World Health Organization

24th MEETING OF THE WHO EXPERT COMMITTEE
ON THE SELECTION AND USE OF ESSENTIAL MEDICINES

OPEN SESSION Monday, 24 2023
World Health Organization, Geneva, Switzerland

Rare diseases
&
Model list of Essential Medicines

Enrico Costa

WHO Collaborating Centre for Pharmaceutical Policy and Regulation

Utrecht University

Essential medicines and rare disease: a debated global health issue

Policy and Practice

"Rare essentials": drugs for rare diseases as essential medicines

Pieter Stolk,[a] Marjolein JC Willemen,[a] & Hubert GM Leufkens[a]

REVIEW

World health dilemmas: Orphan and rare diseases, orphan drugs and orphan patients

Orphan drug legislation: lessons for neglected tropical diseases

Stefano Villa[1]*, Amelia Compagni[1] and Michael R. Reich[2]

Rare Diseases and Essential Medicines

A Global Perspective

Hans V. Hogerzeil

Medicines Policy and Standards, World Health Organization, Geneva, Switzerland

RESEARCH Open Access

Essential list of medicinal products for rare diseases: recommendations from the IRDiRC Rare Disease Treatment Access Working Group

William A. Gahl[1], Durhane Wong-Rieger[2*], Virginie Hivert[3], Rachel Yang[4], Galliano Zanello[5] &
Stephen Groft[6]

Treating Rare Diseases in Africa: The Drugs Exist but the Need Is Unmet

Lucio Luzzatto[1,2] and Julie Makani[1]*

Health Policy Analysis

Access and Unmet Needs of Orphan Drugs in 194 Countries and 6 Areas: A Global Policy Review With Content Analysis

Adrienne Y.L. Chan, MPH, Vivien K.Y. Chan, MMedSc, Sten Olsson, MSc, Min Fan, MPH, Mark Jit, PhD, Mengchun Gong, MD, Shuyang Zhang, MD, Mengqin Ge, MPH, Swathi Pathadka, PharmD, Claudia C.Y. Chung, MSc, Brian H.Y. Chung, MD, Celine S.L. Chui, PhD, Esther W. Chan, PhD, Gloria H.Y. Wong, PhD, Terry Y. Lum, PhD, Ian C.K. Wong, PhD, Patrick Ip, MPH,* Xue Li, PhD*

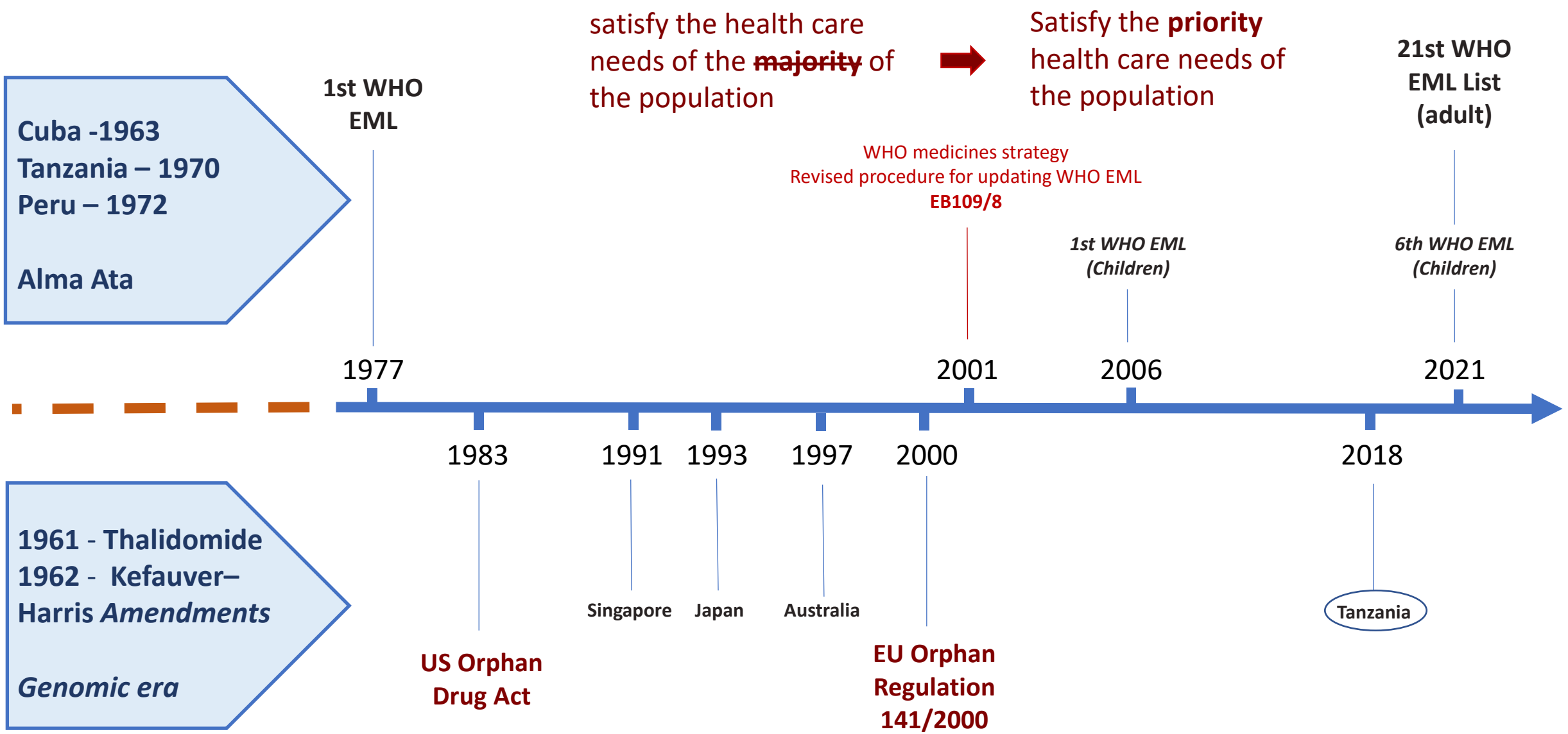
A long-lasting debate within the global health community…

…between those consider the EML a dataset minimum of medicines, who support the ethics of expanding access to cheaper less-effective treatments to target the largest number of people…

…and those consider the EML a goal to strive for in keeping with local priorities and needs, who abide by the principle whereby "**efficiency cannot trump equity in the field of health and human rights***"

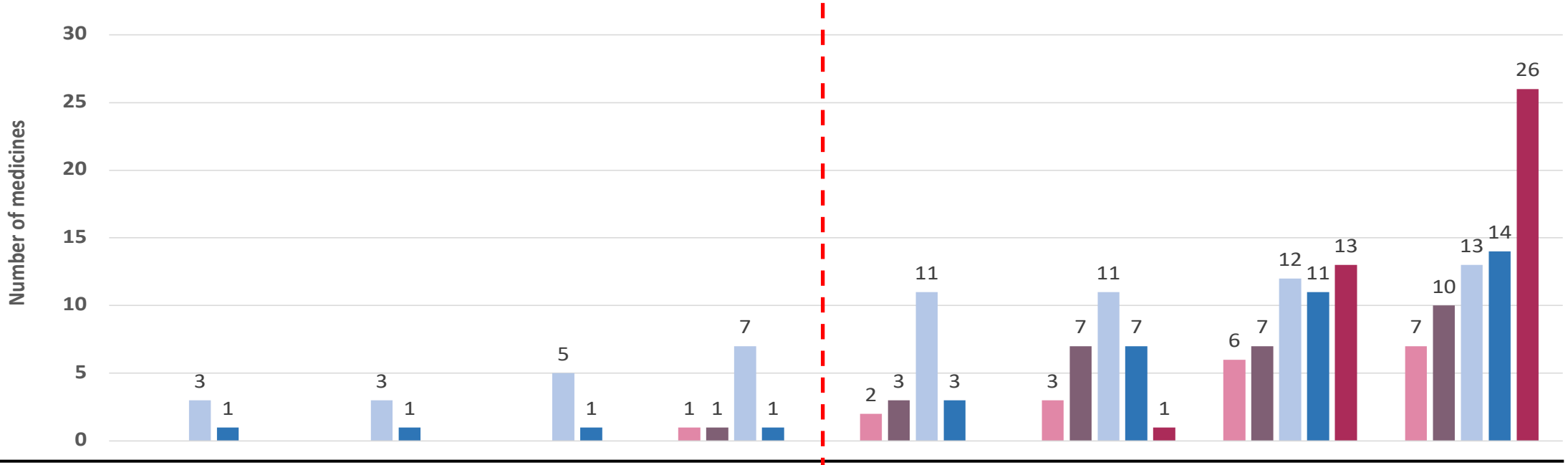
* Persad GC, Emanuel EJ. The ethics of expanding access to cheaper, less effective treatments. *The Lancet* 2016;388(10047):932-934. doi:10.1016/S0140-6736(15)01025-9

Essential medicines and Orphan drug legislations



Framework	Issue	Essential Medicines	Orphan Drugs
Regulation	Reference	WHO Model Lists of Essential Medicines; TRS, No. 615 - 1977 Revision of criteria: WHO Medicines Strategy EB109/8 resolution - 2001	US: Orphan Drug Act - 1983 EU: Regulation (EC) 141/2000
	Definition	Medicines that satisfy the priority health care needs of the population	US: medicines for the treatment of conditions affecting < 200,000 persons, or which will not be profitable within 7 years following approval EU: medicines for the treatment, prevention or diagnosis of life-threatening or chronically debilitating diseases affecting <5 in 10,000 persons, for which no satisfactory methods are authorised, or, if such methods exist, the medicine must be of significant benefit to those affected by the condition.
	Applicant	Academia, Healthcare institutions, International organizations, Scientifc societies, Patient organizations, Individuals, WHO Departments, Pharmaceutical companies	Mainly pharmaceutical companies, but orphan designation is also requested by university centres, consultants, or no-profit organizations
	Evaluation	WHO Expert Committee on the Selection and Use of Essential Medicines	US: FDA Office of Orphan Products Development (OOPD) EU: Committee for Orphan Medicinal Products (COMP)
Policy	Perspective	**From public health to individual health**	**From individual health to public health**
	Target	Mostly LMICs	HICs
	Goal	To provide **effective, safe and affordable medicines to as many patients as possible**	To provide **new therapeutic options to treat rare diseases**
Economics	Incentives	Tax reductions/exemptions at national level; Increasing the likelihood of reimbursement by public payers; Possibility of waivers or donations (e.g. malaria)	US: 7-year market exclusivity, 50% tax credit on CTs, technical assistance and accelerated evaluation, grant funding EU 10-year market exclusivity, fee reductions, technical assistance and accelerated evaluation
	Competition	**High** - Decisions for listing a medicine as essential include the assessment of intellectual property status, the presence of alternatives, comparative effectiveness analyses, and procurement and supply conditions	**Low** - Market exclusivity prevents the approval of competitors for all its duration
	Price	Despite the absolute price of a medicine not being a reason for not including it in the EML, comparative cost-effectiveness within same therapeutic class is considered in the decision-making process	FDA and EMA do not consider price in their decisions; usually orphan medicines are marketed at a high nominal price
Scientific	Selection	**Medicine driven**, although a closer integration with WHO guidelines has been increasingly pursued (e.g. antibiotics, oncological medicines)	**Disease driven**, although in the EU the demonstration of significant benefit over existing therapies is required
	Endpoints	Usually **large magnitude of clinical benefit based on patient-relevant outcomes**	US: approval can be based on **surrogate endpoints or intermediate clinical endpoints** EU: significant benefit over existing therapies must be based on clinically relevant advantage or **major contribution to patient care**
	Clinical evidence	**Cumulative** (systematic reviews and meta-analyses of RCTs, evidence from field testing in , WHO guidelines)	**Pivotal CTs (RCTs, controlled and uncontrolled cohort studies, case series)**

Trends of orphan drugs in the WHO Essential Medicines List 1977 - 2021



	1977	1983	1988	1995	2002	2009	2015	2021
Orphan Drugs	4	4	6	10	19	29	49	70
Essential Meds	208	244	264	279	317	332	410	478
%	1.9%	1.6%	2.3%	3.6%	6.0%	8.7%	12.0%	14.6%

V - Various (e.g. antidotes, chelating agents)

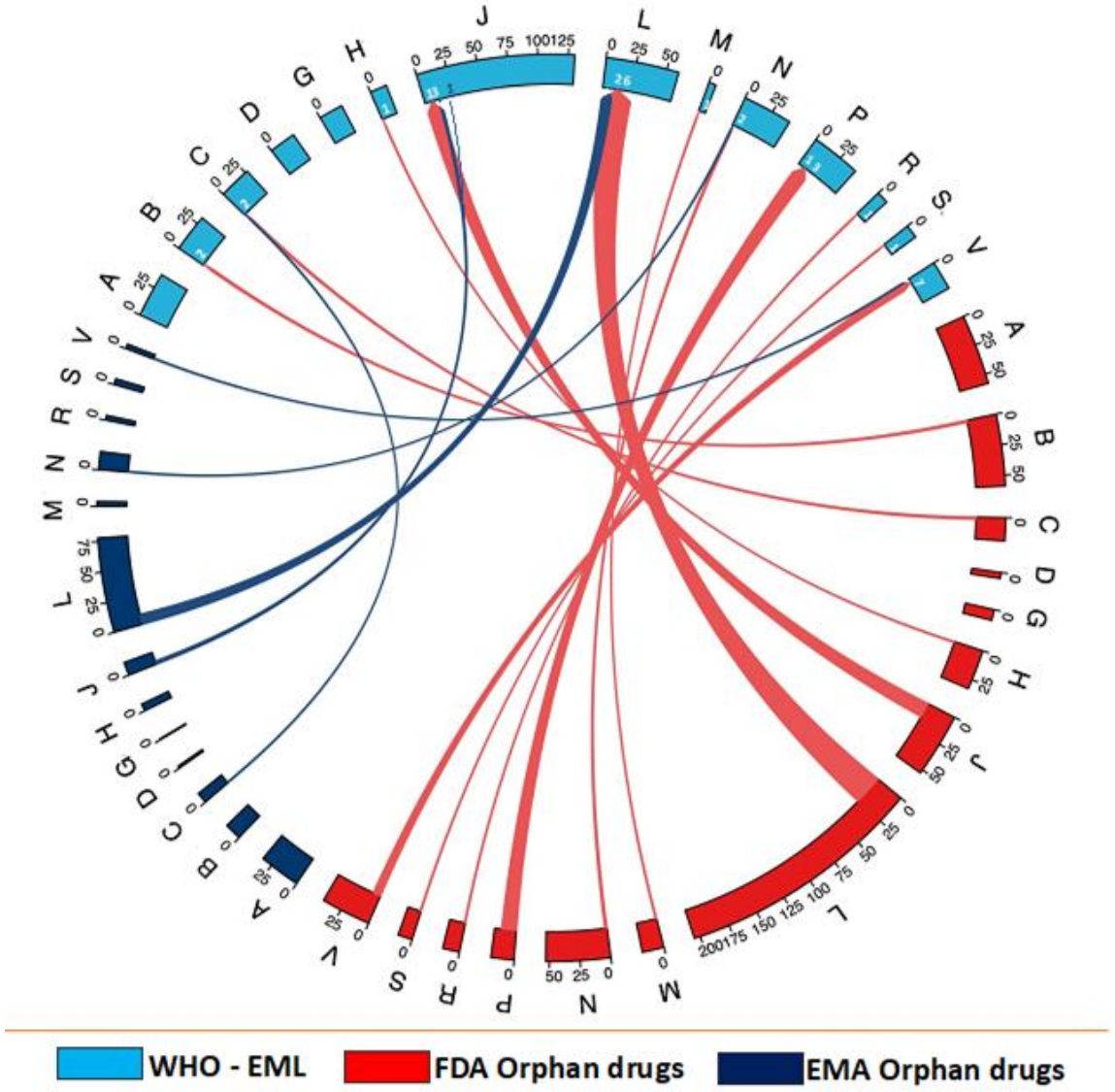
Other categories (B, C, N, H, M, R, S)

P - Antiparasitic products, insecticides and repellents

J - Antiinfectives for systemic use

L - Antineoplastic and immunomodulating agents

The contribution of FDA and EMA's orphan drugs to fuelling the EML (ATC level)



FDA: 69/70 (98%) ;
EMA: 15/70 (21.4%);
FDA&EMA: 14/70 (20%)

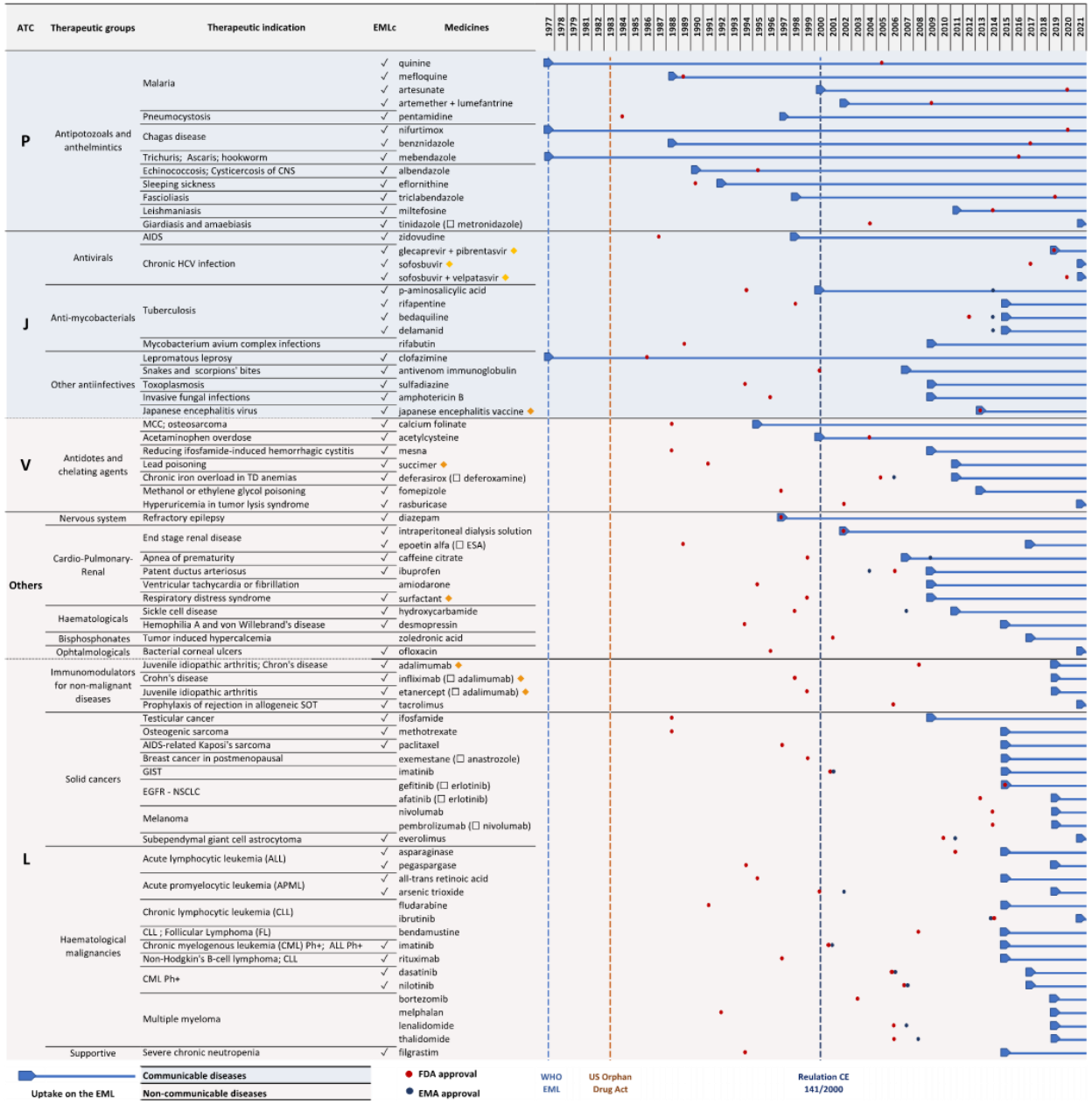
The US and the EU systems have different origins, both conceptually and in terms of timing.

FDA and EMA have different legal frameworks and procedures for granting orphan designations

Characteristics of orphan drugs and non-orphan drugs in the WHO EML

	All Essential Medicines (N=478)		Orphan drugs in the EML (N=70)		Non-Orphan drugs in the EML (N=408)	
	N	%	N	%	N	%
WHO EMLc	351	73.4%	57	81.4%	294	72.1%
List						
Core	351	73.4%	28	40.0%	323	79.2%
Complementary	127	26.6%	42	60.0%	85	20.8%
Product						
Chemical	412	86.2%	61	87.1%	351	86.0%
Biological	62	13.0%	9	12.9%	53	13.0%
Device	4	0.8%	-	-	4	1.0%
Patents (as of 2021)						
Active in most jurisdictions	27	5.6%	11	15.7%	16	3.9%
Main expired but secondary active in some jurisdictions	28	5.9%	8	11.4%	20	4.9%
Expired in most jurisdictions	405	84.7%	51	72.9%	354	86.8%
NA	18	3.8%	-	-	18	4.4%
Time from MEDLINE to EML						
≤20 years	171	35.8%	29	41.4%	142	34.9%
21-50	225	47.1%	24	34.3%	201	49.4%
> 51	72	15.1%	17	24.3%	55	13.5%
NA	10	2.1%	-	-	10	2.5%
ATC Classification						
J - Antiinfectives for systemic use	130	27,2%	14	20,0%	116	28,4%
L - Antineoplastic and immunomodulating agents	60	12,6%	26	37,1%	34	8,3%
P - Antiparasitic products. insecticides and repellents	41	8,6%	13	18,6%	28	6,9%
V - Various (e.g. antidodes, chelating agents)	24	5,0%	7	10,0%	17	4,2%
Others*	223	46,7%	10	14,3%	213	52,2%

Timeframe of orphan drugs listing on the WHO Essential Medicines List (1977 – 2021)



CDs
27 (38.6%)

- 10 neglected tropical diseases,
- 4 malaria,
- 4 tuberculosis,
- 4 hepatitis C
- 4 HIV
- 5 others

The median period for inclusion in the EML after the FDA's or the EMA's approval was **13.5 years (range: 1-28 years).**

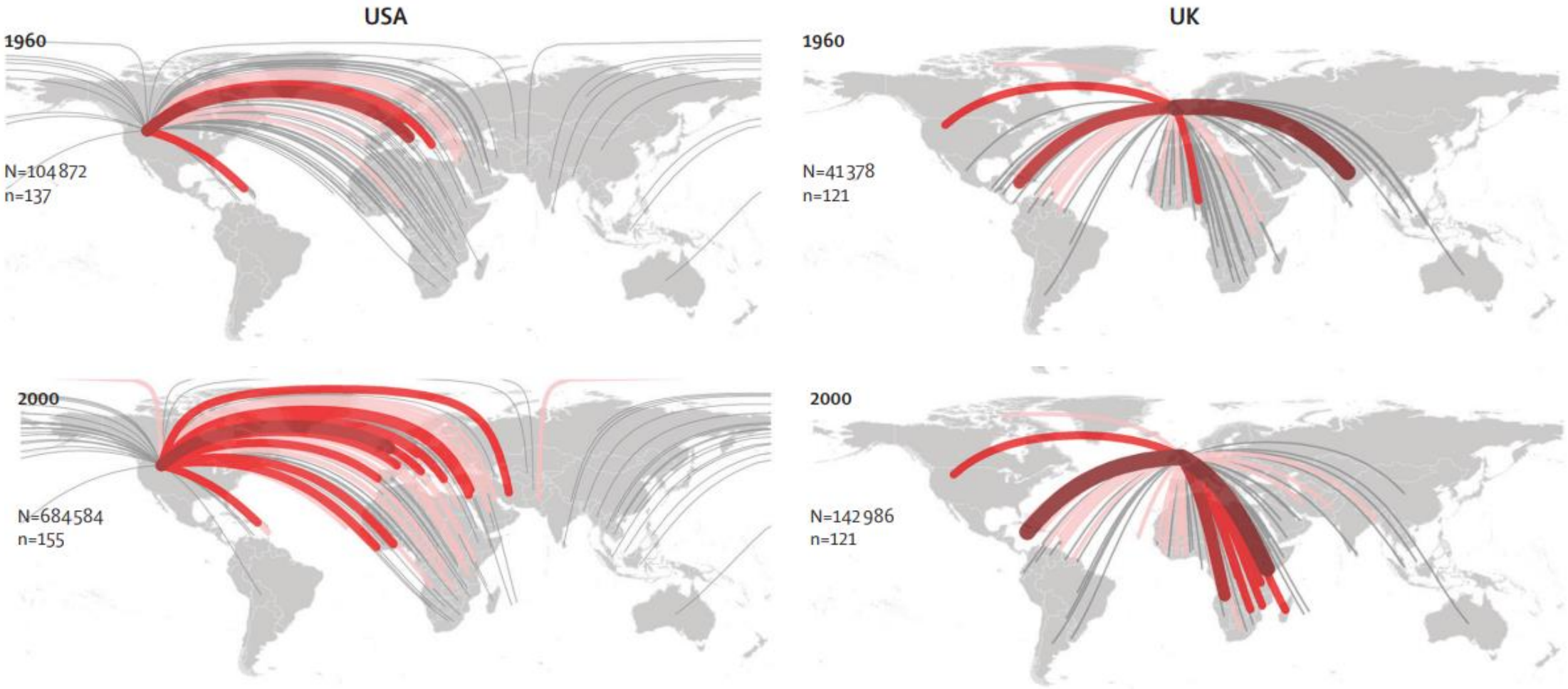
This time lag reflects both an intense learning process, but also the attention paid to the harmonization of scientific backgrounds with the organization of healthcare systems.

NCDs
43 (61.4%)

- 15 haematological malignancies
- 7 solid cancer,
- 4 supportive care
- 17 cover a wide spectrum of acute and chronic conditions

Global migration and the changing distribution of sickle haemoglobin: a quantitative study of temporal trends between 1960 and 2000

Frédéric B Piel, Andrew J Tatem, Zhuojie Huang, Sunetra Gupta, Thomas N Williams, David J Weatherall



Lancet Glob Health 2014; 2: e80–89

Reasons for rejecting the inclusion of orphan drug applications* in the EML

Applications				Re-submission and inclusion	
APIs	**Therapeutic indication**	**Year**	**Reasons**	**Year**	**Motivations**
Artemether + lumefantrine	Malaria due to Plasmodium falciparum	2000	• Use • **Accessibility**	2002	• The increasing of drug-resistant falciparum Malaria has led the use of artemisin and its derivatives to be essential • **Differential prices for developing countries**
Miltefosine	Leishmaniasis	2005	• **Evidence** • Drug • Use • **Accessibility**	2011	• Concerns about evidence have been solved • **Differential prices for developing countries**
Imatinib	Chronic myelogenous leukaemia (CML)	2011	• Disease • **Evidence** • **Accessibility**	2015	• Concerns about evidence have been solved for adults • **Generics are now available in some setting**
Bedaquiline	MDR pulmonary tubercolosis	2013	• Evidence • **Accessibility**	2015	• Significant public health need for new treatments • Availability of data on effectiveness and safety
Dasatinib **Nilotinib**	Chronic myelogenous leukemia	2015	• **Evidence**	2017	• **Relevant clinical benefit**
Gefitinib	Non-small cell lung cancer	2015	• **Evidence** • Use • **Accsessibility**	2019	• Concerns on limited magnitude of benefit have been overcome • **Availability of generic medicines as well as quality-assured diagnostic molecular tests for EGFR-mutations**
Afatinib **Gefitinib**	Alternatives, for the treatment of NSCLC in patients with activating mutations of EGFR	2017	• **Evidence**	2019	• Concerns about limited magnitude of benefits have been overcome • **Availability of generic medicines as well as quality-assured diagnostic molecular tests for EGFR-mutations**

*25 out of 262 (9.5%) applications on orphan drugs – corresponding to 22 medicines - were rejected.

Conclusions

>>> GLOBAL HEALTH NEEDS DRIVE THE UPTAKE OF ORPHAN DRUGS IN THE WHO EML

- We observed a **steep rise in the uptake of orphan drugs** in the EML, from 1.9% in 1977 to 14.6% in 2021, captured by the change of WHO EML criteria in 2000 (and echoing the rising trends of orphan drugs approved in the US and in EU)
- **60% of orphan drugs** included in the EML are listed in the **Complementary List**, thus requiring more specialized expertise and adequate facilities for their appropriate use.
- A major challenge for listing orphan drugs in the EML was dealing with the **uncertainty, mainly of clinical evidence**
- **Price** has still been considered a key issue in the WHO EML decision-making, although the price alone is no longer considered a single criterion to accept or reject the inclusion of a medicinal product in the EML