of regulations has several advantages:

(*a*) Regulatory authorities may benefit from experiences in other countries, both on the organization and the content of risk analysis.

(*b*) It may foster technology transfer as it installs confidence and simplifies the preparation of field trial applications, and

(*c*) It may protect developing countries from being used as a testing ground for field trials that would not be permitted in other countries.

DEVELOPING COUNTRIES

The developing countries, however, do not have regulatory or monitoring procedures, mainly due to lack of monetary enforcement systems, including inadequate institutional facility. India and Philippines which have established regulations and incorporated in their national laws, are exceptions. Other countries *viz.*, Argentina, Bolivia, Brazil, China, Colombia, Costa Rica, Cuba, Indonesia, Malaysia, Thailand and Zimbabwe are in a more or less advanced stage of drafting resolutions, or have formed adhoc committees. Adhoc committees are generally formed to review field trial applications for transgenic plants. Although the number of field trials cannot be matched with that of the OECD countries, it is gradually increasing. In the last three to four years, in Latin America alone, over 60 field trials have been conducted.

COORDINATION AND CAPACITY ESTABLISHMENT

Many of the developing countries are in a process of designing and implementing biosafety regulations. This stage enables opportunities for international coordination of national approaches. Such coordination is carried out by the Inter-American Institute for Cooperation on Agriculture (IICA), for several regions within Latin America, and the International Service for the Acquisition of Agribiotech Applications (ISAAA) for certain selected regions. Harmonization *i.e.*, the regulatory requirement issues were discussed at the "African Regional Conference for International Cooperation on Safety in Biotechnology", held in Zimbabwe in October 1993.

The harmonization processes of IICA and ISAAA are mainly a process building endeavour, since regulation is only as good as the public who develop and enforce it. Thus, capacity building can be defined as (*i*) the training of those nationals who will be developing and

implementing biosafety regulatory mechanisms and (*ii*) the sharing of experience with agencies that are already for many years involved in developing and implementing such regulations. This can be achieved through intensive workshops that would enable participants to gain hands on experience pertaining to the issues and procedures.

There is also a clear-cut way in establishing and harmonizing biosafety regulations in developing countries, by transnational biotech companies. Firstly, if a regulatory system is in place, companies can share responsibility with regulatory authorities in case something misfires. Secondly, supporting regulation may provide a chance to influence the content of the regulation. And finally, implementing and harmonizing regulation can avoid unfair competition from companies established in countries without strict safety regulation. As this is interesting and attractive several international biotech companies contribute to the ISAAA initiative.

BIOSAFETY

RISKS VERSUS BENEFITS

The risk assessment procedures of transgenic plants should provide scientific quantitative information about the chance of any adverse effect leading to an hazard. This information can be gathered through field trials/demonstrations. There is a process of assessing these field trials. This is the state of balancing risks against benefits. In this assessment, ecological effects are to be mainly evaluated. Risk acceptance depends on several factors *viz.*, the expected benefits,

product kinds involved, different possibilities to prevent risks and the need for innovative products through latest technologies. Public perception and reliability of information providing agency, on risks and benefits, also are important. The evaluation of potential risks against expected benefits may vary among different countries. In the application of biotechnology for food production, industrialized countries can easily afford to place higher priority on health and environmental quality management; whereas, developing countries have to concern more with the production and distribution of food. If the application of biotechnology provides enhanced food supplies, developing countries shall accept certain ecological risks. More often the difference is not between south and north, but between entrepreneures and consumers and between biotechnologists and environmentalists. As entrepreneurship is risk oriented, entrepreneurs may accept certain risks than consumers. Consumers can "wait and see"; if their risk perception of some product is too high, they can decide not to buy that product. Biotechnologists focus on the genes of an individual plant and claim that genetic engineering has opened wider options for improvement of plant production. Environmentalists focus their attention on the effect of transgenic plants on ecosystem. Thus, the acceptance of risk and the evaluation of risk against benefit is very much influenced by the position and interests of producer and consumer.This also leads to discussion and deciding on biosafety regulation a very difficult argumet.

HAZARDOUS MATERIALS USED IN BIOTECHNOLOGY — HANDLING AND DISPOSAL

(A) Waste Categories

Hazardous waste can be broadly categorised into four categories: Chemical, radioactive, biohazardous and material that is sharp. Each category has hazards which have an effect on safer handling and safe disposal practices, and a specific waste may have properties of more than one category.

Chemical waste:

Chemical wastes which are hazardous are disposed through a hazardous waste disposal program managed by the safety department. The term "hazardous" refers to materials or chemicals that are corrosive, flammable, reactive, explosive or toxic. The regulatory description of hazardous waste, in a broader sense, includes the majority of known chemicals when they are to be discarded.

The waste disposal of hazardous chemicals is managed in accordance with regulation of the Cregon Department of Environmental Quality (DEQ) and the U.S. Environmental Protection Agency. These regulations suggest specific methods for disposal of different types of hazardous chemical wastes. Therefore, the safety department has specific guidelines which must be strictly followed with reference to packaging, labelling, and disposal of hazardous waste. Since generators are charged for costs associated with waste disposal, guidelines have also been established by the safety department for recycling and waste minimizing methods.

Radioactive waste:

Radioactive substances are most toxic. As compared to organic poisons, infurious effects of radio-nuclides are exceedingly high. For example, radium is 25,000 times more lethal than arsenic. Nuclear war materials, test explosions, craze for power plants, radioisotope use in medicine, industry and research are the main source of radioactive pollution that could threaten our environmental security.

There is no suitable and cheap method of disposal of radioactive waste (spent nuclear fuel

Gaseous effluents and low level wastes). At any time radioactivity is likely to escape from the waste in water bodies, concrete cases and salt formations in high mountains. The nuclear waste is thus likely to get leached into the biosphere.

Pollution control boards and environmental protection agencies must evolve certain foolproof methods to prevent above mentioned pollution by handling radioactive wastes carefully.

Biohazardous waste:

Biological hazard or biohazard means infectious agents causing a risk of death, injury or illness to individuals who handle them. All waste materials which contain such agents must be autoclaved or chemically sterilized before disposing into the general trash. A control *viz.*, sterilizer indicator tape has to be used to assure the effectiveness of treatment.

Toxicity and radioactivity like hazards should not be ignored when disposing of sterilized materials. Provided sterilization is not practical, then biohazardous material must be incinerated in a DEQ-permitted infections waste incinerator.

Sharp materials:

Sharp materials including needles, broken glass, and razor blades provide danger both to initial users and to others who may come in contact with that. Besides causing physical damage, such materials, when contaminated, can provide an entry route into the body for toxic or infectious substances. Therefore, sharp materials should be enclosed in a rigid container and placed in garbage dumpsters.

(B) Instructions for Hazardous Waste Disposal

Proper disposal of chemical wastes is required by central and state governmental laws. For waste generators three steps are suggested: packaging the waste properly, filling out the chemical collection request and sending the request to Linfield Safety Department. However, there is no charge for the pickup service and department billing for hazardous waste disposal will be only for the materials disposed off as billed by the disposal agency.

(a) **Packaging the waste:**

Package the waste in a leak-proof container with a screw-up lid or other secure closer. However, snapcaps (such as those found on milk bottles), wrong size caps, parafilm, or other loose-fitting lids, are not acceptable. Solid debris can be packaged into sealed plastic bags. Biohazard bags are not to be used for chemically hazardous waste.

(b) **Fill up the chemical collection request form:**

The following information has to be filled legibly:

(*i*) Name: Name of the person to be contacted if any questions are to be clarified. He or she should be knowledgeable about the chemical characteristics of the waste and the processes used to generate the waste.

(*ii*) Date: State and federal law allows one to store waste on campus for not more than 90 days. If any container was used to accumulate waste, the date should indicate the last day waste was added.

(*iii*) Department: Departments are charged for waste disposal. Therefore, it has to track who generates a particular area-waste for billing and to help in pollution prevention planning.

(*iv*) Phone details: List the number where the generator can be reached.

(*v*) Building and room. Please mention the building and room where the packed waste product can be located when collectors arrive to pick it up the (not office/corporate office address).

Chemical Contents and Properties

Chemical name and common name:

Used as the basic identifiers for the waste product.

Constituents and percentages: List all the constituents in the container, including solvents and water, by full name, not by abbreviation, initials or chemical formula. Mention their approximate proportions, which should add up to 100%. If the proportions are unknown, indicate that the container holds a mixture and identify the components as well as one can.

Properties, Number of Containers, Container type

Follow the check off and blank fill-in to complete these sections (they are self-explanatory):

Quantity per container: Indicate the amount of waste in the container, not the size of the container, using one of the following units of measure: Litre (including ml etc.), gallon, gram (including kg, etc.), pound. For example, two litres of waste in a four-litre container should be entered as two litres.

- **Total quantity:** Amount in all containers.
- **pH:** Measure the pH and indicate.
- **Major hazards:** Be sure to indicate all hazards.
- **Comments:** Add any comments that you feel would be helpful in classification and handling of the material.

The rest of the form will be completed by the Environmental Health and Safety Department representative picking up the material.

Arranging for waste pickup

Send a copy of the completed request to safety department, unit 4002. Attach a copy of the request to the waste container. The concerned agency will pickup the waste within a week of receiving the request. The marked containers should be left in a visible place in the room noted on the request form.

Problem request forms

While most chemical collection requests the agency receive are usable, there are some common problems that create bad request; further there are some unusually ugly requests.

Common mistakes found on requests include:

(*a*) Signing initials or the name of a laboratory in the column designated for the investigator/generator. A responsible person should be available to clarify any questions regarding the waste.

(*b*) Failure to list the building and room where the waste can be located.

(*c*) Failure to identify 100% of the chemical constituents.

(*d*) Failure to identify any of the constituents at all. Disposing of "unknown" chemicals is extremely expensive.

(*e*) Using chemical formulas to identify the chemical constituents in the waste. For clear communication and to comply with the applicable laws, rules and regulations, the names of the chemical constituents must be written out completely.

(*f*) Using trade names, abbreviations, of waste instead of listing waste chemical constituents. Refer to the MSDS for the chemical constituents, or attach a copy of MSDS within the waste.

Hazardous Waste Disposal Guide

(*a*) *Office and shop waste*

Both office and shop settings typically utilize products that are found also in homes. Environmental regulations allow homeowners greater leeway in disposal of materials than in the workplace environment. What people are used to legally throwing away at home may not be legal to do at work.

(*b*) Aerosol-cans

All aerosol cans are considered hazardous waste until completely empty and punctured. Campus departments may purchase devices to open aerosol cans and drain contents, except for cans with pesticides or other highly toxic materials. Cans will be picked up as with other hazardous wastes. Departments which produce a lot of aerosol cans are encouraged to purchase their own opening device, in consultation with the Linfield College Safety Department.

(*c*) *Office-products*

In the past, correction fluid ("white-out"), duplicating fluid, glues, and various thinners for these products were extensively used in offices. With the advent of word processing systems and photocopiers, the use of these solvent-based products has decreased. Containers that are not completely dry are typically hazardous waste when disposed. In addition, toner fluid (for copiers and printers) may be hazardous, depending on constituents. Inks used for stamp pads or certain pens are typically hazardous.

(*d*) *Cleaning-products*

Many cleaning products have a high or low enough pH to qualify as hazardous waste. Any cleaning product which smells of ammonia is likely to be above the pH allowed for sewer disposal under McMinnville drain disposal regulations. This does not affect the use of these products as intended, but should be kept in mind when getting rid of old or outdated stocks. In addition, many cleaning products contain solvents which may be classified as hazardous waste when disposed.

(*e*) *Rags*

Rags which are to be used for solvent-based purposes should be purchased, when possible, through a laundering service which includes laundering the rags. If this is not feasible, rags with flammable solvents or hazardous constituents should be collected in flammable rag containers and disposed as hazardous waste.

(*f*) *Paint Washers*

Paint washers typically contain flammable or halogenated solvents. Whenever possible, users should set up a recovery system to reclaim the solvent, or arrange for a commercial service which does this. Manufacturers often market replacement solvents which they claim are "non-toxic" or "biodegradable". Their use is encouraged, especially if it results in less chlorinated solvent use. Users must keep in mind, however, that the material they are cleaning may add contaminants to the solvent, such as metals or grease, which make it a hazardous waste.

(*g*) *Paint*

Paint is typically hazardous before drying. The use of lead and mercury in paint has largely disappeared, but the solvents used in both latex and oil-based paints are usually hazardous. Excess unopened or scarcely used paint in good condition should be offered as surplus property. Paint that has been opened should only be thrown away if it is completely dry. If not dry, it can be painted on something or disposed as hazardous waste. There are methods to recycle latex paint to groups that can use it.

Waste Reduction

(*a*) *Waste-costs*

The cost to dispose of hazardous chemical waste will often exceed the original purchase price of a chemical or chemical product. The Linfield College Safety Department encourages waste generators to use waste reduction techniques. If followed, the techniques listed below will help reduce the volume of waste, which will have a corresponding effect on the cost of disposal. Because the costs are variable, they are not listed here. Call the Linfield College Safety Department for current disposal rates. In addition to disposal costs, there are fines from

regulatory agencies for not properly handling waste materials. These fines can be as much as $10,000 per day, and are closely tied into storage and labeling guidelines.

(*b*) *Purchasing*

Purchase chemicals to match anticipated needs. This aspect of waste and cost reduction is frequently overlooked. A substantial portion of hazardous waste generated at Linfield College consists of chemicals that are in original containers, and are unused or of questionable purity due to previous use. Projected savings from purchasing chemicals in a large size are often offset by costs for disposal of unused portions of larger bottles, especially those with a limited shelf life. It may not be possible to exactly determine future needs, but any effort will be beneficial.

(*c*) *Change-procedures*

A procedure which uses a hazardous substance can often be modified to lessen the hazard or amount of waste products resulting from that procedure. In many cases, a less hazardous material can be substituted and perform as well. An example is substituting a commercial lab glass cleaner (*e.g.*, NOCHROMIX) in place of chromic acid cleaning solution. The resulting mixture is still hazardous because of its corrosive properties, but has no toxic chromium and can therefore be neutralized. Reactive substances those that react with water or air or are unstable are especially troublesome disposal items. Disposal costs associated with picric acid, for example, can be as much as ten times the original purchase price.

(*d*) *Unknowns*

Unknowns are difficult and expensive to dispose. Unknowns can be prevented by good record keeping and labeling, which includes designation of constituents and percentages. If unknowns are found, the responsible department must make every effort to identify the material. If this is not possible, then the responsible department will be billed for the cost of identification or classification required for disposal of the unknown chemical, in addition to disposal costs.

(*e*) *Recycling*

Chemical recycling is possible if material is in unopened containers or partially used original containers and of high quality. These materials are made available to interested parties at Linfield College. Be careful not to obliterate any parts of labels. Chemicals and chemical products should not be given or sold to the general public or offered as surplus property. Commercial chemical products may be offered for surplus if reasonable cautions are followed.

(*f*) *Segregate*

Segregate wastes as much as possible. Mixing a low-cost disposal item with a higher one makes the entire lot a higher-cost item.

(*g*) *Storage*

The storage of hazardous materials must be in compliance with federal and state regulations. Your methods of handling waste are subject to unannounced inspections by state regulatory inspectors. All containers need to have a label at all time indicating contents. For waste materials, this could be a simple label such as “WASTE SOLVENT” or “USED ACETONE”. Put the label on the container BEFORE ADDING WASTE. All containers need a lid at all times when not actively adding or removing waste. Evaporation in a hood is not a legal disposal method. Funnels do not count as lids. Secondary containment is advised for liquid containers. Storage limits and locations are the same for waste as for new materials. For example, storage of flammable liquids in excess of 10 gallons requires a flammable liquid storage cabinet. Glass bottles may not be stored on the floor because they can easily be broken by accidental kicking.

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rDNA GUIDELINES

The National Institutes of Health (NIH) *Guidelines for Research Involving Recombinant DNA Molecules* is the reference document for research compliance with recombinant DNA molecules.

SCOPE AND APPLICABILITY

- If your institution receives Federal funding, then it must comply with the NIH Guidelines for recombinant DNA research.

Even if a project is privately sponsored, that research experiment must still be conducted in accordance with the NIH Guidelines.

Definition of recombinant DNA: Recombinant deoxyribonucleic acid (rDNA) by definition involves *in vitro* introduction of different segments of DNA (one being the vector and the others normally unrelated DNA sequences) that are capable of replication in a host cell either autonomously or as an integral part of host's genome and maintenance of their continued propagation. This will include all types of cell fusion, microinjection of DNA or RNA or parts or all of chromosomes, genetic engineering including self cloning and deletion as well as cell hybridation, transformation and other types of virus or pathogen introduction into unnatural hosts.

The organisms involved may belong to these categories:

1. i) Intergeneric organisms

ii) Well defined organisms with non-coding regulatory regions

2. i) Biological agents whose source of DNA is a pathogen

ii) Organisms that are generally recognised as non-pathogenic and may imbibe the characteristics of a pathogen on genetic manipulation.

Recombinant DNA (rDNA):

Defined as either:

1. Molecules constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell; or

2. DNA molecules that result from the replication of those described above.

- **Risk Levels:**

I. Low Risk: risk level of agents and/or operations having minimal effect on personnel, other animal or plants under ordinary use. This classification is restricted to all etiologic agents designated as Biosafety Level 1 by the CDC.

II. Moderate Risk: risk level of agents and/or operations requiring special conditions for control or containment because of (a) known pathogenicity to personnel, other animals or plants; (b) concentration; or c) genetic alteration (synergistic effect) with other materials.

III. High Risk: risk level of agents and/or operations requiring additional control measures beyond those for moderate risk. This classification includes all etiologic agents designated Class 4 or 5 by the CDC and oncogenic viruses classified as high risk by the NCI.

SAFETY CONSIDERATIONS

Risk Group

- 1: not known to cause disease
- 2: rarely serious disease, with therapeutic intervention
- 3: serious, lethal disease with therapeutic intervention
- 4: serious, lethal disease with no therapeutic intervention

RISK ASSESSMENT

- Review classification of organism
- Review research procedures to be performed
- Assess available facility/physical barriers

(biosafety levels)

- Potential for inadvertent release
- Other factors, such as volume, concentration, replication competency

CONTAINMENT

- Standard practices
- Special procedures, equipment
- Available facility/facility design
- Biological barriers

CLASSIFICATION OF EXPERIMENTS

Requires: IBC, RAC, NIH Director Review and Approval prior to the initiation of work

- Drug resistance to organisms
- Prevent compromise to agriculture/medicine

Requires: NIH/OBA, IBC Review and Approval Before Initiation of Work

- Containment determined by NIH/OBA
- Example: Deliberate Cloning of Toxin Molecules Lethal to Vertebrates at an LD50 of Less Than 100 Nanograms/Kg of Body Weight (e.g., Botulinum Toxin)

Requires: RAC Review, IBC, and IRB Review and Approval Before Participant Enrollment

- Requires RAC Review prior to local institutional review.
- Must be reviewed by NIH prior to research participant enrollment.

Requires: IBC Review and Approval prior to the initiation of work

- Involves RG 2-4 agents, host/vector system
- Cloned DNA from RG 2-4 agents into non-pathogenic prokaryotes
- RG 2-4 agents into whole animals, usually transgenic
- Recombinant plants

Requires: IBC notification at the initiation of work (BL-1 containment)

- DNA Contains Less than 2/3 viral genome
- Transgenic Rodents with ABSL1 containment

- Whole Plants-minimal containment required

Exempt from the NIH Guidelines and Does Not Require IBC Review and Approval

Recombinant DNA that is:

- Not in Organisms
- Not a risk to the environment

ROLES AND RESPONSIBILITIES

- Ensure compliance with NIH Guidelines
- Establish IBC
- Appoint a Biosafety Officer
- Ensure IBC has expertise in the research that is reviewed
- Establish a medical surveillance program as needed
- Report all accidents to the NIH

When the institution conducts recombinant DNA research at BL3, BL4, or Large Scale (greater than 10 Liters), ***a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee.***

The Institutional Biosafety Committee must be composed of no fewer than five members so selected that they collectively have experience and expertise in recombinant DNA technology and the capability to assess the safety of recombinant DNA research and to identify any potential risk to public health or the environment.

At least two members shall not be affiliated with the institution (apart from their membership on the IBC) and who represent the interest of the surrounding community with respect to health and protection of the environment (e.g. officials of state or local public health or environmental protection agencies, members of other governmental bodies, or persons active in medical, occupational health, or environmental concerns in the community).

No member of an Institutional Biosafety Committee may be involved (except to provide information requested by the IBC) in the review or approval of a project in which he/she has been or expects to be engaged or has a direct financial interest

Reviewing recombinant DNA research conducted at or sponsored by the institution for compliance with *NIH Guidelines* as specified in Section III, *Experiments Covered by the NIH Guidelines.*

This review shall include:

(i) independent assessment of the containment levels required by the *NIH Guidelines*

(ii) assessment of the facilities, procedures, practices, and training and expertise of personnel involved in recombinant DNA research.

Certain experiments with animals require IBC review and approval:

- Section III-D-4, whole animals
- Section III-E-3, transgenic rodents
- Appendix Q: Containment requirements for large mammals
- Any introduction of biohazardous agents(shedding)
- While the IACUC traditionally examines pain and suffering, euthanasia and vivaria housing, the safe work practices described in Biosafety Levels 1-3 should be followed.

The IBC and IACUC should also ensure:

- biohazard vivaria areas are kept clean
- animal carcasses are properly disposed of
- infected animals are housed separately
- infected animals are transported safely
- infected animals do not infect humans

REPORTING ACCIDENTS AND INCIDENTS

- All **laboratory** accidents or incidents involving recombinant DNA molecules must be reported to NIH, OBA.
- All **adverse events in gene transfer experiments** must be reported to NIH, OBA, even if thought not to be in conjunction with the gene transfer intervention.

RAC APPROVAL

The Institutional Biosafety Committee may not authorize initiation of experiments which are not explicitly covered by the NIH Guidelines until NIH (with the advice of the RAC when required) establishes the containment requirement.

CONCLUSION

This presentation was designed to inform the audience on the key provisions of the NIH Guidelines. The IBC must interact as necessary with other institutional committees and ensure that research involving recombinant DNA molecules is adequately reviewed.

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT – III – Bioethics Biosafety and IPR – SBB1615

UNIT-3 IMPLICATIONS OF BIOSAFETY

Awareness education on genetically engineered organism.-Transgene instability, gene flow, resistance/ tolerance of target organism, increase weedlessness, risks and uncertainty associated with Biotechnology. Containment levels and their impact on Environment- Containment- definition, types of containment, summary of recommended Biosafety levels for infectious agents, detail checklist–premises and lab equipment, Animal facilities, environment.

A **genetically modified organism** (**GMO**) is any organism whose genetic material has been altered using genetic engineering techniques. The exact definition of a genetically modified organism and what constitutes genetic engineering varies, with the most common being an organism altered in a way that "does not occur naturally by mating and/or natural recombination". A wide variety of organisms have been genetically modified (GM), from animals to plants and microorganisms. Genes have been transferred within the same species, across species (creating transgenic organisms), and even across kingdoms. New genes can be introduced, or endogenous genes can be enhanced, altered, or knocked out.

Creating a genetically modified organism is a multi-step process. Genetic engineers must isolate the gene they wish to insert into the host organism and combine it with other genetic elements, including a promoter and terminator region and often a selectable marker. A number of techniques are available for inserting the isolated gene into the host genome. Recent advancements using genome editing techniques, notably CRISPR, have made the production of GMO's much simpler. Herbert Boyer and Stanley Cohen made the first genetically modified organism in 1973, a bacteria resistant to the antibiotic kanamycin. The first genetically modified animal, a mouse, was created in 1974 by Rudolf Jaenisch, and the first plant was produced in 1983. In 1994 the Flavr Savr tomato was released, the first commercialized genetically modified food. The first genetically modified animal to be commercialized was the GloFish (2003) and the first genetically modified animal to be approved for food use was the AquAdvantage salmon in 2015.

Bacteria are the easiest organisms to engineer and have been used for research, food production, industrial protein purification (including drugs), agriculture, and art. There is potential to use them for environmental, purposes or as medicine. Fungi have been engineered with much the same goals. Viruses play an important role as vectors for inserting genetic

information into other organisms. This use is especially relevant to human gene therapy. There are proposals to remove the virulent genes from viruses to create vaccines. Plants have been engineered for scientific research, to create new colors in plants, deliver vaccines, and to create enhanced crops. Genetically modified crops are publicly the most controversial GMOs. The majority are engineered for herbicide tolerance or insect resistance. Golden rice has been engineered with three genes that increase its nutritional value. Other prospects for GM crops are as bioreactors for the production of biopharmaceuticals, biofuels, or medicines.

Animals are generally much harder to transform and the vast majority are still at the research stage. Mammals are the best model organisms for humans, making ones genetically engineered to resemble serious human diseases important to the discovery and development of treatments. Human proteins expressed in mammals are more likely to be similar to their natural counterparts than those expressed in plants or microorganisms. Livestock is modified with the intention of improving economically important traits such as growth rate, quality of meat, milk composition, disease resistance, and survival. Genetically modified fish are used for scientific research, as pets, and as a food source. Genetic engineering has been proposed as a way to control mosquitos, a vector for many deadly diseases. Although human gene therapy is still relatively new, it has been used to treat genetic disorders such as severe combined immunodeficiency, and Leber's congenital amaurosis.

Many objections have been raised over the development of GMOs, particularly their commercialization. Many of these involve GM crops and whether food produced from them is safe and what impact growing them will have on the environment. Other concerns are the objectivity and rigor of regulatory authorities, contamination of non-genetically modified food, control of the food supply, patenting of life and the use of intellectual property rights. Although there is a scientific consensus that currently available food derived from GM crops poses no greater risk to human health than conventional food, GM food safety is a leading issue with critics. Gene flow, impact on non-target organisms, and escape are the major environmental concerns. Countries have adopted regulatory measures to deal with these concerns. There are differences in the regulation for the release of GMOs between countries, with some of the most marked differences occurring between the US and Europe. Key issues concerning regulators include whether GM food should be labeled and the status of gene-edited organisms.

An Overview of the Legal and Socioeconomic Impacts of Biotechnology—Biosafety Regulations

Biosafety, as currently discussed in the International "Convention on Biological Diversity" (CBD) and designed to create internationally binding protocols on biosafety. The application of biotechnology to food and agriculture can bring not only potential risks and benefits as any technology can, but also concerns about the human dimensions coupled with biotechnology. These include both positive and negative impacts on stake holders, social institutions, economy and communities.

Different areas associated with biosafety include:
(*i*) Agriculture and food system issues
(*ii*) Market and consumer issues
(*iii*) Institutional issues, business issues and
(*iv*) Social issues

Agriculture and food system issues.

These include the impact of biotechnology on the organisation, structure and behaviour of agricultural industry; further, the coexistence of conventional organic and biotechnology oriented agriculture; the capacity of the food system to segregate genetically-modified commodity and product of specific markets; impacts on competitions involved, trade in agricultural commodities and the economical impacts of establishing oversight, standard regulations and public policies concerning biotechnology.

Market and consumer issues.

These include various limitations which come to the rescue of consumer demand for overall against the products of agricultural biotechnology, the needs, desires and concerns of consumers in domestic and international markets; the influence of culture, advertising, product labelling, scientific information and recent new events on consumer decision making about the use of biotechnology products; different methods for most effectively increasing the understanding on which publication and primary decision making concerning biotechnology is based.

Institutional issues and business issues.

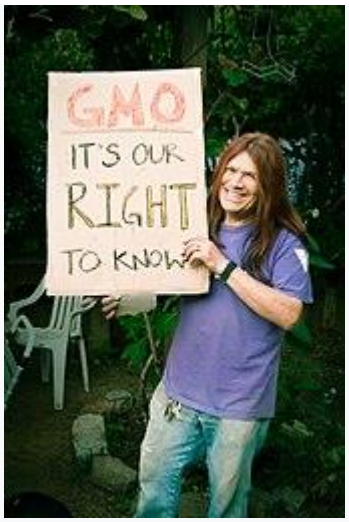
These include the impacts of biotechnology on individual forms or group of forms about buying or selling biotechnology products and processes; changes in business practices, alliances and domestic and international markets including markets in Third World countries.

Social issues.

These include the needs of various public to secure meaningful information for involvement in decision making on development and by use of agricultural biotechnology; the role of civic engagement at the local, state and national levels; perceived and actual risks benefits to consumers and the general environmental protection, agro-terrorism; research vandalism, and their impacts on Third World nations.

Genetically modified food controversies

There is controversy over GMOs, especially with regard to their release outside laboratory environments. The dispute involves consumers, producers, biotechnology companies, governmental regulators, non-governmental organizations, and scientists. Many of these concerns involve GM crops and whether food produced from them is safe and what impact growing them will have on the environment. These controversies have led to litigation, international trade disputes, and protests, and to restrictive regulation of commercial products in some countries.[328] Most concerns are around the health and environmental effects of GMOs. These include whether they may provoke an allergic reaction, whether the transgenes could transfer to human cells, and whether genes not approved for human consumption could outcross into the food supply.[329]



A protester advocating for the labeling of GMOs

There is a scientific consensus[330][331][332][333] that currently available food derived from GM crops poses no greater risk to human health than conventional food,[334][335][336][337][338] but that each GM food needs to be tested on a case-by-case basis before introduction.[339][340][341] Nonetheless, members of the public are much less likely than scientists to perceive GM foods as safe.[342][343][344][345] The legal and regulatory status of GM foods varies by country, with some nations banning or restricting them, and others permitting them with widely differing degrees of regulation.[346][347][348][349]

Gene flow between GM crops and compatible plants, along with increased use of broad-spectrum herbicides,[350] can increase the risk of herbicide resistant weed populations.[351] Debate over the extent and consequences of gene flow intensified in 2001 when a paper was published showing transgenes had been found in landrace maize in Mexico, the crop's center of diversity.[352][353] Gene flow from GM crops to other organisms has been found to generally be lower than what would occur naturally.[354] In order to address some of these concerns some GMOs have been developed with traits to help control their spread. To prevent the genetically modified salmon inadvertently breeding with wild salmon, all the fish raised for food are females, triploid, 99% are reproductively sterile, and raised in areas where escaped salmon could not survive.[355][356] Bacteria have also been modified to depend on nutrients that cannot be found in nature,[357] and genetic use restriction technology has been developed, though not yet marketed, that causes the second generation of GM plants to be sterile.[358]

Other environmental and agronomic concerns include a decrease in biodiversity, an increase in secondary pests (non-targeted pests) and evolution of resistant insect pests.[359][360][361] In the areas of China and the US with Bt crops the overall biodiversity of insects has increased and the impact of secondary pests has been minimal. Resistance was found to be slow to evolve when best practice strategies were followed.[362] The impact of Bt crops on beneficial non-target organisms became a public issue after a 1999 paper suggested they could be toxic to monarch butterflies. Follow up studies have since shown that the toxicity levels encountered in the field were not high enough to harm the larvae.[363]

Accusations that scientists are "playing God" and other religious issues have been ascribed to the technology from the beginning.[364] With the ability to genetically engineer humans now possible there are ethical concerns over how far this technology should go, or if it should be used at all.[365] Much debate revolves around where the line between treatment and enhancement is and whether the modifications should be inheritable.[366] Other concerns

include contamination of the non-genetically modified food supply,[367][368] the rigor of the regulatory process,[369][370] consolidation of control of the food supply in companies that make and sell GMOs,[371] exaggeration of the benefits of genetic modification,[372] or concerns over the use of herbicides with glyphosate.[373] Other issues raised include the patenting of life[374] and the use of intellectual property rights.[375]

There are large differences in consumer acceptance of GMOs, with Europeans more likely to view GM food negatively than North Americans.[376] GMOs arrived on the scene as the public confidence in food safety, attributed to recent food scares such as Bovine spongiform encephalopathy and other scandals involving government regulation of products in Europe, was low.[377] This along with campaigns run by various non-governmental organizations (NGO) have been very successful in blocking or limiting the use of GM crops.[378] NGOs like the Organic Consumers Association, the Union of Concerned Scientists,[379][380][381] Greenpeace and other groups have said that risks have not been adequately identified and managed[382] and that there are unanswered questions regarding the potential long-term impact on human health from food derived from GMOs. They propose mandatory labeling[383][384] or a moratorium on such products.[371][369][385]

Risks of Modern Biotechnology

Article shared by : Aakriti Gupta <="" div="" style="margin: 0px; padding: 0px; border: 0px; outline: 0px; font-size: 16px; vertical-align: bottom; background: transparent; max-width: 100%;">

The following points highlight the four major risks of modern biotechnology. The risks are: 1. Health Risks 2. Environmental Risks 3. Risks to Biodiversity 4. Socioeconomic Risks.

1. Health Risks:

Potential health risks of genetically improved organisms relate to assessing and minimizing the risk of food allergens in genetically improved food. New biotechnology based methods allow the identification, characterization, and minimization of risks of food allergens. Genetically improved crops and food, and the risk of allergens associated with them, are now a concern throughout the world, especially in industrial countries.

More than 90 per cent of food allergens that occur in 2 per cent of adults and 4-6 per cent of children are associated with eight food groups. Allergenicity of genetically improved foods can be raised in crops and foods either by raising the level of endogenous allergen or by introducing a new allergen.

Assessment of the risk of allergens is a challenge. The International Life Sciences Institute (ILSI) has developed a decision tree that provides a framework for risk assessment.

It uses the following criterion: that an introduced protein in a food is not a concern if there is:

(1) No history of common allergenicity,

(2) No similar amino acid sequence to known allergens,

(3) Rapid digestion of the protein, and

(4) The protein is expressed at low levels.

Protocols enable assembly of the data to judge food against this criterion. It is also important to inform consumers of any potential risk. A key concern of consumers is being able to identify where allergens are found.

Consumers want to know where the potential for food allergens exists. Any protein added to food should be assessed for potential allergenicity, whether it is added by genetic engineering or by manufacturing.

There are several related areas of concern with regard to potential human health risks of genetically improved foods: toxicity, carcinogenicity, food intolerances; the risk of the use of gene markers for antibiotic resistance; other macromolecules aside from protein that could be potential allergens; and nutritional value.

Methods of testing and evaluating risks of toxicity and carcinogenicity are well established for food. The question remains as to whether developing countries can implement and use currently available technologies and protocols to assess food allergens and other health risks.

The techniques are well established, and should be readily implementable by trained professionals. Although no clear cases of harmful effects on human health have been

documented from new genetically improved food that does not mean that risks do not exist and they should be assessed on a case by case basis.

2. Environmental Risks:

The risks policymakers and regulators need to assess include the potential for spread of traits from genetically improved plants to the same or related species, plants, the build-up of resistance in insect populations, and the potential threat to biodiversity posed by widespread monoculture of genetically improved crops.

i. A transparent, science-based framework is required, which assesses risks on a case by case basis and takes account of all stakeholder views.

ii. Environment-related issues to be considered in each case include the possibilities for gene transfer, weediness, specific trait effects, genetic and phenotypic variability, and expression of pathogenic genes.

iii. Risk management needs to consider the prospects for managing any specific risks identified with a proposed release.

iv. Experience is accumulating in the management of the Bt genes in transgenic cotton varieties in several countries and this needs to be closely monitored.

v. An agricultural sustainability protocol that balances risks and benefits may have value for the approval and use of new crop varieties.

The risks lie in the management of the cropping system involving soil, water and other inputs. There is a need for the establishment of baseline information in the environment where such introductions are to be made. There is very little known on this, although some understanding has been gained over recent years, and further R&D is required.

The information derived from such an assessment needs to be handled through risk management associated with **"plants as plants."** Risk management involves the consideration of traditional cultural practices that have evolved over time, and new knowledge gained from research in agronomy, plant pathology, entomology, weed science, plant biology, soils, microbiology, and other disciplines.

3. Risks to Biodiversity:

Risks to biodiversity and wildlife are important issues in particular environments. Careful assessment is necessary of the risks associated with the possible creation of new selection pressures coming from the introduction of genetically improved organisms into the environment.

Of special concern is the potential impact on biodiversity of genetically improved organisms as the selection pressures wield influence in the species composition of the ecosystem. These concerns merit further study, especially on the behaviour of genetically improved organisms in the open environment.

The framework for strategic planning in the deployment of genetically improved organisms should be formulated with sustain-ability as the primary concern. Both food safety and biosafety regulations should reflect international agreements and best practice and a given society's acceptable risk levels, including the risks associated with not using biotechnology to achieve desired goals.

The principles and practices for assessing the risks on a case-by-case basis are well established in most Organization for Economic Cooperation and Development (OECD) countries and several emerging economies. These principles and practices have been summarized in a series of OECD reports published over the past decade or more.

National, regional, and international guidelines for risk assessment and risk management provide a basis for national regulatory systems. Biosafety guidelines are available from several international organizations including the OECD, United Nations Environment Program, United Nations Industrial Development Organization, and the World Bank.

Regulatory trends to govern the safe use of biotechnology to date, include undertaking scientifically based, case-by-case, hazard identification and risk assessments; regulating the end product rather than the production process itself; developing a regulatory framework that builds on existing institutions rather than establishing new ones; and building in flexibility to reduce regulation of products after they have been demonstrated to be of low risk.

Biotechnology is not inherently different to other technologies with respect to economic and social impacts, as long as it focuses on the problems that affect poor people.

One important difference is that research on biotechnology has largely taken place in the private sector with proprietary technologies and an orientation to commercial agriculture. This implies the need for a strong role for the public sector, including increased resources, to address developing country priorities.

4. Socioeconomic Risks:

There is a risk that modern science may bypass the needs of poor people. Biotechnology is only one tool in addressing the challenges of food security and poverty. There is a need for biotechnology to be integrated with appropriate policies and other conventional R&D programs.

The positive and negative impacts of biotechnology should be monitored over time in terms of who and what are affected and how they are affected. Monitoring impact will provide guidance for public policymakers in the future.

Unless countries have policies in place to ensure that small farmers have access to delivery systems, extension services, productive resources, markets, and infrastructure, there is a risk that the introduction of agricultural biotechnology could lead to increased inequality of income and wealth.

In such cases, larger farmers are likely to capture most of the benefits through early adoption of the technology, expanded production, and reduced unit costs.

Biotechnology has potential to reduce input use, reduce risk to biotic and abiotic stress, increase yields, and enhance quality-all traits which should enable the development of new crop varieties that are appropriate to poor producers and consumers.

Modern biotechnology is not a silver bullet for achieving food security, but, used in conjunction with other agricultural research, it may be a powerful tool in the fight against poverty.

It has the potential to help enhance agricultural productivity in developing countries in a way that further reduces poverty, improves food security and nutrition, and promotes sustainable use of natural resources. Solutions to the problems facing small farmers in developing countries could benefit both farmers and consumers.

The benefits and risks need to be assessed on a case by case basis, weighing the risks and benefits for each particular situation. The benefits of new genetically improved food to consumers are likely to vary according to how they earn their income and how much of their income they spend on food.

Consumers outnumber farmers by a factor of more than 20 in the European Union, and Europeans spend only a tiny fraction of their incomes on food.

Similarly, in the United States, farms account for less than 2 per cent of all households, and the average consumer spends less than 12 per cent of income on food. In the industrial countries, consumers can afford to pay more for food, increase subsidies to agriculture, and give up opportunities for better tasting and better-looking food.

In developing countries, poor consumers depend heavily on agriculture for their livelihoods and spend the bulk of their income on food. Strong opposition to genetically improved foods in the European Union has resulted in restrictions on modern agricultural biotechnology in some countries.

The opposition is driven in part by perceived lack of consumer benefits, uncertainty about possible negative health and environmental effects, widespread perception that a few large corporations will be the primary beneficiaries, and ethical concerns.

Biocontainment

From Wikipedia, the free encyclopedia

Researchers working in Class III cabinets at the U.S. Army Biological Warfare Laboratories, Camp Detrick, Maryland (1940s). Biocontainment procedures were pioneered at the USBWL in the 1940s and '50s.

One use of the concept of **biocontainment** is related to **laboratory biosafety** and pertains to microbiology laboratories in which the physical containment of pathogenic organisms or agents (bacteria, viruses, and toxins) is required, usually by isolation in environmentally and biologically secure cabinets or rooms, to prevent accidental infection of workers or release into the surrounding community during scientific research.

Another use of the term relates to facilities for the study of agricultural pathogens, where it is used similarly to the term "biosafety", relating to safety practices and procedures used to prevent unintended infection of plants or animals or the release of high-consequence pathogenic agents into the environment (air, soil, or water).

Terminology

The World Health Organization's 2006 publication, *Biorisk management: Laboratory biosecurity guidance*, defines laboratory biosafety as "the containment principles, technologies and practices that are implemented to prevent the unintentional exposure to pathogens and toxins, or their accidental release". It defines biorisk management as "the analysis of ways and development of strategies to minimize the likelihood of the occurrence of biorisks".[1]

The term "biocontainment" is related to laboratory biosafety.[2][3] Merriam-Webster's online dictionary reports the first use of the term in 1966, defined as "the containment of extremely pathogenic organisms (such as viruses) usually by isolation in secure facilities to prevent their accidental release especially during research".[4]

The term laboratory biosafety refers to the measures taken "to reduce the risk of accidental release of or exposure to infectious disease agents", whereas laboratory biosecurity is usually taken to mean "a set of systems and practices employed in legitimate bioscience facilities to reduce the risk that dangerous that dangerous biological agents will be stolen and used maliciously".[5]

Containment types

Laboratory context

Primary containment is the first container in direct contact with biohazardous material[6] as well as protection of personnel and the immediate laboratory environment from exposure to infectious agents. Primary containment requires using proper storage containers, good microbiological technique, and the use of appropriate safety equipment such as biological safety cabinets.

Secondary containment is the protection of the environment external to the laboratory from exposure to infectious materials and is provided by a combination of facility design and operational practices.

Biological safety cabinets (BSC), first commercially available in 1950,[7] are fairly common devices designed to provide effective primary biocontainment in laboratories working with highly infectious agents. Three general levels and types have been devised (Class I, Class II, and Class III).

Biosafety suites are suites of laboratory rooms which are essentially equivalent to large Class III cabinets in which positive pressure personnel suits ("space suits") serve as the "outside" environment for workers. Examples include the biosafety suites at USAMRIID at Fort Detrick, Maryland, USA and the Maximum Containment Facility (MCF) of the CDC in Atlanta, Georgia, USA.

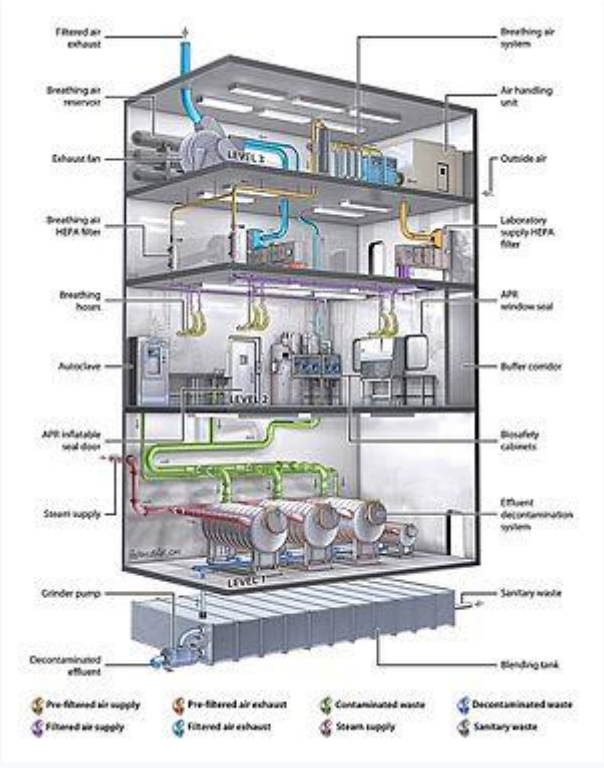
Agricultural context

The term “biocontainment” is used differently in facilities for the study of human pathogens versus those used for the study of agricultural pathogens. In agricultural facilities, the definition for “biocontainment” resembles that for “biosafety,” i.e., the safety practices and procedures used to prevent unintended infection of plants or animals or the release of high-consequence

pathogenic agents into the environment (air, soil, or water). In the agricultural setting, worker protection and public health are always considerations; however, emphasis is placed on reducing the risk that agents under study could escape into the environment.

Biosafety level

From Wikipedia, the free encyclopedia



Essential features of a biosafety level 4 (BSL-4) laboratory[1]

A **biosafety level** (**BSL**), or **pathogen/protection level**, is a set of biocontainment precautions required to isolate dangerous biological agents in an enclosed laboratory facility. The levels of

containment range from the lowest biosafety level 1 (BSL-1) to the highest at level 4 (BSL-4). In the United States, the Centers for Disease Control and Prevention (CDC) have specified these levels.[2] In the European Union, the same biosafety levels are defined in a directive.[3] In Canada the four levels are known as Containment Levels.[4] Facilities with these designations are also sometimes given as **P1** through **P4** (for pathogen or protection level), as in the term *P3 laboratory*.[5]

At the lowest level of biosafety, precautions may consist of regular hand-washing and minimal protective equipment. At higher biosafety levels, precautions may include airflow systems, multiple containment rooms, sealed containers, positive pressure personnel suits, established protocols for all procedures, extensive personnel training, and high levels of security to control access to the facility.

History

The first prototype Class III (maximum containment) biosafety cabinet was fashioned in 1943 by Hubert Kaempf Jr., then a U.S. Army soldier, under the direction of Arnold G. Wedum, Director (1944–69) of Industrial Health and Safety at the United States Army Biological Warfare Laboratories, Camp Detrick, Maryland. Kaempf was tired of his MP duties at Detrick and was able to transfer to the sheet metal department working with the contractor, the H.K. Ferguson Co.[6]

On 18 April 1955, fourteen representatives met at Camp Detrick in Frederick, Maryland. The meeting was to share knowledge and experiences regarding biosafety, chemical, radiological, and industrial safety issues that were common to the operations at the three principal biological warfare (BW) laboratories of the U.S. Army.[7] Because of the potential implication of the work conducted at biological warfare laboratories, the conferences were restricted to top level security clearances. Beginning in 1957, these conferences were planned to include non-classified sessions as well as classified sessions to enable broader sharing of biological safety information. It was not until 1964, however, that conferences were held in a government installation not associated with a biological warfare program.[8]

Over the next ten years, the biological safety conferences grew to include representatives from all federal agencies that sponsored or conducted research with pathogenic microorganisms. By 1966, it began to include representatives from universities, private laboratories, hospitals, and industrial complexes. Throughout the 1970s, participation in the conferences continued to expand and by 1983 discussions began regarding the creation of a formal

organization.[8] The American Biological Safety Association (ABSA) was officially established in 1984 and a constitution and bylaws were drafted the same year. As of 2008, ABSA includes some 1,600 members in its professional association.[8]

In 1977 Jim Peacock of the Australian Academy of Science asked Bill Snowdon, then Chief CSIRO AAHL if he could have the newly released USA NIH and the British equivalent requirements for the development of infrastructure for bio-containment reviewed by AAHL personnel with a view to recommending the adoption of one of them by Australian authorities. The review was carried out by CSIRO AAHL Project Manager Bill Curnow and CSIRO Engineer Arthur Jenkins. They drafted outcomes for each of the levels of security. AAHL was notionally classified as "substantially beyond P4". These were adopted by the Australian Academy of Science and became the basis for Australian Legislation. It opened in 1985 costing $185 million, built on Corio Oval.[9] The Australian Animal Health Laboratory is a Class 4/ P4 Laboratory.

Levels

Biosafety level 1

Biosafety level 1 (BSL-1) is suitable for work with well-characterized agents which do not cause disease in healthy humans. In general, these agents should pose minimal potential hazard to laboratory personnel and the environment.[10] At this level, precautions are limited relative to other levels. Laboratory personnel must wash their hands upon entering and exiting the lab. Research with these agents may be performed on standard open laboratory benches without the use of special containment equipment. However, eating and drinking are generally prohibited in laboratory areas.[10] Potentially infectious material must be decontaminated before disposal, either by adding a chemical such as bleach or isopropanol or by packaging for decontamination elsewhere.[10] Personal protective equipment is only required for circumstances where personnel might be exposed to hazardous material.[10] BSL-1 laboratories must have a door which can be locked to limit access to the lab. However, it is not necessary for BSL-1 labs to be isolated from the general building.[11]

This level of biosafety is appropriate for work with several kinds of microorganisms including non-pathogenic strains of *Escherichia coli* and *Staphylococcus*, *Bacillus subtilis*, *Saccharomyces cerevisiae* and other organisms not suspected to contribute to human disease.[12] Due to the relative ease and safety of maintaining a BSL-1 laboratory, these are the types of laboratories generally used as teaching spaces for high schools and colleges.[11]

Biosafety level 2

At this level, all precautions used at Biosafety Level 1 are followed, and some additional precautions are taken. BSL-2 differs from BSL-1 in that:

- Laboratory personnel have specific training in handling pathogenic agents and are directed by scientists with advanced training.
- Access to the laboratory is limited when work is being conducted.
- Extreme precautions are taken with contaminated sharp items.
- Certain procedures in which infectious aerosols or splashes may be created are conducted in biological safety cabinets or other physical containment equipment.[10]

Biosafety level 2 is suitable for work involving agents of moderate potential hazard to personnel and the environment.[11] This includes various microbes that cause mild disease to humans, or are difficult to contract via aerosol in a lab setting.[13] Examples include Hepatitis A, B, and C viruses, human immunodeficiency virus (HIV), pathogenic strains of *Escherichia coli* and *Staphylococcus*, *Salmonella*, *Plasmodium falciparum*, and *Toxoplasma gondii*.[13][14]

Biosafety level 3

Researcher at US Centers for Disease Control, Atlanta, Georgia, working with influenza virus under biosafety level 3 conditions, with respirator inside a biosafety cabinet (BSC).

Biosafety level 3 is appropriate for work involving microbes which can cause serious and potentially lethal disease via the inhalation route.[10] This type of work can be done in clinical,

diagnostic, teaching, research, or production facilities.[11] Here, the precautions undertaken in BSL-1 and BSL-2 labs are followed, as well as additional measures including:

- All laboratory personnel are provided medical surveillance and offered relevant immunizations (where available) to reduce the risk of an accidental or unnoticed infection.[10]
- All procedures involving infectious material must be done within a biological safety cabinet.[10]
- Laboratory personnel must wear solid-front protective clothing (i.e. gowns that tie in the back). This cannot be worn outside of the laboratory and must be discarded or decontaminated after each use.[10]
- A laboratory-specific biosafety manual must be drafted which details how the laboratory will operate in compliance with all safety requirements.[10]

In addition, the facility which houses the BSL-3 laboratory must have certain features to ensure appropriate containment. The entrance to the laboratory must be separated from areas of the building with unrestricted traffic flow.[10] Additionally, the laboratory must be behind two sets of self-closing doors (to reduce the risk of aerosols escaping).[11] The construction of the laboratory is such that it can be easily cleaned. Carpets are not permitted, and any seams in the floors, walls, and ceilings are sealed to allow for easy cleaning and decontamination.[10] Additionally, windows must be sealed, and a ventilation system installed which forces air to flow from the "clean" areas of the lab to the areas where infectious agents are handled.[10] Air from the laboratory must be filtered before it can be recirculated.[10]

Biosafety level 3 is commonly used for research and diagnostic work involving various microbes which can be transmitted by aerosols and/or cause severe disease. These include *Francisella tularensis*, *Mycobacterium tuberculosis*, *Chlamydia psittaci*, Venezuelan equine encephalitis virus, Eastern equine encephalitis virus, SARS-CoV-1, SARS-CoV-2, MERS-CoV, *Coxiella burnetii*, Rift Valley fever virus, *Rickettsia rickettsii*, several species of *Brucella*, chikungunya, yellow fever virus, West Nile virus, Yersinia pestis.[14][15]

Biosafety level 4

CDC technician dons an older-model positive-pressure suit before entering one of the CDC's earlier BSL-4 labs.

Biosafety level 4 (BSL-4) is the highest level of biosafety precautions, and is appropriate for work with agents that could easily be aerosol-transmitted within the laboratory and cause severe to fatal disease in humans for which there are no available vaccines or treatments.[10] BSL-4 laboratories are generally set up to be either cabinet laboratories or protective-suit laboratories.[10] In cabinet laboratories, all work must be done within a class III biosafety cabinet.[10] Materials leaving the cabinet must be decontaminated by passing through an autoclave or a tank of disinfectant.[10] The cabinets themselves are required to have seamless edges to allow for easy cleaning. Additionally the cabinet and all materials within must be free of sharp edges in order to reduce the risk of damage to the gloves.[10] In a protective-suit laboratory, all work must be done in a class II biosafety cabinet by personnel wearing a positive pressure suit.[10] In order to exit the BSL-4 laboratory, personnel must pass through a chemical shower for decontamination, then a room for removing the positive-pressure suit, followed by a personal shower.[10] Entry into the BSL-4 laboratory is restricted to trained and authorized individuals, and all persons entering and exiting the laboratory must be recorded.[10]

As with BSL-3 laboratories, BSL-4 laboratories must be separated from areas that receive unrestricted traffic. Additionally airflow is tightly controlled to ensure that air always flows from "clean" areas of the lab to areas where work with infectious agents is being

performed.[10] The entrance to the BSL-4 lab must also employ airlocks to minimize the possibility that aerosols from the lab could be removed from the lab. All laboratory waste, including filtered air, water, and trash must also be decontaminated before it can leave the facility.[10]

Biosafety level 4 laboratories are used for diagnostic work and research on easily transmitted pathogens which can cause fatal disease. These include a number of viruses known to cause viral hemorrhagic fever such as Marburg virus, Ebola virus, Lassa virus, and Crimean-Congo hemorrhagic fever. Other pathogens handled at BSL-4 include Hendra virus, Nipah virus, and some flaviviruses. Additionally, poorly characterized pathogens which appear closely related to dangerous pathogens are often handled at this level until sufficient data are obtained either to confirm continued work at this level, or to permit working with them at a lower level.[14] This level is also used for work with Variola virus, the causative agent of smallpox, though this work is only performed at the Centers for Disease Control and Prevention in Atlanta, United States, and the State Research Center of Virology and Biotechnology in Koltsovo, Russia.[16]

- 

Regular inspection of positive-pressure suits to locate any leaks[17]

- 

SPECT machine at BSL-4 imaging facility that separates subjects with pathogens from the machines.[1]

- 

The circular containment tube separates the patient table in the "hot" zone (pathogen present) from the "cold" zone around this MRI machine.

- 

Air pressure resistant (APR) door to separate the hot and cold zones

- 

Working inside a BSL-4 lab with air hoses providing positive air pressure.

- 

Inside a Class III biological safety cabinet with an aerosol control platform

- 

Effluent decontamination system of a BSL-4 lab of NIAID

BSL-4 facilities for extraterrestrial samples

Sample-return missions that bring back to Earth samples obtained from a Category V body must be curated at facilities rated BSL-4. Because the existing BSL-4 facilities in the world do not have the complex requirements to ensure the preservation and protection of Earth and the sample simultaneously,[18] there are currently at least two proposals to build a BSL-4 facility dedicated to curation of restricted (potentially biohazardous) extraterrestrial materials.

The first is the European Sample Curation Facility (ESCF),[19][20] proposed to be built in Vienna, which would curate non-restricted samples as well as perform BSL-4 processing of restricted material obtained from Category V bodies such as Mars, Europa, and Enceladus.[19] The other proposal is by NASA and is tentatively known as the Mars Sample-Return Receiving facility (MSRRF).[21] At least three different designs were submitted in 2009.[18] If funded, this American facility would be expected to take 7 to 10 years from design to completion,[22][23] and an additional two years is recommended for the staff to become proficient and accustomed to the facilities.[22] NASA is also assessing a 2017 proposal to build a mobile and modular BSL-4 facility to secure a sample return capsule at the landing site to conduct preliminary biohazard analyses.[24] After completion of biohazard testing, decisions could be made to sterilize the sample or transport all or portions to a permanent quarantine storage facility anywhere in the world.[24]

The systems of such facilities must be able to contain unknown biohazards, as the sizes of any putative alien microorganisms are unknown. Ideally, it should filter particles down to 10 nanometers, and release of a particle 50 nanometers or larger is unacceptable under any circumstance.[25]

List of BSL-4 facilities

According to a U.S. Government Accountability Office (GAO) report published on 4 October 2007, a total of 1,356 CDC/USDA registered BSL-3 facilities were identified throughout the

United States.[26] Approximately 36% of these laboratories are located in academia. 15 BSL-4 facilities were identified in the U.S. in 2007, including nine at federal labs.[26]

The following is a list of existing BSL-4 facilities worldwide.

Name	Location	Country	year	Description
National Service of Healthcare and Agriculture Quality (SENASA)	Buenos Aires	Argentina		Diagnostic laboratory for Foot-and-mouth disease.[27]
Australian Centre for Disease Preparedness	Geelong, Victoria	Australia	1985	Capable of housing from large experimental animals to insects under conditions that exceed all BSL 4 requirements. The antecedent of all such facilities developed since the 1980s. Arguably the most researched design and construction project ever. AAHL is subdivided into a number of isolation zones that can be managed at differing containment levels concurrently. CSIRO AAHL Project Manager and Architect, William Curnow, provided technical reviews to Canadian, Indian, UK and French Authorities and consulted with Dr Jerry Callis [PIADC] to UN FAO on matters of bio-containment. Formerly known as the Australian Animal Health Laboratory (AAHL) and renamed to

Name	Location	Country	year	Description
				Australian Centre for Disease Preparedness April 2020
University of Melbourne – Doherty Institute for Infection and Immunity	Melbourne, Victoria	Australia	2014	Diagnostic reference lab.[28][29]
National High Security Laboratory	Melbourne, Victoria	Australia		Operates under the auspice of the Victoria Infectious Diseases Reference Laboratory.[30]
Laboratório Nacional Agropecuário de Minas Gerais (Lanagro/MG)	Pedro Leopoldo, Minas Gerais	Brazil	2014	Focus on Agropecuary diseases and diagnostics.[31]
National Microbiology Laboratory	Winnipeg, Manitoba	Canada	1999 [32]	Located at the Canadian Science Centre for Human and Animal Health, it is jointly operated by the Public Health Agency of Canada and the Canadian Food Inspection Agency.[33]

Name	Location	Country	year	Description
Wuhan Institute of Virology of the Chinese Academy of Sciences	Wuhan, Hubei	China	2015	Wuhan Institute of Virology has existed since 1956 and already hosted BSL3 laboratories. A BSL4 facility was completed in 2015, and became the first BSL-4 laboratory in China.[34]
Harbin Veterinary Research Institute of the Chinese Academy of Agricultural Sciences	Harbin, Heilongjiang	China	2018	Harbin Veterinary Research Institute researches prevention and control of major infectious diseases. China's second, and the first for large animals, BSL-4 lab.[35]
Biological Defense Center	Těchonín, Pardubice Region	Czech Republic	1971, rebuilt 2003–2007	Hospital and research facility. Located at the Centrum biologické ochrany (Biological Defense Center). Operated by Army of the Czech Republic.[36]
French Armed Biomedical Research Institute, French	Brétigny-sur-Orge, Essonne	France		French Army laboratory.[37]

Name	Location	Country	year	Description
Defence Health Service				
Jean Mérieux BSL-4 Laboratory	Lyon, Metropolis of Lyon	France	1999	Built and owned by the Fondation Mérieux. Since 2004, operated by INSERM.[38]
Laboratoire de la DGA	Vert-le-Petit, Essonne	France	2013	Operated by the Ministry of Defense.[39]
Centre International de Recherches Médicales de Franceville	Franceville, Haut-Ogooué Province	Gabon		This facility is operated by a research organization supported by both Gabonese (mainly) and French governments, and is West Africa's only P4 lab (BSL-4).[40]
Robert Koch Institute	Berlin	Germany	2015	Diagnostic and experimental lab facility.[41]
Bernhard Nocht Institute for Tropical Medicine	Hamburg	Germany	2014	Part of the Leibniz Center Infection. National reference lab for tropical viruses.[42]
Friedrich Loeffler Institute	Isle of Riems, Greifswald,	Germany	2010	Focus on animal viral diseases and diagnostics.[43]

Name	Location	Country	year	Description
	Mecklenburg-Vorpommern			
Philipps University of Marburg	Marburg, Hesse	Germany	2008	Focuses on hemorrhagic fever viruses.[44]
National Center for Epidemiology	Budapest	Hungary	1998	Division of Virology operates three WHO National Reference Laboratories. The BSL-4 biosafety laboratory provides a modern means to process dangerous imported zoonotic viral pathogens.[45]
University of Pécs	Pécs	Hungary	2016	Opened in 2016, part of "Szentágothai János Kutatóközpont".
High Security Animal Disease Laboratory (HSADL)	Bhopal, Madhya Pradesh	India	1998	This facility deals especially to zoonotic organisms and emerging infectious disease threats.[46]
Centre for Cellular and Molecular Biology	Hyderabad, Telangana	India	2009	National BSL-4 Containment Facility for Human Infectious Diseases.[47]

Name	Location	Country	year	Description
National Institute of Virology	Pune, Maharashtra	India	2012	India's most advanced BSL-4 category lab.[48]
Istituto Nazionale per le Malattie Infettive	Rome, Lazio	Italy	1997	The "National Institute of Infectious Diseases" used to operate within the Lazzaro Spallanzani hospital; the facility is now independent and is home to five BSL-3 labs as well as a single BSL-4 laboratory, which was completed in 1997.[49]
National Institute for Infectious Diseases	Musashimurayama, Tokyo	Japan	2015	Located at National Institute for Infectious Diseases, Department of Virology I. Built in 1981; operated at BSL-3 until 2015 due to opposition from nearby residents.[50]
Institute of Physical and Chemical Research (RIKEN)	Tsukuba, Ibaraki Prefecture	Japan	1984	Facility completed in 1984 but not operated as BSL-4 due to local opposition.[51]
State Research Center of Virology and Biotechnology (VECTOR)	Koltsovo, Novosibirsk Oblast	Russia		One of two WHO-approved facilities for work on variola virus.[16]

Name	Location	Country	year	Description
National Institute for Communicable Diseases	Johannesburg, Gauteng	South Africa	2002	[52]
Korea Centers for Disease Control and Prevention	Cheongju, North Chungcheong Province	South Korea	2017	First BSL-4 Lab in South Korea
Public Health Agency of Sweden	Solna, Stockholm County	Sweden	2001	The only BSL-4 facility in the Nordic region. Constructed for research and diagnostics of hemorrhagic fever viruses.[53]
University Hospital of Geneva	Geneva, Canton of Geneva	Switzerland		"Glove box" type laboratory; primarily for handling clinical samples.[54]
Spiez Laboratory	Spiez, Canton of Bern	Switzerland	2013	Run by Federal Office for Civil Protection and the Federal Department of Defence, Civil Protection and Sports.[55]
The Institute of Virology and Immunology IVI[56]	Mittelhäusern, Canton of Bern	Switzerland		Part of the Food Safety and Veterinary Office (FSVO).[57] Primary purpose is diagnostics of highly pathogenic viruses.[55]

Name	Location	Country	year	Description
Institute of Preventive Medicine	National Defense University	Taiwan	1983	[58]
Francis Crick Institute	Camden, Greater London	United Kingdom	2015	Has BSL-4 space but does not work on human pathogens.[59]
Public Health England's Centre for Infections	Colindale, Greater London	United Kingdom		Department of Health laboratory. Diagnostics for various viral diseases.[60] Part of the European Network of Biosafety-Level-4 Laboratories.[61]
National Institute for Medical Research	Mill Hill, Greater London	United Kingdom		Medical Research Council laboratory. Research and diagnostics for highly pathogenic viruses. Closed in 2017 and work moved to the Francis Crick Institute. Site demolished in 2018. [60]
National Institute for Biological Standards and Control	Potters Bar, Hertfordshire	United Kingdom		Department of Health and Home Office laboratory. Develop assays and reagents for research on virulent pathogens.[60]

Name	Location	Country	year	Description
Animal and Plant Health Agency	Addlestone, Surrey	United Kingdom		Department for Environment, Food and Rural Affairs laboratory. Diagnostics and research for animal diseases.[60]
Institute for Animal Health	Pirbright, Surrey	United Kingdom		Biotechnology and Biological Sciences Research Council laboratory. Research on highly pathogenic animal diseases.[60]
Merial Animal Health	Pirbright, Surrey	United Kingdom		Private lab. Produces vaccines against foot and mouth disease and bluetongue disease.[60]
Centre for Emergency Preparedness and Response	Porton Down, Wiltshire	United Kingdom		Department of Health laboratory. Diagnostics and research for haemorrhagic fever viruses.[60] Part of the European Network of Biosafety-Level-4 Laboratories.[61]
Defence Science and Technology Laboratory	Porton Down, Wiltshire	United Kingdom		Ministry of Defence laboratory. Focuses on protection from biological weapons.[60]
Centers for Disease Control and Prevention,	Fort Collins, Colorado	United States		A BSL 3/4 facility that operates in connection with some of Colorado State University's biomedical research programs.

Name	Location	Country	year	Description
Division of Vector Borne Diseases				The location specializes in arboviral and bacterial diseases.[62]
Centers for Disease Control and Prevention	Atlanta, Georgia	United States		Currently operates in two buildings. One of two facilities in the world that officially hold smallpox.[16]
Georgia State University	Atlanta, Georgia	United States	1997	Research focus on B virus.[63]
National Bio and Agro-Defense Facility (NBAF), Kansas State University	Manhattan, Kansas	United States	2022 (expected)	Under construction. Facility to be operated by the Department of Homeland Security, and replace the Plum Island Animal Disease Center. Expected to be operational by 2022–2023.[64]
National Institutes of Health (NIH)	Bethesda, Maryland	United States		Located on the NIH Campus, it currently only operates with BSL-3 agents.[65]
Integrated Research Facility	Fort Detrick, Maryland	United States		Operated by National Institute of Allergy and Infectious Diseases (NIAID). Focuses on animal models of human diseases.[66]
National Biodefense Analysis and	Fort Detrick, Maryland	United States		Operated by the Department of Homeland Security. Focus on potential bioterrorism threats.[67]

Name	Location	Country	year	Description
Countermeasures Center				
US Army Medical Research Institute of Infectious Diseases (USAMRIID)	Fort Detrick, Maryland	United States	1969	Run by the U.S. Army. Research focuses on biological threats to the U.S. military.[68][69]
National Emerging Infectious Diseases Laboratory (NEIDL), Boston University	Boston, Massachusetts	United States	Built 2008, Opened 2012,[70] BSL-4 Approval in 2017[71]	Focus on potential threats to public health.[72]
Rocky Mountain Laboratories Integrated Research Facility	Hamilton, Montana	United States	2008	NIAID laboratory. Focus on vector-borne diseases.[73]

Name	Location	Country	year	Description
Galveston National Laboratory, National Biocontainment Facility	Galveston, Texas	United States		Opened in 2008, facility is operated by the University of Texas Medical Branch.[74]
Shope Laboratory	Galveston, Texas	United States	2004	Operated by the University of Texas Medical Branch.[75]
Texas Biomedical Research Institute	San Antonio, Texas	United States	1999	The only privately owned BSL-4 lab in the US.[76]

Safety concerns

A North Carolina Mosquito & Vector Control Association (NCMVCA) study highlighted safety concerns. In the United States, laboratories can be funded by federal, state, private, non-profit, or academically. The last accounts for 72% of the funding. There is no central monitoring agency accountable for monitoring laboratories and standards vary according to funding, the age of the laboratory, and is dependent on the size and whether it is SA approved.[77]

High-containment labs that are registered with the Centers for Disease Control and Prevention (CDC) and the U.S. Department of Agriculture's (USDA) Select Agent Program must adhere to Department of Defense standards.[78] No single federal agency, according to 12 agencies' responses to a GSA survey, has the mission to track the overall number of BSL-3 and BSL-4 labs in the United States. This means no agency is responsible for determining the risks associated with the proliferation of these labs.[79]

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UNIT-4 GLP IPR- PATENT WTO TRIPS GATT

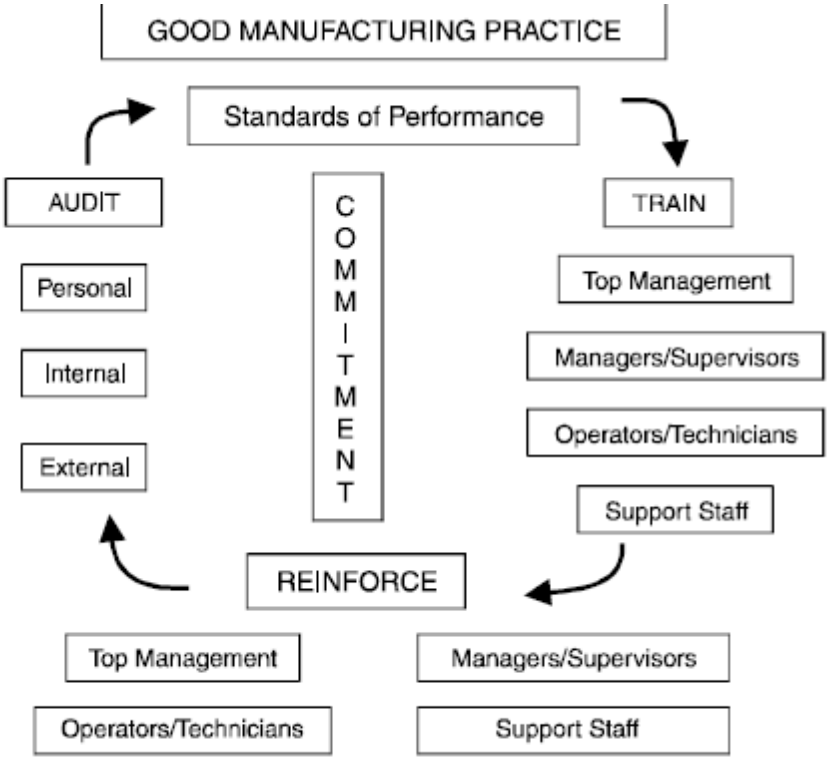
Gene technology laboratory. GLP and Bioethics- introduction, national Good Laboratory Practices (GLP), the GLP authority functions, Good Laboratory Practices- necessity, aspiration and responsibility. Procedure to apply patent, other intellectual properties viz. Copy Rights, Plant Breeder's Rights, Trade Secrets/ Trade Symbol etc. WTO, TRIPS, PCT and GATT. IPR problems and its hindrance.

GOOD MANUFACTURING PRACTICES

What is GMP?

GMP refers to the Good Manufacturing Practice regulations promulgated by the US Food and Drug Administration under the authority of the Federal Food, Drug, and Cosmetic Act (FDA). These regulations, which have the force of law, require that manufacturers, processors, and packagers of drugs, medical devices, some food, and blood take proactive steps to ensure that their products are safe, pure, and effective. GMP regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination, mixups, and errors. This in turn, protects the consumer from purchasing a product which is not effective or even dangerous. Failure of firms to comply with GMP regulations can result in very serious consequences including recall, seizure, fines, and jail time.

GMP regulations address issues including recordkeeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling. Most GMP requirements are very general and open-ended, allowing each manufacturer to decide individually how to best implement the necessary controls.



Example of Good Manufacturing Practices

Approved drug manufacturing equipment

The GMPs require that equipment be of appropriate design to facilitate operations for its intended use and for cleaning and maintenance and, that any equipment surface in contact with components, in-process materials, or drug products not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

GOOD LABORATORY PRACTICES (GLP)

During the 1970s, there were several problems which made some scientific reports unreliable. These reports had been submitted to international regulatory authorities and decisions about the safety of materials to man and the environment were made on the basis of this unreliable information.

Consequently the US Government introduced the first **Good Laboratory Practice (GLP)** regulations in 1978. Other countries followed with different GLP standards and the Organisation for Economic Cooperation and Development (OECD) published the worldwide principles of **Good Laboratory Practice in 1981.** Adherence to these OECD standards permits international acceptability of safety testing from different countries.

In the first part we will examine the nature of the problems that caused the introduction of

GLP and how the international scientific and regulatory community responded to these problems. We will also discuss how international co-operation in GLP is organised. GLP is based on sound, common-sense principles. There is nothing required by GLP that exceeds what any conscientious scientist would do when producing quality research and development.

GLP is concerned with how we organise our laboratories and how we organise our studies. It addresses responsibilities for managing the people, facilities and equipment required for good science and how we plan, perform and report our experiments and studies. Most importantly, GLP does not interfere with the ability of scientists to make scientific decisions.

GOOD LABORATORY PRACTICE PRINCIPLES

1. Test Facility Organisation and Personnel

Management's responsibilities Test facility management should ensure that the principles of good laboratory practice is complied with in the test facility.

2. At minimum it should

(*a*) ensure that qualified personnel, appropriate facilities, equipment, and materials are available;

(*b*) maintain a record of the qualifications, training, experience and job description for each professional and technical individual;

(*c*) ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions;

(*d*) ensure that health and safety precautions are applied according to national and/or international regulations;

(*e*) ensure that appropriate standard operating procedures are established and followed;

(*f*) ensure that there is a Quality Assurance Programme with designated personnel;

(*g*) where appropriate, agree to the study plan in conjunction with the sponsor;

(*h*) ensure that amendments to the study plan are agreed upon and documented;

(*i*) maintain copies of all study plans;

(*j*) maintain a historical file of all Standard Operating Procedures;

(*k*) for each study ensure that a sufficient number of personnel is available for its timely and proper conduct;

(*l*) for each study designate an individual with the appropriate qualifications, training, and experience as the Study Director before the study is initiated. If it is necessary to replace a Study Director during a study, this should be documented;

(*m*) ensure that an individual is identified as responsible for the management of the archives.

Study Director's Responsibilities

1. The Study Director has the responsibility for the overall conduct of the study and for its report.

2. These responsibilities should include, but not be limited to, the following functions:

(*a*) should agree to the study plan;

(*b*) ensure that the procedures specified in the study plan are followed, and that authorization for any modification is obtained and documented together with the reasons for them;

(*c*) ensure that all data generated are fully documented and recorded;

(*d*) sign and date the final report to indicate acceptance of responsibility for the validity of the data and to confirm compliance with these Principles of Good Laboratory Practice;

(*e*) ensure that after termination of the study, the study plan, the final report, raw data and supporting material are transferred to the archives.

Personnel Responsibilities

1. Personnel should exercise safe working practice. Chemicals should be handled with suitable caution until their hazard(s) has been established.

2. Personnel should exercise health precautions to minimise risk to themselves and to ensure the integrity of the study.

3. Personnel known to have a health or medicinal condition that is likely to have an adverse effect on the study should be excluded from operations that may affect the study.

Quality Assurance Programme

General

1. The test facility should have a documented quality assurance programme to ensure that studies performed are in compliance with these Principles of Good Laboratory Practice.
2. The quality assurance programme should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.
3. This individual(s) should not be involved in the conduct of study being assured.
4. This individual(s) should report any finding in writing directly to management and to the Study Director.

Responsibilities of the quality assurance personnel

1. The responsibilities of the quality assurance personnel should include, but not be limited to, the following functions:
(*a*) ascertain that the study plan and Standard Operating Procedures are available to personnel conducting the study;
(*b*) ensure that the study plan and Standard Operating Procedures are followed by periodic inspections of the test facility and/or by auditing the study in progress. Records of such procedures should be retained.
(*c*) promptly report to management and the Study Director unauthorised deviations from the study plan and from Standard Operation Procedures;
(*d*) review the final reports to confirm that the methods, procedures, and observations are accurately described, and that the reported results accurately reflect the raw data of the study;
(*e*) prepare and sign a statement, to be included with the final report, which specifies the dates inspections were made and the dates any findings were reported to management and to the Study Director.

3. Facilities

General

1. The test facility should be of suitable size, construction and location to meet the requirements of the study and minimise disturbances that would interfere with the validity of the study.
2. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study.

Test system facilities

1. The test facility should have a sufficient number of rooms or areas to assure the isolation of test systems and the isolation of individual projects, involving substances known or suspected of being biohazardous.
2. Suitable facilities should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems.
3. There should be storage areas as needed for supplies and equipment. Storage areas should be separated from areas housing the test systems and should be adequately protected against infestation and contamination. Refrigeration should be provided for perishable commodities.

Facilities for handling test and reference substances

1. To prevent contamination or mix-ups, there should be separate areas for receipt and storage of the test and reference substances, and mixing of the test substances with a vehicle.
2. Storage areas for the test substances should be separated from areas housing the test systems and should be adequated to preserve identity, concentration, purity, and stability, and ensure safe storage for hazardous substances.

Archive facilities

1. Space should be provided for archives for the storage and retrieval of raw data, reports, samples, and specimens.

Waste disposal

1. Handling and disposal of wastes should be carried out in such a way as not to jeopardize the integrity of studies in progress.
2. The handling and disposal of wastes generated during the performance of a study should be carried out in a manner which is consistent with pertinent regulatory requirements. This would include provision for appropriate collection, storage, and disposal facilities, decontamination and transportation procedures, and the maintenance of records related to the preceding activities.

4. Apparatus, Material, and Reagents

Apparatus

1. Apparatus used for the generation of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.
2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of procedures should be maintained.

Material

Apparatus and materials used in studies should not interfere with the test systems.

Reagents

Reagents should be labelled, as appropriate, to indicate source, identity, concentration, and stability information and should include the preparation dates, earliest expiration date, specific storage instructions.

5. Test Systems

Physical/Chemical

(*a*) Apparatus used for the generation of physical/chemical data should be suitably located and of appropriate design and adequate capacity.
(*b*) Reference substances should be used to assist in ensuring the integrity of the physical/chemical test systems.

Biological

(*a*) Proper conditions should be established and maintained for the housing, handling and care of animals, plants, microbial as well as other cellular and sub-cellular systems, in order to ensure the quality of the data.
(*b*) In addition, conditions should comply with appropriate national regulatory requirements for the import, collection, care and use of animals, plants, microbial as well as other cellular and sub-cellular systems.
(*c*) Newly-received animal and plant test systems should be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, this lot should not be used in studies and, when appropriate, humanely destroyed.
(*d*) Records of source, date of arrival, and arrival condition should be maintained.

(*e*) Animal, plant, microbial, and cellular test systems should be acclimatised to the test environment for an adequate period before a study is initiated.
(*f*) All information needed to properly identify the test systems should appear on their housing or containers.
(*g*) The diagnosis and treatment of any disease before or during a study should be recorded.

6. Test and Reference Substances

Receipt, handling, sampling and storage
(*a*) Records including substance characterisation, date of receipt, quantities received, and used in studies should be maintained.
(*b*) Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability is assured to the degree possible and contamination or mix-up are precluded.
(*c*) Storage container(s) should carry identification information, earliest expiration date, and specific storage instructions.

Characterisation
(*a*) Each test and reference substance should be appropriately identified (*e.g.*, code, chemical abstract number (CAS), name).
(*b*) For each study, the identity, including batch number, purity, composition, concentrations, or other characterisations to appropriately define each batch of the test or reference substances should be known.
(*c*) The stability of test and reference substances under conditions of storage should be known for all studies.
(*d*) The stability of test and reference substances under the test conditions should be known for all studies.
(*e*) If the test substance is administered in a vehicle, Standard Operating Procedures should be established for testing the homogeneity and stability of the test substance in that vehicle.
(*f*) A sample for analytical purposes from each batch of test substance should be retained for studies in which the test substance is tested longer than four weeks.

7. Standard Operating Procedures

General

(*a*) A test facility should have written Standard Operating Procedures approved by management that are intended to ensure the quality and integrity of the data generated in the course of the study.

(*b*) Each separate laboratory unit should have immediately available Standard Operating Procedures relevant to the activities being performed therein. Published textbooks, articles and manuals may be used as supplements to these Standard Operating Procedures.

Application

1. Standard Operating Procedures should be available for, but not limited to, the following categories of laboratory activities. The details given under each heading are to be considered as illustrative examples.

(*a*) Test and Reference Substance. Receipt, identification, labelling, handling, sampling, and storage.

(*b*) Apparatus and Reagents.Use, maintenance, cleaning, calibration of measuring apparatus and environmental control equipment; preparation of reagents.

(*c*) Record keeping. Reporting, Storage and Retrieval Coding of studies, data collection, preparation of reports, indexing systems, handling of data, including the use of computerised data systems.

(*d*) Test system (where appropriate):

(*i*) Room preparation and environmental room conditions for the test system.

(*ii*) Procedures for receipt, transfer, proper placement, characterisation, identification and care of test system.

(*iii*) Test system preparation, observations examinations, before, during and at termination of the study.

(*iv*) Handling of test system individuals found moribund or dead during the study.

(*v*) Collection, identification and handling of specimens including necropsy and histopathology.

(*e*) Quality Assurance Procedures. Operation of quality assurance personnel in performing and reporting study audits, inspections, and final study report reviews.

(*f*) Health and Safety Precautions. As required by national and/or international legislation or guidelines.

8. Performance of the Study

Study plan

1. For each study, a plan should exist in a written form prior to initiation of the study.

2. The study plan should be retained as raw data.

3. All changes, modifications, or revisions of the study plan, as agreed to by the Study Director, including justification(s), should be documented, signed and dated by the Study Directors, and maintained with the study plan.

Content of the study plan

The study plan should contain, but not be limited to the following information:

1. Identification of the Study, the Test and Reference Substances

(*a*) A descriptive title;

(*b*) A statement which reveals the nature and purpose of the study;

(*c*) Identification of the test substance by code or name (IUPAC; CAS number, etc.);

(*d*) The reference substance to be used.

2. Information Concerning the Sponsor and the Test Facility

(*a*) Name and address of the Sponsor;

(*b*) Name and address of the Test Facility;

(*c*) Name and address of the Study Director.

3. Dates

(*a*) The date of agreement to the study plan by signature of the Study Director, and when appropriate, of the sponsor and/or the test facility management;

(*b*) The proposed starting and completion dates.

4. Test Methods

Reference to OECD Test Guideline or other test guideline to be used.

5. Issues (where applicable)

(*a*) The justification for selection of the test system;

(*b*) Characterisation of the test system, such as the species, strain, sub-strain, source of supply, number, body weight range, sex, age, and other pertinent information;

(*c*) The method of administration and the reason for its choice;

(*d*) The dose levels and/or concentration(s), frequency, duration of administration;

(*e*) Detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed.

6. Records

A list of records to be retained.

Conduct of the study

1. A unique identification should be given to each study. All items concerning this study should carry this identification.

2. The study should be conducted in accordance with the study plan.

3. All data generated during the conduct of the study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialled and dated.

4. Any change in the raw data should be made so as not to obscure the previous entry, and should indicate the reason, if necessary, for change and should be identified by date and signed by the individual making the change.

5. Data generated as a direct computer input should be identified at the time of data input by the individual(s) responsible for direct data entries. Corrections should be entered separately by the reason for change, with the date and the identity of the individual making the change.

9. Reporting of Study Results

General

1. A final report should be prepared for the study.

2. The use of the International System of Units (SI) is recommended.

3. The final report should be signed and dated by the Study Director.

4. If reports of principal scientists from co-operating disciplines are included in the final report, they should sign and date them.

5. Corrections and additions to a final report should be in the form of an amendment. The amendment should clearly specify the reason for the corrections or additions and should be signed and dated by the Study Director and by the principal scientist from each discipline involved.

Content of the final report

The final report should include, but not be limited to, the following information:

1. Identification of the Study, the Test and Reference Substance

(*a*) A descriptive title;

(*b*) Identification of the test substance by code or name (IUPAC; CAS number, etc.);

(*c*) Identification of the reference substance by chemical name;

(*d*) Characterisation of the test substance including purity, stability and homogeneity.

2. Information Concerning the Test Facility

(*a*) Name and address;

(*b*) Name of the Study Director;

(*c*) Name of other principal personnel having contributed reports to the final report.

3. Dates

(*a*) Dates on which the study was initiated and completed.

4. Statement

(*a*) A Quality Assurance statement certifying the dates inspections were made and the dates any findings were reported to management and to the Study Director.

5. Description of Materials and Test Methods

(*a*) Description of methods and materials used;

(*b*) Reference to OECD Test Guidelines or other test guidelines.

6. Results

(*a*) A summary of results;

(*b*) All information and data required in the study plan;

(*c*) A presentation of the results, including calculations and statistical methods;

(*d*) An evaluation and discussion of the results and, where appropriate, conclusions.

7. Storage: The location where all samples, specimens, raw data, and the final report are to be stored.

10. Storage and Retention of Records and Material

Storage and retrieval

1. Archives should be designed and equipped for the accommodation and the secure storage of:

(*a*) the study plans;

(*b*) the raw data;

(*c*) the final reports;

(*d*) the reports of laboratory inspections and study audits performed according to the Quality Assurance Programme;

(*e*) samples and specimens.

2. Material retained in the archives should be indexed so as to facilitate orderly storage and rapid retrieval.

3. Only personnel authorised by management should have access to the archives. Movement of material in and out of the archives should be properly recorded.

Retention

1. The following should be retained for the period specified by the appropriate authorities:

(*a*) The study plan, raw data, samples, specimens, and the final report of each study

(*b*) Records of all inspections and audits performed by the Quality Assurance Programme

(*c*) Summary of qualifications, training, experience and job description of personnel

(*d*) Records and reports of the maintenance and calibration of equipment

(*e*) The historical file of Standard Operating Procedures

2. Samples and specimens should be retained only as long as the quality of preparation permits evaluation.

3. If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archives of the sponsor(s) of the study(s).

Intellectual Property Rights

Intellectual property, often known as IP, allows people to own their creativity and innovation in the same way that they can own physical property. The owner of IP can control and be rewarded for its use, and this encourages further innovation and creativity to the benefit of us all. In some cases, IP gives rise to protection for ideas but in other areas, there will have to be more elaboration of an idea before protection can arise. It will often not be possible to protect IP and gain IP rights (or IPRs) unless, they have been applied for and granted, but some IP protection

such as copyright arises automatically, without any registration, as soon as there is a record in some form of what has been created.

The four main types of IP are:

• Patents for inventions—new and improved products and processes that are capable of industrial application
• Trade marks for brand identity—of goods and services allowing distinctions to be made between different traders
• Designs for product appearance—of the whole or a part of a product resulting from the features of, in particular, the lines, contours, colours, shape, texture or materials of the product itself or its ornamentation
• Copyright for material—literary and artistic material, music, films, sound recordings and broadcasts, including software and multimedia.

However, IP is much broader than this extending to trade secrets, plant varieties, geographical indications, performers rights and so on. To understand exactly what can be protected by IP, you will need to check the four main areas of copyright, designs, patents and trade marks as well as other IP. Often, more than one type of IP may apply to the same creation.

Patent

A patent gives an inventor the right for a limited period to stop others from making, using or selling an invention without the permission of the inventor. It is a deal between an inventor and the state in which the inventor is allowed a short-term monopoly in return for allowing the invention to be made public. Patents are about functional and technical aspects of products and processes. Most patents are for incremental improvements in known technology—evolution rather than revolution. The technology does not have to be complex.

• Specific conditions must be fulfilled to get a patent. Major ones are that the invention must be new. The invention must not form part of the "state of the art". The state of the art is everything that has been made available to the public before the date of applying for the patent. This includes published documents and articles, but can also include use, display, spoken description, or any other way in which information is made available to the public.
• Involve an inventive step, as well as being new, the invention must not be obvious from the state of the art. Obviousness is from the viewpoint of a person skilled in the area of technology that the invention is in.
• Be industrially applicable. This condition requires that the invention can be made or used in any kind of industry.

A patented invention is recorded in a patent document. A patent document must have
• description of the invention, possibly with drawings, with enough details for a person skilled in the area of technology to perform the invention.
• claims to define the scope of the protection. The description is taken into account while interpreting the claims.

The original patent document of a patent application is published by a patent office. The application then adds to the state of the art for later applications and anyone can comment on the application. Often the patent document needs altering or amending to meet the conditions above before a patent can be granted. The final version of the granted patent document is then republished. If more information about the state of the art is discovered after grant, the patent document can be amended and republished again.

Patent rights are territorial; a UK patent does not give rights outside of the UK. Patent rights last for up to 20 years in the UK. Some patents, such as those for medicinal products, may be eligible for a further 5 years protection with a Supplementary Protection Certificate. A patent can be of value to an inventor—as well as protecting his business, patents can be bought, sold, mortgaged, or licenced to others. They also benefit people other than the inventor since large amounts of information can be learnt from other peoples patents — they can stop you from reinventing things or you can monitor what your competitors are doing. Patents also spur you or others on to develop your idea further, and once the term of the patent expires it can be freely performed by anyone which benefits the public and the economy.

TRADEMARK

A trademark is any sign which can distinguish the goods and services of one trader from those of another. A sign includes words, logos, colours, slogans, three-dimensional shapes and sometimes sounds and gestures. A trademark is therefore a “badge” of trade origin. It is used as a
marketing tool so that customers can recognize the product of a particular trader. To be registrable in the UK it must also be capable of being represented graphically, that is, in words and/or pictures.

DESIGN

A design refers to the appearance of the whole or a part of a product resulting from the features of, in particular, the lines, contours, colours, shape, texture or materials of the product or its ornamentation.

In the United Kingdom, designs are protected by three legal rights:

(*a*) Registered designs rights

• gives the owner a monopoly on their product design.

• brings the right to take legal action against others who might be infringing the design and to claim damages.

• may deter a potential infringement.

• also brings the exclusive right to make, offer, put on the market import, export, use or stock any product to which the design has been applied or is incorporated or to let others use the design under the terms agreed with the registered owner, in the UK and the Isle of Man.

Design registration gives the owner a monopoly on their product design, *i.e.*, the right for a limited period to stop others from making, using or selling a product to which the design has been applied, or in which it has been incorporated without their permission and is additional to any design right or copyright protection that may exist automatically in the design.

(*b*) Unregistered design right.

Is not a monopoly right but a right to prevent deliberate copying, and lasts until 10 years after first marketing articles made to the design, subject to an overall limit of 15 years from creation of the design. Unlike design registration, you do not have to apply to register design right. A design right is a property that, like any other business commodity, may be bought, sold or licensed.

(*c*) Artistic copyright.

Work can only be original if it is the result of independent creative effort. It will not be original if it has been copied from something that already exists. If it is similar to something that already exists but there has been no copying from the existing work either directly or indirectly, then it may be original.

The term “original” also involves a test of substantiality—literary, dramatic, musical and artistic works will not be original if there has not been sufficient skill and labour expended in their creation. But, sometimes significant investment of resources without significant intellectual input can still count as sufficient skill and labour.

Ultimately, only the courts can decide whether something is original, but there is much case law indicating, for example, that names and titles do not have sufficient substantiality to be original and that, where an existing work is widely known, it will be difficult to convince a court that there has been no copying if your work is very similar or identical. Sound recordings, films and published editions do not have to be original but they will not be new copyright works if they have been copied from existing sound recordings, films and published editions.

Broadcasts do not have to be original, but there will be no copyright, if, or to the extent that, they infringe copyright in another broadcast.

IMPLICATIONS OF IPRs AND AGRICULTURAL TECHNOLOGY

The dynamics and interplay of IPRs and technological innovations have multiple impacts. These
can be categorized into social, economic and ecological. Due to peculiarities of Indian agriculture, the magnitude of these impacts will be manifold. The IPR regime not only influences research portfolio but also the contours of technology development. Primarily, the underlying motive of protection is to share profits with innovators. Therefore, the economic implications are not only predominant but also most obvious. The other two implications of access to newer technologies are on social and ecological dimensions. These three impacts are not mutually exclusive and often overlap.

Social Implications

Social impact of new technologies is manifested in terms of its influence on equity. Other important issue pertains to “scale effect”. These issues can be explained by the illustration of Green Revolution. This seed-fertiliser technology was predominantly applicable in the areas with assured irrigation. These technologies contributed to the widening of the regional disparity. Viewed from a macro-perspective, however, the revolution was a great success that

helped realize cherished goal of self-sufficiency in food grains. Therefore, the magnitude and nature of
social implications vary according to the category of the technology (Table). Knowledge-based technologies and technologies concerning conservation of natural resources have positive impact
on the society. Because of their nature (public good), the net social welfare increases manifold. Certain technologies like HYVs and hybrids require intensive input use and therefore have a mixed impact on the society. The predominant positive impact (+ + –) clouds the negative effects. Yield enhancement by conventional breeding is an ideal example. By the same yardstick, if conventional breeding aims at preventing yield loss (pest- and disease-resistant varieties) it becomes cost-reducing and has no negative impact (+). There are technologies where the negative component impact is marked (– +). Current levels of technologies (and its costs) in farm machinery and power precludes their accessibility to small and marginal farmers. There is a distinct possibility that in the near future farm machinery is tailor-made to suit small holdings ?

Economic Implications

Most technologies, excluding agricultural biotechnology and crop protection chemicals have a net positive impact on the economy. There are also implicit benefits like savings from potential losses due to pests and diseases. Newer techniques invariably shift production functions thereby improving income of individuals and that of the nation. Research in the public domain will concentrate in cost-reducing technologies that are helpful to the weaker sections. Conservation
of genetic resources have huge positive externalities (both intra and inter generational). Considering the market structure of crop varieties and crop protection chemicals and the nature of potential technologies, the scope for market malpractice such as monopoly and cartelisation is real. Generally embodied technologies are likely to have relatively more apparent impacts. Active presence of the public sector is vital for the provision of disembodied technologies.

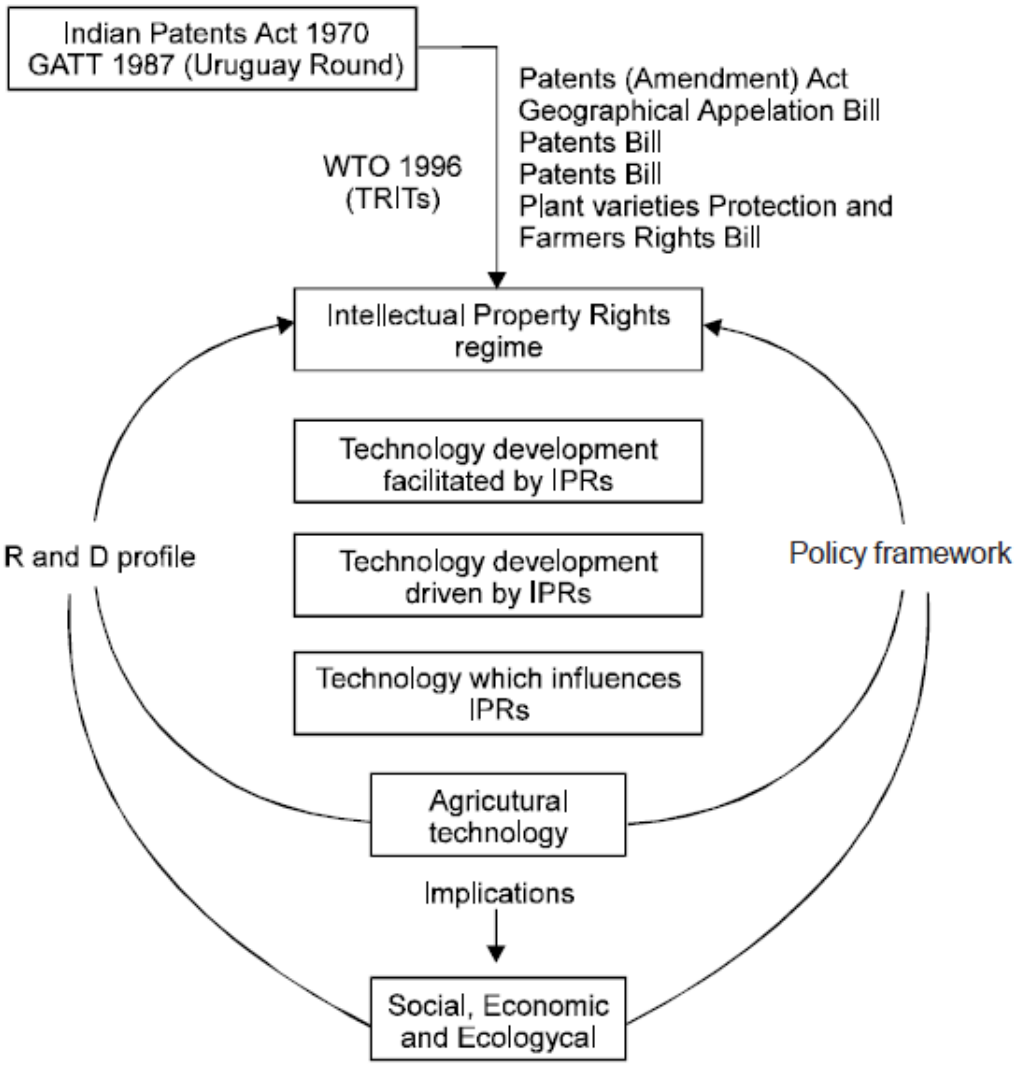


Fig. 2.1. Chemicals used in agriculture.

Ecological implications

Increased use of agrochemicals will accelerate environmental degradation (– – –).Though biotechnological innovations minimise the use of agrochemicals to some extent (+ –), they are feared for their contribution to gene pollution (– ? ?). Development of such resistant varieties by conventional breeding has no negative impacts (++). Any technology encouraging the use of improved varieties is likely to contribute to narrowing of genetic base (–). Increasingly, the use of antibiotics, hormones, unconventional feeds and genetic engineering in livestock and fisheries have raised questions about health hazards and animal biodiversity (– –). Destruction of soil structure and groundwater depletion are serious ecological risks associated with the excessive use of technologies associated with farm machinery and power. Technological advancements in the conservation of soil, water and genetic resources have profound positive

impacts on the ecology (+++). Being locally evolved and practice based, knowledge based technologies optimise resource use thereby imparting positive externalities to the environment.

Protection of Plant Varieties and Farmers' Rights Act, 2001

Introduction

In order to provide for the establishment of an effective system for the protection of plant varieties, the rights of farmers and plant breeders and to encourage the development of new varieties of plants it has been considered necessary to recognize and to protect the rights of the farmers in respect of their contributions made at any time in conserving, improving and making available plant genetic resources for the development of new plant varieties. The Govt. of India enacted "The Protection of Plant Varieties and Farmers' Rights (PPV&FR) Act, 2001" adopting sui generis system. Indian legislation is not only in conformity with International Union for the Protection of New Varieties of Plants (UPOV), 1978, but also have sufficient provisions to protect the interests of public sector breeding institutions and the farmers. The legislation recognizes the contributions of both commercial plant breeders and farmers in plant breeding activity and also provides to implement TRIPs in a way that supports the specific socio-

economic interests of all the stakeholders including private, public sectors and research institutions, as well as resource-constrained farmers.

Objectives of the PPV & FR Act, 2001

1. To establish an effective system for the protection of plant varieties, the rights of farmers and plant breeders and to encourage the development of new varieties of plants.
2. To recognize and protect the rights of farmers in respect of their contributions made at any time in conserving, improving and making available plant genetic resources for the development of new plant varieties.
3. To accelerate agricultural development in the country, protect plant breeders' rights; stimulate investment for research and development both in public & private sector for the development new of plant varieties.
4. Facilitate the growth of seed industry in the country which will ensure the availability of high quality seeds and planting material to the farmers.

Rights under the Act

1. **Breeders' Rights :** Breeders will have exclusive rights to produce, sell, market, distribute, import or export the protected variety. Breeder can appoint agent/ licensee and may exercise for civil remedy in case of infringement of rights.
2. **Researchers' Rights :** Researcher can use any of the registered variety under the Act for conducting experiment or research. This includes the use of a variety as an initial source of variety for the purpose of developing another variety but repeated use needs prior permission of the registered breeder.
3. **Farmers' Rights**
    - A farmer who has evolved or developed a new variety is entitled for registration and protection in like manner as a breeder of a variety;
    - Farmers variety can also be registered as an extant variety;
    - A farmer can save, use, sow, re-sow, exchange, share or sell his farm produce including seed of a variety protected under the PPV&FR Act, 2001 in the same manner as he was entitled before the coming into force of this Act provided farmer shall not be entitled to sell branded seed of a variety protected under the PPV&FR Act, 2001;

- Farmers are eligible for recognition and rewards for the conservation of Plant Genetic Resources of land races and wild relatives of economic plants;
- There is also a provision for compensation to the farmers for non-performance of variety under Section 39 (2) of the Act, 2001 and
- Farmer shall not be liable to pay any fee in any proceeding before the Authority or Registrar or the Tribunal or the High Court under the Act.

Implementation of the Act

To implement the provisions of the Act the Department of Agriculture, Cooperation and Farmers Welfare, Ministry of Agriculture and Farmers Welfare established the Protection of Plant Varieties and Farmers' Rights Authority on 11" November, 2005. The Chairperson is the Chief Executive of the Authority. Besides the Chairperson, the Authority has 15 members, as notified by the Government of India (GOI). Eight of them are ex-officio members representing various Departments/ Ministries, three from SAUs and the State Governments, one representative each for farmers, tribal organization, seed industry and women organization associated with agricultural activities are nominated by the Central Government. The Registrar General is the ex-officio Member Secretary of the Authority.

General Functions of the Authority

1. Registration of new plant varieties, essentially derived varieties (EDV), extant varieties;
2. Developing DUS (Distinctiveness, Uniformity and Stability) test guidelines for new plant species;
3. Developing characterization and documentation of varieties registered;
4. Compulsory cataloging facilities for all variety of plants;
5. Documentation, indexing and cataloguing of farmers' varieties;
6. Recognizing and rewarding farmers, community of farmers, particularly tribal and rural community engaged in conservation and improvement;
7. Preservation of plant genetic resources of economic plants and their wild relatives;
8. Maintenance of the National Register of Plant Varieties and
9. Maintenance of National Gene Bank.

Registration of varieties

A variety is eligible for registration under the Act if it essentially fulfills the criteria of Distinctiveness, Uniformity and Stability (DUS). The Central Government issues notification

in official Gazettes specifying the genera and species for the purpose of registration of varieties. So far, the Central Government has notified 157 crop species for the purpose of registration. To access the list, click here.

The PPV&FR Authority has developed "Guidelines for the Conduct of Species Specific Distinctiveness, Uniformity and Stability" tests or "Specific Guidelines" for individual crop species.

To know the time limit for registration of extant varieties, click here.

To know the registration process, click here

Fees for registration

Application for registration of plant varieties should be accompanied with the fee of registration prescribed by the Authority. Fee for registration for different types of variety is as under:

S.No	Types of Variety	Fees for Registration
1	Extant Variety notified under section 5 of the Seeds Act, 1966	Rs 2000/-
2.	New Variety/Essentially Derived Variety (EDV)/ Extant Variety about which there is common knowledge (VCK)	• Individual Rs. 7000/- • Educational Rs.10000/- • Commercial Rs.50000/-
3.	Farmers Varieties	No Fee

The Registration of a variety is renewable subject to payment of annual and renewal fee as notified in the Plant Variety Journal of India of the Authority and Gazette of India dated 15.06.2015.

DUS Test Centers

Authority has notified DUS test Centers for different crops with a mandate for maintaining and multiplication of reference collection, example varieties and generation of database for DUS descriptors as per DUS guidelines of respective crops. To access the list of DUS test Centers, click here.

Certificate of Registration

The certificate of registration issued will be valid for nine years in case of trees and vines and six years in case of other crops. It may be reviewed and renewed for the remaining period on

payment of renewal fees subject to the condition that total period of validity shall not exceed eighteen years in case of trees and vines from the date of registration of the variety, fifteen years from the date of notification of variety under the Seeds Act, 1966 and in other cases fifteen years from the date of registration of the variety.

Benefit Sharing

The benefit sharing is one of the most important ingredients of the farmers' rights. Section 26 provides benefits sharing and the claims can be submitted by the citizens of India or firms or non-governmental organization (NGOs) formed or established in India. Depending upon the extent and nature of the use of genetic material of the claimant in the development of the variety along with commercial utility and demand in the market of the variety breeder will deposit the amount in the Gene Fund. The amount deposited will be paid to the claimant from National Gene Fund. The Authority also publishes the contents of the certificate in the PVJI for the purpose of inviting claims for benefits sharing.

Rights of Community

1. It is compensation to village or local communities for their significant contribution in the evolution of variety which has been registered under the Act.
2. Any person/group of persons/governmental or non- governmental organization, on behalf of any village/local community in India, can file in any notified centre, claim for contribution in the evolution of any variety.

Convention countries

Convention country means a country which has acceded to an international convention for the protection of plant varieties to which India has also acceded or a country which has law of protection of plant varieties on the basis of which India has entered into an agreements for granting plant breeders' rights to the citizen of both the countries. Any person if applies for the registration of a variety in India within twelve months after the date on which the application was made in the convention country, such variety shall, if registered under this Act, be registered as of the date on which the application was made in convention country and that date shall be deemed for the purpose of this Act to be the date of registration.

Plant Varieties Protection Appellate Tribunal

There is transitory provision by which it is provided that till the PVPAT is established the Intellectual Property Appellate Board (IPAB) will exercise the jurisdiction of PVPAT.

Consequently the Plant Varieties Protection Appellate Tribunal (PVPAT) has been established by appointing Technical Member. All orders or decisions of the Registrar of Authority relating to registration of variety and orders or decisions of the Registrar relating to registration as agent or licensee can be appealed in the Tribunal. Further, all orders or decisions of Authority relating to benefit sharing, revocation of compulsory license and payment of compensation can also be appealed in the Tribunal. The decisions of the PVPAT can be challenged in High Court. The Tribunal shall dispose of the appeal within one year.

Source: Protection of Plant Varieties and Farmers' Rights Authority

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WORLD TRADE ORGANISATION (WTO)

In brief, the World Trade Organisation (WTO) is the only international organisation dealing with the global rules of trade between nations. Its main function is to ensure that trade flows as smoothly, predictably and freely as possible.

Location: Geneva, Switzerland
Established: 1 January 1995
Created by: Uruguay Round negotiations (1986-94)
Membership: 146 countries (as of April 2003)
Budget: 155 million Swiss francs for 2003
Secretariat staff: 560
Head: Director-General, Supachai Panitchpakdi

Functions:

• Administering WTO trade agreements
• Forum for trade negotiations
• Handling trade disputes
• Monitoring national trade policies
• Technical assistance and training for developing countries
• Cooperation with other international organizations

The result is assurance. Consumers and producers know that they can enjoy secure supplies and greater choice of the finished products, components, raw materials and services that they use. Producers and exporters know that foreign markets will remain open to them. The result is also a more prosperous, peaceful and accountable economic world. Decisions in the WTO are typically taken by consensus among all member countries and they are ratified by members' parliaments. Trade friction is channeled into the WTO's dispute settlement process where the focus is on interpreting agreements and commitments, and how to ensure that countries' trade policies confirm with them. That way, the risk of disputes spilling over into political or military conflict is reduced. By lowering trade barriers, the WTO's system also breaks down other barriers between peoples and nations.

At the heart of the system—known as the multilateral trading system—are the WTO's agreements, negotiated and signed by a large majority of the world's trading nations, and gratified in their parliaments. These agreements are the legal ground-rules for international commerce. Essentially, they are contracts, guaranteeing member countries important trade rights.

They also bind governments to keep their trade policies within agreed limits to everybody's benefit. The agreements are negotiated and signed by governments. But their purpose is to help producers of goods and services, exporters, and importers conduct their business. **The goal** is to improve the welfare of the people of the member countries.

A Closer Look at These Principles

Trade without Discrimination

(*a*) Most-favoured-nation (MFN): Treating other people equally. Under the WTO agreements, countries cannot normally discriminate between their trading partners. Grant someone a special favour (such as a lower customs duty rate for one of their products) and you have to do the same for all other WTO members. This principle is known as Most-Favoured-Nation (MFN) treatment. It is so important that it is the first article of the General Agreement

on Tariffs and Trade (GATT), which governs trade in goods. MFN is also a priority in the General Agreement
on Trade in Services (GATS) and the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), although in each agreement the principle is handled slightly differently.

Together, these three agreement cover all the three main areas of trade handled by the WTO. Some exceptions are allowed. For example, countries can set up a free-trade agreement that applies only to goods traded within the group—discriminating against goods from outside. Or they can give developing countries special access to their markets. Or a country can raise barriers against products that are considered to be traded unfairly from specific countries. And in services, countries are allowed, in limited circumstances, to discriminate. But the agreements permit these exceptions only under strict conditions. In general, MFN means that every time a country lowers a trade barrier or opens up a market, it has to do so for the same goods or services from all its trading partners—whether rich or poor, weak or strong.

(*b*) National treatment: Treating foreigners and locals equally. Imported and locally produced goods should be treated equally—at least after the foreign goods have entered the market. The same should apply to foreign and domestic services, and to foreign and local trademarks, copyrights and patents. This principle of "national treatment" (giving others the same treatment as one's own nationals) is also found in all the three main WTO agreements (Article 3 of GATT, Article 17 of GATS and Article of 3 TRIPS), although once again the principle is handled slightly differently in each of these. National treatment only applies once a product, service or item of intellectual property has entered the market. Therefore, charging customs duty on an import is not a violation of national treatment even if locally-produced products are not charged an equivalent tax.

2. *Free Trade: Gradually, Through Negotiation*

Lowering trade barriers is one of the most obvious means of encouraging trade. The barriers concerned include customs duties (or tariffs) and measures such as import bans or quotas that restrict quantities selectively. From time to time other issues such as red tape and exchange rate policies have also been discussed.

Since GATT's creation in 1947-48 there have been eight rounds of trade negotiations. A ninth round, under the Doha Development Agenda, is now underway. At first, these are

focused on lowering tariffs (customs duties) on imported goods. As a result of the negotiations, by the mid-1990s industrial countries' tariff rates on industrial goods had fallen steadily to less than 4%. But by the 1980s, the negotiations had expanded to cover non-tariff barriers on goods, and

to the new areas such as services and intellectual property. Opening markets can be beneficial, but it also requires adjustment. The WTO agreements allow countries to introduce changes gradually, through "progressive liberalization". Developing countries are usually given longer time period to fulfil their obligations.

3. *Predictability: Through Binding and Transparency*

Sometimes, promising not to raise a trade barrier can be as important as lowering one, because the promise gives business a clearer view of their future opportunities. With stability and predictability, investment is encouraged, jobs are created and consumers can fully enjoy the benefits of competition—choice and lower prices. The multilateral trading system is an attempt to governments to make the business environment stable and predictable.

Table 2.1. The Uruguay Round increased bindings. Percentages of tariffs bound before and after the 1986–94 talks

	Before	*After*
Developed countries	78	99
Developing countries	21	73
Transition economies	73	98

(These are tariff lines, so percentages are not weighted according to trade volume or value) In the WTO, when countries agree to open their markets for goods or services, they "bind" their commitments. For goods, these bindings amount to ceilings on customs tariff rates. Sometimes countries tax imports at rates that are lower than the bound rates. Frequently, this is the case in developing countries. In developed countries, the rates actually charged and the bound rates tend to be the same.

A country can change its bindings, but only after negotiating with its trading partners, which could mean compensating them for loss of trade. One of the achievements of the Uruguay

Round of multilateral trade talks was to increase the amount of trade under binding commitments

(see Table 2.1). In agriculture, 100% of products now have bound tariffs. The result of all this: a substantially higher degree of market security for traders and investors.

The system tries to improve predictability and stability in other ways as well. One way is

to discourage the use of quotas and other measures used to set limits on quantities of imports administering quotas can lead to more red-tape and accusations of unfair play. Another is to make countries' trade rules as clear and public (transparent) as possible. Many WTO agreements

require governments to disclose their policies and practices publicly within the country or by notifying the WTO. The regular surveillance of national trade policies through the Trade Policy Review Mechanism provides a further means of encouraging transparency both domestically and at the multilateral level.

4. *Promoting Fair Competition*

The WTO is sometimes described as a "free trade" institution, but that is not entirely accurate. The system does allow tariffs and, in limited circumstances, other forms of protection. More accurately, it is a system of rules dedicated to open, fair and undistorted competition. The rules on non-discrimination—MFN and national treatment – are designed to secure fair conditions of trade. So too are those on dumping (exporting at below cost to gain market share) and subsidies. The issues are complex, and the rules try to establish what is fair or unfair, and how governments can respond, in particular by charging additional import duties calculated to compensate for damage caused by unfair trade.

Many of the other WTO agreements aim to support fair competition: in agriculture, intellectual property, services, for example. The agreement on government procurement (a "plurilateral" agreement because it is signed by only a few WTO members) extends competition

rules to purchases by thousands of government entities in many countries, and so on.

5. *Encouraging Development and Economic Reform*

The WTO system contributes to development. On the other hand, developing countries need flexibility in the time they take to implement the system's agreements. And the agreements themselves inherit the earlier provisions of GATT that allow for special assistance and trade concessions for developing countries.

Over three quarters of WTO members are developing countries and countries in transition
to market economies. During the seven and a half years of the Uruguay Round, over 60 of these countries implemented trade liberalization programmes autonomously. At the same time, developing countries and transition economies were much more active and influential in the Uruguay Round negotiations than in any previous round, and they are even more, so in the current Doha Development Agenda.

At the end of the Uruguay Round, developing countries were prepared to take on most of the obligations that are required of developed countries. But the agreements did give them transition periods to adjust to the more unfamiliar and, perhaps, difficult WTO provisions-particularly so for the poorest, "least-developed" countries. A ministerial decision adopted at the end of the round says better-off countries should accelerate implementing market access commitments on goods exported by the least-developed countries, and it seeks increased technical assistance for them. More recently, developed countries have started to allow duty-free and quota-free imports for almost all products from least-developed countries. On all of this, the WTO and its members are still going through a learning process. The current Doha Development Agenda includes developing countries' concern about the difficulties they face in implementing the Uruguay Round agreements.

WTO AGREEMENTS

How can you ensure that trade is as fair as possible, and as free as is practical? By negotiating rules and abiding by them. The WTO's rules—the agreements—are the result of negotiations between the members.

The current set were the outcome of the 1986-94 Uruguay Round negotiations, which included a major revision of the original General Agreement on Tariffs and Trade (GATT). GATT is now the WTO's principal rule-book for trade in goods. The Uruguay Round also created new rules for dealing with trade in services, relevant aspects of intellectual property, dispute settlement, and trade policy reviews. The complete set runs to some 30,000 pages consisting of about 60 agreements and separate commitments (called schedules) made by individual members in specific areas such as lower customs duty rates and services marketopening.

Through these agreements, WTO members operate a non-discriminatory trading system

that spells out their rights and their obligations. Each country receives guarantees that its exports will be treated fairly and consistently in other countries' markets. Each promises to do the same for imports into its own market. The system also gives developing countries some flexibility in implementing their commitments.

Goods

It all began with trade in goods. From 1947 to 1994, GATT was the forum for negotiating lower customs duty rates and other trade barriers; the text of the General Agreement spelt out important rules, particularly non-discrimination. Since 1995, the updated GATT has become the WTO's umbrella agreement for trade in goods. It has annexes dealing with specific sectors such as agriculture and textiles, and with specific issues such as state trading, product standards, subsidies and actions taken against dumping.

Services

Banks, insurance firms, telecommunications companies, tour operators, hotel chains and transport companies looking to do business abroad can now enjoy the same principles of freer and fairer trade that originally only applied to trade in goods. These principles appear in the new General Agreement on Trade in Services (GATS). WTO members have also made individual commitments under GATS stating which of their services sectors they are willing to open to foreign competition, and how open those markets are.

Intellectual Property

The WTO's intellectual property agreement amounts to rules for trade and investment in ideas and creativity. The rules state how copyrights, patents, trademarks, geographical names used to identify products, industrial designs, integrated circuit layout-designs and undisclosed information such as trade secrete–"intellectual property"–should be protected when trade is involved.

Dispute Settlement

The WTO's procedure for resolving trade quarrels under the Dispute Settlement Understanding is vital for enforcing the rules and therefore for ensuring that trade flows smoothly. Countries bring disputes to the WTO if they think their rights under the agreements are being infringed. Judgements by specially-appointed independent experts are based on interpretations of the

agreements and individual countries' commitments. The system encourages countries to settle their differences through consultation. Failing that, they can follow a carefully mapped out, stage-by-stage procedure that includes the possibility of a ruling by a panel of experts, and the chance to appeal the ruling on legal grounds. Confidence in the system is borne out by the number of cases brought to the WTO—around 300 cases in eight years compared to the 300 disputes dealt with during the entire life of GATT (1947-94).

Policy Review

The Trade Policy Review Mechanism's purpose is to improve transparency, to create a greater understanding of the policies that countries are adopting, and to assess their impact. Many members also see the reviews as constructive feedback on their policies. All WTO members must undergo periodic scrutiny, each review containing reports by the country concerned and the WTO Secretariat.

DEVELOPING COUNTRIES DEVELOPMENT AND TRADE

Over three quarters of WTO members are developing or least-developed countries. All WTO agreements contain special provision for them, including longer time periods to implement agreement and commitments, measures to increase their trading opportunities, provisions requiring all WTO members to safeguard their trade interests, and support to help them build the

infrastructure for WTO work, handle disputes, and implement technical standards. The 2001 Ministerial Conference in Doha set out tasks, including negotiations, for a wide range of issues concerning developing countries. Some people call the new negotiations the Doha Development Round. Before that part in 1997, a high-level meeting on trade initiatives and technical assistance

for least-developed countries resulted in an "integrated framework" involving six intergovernmental agencies, to help least-developed countries increase their ability to trade, and some additional preferential market access agreements.

A WTO committee on trade and development, assisted by a sub-committee on least-developed countries, looks at developing countries' special needs. Its responsibility includes implementation of the agreements, technical cooperation, and the increased participation of developing countries in the global trading system.

TECHNICAL ASSISTANCE AND TRAINING

The WTO organizes around 100 technical cooperation missions to developing countries annually. It holds on average three-trade policy courses each year in Geneva for government officials. Regional seminars are held regularly in all regions of the world with a special emphasis

on African countries. Training courses are also organized in Geneva for officials from countries in transition from central planning to market economies. The WTO set up reference centres in over 100 trade ministries and regional organizations in capitals of developing and least-developed countries, providing computers and internet-access to enable ministry officials to keep

abreast of events in the WTO in Geneva through online access to the WTO's immense database of official documents and other material.

• Assisting developing countries in trade policy issues, through technical assistance and training programmes.

• Cooperating with other international organizations.

THE ORGANIZATION FUNCTIONS

The WTO's overriding objective is to help trade flow smoothly, freely, fairly and predictably. It

does this by:

• administering trade agreements;

• acting as a forum for trade negotiations;

• settling trade disputes;

• reviewing national trade policies.

STRUCTURE

The WTO has nearly 150 members, accounting for over 97% of world trade. Around 30 others are negotiating membership. Decisions are made by the entire membership. This is typically by

consensus. A majority vote is also possible but it has never been used in the WTO, and was extremely rare under the WTO's predecessor, GATT. The WTO's agreements have been ratified
in all members' parliaments.

The WTO's top level decision-making body is the **Ministerial Conference** which meets at least once every two years. The Fifth WTO Ministerial Conference was held in Cancun, Mexico from 10 to 14 September, 2003.

Below this is the **General Council** (normally ambassadors and heads of delegation in Geneva, but sometimes officials sent from members' capitals) which meets several times a year in the Geneva headquarters. The General Council also meets as the Trade Policy Review Body and the Dispute Settlement Body.

At the next level, the **Goods Council, Services Council and Intellectual Property (TRIPS) Council** report to the General Council. Numerous **specialized committees, working groups and working parties** deal with the individual agreements and other areas such as environment, development, membership applications and regional trade agreements.

SECRETARIAT

The WTO Secretariat, based in Geneva has around 560 staff and is headed by a director general. It does not have branch offices outside Geneva. Since decisions are taken by the members themselves, the Secretariat does not have the decision-making role those other international bureaucracies are given.

The secretariat's main duties are to supply technical support for the various councils and committees and the ministerial conferences, to provide technical assistance for developing countries, to analyze world trade, and to explain WTO affairs to the public and media. The Secretariat also provides some forms of legal assistance in the dispute settlement process and advises governments wishing to become members of the WTO. The annual budget is roughly 155 million Swiss francs.

GENERAL AGREEMENT ON TARIFFS AND TRADE (GATT)

The General Agreement on Tariffs and Trade (GATT) was created in 1947. GATT is an agreement between many nations, governing international trade. GATT provides a place for negotiating trade issues and a framework for guiding the conduct of trade. Current GATT

membership includes 123 nations. One of the major beliefs behind GATT is that more liberalized
trade would help the economies of participating nations grow (Banks 35). Some other principles
of GATT are nondiscrimination; what is meant by nondiscrimination is that no member of GATT can discriminate against other nations or who favoritism or give any special privileges to
any nations. This allows all trading partners to be put on an equal basis. A second principle, tariff protection, favors the use of tariffs as a clear way to protect domestic industries, as opposed to no tariff measures such as import quotas. A third and final principle behind GATT is providing a stable basis for trade. This is achieved by binding all participating nations to agree upon tariff levels by listing in "tariff schedules" the negotiated tariffs for each country's products (Banks 35).

There has been eight conferences, referred to as rounds or cycles of GATT, each of these rounds resulted in new trade agreements. The most recent round is referred to as the Uruguay Round because it was launched at a conference in Punte del Este, Uruguay in 1986. These negotiations concluded with the signing by more than 100 of the Uruguay Round "Final Act" in Marrakesh, Morocco in April 1994. The Uruguay Round Agreement has been described as the largest, most comprehensive trade pact in history (Congressional Digest).

The United States had a number of objectives in entering into the Uruguay Round of trade negotiations. These included broadening procedures relating to trade in agricultural products, extending GATT rules to trade in services never before covered by GATT, increasing protection
for patents, copyrights, and trademarks, and an improved way for settling disputes among GATT participants. Most of the objectives that the United States brought to the Uruguay Round were achieved. GATT was expanded to include services and new areas relating to the protection of patents and foreign investment. The Uruguay Round also cut tariffs worldwide by about one third; coverage for agriculture, textiles, and clothing was increased. And a new World Trade Organization was created to administer the agreement, oversee dispute settlements, and review
countries' trade policies and practices (C.D.).

Nations signing the agreement must have it approved by their governments before they can be subjected to its terms. In the U.S. Congress, consideration for the agreement is taking place

under “fast track” procedure, meaning that the House and the Senate must vote up or down on the legislation dealing with the agreement, with no opportunity to introduce or consider amendments. Opponents are concerned that the United States may lose more than it gains. They fear that the World Trade Organization poses a threat to U.S. sovereignty in that the United States may be forced to lower its environmental, health, and safety standards to conform to global rules. An example of this is that a Geneva based trade panel ruled that the U.S. government must halt its boycott of tuna caught with fishing methods that kill large numbers of dolphins (821). The reason that something like this can happen is that nations involved in the GATT are subject to challenges of this sort as illegal trade barriers. The World Trade Organization could also undermine food safety laws by forcing the United States to either accept

food with dangerous pesticide levels or pay a substantial fee. They also argue that new taxes may be needed to offset the loss in tariff revenue. Another concern is that U.S. measures to prevent dumping or selling of a product in a foreign market at a price lower than its fair market value could be weakened. But what the opponents of the World Trade Organization fail to realize is that if the Congress passes the Uruguay Round the U.S. will have a much larger say in environmental and food safety standards and the restriction of dumping. Members of Congress who support the agreement believe that it will bring far reaching economic benefits to the United States, including new employment opportunities and high paying jobs associated with the increased production of goods and services for export (Banks 35).

Supporters also feel that import growth resulting from the agreement will keep prices low and broaden consumer choices. A specific group of Americans that will benefit greatly from the passage to GATT in Congress are the farmers. The United States is by far the most efficient farming country with more prime cropland per capita than any other country in the world. Last

year U.S. farm exports totaled 42.6 billion dollars which is lower than their 1981 peak. The main reason for this has been the increase of Europe’s heavily subsidized farmers (Banks 35). Using 1992 numbers, every one hundred dollars of Europe’s farm exports carried an average twenty five dollar subsidy versus one dollar for the United States (Banks 35). If GATT was to pass the gap wouldn’t disappear but it would shrink significantly.

Another positive aspect of GATT is that it will open up traditionally closed foreign markets. For example, the U.S. will import three percent of its peanuts and Japan will import at

least some of its rice and citrus products, Korea will import some almonds, and so on with other countries. As a positive look to the future for farmers penetrating foreign markets a study shows that Asians eat on average 11 grams of protein a day compared to 52 for Japanese and 72 for Americans. As the Asian countries' standard of living increases the study says so will their protein intake.

With GATT in place, the likelihood is that an increasing amount of it will be American grown. GATT will cost the United States Treasury about fourteen billion dollars over the next five years in revenues lost because of reduced tariffs. Under budget rules, this tax cut for consumers must be paid for with fourteen billion dollars in increased revenues or decreased spending. Republicans feel that the government already has too much money so they are opposed to new taxes. And the Democrats feel that the government could never have too much money to work with so they oppose spending cuts.
GATT is not perfect but I feel that it would be devastating to allow these different outlooks to impede a trade package that may enlarge the U.S. GDP by a cumulative one trillion dollars over the first ten years (76). GATT will increase U.S. competitiveness in foreign markets and create a great number of high paid, highly-skilled jobs for Americans. Because of these positive factors and small speculative risks I feel that the General Agreement on Tariffs and Trade should be supported by all Americans with great enthusiasm towards the economic future of our nation.

The World Intellectual Property Organization (WIPO) is an international organization dedicated to promoting the use and protection of works of the human spirit. These works—intellectual property—are expanding the bounds of science and technology and enriching the world of the arts. Through its work, WIPO plays an important role enhancing the quality and enjoyment of life, as well as creating real wealth for nations. With headquarters in Geneva, Switzerland, WIPO is one of the 16 specialized agencies of the United Nations system of organizations.

It administers 23 international treaties dealing with different aspects of intellectual property protection. The Organization counts 182 nations as member states. As of January 2000, all developed and developing countries who are members of the World Trade Organization (WTO) were obligated to have domestic laws and enforcement mechanisms that comply with

the international standards set forth under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). TRIPS, which is the most comprehensive multilateral agreement on intellectual property, includes a set of provisions dealing with domestic procedures and remedies for the enforcement of intellectual property rights. TRIPS lays down certain general principles applicable to all intellectual property rights enforcement procedures, and contains provisions on civil and administrative procedures and remedies, provisional measures, special requirements related to broader measures and criminal procedures. Because of the January 2000 deadline for TRIPS compliance, during much of that year, USPTO developed and implemented many training programs to help those countries with the January 2000 deadline to implement the TRIPS provisions. The USPTO will continue to cooperate with other US agencies and regional and international organizations in the years to come to provide similar programs to developing countries.

GENERAL PROVISIONS AND BASIC PRINCIPLES

Article 1

Nature and scope of obligations

1. Members shall give effect to the provisions of this Agreement. Members may, but shall not be obliged to, implement in their law more extensive protection than is required by this Agreement, provided that such protection does not contravene the provisions of this Agreement. Members shall be free to determine the appropriate method of implementing the provisions of this Agreement within their own legal system and practice.

2. For the purposes of this Agreement, the term "intellectual property" refers to all categories of intellectual property that are the subject of Sections 1 through 7 of Part II.

3. Members shall accord the treatment provided for in this Agreement to the nationals of other members. In respect of the relevant intellectual property right, the nationals of other members shall be understood as those natural or legal persons that would meet the criteria for eligibility for protection provided for in the Paris Convention (1967), the Berne Convention (1971), the Rome Convention and the Treaty on Intellectual Property in Respect of Integrated Circuits,

were all members of the WTO members of those conventions. Any member availing itself of the possibilities provided in paragraph 3 of Article 5 or paragraph 2 of Article 6 of the Rome Convention shall make a notification as foreseen in those provisions to the Council for Trade-Related Aspects of Intellectual Property Rights (the "Council for TRIPS").

Article 2

Intellectual property conventions

1. In respect of Parts II, III and IV of this Agreement, members shall comply with Articles 1 through 12, and Article 19, of the Paris Convention (1967).

2. Nothing in Parts I to IV of this Agreement shall derogate from existing obligations that members may have to each other under the Paris Convention, the Berne Convention, the Rome Convention and the treaty on Intellectual Property in Respect of Integrated Circuits.

Article 3

National treatment

1. Each member shall accord to the nationals of other members treatment no less favorable than that it accords to its own nationals with regard to the protection of intellectual property, subject to the exceptions already provided in, respectively, the Paris Convention (1967), the Berne Convention (1971), the Rome Convention or the Treaty on Intellectual Property in Respect of Integrated Circuits. In respect of performers, producers of phonograms and broadcasting organizations, this obligation only applies in respect of the rights provided under this Agreement. Any member availing itself of the possibilities provided in Article 6 of the Berne Convention (1971) or paragraph 1(b) of Article 16 of the Rome Convention shall make a notification as foreseen in those provisions to the Council for TRIPS.

2. Members may avail themselves of the exceptions permitted under paragraph 1 in relation of judicial and administrative procedures, including the designation of an address for service or the appointment of an agent within the jurisdiction of a member, only where such exceptions are necessary to secure compliance with laws and regulations which are not inconsistent with the provisions of this Agreement and where such practices are not applied in a manner which would constitute a disguised restriction on trade.

Article 4

Most-favoured-nation treatment

With regard to the protection of intellectual property, any advantage, favour, privilege or immunity granted by a member to the nationals of any other country shall be accorded immediately and unconditionally to the nationals of all other members. Exempted from this obligation is any advantage, favour, privilege or immunity accorded by a member: (*a*) deriving from international agreements on judicial assistance or law enforcement of a general nature and not particularly confined to the protection of intellectual property; (*b*) granted in accordance with the provisions of the Berne Convention (1971) or the RomeConvention authorizing that the treatment accorded be a function not of national treatment but of the treatment accorded in another country; (*c*) in respect of the rights of performers, producers of phonograms and broadcasting organizations not provided under this Agreement;
(*d*) deriving from international agreements related to the protection of intellectual property which entered into force prior to the entry into force of then WTO Agreement, provided that such agreements are notified to the Council for TRIPS and do not constitute an arbitrary or unjustifiable discrimination against nationals of other Members.

Article 5

Multilateral agreements on acquisition or maintenance of protection

The obligations under Articles 3 and 4 do not apply to procedures provided in multilateral agreements concluded under the auspices of WIPO relating to the acquisition or maintenance of intellectual property rights.

Article 6

Exhaustion

For the purposes of dispute settlement under this Agreement, subject to the provisions of Articles 3 and 4 nothing in this Agreement shall be used to address the issue of the exhaustion of intellectual property rights.

Article 7

Objectives

The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conductive to social and economic welfare, and to a balance of rights and obligations.

Article 8

Principles

1. Members may, in formulating or amending their laws and regulations, adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provisions of this Agreement.

2. Appropriate measures, provided that they are consistent with the provisions of this Agreement, may be needed to prevent the abuse of intellectual property rights by right holders or the resort to practices which unreasonably restrain trade or adversely affect the international transfer of technology.

Does the TRIPS Agreement Apply to all WTO Members?

All the WTO agreements (except for a couple of "plurilateral" agreements) apply to all WTO members. The members each accepted all the agreements as a single package with a single signature—making it, in the jargon, a "single undertaking". The TRIPS Agreement is part of that package. Therefore it applies to all WTO members (more on the single undertaking). But the agreement allows countries different periods of time to delay applying its provisions. These delays define the transition from before the agreement came into force (before 1 January, 1995) until it is applied in member countries.

The main transition periods are :

• Developed countries were granted a transition period of one year following the entry into force of the WTO Agreement, *i.e.*, until 1 January, 1996.

• Developing countries were allowed a further period of four years (*i.e.*, to 1 January, 2000) to apply the provisions of the agreement other than Articles 3, 4 and 5 which deal with general principles such as non-discrimination.

• Transition economies, *i.e.*, members in the process of transformation from centrallyplanned into market economies, could also benefit from the same delay (also until 1 January, 2000) if they met certain additional conditions.

• Least-developed countries are granted a longer transition period of a total of eleven years (until 1 January, 2006), with the possibility of an extension. For pharmaceutical patents, this has been extended to 1 January, 2016, under a decision taken by ministers at the Fourth Ministerial Conference in November 2001.

What is the Place of the TRIPS Agreement in the Multilateral Trading System?

One of the fundamental characteristics of the TRIPS Agreement is that it makes protection of intellectual property rights an integral part of the multilateral trading system, as embodied in the WTO.

The TRIPS Agreement is often described as one of the three "pillars" of the WTO, the other two being trade in goods (the traditional domain of the GATT) and trade in services. The TRIPS Agreement is part of the "single undertaking" resulting from the Uruguay Round negotiations. That implies that the TRIPS Agreement applies to all WTO members. It also means that the provisions of the agreement are subject to the integrated WTO dispute settlement mechanism which is contained in the Dispute Settlement Understanding (the "Understanding on Rules and Procedures Governing the Settlement of Disputes").

What is the Relationship between the TRIPS Agreement and the Pre-existing International Conventions that it Refers to?

The TRIPS Agreement says WTO member countries must comply with the substantive obligations of the main conventions of WIPO—the **Paris Convention** on industrial property, and the **Berne Convention** on copyright (in their most recent versions). With the exception of the provisions of the Berne Convention on moral rights, all the substantive provisions of these conventions are incorporated by reference. They therefore become obligations for WTO member countries under the TRIPS Agreement – they have to apply these main provisions, and apply them to the individuals and companies of all other WTO members.

The TRIPS Agreement also introduces additional obligations in areas which were not addressed in these conventions, or were thought not to be sufficiently addressed in them. The TRIPS Agreement is therefore sometimes described as a Berne and Paris-plus Agreement.

The text of the TRIPS Agreement also makes use of the provisions of some other international agreements on intellectual property rights:

• WTO members are required to protect integrated circuit layout-designs in accordance with the provisions of the **Treaty on Intellectual Property in Respect of Integrated Circuits (IPIC Treaty)** together with certain additional obligations.

• The TRIPS Agreement refers to a number of provisions of the **International Convention for the Protection of Performers, Producers of Phonograms and Broad casting Organizations**

(Rome Convention), without entailing a general requirement to comply with the substantive provisions of that Convention. TRIPS Agreement specifies that nothing in Parts I to IV of the agreement shall derogate from existing obligations that members may have to each other under the Paris Convention, the Berne Convention, the Rome Convention and the Treaty on Intellectual Property in respect of integrated circuits.

What is the Role of the TRIPS Council?

The TRIPS Council comprises all WTO members. It is responsible for monitoring the operation of the agreement, and, in particular, how members comply with their obligations under it.

1. Monitoring: Members review each others' laws. The reviews are central to the TRIPS Council's task of monitoring what is happening under the agreement. Each country has to make sure its laws comply with the obligations of the agreement, according to the timetable spelt out in the agreement. Most have to enact laws implementing the obligations. These laws are notified to the TRIPS Council, allowing members to review each others' legislation, and promoting the transparency of members' policies on intellectual property protection. The requirement to notify comes under the TRIPS Agreement. Members have to supply the TRIPS Council with copies of their laws and regulations that deal with the TRIPS Agreements' provisions. These notifications are then used as the basis the Council's reviews of members' legislation. In these reviews, countries supply written questions about each others' laws before the review meetings. The answers are also in writing. Follow-up questions and replies are made orally during the course of the meeting, and further follow-up is possible at subsequent meetings.

PATENTING AND THE PROCEDURES INVOLVED IN THE APPLICATION FOR GRANTING OF A PATENT

Overview of the Patenting Process

A patent is an exclusive right of its owner to exclude others from making, using, or selling the invention as defined in the claims of the patent for a period of time, which in the United States is 20 years from the date of filing the patent application.

There are three types of patents:

1. Utility Patents may be granted to anyone who invents or discovers any new and useful process, machine, article of manufacture, or composition of matter, or any new and useful improvement thereof;

2. Design Patents may be granted to anyone who invents a new, original, and ornamental design for an article of manufacture; and

3. Plant Patents may be granted to anyone who invents or discovers and asexually reproduces any distinct and new variety of plant.

STEPS TO A PATENT

Introduction

There are several steps that help in securing a patent. The steps begin in the lab and move through the legal process of patent prosecution and maintenance. This section describes the steps that you should follow to help maximize the value of your invention and protect your intellectual property rights.

(*a*) Patent success starts in the lab

Documentation is the beginning of strong patents because it authenticates with whom a theory originates (conception) and the steps taken to test and produce results (diligent reduction to practice). These documents are scrutinized to determine inventorship, reduction to practice, and to support a patent's validity.

Well-maintained laboratory records can document the date of conception of an invention and also establish diligence in developing an idea. Such documentation is needed in case of a question about which inventor should be entitled to pursue a patent. Records can be more useful in this regard if the following steps are followed:

• Records have more value if they are meaningful to others. Entries should be complete, accurate, and legible.

• Preface the record of each experiment with a brief purpose or statement of the problem.

• Use a permanently bound notebook with numbered pages.

• Make frequent entries (daily is best) in ink, and design and date each page.
• Start a new page for each new experiment.
• Draw a continuous diagonal line through unused portions of pages remaining at the end of an experiment.
• Don't erase. Instead, where necessary, cross out with a single line.
• Initial and date all major changes.
• Record observations of physical results even if they are not fully appreciated or understood at the time.
• Have work corroborated by having notebooks witnessed by dated signature of an associate who understands the content, but not a co-worker or one who collaborates in the research area and who could be a joint inventor.
• Think carefully before destroying any samples, run sheets, or records related to any inventions.

(*b*) Plan to both publish and patent

Although the timing of publications may sometimes prohibit patenting, planning allows the inventor to both publish and patent. Disclosing the idea to the Office of Technology Transfer as soon as the invention is clearly conceptualized, or at least before submitting abstracts or manuscripts disclosing the invention, allows time to complete a patentability and commercialization assessment before being barred from a patent. In the United States, an inventor has a grace period of one year to file a patent application after disclosure through publication. However, if an invention is publicly disclosed before a U.S. patent application is filed, patent rights in most other countries are lost.

What constitutes publication?

Articles in newspapers, newsletters, bulletins, textbooks, journals, theses, reports, and even letters to the editor all qualify as publications. Oral presentations may constitute publication, as would distribution of a paper at a public meeting. Some legal experts also think that disclosure through electronic communications, such as e-mail, may be considered publication. The key test is that the publication be enabling—it must describe the invention in sufficient detail that it could be duplicated or put into use.

(*c*) Disclosing an invention

The technology transfer process actually begins when the inventor discloses his or her potential invention to the Office of Technology Transfer—a step required by IU's intellectual property policy. Discussions between the inventor and office staff members can help determine whether an invention has been made and whether a formal disclosure should be completed. The office staff supplies inventors with a formal disclosure form and assists in its preparation. An invention disclosure is a written record of an invention containing a complete description of the invention, the inventor's dated signature, and dated signatures of witnesses who fully understand the invention (but are not joint inventors).

(*d*) Invention evaluation

When the completed disclosure form has been reviewed by the Office of Technology Transfer and discussed with the inventor, recommendations are formulated on ownership, patenting, and licensing. Inventions are evaluated for novelty, likelihood of patentability, potential market, usefulness, projected development time, and cost. The most effective way to bring the invention's benefits to the public will be determined, whether through patent, copyright, or placing the invention in the public domain (usually through publication). The probability for an invention's economic success may be roughly gauged by these questions:

• How big is the potential market for the invention? Can the invention be sold to a large section of the public or a large number of manufacturers? Can it be sold to different industries?
• What development will be required before the invention can be sold? How long will development take? What will it cost? What regulatory requirements must be satisfied?
• How will the product be marketed? Can it be distributed through normal commercial channels?
• What is the demand for the invention? Does it fill a real need and not just replace satisfactory article? Does it contribute to the interest?

In most cases, before a patent application is prepared, the Office of Technology Transfer staff will search for potential licensees to determine the level of industrial interest in the technology. (A license is essentially an agreement by the patent owner not to sue the licensee for infringement as long as the licensee abides by the agreement. Licensing is typically the way the

university realizes an invention's commercial potential). In most cases, commercial organizations will underwrite patent expenses in return for the right to a license.

(*e*) Patent prosecution (process of obtaining a patent)

The process of obtaining a patent is called patent prosecution. It consists of preparing and filing the patent application, then filing responses and amendments to the objections of the patent examiner. Patent prosecution will result in either the issuance of a published patent or the rejection or abandonment of the application.

Under U.S. law, individual inventors are allowed to prosecute their own patent applications. However, because the Patent and Trademark Office has specific and often complex rules about the content and examination of applications and because patents are interpreted and

enforced in court, inventors should be represented by a patent attorney or agent.

To qualify as a patent attorney, an individual must have a law degree and a degree in a technical area, and the person must pass the rigorous patent bar exam. To become a patent agent, a person still must pass the patent bar exam, but a law degree is not required. The patent application is prepared by the patent attorney with the help of the inventor and is similar in many respects to a detailed scientific paper (the specifications and drawings) accompanied by one or more claims, which make-up the legal definition of the invention. The patent application must make a full disclosure of the invention to teach others how to make and use the invention and to clearly define the borders of the patent protection. Accomplishing both these objectives requires the close collaboration of the inventor and the patent attorney. Although the make-up of patent applications varies considerably, it is commonly divided into the following headings:

• **Field of the invention —** This describes the general technological field and the broad nature of the invention.

• **Background of the invention —** The background describes the technological problem to be solved and gives a brief description of present technology and its limitations.

• **Objectives of the invention —** The objectives indicate the nature of the improvements the invention seeks to provide.

• **Summary of the invention —** The summary states the essential elements of the invention in broad terms and often introduces the terminology to be used in the main claims of the patent.

• **Detailed description of the invention and/or description of the drawings —**These details include the experimental data, given by way of example, describing the methodology of the invention and the apparatus used (if any).

• **Claims —** Claims define the invention in one or more single-sentence paragraphs and serve as the legal definition of the invention.

When received in the Patent and Trademark Office, the application package is assigned to a patent examiner with expertise in the invention's technical field. Although workloads and response times vary, usually six months or more pass before the application's initial examination.

In the initial examination, the examiner searches both the scientific and the patent literature to determine whether the application discloses and claims new and patentable subject matter, and the examiner judges the allowability of each claim. Most applications are initially rejected. The basis for rejection is most often prior patents or publications which, in the examiner's view, render the new invention obvious. The patent attorney, with the assistance of the inventor, responds to the examiner with arguments about why the invention is patentable. The cycle can be repeated several times and the patent application can be amended, restricted, divided, or continued in the process. On average, the examination of a patent application takes two years in the United States, where the application is considered confidential throughout the process. In many other countries, patent applications are published after a given period of time. The Patent and Trademark Office allows, or approves, around 90,000 patents a year. The total number of patents issued now exceeds 5 million. When the Patent and Trademark Office gives notice of allowance, and the issue fee is paid, the patent is issued, or published in the Patent Gazette.

The cost of the typical U.S. patent prosecution for university, conducted by outside legal counsel, is $15,000 or more.

Summary of Legal Process from the Inventor's Perspective

Filing a Patent Application

Office of Technology Transfer (OTT) submits the invention disclosure to a patent attorney

↓

Patent attorney determines patentability and with the aid of the inventor(s), drafts a application for review

↓

Application is filed along with an assignment, declaration, and power of attorney

↓

Provisional	*Regular*
After 1 year the application must be Converted to a PCT application	After 1 year the foreign placeholder called a PCT application is filed

↓

18 months after the first US filing, the PCT will publish

↓

18 months after the PCT is filed, the PCT must be converted to a separate application per each foreign country ("nationalization"). Because nationalization is extremely expensive, the university does not nationalize without corporate sponsorship.

Examination of a Patent Application

Patent offices worldwide correspond with applicants through official "office actions". The patent attorney and ARTI work with the inventor(s) to answer each office action the time allotted (typically 3 months from the date the examiner issues the action).

↓

A successful prosecution results in a "notice of allowance" from the patent office indicating that the examiner has accepted claims that will "issue" in a patent.

Maintenance of a Patent

Maintenance fees must be paid 3.5, 7.5, and 11.5 years after the patent is issued.

↓

All patent applications filed after June 8, 1995 expire 20 years from the filing, while applications filed before this date expire 17 years from the date the patent was issued.

PATENT COOPERATION TREATY (PCT)

Done at Washington on June 19, 1970, amended on October 2, 1979, and modified on February 3, 1984, and Regulations under the PCT (as in force on January 1, 1985) World Intellectual Property Organization, Geneva 1985.

The Contracting States

↓

Desiring to make a contribution to the progress of science and technology

↓

Desiring to perfect the legal protection of inventions

↓

Desiring to simplify and render more economical the obtaining of protection for inventions where protection is sought in several countries

↓

Desiring to facilitate and accelerate access by the public to the technical information contained in documents describing new inventions

↓

Desiring to foster and accelerate the economic development of developing country through the adoption of measures designed to increase the efficiency of their legal systems, whether national or regional, instituted for the protection of inventions by providing easily accessible information on the availability of technological solution applicable to their special needs and by facilitating access to the ever expanding volume of modern technology

↓

Convinced that cooperation among nations will greatly facilitate the attainment of these aims

↓

Have concluded the present Treaty

Establishment of a Union

1. The States party to this Treaty (hereinafter called "the Contracting States") constitute a Union for cooperation in the filing, searching, and examination, of applications for the protection of inventions, and for rendering special technical services. The Union shall be known as the International Patent Cooperation Union.

2. No provision of this Treaty shall be interpreted as diminishing the rights under the Paris Convention for the Protection of Industrial Property of any national or resident of any country party to that Convention.

Definitions

For the purposes of this Treaty and the regulations and unless expressly stated otherwise:

(*i*) “application” means an application for the protection of an invention; references to an “application” shall be construed as references to applications for patents for inventions, inventors’ certificates, utility certificates, utility models, patents or certificates of addition, inventors’ certificates of addition, and utility certificates of addition;

(*ii)* references to a “patent” shall be construed as references to patents for inventions, inventors’ certificates, utility certificates, utility models, patents or certificates of addition, inventors’ certificates of addition, and utility certificates of addition;

(*iii*) “national patent” means a patent granted by a national authority;

(*iv*) “regional patent” means a patent granted by a national or an intergovernmental authority having the power to grant patents effective in more than one State;

(*v*) “regional application” means an application for a regional patent;

(*vi*) references to a “national application” shall be construed as references to applications for national patents and regional patents, other than applications filed under this Treaty;

(*vii*) “international application” means an application filed under this Treaty;

(*viii*) references to an “application” shall be construed as references to international applications

and national applications;

(*ix*) references to a “patent” shall be construed as references to national patents and regional patents.

Reference:

Sree Krishna, V. 2007. Bioethics and Biosafety in Biotechnology. New Age International (P) Ltd., Publishers, New Delhi – 110002, India.135pp.

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UNIT – V – Bioethics Biosafety and IPR – SBB1615

UNIT 5 GOOD CLINICAL PRACTICES AND ETHICS

Ethics in clinical trials and Good Clinical Practices (GCP) – Definition of clinical trials and GCP, general information about clinical trials, need to conduct clinical trials, Phases of clinical trials, institutional set ups for conducting clinical trials, ethics in clinical Biotechnology

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Good Clinical Practice guidelines and its role in clinical trials

DEFINITION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials. GCP provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are respected and protected [1]. It was finalised in 1996 and became effective in 1997, but was not enforced by law at that time. The Medicines for Human Use (Clinical Trials) Regulations 2004 and the European Union (EU) Directive on Good Clinical Practice changed the world perspective , and compliance with GCP is now a legal obligation in the UK/Europe for all trials involving the investigation of medicinal products [2].

HISTORICAL BACKGROUND

It is very important to understand the background of the formation of the ICH-GCP guidelines as this, in itself, explains the reasons and the need for doing so ((Table 1)). The concept of the ‘good physician‘ dates back to the ancient world and it is evidenced by the Hippocratic Oath (460 BC). In the United States, the first landmark in the regulation of drugs was the Food and Drugs Act of 1906. This was a result of harmful and lethal drugs that could be bought across the counter just like any other consumer product. Some examples are ‘Grandma’s Secret’ and ‘Kopp’s Baby’s Friend’ which contained large doses of morphine, as well as ‘Dr King’s Consumption Cure‘ and ‘Dr Bull’s Cough Syrup‘ which contained morphine and chloroform [3]. In 1938, the Federal Food, Drug and Cosmetic Act was enacted by the Food and Drug Administration (FDA) and for the first time, manufacturers were required to test drugs for safety and present the evidence of safety testing to the FDA prior to marketing [3].

Table 1 **Historical background of GCP**

460BC	Oath of Hippocrates
1930's	U.S. Food, Drugs and Cosmetic Act
1947	Nuremberg Code
Dec. 10th 1948	Declaration of Human Rights
1962	Kefauver-Harris Amendment
1964, revised 2000	Declaration of Helsinki
1979	The Belmont Report
1982	International Guidelines for Biomedical Research Involving Human Subjects
1996	ICH-GCP guidelines issued
1997	ICH-GCP guidelines becomes law in some countries

In 1947, the Nuremberg Code was created as a result of the unethical and horrific experiments carried out during World War II at Nazi war camps by German physicians, who were subsequently tried and charged at the Nuremberg Military Tribunal. This code states the need for a scientific basis in research on human subjects and voluntary consent and protection of participants [4,5]. The Universal Declaration of Human Rights (December 10th 1948) was also adopted and proclaimed by the United Nations after the atrocities of World War II and it further reiterated the human factor involved in medical experiments.

In 1964, the Declaration of Helsinki was developed by the World Medical Association, forming the basis for the ethical principles that underlie the ICH-GCP guidelines we have today. The focus of this declaration is the protection of the rights of human subjects and this is clear in its introduction [6]:

"The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty"

In 1962 the world was once again shocked by the severe foetal limb deformities linked to the use of maternal thalidomide. In fact this drug reaction was only discovered after 10,000 infants were born in over 20 countries worldwide. In response to this, the Kefauver-Harris Amendments were passed which required the FDA to evaluate all new drugs for safety and efficacy [3].

Another important milestone in the formation of the ICH-GCP guidelines was The Belmont Report which was issued in April 1979 by the National Commission for Protection of Human Subjects of Biomedical and Behavioural Research [7]. The principles of this report are as follows:

1. *Respect for Persons*: This principle acknowledges the dignity and freedom of every person. It requires obtaining informed consent from research subjects (or their legally authorised representatives)

2. *Beneficence*: This principle requires that researchers maximise benefits and minimise harms associated with research. Research-related risks must be reasonable in light of the expected benefits.

3. *Justice*: This principle requires equitable selection and recruitment and fair treatment of research subjects.

In 1982, the World Health Organization (WHO) and the Council for International Organizations of Medical Sciences (CIOMS) issued a document entitled 'International Guidelines for Biomedical Research Involving Human Subjects'. This document was released to help developing countries apply the principles of the Declaration of Helsinki and the Nuremberg Code [3]. Worldwide, many organisations and committees issued various documents and guidelines on the same issue, and a decision was taken to consolidate all these guidelines into one universal guideline to be used globally.

In an effort to overcome international GCP inconsistencies throughout the countries, the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued the ICH Guidelines: Topic E6 Guideline for GCP. This guideline was approved on 17 July 1996 and implemented for clinical trials from 17 January 1997. The participants of these guidelines were representatives of authorities and pharmaceutical companies from the EU, Japan and the United States as well as those of Australia, Canada, the Nordic countries and WHO [8].

ICH-GCP

The ICH-GCP is a harmonised standard that protects the rights, safety and welfare of human subjects, minimises human exposure to investigational products, improves quality of data, speeds up marketing of new drugs and decreases the cost to sponsors and to the public. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected and consistent with the principles of the Declaration of Helsinki, and that the clinical trial data is credible [8]. A historical background of the reasons and the importance of GCP is summarised in (Table 2).

Table 2 **Reasons for GCP**

Increased Ethical Awareness
Improved Trial Methods

Clinical Trial Concept Better Understood
Public/Political Concern over Safety Aspects
Frauds and Accidents during Trials
Growing Research and Development Costs
Increasing Competition
Mutual Recognition of Data
New Market Structure

There are 13 core principles of ICH-GCP and they are as follows:

1. Clinical trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interest of science and society.
4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

5. Clinical trials should be scientifically sound, and described in clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethics committee (IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

These principles are self-explanatory and, when summarised, simply mean:

All clinical trials should be conducted in accordance with ethical principles, sound scientific evidence and clear detailed protocols. The benefits of conducting trials should outweigh the risks. The rights, safety and well-being of trial participants are of paramount importance and these should be preserved by obtaining informed consent and maintaining confidentiality. The care must be given by appropriately qualified personnel with adequate experience. Records should be easily accessible and retrievable for accurate reporting, verification and

interpretation. Investigational products should be manufactured according to Good Manufacturing Practice (8).

It is also important to mention the participants of GCP in clinical trials and their respective responsibilities. These are summarised in (Table 3).

Table 3 **GCP participants**

Regulatory Authorities	Review submitted clinical data and conduct inspections
The sponsor	Company or institution/organization which takes responsibility for initiation, management and financing of clinical trial
The project monitor	Usually appointed by sponsor
The investigator	Responsible for conduct of clinical trial at the trial site. Team leader.
The pharmacist at trial location	Responsible for maintenance, storage and dispensing of investigational products eg. Drugs in clinical trials
Patients	Human subjects
Ethical review board or Committee for protection of subjects	Appointed by Institution or if not available then the Authoritative Health Body in that Country will be responsible

Committee to monitor large trials	Overseas Sponsors eg. Drug Companies

GCP IN THE ASIA PACIFIC REGION

Since the conception of the ICH-GCP guidelines, many countries in the Asia-Pacific region realised the need to formulate guidelines of their own based on the framework of the original guidelines [7]. This is clearly seen in (Table 4) that tabulates the adoption of GCP in our country and its neighbours.

Table 4 GCP Adoption in the Asia Pacific Region

Original ICH-GCP Guidelines	1996
Singapore GCP	1998
Chinese GCP	1999
Malaysian GCP	1999, revised 2004
Thailand	2000
Indonesia	2001

In Malaysia, similar guidelines were formulated in the wake of greater demand by the pharmaceutical industry to conduct clinical trials in the country. The Malaysian Guidelines for GCP was first published in October 1999 and the second edition was released in January 2004. The guideline adopts the basic principle outlined by the International Committee on

Harmonization of Good Clinical Practice (ICH-GCP) with some modifications to suit local requirements [1,7].

CONCLUSION

The importance of GCP lies in the question ‘why’ and ‘how’ GCP trials came about. To know the answer to this, we have to look to the historical background that led to the formulation of GCP guidelines in the United States and Europe and also to the formation of the ICH. The events that led up to the culmination of the ICH-GCP guidelines brought forth public awareness that there was a need to control and regulate clinical trials dealing with drugs and human subjects. The violation of human rights played a large role and that is why the Declaration of Helsinki and The Nuremberg Code remain as the framework of the present guidelines. The ICH-GCP guidelines are therefore considered the ‘bible’ of clinical trials, and have become a global law which safeguards humanity as we know it today.

Reference:

Biomed Imaging Interv J. 2008 Jan-Mar; 4(1): e5.
Published online 2008 Jan 1. doi: 10.2349/biij.4.1.e5
A Vijayananthan, MBBS, MRad[*,1] and O Nawawi, MBBS, MRad, FRCR

Clinical trial

A clinical trial participant receives an injection.

Clinical trials are experiments or observations done in clinical research. Such prospective biomedical or behavioral research studies on human participants are designed to answer specific questions about biomedical or behavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. Clinical trials generate data on safety and efficacy.[1] They are conducted only after they have received health authority/ethics committee approval in the country where approval of the therapy is sought. These authorities are responsible for vetting the risk/benefit ratio of the trial—their approval does not mean the therapy is 'safe' or effective, only that the trial may be conducted.

Depending on product type and development stage, investigators initially enroll volunteers or patients into small pilot studies, and subsequently conduct progressively larger scale comparative studies. Clinical trials can vary in size and cost, and they can involve a single research center or multiple centers, in one country or in multiple countries. Clinical study design aims to ensure the scientific validity and reproducibility of the results.

Costs for clinical trials can range into the billions of dollars per approved drug.[2] The sponsor may be a governmental organization or a pharmaceutical, biotechnology or medical device company. Certain functions necessary to the trial, such as monitoring and lab work, may be managed by an outsourced partner, such as a contract research organization or a central laboratory.

Only 10 percent of all drugs started in human clinical trials become approved drugs.[3]

Trials of drugs

Some clinical trials involve healthy subjects with no pre-existing medical conditions. Other clinical trials pertain to people with specific health conditions who are willing to try an experimental treatment. Pilot experiments are conducted to gain insights for design of the clinical trial to follow.

There are two goals to testing medical treatments: to learn whether they work well enough, called "efficacy" or "effectiveness"; and to learn whether they are safe enough, called "safety". Neither is an absolute criterion; both safety and efficacy are evaluated relative to how the treatment is intended to be used, what other treatments are available, and the severity of the disease or condition. The benefits must outweigh the risks.[4][5]:8 For example, many drugs to treat cancer have severe side effects that would not be acceptable for an over-the-counter pain medication, yet the cancer drugs have been approved since they are used under a physician's care and are used for a life-threatening condition.[6]

In the US, the elderly constitute 14% of the population, while they consume over one-third of drugs.[7] People over 55 (or a similar cutoff age) are often excluded from trials because their greater health issues and drug use complicate data interpretation, and because they have different physiological capacity than younger people. Children and people with unrelated medical conditions are also frequently excluded.[8] Pregnant women are often excluded due to potential risks to the fetus.

The sponsor designs the trial in coordination with a panel of expert clinical investigators, including what alternative or existing treatments to compare to the new drug and what type(s) of patients might benefit. If the sponsor cannot obtain enough test subjects at one location investigators at other locations are recruited to join the study.

During the trial, investigators recruit subjects with the predetermined characteristics, administer the treatment(s) and collect data on the subjects' health for a defined time period. Data include measurements such as vital signs, concentration of the study drug in the blood or tissues, changes to symptoms, and whether improvement or worsening of the condition targeted by the study drug occurs. The researchers send the data to the trial sponsor, who then analyzes the pooled data using statistical tests.

Examples of clinical trial goals include assessing the safety and relative effectiveness of a medication or device:

- On a specific kind of patient
- At varying dosages
- For a new indication
- Evaluation for improved efficacy in treating a condition as compared to the standard therapy for that condition
- Evaluation of the study drug or device relative to two or more already approved/common interventions for that condition

While most clinical trials test one alternative to the novel intervention, some expand to three or four and may include a placebo.

Except for small, single-location trials, the design and objectives are specified in a document called a clinical trial protocol. The protocol is the trial's "operating manual" and ensures all researchers perform the trial in the same way on similar subjects and that the data is comparable across all subjects.

As a trial is designed to test hypotheses and rigorously monitor and assess outcomes, it can be seen as an application of the scientific method, specifically the experimental step.

The most common clinical trials evaluate new pharmaceutical products, medical devices, biologics, psychological therapies, or other interventions. Clinical trials may be required before a national regulatory authority[9] approves marketing of the innovation.

Trials of devices

Similarly to drugs, manufacturers of medical devices in the United States are required to conduct clinical trials for premarket approval.[10] Device trials may compare a new device to an established therapy, or may compare similar devices to each other. An example of the former in the field of vascular surgery is the Open versus Endovascular Repair (OVER trial) for the treatment of abdominal aortic aneurysm, which compared the older open aortic repair technique to the newer endovascular aneurysm repair device.[11] An example of the latter are clinical trials on mechanical devices used in the management of adult female urinary incontinence.[12]

Trials of procedures

Similarly to drugs, medical or surgical procedures may be subjected to clinical trials,[13] such as case-controlled studies for surgical interventions.[14]

History

The concepts behind clinical trials are ancient. The Book of Daniel chapter 1, verses 12 through 15, for instance, describes a planned experiment with both baseline and follow-up observations of two groups who either partook of, or did not partake of, "the King's meat" over a trial period of ten days. Persian physician Avicenna, in *The Canon of Medicine* (1025) gave similar advice for determining the efficacy of medical drugs and substances.[15]

Development

Edward Jenner vaccinating James Phipps, a boy of eight, on 14 May 1796. Jenner failed to use a control group.

Although early medical experimentation was performed often, the use of a control group to provide an accurate comparison for the demonstration of the intervention's efficacy was generally lacking. For instance, Lady Mary Wortley Montagu, who campaigned for the introduction of inoculation (then called variolation) to prevent smallpox, arranged for seven prisoners who had been sentenced to death to undergo variolation in exchange for their life. Although they survived and did not contract smallpox, there was no control group to assess whether this result was due to the inoculation or some other factor. Similar experiments performed by Edward Jenner over his smallpox vaccine were equally conceptually flawed.[15]

The first proper clinical trial was conducted by the physician James Lind.[16] The disease scurvy, now known to be caused by a Vitamin C deficiency, would often have terrible effects on the welfare of the crew of long-distance ocean voyages. In 1740, the catastrophic

result of Anson's circumnavigation attracted much attention in Europe; out of 1900 men, 1400 had died, most of them allegedly from having contracted scurvy.[17] John Woodall, an English military surgeon of the British East India Company, had recommended the consumption of citrus fruit (it has an antiscorbutic effect) from the 17th century, but their use did not become widespread.[18]

Lind conducted the first systematic clinical trial in 1747.[19] He included a dietary supplement of an acidic quality in the experiment after two months at sea, when the ship was already afflicted with scurvy. He divided twelve scorbutic sailors into six groups of two. They all received the same diet but, in addition, group one was given a quart of cider daily, group two twenty-five drops of elixir of vitriol (sulfuric acid), group three six spoonfuls of vinegar, group four half a pint of seawater, group five received two oranges and one lemon, and the last group a spicy paste plus a drink of barley water. The treatment of group five stopped after six days when they ran out of fruit, but by then one sailor was fit for duty while the other had almost recovered. Apart from that, only group one also showed some effect of its treatment.[20]

After 1750, the discipline began to take its modern shape.[21][22] John Haygarth demonstrated the importance of a control group for the correct identification of the placebo effect in his celebrated study of the ineffective remedy called *Perkin's tractors*. Further work in that direction was carried out by the eminent physician Sir William Gull, 1st Baronet in the 1860s.[15]

Frederick Akbar Mahomed (d. 1884), who worked at Guy's Hospital in London, made substantial contributions to the process of clinical trials, where "he separated chronic nephritis with secondary hypertension from what we now term essential hypertension. He also founded the Collective Investigation Record for the British Medical Association; this organization collected data from physicians practicing outside the hospital setting and was the precursor of modern collaborative clinical trials."[23]

Modern trials

Austin Bradford Hill was a pivotal figure in the modern development of clinical trials.

Sir Ronald A. Fisher, while working for the Rothamsted experimental station in the field of agriculture, developed his *Principles of experimental design* in the 1920s as an accurate methodology for the proper design of experiments. Among his major ideas, was the importance of randomization—the random assignment of individuals to different groups for the experiment;[24] replication—to reduce uncertainty, measurements should be repeated and experiments replicated to identify sources of variation;[25] blocking—to arrange experimental units into groups of units that are similar to each other, and thus reducing irrelevant sources of variation; use of factorial experiments—efficient at evaluating the effects and possible interactions of several independent factors.[15]

The British Medical Research Council officially recognized the importance of clinical trials from the 1930s. The council established the *Therapeutic Trials Committee* to advise and assist in the arrangement of properly controlled clinical trials on new products that seem likely on experimental grounds to have value in the treatment of disease.[15]

The first randomised curative trial was carried out at the MRC Tuberculosis Research Unit by Sir Geoffrey Marshall (1887–1982). The trial, carried out between 1946 and 1947, aimed to test the efficacy of the chemical streptomycin for curing pulmonary tuberculosis. The trial was both double-blind and placebo-controlled.[26]

The methodology of clinical trials was further developed by Sir Austin Bradford Hill, who had been involved in the streptomycin trials. From the 1920s, Hill applied statistics to medicine,

attending the lectures of renowned mathematician Karl Pearson, among others. He became famous for a landmark study carried out in collaboration with Richard Doll on the correlation between smoking and lung cancer. They carried out a case-control study in 1950, which compared lung cancer patients with matched control and also began a sustained long-term prospective study into the broader issue of smoking and health, which involved studying the smoking habits and health of more than 30,000 doctors over a period of several years. His certificate for election to the Royal Society called him "... the leader in the development in medicine of the precise experimental methods now used nationally and internationally in the evaluation of new therapeutic and prophylactic agents."

International clinical trials day is celebrated on 20 May.[27]

The acronyms used in the titling of clinical trials is often contrived, and has been the subject of derision.[28]

Types

Clinical trials are classified by the research objective created by the investigators.[29]

- In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study.[30]
- In an *interventional study*, the investigators give the research subjects an experimental drug, surgical procedure, use of a medical device, diagnostic or other intervention to compare the treated subjects with those receiving no treatment or the standard treatment. Then the researchers assess how the subjects' health changes.[30]

Trials are classified by their purpose. After approval for human research is granted to the trial sponsor, the U.S. Food and Drug Administration (FDA) organizes and monitors the results of trials according to type:[29]

- *Prevention* trials look for ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include drugs, vitamins or other micronutrients, vaccines, or lifestyle changes.
- *Screening* trials test for ways to identify certain diseases or health conditions.
- *Diagnostic* trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.

- *Treatment* trials test experimental drugs, new combinations of drugs, or new approaches to surgery or radiation therapy.
- *Quality of life* trials (supportive care trials) evaluate how to improve comfort and quality of care for people with a chronic illness.
- *Genetic* trials are conducted to assess the prediction accuracy of genetic disorders making a person more or less likely to develop a disease.
- *Epidemiological* trials have the goal of identifying the general causes, patterns or control of diseases in large numbers of people.
- *Compassionate use* trials or expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomized clinical trials.[31] Usually, case-by-case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.
- Fixed trials consider existing data only during the trial's design, do not modify the trial after it begins, and do not assess the results until the study is completed.
- Adaptive clinical trials use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications include dosage, sample size, drug undergoing trial, patient selection criteria and "cocktail" mix.[32] Adaptive trials often employ a Bayesian experimental design to assess the trial's progress. In some cases, trials have become an ongoing process that regularly adds and drops therapies and patient groups as more information is gained.[33] The aim is to more quickly identify drugs that have a therapeutic effect and to zero in on patient populations for whom the drug is appropriate.[34][35]

Clinical trials are conducted typically in four phases, with each phase using different numbers of subjects and having a different purpose to construct focus on identifying a specific effect.[29]

Phases

Clinical trials involving new drugs are commonly classified into five phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug development process will normally proceed through phases I–IV over many years, frequently involving a decade or longer. If the drug successfully passes through phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population.[29] Phase IV trials are

performed after the newly approved drug, diagnostic or device is marketed, providing assessment about risks, benefits, or best uses.[29]

Phase	Aim	Notes
Phase 0	Pharmacodynamics and pharmacokinetics in humans	Phase 0 trials are optional first-in-human trials. Single subtherapeutic doses of the study drug or treatment are given to a small number of subjects (typically 10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs).[36] For a test drug, the trial documents the absorption, distribution, metabolization, and clearance (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.
Phase I	Screening for safety	Often are first-in-person trials. Testing within a small group of people (typically 20–80) to evaluate safety, determine safe dosage ranges, and identify side effects.[29]
Phase II	Establishing the preliminary efficacy of the drug in a "treatment group", usually against a placebo control group	Phase IIa is specifically designed to assess dosing requirements (how much drug should be given),[29] [37] while a Phase IIb trial is designed to determine efficacy, and studies how well the drug works at the prescribed dose(s), establishing a therapeutic dose range.[37]
Phase III	Final confirmation of	Testing with large groups of people (typically 1,000–3,000) to confirm its efficacy, evaluate its effectiveness, monitor

	safety and efficacy	side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.[29]
Phase IV	Safety studies during sales	Postmarketing studies delineate risks, benefits, and optimal use. As such, they are ongoing during the drug's lifetime of active medical use.[29]

Trial design

A fundamental distinction in evidence-based practice is between observational studies and randomized controlled trials.[38] Types of observational studies in epidemiology, such as the cohort study and the case-control study, provide less compelling evidence than the randomized controlled trial.[38] In observational studies, the investigators retrospectively assess associations between the treatments given to participants and their health status, with potential for considerable errors in design and interpretation.[39]

A randomized controlled trial can provide compelling evidence that the study treatment causes an effect on human health.[38]

Currently, some Phase II and most Phase III drug trials are designed as randomized, double-blind, and placebo-controlled.

- Randomized: Each study subject is randomly assigned to receive either the study treatment or a placebo.
- Blind: The subjects involved in the study do not know which study treatment they receive. If the study is double-blind, the researchers also do not know which treatment a subject receives. This intent is to prevent researchers from treating the two groups differently. A form of double-blind study called a "double-dummy" design allows additional insurance against bias. In this kind of study, all patients are given both placebo and active doses in alternating periods.
- Placebo-controlled: The use of a placebo (fake treatment) allows the researchers to isolate the effect of the study treatment from the placebo effect.

Clinical studies having small numbers of subjects may be "sponsored" by single researchers or a small group of researchers, and are designed to test simple questions or feasibility to expand the research for a more comprehensive randomized controlled trial.[40]

Active control studies

In many cases, giving a placebo to a person suffering from a disease may be unethical.[41] To address this, it has become a common practice to conduct "active comparator" (also known as "active control") trials. In trials with an active control group, subjects are given either the experimental treatment or a previously approved treatment with known effectiveness.

Master protocol

In such studies, multiple experimental treatments are tested in a single trial. Genetic testing enables researchers to group patients according to their genetic profile, deliver drugs based on that profile to that group and compare the results. Multiple companies can participate, each bringing a different drug. The first such approach targets squamous cell cancer, which includes varying genetic disruptions from patient to patient. Amgen, AstraZeneca and Pfizer are involved, the first time they have worked together in a late-stage trial. Patients whose genomic profiles do not match any of the trial drugs receive a drug designed to stimulate the immune system to attack cancer.[42]

Clinical trial protocol

A clinical trial protocol is a document used to define and manage the trial. It is prepared by a panel of experts. All study investigators are expected to strictly observe the protocol.

The protocol describes the scientific rationale, objective(s), design, methodology, statistical considerations and organization of the planned trial. Details of the trial are provided in documents referenced in the protocol, such as an investigator's brochure.

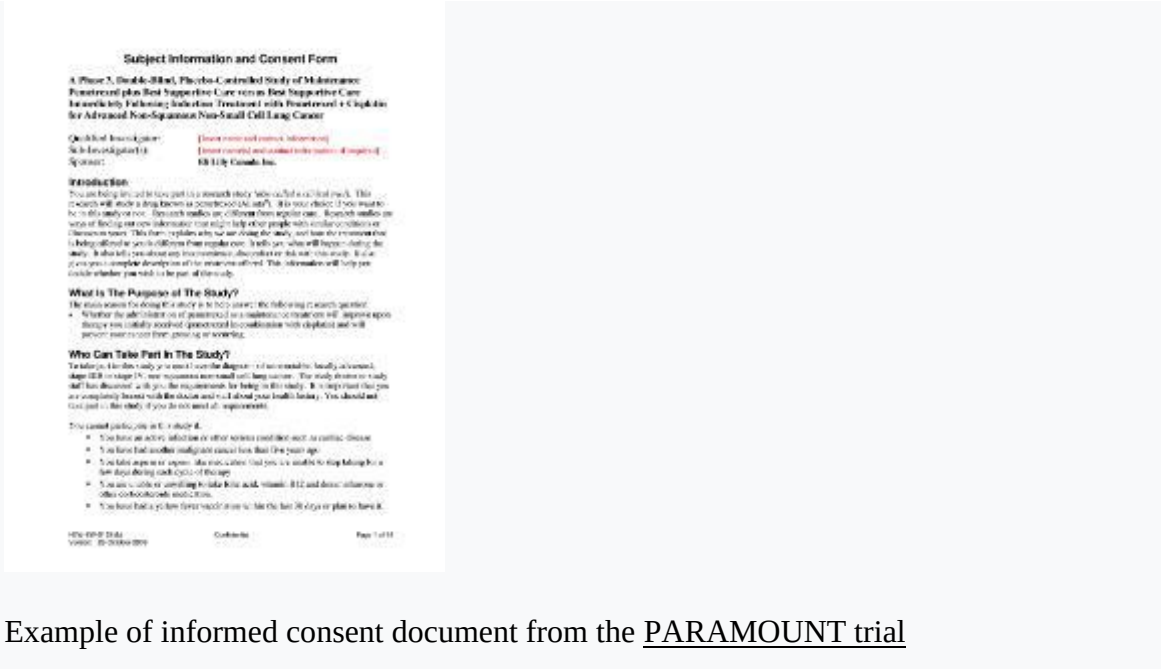
The protocol contains a precise study plan to assure safety and health of the trial subjects and to provide an exact template for trial conduct by investigators. This allows data to be combined across all investigators/sites. The protocol also informs the study administrators (often a contract research organization).

The format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology or medical device companies in the United States, European Union, or Japan have been standardized to follow Good Clinical Practice guidance[43] issued by the

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[44] Regulatory authorities in Canada and Australia also follow ICH guidelines. Journals such as *Trials*, encourage investigators to publish their protocols.

Design features

Informed consent


Subject Information and Consent Form

Example of informed consent document from the PARAMOUNT trial

Clinical trials recruit study subjects to sign a document representing their "informed consent".[45] The document includes details such as its purpose, duration, required procedures, risks, potential benefits, key contacts and institutional requirements.[46] The participant then decides whether to sign the document. The document is not a contract, as the participant can withdraw at any time without penalty.

Informed consent is a legal process in which a recruit is instructed about key facts before deciding whether to participate. Researchers explain the details of the study in terms the subject can understand. The information is presented in the subject's native language. Generally, children cannot autonomously provide informed consent, but depending on their age and other factors, may be required to provide informed assent.

Statistical power

In any clinical trial, the number of subjects, also called the sample size, has a large impact on the ability to reliably detect and measure the effects of the intervention. This ability is described as its "power", which must be calculated before initiating a study to figure out if

the study is worth its costs.[47] In general, a larger sample size increases the statistical power, also the cost.

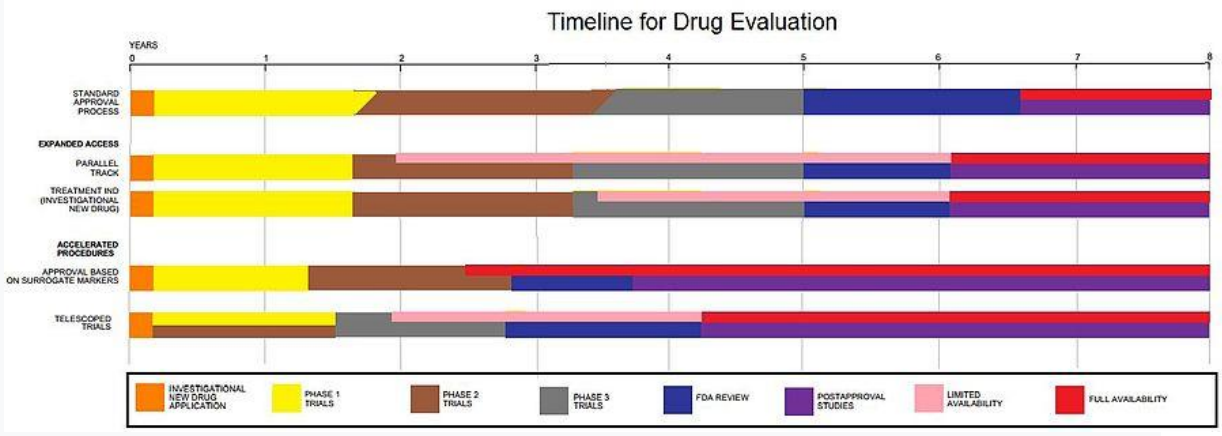
The statistical power estimates the ability of a trial to detect a difference of a particular size (or larger) between the treatment and control groups. For example, a trial of a lipid-lowering drug versus placebo with 100 patients in each group might have a power of 0.90 to detect a difference between placebo and trial groups receiving dosage of 10 mg/dL or more, but only 0.70 to detect a difference of 6 mg/dL.

Placebo groups

Merely giving a treatment can have nonspecific effects. These are controlled for by the inclusion of patients who receive only a placebo. Subjects are assigned randomly without informing them to which group they belonged. Many trials are doubled-blinded so that researchers do not know to which group a subject is assigned.

Assigning a subject to a placebo group can pose an ethical problem if it violates his or her right to receive the best available treatment. The Declaration of Helsinki provides guidelines on this issue.

Duration



Timeline of various approval tracks and research phases in the US

Clinical trials are only a small part of the research that goes into developing a new treatment. Potential drugs, for example, first have to be discovered, purified, characterized, and tested in labs (in cell and animal studies) before ever undergoing clinical trials. In all, about 1,000 potential drugs are tested before just one reaches the point of being tested in a clinical trial.[48] For example, a new cancer drug has, on average, six years of research behind it before it even makes it to clinical trials. But the major holdup in making new

cancer drugs available is the time it takes to complete clinical trials themselves. On average, about eight years pass from the time a cancer drug enters clinical trials until it receives approval from regulatory agencies for sale to the public.[49] Drugs for other diseases have similar timelines.

Some reasons a clinical trial might last several years:

- For chronic conditions such as cancer, it takes months, if not years, to see if a cancer treatment has an effect on a patient.
- For drugs that are not expected to have a strong effect (meaning a large number of patients must be recruited to observe 'any' effect), recruiting enough patients to test the drug's effectiveness (i.e., getting statistical power) can take several years.
- Only certain people who have the target disease condition are eligible to take part in each clinical trial. Researchers who treat these particular patients must participate in the trial. Then they must identify the desirable patients and obtain consent from them or their families to take part in the trial.

A clinical trial might also include an extended post-study follow-up period from months to years for people who have participated in the trial, a so-called "extension phase", which aims to identify long-term impact of the treatment.[50]

The biggest barrier to completing studies is the shortage of people who take part. All drug and many device trials target a subset of the population, meaning not everyone can participate. Some drug trials require patients to have unusual combinations of disease characteristics. It is a challenge to find the appropriate patients and obtain their consent, especially when they may receive no direct benefit (because they are not paid, the study drug is not yet proven to work, or the patient may receive a placebo). In the case of cancer patients, fewer than 5% of adults with cancer will participate in drug trials. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), about 400 cancer medicines were being tested in clinical trials in 2005. Not all of these will prove to be useful, but those that are may be delayed in getting approved because the number of participants is so low .[51]

For clinical trials involving potential for seasonal influences (such as airborne allergies, seasonal affective disorder, influenza, and skin diseases), the study may be done during a limited part of the year (such as spring for pollen allergies), when the drug can be tested.[52][53]

Clinical trials that do not involve a new drug usually have a much shorter duration. (Exceptions are epidemiological studies, such as the Nurses' Health Study).

Administration

Clinical trials designed by a local investigator, and (in the US) federally funded clinical trials, are almost always administered by the researcher who designed the study and applied for the grant. Small-scale device studies may be administered by the sponsoring company. Clinical trials of new drugs are usually administered by a contract research organization (CRO) hired by the sponsoring company. The sponsor provides the drug and medical oversight. A CRO is contracted to perform all the administrative work on a clinical trial. For Phases II–IV the CRO recruits participating researchers, trains them, provides them with supplies, coordinates study administration and data collection, sets up meetings, monitors the sites for compliance with the clinical protocol, and ensures the sponsor receives data from every site. Specialist site management organizations can also be hired to coordinate with the CRO to ensure rapid IRB/IEC approval and faster site initiation and patient recruitment. Phase I clinical trials of new medicines are often conducted in a specialist clinical trial clinic, with dedicated pharmacologists, where the subjects can be observed by full-time staff. These clinics are often run by a CRO which specialises in these studies.

At a participating site, one or more research assistants (often nurses) do most of the work in conducting the clinical trial. The research assistant's job can include some or all of the following: providing the local institutional review board (IRB) with the documentation necessary to obtain its permission to conduct the study, assisting with study start-up, identifying eligible patients, obtaining consent from them or their families, administering study treatment(s), collecting and statistically analyzing data, maintaining and updating data files during followup, and communicating with the IRB, as well as the sponsor and CRO.

Quality

In the context of a clinical trial, quality typically refers to the absence of errors which can impact decision making, both during the conduct of the trial and in use of the trial results.[54]

Marketing

Janet Yang uses the Interactional Justice Model to test the effects of willingness to talk with a doctor and clinical trial enrollment.[55] Results found that potential clinical trial candidates were less likely to enroll in clinical trials if the patient is more willing to talk with their doctor. The reasoning behind this discovery may be patients are happy with their current care. Another reason for the negative relationship between perceived fairness and clinical trial enrollment is the lack of independence from the care provider. Results found that there is a positive relationship between a lack of willingness to talk with their doctor and clinical trial enrollment. Lack of willingness to talk about clinical trials with current care providers may be due to patients' independence from the doctor. Patients who are less likely to talk about clinical trials are more willing to use other sources of information to gain a better insight of alternative treatments. Clinical trial enrollment should be motivated to utilize websites and television advertising to inform the public about clinical trial enrollment.

Information technology

The last decade has seen a proliferation of information technology use in the planning and conduct of clinical trials. Clinical trial management systems are often used by research sponsors or CROs to help plan and manage the operational aspects of a clinical trial, particularly with respect to investigational sites. Advanced analytics for identifying researchers and research sites with expertise in a given area utilize public and private information about ongoing research.[56] Web-based electronic data capture (EDC) and clinical data management systems are used in a majority of clinical trials[57] to collect case report data from sites, manage its quality and prepare it for analysis. Interactive voice response systems are used by sites to register the enrollment of patients using a phone and to allocate patients to a particular treatment arm (although phones are being increasingly replaced with web-based (IWRS) tools which are sometimes part of the EDC system). While patient-reported outcome were often paper based in the past, measurements are increasingly being collected using web portals or hand-held ePRO (or eDiary) devices, sometimes wireless.[58] Statistical software is used to analyze the collected data and prepare them for regulatory submission. Access to many of these applications are increasingly aggregated in web-based clinical trial portals. In 2011, the FDA approved a Phase I trial that used telemonitoring, also known as remote patient monitoring, to collect biometric

data in patients' homes and transmit it electronically to the trial database. This technology provides many more data points and is far more convenient for patients, because they have fewer visits to trial sites.

Ethical aspects

Clinical trials are closely supervised by appropriate regulatory authorities. All studies involving a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial. The local ethics committee has discretion on how it will supervise noninterventional studies (observational studies or those using already collected data). In the US, this body is called the Institutional Review Board (IRB); in the EU, they are called Ethics committees. Most IRBs are located at the local investigator's hospital or institution, but some sponsors allow the use of a central (independent/for profit) IRB for investigators who work at smaller institutions.

To be ethical, researchers must obtain the full and informed consent of participating human subjects. (One of the IRB's main functions is to ensure potential patients are adequately informed about the clinical trial.) If the patient is unable to consent for him/herself, researchers can seek consent from the patient's legally authorized representative. In California, the state has prioritized the individuals who can serve as the legally authorized representative.[59]

In some US locations, the local IRB must certify researchers and their staff before they can conduct clinical trials. They must understand the federal patient privacy (HIPAA) law and good clinical practice. The International Conference of Harmonisation Guidelines for Good Clinical Practice is a set of standards used internationally for the conduct of clinical trials. The guidelines aim to ensure the "rights, safety and well being of trial subjects are protected".

The notion of informed consent of participating human subjects exists in many countries but its precise definition may still vary.

Informed consent is clearly a 'necessary' condition for ethical conduct but does not 'ensure' ethical conduct. In compassionate use trials the latter becomes a particularly difficult problem. The final objective is to serve the community of patients or future patients in a best-possible and most responsible way. See also Expanded access. However, it may be hard to turn this objective into a well-defined, quantified, objective function. In some cases

this can be done, however, for instance, for questions of when to stop sequential treatments (see Odds algorithm), and then quantified methods may play an important role.

Additional ethical concerns are present when conducting clinical trials on children (pediatrics), and in emergency or epidemic situations.[60][61]

Ethically balancing the rights of multiple stakeholders may be difficult. For example, when drug trials fail, the sponsors may have a duty to tell current and potential investors immediately, which means both the research staff and the enrolled participants may first hear about the end of a trial through public business news.[62]

Conflicts of interest and unfavorable studies

In response to specific cases in which unfavorable data from pharmaceutical company-sponsored research were not published, the Pharmaceutical Research and Manufacturers of America published new guidelines urging companies to report all findings and limit the financial involvement in drug companies by researchers.[63] The US Congress signed into law a bill which requires Phase II and Phase III clinical trials to be registered by the sponsor on the clinicaltrials.gov website compiled by the National Institutes of Health.[64]

Drug researchers not directly employed by pharmaceutical companies often seek grants from manufacturers, and manufacturers often look to academic researchers to conduct studies within networks of universities and their hospitals, e.g., for translational cancer research. Similarly, competition for tenured academic positions, government grants and prestige create conflicts of interest among academic scientists.[65] According to one study, approximately 75% of articles retracted for misconduct-related reasons have no declared industry financial support.[66] Seeding trials are particularly controversial.[67]

In the United States, all clinical trials submitted to the FDA as part of a drug approval process are independently assessed by clinical experts within the Food and Drug Administration,[68] including inspections of primary data collection at selected clinical trial sites.[69]

In 2001, the editors of 12 major journals issued a joint editorial, published in each journal, on the control over clinical trials exerted by sponsors, particularly targeting the use of contracts which allow sponsors to review the studies prior to publication and withhold publication. They strengthened editorial restrictions to counter the effect. The editorial noted that contract research organizations had, by 2000, received 60% of the grants

from pharmaceutical companies in the US. Researchers may be restricted from contributing to the trial design, accessing the raw data, and interpreting the results.[70]

During public health crises

Conducting clinical trials of vaccines during epidemics and pandemics is subject to ethical concerns. For diseases with high mortality rates like Ebola, assigning individuals to a placebo or control group can be viewed as a death sentence. In response to ethical concerns regarding clinical research during epidemics, the National Academy of Medicine authored a report identifying seven ethical and scientific considerations. These considerations are:[71]

- Scientific value
- Social value
- Respect for persons
- Community engagement
- Concern for participant welfare and interests
- A balance towards benefit over risks
- Post-trial access to tested therapies that had been withheld during the trial

Pregnant women and children

Pregnant women and children are typically excluded from clinical trials as vulnerable populations, though the data to support excluding them is not robust. By excluding them from clinical trials, information about the safety and effectiveness of therapies for these populations is often lacking. During the early history of the HIV/AIDS epidemic, a scientist noted that by excluding these groups from potentially life-saving treatment, they were being "protected to death". Projects such as Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) have advocated for the ethical inclusion of pregnant women in vaccine trials. Inclusion of children in clinical trials has additional moral considerations, as children lack decision-making autonomy. Trials in the past had been criticized for using hospitalized children or orphans; these ethical concerns effectively stopped future research. In efforts to maintain effective pediatric care, several European countries and the US have policies to entice or compel pharmaceutical companies to conduct pediatric trials. International guidance recommends ethical pediatric trials by limiting harm, considering varied risks, and taking into account the complexities of pediatric care.[71]

Safety

Responsibility for the safety of the subjects in a clinical trial is shared between the sponsor, the local site investigators (if different from the sponsor), the various IRBs that supervise the study, and (in some cases, if the study involves a marketable drug or device), the regulatory agency for the country where the drug or device will be sold.

A systematic concurrent safety review is frequently employed to assure research participant safety. The conduct and on-going review is designed to be proportional to the risk of the trial. Typically this role is filled by a Data and Safety Committee, an externally appointed Medical Safety Monitor,[72] an Independent Safety Officer, or for small or low-risk studies the principal investigator.[73]

For safety reasons, many clinical trials of drugs[74] are designed to exclude women of childbearing age, pregnant women, or women who become pregnant during the study. In some cases, the male partners of these women are also excluded or required to take birth control measures.

Sponsor

Throughout the clinical trial, the sponsor is responsible for accurately informing the local site investigators of the true historical safety record of the drug, device or other medical treatments to be tested, and of any potential interactions of the study treatment(s) with already approved treatments. This allows the local investigators to make an informed judgment on whether to participate in the study or not. The sponsor is also responsible for monitoring the results of the study as they come in from the various sites as the trial proceeds. In larger clinical trials, a sponsor will use the services of a data monitoring committee (DMC, known in the US as a data safety monitoring board). This independent group of clinicians and statisticians meets periodically to review the unblinded data the sponsor has received so far. The DMC has the power to recommend termination of the study based on their review, for example if the study treatment is causing more deaths than the standard treatment, or seems to be causing unexpected and study-related serious adverse events. The sponsor is responsible for collecting adverse event reports from all site investigators in the study, and for informing all the investigators of the sponsor's judgment as to whether these adverse events were related or not related to the study treatment.

The sponsor and the local site investigators are jointly responsible for writing a site-specific informed consent that accurately informs the potential subjects of the true risks and potential benefits of participating in the study, while at the same time presenting the material as briefly as possible and in ordinary language. FDA regulations state that participating in clinical trials is voluntary, with the subject having the right not to participate or to end participation at any time.[75]

Local site investigators

The ethical principle of *primum non-nocere* ("first, do no harm") guides the trial, and if an investigator believes the study treatment may be harming subjects in the study, the investigator can stop participating at any time. On the other hand, investigators often have a financial interest in recruiting subjects, and could act unethically to obtain and maintain their participation.

The local investigators are responsible for conducting the study according to the study protocol, and supervising the study staff throughout the duration of the study. The local investigator or his/her study staff are also responsible for ensuring the potential subjects in the study understand the risks and potential benefits of participating in the study. In other words, they (or their legally authorized representatives) must give truly informed consent.

Local investigators are responsible for reviewing all adverse event reports sent by the sponsor. These adverse event reports contain the opinions of both the investigator (at the site where the adverse event occurred) and the sponsor, regarding the relationship of the adverse event to the study treatments. Local investigators also are responsible for making an independent judgment of these reports, and promptly informing the local IRB of all serious and study treatment-related adverse events.

When a local investigator is the sponsor, there may not be formal adverse event reports, but study staff at all locations are responsible for informing the coordinating investigator of anything unexpected. The local investigator is responsible for being truthful to the local IRB in all communications relating to the study.

Institutional review boards (IRBs)

Approval by an Institutional Review Board (IRB), or ethics board, is necessary before all but the most informal research can begin. In commercial clinical trials, the study protocol is not approved by an IRB before the sponsor recruits sites to conduct the trial. However,

the study protocol and procedures have been tailored to fit generic IRB submission requirements. In this case, and where there is no independent sponsor, each local site investigator submits the study protocol, the consent(s), the data collection forms, and supporting documentation to the local IRB. Universities and most hospitals have in-house IRBs. Other researchers (such as in walk-in clinics) use independent IRBs.

The IRB scrutinizes the study both for medical safety and for protection of the patients involved in the study, before it allows the researcher to begin the study. It may require changes in study procedures or in the explanations given to the patient. A required yearly "continuing review" report from the investigator updates the IRB on the progress of the study and any new safety information related to the study.

Regulatory agencies

In the US, the FDA can audit the files of local site investigators after they have finished participating in a study, to see if they were correctly following study procedures. This audit may be random, or for cause (because the investigator is suspected of fraudulent data). Avoiding an audit is an incentive for investigators to follow study procedures. A 'covered clinical study' refers to a trial submitted to the FDA as part of a marketing application (for example, as part of an NDA or 510(k)), about which the FDA may require disclosure of financial interest of the clinical investigator in the outcome of the study. For example, the applicant must disclose whether an investigator owns equity in the sponsor, or owns proprietary interest in the product under investigation. The FDA defines a covered study as "... any study of a drug, biological product or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety."[76]

Alternatively, many American pharmaceutical companies have moved some clinical trials overseas. Benefits of conducting trials abroad include lower costs (in some countries) and the ability to run larger trials in shorter timeframes, whereas a potential disadvantage exists in lower-quality trial management.[77] Different countries have different regulatory requirements and enforcement abilities. An estimated 40% of all clinical trials now take place in Asia, Eastern Europe, and Central and South America. "There is no compulsory registration system for clinical trials in these countries and many do not follow European

directives in their operations", says Jacob Sijtsma of the Netherlands-based WEMOS, an advocacy health organisation tracking clinical trials in developing countries.[78]

Beginning in the 1980s, harmonization of clinical trial protocols was shown as feasible across countries of the European Union. At the same time, coordination between Europe, Japan and the United States led to a joint regulatory-industry initiative on international harmonization named after 1990 as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[79] Currently, most clinical trial programs follow ICH guidelines, aimed at "ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost-effective manner. These activities are pursued in the interest of the consumer and public health, to prevent unnecessary duplication of clinical trials in humans and to minimize the use of animal testing without compromising the regulatory obligations of safety and effectiveness."[80]

Aggregation of safety data during clinical development

Aggregating safety data across clinical trials during drug development is important because trials are generally designed to focus on determining how well the drug works. The safety data collected and aggregated across multiple trials as the drug is developed allows the sponsor, investigators and regulatory agencies to monitor the aggregate safety profile of experimental medicines as they're developed. The value of assessing aggregate safety data is: a) decisions based on aggregate safety assessment during development of the medicine can be made throughout the medicine's development and b) it sets up the sponsor and regulators well for assessing the medicine's safety after the drug is approved.[81][82][83][84][85]

Economics

Clinical trial costs vary depending on trial phase, type of trial, and disease studied. A study of clinical trials conducted in the United States from 2004 to 2012 found the average cost of Phase I trials to be between $1.4 million and $6.6 million, depending on the type of disease. Phase II trials ranged from $7 million to $20 million, and Phase III trials from $11 million to $53 million.[86]

Sponsor

The cost of a study depends on many factors, especially the number of sites conducting the study, the number of patients involved, and whether the study treatment is already approved for medical use.

The expenses incurred by a pharmaceutical company in administering a Phase III or IV clinical trial may include, among others:

- production of the drug(s) or device(s) being evaluated
- staff salaries for the designers and administrators of the trial
- payments to the contract research organization, the site management organization (if used) and any outside consultants
- payments to local researchers and their staff for their time and effort in recruiting test subjects and collecting data for the sponsor
- the cost of study materials and the charges incurred to ship them
- communication with the local researchers, including on-site monitoring by the CRO before and (in some cases) multiple times during the study
- one or more investigator training meetings
- expense incurred by the local researchers, such as pharmacy fees, IRB fees and postage
- any payments to subjects enrolled in the trial
- the expense of treating a test subject who develops a medical condition caused by the study drug

These expenses are incurred over several years.

In the US, sponsors may receive a 50 percent tax credit for clinical trials conducted on drugs being developed for the treatment of orphan diseases.[87] National health agencies, such as the US National Institutes of Health, offer grants to investigators who design clinical trials that attempt to answer research questions of interest to the agency. In these cases, the investigator who writes the grant and administers the study acts as the sponsor, and coordinates data collection from any other sites. These other sites may or may not be paid for participating in the study, depending on the amount of the grant and the amount of effort expected from them. Using internet resources can, in some cases, reduce the economic burden.[88]

Investigators

Investigators are often compensated for their work in clinical trials. These amounts can be small, just covering a partial salary for research assistants and the cost of any supplies (usually the case with national health agency studies), or be substantial and include "overhead" that allows the investigator to pay the research staff during times between clinical trials.[*citation needed*]

Subjects

Participants in Phase I drug trials do not gain any direct health benefit from taking part. They are generally paid a fee for their time, with payments regulated and not related to any risk involved. In later phase trials, subjects may not be paid to ensure their motivation for participating with potential for a health benefit or contributing to medical knowledge. Small payments may be made for study-related expenses such as travel or as compensation for their time in providing follow-up information about their health after the trial treatment ends.

Participant recruitment and participation

Newspaper advertisements seeking patients and healthy volunteers to participate in clinical trials

Phase 0 and Phase I drug trials seek healthy volunteers. Most other clinical trials seek patients who have a specific disease or medical condition. The diversity observed in society should be reflected in clinical trials through the appropriate inclusion of ethnic minority populations.[89] Patient recruitment or participant recruitment plays a significant role in the activities and responsibilities of sites conducting clinical trials.[90]

All volunteers being considered for a trial are required to undertake a medical screening. Requirements differ according to the trial needs, but typically volunteers would be screened in a medical laboratory for:[91]

- Measurement of the electrical activity of the heart (ECG)
- Measurement of blood pressure, heart rate, and body temperature
- Blood sampling
- Urine sampling
- Weight and height measurement
- Drug abuse testing
- Pregnancy testing

It has been observed that participants in clinical trials are disproportionately white. This may reduce the validity of findings in respect of non-white patients.[92]

Locating trials

Depending on the kind of participants required, sponsors of clinical trials, or contract research organizations working on their behalf, try to find sites with qualified personnel as well as access to patients who could participate in the trial. Working with those sites, they may use various recruitment strategies, including patient databases, newspaper and radio advertisements, flyers, posters in places the patients might go (such as doctor's offices), and personal recruitment of patients by investigators.

Volunteers with specific conditions or diseases have additional online resources to help them locate clinical trials. For example, the Fox Trial Finder connects Parkinson's disease trials around the world to volunteers who have a specific set of criteria such as location, age, and symptoms.[93] Other disease-specific services exist for volunteers to find trials related to their condition.[94] Volunteers may search directly on ClinicalTrials.gov to locate trials using a registry run by the U.S. National Institutes of Health and National Library of Medicine.

Research

The risk information seeking and processing (RISP) model analyzes social implications that affect attitudes and decision making pertaining to clinical trials.[95] People who hold a higher stake or interest in the treatment provided in a clinical trial showed a greater likelihood of seeking information about clinical trials. Cancer patients reported more

optimistic attitudes towards clinical trials than the general population. Having a more optimistic outlook on clinical trials also leads to greater likelihood of enrolling.[95]