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Clinical trials

Emilio N. Vogelius

Legal frame

The Argentine Republic adopted a federal System.

Due to such system health matters fall under national, provincial or the City of Buenos Aires, regulation scope.

Each system has the possibility to issue individual regulations that would apply only in its territory.

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Rules to consider

The rules to be considered are:

1. Constitution
2. Civil and Commercial National Code
3. Law regulating Patients' Rights
4. Disposition of ANMAT 6677 (The local board of Health is referred to as ANMAT) partially modified by Disposition 4008/17.

If the trial is performed in a province or provinces, provincial rules would apply

Most of our speach will be focused in the latter.

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Disposition 6677/2010

Disposition 6677 issued by ANMAT follows a previous identified as Disposition 5330 that was in place since 1997, until its replacement by Disposition 6677 on November 1st. 2010.

The correct name of Disposition 6677 is: Good Clinical Practice Regulation for Clinical Pharmaceutical Studies. (GCP)

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General controls

Clinical trials to be performed in Argentina fall under several controls:

1. ANMAT has to approve the trial and it further keeps title to audit its execution
2. Research Ethics Committees have identical faculties.
3. There should be no relation between the Ethics Committee and the Sponsor.

The different provinces and the City of Buenos Aires have their own Central Ethics Committees to accredit Institutional Ethics Committees in their jurisdiction. Since 2016 there is a National Advisory Ethics Committee in place that assist Central Ethics Committees.

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Trials that request approval

All trials are subject to be approved, exception made of certain phase 4 trials.

Phase 4 trials are to be approved when products already commercialized are subject to relevant modifications, such as a new strength or dosage form.

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Scope of the speach

We will consider in this speach certain aspects that create tension between local and compliance regulations or that may be subject to problems, such as:

1. The informed consent
2. The investigators qualifications
3. Certain matters related to subjects
4. The supply of the product

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Informed Consent Form

The Informed Consent Form is highly regulated. It should be highlighted that the informed consent is used to inform the subject not only for the purpose of protecting the investigator or the sponsor.

Mandatory use of specific phrases is established by Disposition 6677/2010. Of course, forms ought to be signed.

Exception made of cases in which a study potential participant, is economic, socially, cultural or educationally vulnerable, a witness signature is not required. In the cases mentioned above the witness has to be unrelated to the investigator and his/her team.

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Signature of the informed consent (general scope)

Due to modifications resulting from the New National Civil and Commercial Code we will refresh the identification of who should be giving the consent:

1. Majority of age is reached at 18 years old.
2. Minors up to 13 years old require the consent to be signed by who exercises the parental rights.
   a. Both parents. A non-settled criteria accepts that the signature of one of the parents assumes the consent of the other one.
   b. Only the one that keeps such rights (cases of widows, sole parents, judicial declaration removing parental rights).
3. Minors from 13 to 16 years old should give their consent to the trial with the assistance of who keeps parental rights in trials involving high risks or invasive trials.
4. Minors older than 16 years are these who should give their consent, nevertheless to have the parental assistance registered is advisable.

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Signature of the informed consent (exceptions)

1. The sole parent that exercises custody of the minor.
2. The Court appointed representative (tutor).
3. In case of under-aged parents, these keep the parental rights, although it is advisable to request an adult grand-parent consent.
4. In case of a double bond (e.g. parents that late recognize their sons, or other situations) the main consent should be the one of the parent that exercises parental rights

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Opinion

Not all the country is socially prepared and ordered under rules as the ones established by the Congress, which are written by educated people.

Not all individuals subject to trials live in cities where advice is available.

Usually those that live in a more vulnerable environment are those more needed of medical attention.

In practice, and having the Consent signed by a witness, when dealing with vulnerable population it is convenient to highlight the vulnerability of the population involved. This could be done by the Investigator or the Ethics Committee

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Investigators

The regulations require that investigators should be knowledgeable on the matter under trial.

In our country a great number of doctors work in public hospitals. In many cases they do it for free or for a symbolic fee.

Working in public hospitals may authorize to catalog these doctors as public agents.

Compliance rules oppose to make payments to public agents.

Said situation creates a conflict which, in my opinion, is not resolved.

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Centers and investigators

It should be stated that doctors not only perform their work in hospitals, but also keep a private practice.

It should be noticed that public hospitals are an important source of potential subjects of clinical trials (cases of sickness are more usual attended in public hospitals than in private clinics).

Public hospitals can be appointed as Centers where the research is to be followed, but this does not mean that private trials can be performed in public hospitals for free.

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Centers and investigators

When appointed as Centers, public hospitals, or the Ministry of Health, or the University of Buenos Aires, as the case may be, collect for the use of its assets and space.

When Public Hospitals act as Centers an agreement is signed by the Sponsor, the Investigator, the Chief of Department of the Hospital and the Hospital Director. Public Hospitals usually have established a cost to compensate the performance of the Study.

Some Centers work through Foundations to collect the amounts to be paid in connection to the trials. This is not objected when there is a clear link between both entities.

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Payment to investigators

Payment to doctors for carrying on clinical trials is clearly allowed. It is a professional work.

However: payment should be reasonable in its amount and installments.

Never forget that doctors are potential prescribers of the products.

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Payment to patients

Disposition 6677/2010 allows to compensate the patients for all inconveniences the trial may cause.

Payments may be reasonable and cover travel expenses, accommodation and meals during the trial.

Please bear in mind that Argentina is a large country in which not all areas are of easy access and that certain areas are not duly covered by medical assistance

No payments for the mere fact of participating in the trial are allowed. Exception are payments to healthy or patient volunteers participating in Phase I investigations, which are allowed since there are no expectations for them to receive any benefit from the trial.

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Supply of products

There is no doubt that products for performing clinical trials must be supplied by the sponsors free of charge

Should the products be not authorized in the country the ANMAT when authorizing the trial would also commit to authorize the import of the necessary number of products.

If the case requires contraceptives these must also be provided. Same occurs in cases in which additional products are needed to perform the trial.

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Supply of products

An insurance coverage should also be provided by the sponsor to cover any eventual damage to the participating subjects.

The problem still not settled is until when should the trial products be supplied.

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Supply of products

Disposition 6677 including the Guidelines to be followed in Clinical Trials state that:

Participants requiring to continue their treatment after the study completion shall have access to the intervention that turned to be beneficial or to an alternative intervention or to another proper benefit, which shall be approved by the Ethics Committee for the time it decides or until such access is ensured by any other means.

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Supply of products

The investigator and the sponsor should ensure the patient that he/she will receive proper medical care in the event of injury related to his/hers participation in the study.

What can create some confusion is the time until when the product under trial should be provided or even imported.

Our interpretation is that, according to the Ethics Committee opinion, this should be provided until the participant has access to the product, or an equivalent effective treatment, by any other mean other than the provision under the terms of the trial.

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Thank you!

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INNOVATION IN THE BIOPHARMACEUTICAL INDUSTRY

Clinical Research Compliance & Its Challenges

A Closer Look to Legal Protection to Test Data in Clinical Trials

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AGENDA

I. Innovation

II. Protecting Innovation

III. How to foster Innovation?

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I. Innovation

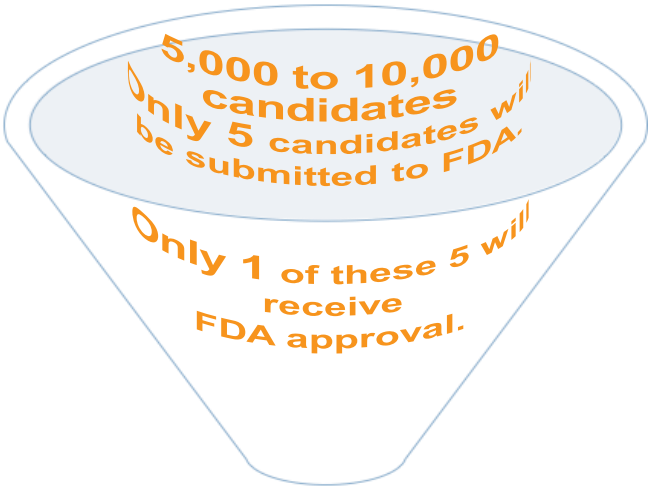
What does Innovation mean for patients? (*)

- ✓ Innovation means better Prevention
- ✓ Innovation means better Treatments
- ✓ Innovation means better Medicine

(*) 2017. Pharma Innovation Hub. Retrieved from http://www.phrma.org/advocacy/intellectual-property

I. Innovation

The Process of Innovation



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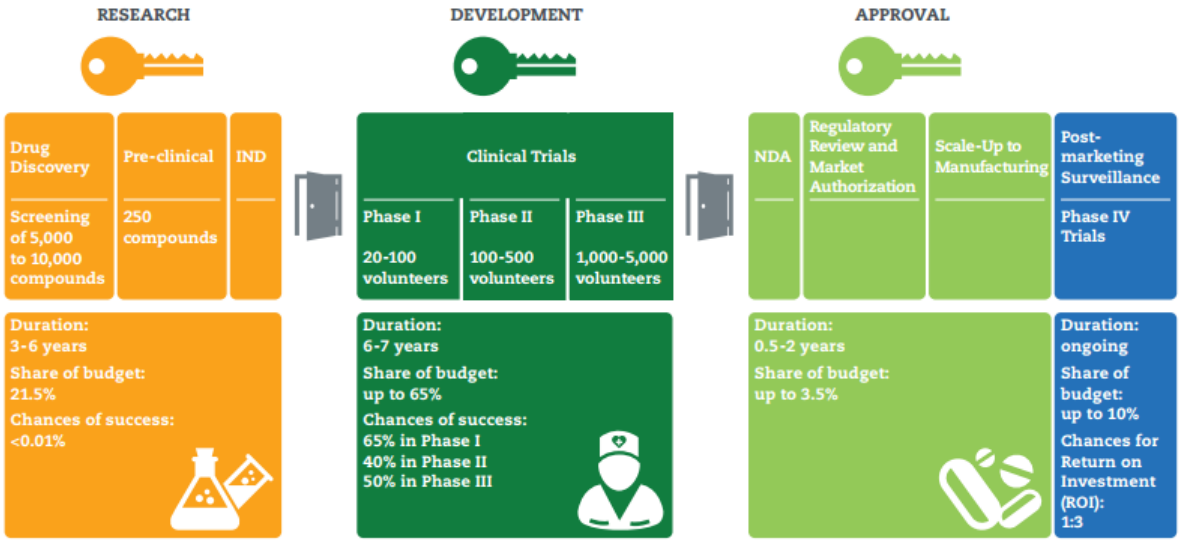
11. Protecting Innovation (*)



(*) https://www.ifpma.org/wp-content/uploads/2017/02/IFPMA-Facts-And-Figures-2017.pdf

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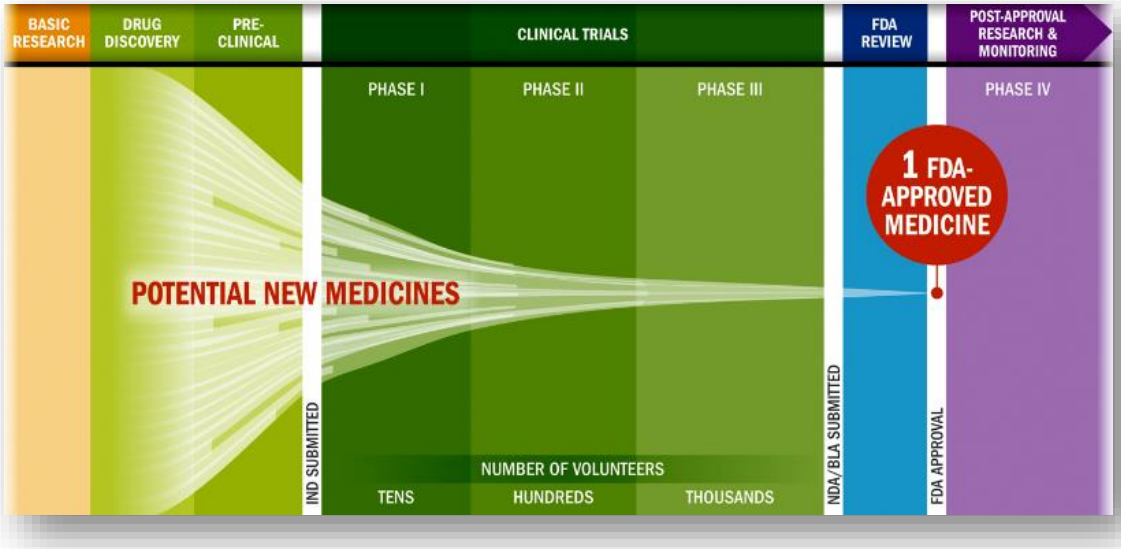
I. Innovation

The Process of Innovation (*)



(*) 2017. Phrma Innovation Hub. Retrieved from http://www.phrma.org/advocacy/research-development/clinical-trials

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II. Protecting Innovation

- Protecting proprietary test data of new medicines is a key starting point in order to create core competitiveness in pharmaceuticals and biotechnology;
- Protecting proprietary test data provides incentives beyond the traditional intellectual property protection to stimulate companies to continue investing in research and development of new drugs:
- In countries where patents are not available, protecting proprietary data becomes particularly relevant.

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II. Protecting Innovation

- Innovator obtains approval of commercialization of a drug for certain period of time;
- The regulatory agency should not access innovator´s test data, without its consent, when reviewing a filing for approval of commercialization of a generic or biosimilar requesting reliance on innovator´s data;
- Applicants of non-innovative drugs can request approval of commercialization according to their own tests of efficacy and safety;

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II. Protecting Innovation. Argentina

Dec. 150/92	TRIPS 1995	Confidentiality Law	Confidentiality Law	Resol 6677 /2010
• Decree No. 150/92: provides that as long as the product for which marketing approval is sought has been approved in any of the countries included in Annex I of Decree 150/92, any person may apply for marketing approval without time limitations, submitting minimum information (bioavailability data and a project of label, leaflet and prospect). The list of countries includes, among others, Denmark, Japan, the U.S.A., Germany, the U.K., Spain, Italy and France	• Art. 39.3: "Members, when requiring, as a condition for granting the marketing authorization of pharmaceutical or of agricultural chemical products containing a new chemical entities, the submission of undisclosed test or other data, that involves a considerable effort, shall protect such data against unfair commercial use."	• Section 4 Law 24.766: For those cases which require approval of registration or marketing authorization of products that contain new chemical entities that do not have a previous registration in Argentina or in any other country, it is compulsory to submit to ANMAT information that guarantees the efficacy and safety of the product. As long as such information includes the requirements of Section 1 and is the result of a significant technical and economical effort, it shall be protected against any unfair commercial use as it is defined in the present law and cannot be disclosed.	• Section 5: grants ANMAT the power to authorize marketing authorization of drugs previously approved without requiring the production of data on clinical trials provided the data had already been filed by the innovator.	• Section 8:The sponsor shall submit the final result within one-year period after the study termination.

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II. Protecting Innovation. Argentina

Copy  Innovator

Unfair competition

A.N.M.A.T.

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ıg Innovation. Argentina

- Test data protection (based on clinical and pre-clinical trials) is not contemplated in Argentine Legislation, thus there are no legal requirements on this regard.
- There is legal protection under Trade Secret Law (Argentine Legislation N° 24,766), which has been invoked in many legal actions but so far interpreted in a very narrow way.
- Local judiciary has been very reluctant to grant legal protection to test data so far.

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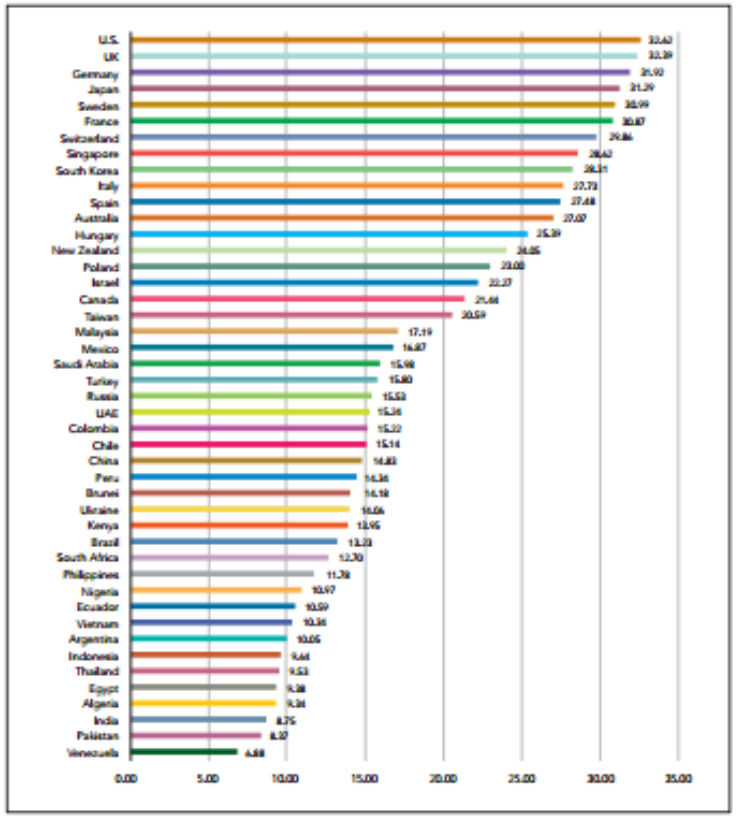

(*) http://www.theglobalipcenter.com/wp-content/uploads/2017/02/GIPC_IP_Index_2017_Report.pdf

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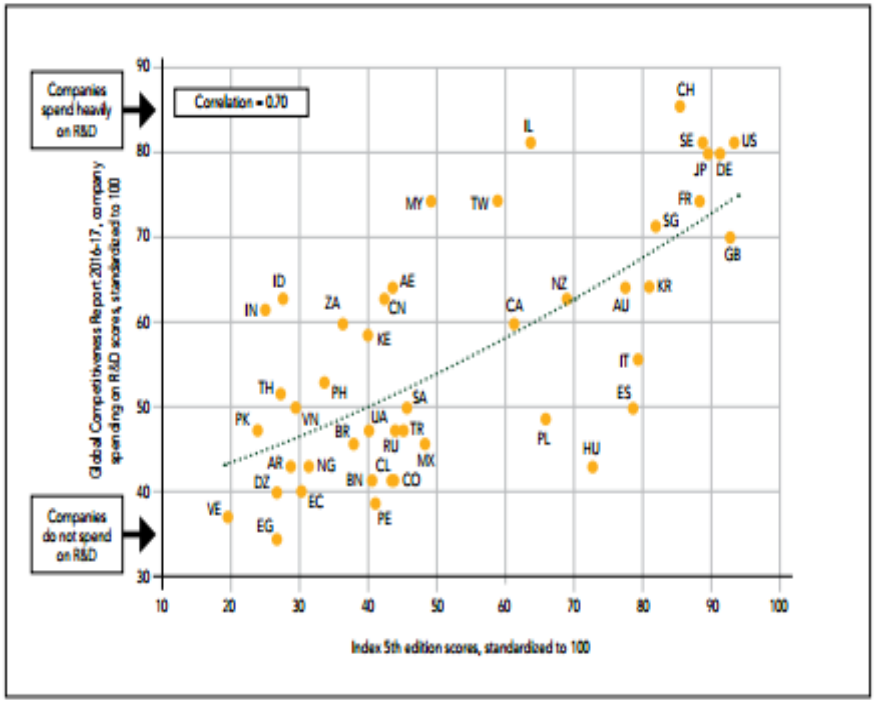

Sources: World Economic Forum/Executive Opinion Survey (2016); GIPC (2017)
Legend: AE – United Arab Emirates, AR – Argentina, AU – Australia, BN – Brunei, BR – Brazil, CA – Canada, CH – Switzerland, CL – Chile, CN – China, CO – Colombia, DE – Germany, DZ – Algeria, EC – Ecuador, EG – Egypt, ES – Spain, FR – France, GB – United Kingdom, HU – Hungary, ID – Indonesia, IL – Israel, IN – India, IT – Italy, JP – Japan, KE – Kenya, KR – South Korea, MX – Mexico, MY – Malaysia, NG – Nigeria, NZ – New Zealand, PE – Peru, PH – Philippines, PK – Pakistan, PL – Poland, RU – Russia, SA – Saudi Arabia, SE – Sweden, SG – Singapore, TH – Thailand, TR – Turkey, TW – Taiwan, UA – Ukraine, US – United States, VE – Venezuela, VN – Vietnam, ZA – South Africa.

(*) http://www.theglobalipcenter.com/wp-content/uploads/2017/02/Statistical_Annex.pdf

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III. How to Foster Innovation?

Drug research and development lead to the discovery of tomorrow's life-changing and life-saving new medicines.

Biopharmaceutical intellectual property (IP) protection, in particular, test data protection, fosters research and development.

Test data protection encourages innovative biopharmaceutical companies to invest in life-saving medicines.

Test data protection also allows companies to secure the resources for future investments in R&D, providing hope to patients who await tomorrow's innovative medicine.

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III. How to Foster Innovation?

There are three key elements for an effective test data protection system:

1. It must provide *fair* and *effective motivation* for innovation;

2. It must provide innovators *certainty* regarding their rights; and

3. It must offer test data owners *strong enforcement tools* to defend themselves against infringements to data protection rights.

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Questions?