Malattie rare e pediatria:
innovazione terapeutica e misure nazionali ed europee di attrazione degli investimenti

In collaborazione con Farmindustria

Ore 10.00-13.20

Palazzo Wedekind
Piazza Colonna, 366

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ALTEMS
ALTA SCUOLA DI ECONOMIA E MANAGEMENT DEI SISTEMI SANITARI

UNIVERSITÀ CATTOLICA del Sacro Cuore

Introduction

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The EU Orphan Regulation

Objectives

- To ensure a high level of health protection for all
- To ensure the same quality of treatment to patients with rare diseases
- To restore the equilibrium between supply (industry) and demand (patients with rare diseases)
- To provide incentives for industry to develop and market orphan medicinal products
- To ensure better functioning of the internal market and preserve fair competition
- To encourage innovation

Not all of these objectives are entirely within the competences of the EC. Access to treatment depends also on national health policies, as health care is a national responsibility of the Member States.

Orphan Regulation

Designation criteria Art. 3 of Reg 141/2000

A product is eligible if a sponsor can establish:

1. that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition **affecting not more than five in 10 thousand persons** in the Community when the application is made, or
2. that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is **unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment**.

and

3. That there exists **no satisfactory method** of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

Follow-up actions

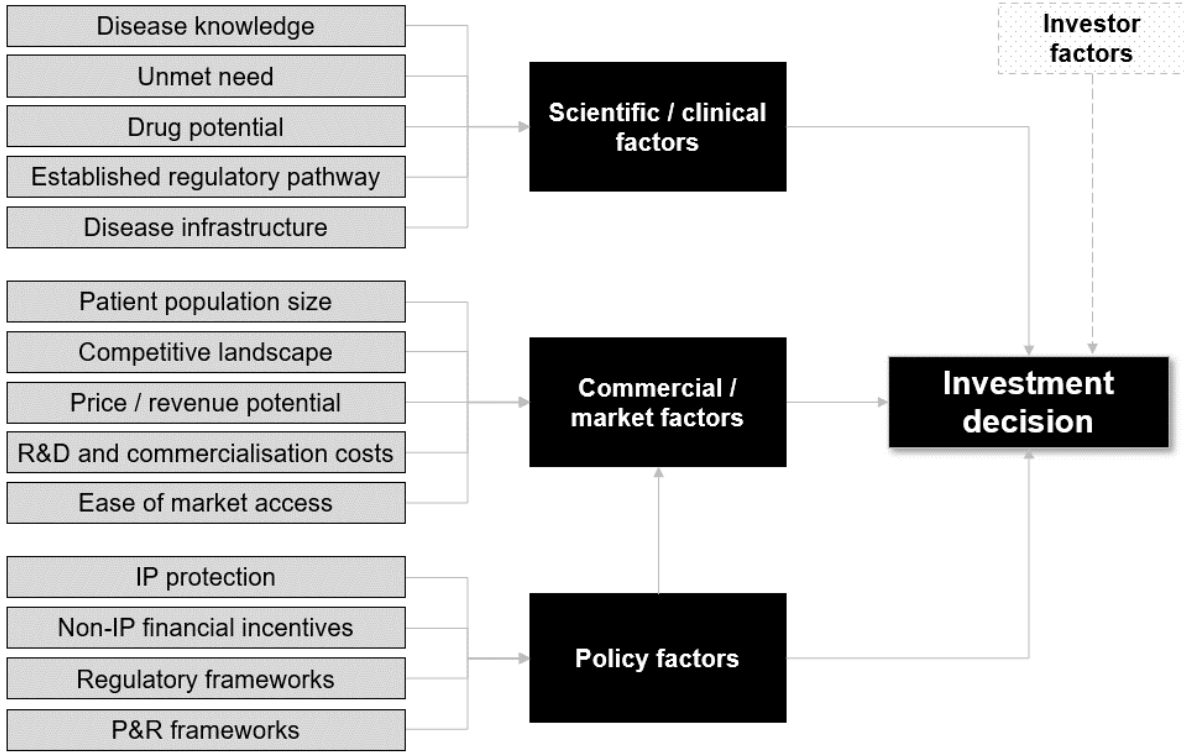
- Implementing **Regulation No 847/2000**
- **2006 Paediatric Regulation** created the possibility for orphan paediatric medicines to be granted two additional years of market exclusivity

- Criteria for designation (Commission Notice 2016/C 424/03)
- Centralised authorisation procedure (Regulation (EC) No 726/2004)
- Fee reductions and exemptions for SMEs (Regulation (EC) No 2049/2005)
- Conditional marketing authorisations (Regulation (EC) No 507/2006)
- Extension of market exclusivity for orphan paediatric drugs (Regulation (EC) No 1901/2006)
- Clarification of the COMP procedure (Guideline 2008/C 242/07)
- Concepts "similar medicinal product" and "clinical superiority" (Commission Regulation (EU) 2018/781)

Implementation

Demonstrating insufficient return on investment

- Lack of product development for rare diseases is significantly related to expectations of low return on investment on these products.
- 'Expectation of insufficient return' represents the real *raison d'être*' of the Regulation, whereas prevalence could be seen more as a proxy measure by linking the former to the limited size of the market.



Simplified taxonomy of investment decision factors (non-exhaustive)
Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions July 2021. Dolon for EPFIA

Implementation

Demonstrating medical plausibility & significant benefit

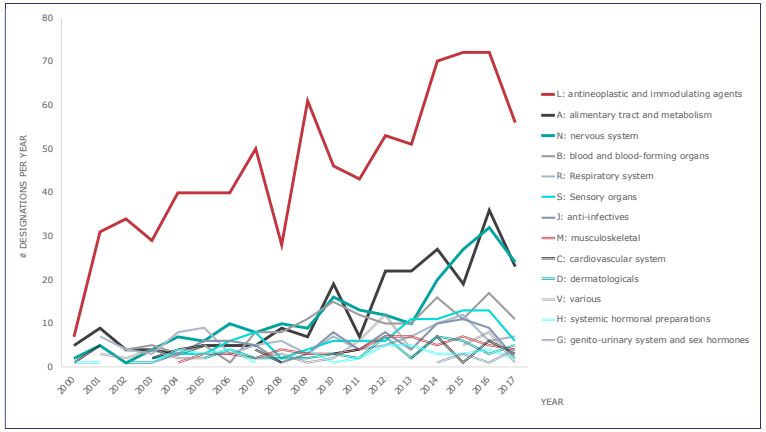
- For a product to be granted OD it must also be demonstrated that "there is no satisfactory treatment for the condition in question in the EU or, if there is, the product in question will be of **significant benefit** to patients affected by that condition." The EU Orphan Regulation thus requires a sponsor to provide details of "**existing methods**, which may include authorised medicinal products, medical devices or other methods of diagnosis, prevention or treatment, which are used in the Community [European Union]'.

- *Existing methods: Only authorised products should be taken into account. Non-pharmacological methods could be considered as a satisfactory method. In certain cases, 'magistral formulae' and 'officinal formulae', may be considered as satisfactory treatment if they are well known and safe and are in general practice in the EU*
- *A product can be said to provide significant benefit if it confers a clinically relevant advantage or offers a major contribution to patient care over existing authorized medicinal products or methods at the time of designation*

State of play

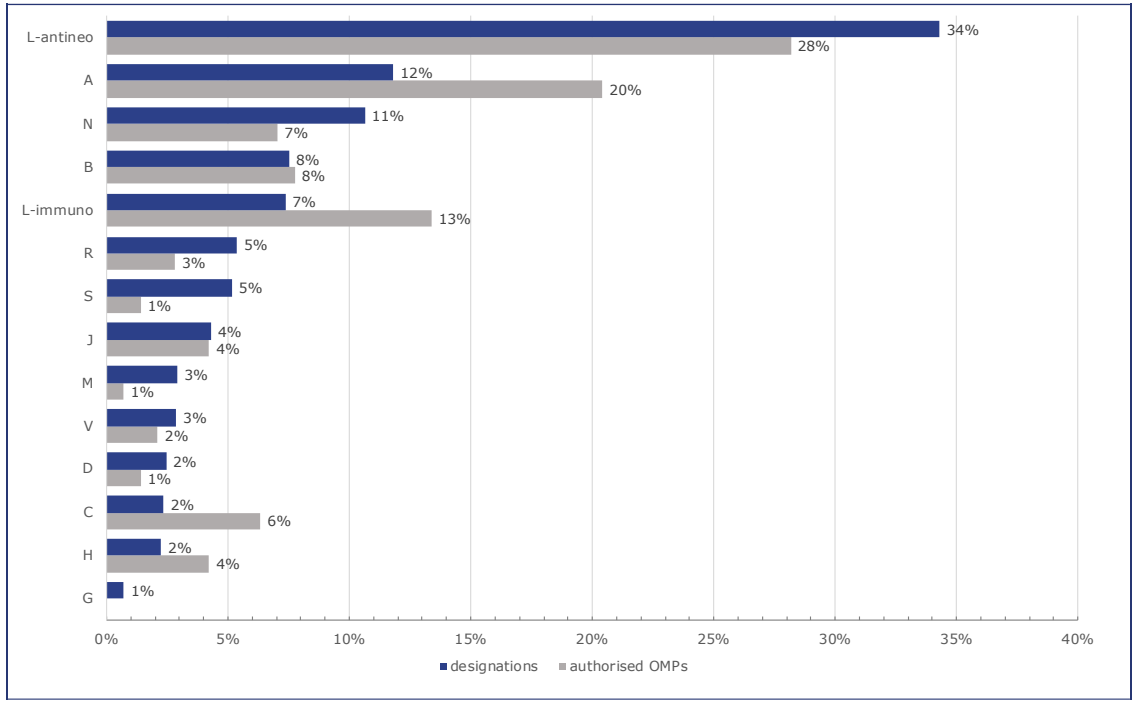
Orphan Designation by ATC code

Designations & OMP by target population



Source: EMA, 2018. Includes data up to end 2017.

	L-ant	A	N	B	L-imm	R	S	J	M	V	D	C	H	G	Total
Designated	671	231	208	147	144	105	101	84	57	56	48	46	44	14	1,956
Authorised	40	29	10	11	19	4	2	6	1	3	2	9	6		142



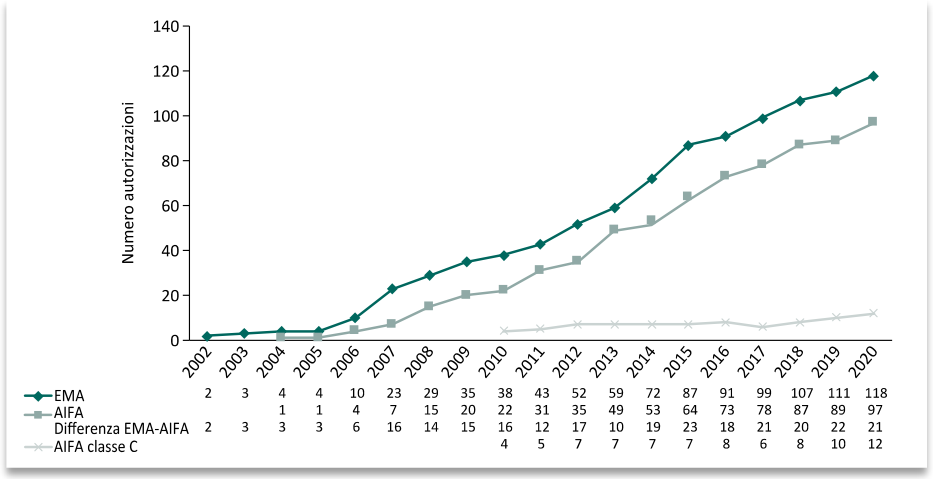
Source: EMA, 2018. Includes data up to end 2017. L-antineo = antineoplastic agents, A = alimentary tract and metabolism, N = nervous system, B = blood & blood-forming organs, L-immuno = immunomodulating agents, R = respiratory system, S = sensory organs, J = anti-infectives, M = musculoskeletal, V = various, D = dermatological, C = cardiovascular, H = systemic hormonal preparations, G = genito-urinary system & sex hormones.

Population affected by the condition	Designated	%	Authorised	%
Adult & paediatric	1,324	68%	97	68%
Only paediatric	166	8%	14	10%
Only adults	466	24%	31	22%
Total	1,956		142	

Source: EMA, 2018.

03
State of play

National (Italian) Context

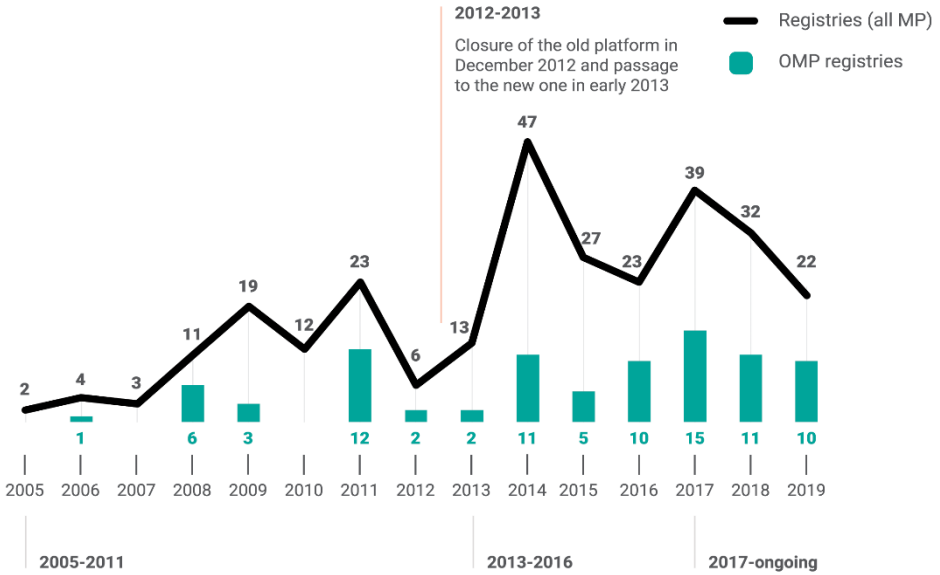


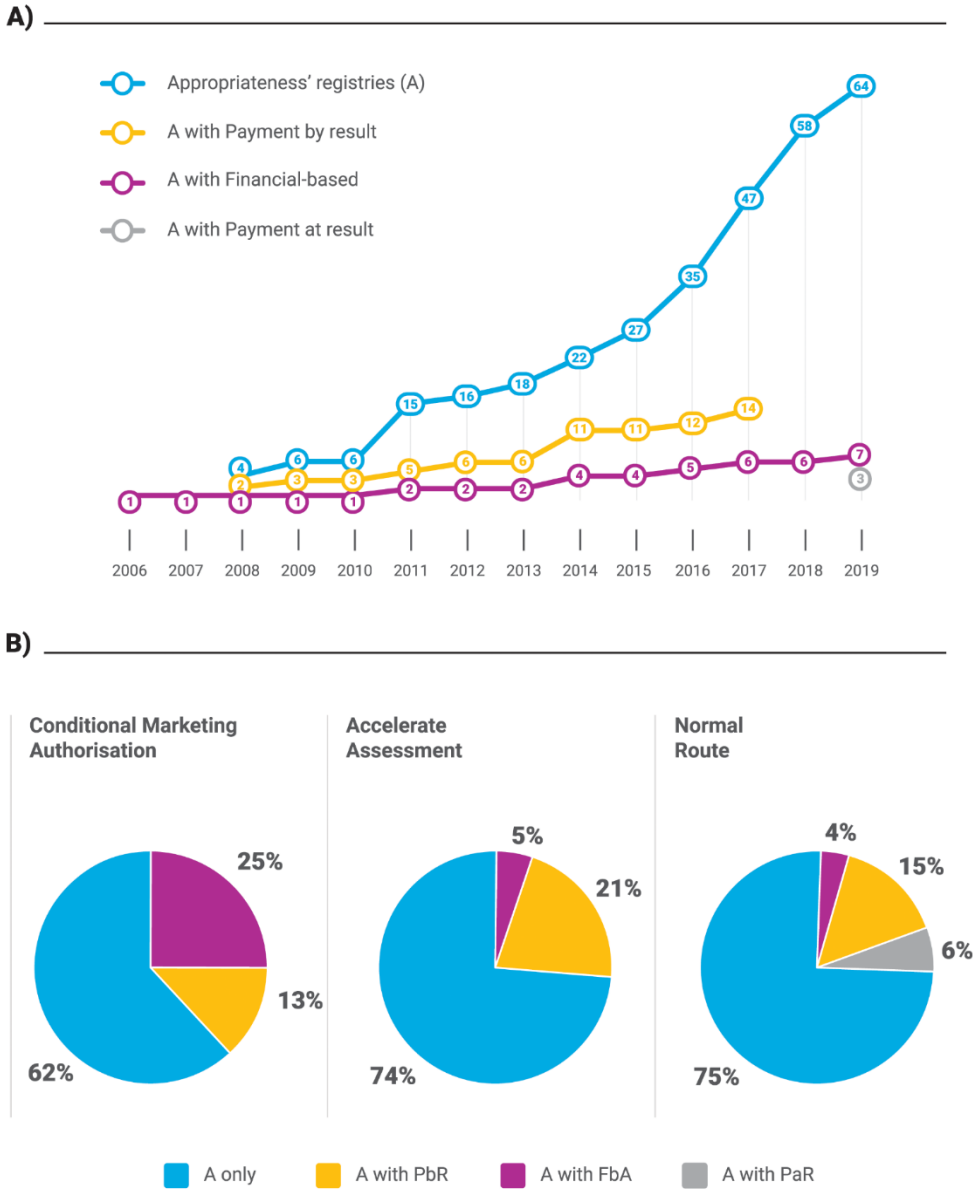
Comparison of drugs authorised with centralised EMA procedure and available in Italy (cumulative data 2002-2020)

- Strumenti di *early access:* 648/96 Law, 5% AIFA Fund, Compassionate use etc
- P&R Fast-track procedure
- AIFA Innovation framework specificities for OMP & rare disease treatments
- Performance-based risk-sharing agreement and other entry agreements to manage clinical uncertainty
- AIFA registries for the appropriateness verification and support price definition and pharmaceutical expenditure

- National Plan of Rare Diseases (incoming the update)
- National Network of Rare Diseases
- Testo Unico Rare Disease

AIFA OMP Registries & MEA





Xoxi E, Facey KM, Cicchetti A. The Evolution of AIFA Registries to Support Managed Entry Agreements for Orphan Medicinal Products in Italy. Front Pharmacol. 2021

Early access

Medicinali inseriti nella lista 648 nell'anno 2020, destinati al trattamento delle malattie rare, senza qualifica di orfano e con qualifica di orfano

Principio attivo	Indicazione terapeutica
bevacizumab (originator o biosimilare)	Trattamento della neurofibromatosi di tipo 2
associazione carboplatino + paclitaxel	Trattamento del carcinoma del timo
ibrutinib	Trattamento dei linfomi non Hodgkin B della zona marginale recidivati/ refrattari dopo almeno una linea di chemio-immunoterapia con anti-CD20
infliximab (originator o biosimilare)	Trattamento dei pazienti con sarcoidosi severa e/o con localizzazioni potenzialmente fatali che hanno fallito la I e II linea di trattamento (steroidi e agenti citotossici)
peginterferone alfa 2a	Trattamento delle forme refrattarie della malattia di Behçet
lenvatinib	Trattamento del carcinoma adenoide cistico
onasemnogene abeparvovec (Zolgensma)	Trattamento entro i primi sei mesi di vita di pazienti con diagnosi genetica (mutazione biallelica nel gene SMN1 e fino a 2 copie del gene SMN2) o diagnosi clinica di atrofia muscolare spinale di tipo 1 (SMA1)
plasminogeno	Trattamento della congiuntivite lignea
regorafenib	Trattamento del glioblastoma multiforme recidivato
rituximab (originator o biosimilare)	Trattamento della leucemia linfoblastica
trastuzumab (originator o biosimilare)	Trattamento dei tumori sierosi dell'endometrio metastatico, HER2 amplificati in associazione con carboplatino e paclitaxel
venetoclax	Trattamento di pazienti adulti con leucemia mieloide acuta di nuova diagnosi non candidabili a chemioterapia intensiva di induzione o con età ≥75 anni, in combinazione con azacitidina o decitabina

Nota: in rosso sono riportati i farmaci presenti nella lista 648 indicati per il trattamento delle malattie rare e che possiedono anche il requisito di farmaco orfano

Numero di richieste di accesso al fondo e numero di effettivi accessi ottenuti nell'anno 2020

	Numero di pazienti che hanno presentato richiesta per l'accesso al fondo AIFA		Numero di pazienti che hanno avuto risposta positiva alla richiesta di accesso al fondo AIFA	
Anno	Con malattia rara	Con tumore raro	Con malattia rara	Con tumore raro
2020	1.641	1.293	1.361	937

Medicinali destinati al trattamento delle malattie rare per i quali è stato attivato nell'anno 2020 un programma ai sensi del D.M. 7 settembre 2017

Principio attivo (nome commerciale)	Indicazione terapeutica
tafamidis (Vyndaqel)	Trattamento dell'amiloidosi da transtiretina wild-type o ereditaria nei pazienti adulti affetti da cardiomiopatia (ATTR-CM)
niraparib (Zejula)	Trattamento di mantenimento di pazienti con carcinoma dell'ovaio avanzato in risposta dopo trattamento di prima linea con chemioterapia a base di platino, che non possono essere trattate con alternative terapeutiche autorizzate
risdiplam (Evrysdi)	Trattamento dell'atrofia muscolare spinale (SMA) di tipo 1, in pazienti non candidabili a terapie autorizzate o che, a giudizio del medico curante, non siano in grado di continuare il trattamento in corso con la terapia autorizzata
risdiplam (Evrysdi)	Trattamento dell'atrofia muscolare spinale (SMA) di tipo 2, in pazienti non candidabili a terapie autorizzate o che, a giudizio del medico curante, non siano in grado di continuare il trattamento in corso con la terapia autorizzata
pemigatinib (Pemazyre)	Trattamento di pazienti adulti con colangiocarcinoma metastatico o localmente avanzato
belantamab mafodotin (Blemrep)	In monoterapia per il trattamento di pazienti adulti con mieloma multiplo recidivato/refrattario, che hanno ricevuto almeno quattro precedenti terapie, la cui malattia è refrattaria ad almeno un inibitore del proteasoma, un agente immunomodulatore e un anticorpo monoclonale anti-CD38
lumasiran (Oxlumo)	Trattamento di pazienti con iperossaluria primitiva di tipo 1 (PH1), privi di una valida alternativa terapeutica
pevonedistat	Trattamento di prima linea di pazienti con sindromi mielodisplastiche acute ad alto rischio, o Low Blast Acute Myelogenous Leukemia
luspatercept (Reblozyl)	Trattamento dell'anemia trasfusione-dipendente, associata a beta-talassemia
luspatercept (Reblozyl)	Trattamento dell'anemia trasfusione-dipendente dovuta a sindrome mielodisplastica (SMD) a rischio molto basso, basso e intermedio, nei pazienti che presentano sideroblasti ad anello con risposta insoddisfacente o non idonei a terapia basata su eritropoietina
elexacaftor/tezacaftor/ ivacaftor (Kaftrio)	Trattamento di pazienti di almeno 12 anni con fibrosi cistica, omozigoti per la mutazione F508del

Results of EU Orphan Regulation

Relevance
Effectiveness
Efficiency
Coherence
EU added value

	1 956 designations for 698 unique conditions
	142 authorised orphan medicines for 107 unique conditions
	55 Orphan medicines approved for use in children
	Designations and authorised medicines in nearly all major therapeutic areas
	Around 1/3 of designations for conditions with prevalence <5 in 100,000
	76% of authorised orphan medicines are new active substances
	~1,000 Sponsors, 96 marketing autorisation holders
	168x Market exclusivity granted, 1,272 requests for protocol assistance

Revision of the EU Legislation on medicines for children and rare diseases

Ref. Ares(2020)7081640 - 25/11/2020

European Commission

INCEPTION IMPACT ASSESSMENT	
Inception Impact Assessments aim to inform citizens and stakeholders about the Commission's plans in order to allow them to provide feedback on the intended initiative and to participate effectively in future consultation activities. Citizens and stakeholders are in particular invited to provide views on the Commission's understanding of the problem and possible solutions and to make available any relevant information that they may have, including on possible impacts of the different options.	
TITLE OF THE INITIATIVE	Revision of the EU legislation on medicines for children and rare diseases
LEAD DG (RESPONSIBLE UNIT)	SANTE (Unit B5: Medicines: policy, authorisation and monitoring)
LIKELY TYPE OF INITIATIVE	Legislative proposal of the European Parliament and of the Council
INDICATIVE PLANNING	Q1 2022
ADDITIONAL INFORMATION	Evaluation of the legislation for medicines for rare diseases and children
The Inception Impact Assessment is provided for information purposes only. It does not prejudge the final decision of the Commission on whether this initiative will be pursued or on its final content. All elements of the initiative described by the Inception impact assessment, including its timing, are subject to change.	