GOVERNO DE PORTUGAL
MINISTÉRIO DA SAÚDE

infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde I.P.

P-BIO
Portugal's Biotechnology Industry Organization
Associação Portuguesa de BioIndústria

HEALTHCARE BUSINESS SUMMIT

INL, Braga, 16-17 October 2019

Life Science Start-up: From Inception to Exit

IMP (IND) Enabling

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INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

National Authority of Medicines and Health Products, I.P. - Portugal

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INFARMED
Regulatory Scientific Advice Office (GARC)
gives advice for medicines and health products.

- To facilitate the development and availability of high-quality, effective and acceptably safe medicines an health products
  R&D / CLINICAL TRIAL / MA SUBMISSIONS / REIMBURSEMENT

- promotion of an early dialogue aims to reduce duplication and to streamline and improve efficiency and quality of processes optimize the whole development process for the benefit of public health.
  Q / S / E / SCIENTIFIC / REGULATORY/ GXP

- for the quality of the submissions and increase of competences in the different specific areas of activity of the medicines and health products along the lifecycle of a medicine or health products.
  PREPARE EUROPEAN AND INTERNACIONAL TRANSITION

BELOW THE TIP OF ICEBERG

- Finalized requests versus total scientific advice requests:
- 2007 – 9 (13); 2008 – 8 (13); 2009 – 18 (22); 2010 – 34 (44);
- 2011 – 27 (29); 2012 – 31(35); 2013 - 29 (54); 2014 - 51 (80); 2015 – 59 (74)
- 2016- 50 (65); 2017- 80 (80); 2018 -76 (80); 2019*- 48 (49).

*to September 2019

- Most unfinished requests were submissions for information and requiring basic regulatory responses provided through CIMI.
- Accepted as Scientific Advice represent half of total regulatory requests – sent mostly to CIMI to provide regulatory responses.

cimi@infarmed.pt

Information center provides regulatory information

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DURING INITIAL DEVELOPMENT and DURING POST-MARKETING

NOT DURING ASSESSMENT

MEDICINAL PRODUCTS

• Development, manufacture and monitoring in the areas of quality, non-clinical and clinical safety, including pharmacovigilance and risk minimisation, efficacy, economic assessment, licensing, inspection and publicity.

MEDICAL DEVICES

• Development and manufacture of in the areas of quality, non-clinical and clinical safety, including vigilance and risk minimisation, performance and publicity.

COSMETICS

• Development and manufacture of products in the areas of quality, safety, including vigilance and publicity.

INFARMED
Regulatory Scientific Advice Office (GARC)

- Scientific Advice procedures annually (2019 *to September)

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
TOTAL COMPLETED	8	9	8	18	34	27	31	29	51	59	50	78	76	48
MEDICAL DEVICES									14	30	25	28	20	12

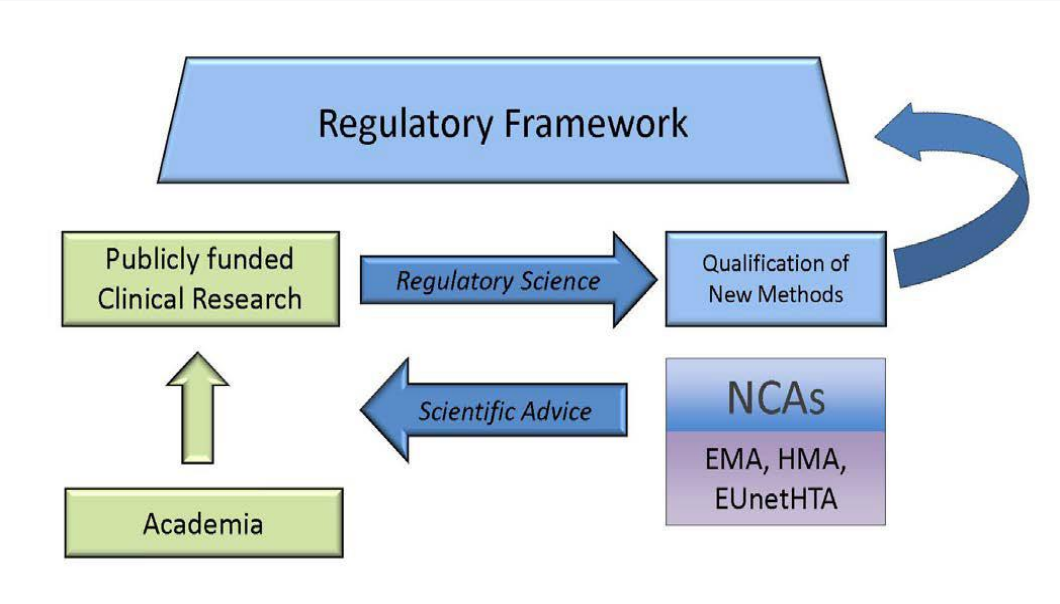
total mean 3 years (2013-15)	31
concluded	80%
academic / hospital	15%
national	70%
clinical trials / studies	10%
medical devices	40%
cosmetics	5%
ATMP	12%
GMP	12%
Regulatory only	30%

- Academic / hospital clinical trials

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
CLINICAL TRIALS ACADEMIC NON PROFIT									12	13	10	5	11	

STARS - Strengthening training of academia in regulatory sciences and supporting regulatory scientific advice - Consortium of innovation offices from 18 medicines agencies

- Duration *36* months
- Keywords: Drug development, clinical phases, Translational medicine, Drug development, late phases, Pharmacology, pharmacogenomics, drug discovery and design, *Regulation, Regulatory Science*



GARC - Margarida Menezes Ferreira e Helena Beaumont

favouring development

INNOVATION TASK FORCE

- Briefing meetings with selected EXPERTS and EMA
  - Forum for early dialogue with applicants
  - Advice prior to submission for scientific advice,
  - Free

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800ba1d9

SCIENTIFIC ADVICE

- EU-wide advice for all medicinal products

On development & quality aspect, non-clinical testing, clinical trials and post-marketing issues

- Written procedure (normally 40 days, extended to 70 days if oral hearing)
- Fee reduction for Advanced Therapy Medicinal products
- Free for Orphan Medicinal Products (Protocol Assistance)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800229b9&jsenabled=true

National Authorities – regulatory and scientific advice

Briefing Meetings

Type of issues discussed:

- Profile of the product/technology
- Development strategy/program: quality, safety, efficacy, manufacturing, Risk Management Plan (as applicable)
- Key scientific or regulatory areas
- Guidance is provided by ITF towards relevant related guidelines, services (e.g. SMEs office) or scientific procedures (e.g. Scientific Advice, OMP designation) in line with the presented strategy of the company
- Identified areas for further reflection and on the regulatory opportunities discussed

Since 2009, there have been 66 meetings with ATMP developers; in 47 of them CAT/CPWP or GTWP members were present

Scientific advice Working Party (SAWP)

- **Incentive: early – late / scientific certainty**

- Open to all applicants
  - Fee reduction for SMEs
  - Fee reduction for ATMP developers (non-SMEs)
  - Protocol assistance (free) for Orphan medicinal products

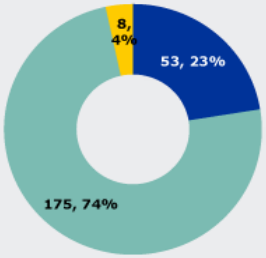
- Scientific advice is given from the scientific advice working party (SAWP) of the CHMP in collaboration with the CAT (+ other committees & working parties)
- Simple, fast procedure: 40 or 70 days (incl. face to face meeting with the Applicant)
- Possibility for parallel SA with FDA
- …

information kept confidential

Slide gently provided by Lisbeth Barkholt (MPA, SE / EMA)

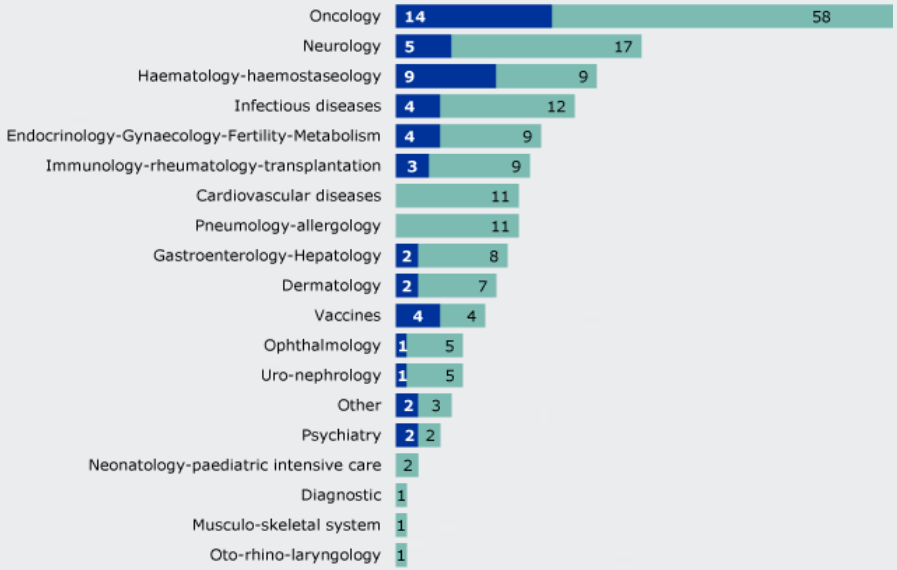
PRIME start 4/16 to 12/19

Applications and eligibility decisions



Type of applicant

Therapeutic areas



Recommendations adopted by 28 March 2019.

* Out of scope applications are not included in the detailed charts.

Granted Denied Out of scope*

42 PRIME granted:
18 for ATMPs (43%)
-
17 GTMP 1 TEP

8 Oncology
4 Haematology
1 Transplantation
1 Neurology

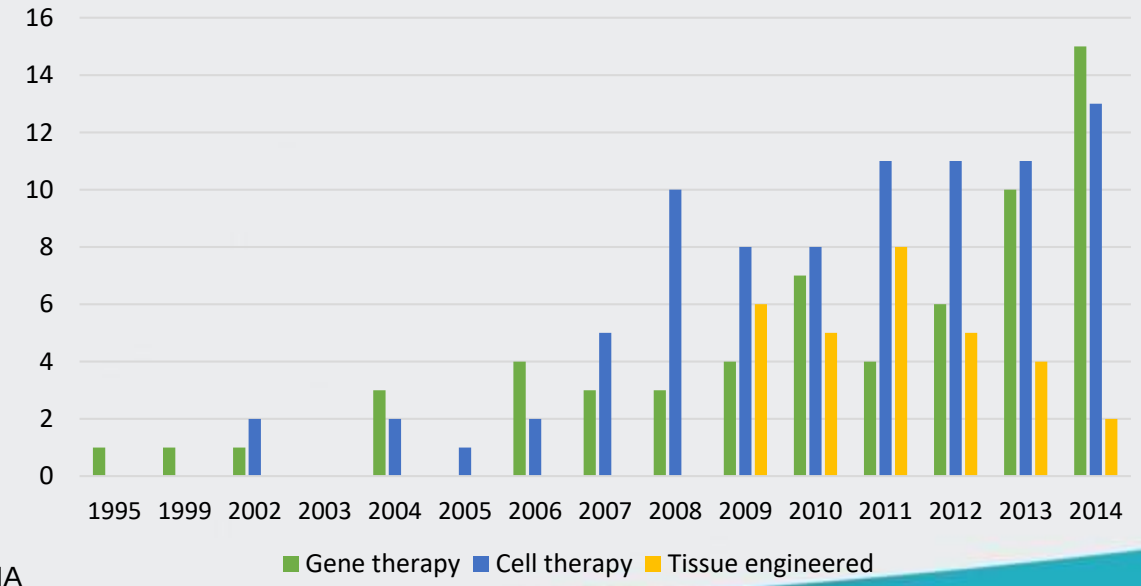
Adapted from Patrick Celis CAT statistics 2009-2017

	Name* **MARCH 2019**	Substance type	Therapeutic area	Therapeutic indication	Type of data supporting request	Type of applicant	Date of granting PRIME eligibility
AAV	Adeno-associated viral vector containing factor IX gene variant (PF-06838435/SPK-9001)	Advanced therapy	Haematology - Hemostaseology	Treatment of haemophilia B	Nonclinical + Clinical exploratory	Other	23/02/2017
AAV	Adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene (BMN 270)	Advanced therapy	Haematology - Hemostaseology	Treatment of haemophilia A	Nonclinical + Clinical exploratory	Other	26/01/2017
AAV	Adeno-associated viral vector serotype 5 containing human factor IX gene or variant (AMT-060, AMT-061)	Advanced therapy	Haematology - Hemostaseology	Treatment of severe haemophilia B	Nonclinical + Clinical exploratory	SME	21/04/2017
AAV	Adeno-associated viral vector serotype 8 containing the human MTM1 gene (AT132)	Advanced therapy	Other	Treatment of X-linked Myotubular Myopathy	Nonclinical + Clinical exploratory	SME	31/05/2018
AAV	Adenovirus associated viral vector serotype 8 containing the human CNGB3 gene (AAV2/8-hCARp.hCNGB3)	Advanced therapy	Ophthalmology	Treatment of achromatopsia associated with defects in CNGB3	Nonclinical + Tolerability first in man	SME	22/02/2018
LENTI/ RETRO	Autologous CD34+ cells transduced with lentiviral vector encoding the human beta globin gene (OTL-300)	Advanced therapy	Haematology-haemostaseology	Treatment of transfusion-dependent β-thalassemia	Nonclinical + Clinical exploratory	SME	20/09/2018
LENTI/ RETRO	Autologous CD4 and CD8 T cells transduced with lentiviral vector containing an affinity-enhanced T cell receptor to target the cancer-testis tumour antigen NY-ESO-1 (NY-ESO-1c259T)	Advanced Therapy	Oncology	Treatment of HLA-A*0201, HLA-A*0205, or HLA-A*0206 allele positive patients with inoperable or metastatic synovial sarcoma who have received prior chemotherapy and whose tumour expresses the NY-ESO-1 tumour antigen	Nonclinical + Clinical exploratory	Other	21/07/2016
LENTI/ RETRO	Autologous CD4+ and CD8+ T cells Expressing a CD19-Specific Chimeric Antigen Receptor (JCAR017)	Advanced therapy	Oncology	Treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL)	Nonclinical + Clinical exploratory	Other	15/12/2016
LENTI/ RETRO	Autologous haematopoeitic stem cells transduced with lentiviral vector Lenti-D encoding the human ATP-binding cassette, sub-family D (ALD), member 1 (ABCD1) from cDNA	Advanced therapy	Neurology	Treatment of cerebral adrenoleukodystrophy	Nonclinical + Clinical exploratory	Other	26/07/2018
LENTI/ RETRO	Autologous human T cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor (CAR) for B-cell maturation antigen (BCMA) (JNJ-68284529)	Advanced therapy	Oncology	Treatment of adult patients with relapsed or refractory multiple myeloma, whose prior regimens included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on the last regimen	Nonclinical + Clinical exploratory	Other	28/03/2019
LENTI/ RETRO	Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor (KTE-X19)	Advanced therapy	Oncology	Treatment of adult patients with relapsed or refractory mantle cell lymphoma	Nonclinical + Clinical exploratory	Other	31/05/2018
LENTI/ RETRO	Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains (bb2121)	Advanced Therapy	Oncology	Treatment of relapsed and refractory multiple myeloma patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody	Nonclinical + Clinical exploratory	Other	09/11/2017
HSV	Genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII (KB103)	Advanced therapy	Dermatology	Treatment of Dystrophic Epidermolysis Bullosa	Nonclinical + Clinical exploratory	SME	28/03/2019

The relevance of SAWP for ATMP development

	Total	2009	2010	2011	2012	2013	2014
MAA's	15	3	1	2	3	2	4
Classification	123	22	19	12	17	20	28
Certification	6	1	0	0	1	3	1
SA	132	17	19	21	19	23	33
PIP	30	3	4	4	8	5	6

SA and PA for ATMP per type



Data provided by Patrick Celis - CAT secretariat / EMA

Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency

Eur J Clin Pharmacol (2010) 66:39–48

Table 5 Summary of the results of the simple logistic regression analysis of variables associated with having received SA and compliance with SA

Independent variables	Analysis SA			Subgroup Analysis Compliance		
	SA-given/total, n=69/188 (%)	Odds ratio[a] [95% CI]	p value	Compliant/total, n=39/59 (%)	Odds ratio[a] [95% CI]	p value
CHMP outcome year		1.447 [1.093; 1.915]	0.0098		0.742 [0.425; 1.294]	0.293
2004	8/36 (22%)			5/7 (71%)		
2005	11/36 (31%)			7/9 (78%)		
2006	19/50 (38%)			12/17 (71%)		
2007	31/66 (47%)			15/26 (58%)		
Product type			0.0064			0.775
Biologic	29/61 (48%)	4.66 [1.797; 12.085]		14/22 (64%)	1.313 [0.233; 7.409]	
New chemical substance	33/84 (39%)	3.328 [1.326; 8.353]		21/30 (70%)	1.750 [0.323; 9.469]	
Known chemical substance	7/43(16%)	1		4/7 (57%)	1	
Orphan drug status			0.8241			0.0068
Orphan	19/50 (38%)	1.079 [0.553; 2.104]		6/16 (38%)	0.182 [0.053; 0.625]	
Non-orphan	50/138 (36%)	1		33/43 (77%)	1	
Therapeutic area			0.96			0.87
Infectious disorders	14/39 (36%)	0.95 [0.413; 2.184]		6/11 (55%)	0.600 [0.135; 2.673]	
Oncology	14/35 (40%)	1.13 [0.483; 2.645]		7/11 (64%)	0.875 [0.190; 4.030]	
Endocrine and metabolic disorders	9/29 (31%)	0.763 [0.298; 1.954]		6/8 (75%)	1.500 [0.238; 9.438]	
Neurologic and psychiatric disorders	9/23 (39%)	1.09 [0.408; 2.914]		6/8 (75%)	1.500 [0.238 9.438]	
Others	23/62 (37%)	1		14/21 (67%)	1	
Company size		1.566 [1.083; 2.264]	0.0172		3.975 [1.799; 8.781]	0.0006
Small pharmaceutical	14/54 (26%)			3/12 (25%)		
Medium pharmaceutical	17/51 (33%)			9/15 (60%)		
Large pharmaceutical	38/83 (46%)			27/32 (84%)		

[a] For categorical explanatory variables, the reference group for the calculation of the OR is indicated by OR=1. An OR>1 means that an event is more likely in this group compared to the reference group. An OR<1 means that an event is less likely in this group compared to the reference group. Outcome year and company size (small=1, medium=2, large=3) were used as continuous explanatory variables.

Market Authorisation Applications

CAT 2009-2019

APPROVED AND LATER WITHDRAWN:

ChondroCelect - for cartilage repair, 2009 *(withdrawn 06/2016)

MACI - for cartilage repair, 2012 *(closure of EU manufacturing site 09/2014)

Provenge advanced prostate cancer, 2013 *(withdrawn 05/2015)

Glybera - LPL deficiency, 2013 ..... withdrawn 10/2017

APPROVED :

Holoclar - limbal stem cell deficiency, 2015

Imlygic - advanced melanoma, 2015

Strimvelis - ADA-SCID, 2016

Zalmoxis - high-risk haematological malignancies (adjunctive to HSCT), 2016

Spherox - for cartilage repair < 10 cm^2, 2017

Alofisel - complex anal fistulas in Crohn's disease, 2018

Kymriah - children + adult <25yo ALL and adult DLBCL, 08/2018

Yescarta - adult DLBCL and PMBCL, 08/2018

Luxturna - children and adult retinal dystrophy biallelic RPE65 mutations, 09/2018

Zynteglo – β Thalassemia - >12yo, non β0/β0, 03/2019

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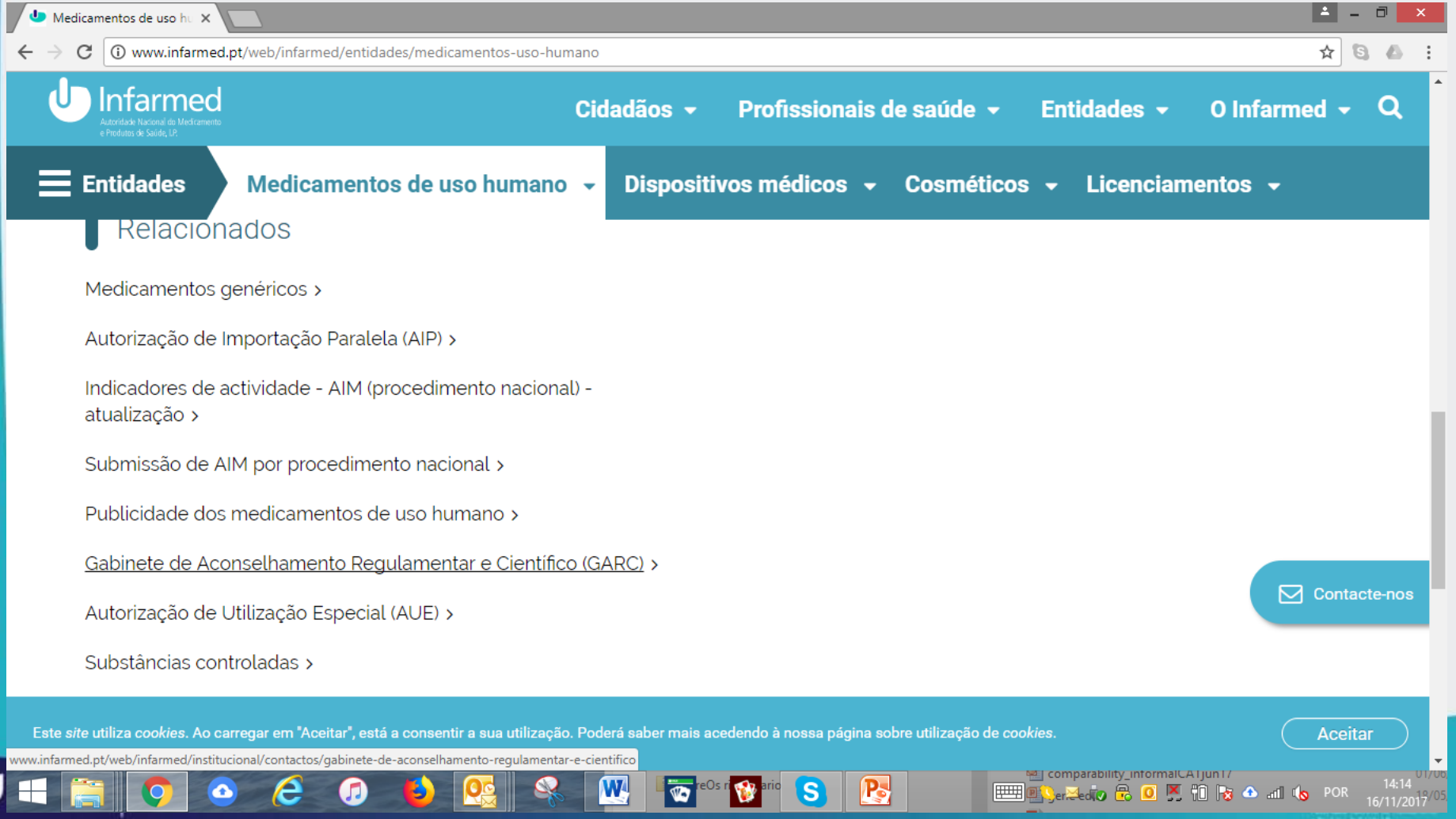

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