Working group - Pharmaceuticals in the Environment

Pharmaceutical Committee – 23 November 2023

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- Chair EC Working Group Pharmaceuticals in the Environment

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Challenges – active pharmaceutical ingredients reach the environment

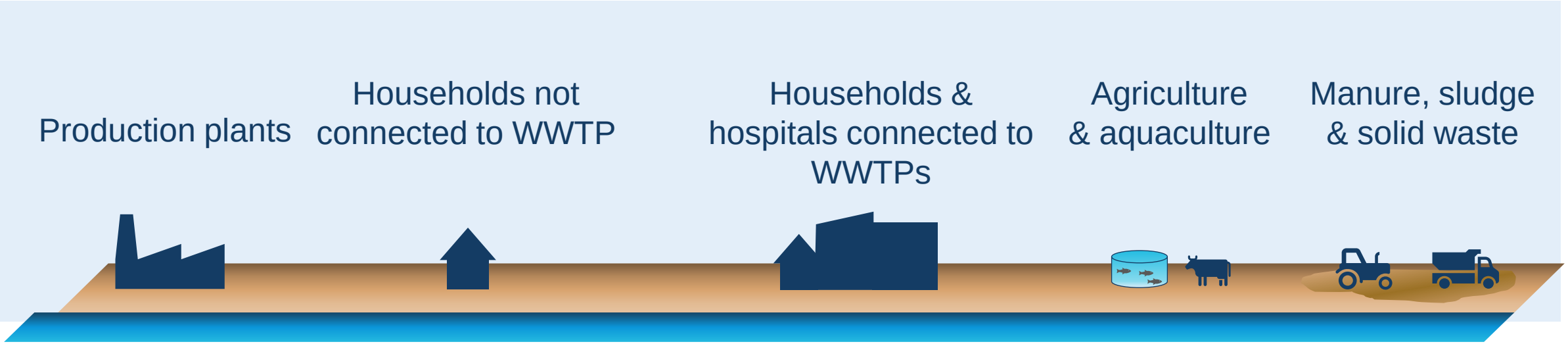
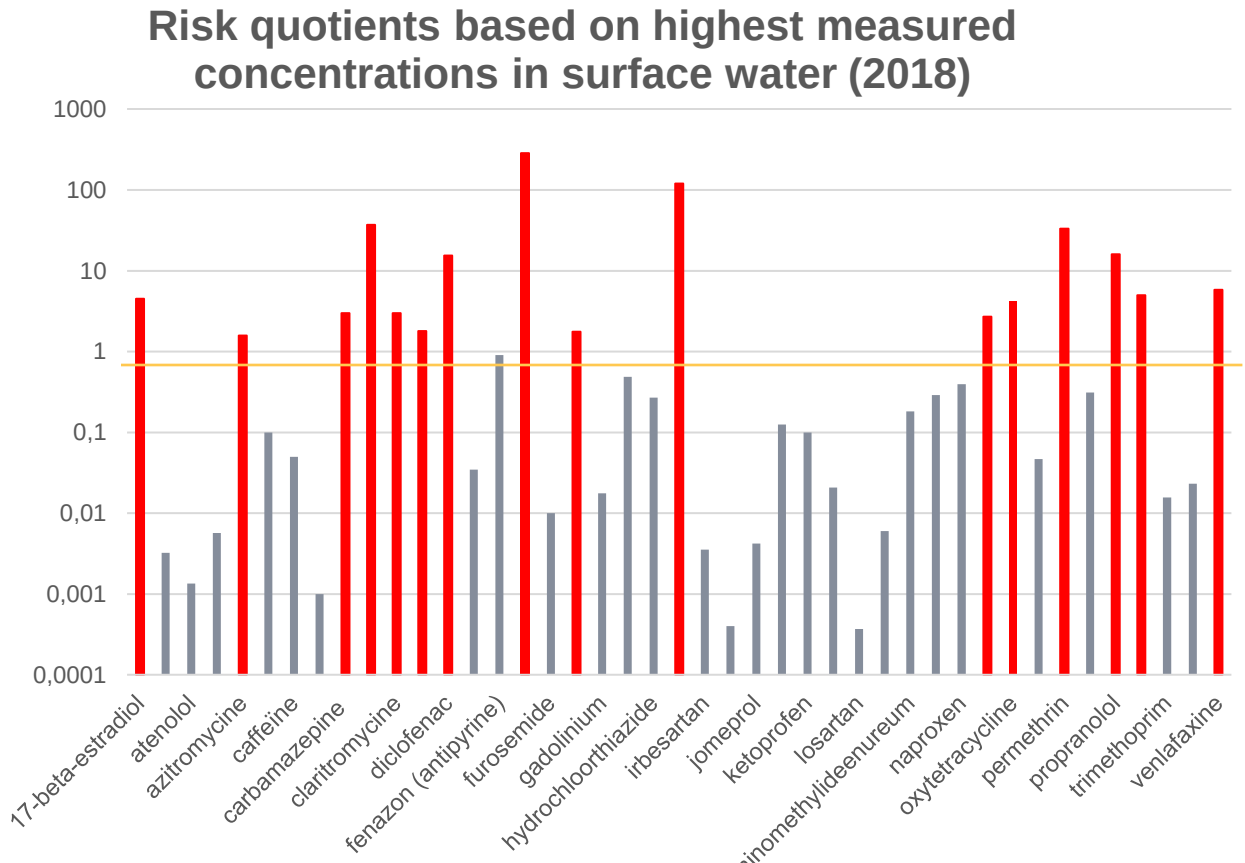


Image: Knowledge Centre on Pharmaceuticals in the Environment at Swedish MPA

- Chemical mixtures are present in our waters
- Ecosystems related to water resources may therefore be exposed to mixtures during their whole life-cycle – 24 / 7
- Antimicrobial agents pose an additional risk by adding pressure towards increased antimicrobial resistance

Conclusions from NL inquiry – complex mixtures in the environment

- At least 190 tonnes of API residues reach Dutch surface water annually
- 16 of 43 measured APIs had a risk quotient (RQ) exceeding 1 - indicating potential risk for aquatic organisms
- Dutch surface water environments are potentially at risk of adverse effects



Källa: Netherlands National Institute for Public Health and the Environment (RIVM). Medicijnresten en waterkwaliteit: een update (2020)

33 pharmaceutical substances in insects in river in Uppsala, Sweden

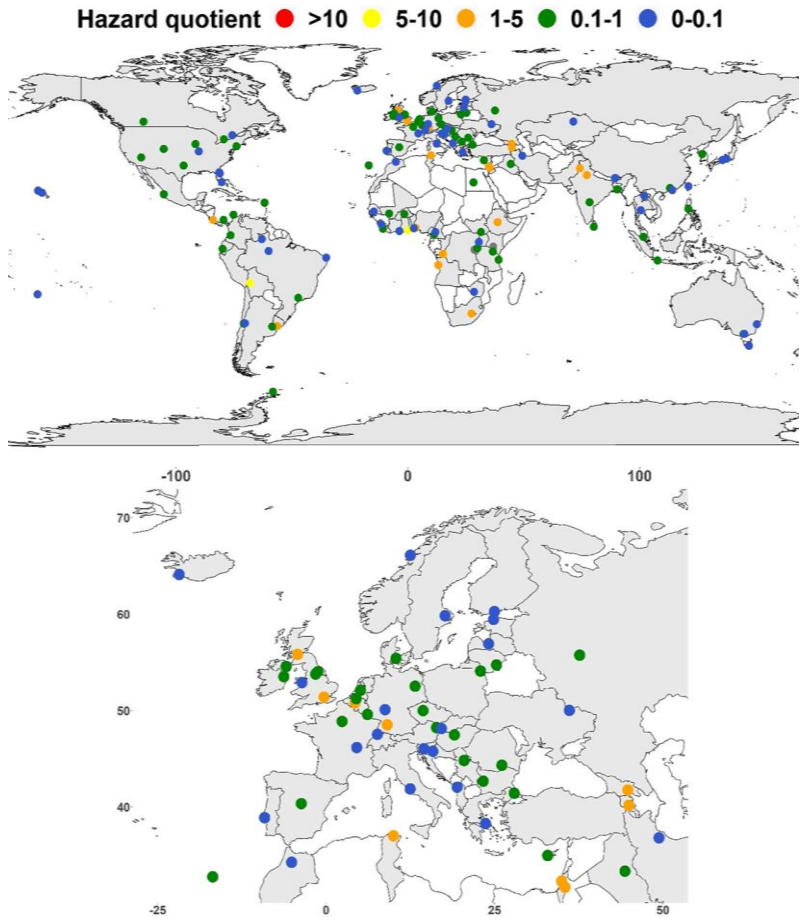
- In the insects in the river – 33 different pharmaceuticals prescribed at the hospitals
- Highest concentration of tetracyklin (overuse leads to antimicrobial resistence)
- Also antidepressive and antipsycotic pharmaceuticals alongside antihistamines - effects the insects behavior and balance in the ecosystem

Pharmaceuticals are identified in insects in River Fyris – A study with both tandem quadrupole and quadrupole-time-of-flight mass spectrometry (*Environmental Advances*)

Nytt vid farmaceutiska fakulteten - Institutionen för Läkemedelskemi - Uppsala universitet (uu.se)

Survey - 61 high-use APIs in rivers from 104 countries

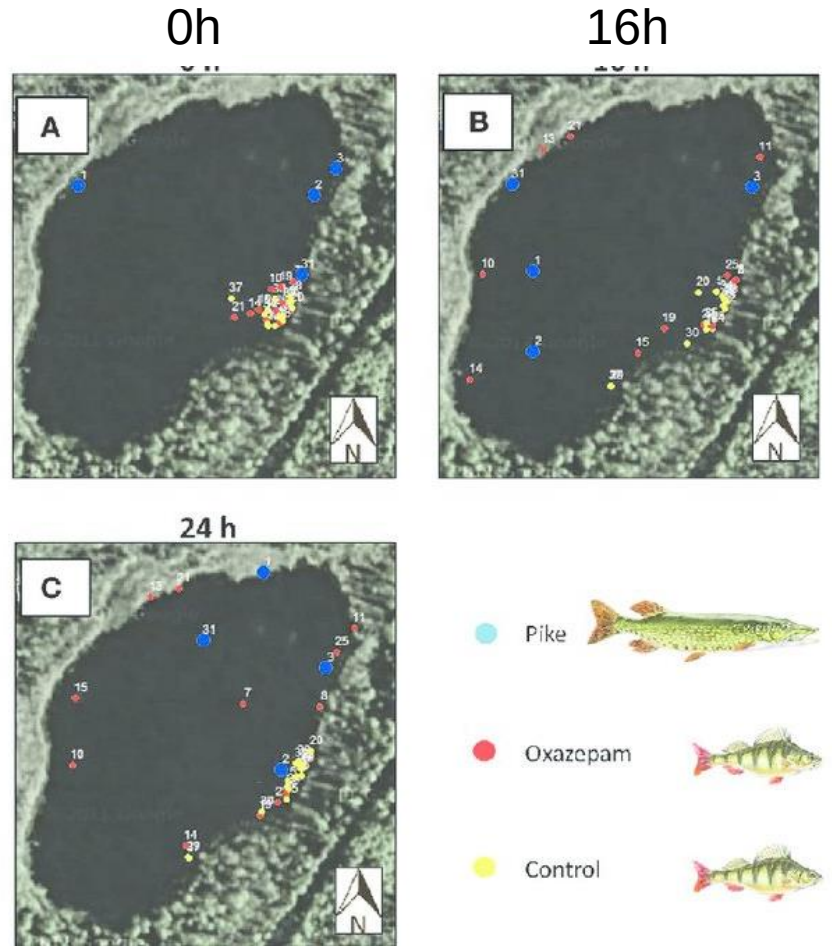
- First truly global holistic assessment of their potential ecotoxicological effects
- 34.1% of the 137 sampling campaigns had at least one location where concentrations were of ecotoxicological concern
- 23 APIs occurred at concentrations exceeding “safe” concentrations, (including substances from the compound classes)
  - antidepressant, antimicrobial, antihistamine, β-blocker, anticonvulsant, antihyperglycemic, antimalarial, antifungal, calcium channel blocker, benzodiazepine, painkiller, progestin
- Overall, the results show that API pollution is a global problem that is likely negatively affecting the health of the world's rivers and ecosystems



- Assessment of the Potential Ecotoxicological Effects of Pharmaceuticals in the World's Rivers - Bouzas-Monroy - 2022 - Environmental Toxicology and Chemistry - Wiley Online Library

Potential Ecological Effects

Oxazepam (Sobril)-treated pearch
Becomes less afraid of the pike
https://www.frontiersin.org/articles/10.3389/fenvs.2016.00081/full



Ecological effects

Birth Control Pills caused collapse of fish populationen in Canadian lake

Kidd et al., (2007) PNAS 104:21

Overall Conclusion

To meet the United Nations' Sustainable Development Goal and effects on the local communities, our long-term health and our ecosystems…

work is urgently needed to tackle the problem and bring concentrations down to an acceptable level of pharmaceuticals in the environment

Introduction – Ad hoc Working Group on PiE

- An ad-hoc working group, to address parts of the EU Strategic Approach to Pharmaceuticals in the Environment, established in February 2020
- The Pharmaceutical Committee endorsed in the March 2020 the mandate of the working group (WG) to focus on the EU strategic Approach on pharmaceuticals in the environment
- In particular on the actions and measures that fall under the competence of the Member States

Introduction

- 13 Member States, European Medicinal Agency (EMA) and the Commission participating, and 7 sub-working groups was established
- An action plan was elaborated by the working group and adopted by Pharmaceutical Committee
- The mission - propose recommendations, exchange of examples and good practices, and possible guidelines to implement the EU strategic approach – linked to the Pharmaceutical Strategy
- Report will focus on good practices and conclusions - ready in March 2024

How have we worked

- An inventory was made in participating member states on the situation
- A questionnaire was sent out through the Pharmaceutical Committee in 2021 and a compilation of the questionnaire was made in 2022 - as input to the work
- A new assignment from the Pharmaceutical Committee autumn 2021 and a prolonged assignment to the working group to 31 Mars 2024 – Concept papers for development of new legislation
- Concept Paper with legislative proposals in *Strengthening the environmental risk assessment (ERA) requirements and conditions of use for medicines*
- The concept paper was submitted in March 2022 and will not part of the final report

- A draft proposal of a final report presented and discussed at meeting in Sweden in May 2023 during the Swedish Presidency to the EC
- Presentation of the work and the propoals in pharmaceutical legislation on the Pharmaceutical Committee on the 23th of November
- Finalization of the collaboration for pharmaceuticals in the environment, including stakeholder involvement, recommendations, good practices and conclusions are to be done until March 2024

Topics – recommendation and best practice in 7 areas

Guidelines for healthcare professionals on the prudent use of pharmaceuticals *(Leader: NL Collaborators: CZ, ES, FR, FI, SE)*

Environmental aspects as a part of medical training and professional development programs *(Leader: NL Collaborators: CZ, ES, FR, NL, SE)*

Environmental considerations in the advertising and prescription of medicinal products *(Leader: FR Collaborators: EMA, FI, SE)*

Reduce medical waste *(Leader: FR Collaborators: Commission, DE, EMA, ES, IT, SE)*

Exchange of best practices on the on the environmentally safe disposal of medicinal products and clinical waste *(Leader: RO Collaborators: NL, SE)*

Waste collection schemes of unused pharmaceuticals *(Leader: ES Collaborators: FI, NL, SE)*

Improve the level of environmental expertise in the Committees and networks *(Leader: DE Collaborators: AT, CZ, EMA, ES, IE, NL, SE, SI)*

Results

- Will be presented at the end of the mandate period (31 of mars 2024) to the pharmacetical committee
- Next steps after that is to be decided on
- Communication of the proposals and continuation of the work on pharmaceuticals in the environment at a european level
- Could be a assignement to the ad hoc working group or to another part
- However not in the present mandate for the WG

Pharmaceutical legislation - Take home messages (revised Directive 2001/83/EC - Chairmans view)

+ Possibilty to refuse an application if ERA is incomplete and environmental risk is ground for refusal or revoked marketing authorization
+ Environmental data collected and made publicly available
+ Legacy products - approved before 2006– catch up procedure
+ Long term perspective (25 years since 2010)

Pharmaceutical legislation - Take home messages - (Missing parts - Chairmans view)

- Risk of emissions from manufacturing needs to be part of the ERA for all pharmaceuticals posing a risk to the environment, not only for antibiotics
- Control of emissions to the environment in manufacturing should be included in the legislation or in Good Manufacturing Practice (GMP)
- Prescription should be possible for all pharmaceuticals posing a risk to the environment not only for antibiotics and persistent bioacumulative, mobile toxic substances for example hormones
- Make amendments for better data transparency: include defined principles on data sharing and clear requirements for publicly availability of data

Pharmaceutical legislation - Take home messages - (Missing parts - Chairmans view)

- Identified risk (not serious risk) to the environment or public health should be a ground for suspending, revoking or varying a marketing authorisation and withdrawal from the market
- Limiting advertising for medicinal products for which risk to the environment or public health is identified

MPA:s comments regarding manufacturing on the proposal for new pharmaceutical legislation

- It is important that the risk to the environment in the entire manufacturing supply chain, inside and outside EU, is included in the environmental risk assessment for all pharmaceuticals that might pose an environmental risk.
- The Swedish MPA believes that environmental aspects should be included as part of Good Manufacturing Practice (GMP) to enable verification of the environmental aspects for example by third-party inspections.
- The environmental risk assessment should not be restricted to antimicrobials but include all pharmaceuticals that might pose a risk to the environment.

Release of active substances from production need to be adressed

- More local, easier to identifiy and to control – low hanging fruit – linked to AMR
- To minimize environmental pollution - Controlled processes of production and introducing of more advanced handling of wastewater needed
- Local Hot Spots – causing very high concentration effecting the local population and the local environment
  - For example - Larsson et al. – Concentration of antibioic Ciprofloxacin på 31 mg/L in treated sewage water from a ordinary treatment plant in Patancheru i Indien,)
  - exceeds levels toxic to some bacteria by over 1000-fold
  - 200 mg daily dose for treatment of urinery tract infections also used for lots of other conditions

Proposal for legislative changes in Directive 2001/83/EC, based on Concept paper on environmental challenges

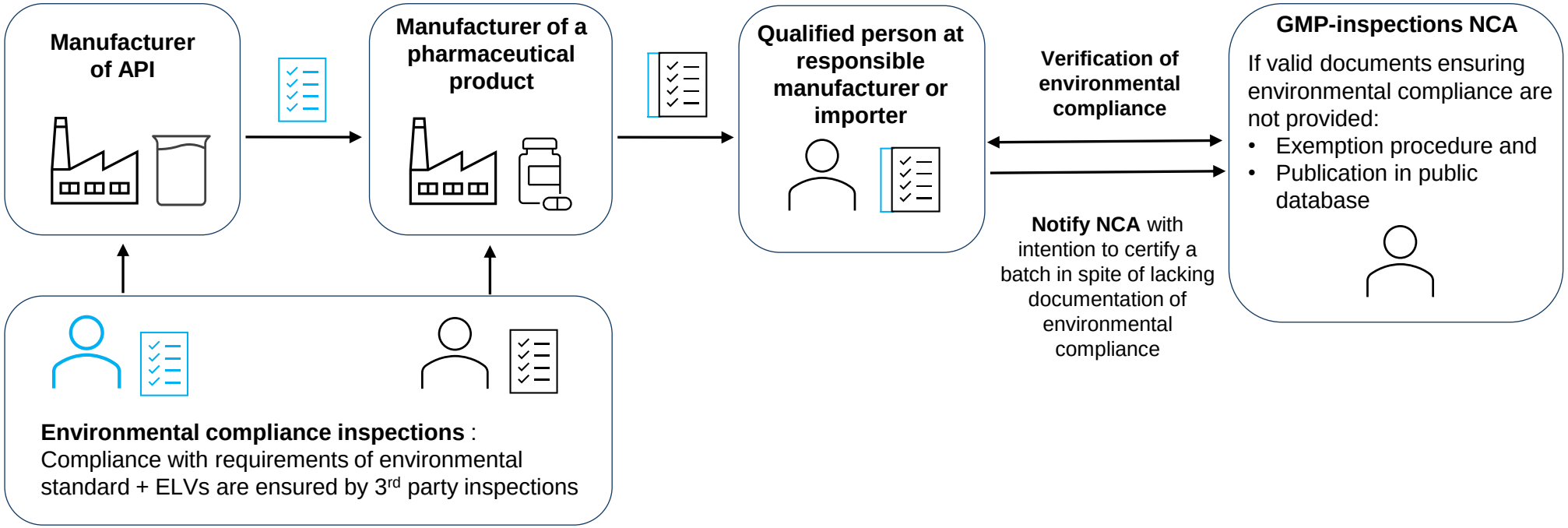


Figure 1. Process of information and inspections from manufacturing to certification of batches of pharmaceutical products. These steps are applicable for substances produced and used in the manufacturing for which the EU Commission has adopted emission limit values (ELVs) within the new EU human pharmaceutical legislation. Each batch must be accompanied by a document ensuring *compliance of the manufacturing site*. The documents are valid for X years. The 3rd party inspectors and its organisation must meet specified qualifications. API = active pharmaceutical ingredient.