INTRODUCTION

The subject of ETHICS holds center stage in every facet of the pharmaceutical value chain, with each department responsible to drive the business via an ethical approach, thereby impacting every single employee employed. This necessitates an ethical behavior in a setting that ensures highest standards of ethical conduct.

The purpose of this review is to provide a summary on the subject of ethics related to clinical research and to bring together individuals who continue to strive and bring ethics at the center of our everyday day operations and help differentiate right and wrong behavior.

What defines as ethical?

According to Resnik,[1] when most people think of ethics (or morals), they think of rules for distinguishing between right and wrong, such as the Golden Rule (“Do unto others as you would have them do unto you”), a code of professional conduct like the Hippocratic Oath (“First of all, do no harm”), religious creed like the Ten Commandments (“Thou Shalt not kill”), or a wise aphorisms like the sayings of Confucius. Thus the most common way of defining “ethics”: Norms for conduct that distinguish between acceptable and unacceptable behavior.

Medical ethics: Historical perspectives

The first basic guideline for medical ethics was introduced during the life of Hippocrates, a classical Greek physician who lived between 460 and 377 BC. Hippocrates’ three-word “Do NO harm” phrase created the first ethical law in the field of medicine that has evolved into the 181-word vow recited at modern medical school graduation ceremonies.

Ancient medical texts in cultures of India and China established groundwork of morals and virtues to be exemplified by medical practitioners. These first guidelines established models of physician humility, concern, and compassion for patients. Religions of this time influenced the creation of this code of behavior by establishing a basic understanding of the sacred relationship between medical practitioners and their patients.[2]

It was during the intellectual revolution of the 18th century that numerous medical advances took place in the West, including the publishing of the first book discussing medical ethics.[3] Thomas Percival, a British physician, published his book “Code of Medical Ethics,” in the year 1803. At nearly the same time, medical students attending the University of Pennsylvania began to be lectured by physician Benjamin Rush regarding the importance of medical ethics. In 1847, the American Medical Association was formed in order to establish a definite code of medical ethics because no government laws established medical regulations.

For the past 60 years, the main sources of guidance on the ethical conduct of clinical research have been the Nuremberg code,[4] Declaration of Helsinki,[5] Belmont Report,[6] International Ethical Guidelines for Biomedical research involving human subjects,[7] and closer home in India, the Indian Council of Medical Research (ICMR) Guidelines for clinical research.[8]
drug development. Large pharmaceutical companies set extensive research facilities within their firms to conceptualize and implement research protocols. Major spending was planned around clinical development. In 2010 alone, 60 billion USD was invested by the industry in clinical development projects. The pharmaceutical company does sponsor a large number of discovery and development projects with annual budgets ranging between 10 and 21% of the total sales for the company.

As a sponsor for major clinical development projects, the industry therefore is the uncrowned champion of ethics, by virtue of the large spends alone. This large spend is primarily aimed to ensuring not only in just developing drugs but also in hiring top scientific talent that is ethically oriented and ensures patient safety at every stage of the clinical trial process. The scientific talent within the industry sponsor organizations serves as custodians of ethical principles.

This review is aimed at presenting the industry viewpoint as a custodian and driver of all ethical principles.

**Pharmaceutical industry and public perception**

The subject of ethics is phenomenally huge in the context of pharmaceutical industry, and the attitudes of the public. There are various ethical dilemmas faced by the industry related to drug pricing and marketing, role of intellectual property rights and patent protection, moral and economic requisites of research and clinical trials. The focus of this review is on clinical development as one aspect that ensures patient safety, although one could argue that good manufacturing practices and other technical operations are also mandatory for ensuring patient well-being.

*In a study* to analyze newspaper coverage of ethical issues in the pharmaceutical industry, top five US newspapers were audited over 2 years and yielded 376 articles, which appeared as front-page stories or editorials. The study found analysis of the ethical issues, which revealed different results for the 2 years. In one year, 2004 the most common issues covered were drug pricing, data disclosure, and importation/reimportation. In 2005, drug safety was the number one issue, due to Vioxx® with drug pricing a distant second. The study concluded that Pharmaceutical companies need to take action to address the negative impression about them.[9]

**Patient attitudes to clinical trials**

In a study to review the attitudes of the public and the out-patients to ethical aspects of clinical trials, positive attitudes toward medical research were disclosed.[10] The majority found scientific testing necessary, although only a minority considered participation a moral obligation.

**Ethics and interpretations: Industry viewpoint**

The industry is aligned to the philosophy of the World Medical Assembly (WMA) and the Declaration of Helsinki. Since the World Medical Assembly’s Declaration of Helsinki first reference in 1964, further amendments until 2008 reflect the growing importance in our ability to apply ethical principles. Here, the declaration binds the physician with the international code of medical ethics declaring that the physician shall act in the patient’s best interest while providing medical care. The declaration is categorical in the assumption that the physician's knowledge and conscience are dedicated to the fulfillment of the duty; the duty to promote and safeguard the health of the patient.

With globalization and marginal shift in the clinical trial footprint to developing countries there have been a number of ethical issues especially with reference to recruitment of vulnerable population. The WMA clearly confirms that populations that are underrepresented should be provided appropriate access to medical research. Therefore, all the concerns and reports suggesting that it is unethical to go to developing countries for exposing vulnerable population as ‘unethical’ is unjustified. A large proportion from developing countries will be prescribed pharmaceutical products prescribed in the West.

Further the WMA also prescribes as ethical that the currently available interventions must also be under continuous evaluation. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating, and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for poststudy access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

The highlight of the WMA, Declaration confirms that in both medical practice and medical research, most interventions involve risks and burden. Table 1 reviews the Global and Indian guidelines that the industry adopts in applying ethical principles.

**What constitutes a research as “Ethical”**

Ethical requirements for clinical research aim to minimize the possibility of exploitation by ensuring that research subjects are not merely used but are treated with respect while they contribute to the social good.[11]

Emanuel EJ[12] has detailed very vividly the various constituents that define the ethics of a research proposal. He questions the overreliance on informed consent as a basis for ethical trial conduct.
In an interesting article published in *JAMA*,[12] outlining the need to limit the obsession with Informed Consent, Emanuel draws us to interesting list of seven ethical requirements that are mandatory in addition to the ethical obligation to ensure human protection whilst participation in a clinical trial.

The seven requirements are designed to provide a systematic and coherent framework for determining whether clinical research is ethical.

**Social or scientific value**

To be ethical, clinical research must be valuable,[4,13] meaning that it evaluates a diagnostic or therapeutic intervention that could lead to improvements in health or well-being.

**Industry viewpoint**

That drug development is expensive is well known. Therefore, Industry is judicious to invest in research practices that offer specific answers. Clinical Research Protocols are very specific in the endpoints.

The Clinical Development Plans aim to develop a clearly scientific and differentiated compound in terms of efficacy, safety, compliance or cost. Otherwise, the new drug would not be investigated. The approach of the industry has been to perform extensive feasibilities. These feasibilities do offer significant insights in terms of the standard of care, unmet needs with available standards of care, and help select sites that have the infrastructure and personnel to initiate the study. The industry enters into extensive and in depth negotiations with regulatory stakeholders and experts early on that help address key fundamental questions in a study protocol and ensure that the risk to patient is minimized. Industry also conducts extensive Phase IV programs to continuously review the safety and efficacy of the product even after its entry into the market.

Industry also ensures that the results of clinical trials, whether positive or negative are shared with the society thereby justifying the social value.

**Scientific validity**

To be ethical, valuable research must be conducted in a methodologically rigorous manner.[13] The council for international organization of medical sciences (CIOMS) guidelines clearly states: “Scientifically unsound research on human subjects is *ipso facto* unethical in that it may expose subjects to risks or inconvenience to no purpose.”[7]

Industry approach to scientific validity;

**Science**

Industry sponsored clinical research protocols have a clear scientific objective; are designed using accepted principles, methods and reliable practices; have sufficient power to definitively test the objective; and offer a plausible data analysis plan. Every study protocol is embedded in the clinical development plan.

**Talent**

The industry now hires some of the brightest academic talent from the top universities of the world. The proof of quality of the talent is testament to the various drugs that have been discovered and developed by the industry. Many scientists working for R and D departments for the industry confirm the attrition of many compounds and they have the experience and courage to ‘kill’ the project early on. This minimizes the risk to unnecessarily exposing humans and is the ethical standard adopted by biopharmaceutical companies.

**Fair selection of subjects**

The selection of subjects must be fair.[6,11] Subject selection encompasses decisions about who will be included both through the development of specific inclusion and exclusion criteria and the strategy adopted for recruiting subjects, such as which communities will be study sites and which potential groups will be approached. There are several facets to this requirement.
Industry Practices

Industry Practices fair selection of subjects by incorporating a extensive inclusion and exclusion criteria. This extensive list takes into account various factors that help in minimizing patients at risk. There are several in-house teams with the industry research centers that deliberate at length the exclusion criteria. Moreover, it is the scientific goals of the study that forms the basis of selection of subjects and not vulnerability, privilege or any other factor not related to the purpose of the study.

Favorable risk-benefit ratio

Assessment of the potential risks and benefits of clinical research by researchers and review bodies typically involves multiple steps. First, risks are identified and, within the context of good clinical practice, minimized by using procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.12

Industry approach

At the outset, before any investigational drug is tested in human beings, it has to pass through rigorous in-vivo and in-vitro preclinical tests just to make sure that it is safe enough to be administered to humans.

A strict “No-waiver” to protocol deviation policy is the standard practice adopted by the industry research teams to ensure that the risk-benefit ratio is ensured in favor of benefit for the human participant.

Monitoring resources by the industry research teams monitor compliance to the study drug and protocol, ensure timely reporting of adverse events and serious adverse events and that these are followed until resolution or stabilization. This ensures a fair amount of minimization of risks to human participants.

Further the use of centralized laboratories that ensure that the values are harmonized and clinically significant values flagged off to the sponsors and the site teams does help alleviate some concerns with the risks associated with study drug.

Adoption of adaptive trials, establishing the Independent Data Monitoring Boards, having interim analysis are other steps that industry follows to ensure that the risks to the patient are minimized.

Independent review

Investigators inherently have multiple, legitimate interests to conduct high-quality research, complete the research expeditiously, protect research subjects, obtain funding, and advance their careers. These diverse interests can generate conflicts that may unwittingly distort the judgment of even well-intentioned investigators regarding the design, conduct, and analysis of research.14-17 Wanting to complete a study quickly may lead to the use of questionable scientific methods or readily available rather than the most appropriate subjects.

Industry practices

Industry ensures that the independent review is established via the institutional review boards/independent ethics committees who have the authority to approve, amend or terminate the study. Further there is the independent data safety monitoring board which also helps in evaluating, interim, ad-hoc and continuous data review if applicable for study drugs and research protocols.

Informed consent

Of all requirements, none has received as much explication as informed consent.14,17,15 The purpose of informed consent is 2-fold: To ensure that individuals control whether or not they enroll in clinical research and participate only when the research is consistent with their values, interests, and preferences.

The industry has an extensive checklist of items that help in ensuring the informed consent procedures as laid out by various guidelines are adhered to at the site. Special care is taken for research studies involving nonautonomous persons like children, adults with diminished mental capacity, etc., to ensure that research participation is consistent with their interests and values. Training of all in-house research personnel, ensure training and assessment of site personnel, monitoring for informed procedures at the site in 100% for all patients, training and retraining as necessary, continuous revision of standard Operating Procedures (SOPS), audits, co-monitoring etc are some of the measures adopted by the industry to adhere and champion the rights of the patients.

Respect for potential and enrolled subjects

Respect for potential and enrolled subjects is justified by multiple principles including beneficence, nonmaleficence, and respect for persons.18 Permitting subjects to withdraw and providing them additional information learned from the research are key aspects of respecting subject autonomy.6,19 Protecting confidentiality and monitoring well-being are motivated by respect for persons, beneficence, and nonmaleficence.

Industry ensures that only qualified and trained investigators recruit patients for a study. This ensures the ethics related to permitting subjects to withdraw from the study are truly incorporated in both letter and spirit. The review of the
Informed consent document developed must ensure that the clauses related to patient withdrawal are adhered to.

**Indian clinical research and ethics**

Undoubtedly, India has a great potential to deliver on the promise of clinical development. The past few years have witnessed some progress made in establishing a culture of research and aligned stakeholders who speak the common language of ethics.

To study the perception of investigators attitudes and knowledge of ethics in India, a specially designed survey questionnaire was served to 29 investigators, having prior experience of participating in drug development studies with pharmaceutical companies. The survey confirmed that majority believed that the research they conducted was relevant to the needs of society and concluded that, at well established and well trained sites, there exists a good understanding of the ethical issues around conduct of clinical research in a developing country.[19]

According to an online survey to study the perception of various stakeholders regarding clinical trial drug industry in India, 78.5% respondents confirmed that India is not delivering on the potential for research and development.[20]

**DISCUSSION**

**The pharmaceutical industry and contributions to diseases of the developing world**

Progress helps each individual patient who benefits from innovative new medicines, but it also can improve health care overall by helping patients maintain their health and by cutting overall costs. One study found that the development of a new treatment that delays the onset of Alzheimer’s could reduce Medicare and Medicaid spending on patients with Alzheimer’s by more than $100 billion annually by 2030.[21] A separate study found that annual costs for diabetes care can be up to 48% lower for patients who take their diabetes medicines properly.[21] In a population of 24 million patients with diabetes-among whom only one-quarter control the disease-the potential cost savings associated with better diabetes care could be significant.

Research and the progress that it yields are ongoing, with more than 2900 medicines currently in development. Today’s potential new medicine may become tomorrow’s new cure.

Despite the pharmaceutical industry’s notable contributions to human progress, Government officials, physicians, and social critics have questioned whether the multibillion dollar industry is fulfilling its social responsibilities. According to a October 2004 report[22] submitted by the Hudson Institute Report by Center for Science in Public policy, Washington DC, USA, pharmaceutical company contributions to tuberculosis (TB), Human Immunodeficiency Virus (HIV), malaria, and other infectious diseases were substantial and significant. In 2004 alone, more than contributions amounting to 2 billion USD were invested in the understanding of these diseases.

In the past 10 years over 300 new medicines have been approved by the FDA. These medicines are helping patients live longer, healthier lives. They are transforming many cancers into treatable conditions, reducing the impact of cardiovascular disease, offering new options for patients with hard-to-treat diseases like Alzheimer’s and Parkinson’s, and fighting even the rarest conditions.

A Boston Healthcare report published a white paper in June 2012 confirming the dramatic advances in overall cancer survival that has been realized by the cancer community in recent years.[23]

The medicines developed over the past several decades—and the medical advances they represent—have revolutionized the battle against disease and have saved and improved lives around the world.

According to one study, medicines and intervention treatments contributed to a 45% decline in deaths by heart attack and heart failure from 1999 to 2005. Death rates from cancers also have steadily declined, with one major study reporting that new medicines account for 50-60% of survival increases[24].

One particularly compelling example is Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS). Just 15 years after the disease was first reported in the United States, highly active antiretroviral treatment became widely available, drastically lowering the number of US AIDS deaths. In 1995, there were 16.2 AIDS deaths per 100,000 people in America. Within 2 years, that number had dropped to six, and by 2007, it was 3.7. Now, thanks to continued advances in HIV/AIDS therapies, the disease that was first seen as a death sentence is now a controllable condition.[21]

Sometimes, the health progress from medicines is seen in improvements to quality of life as much as in survival. After 3 years, half of untreated Alzheimer’s disease patients are placed in nursing homes, compared with just 11% of patients receiving treatment.[21].

Perhaps above all else, real advances give patients one essential ingredient for survival: hope.
INDUSTRY VIEWPOINT-CONCLUSION

Development of robust clinical research proposals, ensuring sufficient time for thorough and extensive feasibility, hiring and training top talent that is oriented to ethics as well as selecting qualified and experienced sites/contract research organization (CRO) and personnel, establishing a clear and robust monitoring mechanism to review informed consent, protocol deviations, adverse event reporting, and study close-out procedures will ensure application of ethical principles as laid out in the various guidelines of Good Clinical Practice.

Finally, ethics in clinical research is an evolving journey, never a destination.

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