GMP expectations at antimicrobial manufacturing sites

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Agenda

01 Background: The rising concerns with antimicrobial resistance and WHO's involvement

02 Outcome of a recent manufacturer's survey

03 Way forward / Conclusion

Background

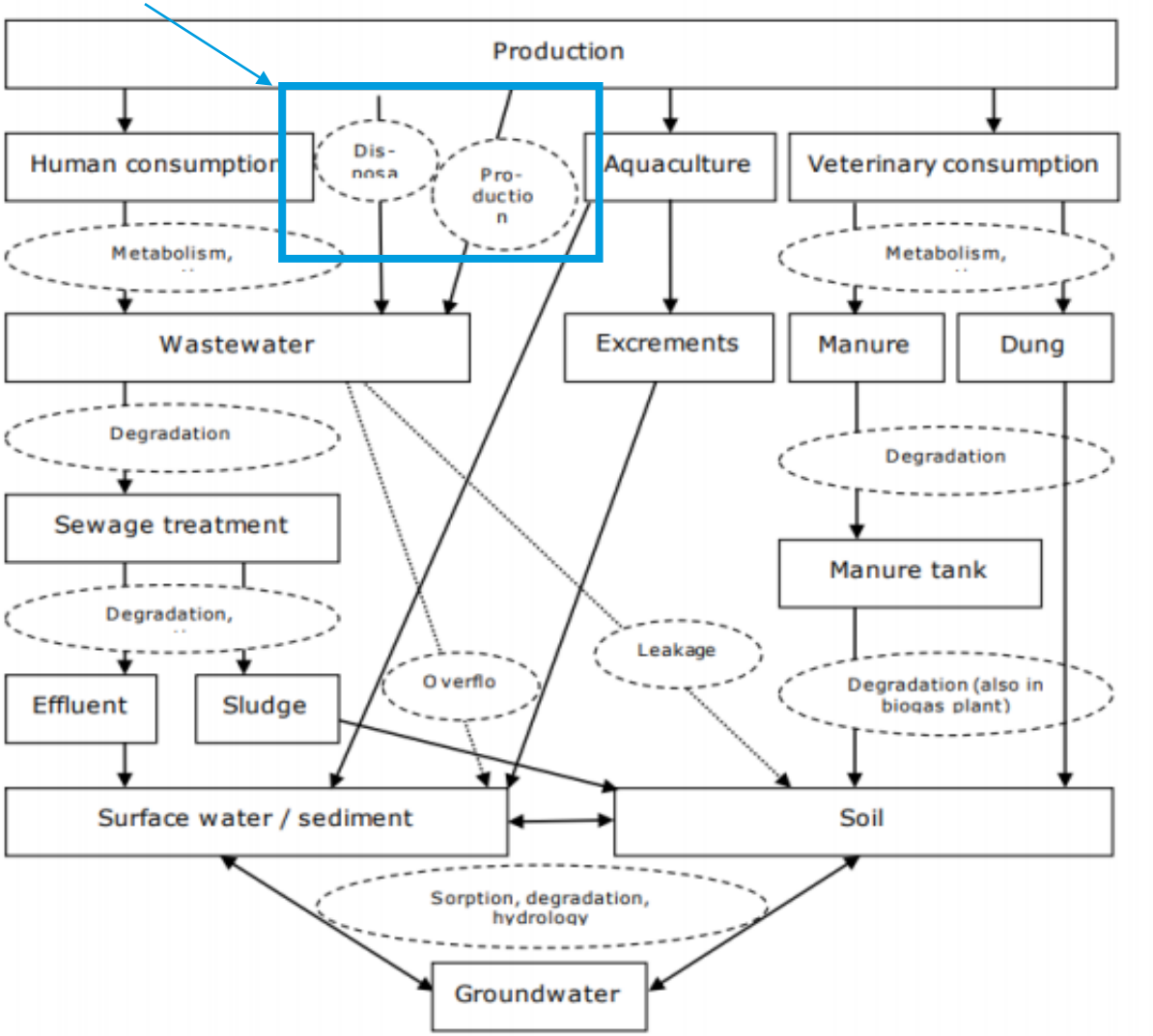
The triggers to consider GMP as a tool to environmental protection to tackle AMR

- AMR was identified as a priority at the WHA since 1998.
- Several WHA resolutions[1] on AMR exist and 1 resolution from 71st UN General Assembly[2] in 2016
- GPW13 (2019-2023) highlights the urgency of tackling antimicrobial resistance
- UN Ad hoc Interagency Coordinating group on antimicrobial resistance, April 2019 – All are URGED to ACT!

Source 1 : see notes below for full listing. Source 2: :https://www.who.int/antimicrobial-resistance/events/UNGA-meeting-amr-sept2016/en/

Target (for WHO PQT Inspections)

Emissions and fate of antimicrobials in the environment



Source: Schmitt et 334 al., 2017

Excerpts from the literature

Infection
DOI 10.1007/s15010-017-1007-2

ORIGINAL PAPER

Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens

Christoph Lübbert[1,2] · Christian Baars[3] · Anil Dayakar[4] · Norman Lippmann[2,5] · Arne C. Rodloff[2,5] · Martina Kinzig[6] · Fritz Sörgel[6,7]

Received: 27 February 2017 / Accepted: 8 March 2017

53rd ECSPP recommendations

Update and recommendations from inspectors' meeting, including those on GMP and environmental issues.

In 2018, the WHO Secretariat sought the Expert Committee's opinions on the **need for revision of GMP to address environmental protection** from emissions when manufacturing pharmaceutical products, and the **role of GMP inspectors** in environmental protection and AMR control.

A pilot project on AMR and environmental control enforced through GMP was viewed as a possibility to start focused surveillance, beginning with a few antibiotics, such as those identified by the WHO Expert Committee on the Selection and Use of Essential Medicines as the antibiotics "RESERVE" group.

The Expert Committee acknowledged the concern about AMR and supported the **preparation of a text** on points to be considered in relation to prevention of AMR**.** This could **include reference to the role that inspectors** can play during inspections.

Source: 53rd *ECSPP report TRS 1019, 2018*

54th ECSPP recommendations

In 2019, the Expert Committee adopted the Points-to-consider document entitled *Environmental Aspects of Manufacturing for the Prevention of Antimicrobial Resistance* revised according to the indications provided; and agreed to:

- a study on the practices currently in use at pharmaceutical manufacturing facilities regarding waste and wastewater management (the sites eligible are those participating in WHO Prequalification producing antimicrobials) and on the current controls on antimicrobial levels in effluents and other relevant types of waste. This would be done through the means of a survey.

Steps taken after the 54th ECSPP

1. Publication of "***Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance***" (May 2020, Technical report series 1025, Annex 6 https://www.who.int/publications/m/item/trs-1025-annex-6-manufacturers-inspectors-environmental-aspects-manufacturing-amr).
2. A survey was drafted and circulated to API manufacturers of antimicrobials participating in WHO Prequalification (July to September 2020).
3. Data from the survey was analyzed and compiled in a report.

Overview of the Points to Consider document

World Health Organization

Annex 6

Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance

Overview of the survey

Purpose:

- Verify implementation of recommendations in the Points-to-Consider document on waste and wastewater management and on the current controls for antimicrobial levels in effluents and other relevant types of waste;
- Sensitize manufacturers of antimicrobials as to WHO's new expectations on the practices currently in use at pharmaceutical manufacturing facilities;

Source: *Comments on working document QAS/19.802*

Purpose of the survey

- Emphasize the importance of all aspects of GMP implementation, taking into account specific clauses of GMP that may not have a direct impact on product quality but will safeguard the environment through their enforcement; and
- Notify manufacturers of antimicrobials that these items may be covered during the next scheduled on-site inspection of their manufacturing facilities.

Note: In order to complete the survey, pharmaceutical manufacturers were advised to read it in conjunction with the WHO policy document *Points to consider for manufacturers and inspectors: environmental aspects of manufacturing practices for the prevention of antimicrobial resistance (1)*.

Source: *Comments on working document QAS/19.802*

Survey for Pharmaceutical Manufacturers of Antimicrobials

This survey shall be read in conjunction with the WHO "Points to consider for manufacturers and inspectors: environmental aspects of manufacturing practices for the prevention of antimicrobial resistance" (WHO Technical Report Series, N 1025, 2020, Annex 6).

This survey is intended to collect information on the type of waste being generated by manufacturers in the WHO Prequalification programme. Please refer to the article entitled "Environmental Aspects of Manufacturing for the Prevention of Antimicrobial Resistance", WHO Drug Information, Vol 33, No. 4, 2019 (https://www.who.int/medicines/publications/druginformation/issues/DrugInformation2019_Vol33-4/en/) for more details on this initiative.

Kindly note that your responses to this survey might be verified during the next onsite inspection. Results of this survey may be used for publications by the WHO, without publishing any information on the name or address of the manufacturer.

Thank you for your participation in the survey.
There are 24 questions in this survey.

Identification

1. Company name and manufacturing site name. *

Please write your answer here:

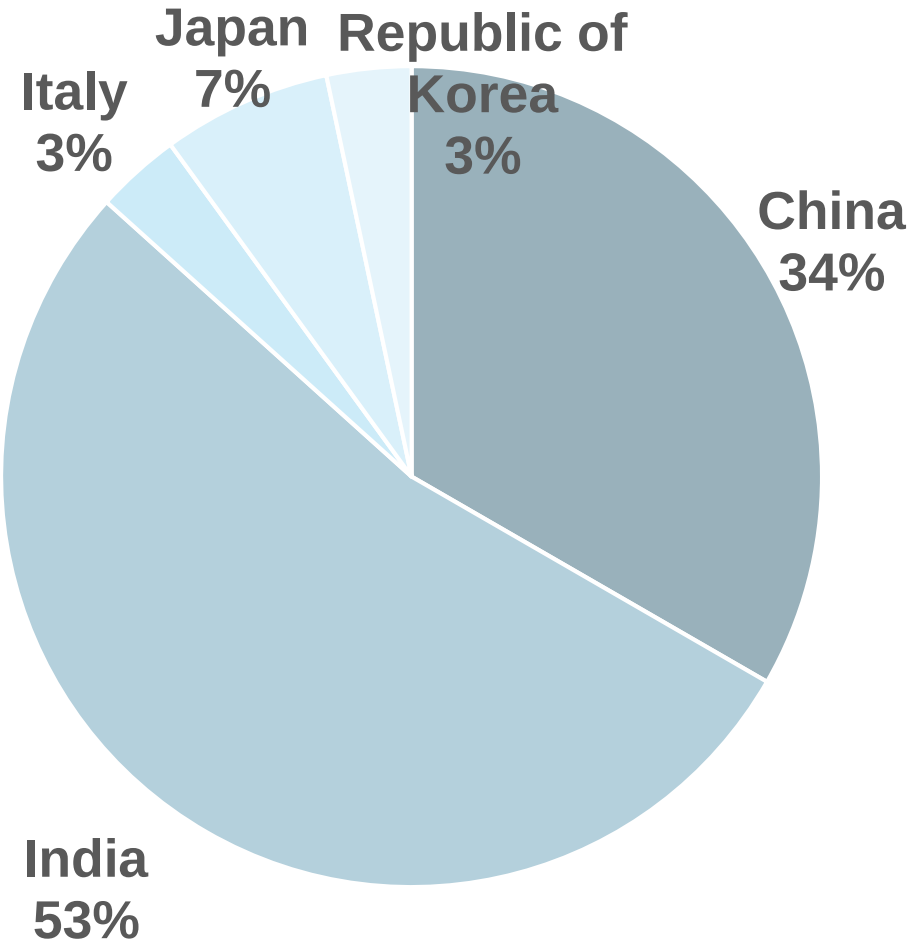
Outcome of the survey

Survey circulated: July to September 2020

- N of manufacturers who received the survey: 38
- N of manufacturers who responded: 30

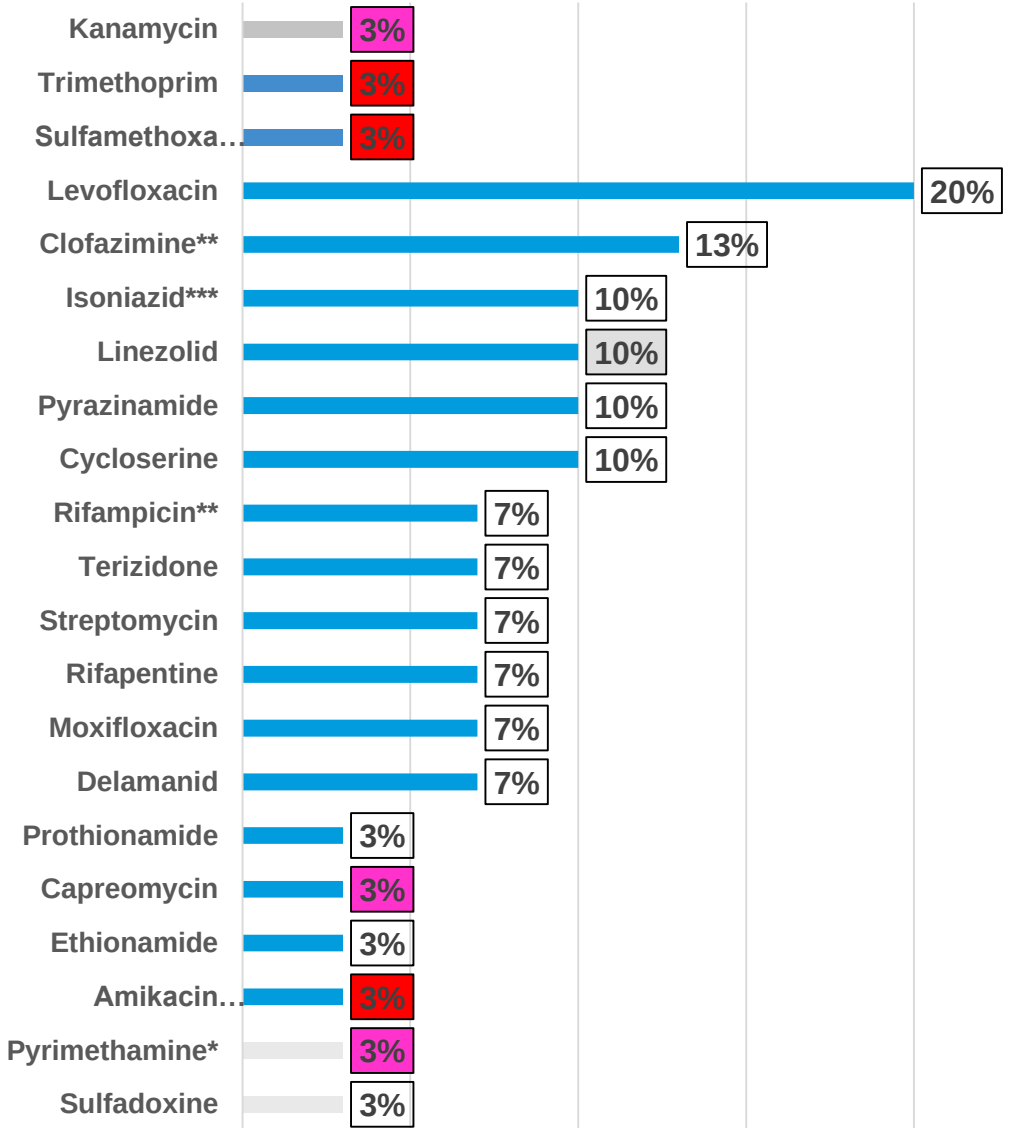
Outcome of the survey

1. Geographical location of respondents



Outcome of the survey

2. Antimicrobial APIs manufactured and their EML classification



% legend

- Access group antibiotics
- None
- non-EML
- Reserve group antibiotics

Bar legend

- Antimalarial medicines
- Antituberculosis medicines
- Lower urinary tract infections
- Serious bacterial infection

* also Antipneumocystosis and antitoxoplasmosis medicines

** also Antileprosy medicines

*** also Medicines for prevention of HIV-related opportunistic infections

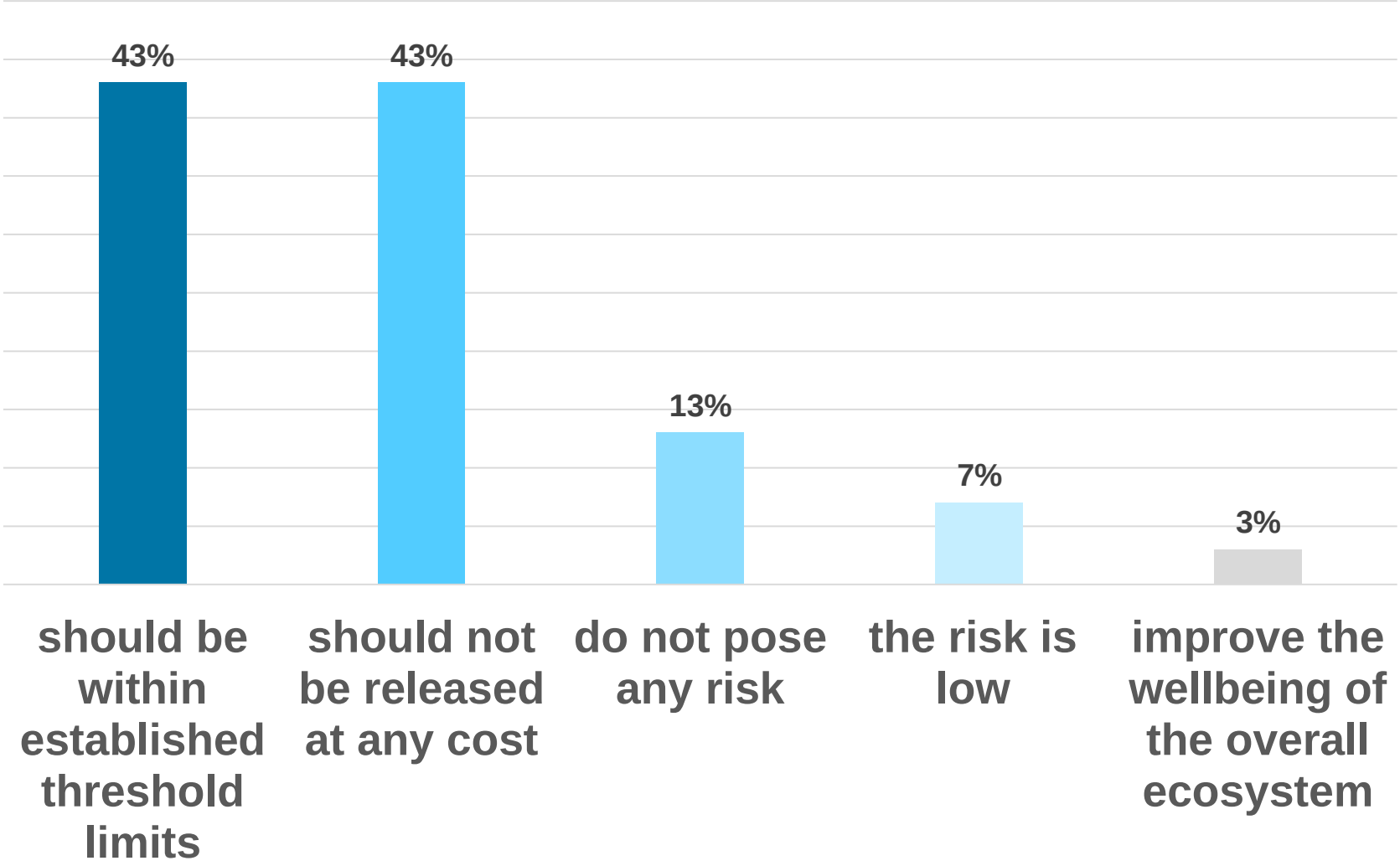
Outcome of the survey

3. Other antimicrobial APIs also made by the same manufacturers

WHO Antibiotics Classification (Aware)	Active Pharmaceutical Ingredients	Number of sites	%*
Access group antibiotics	Chloramphenicol, Clindamycin, Nitrofurantoin	3	9%
Watch group antibiotics	Azithromycin, Ciprofloxacin, Cefuroxim, Cefixime axetil, Ofloxacin, Tazobactam, Vancomycin Hydrochloride, Piperacillin	16	53%
None – Anti-infective	Erythromycin	4	14%
None - Antifungal	Voriconazole	1	3%
None - Intestinal anthelmintics	Mebendazole	1	3%
None - Antifungal-antileishmaniasis	Amphotericin B	1	3%
None	Bacitracin, Colistimethate sodium, Cephalexin, Cefaclor, Cefpodoxime proxetil, Cefprozil, Cefadroxil, Cefdinir, Dalbavancin, Daptomycin, Dihydrostreptomycin sulfate, Enrofloxacin, Fenticonazole Nitrate, Milbemycin oxime, Minocycline HCl, Rifaximin, Spiramycin, Teicoplanin, Tigecycline, Tioconazole, Tobramycin,	21	61%

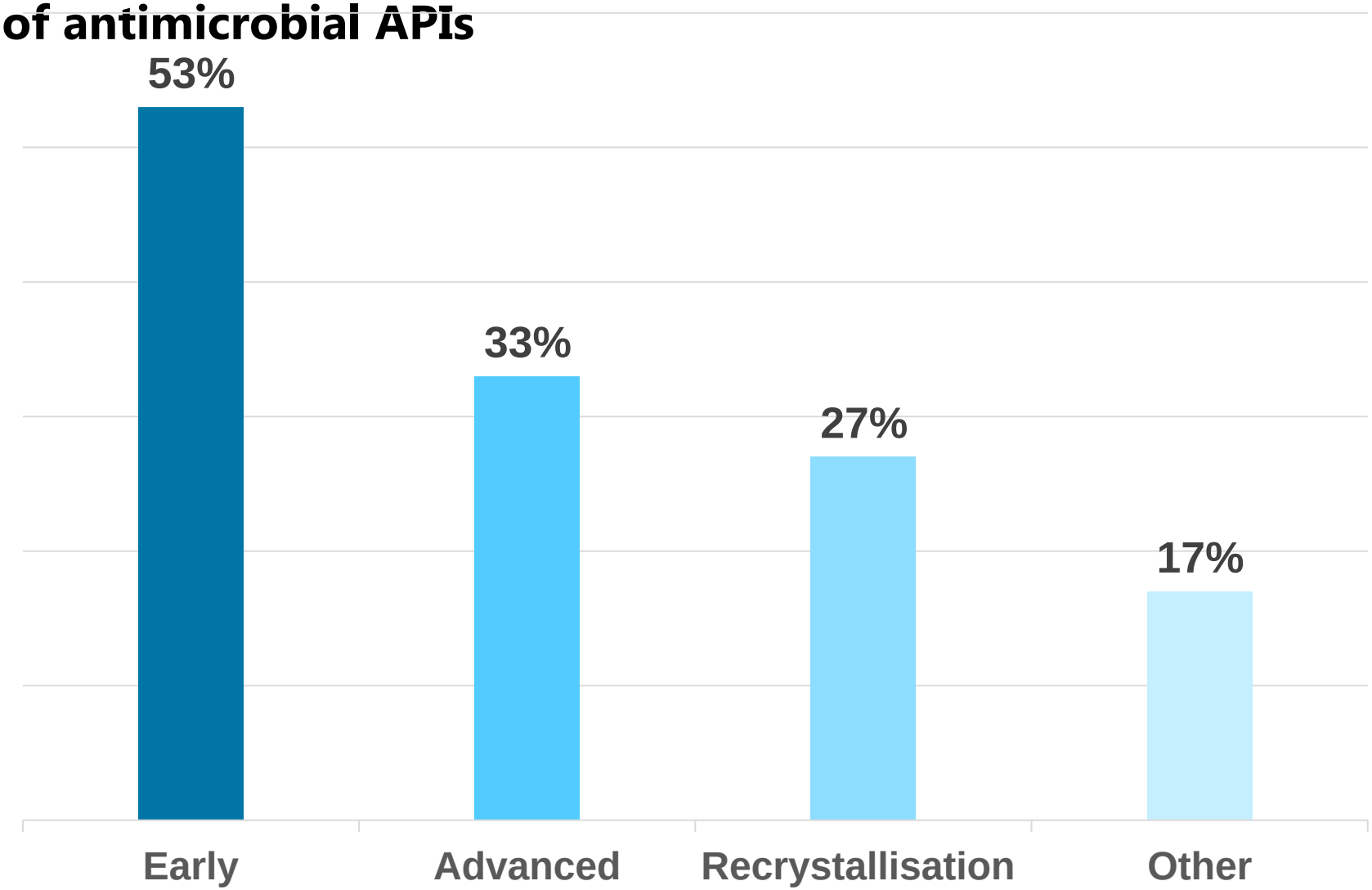
Outcome of the survey

4. Which statement reflects the company's current understanding of the potential impact of releasing antimicrobial residues into water streams/the environment?



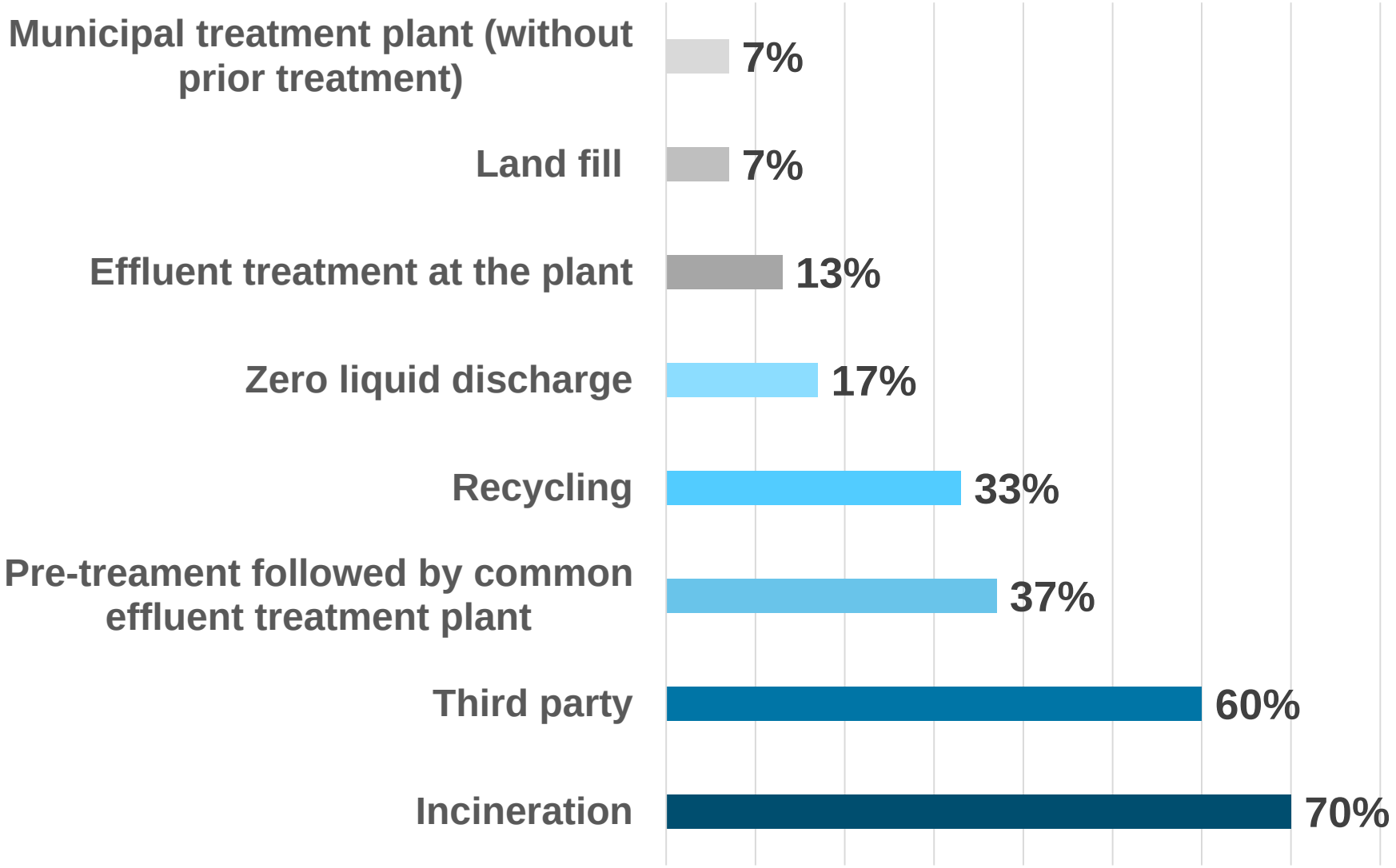
Outcome of the survey

5. Main sources of waste released during stages of production of antimicrobial APIs



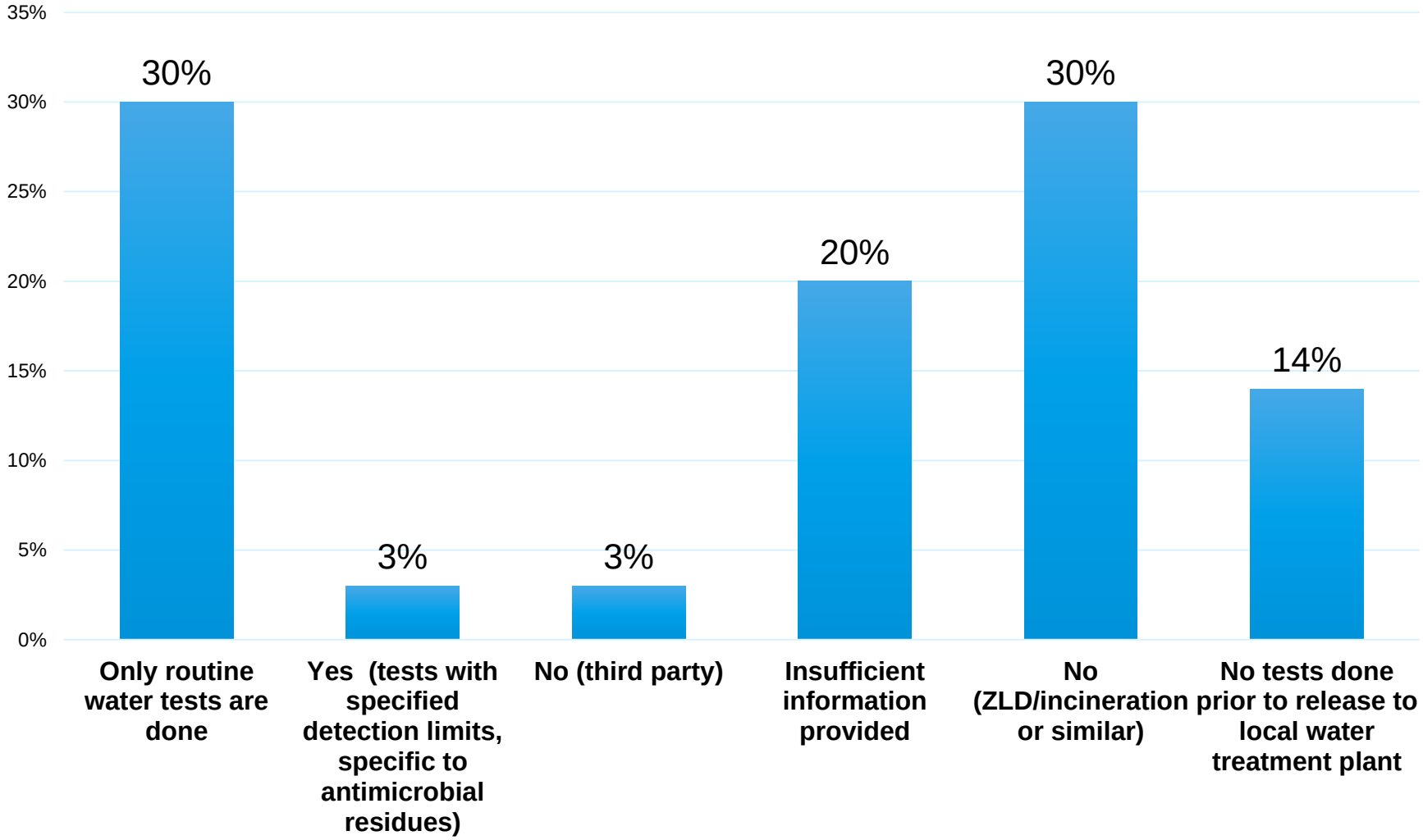
Outcome of the survey

6. Treatment/disposal methods of antimicrobial waste



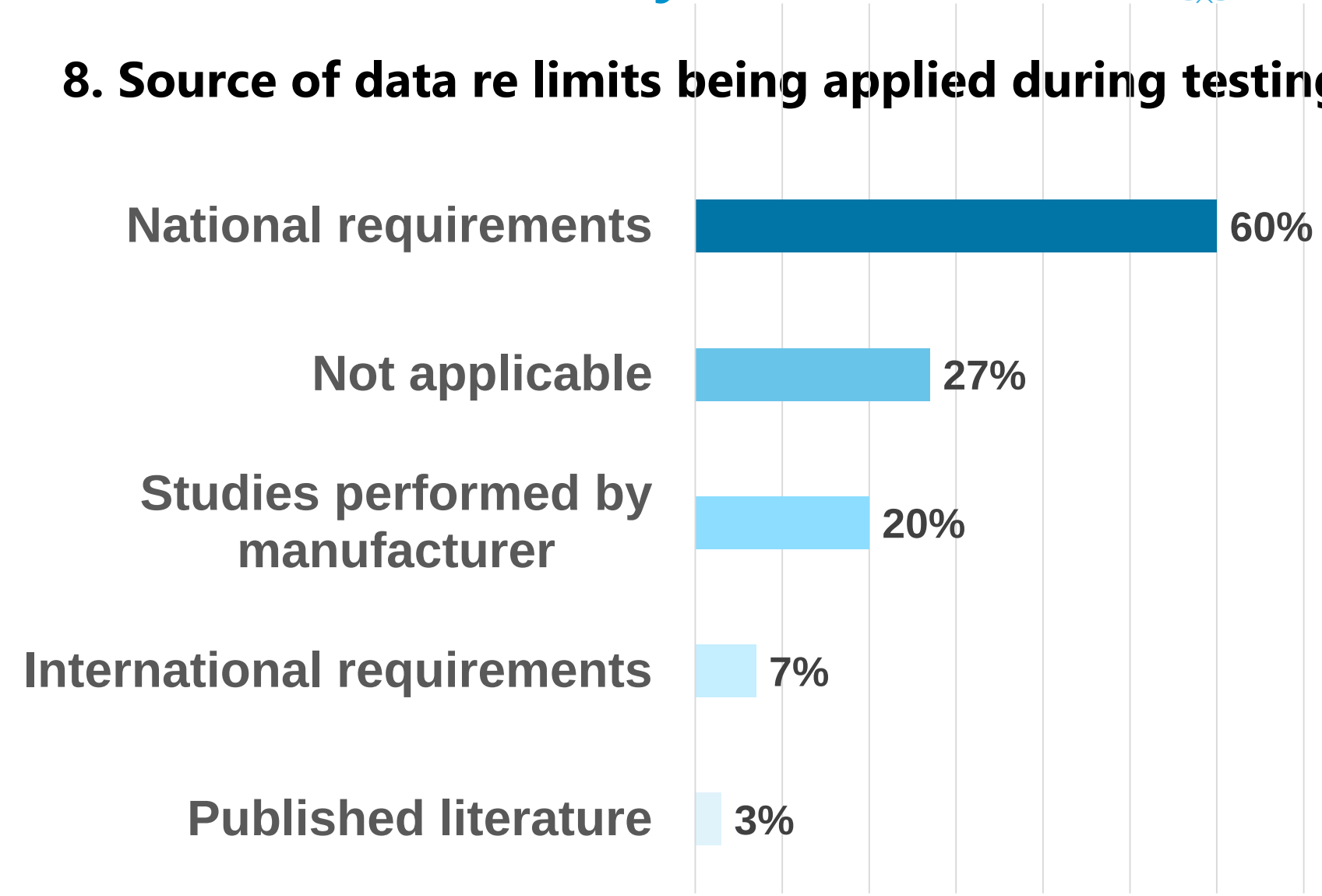
Outcome of the survey

7. Testing of waste prior to its release



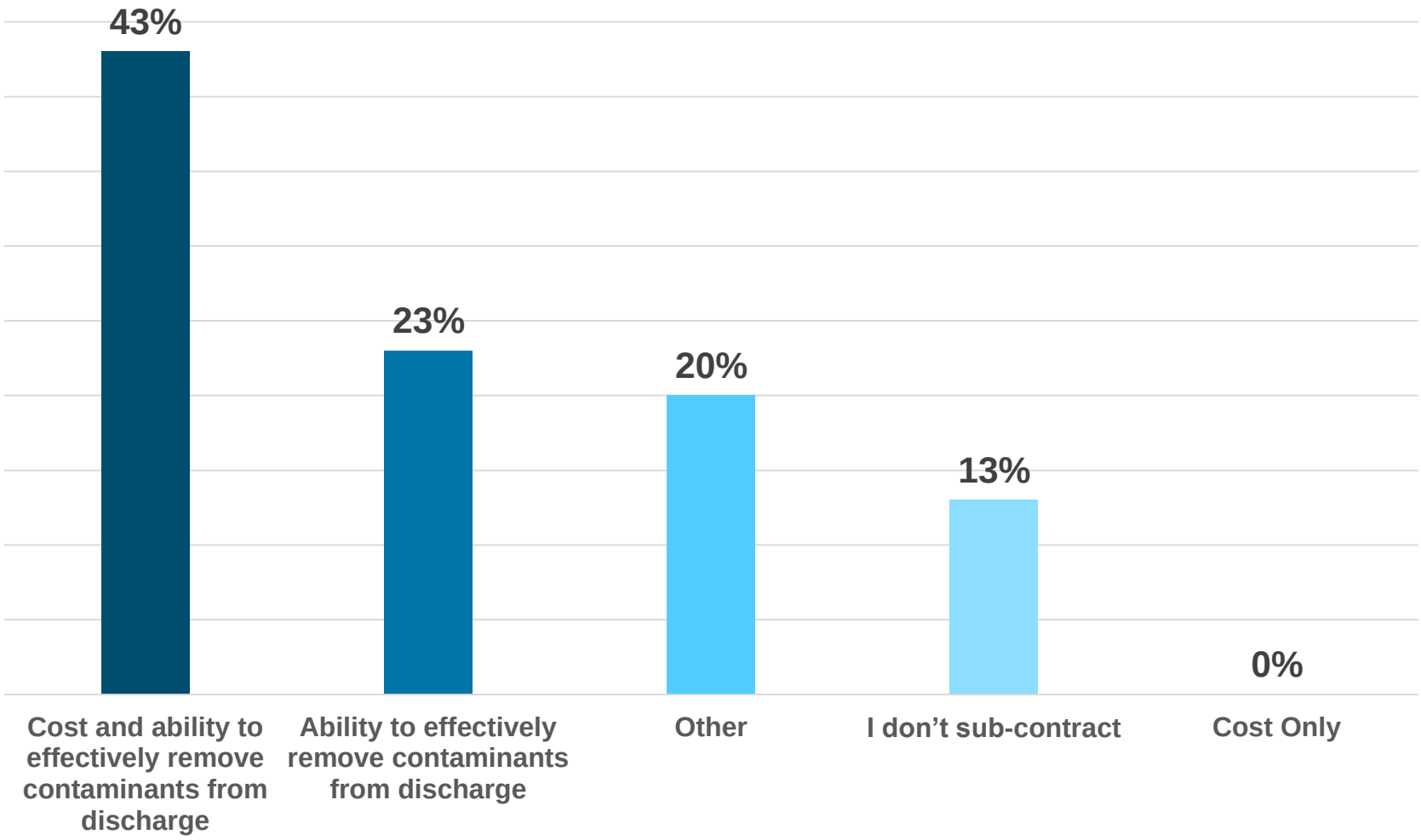
Outcome of the survey

8. Source of data re limits being applied during testing



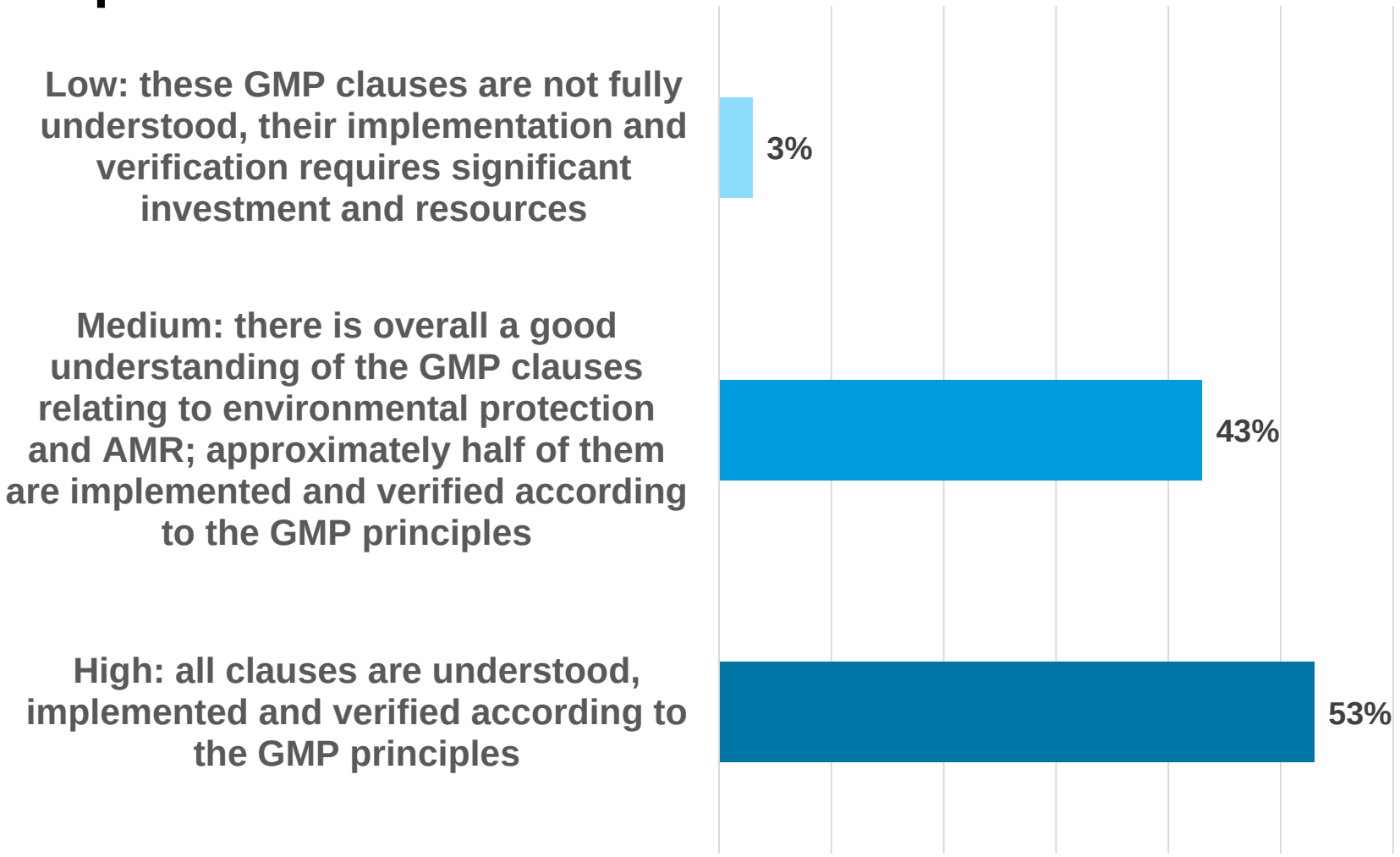
Outcome of the survey

9. Criteria used for selection of subcontractors for waste



Outcome of the survey

10. Manufacturer's opinions of their own understanding and compliance levels



Outcome of the survey

This survey revealed that:

- Several manufacturers are operating under the principle of zero-liquid discharge or use recycling and/or incineration as means of reducing environmental contamination with antimicrobials.
  - ➢ Note: When recycling is used, there may be the need to verify that the contamination is still adequately contained.
- Most of the manufacturers surveyed were unable to provide a clear scientific rationale or justification for their decontamination procedures.

Outcome of the survey

This survey revealed that:

- Most were unable to demonstrate that the concentration of antimicrobials in wastewater from the manufacturing processes at their site did not exceed scientifically derived discharge targets for antimicrobial residues.

Way forward

Next steps:

- Performing a gap analysis between what is covered by environmental inspectors and GMP inspectors
- Training of API GMP inspectors and regulators (December 7, 9:30 -15:30 Geneva time, Registration still possible at: https://who.zoom.us/webinar/register/WN_BfHClr6eQsm44kjM5NzrSQ or email crofts@who.int)

Way forward

Next steps:

- Creation of inspection tools (Aide-Memoire to cover waste management aspects during GMP inspections)
- Working with manufacturers and providing training on new expectations and how to improve waste management practices for AMR

Thank you

WHO

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