Good Clinical Practice and Regulatory Aspects

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- Member of the Ethics Committee of Hospital Nacional Dos de Mayo

www.diahome.org

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MINISTERIO DE SALUD
INSTITUTO NACIONAL DE SALUD

- In Peru, until 2003, clinical trials were approved by the Directorate General of Health of the People, the Ministry of Health.

- Since 2004, this function was transferred to the National Institute of Health (NIH), executing public organization whose mission is the promotion, development and dissemination of scientific and technological research through the General Office of Research and Technology Transfer (OGITT) .

MANAGEMENT DOCUMENTS

- Decreto Supremo Nº 017-2006-SA (National Regulation for CT)
- Decreto Supremo Nº 006-2007-SA y D.S. 011-2007-SA, (Second version of the National Regulation for CT)
- Procedures Manual for Clinical Trials

- Regulate clinical research
- Define the rules for approval and monitoring clinical trials

- **Article 8 .- Conditions on the clinical trial.**

  All clinical trials must be conducted under conditions of respect to dignity, protection of the rights and welfare of subjects research, it must safeguard their physical and mental well as their privacy and data protection.

- **Article 69 .- Authorization of the trial.**

  NIH issue Resolution Clinical Trial Authorization, after evaluation of the protocol, Technical Report of the General Directorate of Medicines, Supplies and Drugs (DIGEMID) or other indicated in Article 66 of this regulation, within a maximum of forty (40) working days (including 30 days of the evaluation of the safety profile for DIGEMID).

  In case Controversial situations should involve the convening of technical committees, the deadline for the approval of the trial shall be sixty (60) days (including 45 days of the evaluation of the safety profile for DIGEMID).

PERUVIAN MINISTRY OF HEALTH

PERUVIAN INSTITUTE OF HEALTH

GENERAL OFFICE OF RESEARCH AND TECHNOLOGICAL TRANSFERENCE (OGITT)

DIGEMID

Artículo 6º Responsabilidades de DIGEMID.-

PHARMACEUTICAL COMPANY

CT

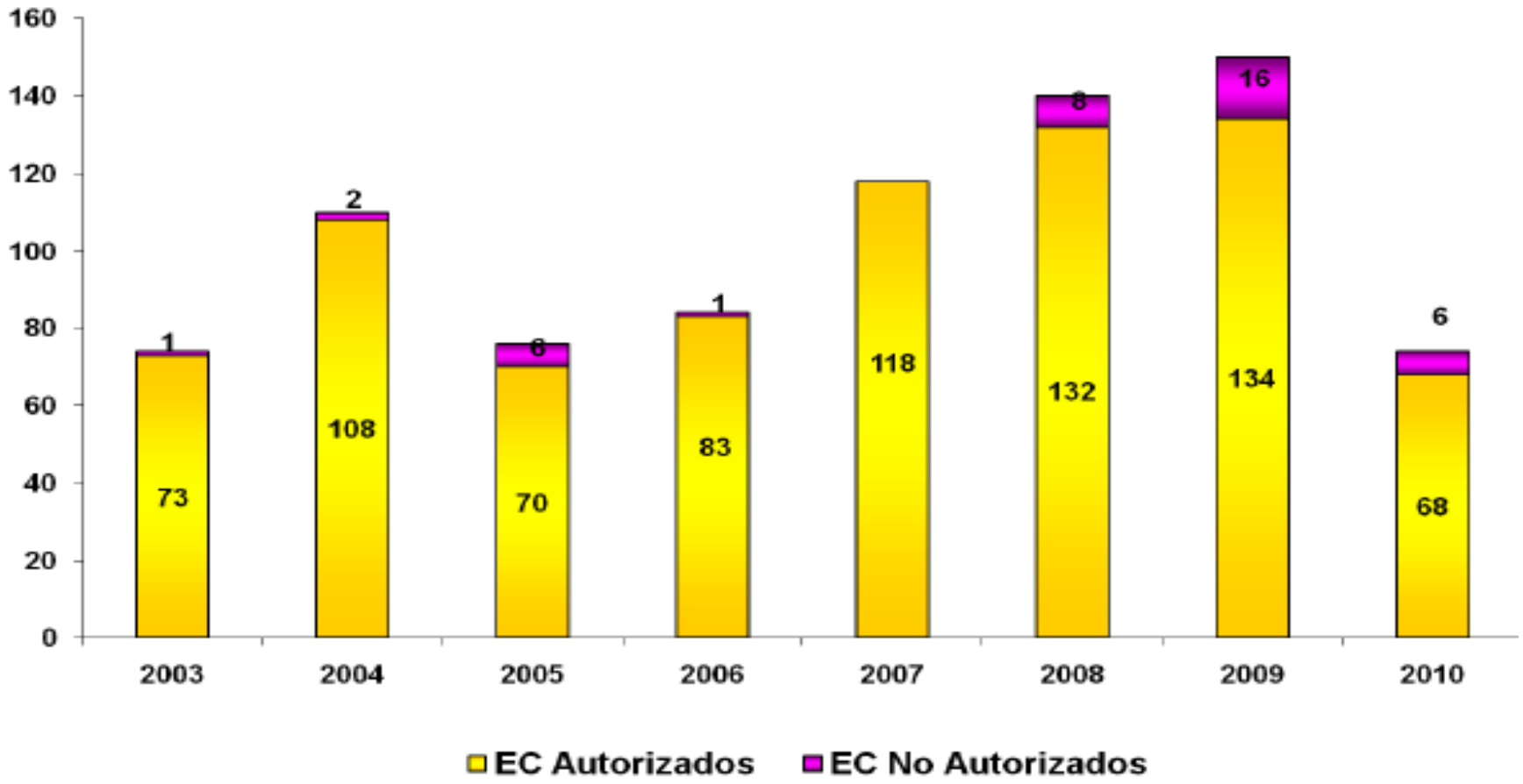
CROs,

UNIVERSITIES, INSTITUTES, CONSORCIUM

The National Institute of Health is the national authority is in charge of regulating CT in Peru: authorization, recording, monitoring, and auditing clinical trials

DIGEMID (General Direction of Drugs) is in charge of evaluating IP safety, and importation

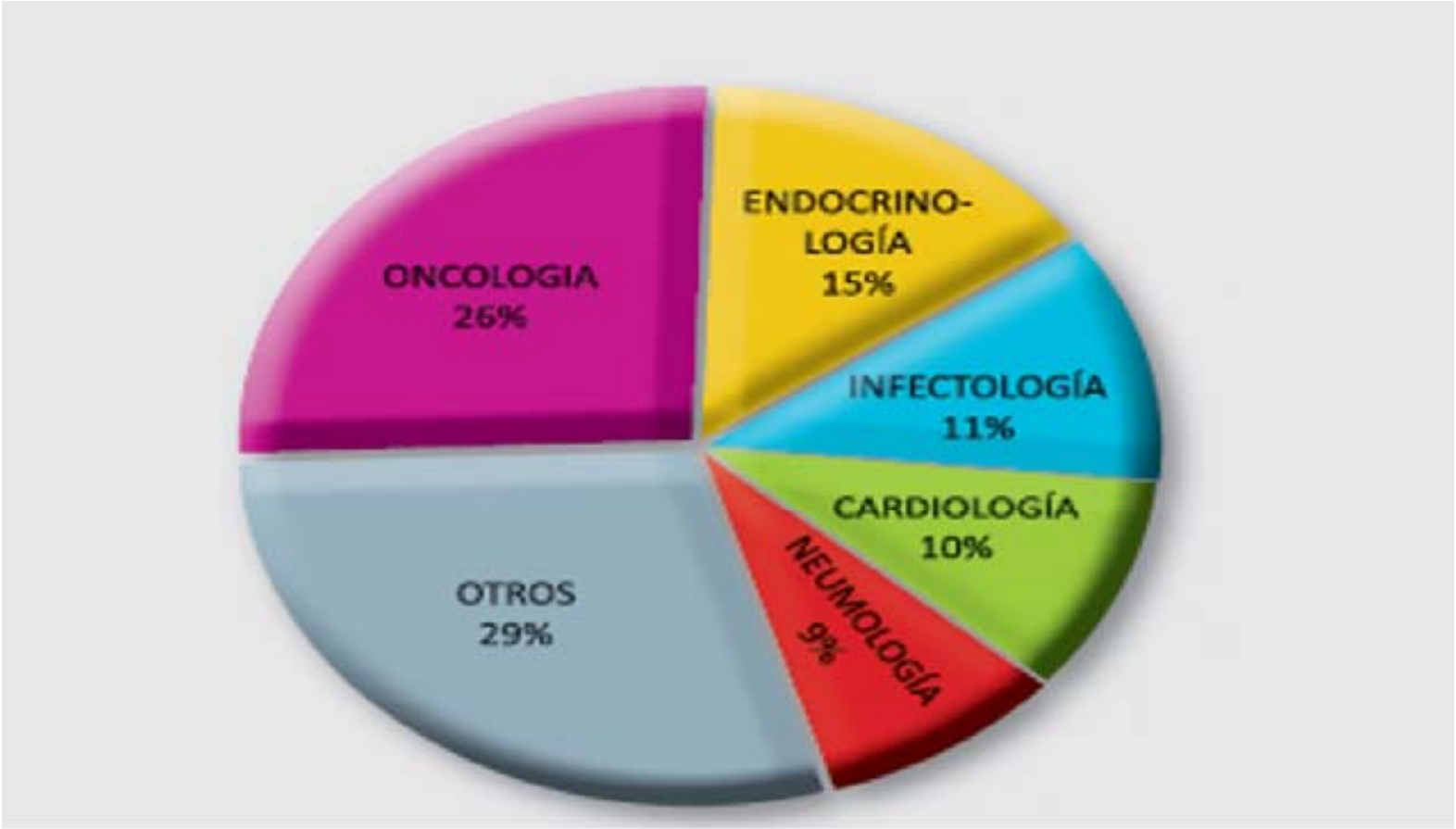
Clinical trials evaluated. Peru 2003-2010



Source: INS/OGITT

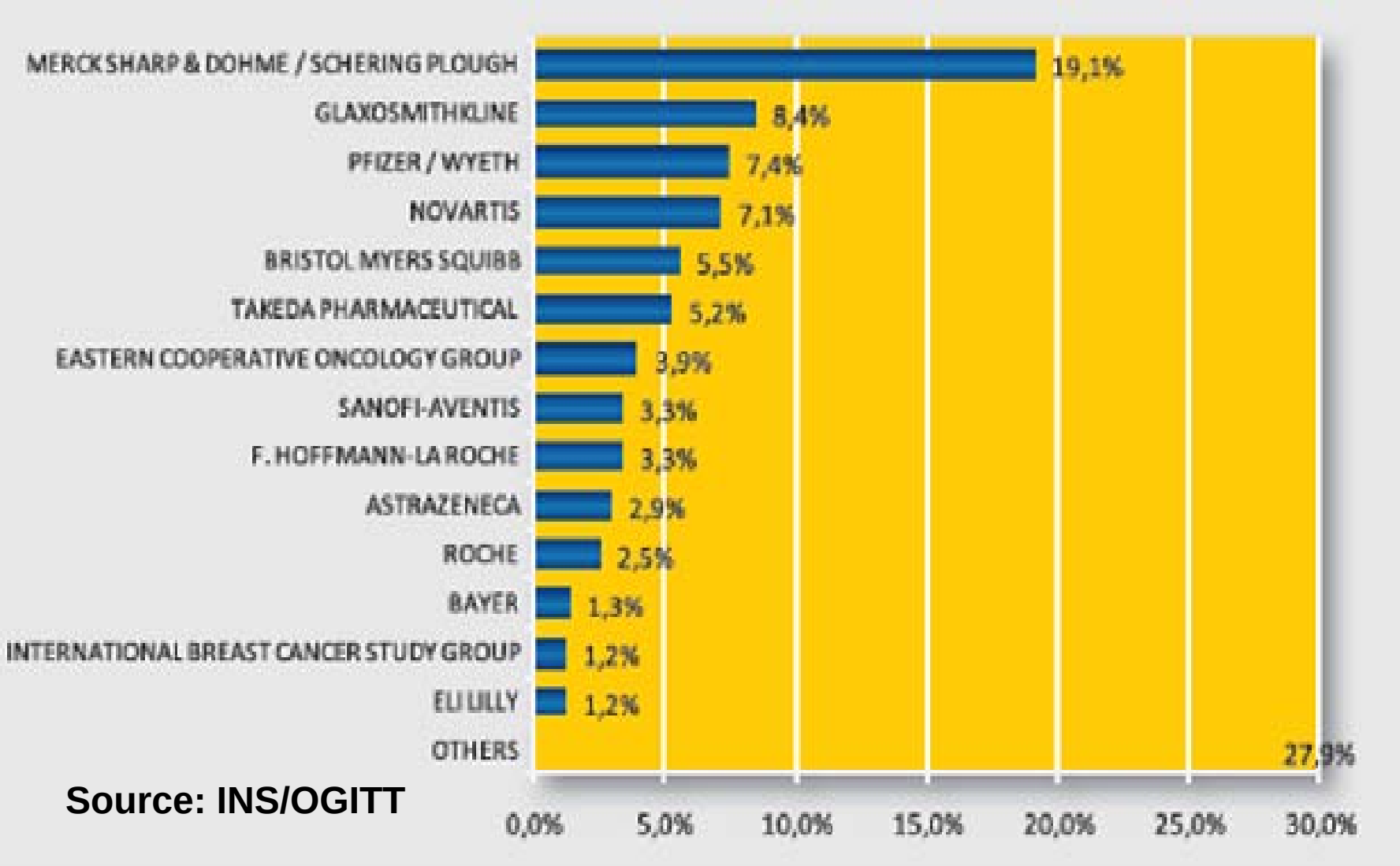
(*) Until 07/30/2010

According the specialty. Clinical trials 2004 - 2010



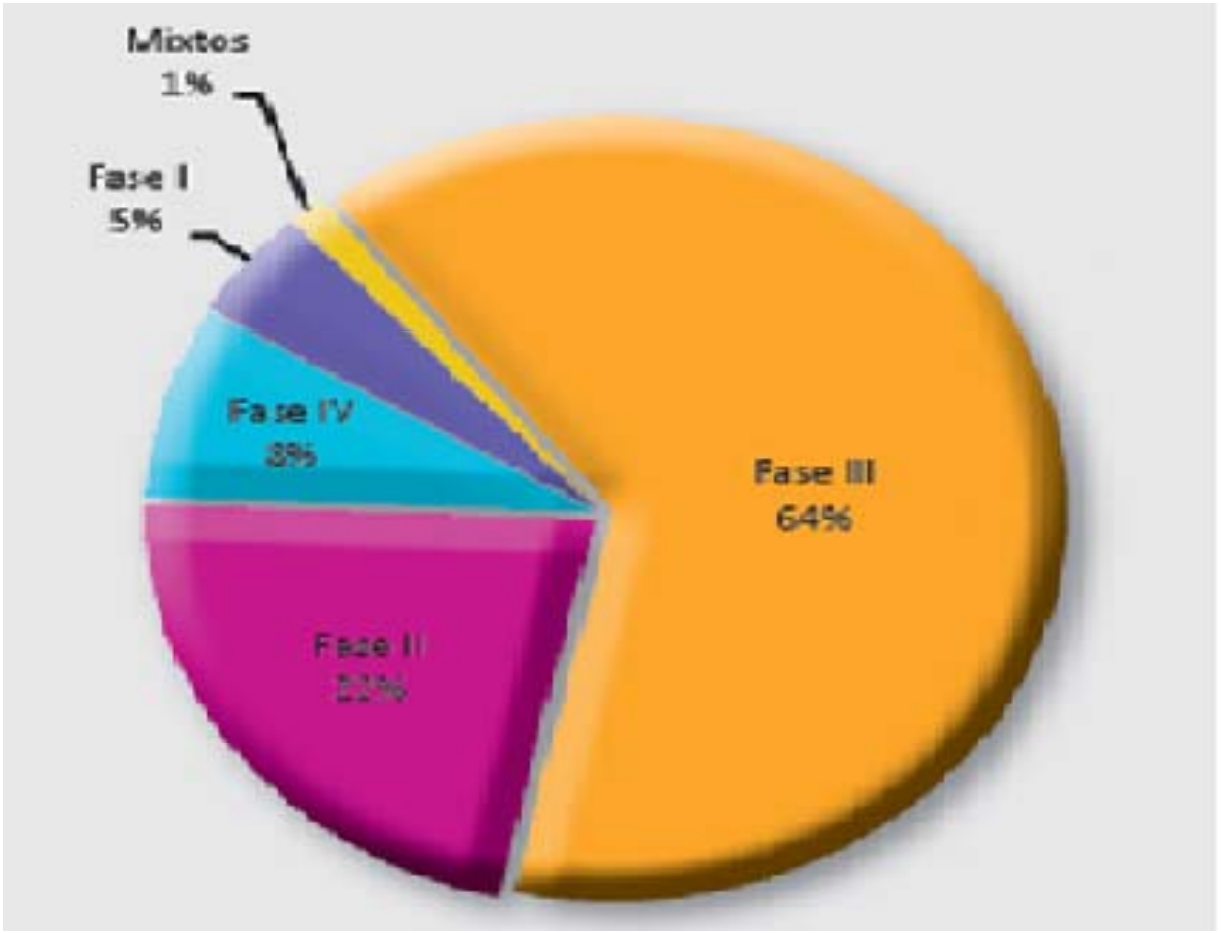
Source: INS/OGITT

According the sponsor. Clinical trials 2004 - 2010



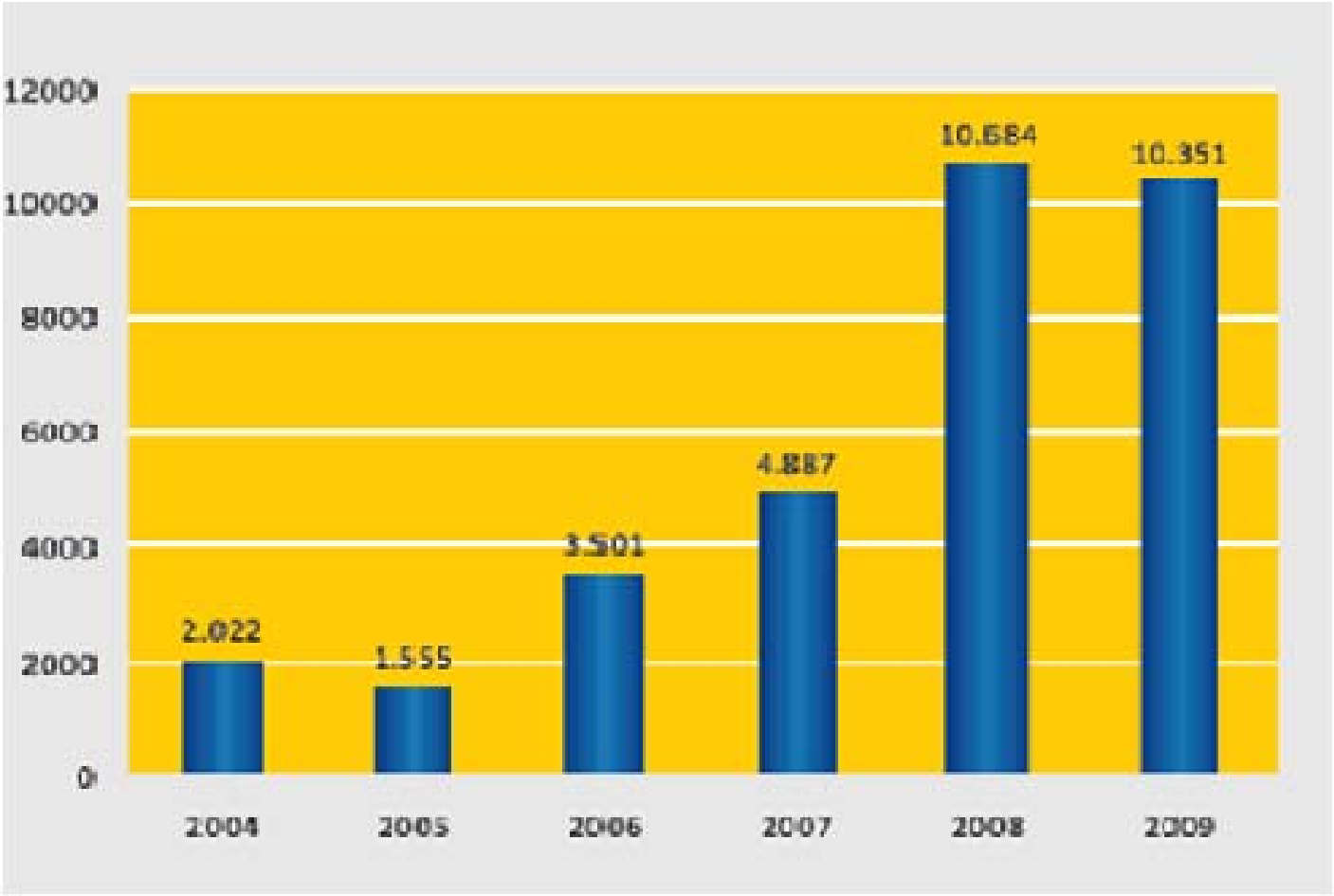
Source: INS/OGITT

According Phase. Clinical Trials 2004 - 2010



Source: INS/OGITT

Participants in clinical trials. 2004 - 2009



Source: INS/OGITT

According to their location. Research Center 2009

Departamento	Cantidad	Porcentaje
Lima	319	83,50%
Arequipa	21	5,50%
Lambayeque	9	2,40%
La Libertad	8	2,10%
Cusco	6	1,60%
Piura	6	1,60%
Callao	4	1,00%
Loreto	3	0,80%
Ica	2	0,50%
Amazonas	1	0,30%
Ancash	1	0,30%
Cajamarca	1	0,30%
Junín	1	0,30%
Total	**382**	**100%**

Source: INS/OGITT

Distribution of professional staff by year CT Area

Year	Doctors	Pharmaceutica lChemical	Statistical	Lawyer
2004	3	0	1	0
2005	3	1	1	0
2006	1	1	1	0
2007	4	1	1	0
2008	4	1	1	0
2009	9	5	1	1
2010	15	7*	1	2

Source: INS/OGITT

Processes associated with clinical trials.
OGITT-INS, 2003-2010*

PROCEDIMIENTOS	2003	2004	2005	2006	2007	2008	2009	2010
Autorizaciones	73	108	70	83	118	132	134	68
No autorizaciones	1	2	6	1	0	8	16	6
Renovaciones	11	41	56	63	101	109	124	79
Ampliación de Centro	41	41	33	38	117	170	241	181
Informe de Enmienda	0	0	1	0	109	212	458	336
Extensión de Tiempo	15	16	21	18	25	50	51	29
Listado Suministros (Ampliación / Modificación)	2	44	46	97	220	307	434	256
Solicitud de Enmienda	30	15	1	12	11	8	6	4
Cierre de Centro	-	6	1	21	21	29	55	23
Cambio de Investigador	-	3	1	18	12	7	21	4
Cambio de Patrocinador / OIC	-	-	2	3	5	7	7	7
Suspendidos por el patrocinador	05	5	9	13	17	16	39	23

Source: INS/OGITT

(*) Until 07/30/2010

- **Article 27 .- Responsibility of the Sponsor: Safe for the research subject.**

  Insurance with coverage in the country (or have a legal representative in Peru in case of an insurance policy of a foreign company) that would cover compensation risks associated with a clinical trial.

  In exceptional cases described in the manual of procedures, may provide a similar means of compensation appropriately endorsed by the sponsor.

Sponsors directly cover any adverse event, not using the policy.

Severe adverse events are rare.

Having a legal representative in Peru during the time of the execution of the clinical trial, if the sponsor is a foreigner. No problem

- **Article 49 º .- The requirements of the Principal Investigator.**

  a) Be professional surgeon or dental surgeon to investigate in the area of expertise and competence, registered and qualified to exercise the respective professional association.

  b) Having enough time to properly conduct the study within the agreed period.

  c) Meet the guidelines of Good Clinical Practice and Peruvian legislation for clinical trials.

- Physician without a specialty or a specialty not related to that of the CT are not allowed to be main investigator
- Some main investigators have many ongoing studies (one of them: 15)
- Some main investigators have poor training in ethics in research

Number of clinical trials and principal investigators

N° EC	N° - IP	
	N	%
1	172	46,1
2	56	15,0
3	47	12,6
4	25	6,7
5	21	5,6
6	11	2,9
7	9	2,4
8	6	1,6
9	7	1,9
10	4	1,1
11	4	1,1
12	2	0,5
13	4	1,1
14	1	0,3
15	1	0,3
16	1	0,3
18	1	0,3
29	1	0,3
Total	373	100,0

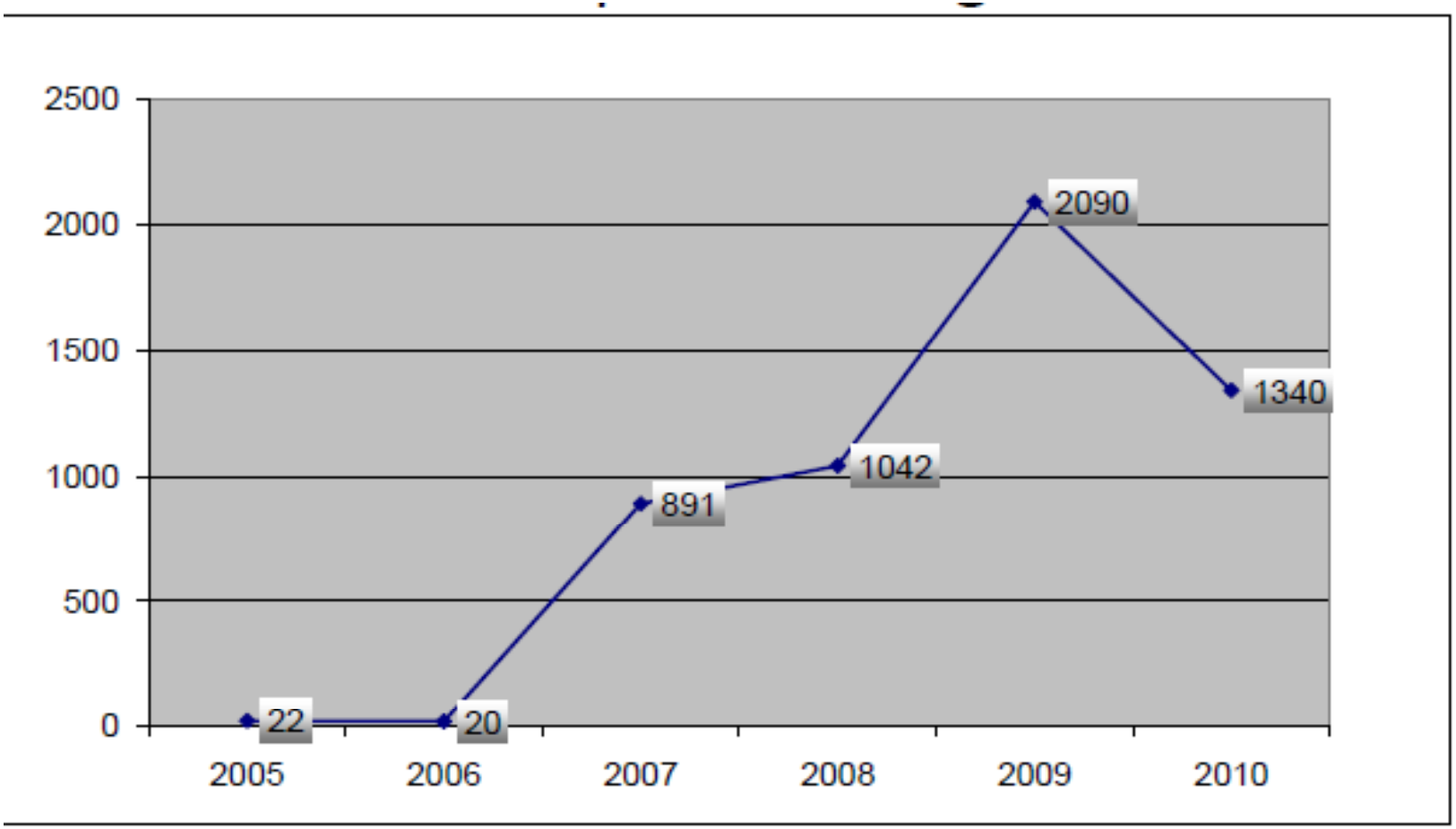
Source: INS/OGITT

(*) Until 12/31/2009

- **Article 107 .- responsibility of the Sponsor or Contract Research Organization.**

  a) Notify NIH, and the Institutional Research Ethics for all serious adverse events and unexpected adverse reactions occurred in a clinical trial authorized in a maximum of seven (07) days after the done happened

Number of notifications reported adverse events by year



Source: INS/OGITT

(*) Until 06/01/2010

ACERCANDO LA CIENCIA A LAS PERSONAS

MINISTERIO DE SALUD
INSTITUTO NACIONAL DE SALUD

Sistema de Reporte de Eventos Adversos Serios
REAS - NET

Reas-Net

es el Sistema Virtual del Instituto Nacional de Salud para el Reporte de Eventos Adversos Serios que se presentan durante el desarrollo de un ensayo clínico. Este es un sistema que funciona a través del internet desde cualquier lugar del país para el envío de los reportes con oportunidad y confidencialidad.

Los usuarios de este sistema son: los investigadores, patrocinadores y organizaciones de investigación por contrato (OIC) de ensayos dínicos autorizados y los profesionales de la Oficina General de Investigación y Transferencia Tecnológica del INS.

INGRESO PARA INVESTIGADORES/ PATROCINADORES / OIC

Nombre de usuario:

Contraseña:

Código EC INS:

Ingresar

INGRESO PARA PROFESIONALES INS Y DIGEMID

Nombre de usuario:

Contraseña:

Ingresar

Si tiene alguna consulta o sugerencia comunicarse con nosotros a través del correo electronico reasnet@ins.gob.pe o haciendo click Aqui>>>

- **Article 43 º .- Registration of Contract Research Organizations.**
  a) Application for registration and
  b) Authenticated copy of public write.

  Article 52 º .- Registration of Research Centers.

- **Article 62 º .- Registration of the IRB.**

  a) Application for registration addressed to the NIH,
  b) Resolution of the highest authority of the Research Institution which authorizes the operation of the IRB.

  c) A copy of the Rules and Procedure Manual approved by the Research Institution.

  The record is temporary, must be renewed every two (02) years

Registries related to clinical trials, Peru until 2011

Type of Institution	Registered Until 2011
Research centers	425
Contract Research Organizations	30
IRBs	27

Source: INS/OGITT

- **Article 73 .- Public Information Clinical Trials.**

  Once concluded the authorization process, the National Institute of Health put through its website the following information about clinical trials authorized and unauthorized: Title of the research protocol, protocol code, study phase, Sponsor, Principal Investigator, Research Centers, IRB and clinical trial situation.

Registration system and monitoring of clinical trials

Instituto Nacional de Salud

REGISTRO DE ENSAYOS CLINICOS

FICHA DE DATOS

REGISTRO NACIONAL DE ENSAYOS CLINICOS

NRO EC INS :	001-11

INFORMACIÓN GENERAL DEL ENSAYO CLÍNICO

Titulo:
UN ESTUDIO DE EXTENSION, ABIERTO, SOBRE LA SEGURIDAD DE PREGABALINA EN SUJETOS CON DOLOR NEUROPÁTICO ASOCIADO CON NEUROPATÍA POR VIH (PREGABALINA A0081251)

Patrocinador :	**TIPO PATROCINADOR**
1.- PFIZER S.A	LABORATORIO(INDUSTRIA FARMACEUTICA)
Empresa / Institución / Otra ejecutora	
1.- PFIZER S.A	LABORATORIO(INDUSTRIA FARMACEUTICA)

Fase Clínica del estudio:	III	**Código de Protocolo:**	A0081251

CENTRO DE INVESTIGACION, INVESTIGADOR PRINCIPAL, COMITE DE ETICA

Centro de Investigación donde se realizará el ensayo clínico		**Investigador Principal**	**Comité Institucional de Ética en Investigación (CIEI) que aprobó el ensayo para el centro**		**Observaciones**
Institución de Investigación	**Centro de Investigación**	**Nombres y Apellidos**	**Nombre de Comite de Etica**	**Datos de contacto**	
HOSPITAL NACIONAL DOS DE MAYO	UNIDAD DE INVESTIGACIÓN CLÍNICA SERVICIO DE ENFERMEDADES INFECCIOSAS Y TROPICALES	EDUARDO ROMULO TICONA CHAVEZ Correo electronico: eticonacrg@terra.com.pe Telefono:	HOSPITAL NACIONAL DOS DE MAYO - COMITÉ DE ETICA EN INVESTIGACIÓN BIOMÉDICA	Fernando Carballo Ordoñez Correo Electronico: hdosdemayo@hotmail.com Telefono:328-0028	

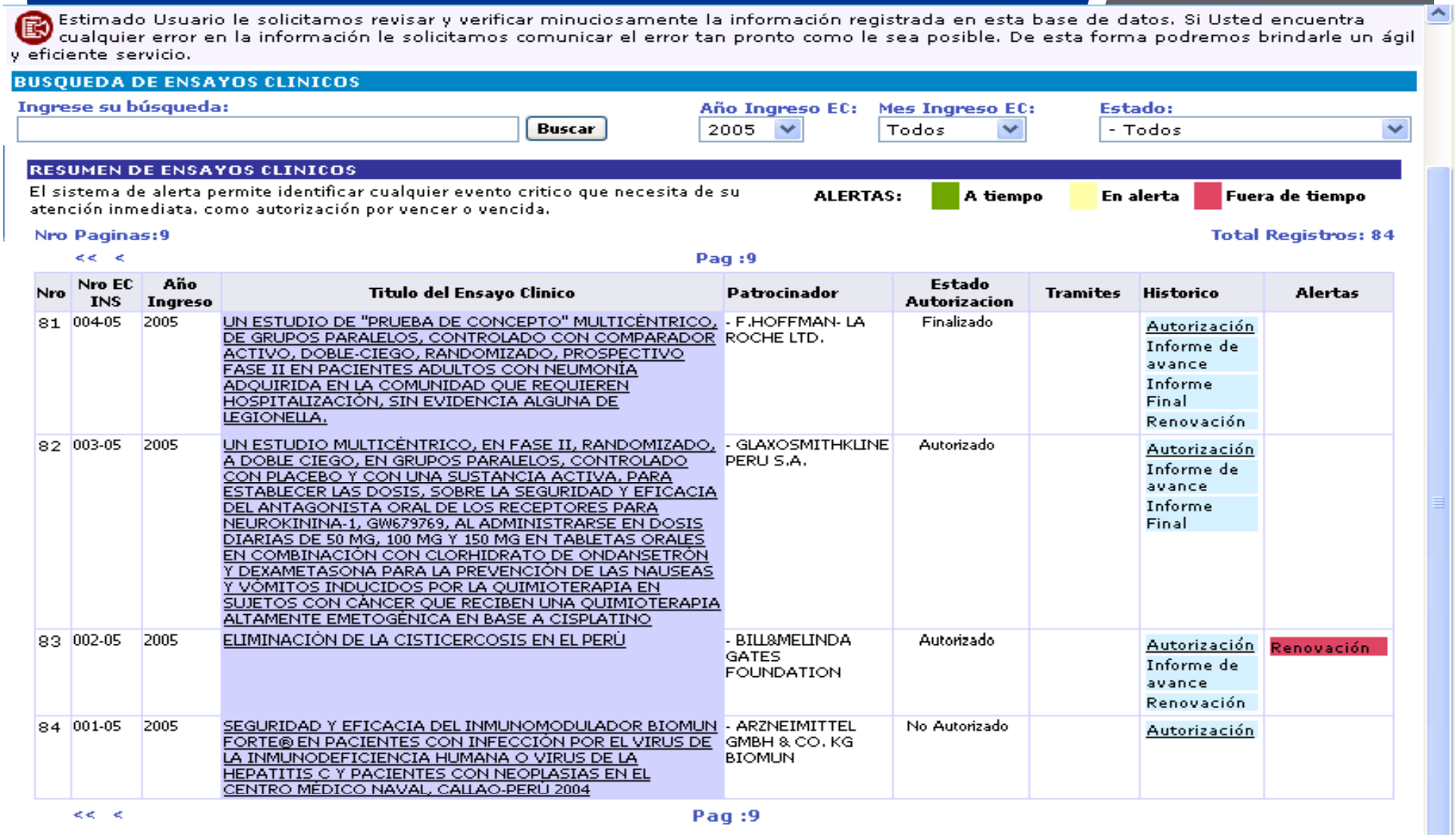
INFORMACIÓN DE PERSONAS DE CONTACTO DEL ENSAYO CLÍNICO

Nombres y Apellidos	**Correo Electronico**	**Telefono**
Martin Nizama Garcia	martin.nizama_overallout@pfizer.com	997577925

SITUACIÓN DEL ENSAYO CLINICO

Ensayo Clinico Autorizado y Activo

Registration system and monitoring of clinical trials



Estimado Usuario le solicitamos revisar y verificar minuciosamente la información registrada en esta base de datos. Si Usted encuentra cualquier error en la información le solicitamos comunicar el error tan pronto como le sea posible. De esta forma podremos brindarle un ágil y eficiente servicio.

BUSQUEDA DE ENSAYOS CLINICOS

Ingrese su búsqueda: [Buscar] Año Ingreso EC: 2005 Mes Ingreso EC: Todos Estado: - Todos

RESUMEN DE ENSAYOS CLINICOS

El sistema de alerta permite identificar cualquier evento critico que necesita de su atención inmediata. como autorización por vencer o vencida.

ALERTAS: A tiempo | En alerta | Fuera de tiempo

Nro Paginas:9 Total Registros: 84

<< < Pag :9

Nro	Nro EC INS	Año Ingreso	Titulo del Ensayo Clinico	Patrocinador	Estado Autorizacion	Tramites	Historico	Alertas
81	004-05	2005	UN ESTUDIO DE "PRUEBA DE CONCEPTO" MULTICÉNTRICO, DE GRUPOS PARALELOS, CONTROLADO CON COMPARADOR ACTIVO, DOBLE-CIEGO, RANDOMIZADO, PROSPECTIVO FASE II EN PACIENTES ADULTOS CON NEUMONÍA ADQUIRIDA EN LA COMUNIDAD QUE REQUIEREN HOSPITALIZACIÓN, SIN EVIDENCIA ALGUNA DE LEGIONELLA.	- F.HOFFMAN- LA ROCHE LTD.	Finalizado		Autorización Informe de avance Informe Final Renovación	
82	003-05	2005	UN ESTUDIO MULTICÉNTRICO, EN FASE II, RANDOMIZADO, A DOBLE CIEGO, EN GRUPOS PARALELOS, CONTROLADO CON PLACEBO Y CON UNA SUSTANCIA ACTIVA, PARA ESTABLECER LAS DOSIS, SOBRE LA SEGURIDAD Y EFICACIA DEL ANTAGONISTA ORAL DE LOS RECEPTORES PARA NEUROKININA-1, GW679769, AL ADMINISTRARSE EN DOSIS DIARIAS DE 50 MG, 100 MG Y 150 MG EN TABLETAS ORALES EN COMBINACIÓN CON CLORHIDRATO DE ONDANSETRÓN Y DEXAMETASONA PARA LA PREVENCIÓN DE LAS NAUSEAS Y VÓMITOS INDUCIDOS POR LA QUIMIOTERAPIA EN SUJETOS CON CÁNCER QUE RECIBEN UNA QUIMIOTERAPIA ALTAMENTE EMETOGÉNICA EN BASE A CISPLATINO	- GLAXOSMITHKLINE PERU S.A.	Autorizado		Autorización Informe de avance Informe Final	
83	002-05	2005	ELIMINACIÓN DE LA CISTICERCOSIS EN EL PERÚ	- BILL&MELINDA GATES FOUNDATION	Autorizado		Autorización Informe de avance Renovación	Renovación
84	001-05	2005	SEGURIDAD Y EFICACIA DEL INMUNOMODULADOR BIOMUN FORTE® EN PACIENTES CON INFECCIÓN POR EL VIRUS DE LA INMUNODEFICIENCIA HUMANA O VIRUS DE LA HEPATITIS C Y PACIENTES CON NEOPLASIAS EN EL CENTRO MÉDICO NAVAL, CALLAO-PERÚ 2004	- ARZNEIMITTEL GMBH & CO. KG BIOMUN	No Autorizado		Autorización	

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Registration system and monitoring of clinical trials

- Hosted on the website of the NIH http://www.ins.gob.pe. Provides information about regulations and rules of the CT, record IRB, research centers and CRO.

- Have different access levels: staff of Evaluation of the NIH, sponsors and CRO, researchers and the general public, with free access.

- The CT registration is done electronically. The data is automatically stored in a database from the time the sponsor fills out the application form for approval.

- This database facilitates the search for the title of the study protocol, the sponsor, the investigational product or the code of the CT and have statistics.

Registration system and monitoring of clinical trials

- The sponsor can download the forms from the website (authorization, EC renewal, suspension, extension of time expanded center, request for amendment, change of research or contract research organization, center closing and final report). view the status of their case and communicating electronically with staff of the NIH.

- NIH can monitor clinical trials process from authorization until the final report.

- The system issues alerts: yellow 20 days before the expiration of the authorization of CT and red at the end of the authorization.

Registration system and monitoring of clinical trials

- The ordinary citizen can access information such as title, protocol code, sponsor, name of the executor or CRO, name of investigator and institution research center, specialty of the study, phase of the study, duration of the trial, number of research, subjects to include in Peru and the world, number of participants by gender, duration of treatment of subjects, age range of subjects , ethics committee approved the study, number of Director's Resolution that was approved, name of the monitor, phone and email and statistical tables.

Registration system and monitoring of clinical trials

- This registration system and monitoring of clinical trials was considered as one of the good governmental practices in Peru in the category or transparency (2008)

Article 105 º .- Publication of Results of Clinical Trials authorized and performed.

Submitting to the NIH a copy of the publication showing the results of the authorized clinical trial.

Not accomplished

- **Article 124 ° .- Regular Inspection Scheduling.**

Routine inspections will be scheduled based on the following criteria:

a) For research protocol:

Vulnerable population

Research phase.

Research with more than the minimum risk

Impact on public health study

Criteria of safety of the product in research.

b) For research center:

High recruitment.

Background Investigator

Large number of clinical trial

Relevant information received safety reports and / or progress reports.

- **Article 125 ° .- Extraordinary Inspections.**

  Extraordinary inspections are performed at any time in order to anticipate or correct any situation that endangers the health of the subject in research and to a complaint.

INSPECTION - CLINICAL TRIALS

YEAR	Regular inspections	Extraordinary Inspections	Ethics Committees	Research Centers	CRO	TOTAL
2004	30	0	0	0	0	30
2005	26	0	0	0	0	26
2006	0	6	0	0	0	6
2007	16	0	0	0	0	16
2008	6	2	0	0	1	9
2009	35	7	49	82	2	175
2010	12	13	1	65	4	95

Source: INS/OGITT

(*) Until 10/31/2010

Clinical trials inspected by phase in 2009

PHASE C. T.	C.T. Active	C. T. Inspected	%
Phase I	15	9	60
Phase II	61	14	23
Phase III	178	14	7.8
Phase IV	24	0	0
Total	278	37	13.3

Source: INS/OGITT

Inspections 2009 (n = 38 clinical trials) INS/ OGITT

	Type of findings	No. CT
Documentation	Inconsstent data source and case report *form*	7
	Protocol deviations	4
	Delegation of functions without documents	3
	Lack of monitoring reports	3
	Inadequate documentation file	2
	Inadequate patient monitoring	1
	Lack of Authorization renewals	1
	Initiation of CT without authorization	1

	Type of findings	No. CT
Research Team	Without proper training (clinical experience, legislation Peru, GCP, ethics in research)	9
	Absence of the principal investigator in the center, failure to perform its functions	4
	It does not have complete equipment, or human resources to deal with emergencies and urgencies.	2
Informed Consent	Does not indicate the research center where the study was conducted and the time of taking the IC	3
	Using different versions than those authorized	3
	Lack of documentation sustaining credible impossibility	2
	screening, prior procedures without informed consent	2

Source: INS/OGITT

Research Products	Improper storage (temperature control)	8
	Lack training in management by Sponsor	2
Medical equipment	Lack of calibration	3
Bio-security	Improper handling of samples and waste (water shortage)	1
EAS notification	Report inappropriate times	3
	No report of the investigator-sponsor	2
	Inappropriate coding of patients	1
	Errors in the administration of the investigational product	1
Compensation (Insurance)	SAE that should cover the Sponsor (medication error, lack of effect)	2
	There is no contract with handling medical center in case of SAE in medical office	2
Infrastructure	Inadequate environments	10
	Laboratories use the State without prior contracts	1

Inspections Ethics Committees Research (IRB)

- From March 30 to July 31, 2009 was conducted visits to 27 IRB.

  - 24 already had registration..

  - 3 in the registration process.

- Of the 27 inspected IRB:

  - 22 are located in Lima.

  - 5 are located in other regions: 2 in Arequipa, 2 in Trujillo and 1 in Piura.

Source: INS/OGITT

- **Article 60 .- Establishment of the Institutional Research Ethics**
- This should be composed of at least five (5) members:

  a) At least one (1) member of the Research Institution.

  b) At least one (1) member not belonging to the institution and is not an immediate relative of a member of the Research Institution.

  c) At least one (1) community member, who has no profession of health sciences and not belonging to the research institution.

  d) It should be alternate members whose number shall establish the rules of procedure IRB.

  Most of the members must have expertise and experience in relation to the scientific, ethical and legal research. Both genders should be represented. <u>All members must have at least a certificate of basic training in research ethics and one of its members have had training in bioethics.</u>

- **Article 59 .- Functions of the IRB.**

  a) Assess the methodological, ethical and legal research protocols that are referred.

  b) Assess the amendments to the approved research protocols.

  c) Assess the adequacy of the principal investigator and his team.

  d) Assess the adequacy of installations for research centers.

  e) Carry out supervision of the research protocols approved by the National Institute of Health since its beginning until the receiving the final report at appropriate intervals according to the degree of risk to study participants at least once a year.

  g) Evaluate reports of serious adverse events and international security reports submitted by the Principal Investigator, Sponsor or CRO.

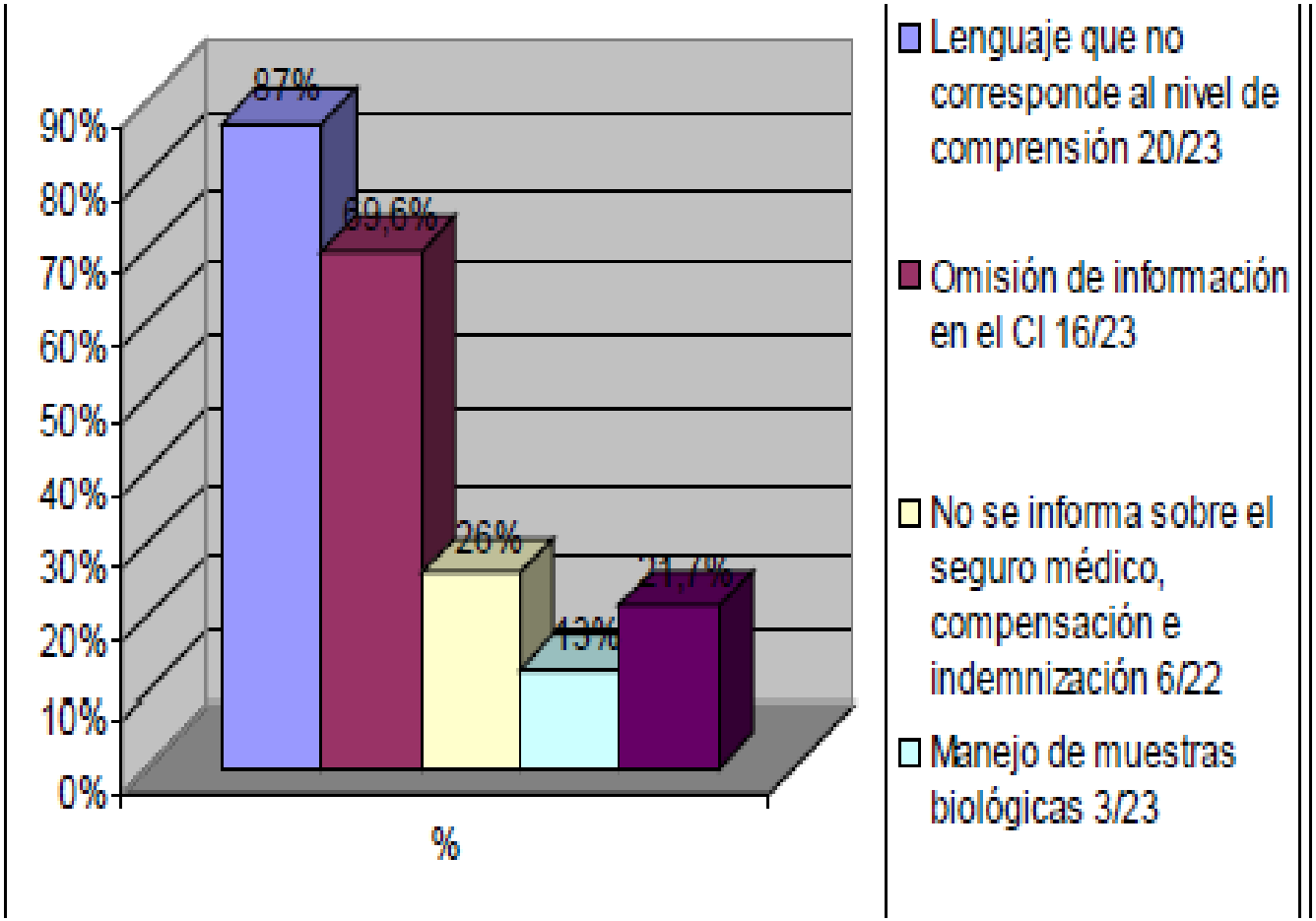
  h) To suspend a clinical trial, temporarily or permanently, when they have evidence that research subjects would be exposed to uncontrolled risk that threaten life, health or safety, or other reasons defined in the rules of the IRB.

Observed indicators for the IRB in Peru Inspections

Total time elapsed between the presentation of the protocol to the IRB and the emissions of the final report	7 to 123 days (range)	25.8 (average)
IRB monitoring visit conducted between 2006-2009	6 / 27	22.2%
IRB who failed at least one clinical trial between 2006-2009	6 / 27	22.2%
IRB to have a member trained in Bioethics	13/27	48.1%

Source: INS/OGITT

Observations on the informed consent



- language does not correspond to the level of understanding

Source: INS/OGITT

RESULTS OF INSPECTIONS RESEARCH CENTER 2009. Source INS/OGITT

CATEGORY	No. RC
NO EQUIPMENT CALIBRATED	8
IN THE PROCESS OF IMPLEMENTATION FOR DOCUMENTATION FILES	5
THE CENTER DOES NOT HAVE EQUIPMENT FOR EMERGENCY CARE OF AE	5
THE CENTER IS NOT IMPLEMENTED	4
IMPLEMENTATION PROCESS IN PRODUCT RESEARCH AREA	4
NO AGREEMENT FOR HOSPITAL IN CASE OF ADVERSE EVENTS	4
NO EMERGENCY CARE AREA ADVERSE EVENTS	4
ABSENCE OF THE PRINCIPAL INVESTIGATOR	3
DO NOT KNOW WHO PROCESSED BIOLOGICAL SAMPLES	3
DO NOT HAVE AREA FOR MONITORING	3
NO FILES ARE KEY	2
THE CENTER DOES NOT HAVE AN AREA TO FILE DOCUMENTS	2
EQUIPMENT STILL PACKED	1
FRIDGE IN PURCHASING PROCESS	1
DO NOT SUBMIT LICENSE MINSA	3

Regulatory issues considered for review

- Insurance for the research subject.
- Joint responsibility of the research institution.
- Requirements for the approval of CT (contracts..).
- CT approval time.
- Exhortation PI: sufficient time.
- National Commission on Research Ethics.
- Scale of penalty for infractions

Source: INS/OGITT

Outstanding aspects in legislation

- Biological samples Norm.
- Norm for the manufacture of investigational products in the country.
- Fund for research intangible.
- Norm of therapeutic equivalence of pharmaceutical products.
- Clinical trials and medicinal plants.
- Dispensing units for research products

Source: INS/OGITT

Challenges of clinical research in Peru

- Improve the quality and timeliness of the Evaluation of Clinical Trials.
- Improve and increase inspections of clinical trials priority in early phases and CT with vulnerable populations.
- Improve coordination with DIGEMID for the timely evaluation of the safety profile and list of imported inputs.
- Promote the exchange of experiences and information with other regulatory agencies in America and Europe.
- Promote ongoing training in Good Clinical Practice, bioethics and research methodology.

Source: INS/OGITT

- *Thank you*