INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

Harmonization of bioequivalence ICH process and implementation considerations: a generic industry point of view

Susana Almeida, PhD
Secretary General IGBA

2024

About IGBA

- Founded in March 1997 as the International Generic Pharmaceutical Alliance (IGPA)
- Renamed International Generic and Biosimilar Medicines Association (IGBA) in September 2015; Legally incorporated in Geneva, Switzerland
- Admitted as ICH Assembly Member in 2016 and ICH Management Committee since 2017
- Accredited WIPO Observer since September 2019
- Non-State actor in official relations with WHO since January 2022
- Maintains constant dialogue with the WHO, WTO, WIPO and other national, regional and international bodies

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Full Members

Associate Members

Observer Status

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Recent developments

- May 2025 – CEO Advisory Committee met in Vienna

INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Recent developments

- IGBA reelected to the Management Committee of ICH

INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Vision for Single Global Development

- Enabling off-patent medicines to prepare a **single data package globally, acceptable in all jurisdictions,** would support more timely and equitable access to affordable therapies.

Link to patient access

- Regulatory processes and requirements influence development timelines and the resources involved

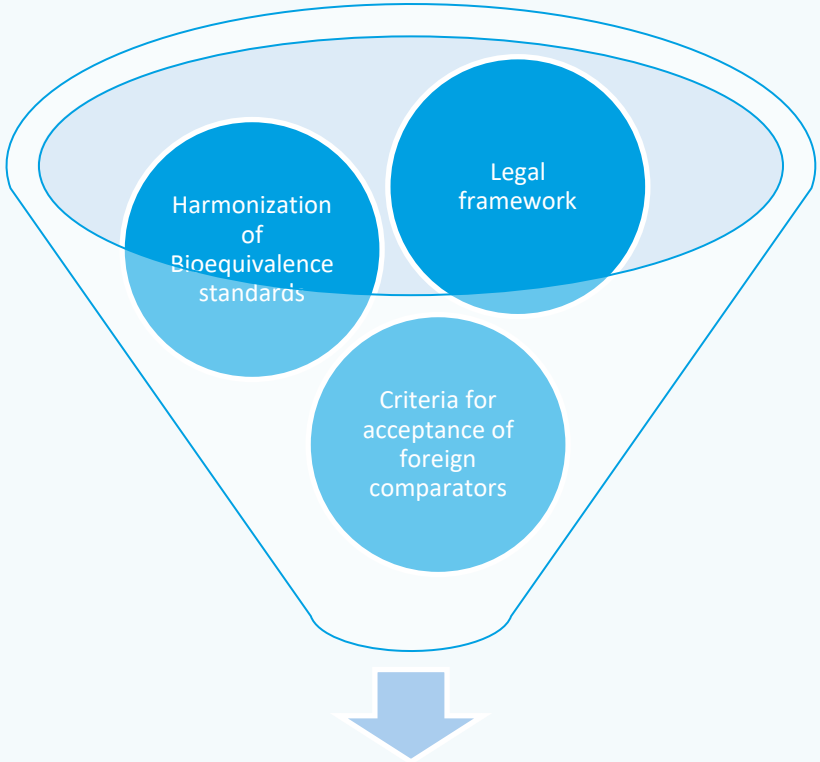
- Disparate requirements between countries delay or inhibit patient access to medicines:

↑ development timelines

↑ resources needed

INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

3 Pillars of Single Global Development that must advance simultaneously



INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Single global development of off patent medicines

IPRP: Mapping the barriers to FRPs

J Pharm Pharm Sci (www.cspsCanada.org) 22, 28 - 36, 2019

A Survey of the Regulatory Requirements for the Acceptance of Foreign Comparator Products by Participating Regulators and Organizations of the International Generic Drug Regulators Programme

Alfredo García-Arieta[1], Craig Simon[2], Gustavo Mendes Lima Santos[3], Iván Omar Calderón Lojero[4], Zulema Rodríguez Martínez[4], Clare Rodrigues[5], Sang Aeh Park[6], Ji Myoung Kim[6], Ryosuke Kuribayashi[7], Yusuke Okada[7], Arno Nolting[8], Chantal Pfäffli[8], Wen-Yi Hung[9], Christopher Crane[10], April C. Braddy[11], Joy van Oudtshoorn[12], Diego Gutierrez Triana[13], Mitch Clarke[14]

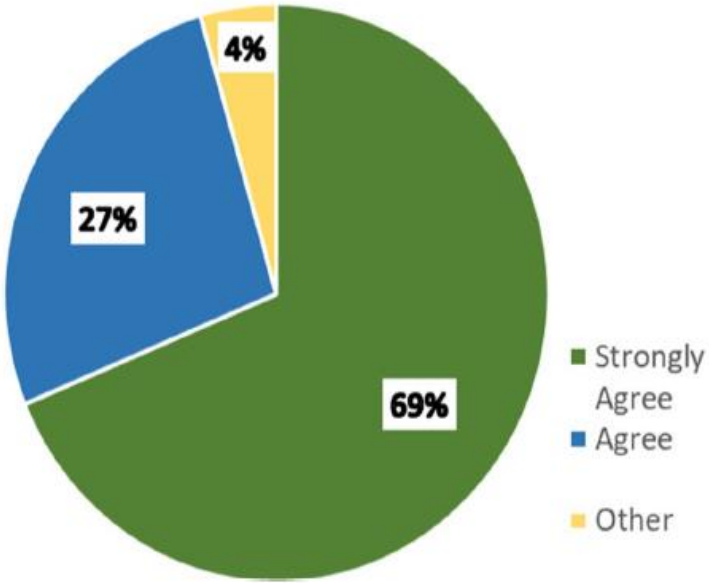
IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Swiss example

- Guidance document
- Authorisation of human medicinal product with known active pharmaceutical substance (v5.1, 2024)

- Comparability of a foreign comparator product with the Swiss reference product (pharmaceutical bridging)

Harmonization of BE: does it matter?



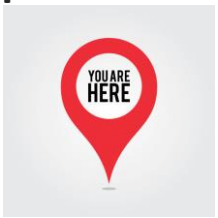
- It matters A LOT!
- Recent international survey on complex generics:
- **96% Agree or Strongly Agree** on the importance of a harmonized international approach for complex generics

Stern S, Coghlan J, Krishnan V, Raney SG, Babiskin A, Jiang W, Lionberger R, Xu X, Schwendeman A, Polli JE. Research and Education Needs for Complex Generics. Pharm Res. 2021 Dec;38(12):1991-2001. doi: 10.1007/s11095-021-03149-y. Epub 2021 Dec 24. PMID: 34950975.

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

ICH harmonization of bioequivalence standards

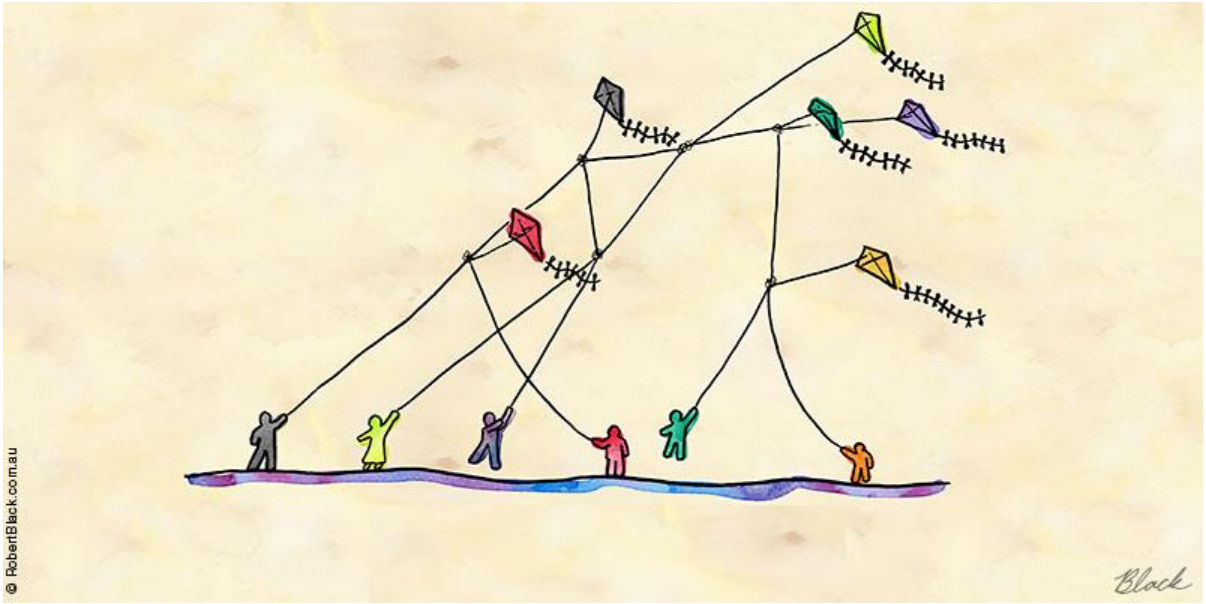
- Ongoing and advancing
- M13 (immediate release) progressing (latest workplan available at the ICH website):
  - M13A – Step 5 reached – implementation phase
  - M13B ongoing development



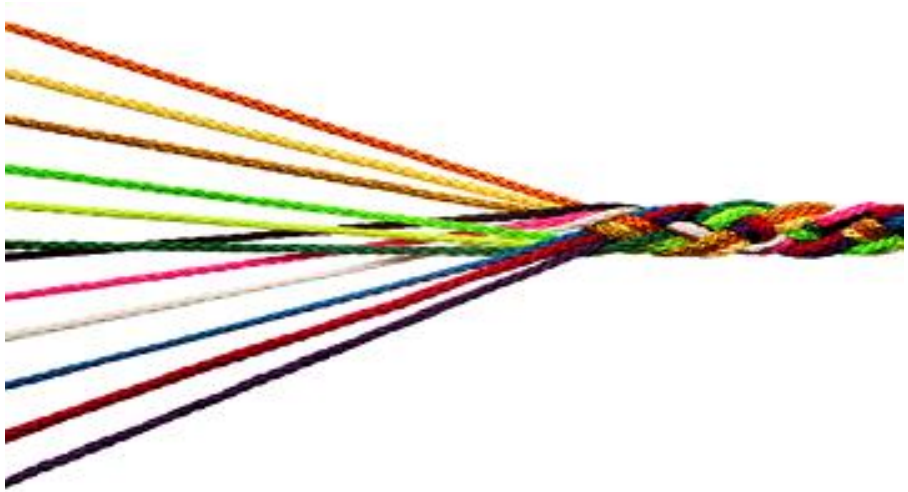
  - M13C
- Harmonization of BE for Modified Release: new topic adopted by ICH in June 2023

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Before M13:
multiple standards (a tangled mess)



After M13:
Harmonization and convergence



INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

Implementation of a new ICH guideline

~~(Local guideline)~~  New ICH Guideline

Example: ICH M10 bioanalytical guideline

INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

M13 guideline series – staggered approach

M13A

- BE IR solid oral dosage forms
- Step 5 (implementation)

M13B

- Strength biowaivers
- Step 1 (consensus building)

M13C

- data analysis and BE assessment for 1) highly variable drugs, 2) drugs with narrow therapeutic index, and 3) advanced BE study design and data analysis considerations.
- (yet to be started)

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Scope and Organization of M13 (B)

- **Tier 2 → M13B: Second guideline in the series**

  BE for additional strengths of a product line including biowaiver considerations

  - BE study(ies) conducted with one strength (bio-strength)
  - Relationship to bio-strength
  - Biowaiver from requirement for additional studies
    - Dose proportionality in the pharmacokinetics of the comparator product
    - Qualitative and quantitative composition comparison among strengths
    - Comparative in vitro dissolution
    - Assessment of similarity between dissolution profiles

Scope and Organization of M13 (C)

- **Tier 3 → M13C: Third guideline in the series**

  BE study design, analysis, and assessment for

  - Highly variable drugs
  - Drugs with narrow therapeutic index (NTI)
  - Complex BE study design and analysis considerations

Implementation of a new ICH guideline

~~(Local guideline)~~

Tier 1
Tier 2
Tier 3

- It is difficult to replace the local guidelines completely at once
- Some regions/countries cover the topics in M13A in more than one guideline (an example Canada)
- Clear mapping of what parts of existing guidelines will be replaced as M13 documents reach Step 5 is required: what remains in force, what is superseded?

Implementation strategy

- **EMA example**

On 25 January 2025, the date of coming into effect, ICH M13A will supersede applicable parts of the EMA Guideline on the investigation of bioequivalence related to bioequivalence study considerations and data analysis for a non-replicate study design (see Tier 1 in the ICH M13 Concept_Paper - ich.org).

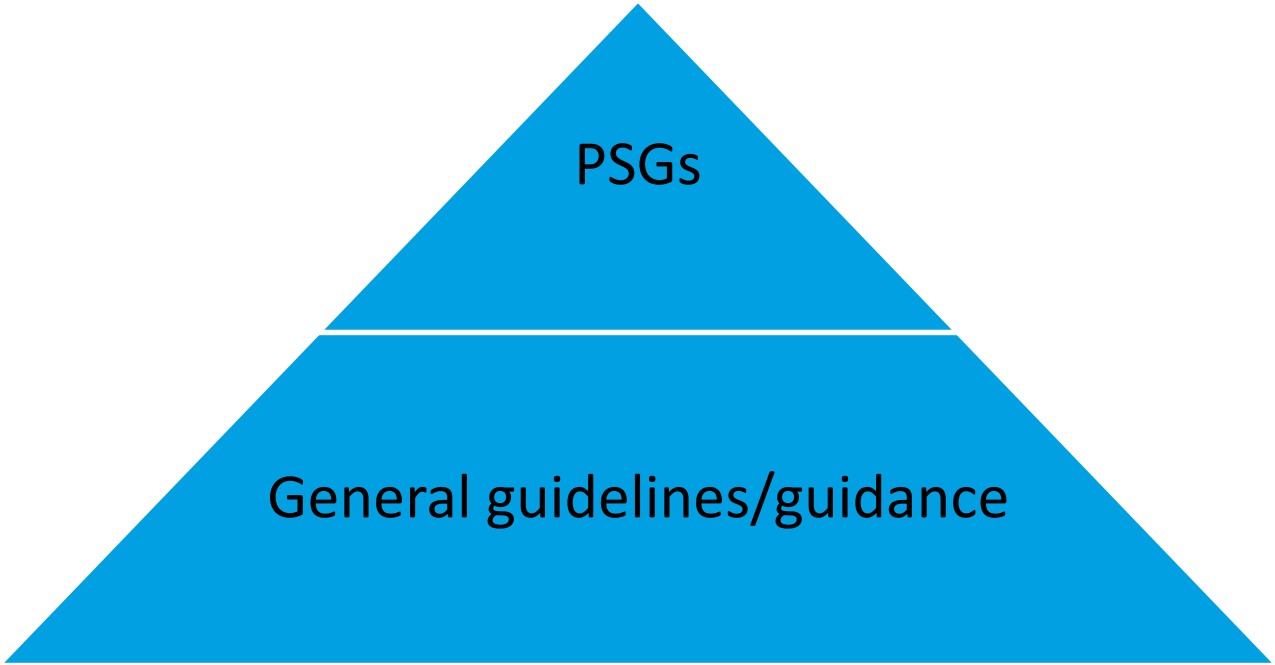
Note: Appendix III of the EMA guideline is already superseded by the ICH M9 Guideline on biopharmaceutics classification system-based biowaivers.

Further EMA guidance on how the ICH M13 series will replace the EMA guideline will be published in due course.

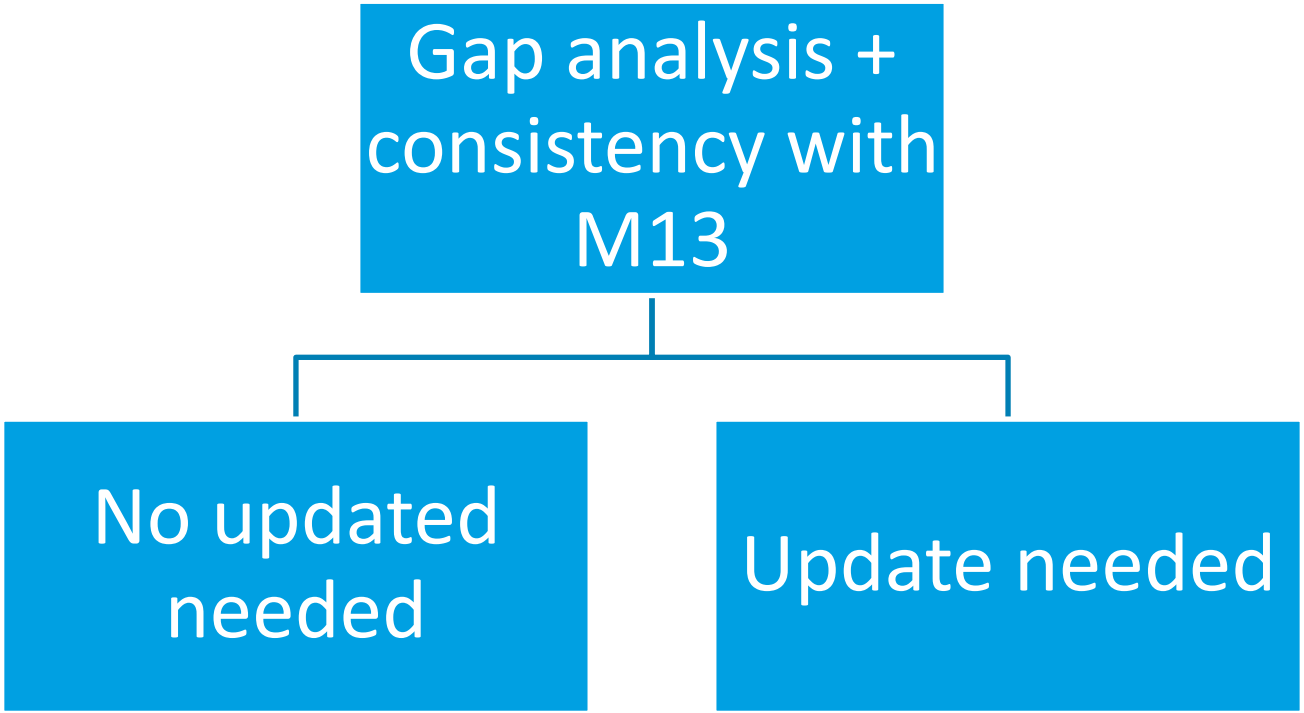
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Product specific guidance (PSG)

- Available in some regions/countries – they may also need some updating to reflect international harmonization process



For each PSG



INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Some examples

Early exposure for IR

For orally administered IR drug products, BE can generally be demonstrated by measurement of rate and extent of absorption, i.e., Cmax and AUC(0-t). However, in some situations, Cmax and AUC(0- t) may be insufficient to adequately assess the BE between two drug products, e.g., when the early onset of action is clinically relevant.

In these cases, an additional PK parameter, such as area under the concentration vs. time curve between two specific time points (pAUC) or tmax, may be applied. In the case of pAUC, it is typically evaluated from the time of drug administration until a predetermined time point that is related to a clinically relevant pharmacodynamic measure. Samples should be spaced such that the pAUC can be estimated accurately.

ICH M13A

Recent IPRP publication

Argentina, Australia, Brazil, Colombia, the EU, Japan, Israel, Mexico, New Zealand, Republic of Korea, Saudi Arabia, Singapore, South Africa, Switzerland, Chinese Taipei, and the WHO **do not have requirements for *pAUC* for IR products**

#Team *pAUC*

Canada and US *pAUC* may be necessary

#Team t_{max}

Colombia, the EU, Republic of Korea, South Africa, Switzerland, and the WHO stated that if differences in the time required for the manifestation of the drug effect could affect its clinical usefulness: t_{max}

INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

J. pharm. pharm. sci., 21 March 2024 https://doi.org/10.3389/jpps.2024.12398

Two points need to be addressed to design a study

- Selecting the metric is only half of the problem…
- Second half is how you analyze it and how you define the acceptance criteria

- It is not possible to discuss one without reflecting on the other

And also

- The situations where early exposure is relevant for IR products are rare
- Any approach used to assess early exposure in IR products has significant challenges – clinical relevance is always key
- One size will not fit all – very difficult to determine a single approach that will work in all cases since clinical relevance is not uniform even for drugs where early exposure matters

Tadalafil, some examples

EMA PSG - Comparable median (≤ 20% difference, 80.00–125.00%) and range for Tmax

FDA PSG – Fasted + fed Bioequivalence based on (90% CI): Tadalafil

SFDA PSG – Fasted + fed Bioequivalence based on (90% CI): Tadalafil

INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Another example

Could agencies come to different conclusions on e.g. PK linearity in some occasions during the revision of existing PSGs, now that we also have Cmax as a decision criterion for assessment of linear/non-linear PK and also that mainly single dose studies are supposed to be considered?

INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Main open questions

- What parts of existing guidelines from each country/region will be superseded and what parts remain in force?
- For countries/regions with PSGs: what will be the strategy to update PSGs if discrepancies exist vs. the harmonized guideline?
- In case of conflict between an existing PSG and new ICH text, what takes precedence? How should the applicants proceed in the interim (until clear directions are known and harmonization is completed)?
- Are there any plans to consider harmonization of PSGs?

Relevance for the generic industry

- What are the applicable requirements for the development of a new generic medicine?
- Which guidelines are applicable now?

- A clear mapping throughout the process would be very helpful to guide sponsors/applicants

INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

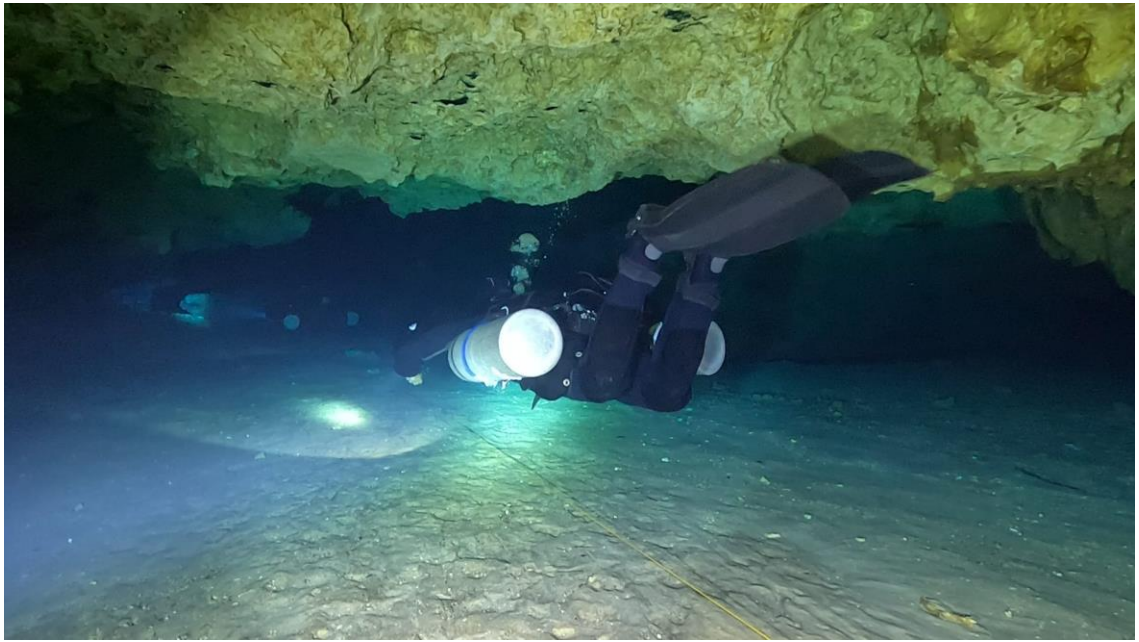
What can you do about this?

- Pay close attention
- Discuss with your peers (e.g. via the trade associations)
- Highlight any areas of potential concern
- Participate in the discussions

- Mark your calendar 26 Feb 2025, Amsterdam

salmeida@igbamedicines.org

INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION



INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

Thank you

Do at least one thing that scares you every day!

(E. Roosevelt)

Acknowledgments:
IGBA's M13 support group