All the things you always wanted to know about INNs

PTMG Athens, Oct 5, 2023

World Health Organization

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INN/HPS/MHP

World Health Organization

Geneva, Switzerland

NOVARTIS

Antoinette Lachat

Sr. IP Counsel Immunology

Legal Brand Protection

Novartis Pharma AG

Basel, Switzerland

Agenda

- Who is WHO?
- The INN: what it is and does
- The pharma trademark: what it is and does
- INN and Trademarks: allies or aliens?
- What’s new from WHO’s side?
- Similarity Assessments
- Q&A

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World Health Organization

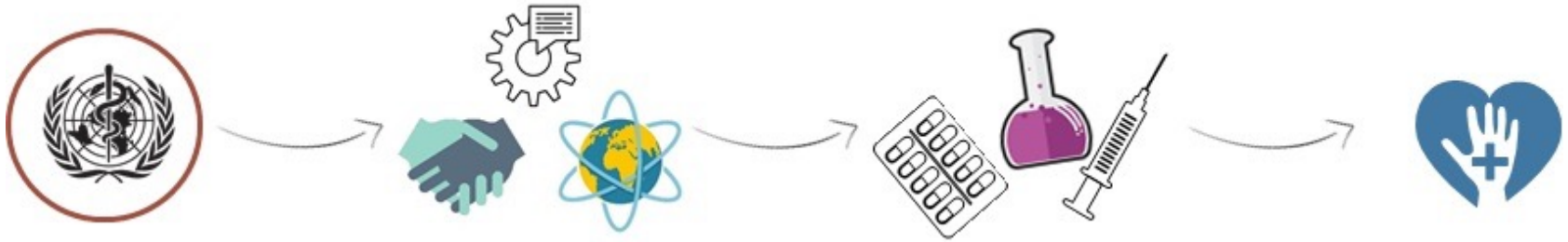
WHO is a specialised agency of the UNs serving as the directing and coordinating authority for international health matters and public health on behalf of its 194 Member States.

WHO is operating at 3 levels, HQ in Geneva, 6 regional offices and 150 country offices

Principle objective - ***the attainment by all people of the highest possible level of health.***

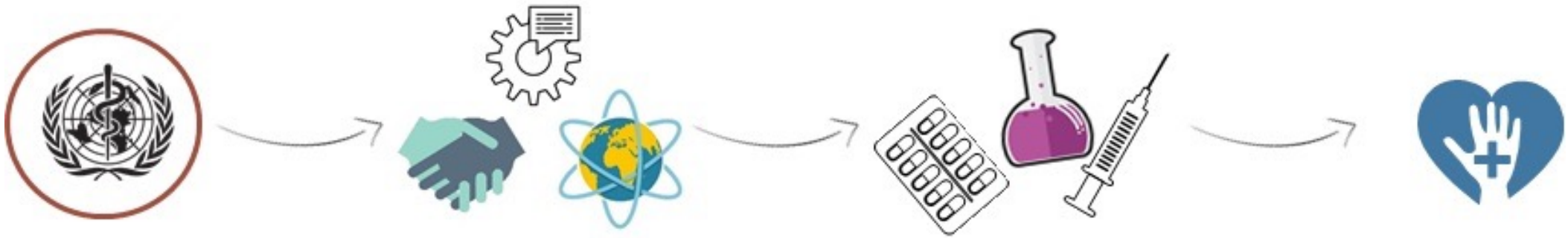
WHO is responsible for providing leadership on global health matters, shaping the health research agenda, **setting norms and standards**, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.

Setting norms and standards and promoting their implementation is affirmed as **a core function** of WHO.



Norms & Standards: WHO Core Business

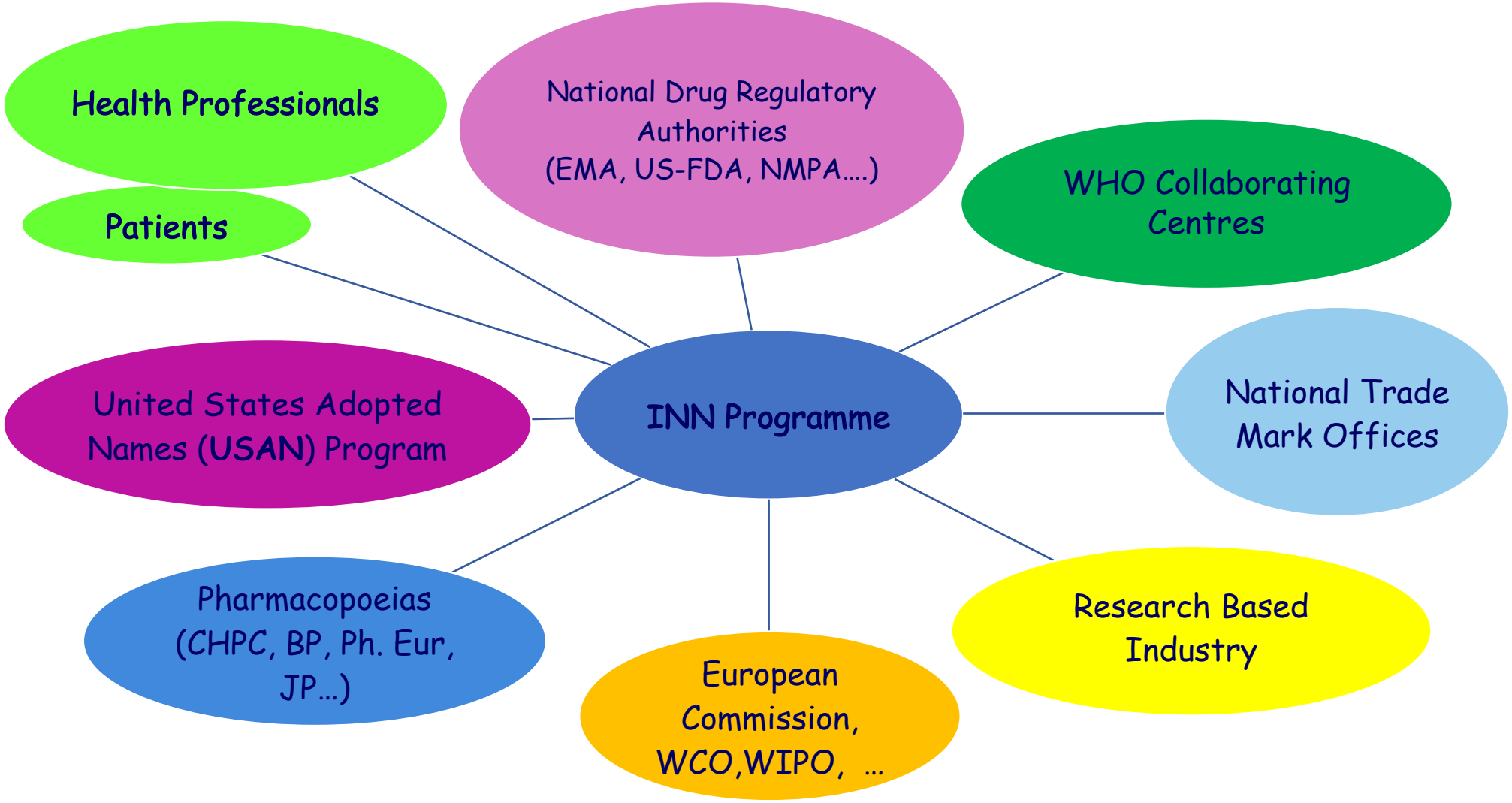
The Constitution requires WHO“ to develop, establish and promote **INTERNATIONAL STANDARDS** with respect to biological and pharmaceutical products”.



International Nonproprietary Name (INN)

- Unique name
- Distinctive in sound and spelling
- Not liable to confusion with other names in common use
- Formally placed by WHO in the public domain
- Can be used without any restriction to identify pharmaceutical substances

INN Stakeholders



INN

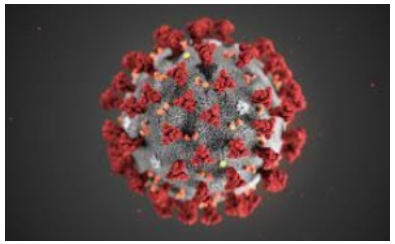
Ebola

galidesivir

Hepatitis C

sofosbuvir
(now in EML)

COVID-19



tozinameran, elasomeran

Nonproprietary Name & Proprietary Name
(valsartan) (Diovan®)

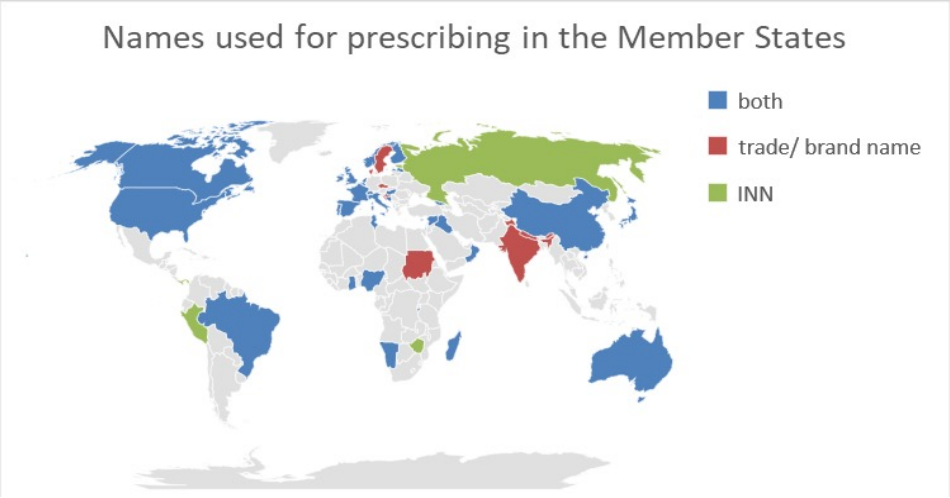
Identifies active pharmaceutical ingredient

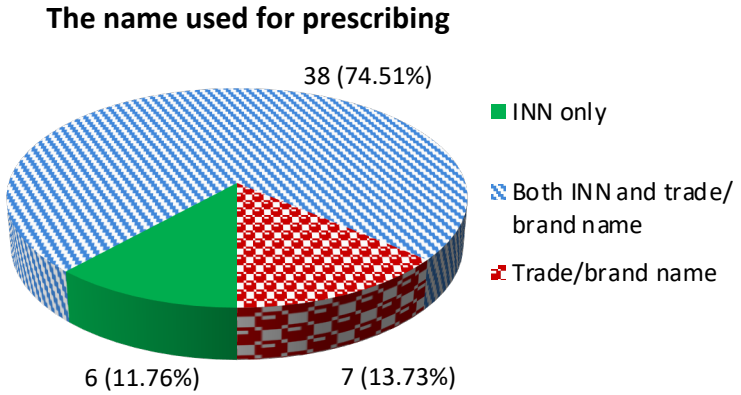
®/™ identifies product of a specific source

In most Member States, INN are used for prescribing

WHO Drug Information, Vol.35No.4, 2021 - WHO Drug Information - Volume 35, No. 4

- INN are mandatory in Armenia, Estonia, Panama, Peru, Russian Federation and Zimbabwe.
- Brand / trade names are obligatory in Croatia, Czech Republic, Denmark, India, Nepal, Sudan and Sweden.

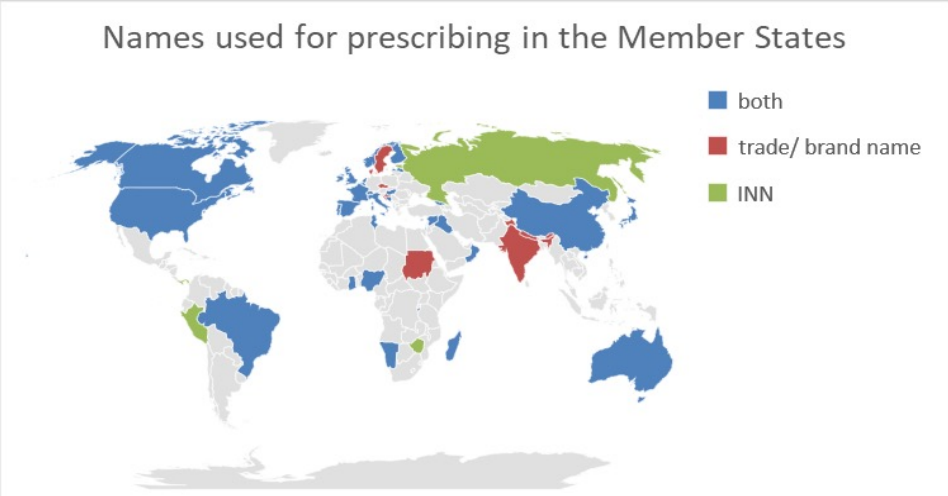


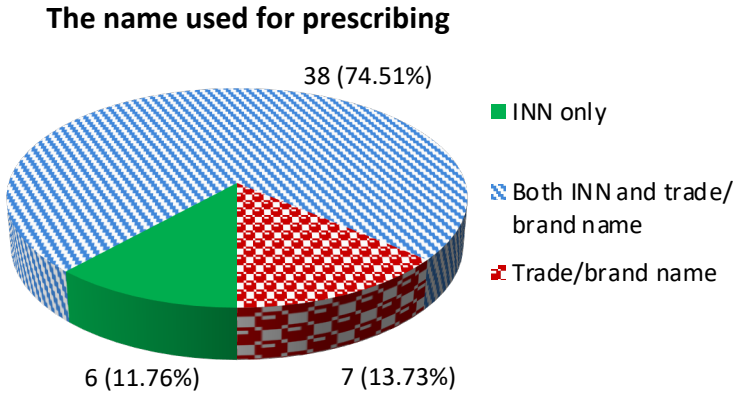


INN in USA, Switzerland and Greece

WHO Drug Information, Vol.35No.4, 2021 - WHO Drug Information - Volume 35, No. 4

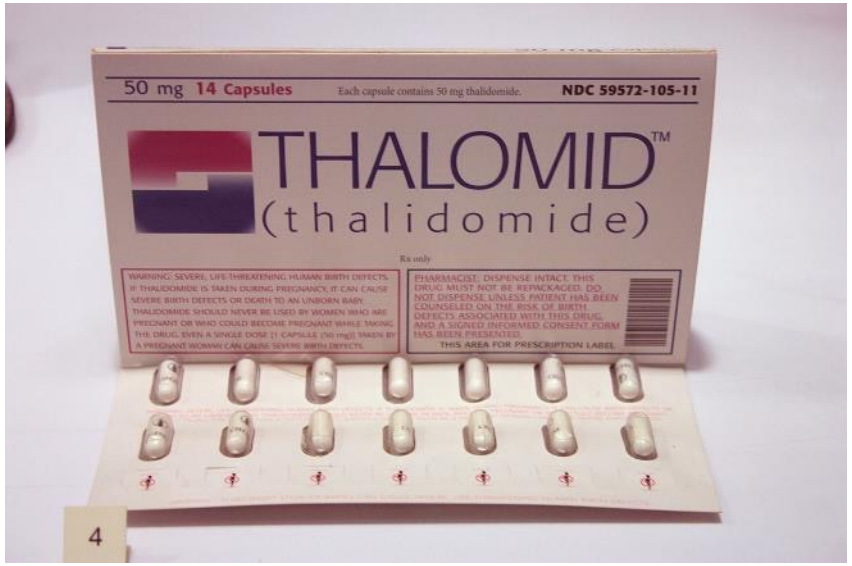
- INN and brand names can be used in **USA**, **Switzerland** and **Greece** for prescription, however in Greece brand name's use is restricted,





INN is a global name for the entire lifecycle of a molecule

thalidomide (8)(4)



Contergan® … And …. Immunoprin®, Talidex®, Talizer®, Neurosedyn®, Distaval® and many others

One INN can get various Trademarks

Global mark in Transplantation

CERTICAN® everolimus

ZORTRESS® (everolimus) Tablets 0.25 mg, 0.5 mg, 0.75 mg

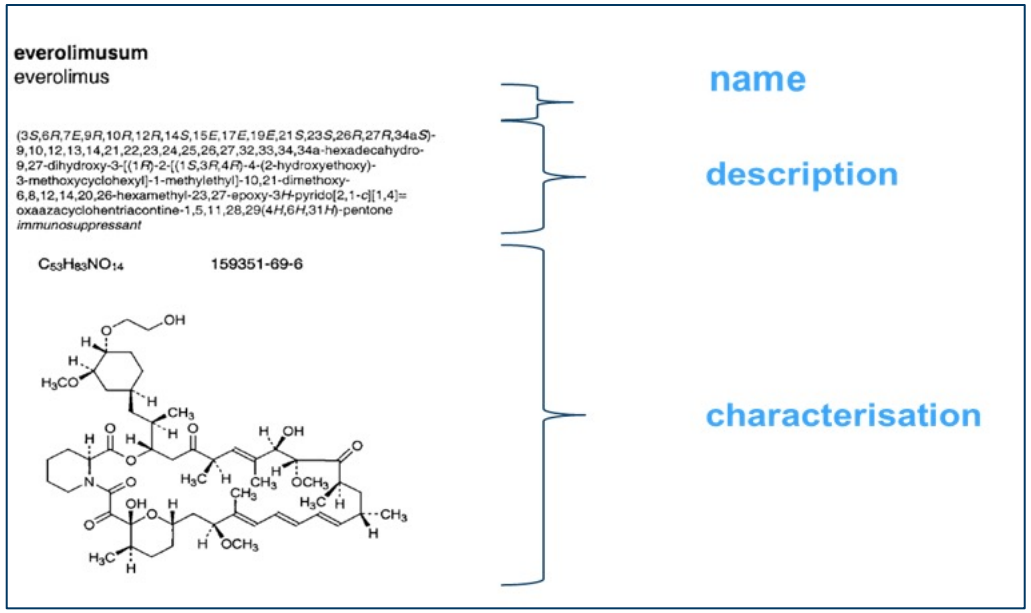
2nd indication: diff. Strength in Onco

AFINITOR® (everolimus) tablets

VOTUBIA® (everolimus) tablets

2nd Onco Indication in EU

Comparison



Passport / Trilogy of the INN: Name (in 6 languages) + Description (IUPAC name) + Characterisation; change in Characterisation may affect the name! Available for anybody's use as long as all 3 components apply.

Analogy: Name + Description of protected scope + bibliographic data consisting of owner, birthdate & nr.

INN & Trademarks are 2 different Species

INN

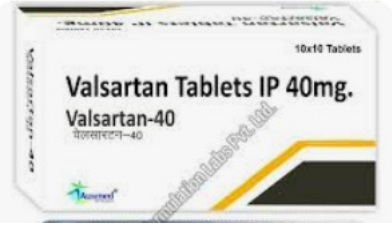
- Unique Identifier of the active molecule; *scientific concept*
- **Eternal Vehicle for Patient Safety**

Trademark

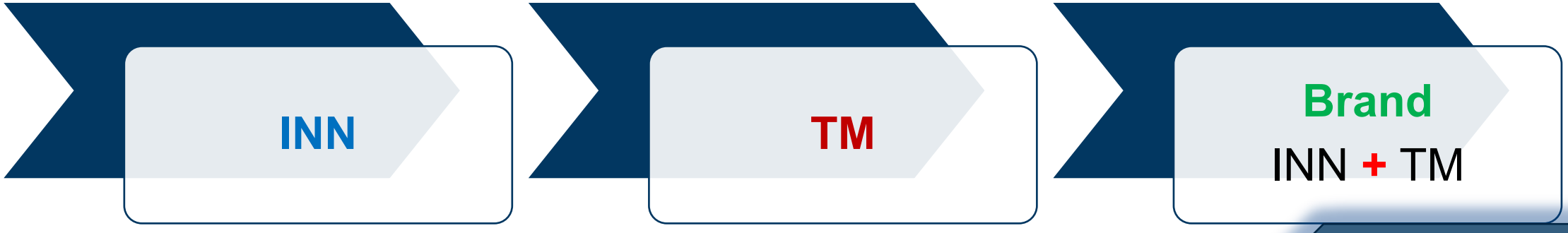
- Unique Identifier of the origin; *legal concept*
- **Eternal Vehicle for Quality**

Product

- Keep them separate; do not add or remove any letters (Proper Trademark Use = Proper INN Use)
- **Blurring / Mixing them results in redundancy and risks**



Where INN & TM fit in the drug development path



How to create?
How to characterize?
Similarity INN – INN
Similarity INN – INN stem
Similarity INN - TM

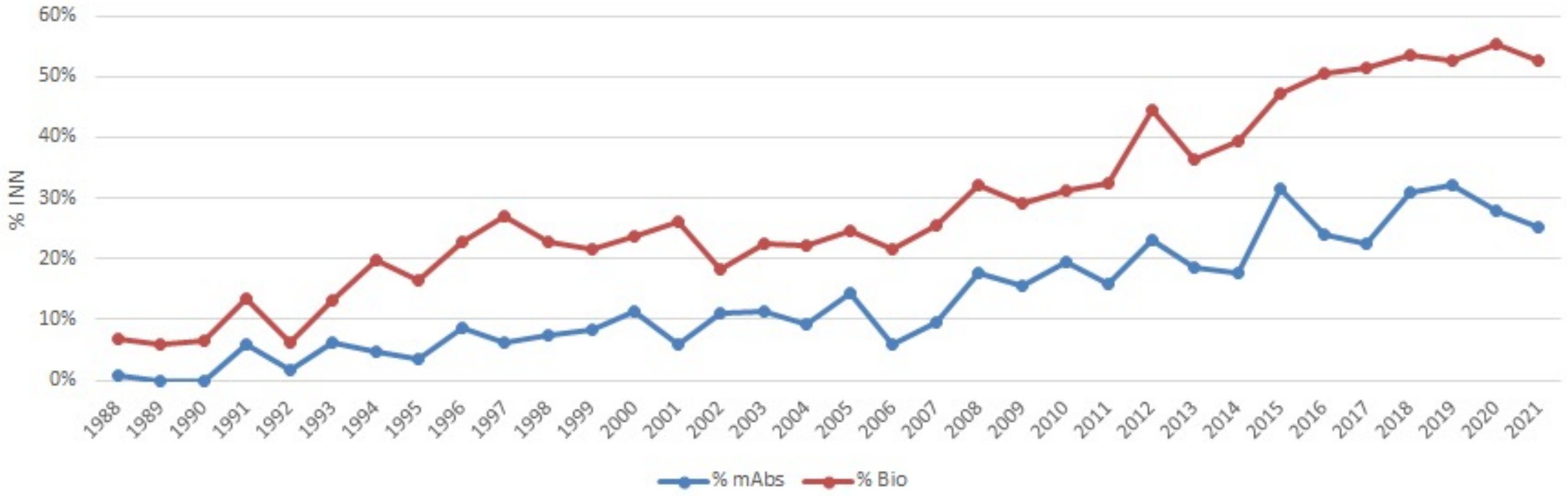
We create distinct candidates
We search & identify potentially viable ones
We understand case law
We file, defend, pressure test them

pre-approval from HAs

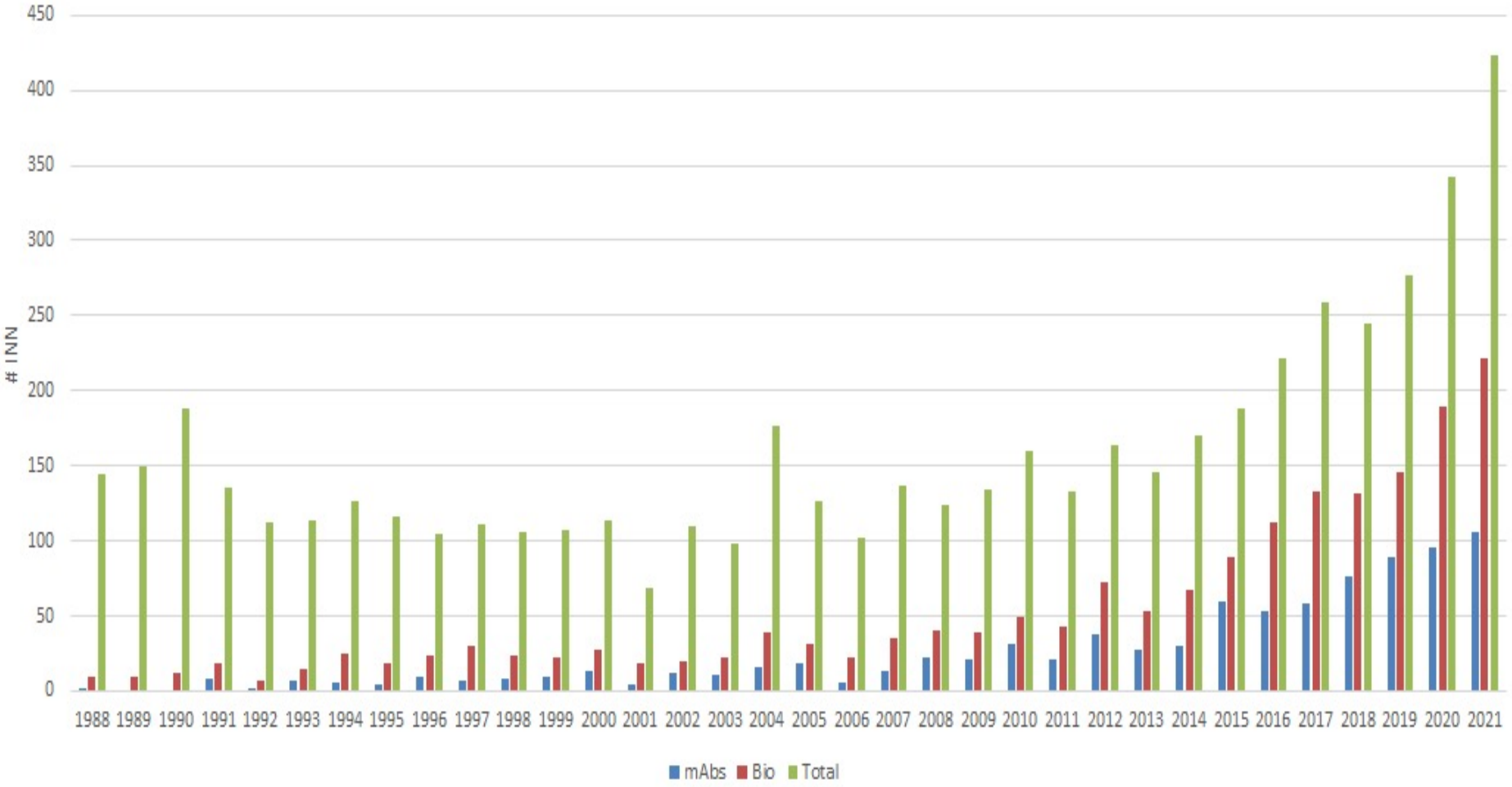
Confidential Data

New INNs, new INN stems, TM with Health Authority for (pre-) approval & launch

Percentage of published INN for biological requests and monoclonal antibodies through the years.

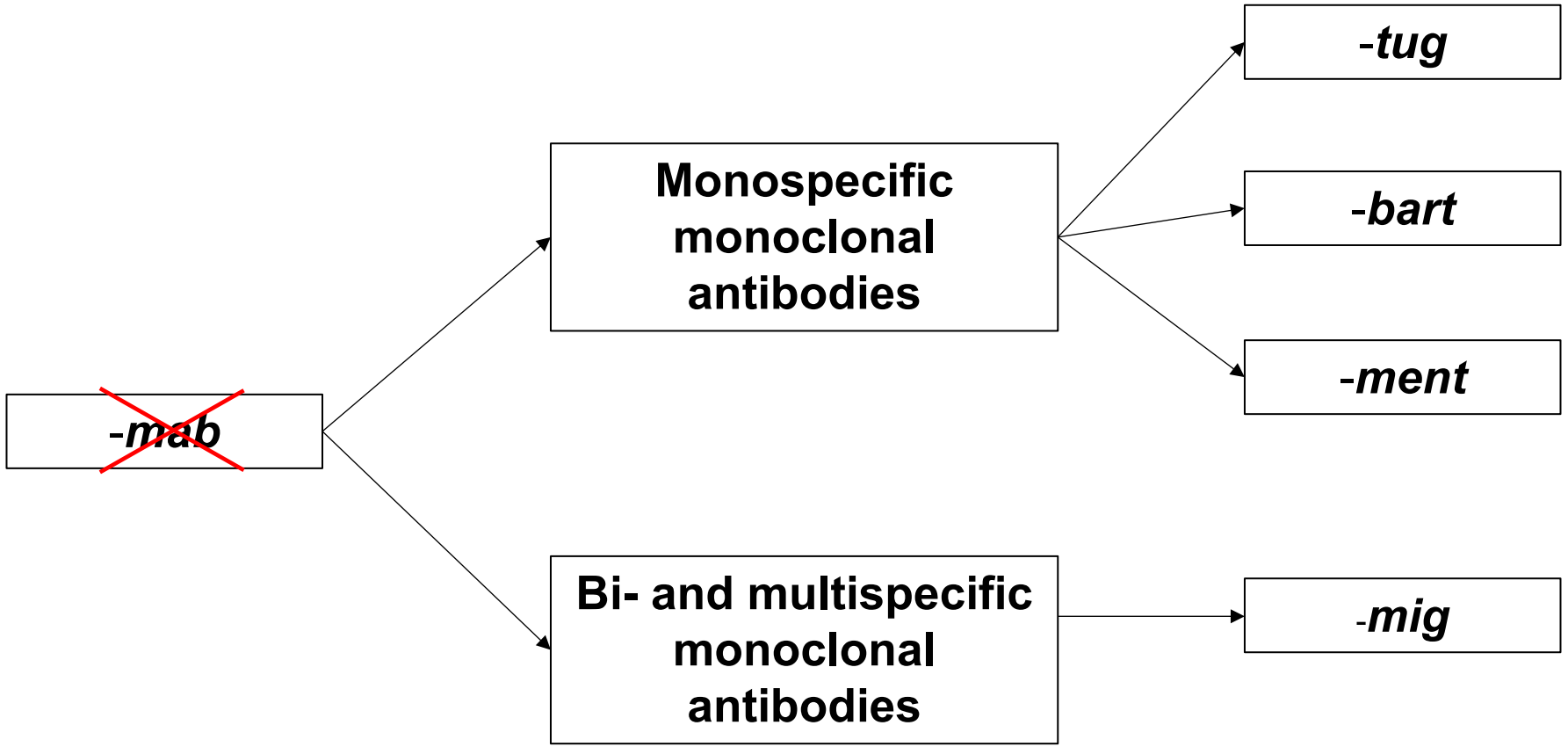


879 INN with the stem -mab have been assigned until 2021



Discontinuing the stem “-mab” and its replacement with four new stems

New INN nomenclature for monoclonal antibodies - The Lancet
Full article: International nonproprietary names for monoclonal antibodies: an evolving nomenclature system (tandfonline.com)

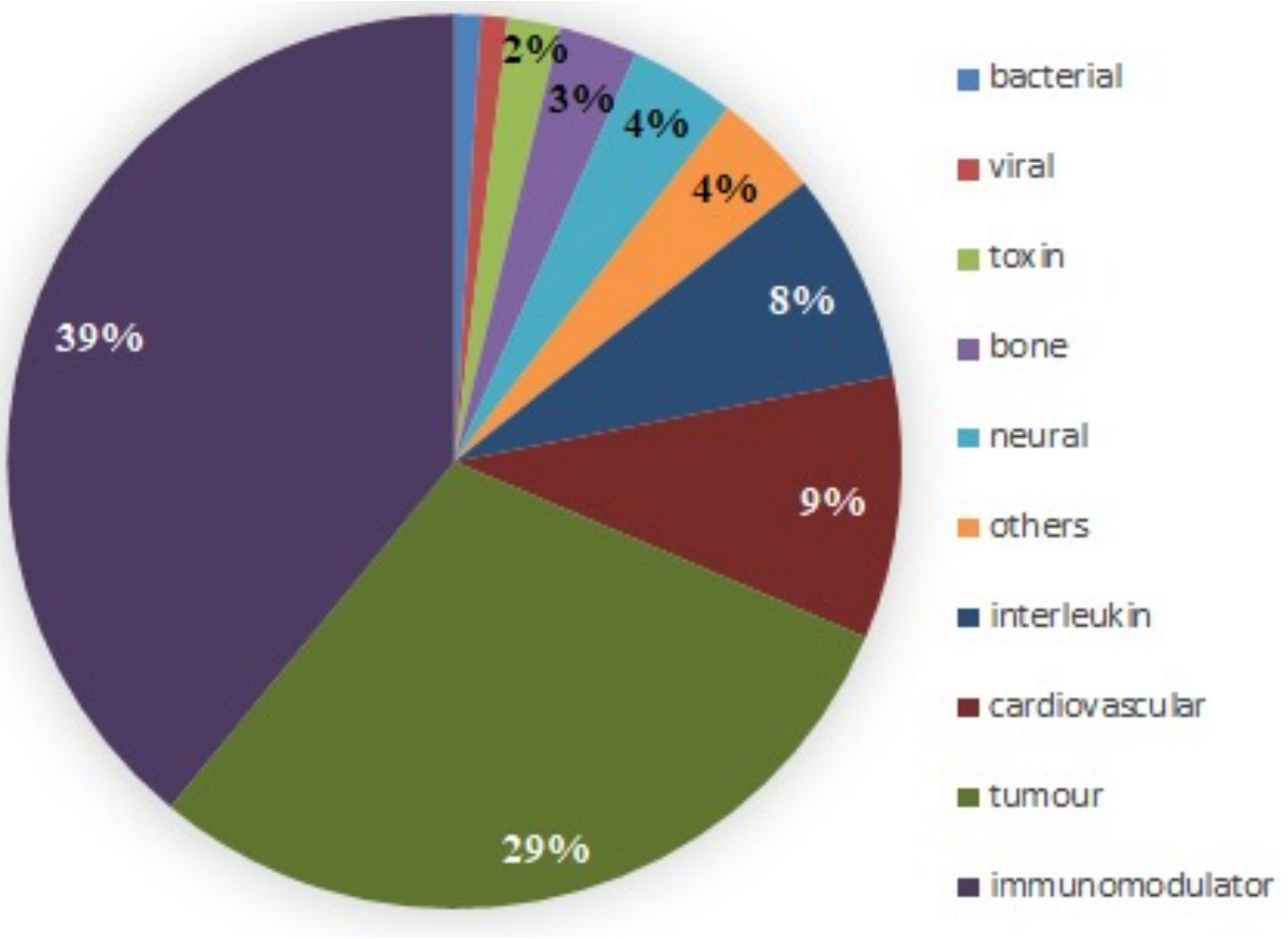


And new stem categories like:

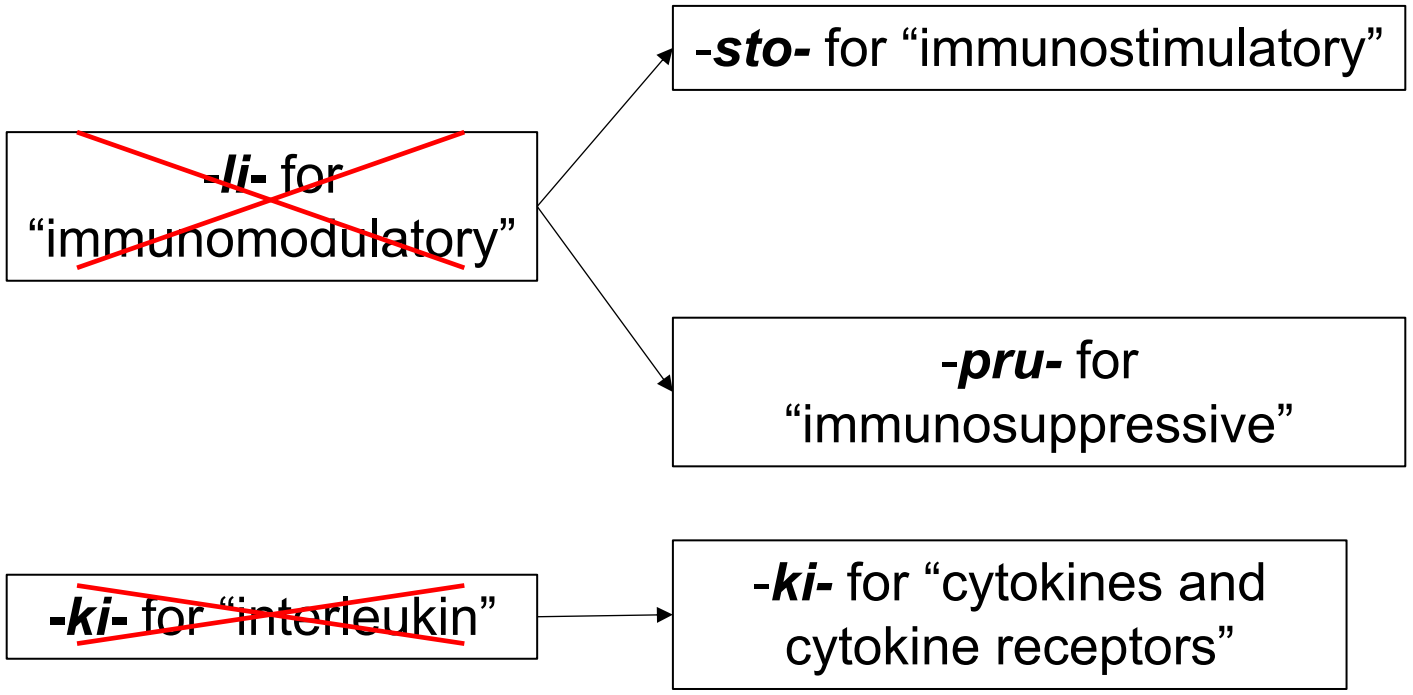
- ***tug***
- ***bart***
- ***ment***
- ***mig***

- ***Can we object?***
- ***How to conceive?***

Marketed INN for monoclonal antibodies by target infix.



Further changes to infixes

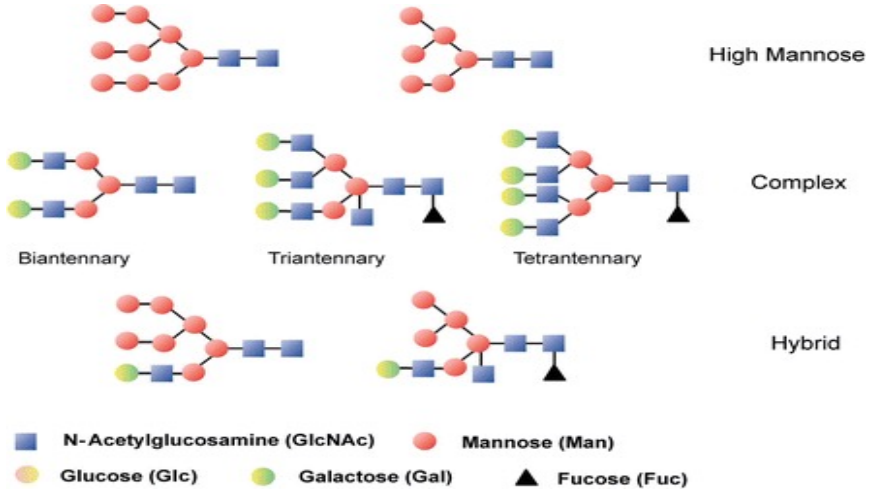


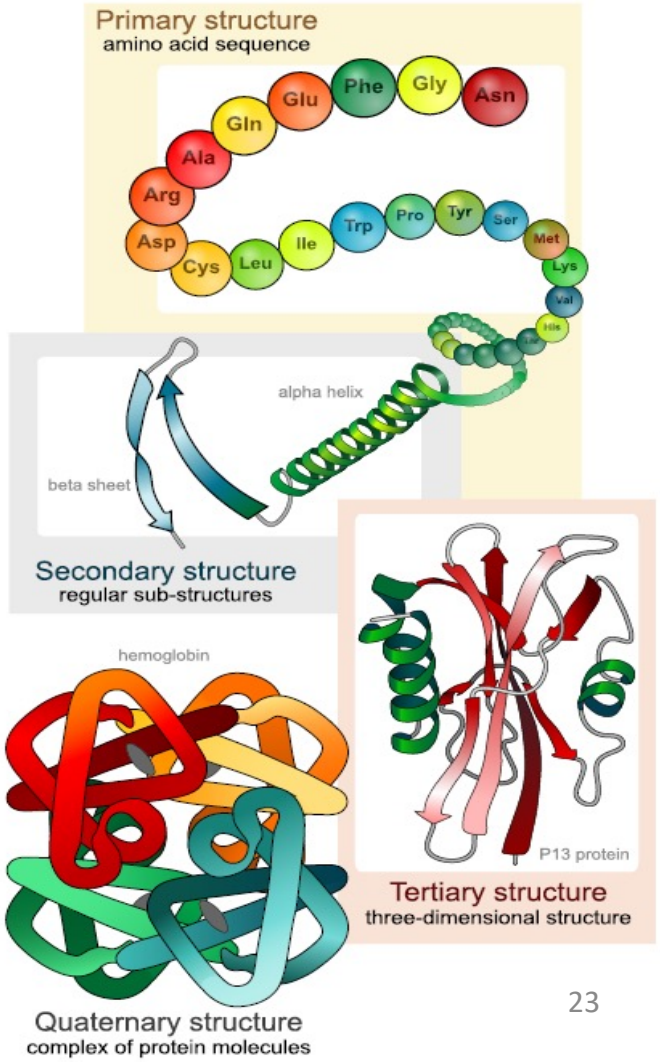
[INN Working Doc. 22.542: New INN nomenclature scheme for monoclonal antibodies]

Background BQ

Biotherapeutic proteins are very different to chemical medicines::

- Size
- Complexity – structure

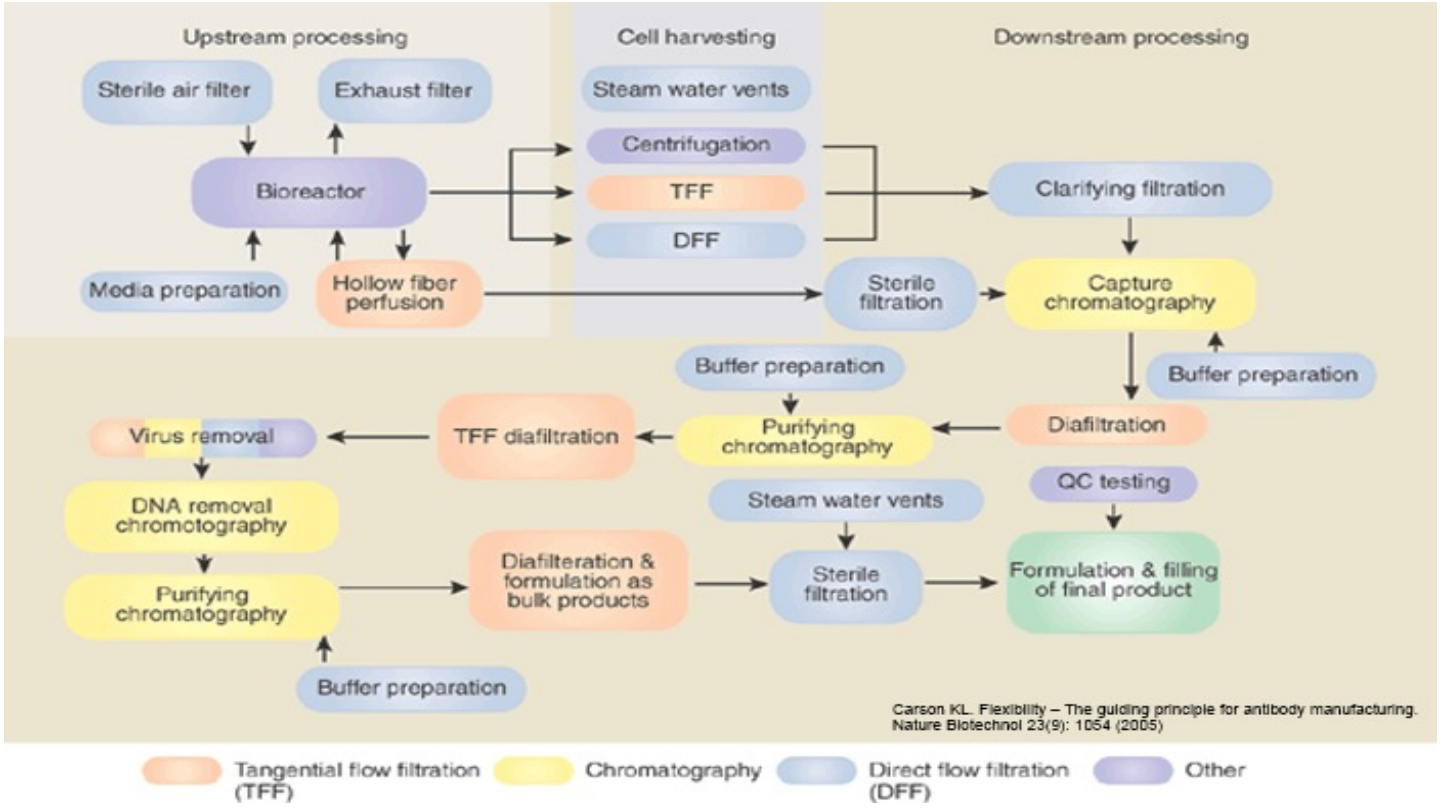




Background BQ

Biotherapeutic proteins are very different to chemical medicines::

- Size
- Complexity – structure
- Complexity – manufacture

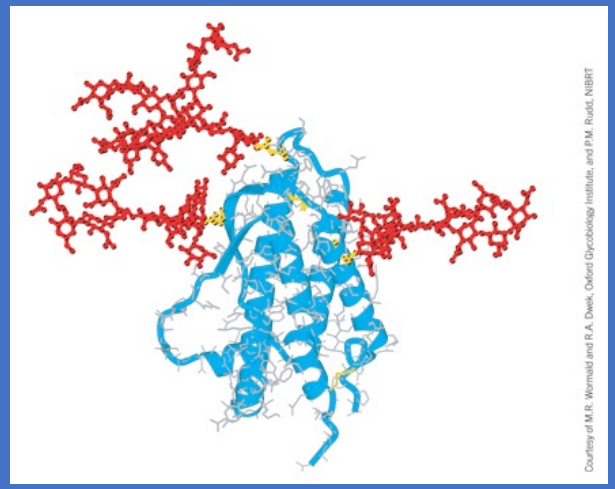


Background BQ

Biotherapeutic proteins are very different to chemical medicines::

- Size
- Complexity – structure
- Complexity – manufacture
- Heterogeneity

EPO



- Mass = 27948±285 deglycosylated 18240±4
- 2 disulphide bonds
- 3 N-glycosylation
- 2 O-glycosylation sites
- Many types of glycans
- C-terminal truncation

Even the most controlled biotechnological process produces a spectrum of 100 000s of molecules – all potentially having different activity, circulatory half-life and potential to induce an immune reaction. Therefore every different process effectively produces a different product.

National biological identifier schemes

NRA (Country)	Issue	Approach	Pros and Cons
FDA (USA)	Pharmacovigilance of all new biological medicines	Addition of a four-letter (with vowels) suffix hyphenated to USAN (e.g. infliximab-dyyb or -abda & epoetin alfa-epbx).	Simple and easy to administer. Use of vowels incompatible with BQ. At least one suffix is commercial (–sndz).
EMA (European Union)	Pharmacovigilance of all new biological medicines	No separate scheme, use of tradenames & 2D barcode tracing is sufficient.	2D barcode more complex & expensive to implement esp. in developing countries.
PMDS (Japan)	Distinguishing biosimilar from reference medicines	Addition of suffix (BS1, BS2 etc.) for biosimilars.	Simple. Potential for confusion with many biosimilars
TGA (Australia)	Distinguishing a medicine with differing glycosylation profile.	Insistence on the use of a different Greek letter to that assigned by WHO.	Non-compliance with WHO naming convention.

WHO International Nonproprietary Name

Because INNs are allocated on the basis of the amino acid sequence, the sole use of the INN is not able to distinguish between these differing products.

It was concluded that some kind of distinguishing identifier should be used with the INN. In July 2014 a proposal was published for a Biological Qualifier (BQ). After extensive consultation, the Proposal was finalised in June 2015 and adopted in April 2016, but was shelved shortly afterward.

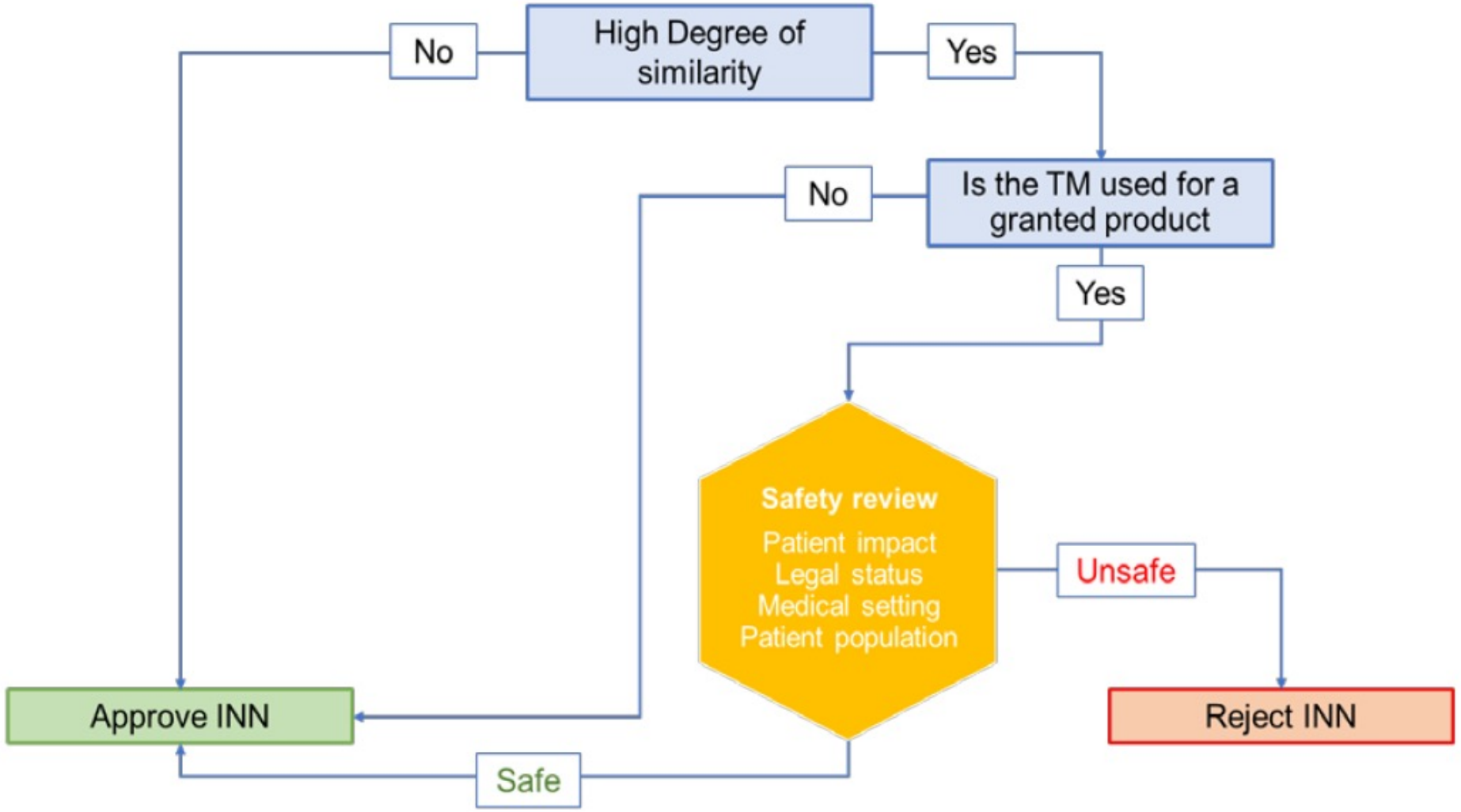
The aim of the BQ is to uniquely identify ALL biological medicines with a unique code.

Similarity

➢When is similar too similar? And in what pronunciation? Human or artificial?

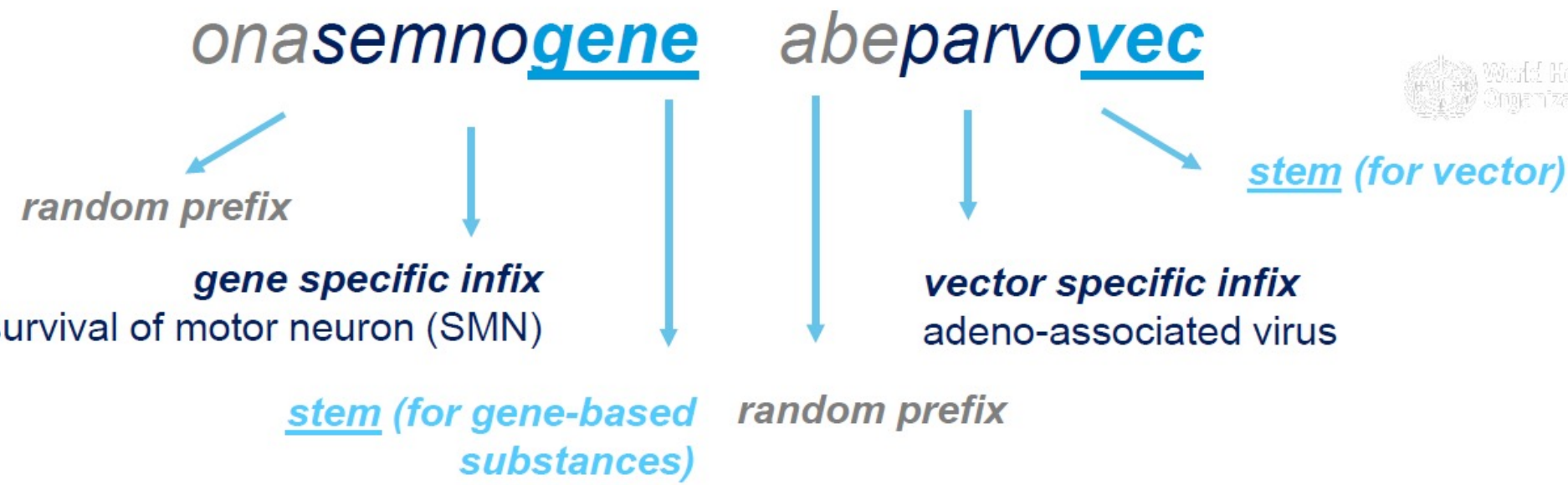
Same stem category	Different stem category	Overall similarity
Rodabrutinib/radotinib	ersodetug / erzotabart	avapritinib – evo**brutinib**
Vialumab/avelumab	tinodasertib / tinocabtagene autoleucel	Axal® - axaltenibart (alprazolam)
Bafilumab/namilumab	Vidofludimus / vidoflufolastat (18F)	Bevit® - bevitug (thiamine hydrochloride)
Rivulumab/rilotumumab	Ronactolol / ronacaleret	
	Alirenitide / alizapride	

WHO's Flowchart



Nomenclature scheme for gene therapy substances

Two-word scheme



What is in the name: gene therapy substance, gene of interest, non-replicating viral vector, virus vector type

What is not included: details of the vector

Nomenclature scheme for cell therapy substances

One-word scheme

darvadstrocel

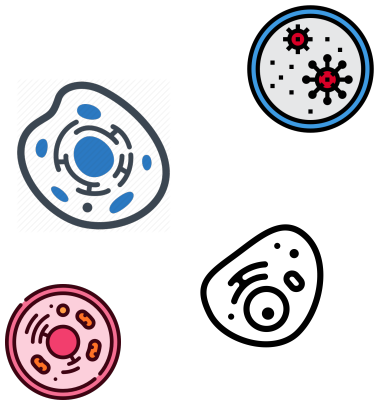
random prefix

cell type specific infix

stem (for cell-based substances)

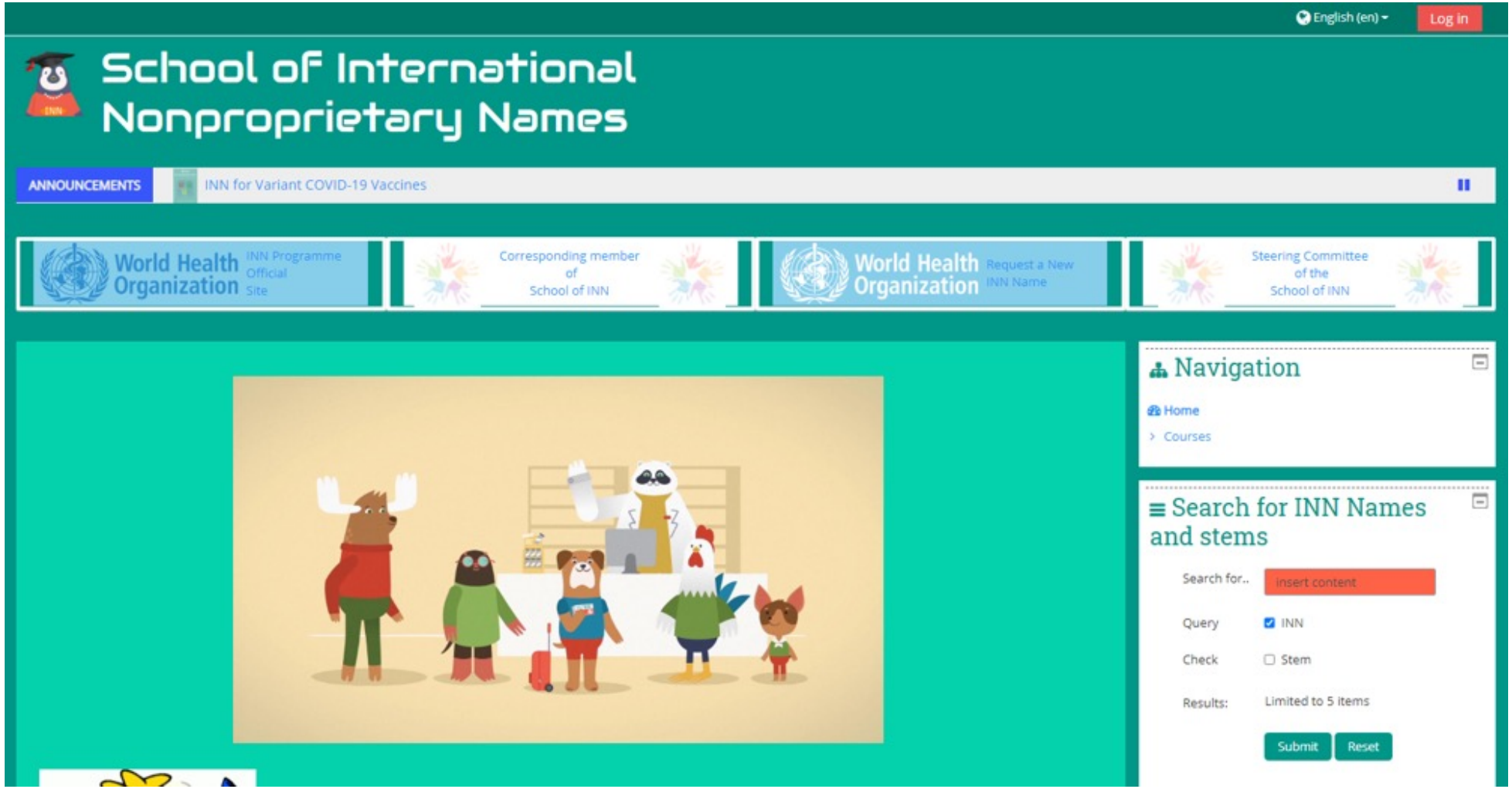
What is in the name: cell therapy substance, not genetically manipulated, primary cell type

What is not included: autologous or allogeneic substance, cell manipulation, composition of the final cell substance



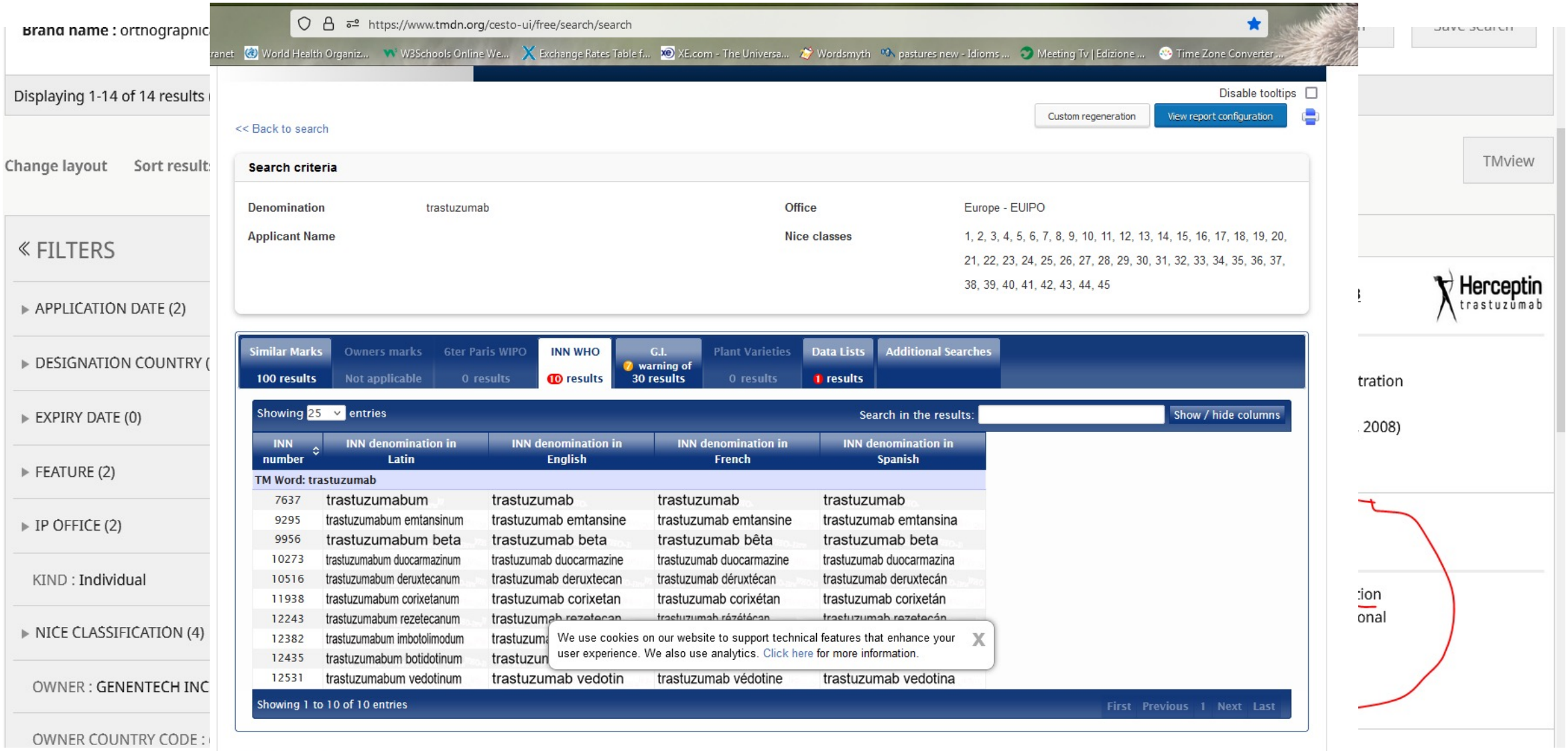
School of INN (SoINN) Platform

https://extranet.who.int/soinn



https://www.youtube.com/embed/lv51EVLmess?rel=0&autoplay=1

INN Global Data Hub



INN MedNet

- **Mednet Search Tool**
  https://extranet.who.int/soinn/
- On-line queries of WHO INN data for lists of Proposed and Recommended INN
  Example: **“beglogene”**

		INN N°	Substance name click to see names in multiple languages	Proposed list	Recommended list
		10505	betibeglogene darolentivec	116	78
		10900	betibeglogene autotemcel	125	86
		11826	lovotibeglogene autotemcel	125	87
		12025	nulabeglogene autogedtemcel	126	

WHO Drug Information: https://www.who.int/teams/health-product-and-policy-standards/inn/inn-lists/

What's in an International Non-Proprietary Name?

12102	volamcabtagene durzigedleucel	126	88
12108	laruparetigene zovaparvovec	126	88
12109	ixoberogene soroparvovec	127	89
12119	dalucabtagene autoleucel	126	88
12142	equecabtagene autoleucel	127	89
12143	cretostimogene grenadenorepvec	127	89
12186	anbalcabtagene autoleucel	127	89
12196	linvekinogene treniplasmid	127	89
12208	varnimcabtagene autoleucel	127	89
12215	satricabtagene autoleucel	127	89
12220	alvamemugene sulseparvovec	127	89
12223	ninsipapogene sibarnarepvec	127	89
12224	esepapogene zalarnarepvec	127	89
12225	seglebegagene dasniparvovec	127	89
12226	alnugranogene aldeparvovec	127	89
12227	crosigalcogene omlixparvovec	127	89
12248	zocaglusagene nuzaparvovec	127	89
12254	pomlucabtagene autoleucel	127	89
12261	vixicovtogene oboplasmid	126	88
12263	tremtelectogene empogeditemcel	127	89
12276	umitrelimorgene autodencel	127	89

Do these really meet the objectives to simplify identification?

If the nomenclature imposes '-cabtagene autoleucel' – we can create xyzcabtagene autoleucel only?

Results Counter (max 850) = 25

		INN N°	Substance name click to see names in multiple languages	Proposed list	Recommended list
		11110	tebrocabtagene autoleucel	121	83
		11131	ciltacabtagene autoleucel	122	84
		11274	orvacabtagene autoleucel	122	84
		11372	relmacabtagene autoleucel	123	85
		11437	gavocabtagene autoleucel	123	85
		11486	obecabtagene autoleucel	123	85
		11574	zamtocabtagene autoleucel	124	86
		11704	zevorcabtagene autoleucel	125	87
		11832	acmucabtagene autoleucel	125	87
		11886	brexucabtagene autoleucel	125	87
		11887	itezocabtagene autoleucel	125	87
		11931	plixacabtagene autoleucel	126	88
		11974	rapcabtagene autoleucel	126	88
		12119	dalucabtagene autoleucel	126	88
		12142	equecabtagene autoleucel	127	89
		12186	anbalcabtagene autoleucel	127	89
		12208	varnimcabtagene autoleucel	127	89
		12215	satricabtagene autoleucel	127	89

These lengthy INN result in INN Abbreviations

2. Tumor-Specific CAR-T Cell Immunotherapy

2.1. Hematologic Malignancies

Since the first FDA approval in 2017, there are five CAR-T cell therapies are available to date. They are tisagenlecleucel (tisa-cel, Novartis: refractory and relapsed (r/r) B-ALL, r/r DLBCL, CD19-41BB-CD3z CAR-T, cryopreserved PBMC), axicabtagene ciloleucel (axi-cel, Kite Pharma: r/r DLBCL, CD19-CD28-CD3z CAR T, fresh PBMC), brexucabtagene autoleucel (brex-cel, Kite Pharma: r/r mantle cell lymphoma, CD19-CD28-CD3z CAR T, enriched T cell), lisocabtagene maraleucel (liso-cel, Juno Therapeutics & Bristol Myers Squibb: r/r DLBCL, CD19-41BB-CD3z CAR T, 1:1 mixture of CD4:CD8 T cell), and idecabtagene vicleucel (ide-cel, Bristol Myers Squibb: r/r MM, BCMA-41BB-CD3z CAR T, CD8 T cell) [5]. CAR-T cells developed by Kite Pharma, axi-cel and brex-cel, consist of CD28

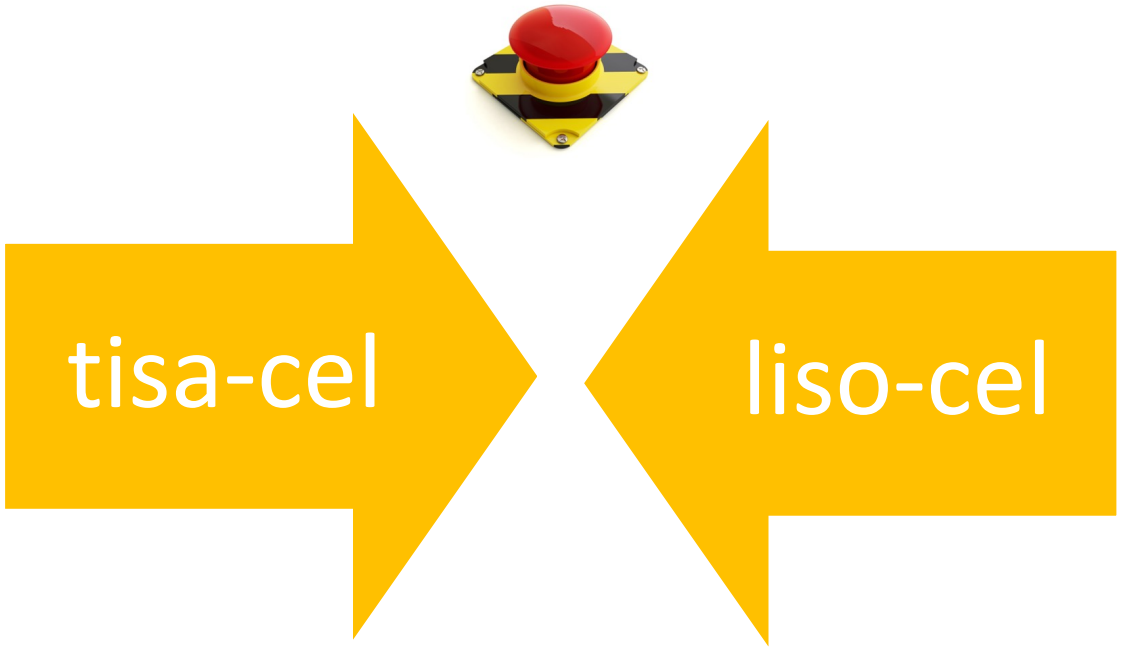
Sponsors & Journals abbreviate them!

Chimeric antigen receptor (CAR) T-cell therapies are adoptive cell immunotherapies that have led to remarkable patient outcomes and transformed the treatment landscape in relapsed or refractory (R/R) B-cell malignancies and multiple myeloma [1,2,3,4,5]. Currently, 6 CAR T-cell products are approved by the Food and Drug Administration (FDA): tisagenlecleucel (tisa-cel; Kymriah®), axicabtagene ciloleucel (axi-cel; Yescarta®), brexucabtagene autoleucel (brex-cel; Tecartus®), lisocabtagene maraleucel (liso-cel; Breyanzi®), idecabtagene vicleucel (ide-cel; Abecma®), and ciltacabtagene autoleucel (cilta-cel; Carvykti®).

Problematic Result:

tisagenlecleucel

lisocabtagene maraleucel



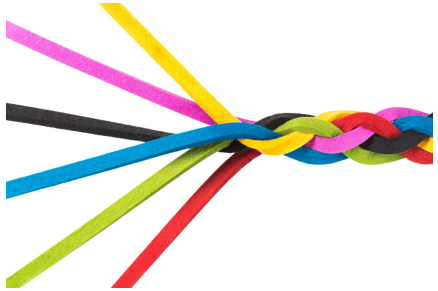
PL126: Example of a cell therapy definition paragraph

World Health Organization

evencaleucelum
evencaleucel

autologous lymphocytes enriched in activated natural killer cells (NK), derived from peripheral blood mononuclear cells (PBMCs). The cells are cultured in medium supplemented with human serum and interleukin 2 (IL-2), and activated by addition of the anti-CD3 antibody *muromonab-CD3*. At least 10% of the cells are NK cells (CD3-CD56+), but the substance also contains T cells (CD3+CD56-) and NK-like T cells (CD3+CD56+). At least 30% of the NK cells show cytotoxic activity and respond in a functional test against the leukemia cell line K562 with surface expression of lysosomal-associated membrane protein 1 (LAMP-1, CD107a).
cell therapy (antineoplastic)

That black box is a real concern!



We are Allies – not Aliens!

- **FDA, EMA and INN Experts** all have access to ***confidential*** information:
  - **to be launched product identifiers (trademarks)**
  - **to be published INN data (INN stems/substems, pINN).**
- WHO's policy to compare to ***in market*** trademarks only remains a concern. A pINN can be amended with less effort than a close to launch trademark.
- INN / stems that are published later than the trademark has been filed should not be a stumbling block for a launch trademark. The trademark should actually prevail in the regulatory review. The 'grace period of non-use' governing trademark oppositions could also be respected in INN – TM conflicts.
- Adoption of a conflicting non-proprietary name or stem can destroy exclusivity of a pre-approved trademark & jeopardize uniqueness of both

Trademarks derived from INN…

Numéro de dépôt : TN/E/ 2022/76
Date de dépôt : 09/02/2022
Titulaire : SUN PHARMACEUTICAL INDUSTRIES LIMITED
Adresse : 1 rue de Stockholm F-75008 Paris, France
Mandataire : Abdelmattaleb NASR
NASRIP, Carthage Innovation, Ecole Polytechnique de Tunisie BP 743, La Marsa 2070 -Tunisie
Produits ou services désignés :
Classe 5 Préparations et substances pharmaceutiques; préparations et substances médicinales;

ROSUVAS

rosuvastatinum **rosuvastatin**	(3*R*,5*S*,6*E*)-7-[4-(*p*-fluorophenyl)-6-isopropyl-2-(*N*-methylmethane sulfonamido)-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid *antihyperlipidaemic*
rosuvastatine	acide (3*R*,5*S*,6*E*)-7-[4-(4-fluorophényl)-6-(1-méthyléthyl)-2-[méthyl (méthylsulfonyl)amino]pyrimidin-5-yl]-3,5-dihydroxyhept-6-énoïque *antihyperlipidémiant*
rosuvastatina	ácido (3*R*,5*S*,6*E*)-7-[4-(*p*-fluorofenil)-6-isopropil-2-(*N*-metilmetano sulfonamido)-5-pirimidinil]-3,5-dihidroxi-6-heptenoico *antihiperlipémico*

Tipo de Marca: Marca de Fábrica y Comercio
Signo solicitado:

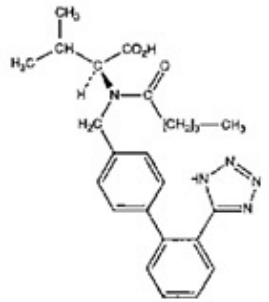
VALSAN

Clasificación internacional de Niza:
Clase: 5
Productos/Servicios:
Productos farmacéuticos del sistema nervioso central.
Número de expediente: 2022-002863
Fecha de Presentación de la Solicitud: 8 de noviembre del 2022.
El presente aviso tiene una vigencia de 15 días hábiles, contados, a partir de su entrega. Emitido en la ciudad de Managua, Nicaragua siete de diciembre, del año dos mil veintidos. Opóngase. Registrador.

≠

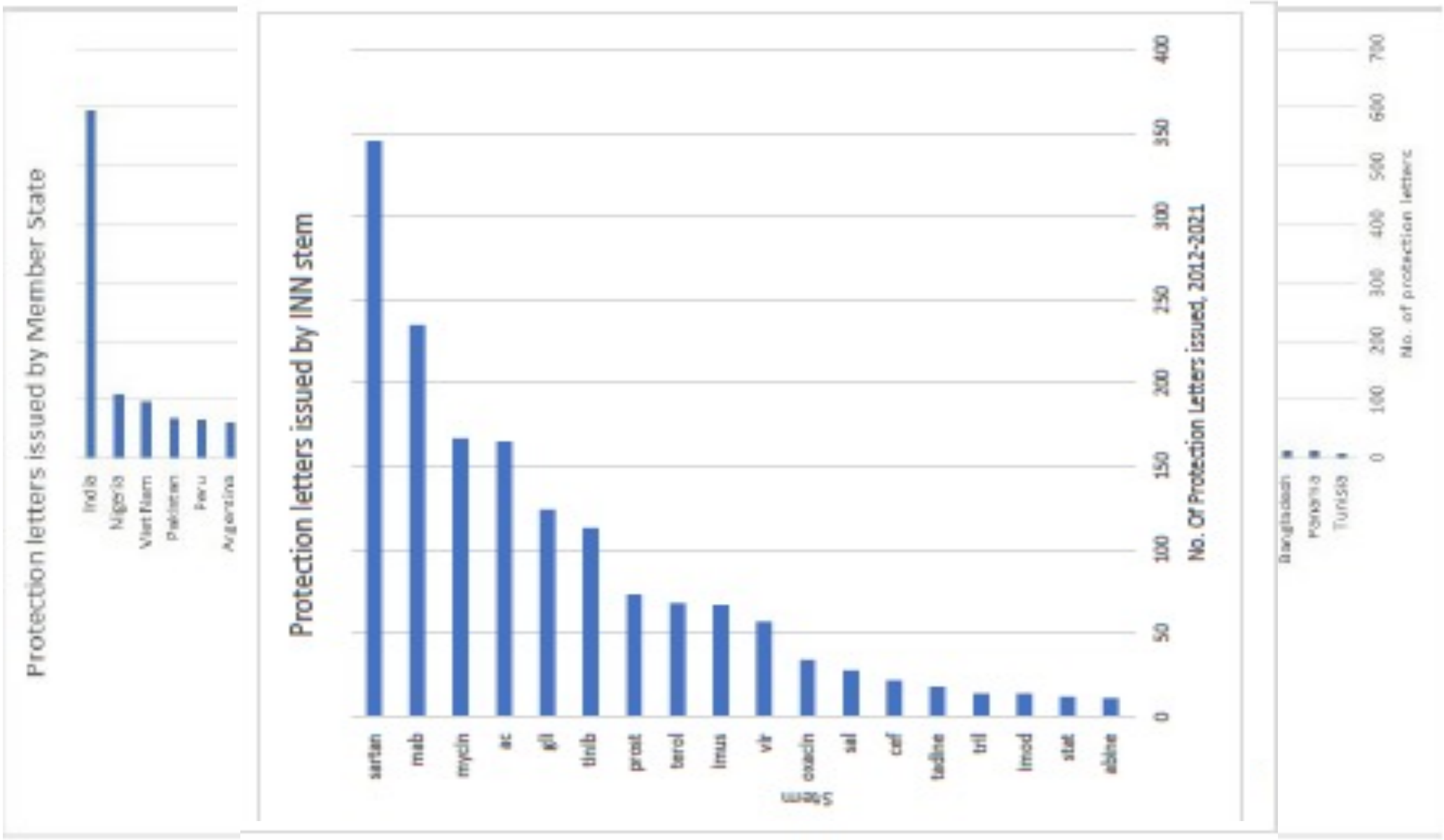
valsartanum
valsartan

N-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-*N*-valeryl-L-valine
$C_{24}H_{29}N_5O_3$ 137862-53-4 *antihypertensive*

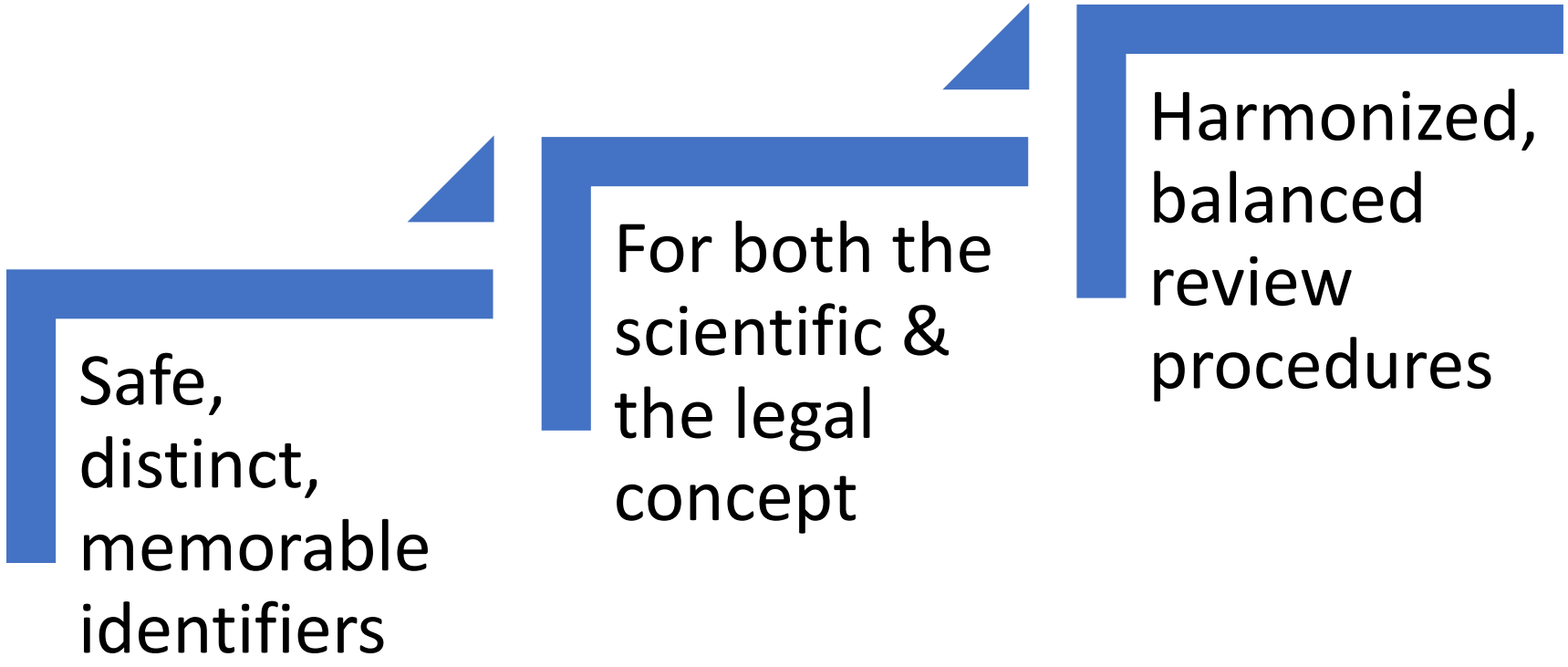


… violate the scientific concept, the legal concept AND the trilogy of the INN (Name, description & structure)

Protection Letters – Statistics and Publication



Allies! Aligned on the same objective



Concluding

Oracle of Delphi – aka ‘Q&A session’

World Health Organization

Thank you

WHO

20, Avenue Appia
1211 Geneva

Switzerland