Ethics assessment in different fields

Pharmaceutics

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Annex 2.c.2
Ethical Assessment of Research and Innovation: A Comparative Analysis of Practices and Institutions in the EU and selected other countries
Deliverable 1.1

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Contents

1 Abbreviations

EFPIA - the European Federation of Pharmaceutical Industries and Associations

IFPMA - the International Federation of Pharmaceutical Manufactures and Associations

MNCs – Multinational Corporations/Companies

NCE - new chemical entity

POM - Prescribing of Pharmacy Only Medicines

TNC – Transnational Corporations/Companies

WHO - the World Health Organization

2 Pharmaceutics

2.1 Basic description

Pharmaceutics is a discipline of pharmacy dealing with the development, manufacture and delivery of new medicinal drugs and the clinical response for a new medication. Pharmaceutics concerns the relation between these four phases of a medication process. It is an applied science of dosage form design concerning all phases of the process of turning a new chemical entity (NCE) into an effective medicine that can be safely and in a convenient manner used by patients in the community.[1] Pharmaceutics applies such disciplines as chemistry, physics, mathematics and other related disciplines to produce medicines.[2]

The objective of pharmaceutics is to formulate a drug substance and translate it to commercialised over-the-counter or prescription products.[3] These raw chemicals may be turned into a medication in such forms as tablets, capsules, creams, gels, ointments, transdermal and transmucosal patches, solutions, sprays, eye and eardrops, and many others.[4]

Some of the sub disciplines of pharmaceutics include the following:

- Pharmaceutical formulation
- Pharmaceutical manufacturing
- Dispensing Pharmacy
- Pharmaceutical Technology
- Physical Pharmacy
- Pharmaceutical Jurisprudence[5]

[1] The University of Mississippi, School of Pharmacy. http://www.pharmacy.olemiss.edu/pharmaceutics/
[2] University of the Western Cape, "Discipline of Pharmaceutics". http://www.uwc.ac.za/Faculties/NS/Pharmacy/Pages/Pharmaceutics.aspx.
[3] The University of Mississippi, School of Pharmacy. http://www.pharmacy.olemiss.edu/pharmaceutics/
[4] Ibid.
[5] Wikipedia, 'Pharmaceutics". http://en.wikipedia.org/wiki/Pharmaceutics

2.2 Values and Principles

Ethical values and principles of pharmaceutics are strictly related to the professional responsibilities of a pharmacist. In general, pharmacists as professionals are responsible for:

Dispensing and compounding drugs or preparing suitable dosage forms for administration of drugs where overall these include patient pharmaceutical care in the clinical area, manufacturing, community pharmacy and research, with the latter including collection, identification, purification, isolation, synthesis, clinical trials, standardisation and quality control of medicinal substances.[6]

Pharmaceutics, as a discipline strictly related to medicine, has been firstly influenced by **deontological ethics focusing on 'a duty',[7] therefore professionalism** in pharmacy; and secondly by **the four principle approach to bioethics ('principlism')** including the following principles:[8]

1. Autonomy (an individual is a moral agent having the capacity to understand and make ethical decisions, having rights, duties and obligations)
2. Beneficence (principle of 'doing good')
3. Non-maleficence (principle of avoiding harms)
4. Justice (all individual should be treated fair)

In professional ethics, decision-making gets involved in procedural rather than normative ethics and is based on moral reasoning.[9] The main ethical values and principles of pharmaceutics include **respect for patient's dignity and autonomy, beneficence, non-maleficence, justice, empathy, honesty, cooperation, and excellence**.[10]

The 20th century has brought a great change in pharmaceutics. The discipline dealing with compounding and dispensing medications by pharmacists has become a great market run by corporations. **Pharmaceutics is dominated by industry**, where physicians and patients rely on pharmaceutical companies to provide medications needed to address patient health concerns.[11] However, the pharmaceutical industry as any other branch of industry is business oriented, aiming at maximising profits from the drugs they sell. They have therefore an obvious interest in influencing consumers to buy the drugs they manufacture.[12] These efforts

[6] Noordin M. I., "Ethics in Pharmaceutical Issues", in P.A Clark (ed.), *Contemporary Issues in Bioethics*, InTech, 2012. pp. 83-102, [p. 84].
[7] Cahana A., A. Mauron, "The story of Vioxx—no pain and a lot of gain: ethical concerns regarding conduct of the pharmaceutical industry", *Journal of Anesthesia*, 2006 (20), pp. 348–351, [p.350].
[8] Beauchamp, T.L, J. F. Childress, *Principles of biomedical ethics*, 5th Edition, 2001.
[9] Pooneh, Salari, P. S. Sharif, M. Javadi, and F. Asghari, "Pharmacy ethics: evaluation pharmacists' ethical attitude", *Journal of Medical Ethics and History of Medicine*, 4:5, 2011. http://journals.tums.ac.ir/full_text.aspx?org_id=59&culture_var=en&journal_id=24&issue_id=2086&manuscript_id=18167&segment=en
[10] Salari P., H. Namazi et al, "Code of ethics for national pharmaceutical system: Codifying and compilation", *Journal of Research in Medical Sciences*, 18(5), May 2013, pp. 442–448. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3810583/?report=printable
[11] Haque O. S., J. De Freitas et al, "The Ethics of Pharmaceutical Industry: Influence in Medicine", The UNESCO Chair of Bioethics, May 2013, p. 13. http://medlaw.haifa.ac.il/index/main/4/EthicsofPharmaceutical.pdf
[12] Ibid.

may lead to a **conflict of interest** between 'the objective of pharmaceutical companies to maximise profits and the need of patients to receive the most safe, effective, and individualised medications at any given time'.[13] Eventually, the primary ethical interest within medicine should focus on maximising the health and wellbeing of patients not the corporate profits.[14]

Not only patients but also physicians are the consumers of the pharmaceutical industry.[15] Pharmaceutical companies, therefore, seek to influence both physicians and patients through "provider-directed" and "direct-to-consumer" approaches, respectively.[16]

Industrialisation and commercialisation of pharmaceutics have led to the emergence of new challenges related to the clash between professional duties of an individual pharmacist as a moral agent versus the business milieu.[17] The values and principles of pharmaceutics, therefore, have evolved by including the values and principles of actors engaged in providing pharmaceutical care, rising questions of scientific integrity, institutional integrity, and funding of research and innovation in pharmaceutics.

Competition is a great driver for research and innovation in medicine. The cooperation between pharmaceutical corporations and physicians and pharmacists is an inevitable factor necessary for development in pharmaceutics. However, even though the pharmaceutical industry, physicians and pharmacists share a number of common interests, the parties have different emphasis and focus on different stakeholders.[18] Health-care providers focus primarily on patient care and scientific advance, while industry strives primarily for commercial outcomes.[19] Notwithstanding, **pharmaceutical companies** have the responsibility towards clients, patients, healthcare providers (physicians), community and environment.[20] Ethics, honesty, and accuracy in publishing the results of investigations, privacy, confidentiality, justice in resource allocation should be some of the reference points for business.[21]

Regarding the **policy-making** in the area of pharmaceutics, the international, regional and national regulations should always take into consideration equity in access to drugs (including accessibility and affordability), drug efficacy, quality and safety, and rational use of drugs.[22] Equity in access to drugs is related, among the other issues, to the question of which drug should be added to country's drug list. Therefore, public officials in relation with

[13] Haque et al, op. cit., 2013.
[14] Haque et al, op. cit., 2013.
[15] Haque et al, op. cit., 2013.
[16] Haque et al, op. cit., 2013.
[17] Cahana A., A. Mauron, "The story of Vioxx—no pain and a lot of gain: ethical concerns regarding conduct of the pharmaceutical industry", *Journal of Anesthesia*, 2006 (20), pp. 348–351, [p.350].
[18] Pharmainfo.net, "Ethical Issues Concerning the Relationships between Medical Practitioners and the Pharmaceutical Industry". http://www.pharmainfo.net/sameer-rastogi/publications/ethical-issues-concerning-relationships-between-medical-practitioners-an.
[19] Ibid.
[20] Salari P., H. Namazi, et al, "Code of ethics for national pharmaceutical system: Codifying and compilation", Journal of Research in Medical Sciences, 18(5), May 2013, pp. 442–448. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3810583/?report=printable
[21] Ibid.
[22] Salari & Namazi, op. cit, 2013.

pharmaceutics corporations should be hold accountable (bribery), uphold the principle of predictability, and provide unbiased and justified services and legal obligations.[23] Furthermore, policy-makers should have responsibilities towards consumers, including ensuring the standard quality of drugs, controlling the quantity and quality of drug production, monitoring packaging and importation as well as trying to facilitate drug availability and revealing any issue relate to drug safety to the public.[24]

3 Ethical Issues

Over time, the role of pharmacists has changed significantly. They have evolved from medicine sellers, dealing mostly with compounding and dispensing medications to global players playing a crucial role in the adoption of global standards and creating trends in the pharmaceutics industry.[25]

Pharmaceutics raises a variety of ethical questions. As these issues are related to different aspects of the discipline, the ethical questions need to be analysed taking into consideration on the one hand, the different phases of medicine development and distribution, and on the other, the relations of the actors engaged in this process. Noordin (2012) identifies nine areas of pharmaceutical activity inevitably entailing ethical considerations.[26] This report follows his division, although expands the list by discussing the actors engaged in pharmaceutics and their relations, academic freedom and professional autonomy, including funding of a pharmaceutical development.

3.1 Clinical Pharmacy Practice

3.1.1 Patients pharmaceutical care

The ethical issues may occur in a daily clinical practice in hospitals. Pharmaceutical care refers to the responsibility of a pharmacist for a drug therapy in order to achieve the best outcomes that promote a patient's quality of life.[27] Some of the ethical issues in pharmaceutical care practice include as following: a patient's confidentiality, privacy, and autonomy, a duty to warn and competencies in deciding about the best medication to be procured.[28] **Confidentiality and privacy** are related to disclosure of a patient's sensitive data by a pharmacist. Lack of assurance of confidentiality may cause a reluctance to disclose information by a patient, resulting in obstacles to effective pharmaceutical care.[29] The autonomy requires from a pharmacist to inform a patient about possible side effects of a

[23] Salari & Namazi, op. cit, 2013.
[24] Salari & Namazi, op. cit, 2013.
[25] Noordin M. I., "Ethics in Pharmaceutical Issues", in P.A. Clark (ed.), *Contemporary Issues in Bioethics*, InTech, 2012, pp. 83-102 [p. 84]. http://www.intechopen.com/books/contemporaryissues-in-bioethics/ethics-in-pharmaceutical-issues
[26] Noordin M. I., "Ethics in Pharmaceutical Issues", in P.A. Clark (ed.), *Contemporary Issues in Bioethics*, InTech, 2012, pp. 83-102. http://www.intechopen.com/books/contemporaryissues-in-bioethics/ethics-in-pharmaceutical-issues
[27] Ibid., p. 85.
[28] Noordin, op. cit., 2012.
[29] Noordin, op. cit., 2012.

medicine. This, however, may collide with the success of the therapy as a patient may resign from it due to a fear of the side effects.[30]

Another aspect is that pharmacists play a crucial role in choosing the **best medications** to ensure the quality of life. They need to balance different objectives such as minimising drug costs, cost effectiveness of drugs, cost utility, cost-benefit, overall cost of illness, cost consequences (pharmacoeconomics).[31] Their decisive position may raise ethical questions of **relations with pharmaceutical industry**, such as divided loyalties of doctors and pharmacists. A conflict may result from an advertising activity, gift giving and support for medically related activities such as travel to meetings, particularly in case of a sponsorship of meetings, conferences, workshops and pharmaceutical support for continuing medical education.[32]

3.1.2 Interaction with other medical professionals

The ethical issue may arise in the situation when a pharmacist only assists a physician in a therapy, but is not allowed to comment on shortcomings involving other professionals.[33]

3.2 Community Pharmacy Practice

3.2.1 Dispensing of drugs

The role of the pharmacists is dispensing a medicine in a professional manner. This means providing adequate information on the appropriate drug dosage based on various factors, side effects, warnings, precautions and contraindications, interactions with other medicines or food etc.[34] Most of the legal regulations allow pharmacists to refuse selling a medicine, which may put a patient's life or health at risk according to their professional judgment.[35] As far as this regulation does not raise controversy, some countries allow pharmacists to refuse dispensing a drug because of their **personal beliefs**[36] (e.g. pharmacists' religion and prescribing contraceptives). In such situation, moral values of a pharmacist remain in conflict with autonomy of a patient, and sometimes even with respect for a patient's dignity. Literature emphasises a new trend of **online pharmacies**. Internet pharmacies, admittedly, increases access to medicines, lowers transaction and product costs and greater anonymity.[37] Nevertheless, some controversies arise, including potential harms caused by "cyberdoctors" and selling medications without prescriptions.[38]

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[30] Noordin, op. cit., 2012.
[31] Noordin, op. cit., 2012, p. 86.
[32] Pharmainfo.net, "Ethical Issues Concerning the Relationships Between Medical Practitioners and the Pharmaceutical Industry". http://www.pharmainfo.net/sameer-rastogi/publications/ethical-issues-concerning-relationships-between-medical-practitioners-an
[33] Noordin M. I., "Ethics in Pharmaceutical Issues", in P.A. Clark (ed.), *Contemporary Issues in Bioethics*, InTech, 2012, pp. 83-102, [p. 86]. http://www.intechopen.com/books/contemporaryissues-in-bioethics/ethics-in-pharmaceutical-issues
[34] Ibid., p. 87.
[35] Noordin, op. cit., 2012.
[36] Noordin, op. cit., 2012.
[37] Noordin, op. cit., 2012.
[38] Noordin, op. cit., 2012.

3.2.2 Prescribing of Pharmacy Only Medicines (POM)

Depending on a country regulation, pharmacists are allowed to sell some of the medicines without a prescription from a physician. Some of the 'medicines' are available also in a commercial sell. This requires setting guidelines by the authority to ensure public safety. In some countries, oral contraceptives are available without a prescription.[39] A pharmacist, therefore, has to make a decision whether to sell a medicine to youngster or not. **Self-medication and non-prescription drugs** are a new challenge in medicine as improper dosing may cause a serious harm.[40] Pharmacists have a role to play to provide a patient with adequate information about the medicine. A serious problems lies on a decision, which medication should be sold without a prescription and sufficient information about a drug, including dosage and possible side effects. Governments and a great lobby of pharmaceutical corporations have their role to play in ensuring wellbeing and safety of the public.

3.2.3 Patients' drug consultations

Pharmacists are professionals, expected to have a comprehensive knowledge on medicines and to provide the public with adequate information on a medicine in an ethical manner.[41] Most of the national regulations require pharmacists to record all the transactions, including **individual records of patients**.[42] This procedure needs to fulfil requirements of privacy and confidentiality.

3.2.4 Extemporaneous pharmaceutical preparations

Extemporaneous pharmaceutical preparations are unlicensed drugs. Most of the national regulations do not require them to be concerned with quality, stability, bioavailability, efficacy and safety.[43] There is a problem with assuring quality in extemporaneous preparations, because there are no requirements on submission for registration, and with stability of extemporaneous preparations.[44] Pharmacists need to prepare these medicines according to their professional knowledge and providing adequate information in order to avoid unintended harms.

3.3 Manufacturing of Pharmaceutical Products

Manufacturing of pharmaceutical products is regulated by a variety of laws, both at the national and international level regarding testing and ensuring quality, safety and efficacy and by marketing of drugs.[45] Manufacturing includes not only a production of medicines, but also development and licensing for use as medications.[46]

[39] Noordin, op. cit., 2012, p. 88.
[40] Noordin, op. cit., 2012.
[41] Noordin, op. cit., 2012.
[42] Noordin, op. cit., 2012, p. 89.
[43] Ibid
[44] Noordin, op. cit., 2012.
[45] Noordin, op. cit., 2012, p. 90.
[46] Ibid.

3.3.1 Quality assurance in pharmaceutical manufacturing

Quality assurance includes four aspects: quality control, production, distribution and inspections.[47] Ethics is inevitably linked to quality assurance and requires an effective management of an organisation but also of a whole business process. It focuses on prevention.[48]

3.3.2 Good manufacturing practice

Good manufacture practice is part of a quality assurance.[49] The system should be design in a way ensuring identification of any batch of the product and that 'complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence of the defect'.[50] Corrective and preventive measures should be implemented.[51]

3.3.3 Good storage practice and good distribution practice

Any actors dealing with the storage and distribution of pharmaceutical products are ethically responsible. These actors include manufacturers of finished products, brokers, suppliers, distributors, wholesalers, traders, transport companies and forwarding agents.[52] The problem that may occur is **tracking a supply chain and identifying an actor responsible** for harm. Good storage is especially crucial in case of vaccines, where the improper treatment may affect safety, efficacy and quality of a product.[53]

3.3.4 Handling Product Complaints and Product Recalls

Pharmacists are the first to react for product **safety alerts** if a product does not fulfil the safety specifications. If a product may cause a serious hazard to consumers, pharmacists should inform public officials and disseminate the safety alert.[54] In such situation, an adequate reaction of public officials is crucial to **ensure public health and safety**. However, relations between the state and pharmaceutical industry may raise ethical questions. An extreme example is when a company advocates for hiding the risk from society.

4 Wholesale, Supply, Import and Export of Drugs

The overall concern in a supply chain is that some of the **pharmaceutical products may be misused**, threatening health, safety, or even life of society. It is relevant for dangerous drugs such as morphine, and for psychotropic substances. The import and export of dangerous drugs should be strictly controlled, monitored and authorised.[55]

[47] Noordin, op. cit., 2012, pp. 90-91.
[48] Ibid.
[49] Noordin, op. cit., 2012.
[50] Noordin, op. cit., 2012.
[51] Noordin, op. cit., 2012.
[52] Noordin, op. cit., 2012, p. 92.
[53] Ibid.
[54] Noordin, op. cit., 2012.
[55] Noordin, op. cit., 2012, pp. 93-94.

5 Research and Clinical Trials

In the European context, a clinical trial according to the Clinical Trial Directive of the European Parliament and the Council, is:

any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.[56]

Overall objective of a clinical trial should be added value; hence 'enhancement of health or knowledge must be derived from the research -positive contribution to knowledge about health and well being'.[57] Clinical trials should be conducted in a transparent manner, which results should serve for the good of humanity.[58]

Research should be well planned, appropriately designed and ethically approved by ethics committee, especially when an **animal or human subject** is involved in research. One of the greatest ethical problems in pharmaceutics is that companies invest in drugs that are likely to be more lucrative in their sales. Pharmaceutical companies prefer to invest in developed countries' diseases, while diseases such as AIDS are not of a particular interest, because the vast majority of AIDS sufferers are from poorer countries, and cannot afford treatment (question of resource allocation).[59]

5.1 Preclinical Research

Preclinical research is a study of a product before it is approved for studies on human subjects. In many cases, preclinical studies involve **research on animals**, which as such raises controversies. In 1959, William Russell and Rex Burch published *The Principles of Humane Experimental Technique* identifying the basic principles guiding animal use in research, teaching and testing.[60] The '3Rs' have become a global standard in animal research. These principles are as follows:

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[56] European Parliament and the Council, "Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" (the Clinical Trials Directive). http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm.
[57] Torres, C.E., "Ethical Issues in Clinical Trials", Forum for Ethical Review Committees in Asia and the Western Pacific. http://www.jirb.org.tw/DB/File/Download/970128-01_Ethics%20Issues%20in%20Clinical%20Research_Benjamin%20Kuo.pdf
[58] Noordin, M. I., "Ethics in Pharmaceutical Issues", in P.A. Clark (ed.), *Contemporary Issues in Bioethics*, InTech, 2012, pp. 83-102 [p. 97]. http://www.intechopen.com/books/contemporaryissues-in-bioethics/ethics-in-pharmaceutical-issues
[59] Noordin M. I., "Ethics in Pharmaceutical Issues", in P.A. Clark (ed.), *Contemporary Issues in Bioethics*, InTech, 2012, pp. 83-102 [p. 94]. http://www.intechopen.com/books/contemporaryissues-in-bioethics/ethics-in-pharmaceutical-issues
[60] Novo Nordisk, "Bioethics in action: Animals in pharmaceutical research and development", p. 5. http://www.novonordisk.com/images/science/Bioethics/Downloads/Bioethics_Animals%20UK_25-09.pdf

- Reduce the number of animals used to obtain the same results,
- Refine the living conditions for the animals or
- Replace the animals by using *in vitro* methods.

5.2 Clinical Trials for New Drugs

Clinical trials include research on trial on **human subjects** in the last phase of research. Clinical trials deal with human beings, therefore they have to be carried out with respect for human rights and dignity of people participating in clinical trials. According to ICH GCP Guideline:

A trial should be initiated and continued only if anticipated benefits justify the risks. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.[61]

The trail should be conducted upholding the principles of:

- Respect for patient autonomy
- Informed consent prior to participation in trial
- Privacy protection
- Confidentiality (e.g. in publication or dissemination of data and results)
- Opportunity to withdraw
- Well-being monitored

Literature argues that participation in the trial should be voluntary where informed consent is obligatory. Voluntary character and informed consent may be questioned if we take into consideration **trials including children, people with disabilities, or conducting trails in developing countries**. The history only confirms these concerns. Striving for high ethical standard of multi-national clinical trials, they should be regulated with respect to the following principles:[62]

- Social Value
- Scientific Validity
- Fair Selection of Subjects & Communities
- Favourable Risk-Benefit Ratio
- Independent Review
- Individual Informed Consent
- Respect for Enrolled Subjects & Communities
- Collaborative Partnership

[61] INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE ICH HARMONISED TRIPARTITE GUIDELINE GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1) Current Step 4 version dated 10 June 1996.
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf

[62] A list based on the presentation of Torres, C.E., "Ethical Issues in Clinical Trials", Forum for Ethical Review Committees in Asia and the Western Pacific. http://www.jirb.org.tw/DB/File/Download/970128-01_Ethics%20Issues%20in%20Clinical%20Research_Benjamin%20Kuo.pdf

6 Marketing of Pharmaceutical Products

Marketing of pharmaceutical products is of serious ethical concerns. Companies' sales representatives should be 'adequately trained and possess sufficient medical and technical knowledge to present information about the products in an accurate and responsible manner'.[63] Sales representatives are not allowed to exaggerate the capabilities of the product.[64] Marketing of pharmaceutical products may bring potential risks in relation between pharmaceutical company, sales representative, pharmacists and physicians. As was already mentioned above, this risk is related to gift giving by the companies, support for medically related activities such as travel to meetings, particularly in case of a sponsorship of meetings, conferences, workshops and pharmaceutical support for continuing medical education.[65]

6.1 Complementary & Alternative Medicines

Complementary and alternative medicines are 'health practices that have the component of pharmaceutical preparations, dietary supplements, and traditional forms of health practice such as acupuncture, Chinese medicine, homeopathy, etc.[66] However, ensuring efficacy of these medicines is extremely hard.

6.2 Advertising

There is a serious question of providing consumers and/or physicians and pharmacists with free samples or medicines.[67] Furthermore, there is a great discussion on the **real cost of medicines**. Widely advertised drugs will be more costly to the consumers, because of the expenditure on advertisements.[68] As a result, the consumers pay advertisement costs.[69]

6.3 Intellectual Property

The ethical question that arises is related to licensing, **patents and respect for intellectual property laws**. Intellectual property regulations strive for protecting intellectual goods and services of creators and producers by granting them certain time-limited rights to control the production and sales.[70] On the one hand, property rights are incredibly important individual human rights. On the other hand, patents emerged as a great **challenge for the principles of justice, including fairness, equality, inclusion and non-discrimination**, and can even lead to the violation of human rights. It is because patents not only protect intellectual property of creators and producers, but are also a great source of profits. It is worth quoting 't Hoen:

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[63] Noordin, M. I., "Ethics in Pharmaceutical Issues", in P.A. Clark (ed.), *Contemporary Issues in Bioethics*, InTech, 2012, pp. 83-102 [p.98]. http://www.intechopen.com/books/contemporaryissues-in-bioethics/ethics-in-pharmaceutical-issues
[64] Ibid.
[65] Pharmainfo.net, "Ethical Issues Concerning the Relationships Between Medical Practitioners and the Pharmaceutical Industry". http://www.pharmainfo.net/sameer-rastogi/publications/ethical-issues-concerning-relationships-between-medical-practitioners-an.
[66] Noordin M. I., "Ethics in Pharmaceutical Issues", in P.A. Clark (ed.), *Contemporary Issues in Bioethics*, InTech, 2012, pp. 83-102 [p.100]. http://www.intechopen.com/books/contemporaryissues-in-bioethics/ethics-in-pharmaceutical-issues
[67] Ibid.
[68] Noordin, op. cit., 2012, p 100.
[69] Ibid.
[70] Noordin, op. cit., 2012, p. 101.

The reasons for the lack of access to essential medicines are manifold, but in many cases the high prices of drugs are a barrier to needed treatments. Prohibitive drug prices are often the result of strong intellectual property protection. Governments in developing countries that attempt to bring the price of medicines down have come under pressure from industrialised countries and the multinational pharmaceutical industry.[71]

Patents are a great challenge especially for developing countries. Patent-holder, e.g. a pharmaceutics company, has monopolistic control over the usage and sale of a drug.[72] Hence, it can decide on the prices of medicines. Intellectual property is based on TRIPS (Agreement on Trade-Related Aspects of Intellectual Property Rights) within the WTO (the World Trade Organisation) system.[73] Developing countries are under pressure from more powerful countries and trans- and multi- national corporations (TNCs MNCs) to implement patent regulations that favour these corporations to accept and go beyond requirements of regular TRIPS.[74] These new strict regulations limit possibility to produce and disseminate **generics**,[75] cheaper alternatives for patented medicines manufactured by international corporations. In this way, access to medication is limited.

6.4 Academic Freedom and Professional Autonomy

Academic freedom and professional autonomy is a great challenge in terms of funding.

Industry-sponsored research may cause ethical questions. In any research, 'a scientist must have freedom to inform the subjects and patients and the scientific community about any concerns with respect to the treatment under review'.[76] The company may disagree with the results of research and strive for hiding or deceive them. Disagreement, however, should be expressed in a forum during an open and transparent debate.[77] Companies may also want to influence researchers to conduct research towards their expectations and indicate that the results should confirm their expectation. This practice may limit academic freedom and professional autonomy. This refers also to preventing from publishing articles, where reviewers and editors may have financial or personal relationships with organisations that could influence their actions (conflict of interests).[78]

[71] 'T Hoen, E.F.M., "TRIPS, Pharmaceutical Patents and Access to Essential Medicines: Seattle, Doha and Beyond", 2003. http://cdrwww.who.int/intellectualproperty/topics/ip/tHoen.pdf.
[72] Joseph, S., "Pharmaceutical Corporations and Access to Drugs: 'The Fourth Wave' of Corporate Human Rights Security", *Human Rights Quarterly,* 25, 2, May 2003, pp. 425-452, [p. 428].
[73] Ibid., p. 429.
[74] 'T Hoen, op. cit., 2003.
[75] "Parallel imports are cross-border trade in a patented product, without the permission of the manufacturer or publisher. Parallel imports take place when there are significant price differences for the same good in different markets" in 'T Hoen, op. cit., 2003.
[76] Glancy, G. D., R. J. O'Shaughnessey, "Ethics in Psychopharmacological Research". http://ww1.cpa-apc.org/Publications/Archives/Bulletin/2002/october/glancy.asp
[77] Ibid.
[78] Glancy, op. cit.

7 Organisations

- European Federation of Pharmaceutical Industries and Associations (EFPIA) http://www.efpia.eu/
    - *EFPIA brings together 33 European national pharmaceutical industry associations as well as 40 leading companies undertaking research, development and the manufacture in Europe of medicinal products for human use.*
- The International Federation of Pharmaceutical Manufactures and Associations (IFPMA) http://www.ifpma.org/
    - *Founded in 1968, the IFPMA is a global, non-profit, nongovernmental organisation. With members across the globe and a secretariat based in Geneva, Switzerland, the IFPMA represents the research-based pharmaceutical industry, including the biotechnology and vaccine sectors.*
- World Health Organisation (WHO) http://www.who.int/en/
    - *WHO is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.*
- Pharmaceutical Medicine Ethics Council (PMEC) of the International Federation of Associations of Pharmaceutical Physicians & Pharmaceutical Medicine (IFFAPP) http://ifapp.org/Ethics/About-pmec
    - *PMEC members are appointed by the IFAPP Officers, Executive Committee and/or the IFAPP House of Delegates to provide independent medical scientific ethical advice on Pharmaceutical Therapeutics Development to the IFAPP Executive Committee [IFAPP] on the safety, quality and performance of Pharmaceutical development of drugs and devices, including issues relating to manufacture, preclinical and clinical research, pre-market conformity assessment and post marketing monitoring.*
- UK Department of Health
- King's Fund Forum for Consensus and Controversies in Medicine
    - *Its purpose is to stimulate good practice and innovation in health care.*
- Medicines and Healthcare Products Regulatory Agency (MHRA) http://www.mhra.gov.uk/Aboutus/index.htm
    - *The MHRA is responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe.*

- National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.ncchta.org/
    - *To create a research system that provided reliable and relevant information to help inform decisions on health policy, clinical practice and the management of services.*
- National Horizon Scanning Centre http://www.haps.bham.ac.uk/publichealth/horizon/
    - *The National Horizon Scanning Centre aims to provide advanced notice to the English Department of Health and national policy makers of selected key new and emerging health technologies that might require evaluation, consideration of clinical and cost impact or modification of clinical guidance around 2-3 years prior to launch on the National Health Service. The scope of the horizon scanning activity includes pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitation and therapy, and public health and health promotion activities.*
- AFSSAPS (Agence Française de Securité Sanitaire des Produits de Santé) http://www.afssaps.fr/Les-contacts-utiles-a-l-Afssaps#Mail
    - *This is the authority for all safety decisions taken concerning health products from their manufacturing to their marketing.*
- College des Economistes de la Sante-CES http://www.perso.wanadoo.fr/ces/
- Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT) http://cedit.aphp.fr/english/index_present.html
    - *The CEDIT is a hospital-based agency for the assessment of medical technology.*
- European Health Economics SAS http://www.medscinet.com/ehe/fr
    - *This is a consultancy specialising in economic evaluations of health interventions.*
- Haute Autorité de santé (HAS) http://www.has-sante.fr
    - *Its purpose is to improve the quality of care delivered to patients through measures such as the production of good practice guidelines, the development of disease management programs for chronic conditions, continuing professional development (CPD), and accreditation of health care organisations.*
- L'Agence Nationale pour l'Accreditation et l'Evaluation en Sante
    - *Its purpose is to promote and develop health technology assessment projects.*
- Mapi-Trust http://www.mapi-trust.org

  - *This is a non-profit organisation facilitating access to information in the fields of Patient-Reported Outcomes (PRO) and Pharmaco-Epidemiology, promoting the use of scientific approaches in these fields and encouraging exchanges between academics, companies, and international organisations.*

- Societe Francaise d'Economie de la Sante-SFES http://www.sfes.info/
- German Agency for HTA at the German Institute for Medical Documentation and Information http://www.dimdi.de
  - *Its purpose is to implement and manage information related to Health Technology Assessment (HTA) and Evidence Based Medicine (EMB).*
- Institut fur Qualitat und Wirschaftlichkeit im Gesundheitswesen (IQWIG) http://www.iqwig.de/contact.47.en.html
  - *The Institute for Quality and Efficiency in Health Care is an independent scientific institute that evaluates the quality and efficiency of health care. The Institute investigates what therapeutic and diagnostic services are feasible and meaningful, and communicates its findings to the health care professions, patients and the general public.*
- Office of Technology Assesment of the German Parliament-MHH Hannover Medical School http://www.tab.fzk.de/home.html
  - *Its purpose is to provide technology related advice to German Parliament.*
- Health Council of the Netherlands http://www.gr.nl
  - *The Health Council of the Netherlands (Gezondheidsraad) is an independent scientific advisory body whose task is to advise Ministers and Parliament in the field of public health. Ministers ask the Health Council for advice on which to base policy decisions. In addition, the Health Council has an "alerting" function, which also allows it to give unsolicited advice.*
- Health Organisation Policy Economics (HOPE)-University of Maastricht
  - *HOPE conducts research in medical technology assessment.*
- The Netherlands Organisation for Health Research and Development (ZonMW) http://www.zonmw.nl
  - *ZonMw manages national research programmes in the areas of genomics, gene therapy, pharmaceutical research and development, vaccines and tissue engineering.*
- Institute for Medical Technology Assessment (iMTA) http://www.bmg.eur.nl/imta/

  - *The iMTA is a university-based scientific institute that conducts research in medical technology assessment, including health economics and health outcomes research.*

- Uiversity of Nymegen, School of Medicine, Medical Technology Assessment Unit http://www.ehm.kun.nl/ehm/mies/mta
- The Netherlands National Institute of Public Health and the Environment http://www.rivm.nl
- The Netherlands Organisation for Applied Scientific Research http://www.tno.nl
- UCLA Pharmaceutical Economics and Policy of the University of California, Los Angeles, Jonathan and Karin Fielding School of Public Health, Department of Health Policy and Management http://hpm.ph.ucla.edu/upcoming-events/ucla-pharmaceutical-economics-and-policy
  - *This program promotes teaching and research on issues related to pharmaceuticals and the pharmaceutical industry. It trains professionals seeking careers in the area, and supports the work of industry and government.*
- School of Public Health University of Washington http://sphcm.washington.edu/
- Pan American Health Organisation http://devserver.paho.org/
- Office of Medical Applications of Research (OMAR) http://odp.od.nih.gov/omar/
  - *The Office of Medical Applications of Research (OMAR) within the National Institutes of Health (NIH) is the focal point for evidence-based assessments of medical practice and state-of-the-science on behalf of the medical community and the public.*
- Lister Hill Center for Health Policy https://www.soph.uab.edu/listerhill
  - *This endowed Center has a university wide mission to facilitate the conduct of health policy research and to disseminate the findings of that research beyond the usual academic channels.*
- Johns Hopkins Bloomberg School of Public Health http://www.jhsph.edu/
- Institute for Healthcare Studies http://www.feinberg.northwestern.edu/ihs/index.html
  - *Its purpose is to promote, coordinate, and originate multi-disciplinary and multi-departmental research, and education for the purpose of improving safety, equity, quality, and policy in health care.*
- Department of Defense Pharmacoeconomic Center (ECRI) http://www.pec.ha.osd.mil/

- *Its purpose is to improve the clinical, economic, and humanistic outcomes of drug therapy in support of the readiness and managed healthcare missions of the MHS.*

- Agency for Healthcare Research and Quality http://www.ahrq.gov/
  - *The Agency for Healthcare Research and Quality (AHRQ) is the lead Federal agency charged with improving the quality, safety, efficiency, and effectiveness of health care for all Americans. As one of 12 agencies within the Department of Health and Human Services, AHRQ supports health services research that will improve the quality of health care and promote evidence-based decision-making.*

- Canadian Agency for Drugs and Technologies in Health CADTH http://www.cadth.ca/index.php/en/home
  - *Its purpose is to facilitate the appropriate and effective utilisation of health technologies within health care systems across Canada. To provide timely, relevant, rigorously derived, evidence-based information to decision makers and support for the decision-making processes.*

- Centre for Evaluation of Medicines http://www.thecem.net/index.php
  - *The Centre for Evaluation of Medicines (CEM) has been in operation since 1992. It is an academic research and educational unit. The CEM mission is to evaluate drug and technology use in the real world in order to improve patient health outcomes and policy decisions.*

- Drug Quality and Therapuetics Committee http://www.health.gov.on.ca/english/public/pub/drugs/dqtc.html
  - *The DQTC's key functions are to assess the suitability of drug products for government funding by evaluating the therapeutic value of drug products, interchangeability of generic drug products, value for money of drug products.*

- Health Policy, Management, and Evaluation http://www.hpme.utoronto.ca/site3.aspx
  - *The Department bridges all three levels of health care – clinical, organisational and policy – and is committed to translating innovative ideas into practices that improve health care. HPME is called upon to contribute ideas, information and analysis to discussions and decision-making at a local, regional, national and international level.*

- Pharmaceutical Benefits Advisory Committee (PBAC) http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pbs-general-listing-committee3.htm
  - *Required by the National Health Act to consider the effectiveness and cost of a proposed benefit compared to alternative therapies.*

- CDE - Center for Drug Evaluation http://www.cde.org.tw/eng/default.html
    - *Its purpose is to enhance the efficiency and quality of drug evaluation, thus promote public health and welfare including timely access to innovative medicines.*
- Pharmacoeconomics Research Unit http://healtheconomics.utoronto.ca/
    - *Pharmacoeconomics Research Unit supports the Ontario Ministry of Health and Long Term Care and Cancer Care Ontario, the Ontario Public Drug Programs (OPDP), the Committee to Evaluate Drugs/Cancer Care Ontario (CED-CCO) subcommittee and the New Drug Funding Program (NDFP) in their pharmacoeconomic (PE) needs*
- Pharmacy Law and Ethics Association http://www.rpharms.com/management--law-and-ethics/pharmacy-law-and-ethics-association.asp
    - *The Pharmacy Law and Ethics Association (PLEA) is an independent group for pharmacists who are interested in law and ethics and lawyers or ethicists who are interested in pharmacy.*
- Council for International Organisations of Medical Sciences (CIOMS) http://www.cioms.ch/
    - *CIOMS assesses and monitors of adverse drug reactions and pharmacogenetics.*
- Pharma Compliance Monitor (PCM) http://www.pharmacompliancemonitor.com/about/
    - *Pharma Compliance Monitor (PCM) is only publication that spotlights regulatory and compliance news and developments for the pharmaceutical and biotechnology communities.*
- Cancer Care Ontario's Pharmacoeconomics Research Unit https://www.cancercare.on.ca/research/pharmacoeconomicsresearchunit/
    - *In an effort to support drug policy decision making, Cancer Care Ontario established a Pharmacoeconomics Research Unit to help decision makers use health economics to make better decisions about cancer treatments.*
- World Medical Association http://www.wma.net/en/10home/index.html
- China Pharmaceutical Industry Association http://www.cpia.org.cn/en/about.html
- PharmaceuticalEthics.com http://www.pharmaceuticalethics.com/
    - *PharmaceuticalEthics.com is a specialist consultancy providing advice and education in pharmaceutical business ethics and.*

- The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/about-ispor.asp
    - *The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) promotes the science of pharmacoeconomics (health economics) and outcomes research (the scientific discipline that evaluates the effect of health care interventions on patient well-being including clinical, economic, and patient-centered outcomes) and facilitates the translation of this research into useful information for health care decision makers to increase the efficiency, effectiveness, and fairness of health care to improve health. Founded in 1995, ISPOR is a non-profit 501(c)(3) public organisation for educational and scientific purposes, as defined by the US IRS, and a non-profit research organisation under the European Commission 7th Framework Programme.*

8 Institutionalisation and international frameworks and protocols

Access to medicines is a human right expressed in the Article 12 of the UN *International Covenant on Economic, Social and Cultural Rights* ('(...) the right of everyone to the enjoyment of the highest attainable standard of physical and mental health'[79]). Therefore, the states (parties of the Covenant) must ensure that pharmaceutical system is:

- Institutionally sound
- Transparent
- Mechanisms to reduce likelihood of corruption or undue influence and
- That sufficient regulation of the pharmaceutical industry ensures "ethical" corporate behaviour.[80]

A good governance of the pharmaceutical system requires, therefore, upholding the principles of transparency, accountability, institutional pluralism, participation and rule of law.[81] As pharmaceutical industry is strictly related to the academics and regulatory bodies, the regulatory framework must capture the relations between these actors. These regulations include regulations adapted to accommodate drug innovation and development, and to protect patient and research subject safety. Regulating pharmaceutical activities focuses therefore on expenditure control, quality, and access.[82] Nevertheless, these concepts are vogue and

[79] UN General Assembly, International Covenant on Economic, Social and Cultural Rights, Adopted and opened for signature, ratification and accession by General Assembly Resolution 2200A (XXI) of 16 December 1966 entry into force 3 January 1976, in accordance with Article 27. http://www.ohchr.org/EN/ProfessionalInterest/Pages/cescr.aspx

[80] Cohen ,J. C., L. C. Esmail, "Creating Ethical Incentives for the Pharmaceutical Industry: Reality or Fantasy?", Presentation at Conference on 'Self-Regulation in the Pharmaceutical Industry – What can it achieve?', 21 April 2005. http://www.baselgovernance.org/events/past-events/self-regulation-in-the-pharmaceutical-industry-2005/self-regulation-in-the-pharmaceutical-industry-abstracts/

[81] Ibid.

[82] Maynard, A., K. Bloor, "Dilemmas in Regulation of the Market for Pharmaceuticals", *Health Affairs,* Volume 22, Nr 3, 2003. http://www2.lawrence.edu/fast/finklerm/Maynard_Bloor.pdf

ambiguous, so regulatory frameworks not always capture their nature. Regulations are directed towards influencing patients, doctors and/or industry.[83]

Pharmaceutics is a discipline regulated to some extent at different levels, international, regional and national.

Figure 1 (see Figure 1[84]) presents the levels of legislative, regulatory, and code-based compliance control mechanisms, including the 2006 and 2012 revised versions of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Code of Practice. The scheme focuses on the promotion activities; nevertheless, it can be expanded to a more general perspective.

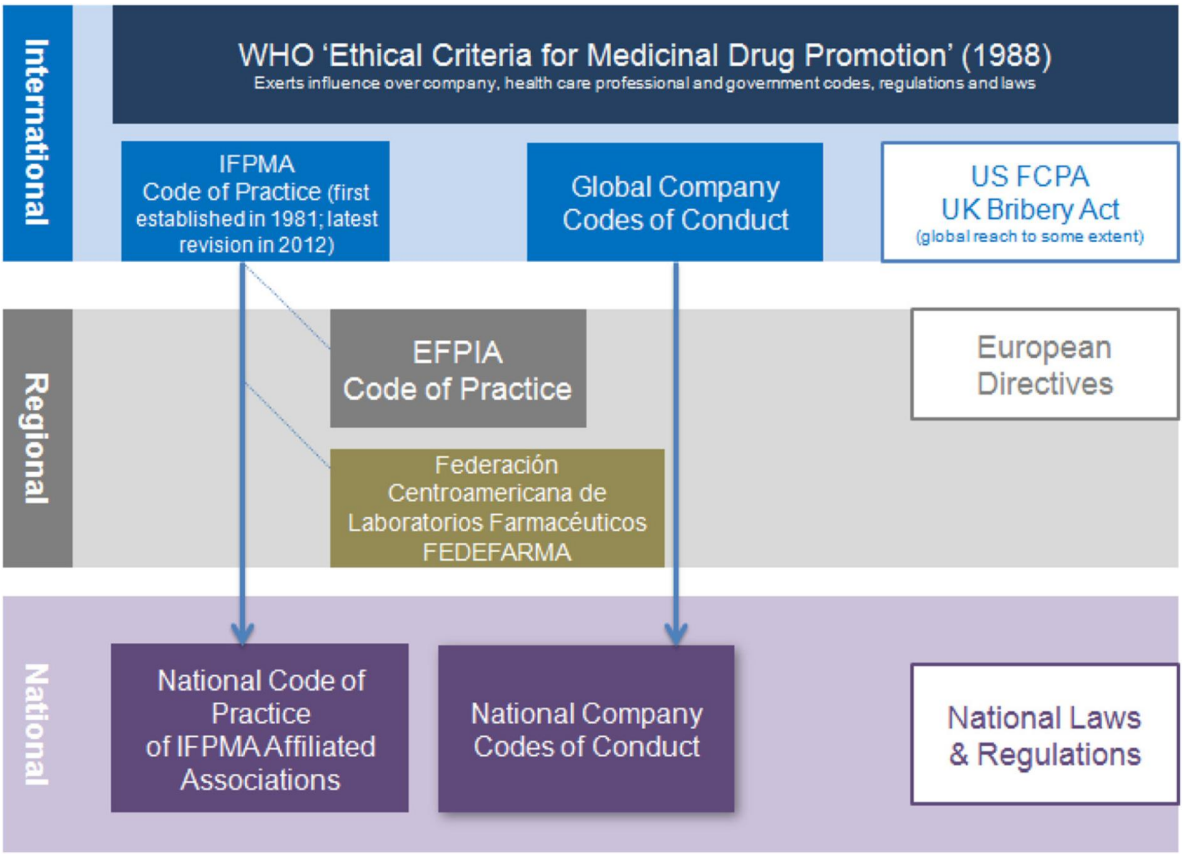

Figure 1: Summary of different code and regulatory mechanisms applying to international pharmaceutical companies

8.1 National level

The reference point for a pharmacist regarding ethical conduct is a professional code. Until today, pharmaceutics is a discipline that has not been regulated yet in one ethical code.

[83] Ibid.
[84] Source: Francer, J., J. Zamarriego Izquierdo, T. Music, K. Narsai , C. Nikidis, H. Simmonds, and P. Woods, "Ethical pharmaceutical promotion and communications worldwide: codes and regulations", *Philosophy, Ethics, and Humanities in Medicine,* 9:7, 2014, p. 2. http://www.peh-med.com/content/9/1/7

Nevertheless, various pharmaceutical activities are regulated on different levels. Most of the countries have national guidelines on the code of ethics or code of conduct for pharmacists.[85] At the national level, a pharmacy professional body, board or council safeguards the profession following a code of ethics or a code of conduct.[86] These codes of ethics or codes of conduct provide guidance on actions to be taken by a board or council in case of misconduct of pharmacists.[87] The pharmacists' codes of ethics ensure that patients/consumers 'receive the highest quality drug products with assured safety and efficacy'.[88]

National legislations towards pharmaceutics regulate such areas as: the practice of pharmacy, including professional codes of conduct, the sale of medicines, the dispensing of narcotics and other drugs of abuse, sale of drugs, quality assurance on medicine manufacturing, wholesale, supply, import and export of drugs, advertising of drugs and medical devices.[89] An important part of a regulation is devoted to standardise procedures of clinical trials including human subjects and animals. A pharmacist should dispense drugs in compliance with the provisions of the legislation of the country in which she or he practices and following professional ethical code.[90] In general, pharmacists are hold legally accountable for their actions. National legislations recognise the national pharmacopoeia (e.g. the United States Pharmacopoeia (USP), British Pharmacopoeia (BP)).[91] Pharmacopoeias define and ensure the standard for drugs in term of quality, safety and efficacy.[92]

8.2 International level

At the International level, **the World Health Organisation (WHO),** the directing and coordinating authority for health within the United Nations system, traditionally plays an important role in promoting public health and ensuring drug safety in the global market and affordability by poorer nations.[93] The WTO is 'responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends'.[94] The organisation provides recommendations and guidelines on specific topics, such as child health, HIV/AIDS, Tuberculosis, or patent safety.[95] The WTO also plays a role in encouraging developed nations to harmonise their standard requirements to facilitate drug accessibility.[96]

[85] Noordin M. I., "Ethics in Pharmaceutical Issues", in P.A. Clark (ed.), *Contemporary Issues in Bioethics*, InTech, 2012, pp. 83-102 [pp. 83-84]. http://www.intechopen.com/books/contemporaryissues-in-bioethics/ethics-in-pharmaceutical-issues
[86] Ibid.
[87] Noordin, op. cit., 2012, pp 83-84.
[88] Ibid.
[89] Noordin, op. cit, 2012, p. 85.
[90] Ibid
[91] Noordin, op. cit, 2012, p. 85.
[92] Noordin, op. cit, 2012, p. 85.
[93] Noordin, op. cit, 2012, p. 85.
[94] WTO. http://www.who.int/about/en/.
[95] WTO, "WHO guidelines approved by the Guidelines Review Committee". http://www.who.int/publications/guidelines/en/
[96] Noordin, op. cit, 2012, p. 85.

Pharmaceutics is an **industry-dominated discipline**, particularly by trans- and multi- national corporations (TNCs and MNCs). The activity of pharmaceutical companies is not regulated by law at the global level, but mostly at the national and regional level.

Companies and their associations strive for self-regulation. Most of the pharmaceutical companies have their own codes of conducts regarding different areas of pharmaceutical activities. (See Appendix 1 – List of pharmaceutical manufacturers).

Pharmaceutical industry provides an interesting example of self-regulation in marketing practices. The attempt to regulate these activities was triggered already in the 1960s, mostly due to the raising awareness of the pharmaceutical companies' misconduct and the WHO policy on the ethical criteria in marketing.[97]

It is worth mentioning the **International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)** and voluntarily adopted code of practice (first adopted as the foundation of a global approach self-regulation by the pharmaceutical industry in 1981; the last revision in 2012). The revised version of the IFPMA Code covers not only marketing practices but also interactions with healthcare professionals, medical institutions, patient organisations and marketing activities.[98]

The IFPMA was founded in 1968 and is a global, non-profit, nongovernmental organisation representing the research-based pharmaceutical industry, including the biotechnology and vaccine sectors[99] and account for about 80% of world trade in pharmaceuticals by value.[100] According to the IFPMA, self-regulation is very effective and compared with hard-law, is wider in the scope, often quicker in application and more responsive to current good practice.[101] Initially, the IFPMA code was introduced by the pharmaceutical companies in response to 'an emerging and growing public concern about the harmful effects of unethical pharmaceutical promotion on public health'.[102] However, voluntary codes of conduct are accused to be a backdoor to evade binding regulations towards companies. At that time, the industry has seen the IFPMA Code as 'an important aim (...) to avoid the more imminent threat of public regulation at the international level and to avoid, therefore, surrendering the issue unconditionally to the WHO'.[103] On the wave of this criticism, the IFPMA code was

[97] Ronit, K., V. Schneider, "Global Governance through Private Organisations", *Governance: An International of Policy and Administration*, Vol. 12, No. 3, July 1999, pp. 243-266 [p. 254].
[98] http://www.ifpma.org/ethics/ifpma-code-of-practice/about-ifpma-code-of-practice.html
[99] International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). http://ifpma.org/about-ifpma/welcome.html.
[100] The World Health Organization (WHO) and Health Action International (HAI), "Understanding and Responding to Pharmaceutical Promotion: A Practical Guide", Chapter 7, also available at http://www.politicsofmedicines.org/articles/regulation-of-pharmaceutical-promotion-why-does-regulation-matter
[101] International Federation of Pharmaceutical Manufacturers and Associations, "Annex 3: Debate on self-regulation of promotion. The case for self-regulation by the pharmaceutical industry' in 'Regulation of Pharmaceutical Promotion: Why Does Regulation Matter?" http://www.politicsofmedicines.org/articles/regulation-of-pharmaceutical-promotion-why-does-regulation-matter
[102] The World Health Organization (WHO) and Health Action International (HAI), "Understanding and Responding to Pharmaceutical Promotion: A Practical Guide", Chapter 7, available also at http://www.politicsofmedicines.org/articles/regulation-of-pharmaceutical-promotion-why-does-regulation-matter
[103] Ronit, K., V. Schneider, "Global Governance through Private Organisations", *Governance: An International of Policy and Administration*, Vol. 12, No. 3, July 1999, pp. 243-266.

described by a network of consumer health organisations, Health Action International (HAI) as:

> A bid to prevent WHO or national pharmaceutical regulatory agencies from taking stronger measures to control pharmaceutical promotion (Health Action International, 1987), and was highly critical of the code's content because of the weakness of standards and lack of active enforcement procedures (Health Action International, 1988).[104]

This criticism is not ill founded, as the Code even after the 2012 revision retains adverse publicity as its only sanction.[105] Joel Lexchin explains the weakness of this solution:

Although the Rx&D code does provide for fines, the maximum amount after three violations is CAN$50,000 a trivial amount for companies that spend tens of millions or more annually promoting their products. Furthermore, the IFPMA and R&D decisions about whether or not the codes have been broken are made either entirely by industry personnel or with only token representation from outside the industry.[106]

At the European level, **the European Federation of Pharmaceutical Industries and Associations (EFPIA)** brings together 33 European national pharmaceutical industry associations, hence organisations representing pharmaceutical manufacturers at the national level as well as 40 leading companies, research-based pharmaceutical companies, developing and manufacturing medicines in Europe for human use.[107] The EFPIA prepares position papers that provide guidelines on specific areas of pharmaceutics (http://www.efpia.eu/library/position-papers). In 1991, the EFPIA developed 'European Code of Practice for the Promotion of Medicine' (revised in 1993). The European Community welcomed this initiative enthusiastically.[108] The directive on the advertising of medical products for human use confirms this, emphasising the role of self-regulation stating that 'this article shall not exclude the voluntary control of advertising of medicinal products by self-regulatory bodies and recourse to such bodies, if proceedings before such bodies are possible in addition to the judicial or administrative proceedings'.[109]

The newest international initiative in the pharmaceutical field is **a Consensus Framework for Ethical Collaboration** signed by five global healthcare organisations on 13 January 2014.[110] The signatories are the International Alliance of Patients' Organisations (IAPO), International

[104] The World Health Organisation (WHO) and Health Action International (HAI), "Understanding and Responding to Pharmaceutical Promotion: A Practical Guide", Chapter 7, available also at http://www.politicsofmedicines.org/articles/regulation-of-pharmaceutical-promotion-why-does-regulation-matter
[105] Lexchin, J., "The case against self-regulation by industry", *Regulation of Pharmaceutical Promotion: Why Does Regulation Matter?* http://www.politicsofmedicines.org/articles/regulation-of-pharmaceutical-promotion-why-does-regulation-matter
[106] Ibid.
[107] EFPIA. http://www.efpia.eu/about-us.
[108] Ronit, K., V. Schneider, "Global Governance through Private Organisations", *Governance: An International of Policy and Administration*, Vol. 12, No. 3, July 1999, pp. 243-266 [p. 254].
[109] Art. 12 par. 4, Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use.
[110] IFPMA, "Putting patients first: five global healthcare organisations sign Consensus Framework for Ethical Collaboration", News Release,13 January 2014, Geneva. http://ifpma.org/fileadmin/content/News/2014/EN-News_Release_-_Consensus_Framework_-_13_Jan_2014.pdf

Council of Nurses (ICN), International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), International Pharmaceutical Federation (FIP), and the World Medical Association (WMA).[111] The Consensus Framework is based on five principles: putting patients first, supporting ethical research and innovation, ensuring independence and ethical conduct, and promoting transparency and accountability.[112]

Self-regulation includes not only multi-national initiatives, but also codes of conduct developed at the **national level**. For instance, **the German industry (*Bunderesverband der PharmazeutischenIndustrie (BPI)*)** elaborated its own code of conduct already in 1969.[113] In the same year, **Swiss producers and *Schweizerische Gesellschaft für Chemische Industrie (SGCI)*** developed a similar regulation. At this time, most of the national private initiatives were so called a 'VIP club', strictly reserved for producers. Nevertheless, the EFPIA code had a strong influence on these industry-driven initiatives and forced them to include experts and to establish independent bodies to oversee the market.[114] On a wave of self-regulatory initiatives, a new committee was established under the aegis of EFPIA 'to pool expertise and act as a relevant partner for the European Commission'.[115] However paradoxically, the EFPIA has not included non-industry stakeholders into the monitoring process.[116] Since many of the EFPIA members had already developed compatible codes recognised by national authorities, EFPIA used this 'self-regulatory package' to avoid a hard-law European regulation[117] and keep the control over their business.

9 Conclusions

Sceptics of the self-regulation (also in other industry branches) emphasise vague or ambiguous character of provisions that in many cases is deliberately intended. This leads to lack of effectiveness of soft law regulations. Ineffectiveness also results from a voluntary character of codes of conduct, as companies may opt out these regimes without any consequences. Furthermore, private initiatives are accused to be a backdoor to evade binding regulations towards companies and a 'VIP club' where non-industry stakeholders' perspective is not taken into account, even if they are invited, e.g. multi-stakeholder initiative. Lastly, critics call into question a classification of self-regulation as part of the law.

Despite the criticism towards self-regulation, such initiatives as the IFPMA Code or the EFPIA bring together the largest and the most powerful companies creating a forum for discussion on the global health issues. The relationship between the WHO and the pharmaceutical industry was never easy one.[118] Nevertheless, the WHO admits that in many cases self-regulation is more successful than hard-law, as public regulation is not always

[111] Ibid.
[112] IFPMA, op. cit. 2014.
[113] Ronit & Schneider, op. cit, 1999, p. 254.
[114] Ibid.
[115] Ronit & Schneider, op. cit, 1999, p. 254.
[116] Ronit & Schneider, op. cit, 1999, p. 255.
[117] Ibid.
[118] Ronit & Schneider, op. cit, 1999, p. 251.

possible to establish, or could not be the exclusive instrument of regulation.[119] Therefore, the WHO encourages private initiatives.[120]

Effective regulation of the pharmaceutical industry requires overlapping and/or complementary hard-law and soft-law regulations, and the ability of national authorities to monitor private arrangements (e.g. report or sanction in case of incompliance with the IFPMA Code).[121] Currently, the most serious problem of global governance is monitoring of companies' cross-border activity in the countries with poor regulatory framework. This includes compliance with voluntary codes of conduct that companies declared to apply in their operations.

9.1 Regional level - Europe

In the European context, the main directives regulating pharmaceutical activity include the followings:

- DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;
- DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use;
- COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.
- The Council of Europe's Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (ETS No. 123) revised and adopted in 2006

These directives focus mostly on **clinical trials.** They are followed by internationally recognised frameworks and guidelines on clinical trials such as:

- The Declaration of Helsinki,
- The Nuremberg code,
- The Belmont report
- The International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice

[119] Ibid.
[120] Ronit & Schneider, op. cit, 1999, p. 251.
[121] Ronit & Schneider, op. cit, 1999, p. 251.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf.

- The rules governing medicinal products in the European Union http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm.

Regarding defining and ensuring the standard for medicines in term of quality, safety and efficacy, at the European level European Pharmacopoeias is responsible for facilitating the free movement of medicinal products in Europe, ensuring the quality of medicinal products and their components imported into or exported from Europe.[122] Legal framework and guidelines on **quality of medicines**:

- The Convention developed by the Council of Europe on the Elaboration of a European Pharmacopoeia,
- A Protocol adopted in 1994 and amending the Convention to prepare for the accession of the European Union and defining the respective powers of the European Union and its member states within the European Pharmacopoeia Commission,
- European Union Directives 2001/82/EC, 2001/83/EC, and 2003/63/EC, as amended, on medicines for human and veterinary use. These maintain the mandatory character of European Pharmacopoeia monographs when requesting marketing authorisation (MA).
- European Commission: Quality of medicines and Good Manufacturing Practices (GMP) http://ec.europa.eu/health/human-use/quality/index_en.htm.

Other legislative issues related to pharmaceutics**:**[123]

- Transparency Directive
- Clinical Trials on Medicinal Products for Human Use
- Growth Programme in the field of Health 2014 – 2020
- Medical Devices Regulation
- In vitro diagnostic medical devices Regulation
- Access to genetic resources and the fair and equitable sharing of benefits arising from their utilisation in the Union
- eHealth Action Plan 2012-2020
- Fees payable to the EMA for the conduct of pharmacovigilance activities
- Innovative Medicines Initiative 2

[122] Eurpean Pharmacopeia. https://www.edqm.eu/en/european-pharmacopoeia-background-50.html.
[123] The list is based on the European Federation of Pharmaceutical Industries and Associations, "EU Legislation". http://www.efpia.eu/eu-legislation

- Personal Data Protection Regulation
- Community Trademark Regulation

10 Journals and conference series

10.1 Journals:

- American Journal of Bioethics - http://www.bioethics.net/
- Journal of Bioethical Inquiry - http://www.springer.com/medicine/journal/11673
- Journal of Medical Ethics - http://jme.bmj.com/
- Princeton Journal of Bioethics - http://www.princeton.edu/~pjb/
- Ethics & Medicine – International Journal of Bioethics - http://www.ethicsandmedicine.com/
- Eubios Journal of Asian and International Bioethics - http://www.eubios.info/
- South African Journal of Bioethics and Law - http://www.sajbl.org.za/
- Health Affairs - http://www.healthaffairs.org/1500_about_journal.php
- The Journal of Law, Medicine & Ethics - http://onlinelibrary.wiley.com/doi/10.1111/jlme.2013.41.issue-4/issuetoc
- New England Journal of Medicine - http://www.nejm.org/
- The Pharmaceutical Journal - http://www.pharmpress.com/product/00316873/pj
- Journal of Pharmaceutical Policy and Practice - http://www.joppp.org/content/6/1/11
- Asian Journal of Pharmaceutical and Clinical Research - http://www.ajpcr.com
- International Journal of Pharmaceutical Sciences and Drug Research - http://www.ijpsdr.com/
- The Internet Journal of Law, Healthcare and Ethics - http://www.ispub.com/IJLHE
- International Journal of Pharmaceutical Sciences and Research - http://www.ijpsr.com/aboutus.htm
- European Journal of Pharmaceutics and Biopharmaceutics - http://www.sciencedirect.com/science/journal/09396411

- International Journal of Pharmaceutical and Healthcare Marketing - http://www.emeraldinsight.com/journals.htm?articleid=1742592
- American Journal of Pharmaceutical Sciences and Nanotechnology - http://ajpsn.uscip.us
- Journal of Pharmacy & Pharmaceutical Sciences - http://ejournals.library.ualberta.ca/index.php/JPPS
- Journal of Ethics in Mental Health - http://www.jemh.ca/

10.2 Conference series:

- Pharmaceutical Regulatory and Compliance Congress - http://www.pharmacongress.com/
- Eighth International Pharmaceutical Compliance Congress - http://www.internationalpharmacongress.com/
- Pharmaceutical Law Conference - http://www.healthcareconferences.com.au/healthcare-conferences/healthcare/pharmaceutical-law-conference
- Corporate Compliance & Transparency in the Pharmaceutical Industry - http://pharma.flemingeurope.com/corporate-compliance-conference
- International Conference on Opioids - http://opioidconference.org/Home_Page.html
- American Society for Bioethics and Humanities Annual Meeting - http://www.asbh.org/meetings/annual/annualmeeting.html
- International Conference on Ethics Review of Clinical Research in Pharmaceuticals - http://www.coe.int/t/dg3/healthbioethic/conferences_and_symposia/Programme_Mow_enx.pdf
- Canadian Bioethics Society's annual conference - https://www.bioethics.ca/ethics/conference.html
- UNESCO Chair in Bioethics World Conference on BIOETHICS, MEDICAL ETHICS & HEALTH LAW - https://www.isas.co.il/bioethics2013/
- International Bioethics Forum - http://www.btci.org/bioethics/
- World Congress on Bioethics - http://bioethicsmexico.mx/

11 Key publications

- The Future of Drug Discovery: Who Decides Which Diseases to Treat? by Tamas Bartfai and Graham V. Lees (May 18, 2013) http://www.amazon.com/The-Future-Drug-Discovery-Diseases-ebook/dp/B00D6LW02G/ref=sr_1_2?ie=UTF8&qid=1397166854&sr=8-2&keywords=ethics+pharmaceutics

- Global Pharmaceuticals: Ethics, Markets, Practices by Adriana Petryna, Andrew Lakoff and Arthur Kleinman (Mar 15, 2006) http://www.amazon.com/Global-Pharmaceuticals-Ethics-Markets-Practices/dp/082233741X/ref=sr_1_sc_1?ie=UTF8&qid=1397166854&sr=8-1-spell&keywords=ethics+pharmaceutics

- Ethics and the Pharmaceutical Industry by Michael A. Santoro and Thomas M. Gorrie (Jul 23, 2007) http://www.amazon.com/Ethics-Pharmaceutical-Industry-Michael-Santoro/dp/0521708885/ref=sr_1_sc_2?ie=UTF8&qid=1397166854&sr=8-2-spell&keywords=ethics+pharmaceutics

- Pharmaceutical Ethics by Sam Salek and Andrew Edgar (Oct 11, 2002) http://www.amazon.com/Pharmaceutical-Ethics-Sam-Salek/dp/0471490571/ref=sr_1_sc_4?ie=UTF8&qid=1397166854&sr=8-4-spell&keywords=ethics+pharmaceutics

- Hooked: Ethics, the Medical Profesion, and the Pharmaceutical Industry by Howard Brody (Dec 1, 2006) http://www.amazon.com/Hooked-Medical-Profesion-Pharmaceutical-Industry/dp/0742552187/ref=sr_1_sc_5?ie=UTF8&qid=1397166854&sr=8-5-spell&keywords=ethics+pharmaceutics

- Case Studies in Pharmacy Ethics by Robert Veatch and Amy Haddad (Mar 26, 2008) http://www.amazon.com/Studies-Pharmacy-Ethics-Robert-Veatch/dp/0195308123/ref=sr_1_sc_6?ie=UTF8&qid=1397166854&sr=8-6-spell&keywords=ethics+pharmaceutics

- The Law and Ethics of the Pharmaceutical Industry by M.N.G. Dukes (Dec 31, 2005) http://www.amazon.com/The-Law-Ethics-Pharmaceutical-Industry/dp/0444518681/ref=sr_1_sc_7?ie=UTF8&qid=1397166854&sr=8-7-spell&keywords=ethics+pharmaceutics

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- The New Medicines: How Drugs are Created, Approved, Marketed, and Sold by Bernice Z. Schacter (Dec 30, 2005) http://www.amazon.com/The-New-Medicines-Approved-Marketed/dp/027598141X/ref=sr_1_29?ie=UTF8&qid=1397167181&sr=8-29&keywords=ethics+pharmaceutical

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13 Appendix 1

The list of pharmaceutical manufacturers[124]

- Adams Laboratories
- Abbott Laboratories
- Acadia Pharmaceuticals
- Aeterna Laboratories
- Agfa, Inc
- Alcon
- Allergan Pharmaceuticals
- Alliance Pharmaceutical Corp.
- Allos Therapeutics
- ALZA Corporation
- Amgen, Inc
- Amylin Pharmaceuticals, Inc
- Applied Genetics
- Ariad
- Astra Zeneca
- Barr Laboratories
- BASF Group
- Bausch and Lomb
- Baker Norton
- Bayer, Inc
- Becton Dickinson (BD)
- Berlex Laboratories
- Janssen Pharmaceutica
- Johnson & Johnson, Inc
- Kendle, Inc
- King Pharmaceuticals
- Konsyl Pharmaceuticals, Inc
- LabCorp, Inc
- Lampire Biological Laboratories
- 3M Pharmaceuticals
- MGI Pharma
- Mabtech AB
- MedImage, Inc.
- MEDMarket Virtual Industrial Park
- Merck & Co., Inc.
- Merck KGaA, Inc
- Merck Singulair
- Meridian Medical Technologies
- Monsanto Corporation
- Morton Grove Pharmaceuticals
- MWG BIOTECH GmbH
- Mylan Pharmaceuticals Inc
- Myriad Genetics Laboratories, Inc.
- Neoprobe Corporation

[124] The list based on the Samfor University, McWorther School of Pharmacy, http://pharmacy.samford.edu/msop_dic.aspx?id=2147483879.

- Bertek
- Berna Products
- Beutlich Pharmaceuticals
- Biogen, Inc
- BlaineBaxter Healthcare Corp
- Bioscan, Inc.
- Boehringer Ingelheim Pharmaceuticals, Inc
- Braun Medical
- Brisol-Meyers Squibb Co
- Celgene
- Cell Genesys
- Centocor
- Chemical Institute of Toxicology
- Chiron Therapeutics
- Chugai Pharma
- Codonics Inc
- CollaGenex
- CTI, Inc
- CytogenCorporation
- Cytokines
- Datagen Ltd
- Del Laboratories
- Dermik Laboratories
- Diagnostix Plus, Inc.
- Dartmouth
- Dow Hickam Pharmaceuticals
- Nephron Pharmaceuticals
- Novartis, Inc
- Novo Nordisk A/S, Inc
- Nutramax Laboratories, Inc
- Omicron Biochemicals, Inc.
- Ortho-McNeil
- Ortho Biotech
- Otsuka America Pharmaceutical
- OXiGENE
- Paddock Laboratories
- Parnell Pharmaceuticals, Inc
- Perkin-Elmer
- Pharmaceutical Specialties
- Pfizer,Inc.
- Pharmaceutical Profiles-UK
- PharMingen Inc.
- PhRMA:
- Pliva
- Polaroid: Medical Devices
- P and G
- Protein Design Labs, Inc.
- ProZyme:Manufacturer of Protein & Enzymes
- Purdue
- QuadraMed Corporation
- Research Genetics
- Roche Group, Inc

- Dupont Pharmaceutical
- Eli Lilly and Company
- Endo Pharmaceuticals
- Enzon
- Eon Labs
- Eppendorf, Inc
- Ethex
- Ferring
- Fougera
- Gebauer
- GE Medical Systems, Inc
- Genaera Corporation
- Genentech, Inc.
- Genetronics Biomedical,Inc
- Genesis Nutrition
- Genta
- Genzyme Corporation
- Gilead Sciences
- Glades Pharmaceutical
- GlaxoSmithKline
- Hampton Research
- HemoStat Laboratories
- Hoechst Pharmaceuticals
- Hollister-Stier
- Imation Corporation
- ImClone Systems
- Roxane Laboratories, Inc
- Sanofi-Aventis
- Savage Laboratories
- Schein
- Schering-Plough
- Schwarz Pharma
- SEQwright, Inc
- Sequus Pharmaceuticals
- Sepracor
- Shaw Pittman
- Siemens In the USA
- Sigma-Tau Pharmaceuticals, Inc
- Signature Immunologics
- Sirna
- Solvay Pharmaceuticals, Inc
- Sosei Company, Ltd.
- Talent s.r.l
- Takeda Chemical Industries
- Tanox Biosystems, Inc.
- Taro Pharmaceutical Industries Ltd.
- Teva Pharmaceuticals USA
- Titan Pharmaceuticals
- UCB Pharma
- Upsher-Smith Laboratories
- Valeant
- Vertex Pharmaceuticals Incorporated

- ImmunoGen
- Immunomedics, Inc.
- ImmunoScience, Inc.
- Incyte Pharmaceuticals, Inc
- Innovative Research of America
- INOVA Diagnostics, Inc
- Isis Pharmaceuticals, Inc.
- Vion Pharmaceuticals
- Watson Laboratories
- Worthington Biochemical Corporation
- Wyeth-Ayerst Laboratories
- YSI Incorporated
- Xoma Pharmaceuticals, Inc
- Zila