2024-04-10 Krister Halldin, Swedish Medical Products Agency

Environmental premium in the Swedish national pharmaceutical benefits system

4-years pilot

Agenda

- Which pharmaceuticals will be included?
- What is the idea behind the environmental premium?
- What will be required to qualify?
- How will applications be done?

Pharmaceuticals included should

- be in the Swedish **product-of-the-month system**
- belong to pharmaceutical subgroup:
  - antibiotics (with limitations)
  - non-steroidal anti-inflammatory drugs (NSAIDs)
  - sex hormones

Around 70 companies sell products that are included

Around 460 products with a total sale of 4.9 million packages per year

The products-of-the-month

TLV THE DENTAL AND PHARMACEUTICAL BENEFITS AGENCY

- the available generic substitutable pharmaceuticals with the lowest prices that pharmacies must offer customers when substituting pharmaceuticals
- the product in each package size group with the lowest sales price per unit that can be provided to the entire market with a sufficient shelf life for the entire price period becomes the product-of-the-month

Main idea with the environmental premium

Production with low environmental (API emissions)

► environmental premium

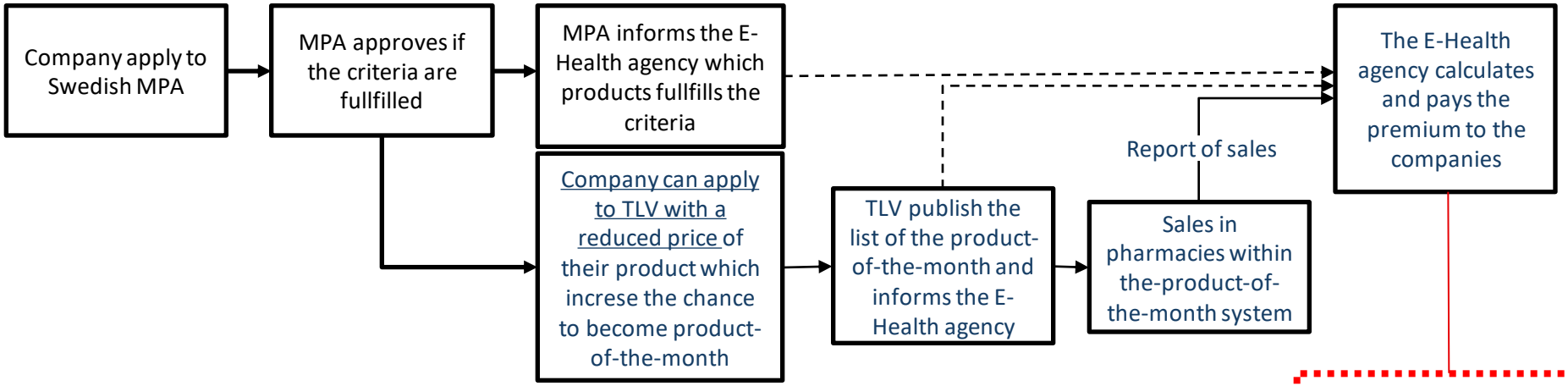
► possibility for company to lower the prize

► win the bid for product-of-the-month ► more sales/income

► larger market share for products with less risks

“to incentivize more sustainable production”

Explanation of the system with the premium



The premium is a fixed amount per sold package of products in the product-of-the-month system. Intended to stimulate the companies to lower their price

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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eHälsomyndigheten

Overview of criteria

All production sites:
Production of API
Formulation of Drug

Audit

Verified report

Application
Sent by the company applying for the environmental premium

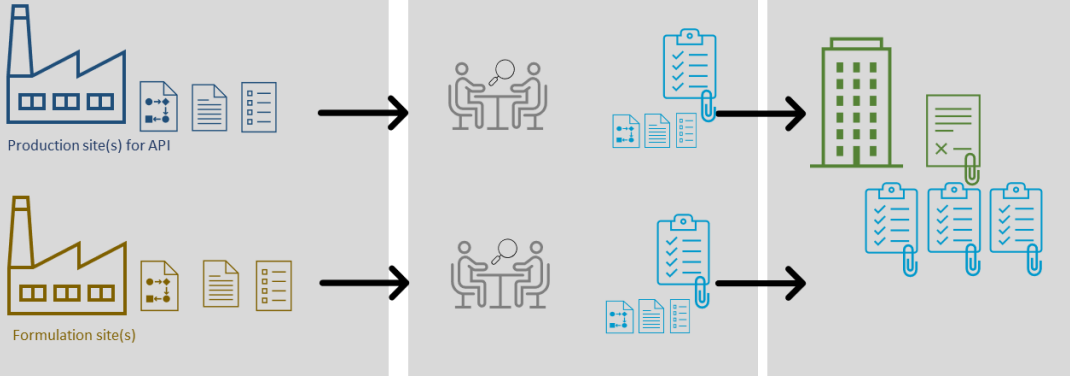
Handling and decision
Swedish MPA

Requirements:
1. Mapping and handling of waste streams
2. Sampling, analysis and calculations
3. Emission limit values, compliance

Requirements :
Physical visit
Verification of documentation and calculations
Competence and experience

Requirements :
Certificates of compliance and validity of documentation

Requirements :
Application form
All verified reports
Competence and experience of auditor
CV



Requirements – descriptions and documentation

- Schematic image or description of sites in the production chain
  - Production units
  - Waste water treatment units
  - Inventory of all waste streams

- Mapping of waste streams where API can occur (API production and formulation of drug)
  - Synthesis scheme (for API, GMP steps)
  - Flowchart (all chemicals and solvents that can affect presence of API in waste streams)
  - Presence of API in each waste stream (moles, kg and %)
  - Mass balance calculation

Requirements – descriptions and documentation

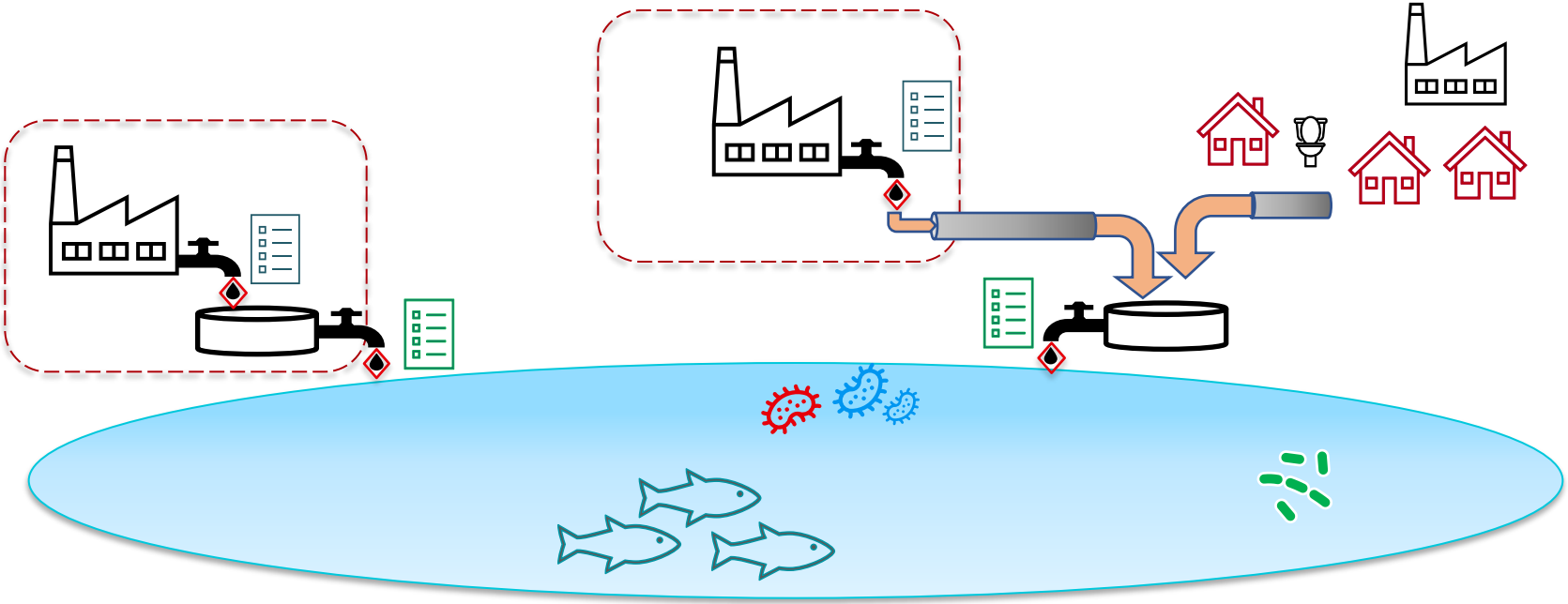
- Handling of process wastewater containing API
  - Calculation of the average concentration of API in the process wastewater during production of a representative batch
  - Description and justification of selected techniques for wastewater treatment
  - Information on how process wastewater is *transported* to WWTP without leakages

- Handling of solid waste
  - All sources of solid waste with API should be listed
  - Information on how solid waste is handled and stored to avoid leakages
  - Information on final processing of solid waste and how leakages are avoided

Requirements - emission of API to recipients

- Identification of a representative batch
  - A batch manufactured, including cleaning of equipment, according to the method that results in the highest concentration of API in process wastewater
- Hourly sampling when a representative batch is manufactured – merged to a composite sample every 24th hour
- Chemical analysis of API in composite samples by an accredited analytical laboratory
- Average concentration in the wastewater during production of a representative batch should be below the emission limit value (ELV)

Sampling points



Suggested ELVs – in wastewater

Drug group	Active pharmaceutical ingredient		Limit value in wastewater and process wastewater (µg/L)	
			To inland waters	To coastal waters
Antibiotics	Azithromycin		0.50	0.50
	Ciprofloxacin*		0.10	0.10
	Clarithromycin		0.25	0.25
	Moxifloxacin		0.125	0.125
Sex hormones	Potent sex hormones (estrogens and progestogenes)	Ethinylestradiol*	0.00007	0.00070
		Estradiol*	0.00080	0.00800
		Others	0.0007	0.0070
	Other sex hormones		0.15	1.50
NSAIDs	Diklofenac*		0.10	1.00
	Other NSAIDs		0.15	1.50

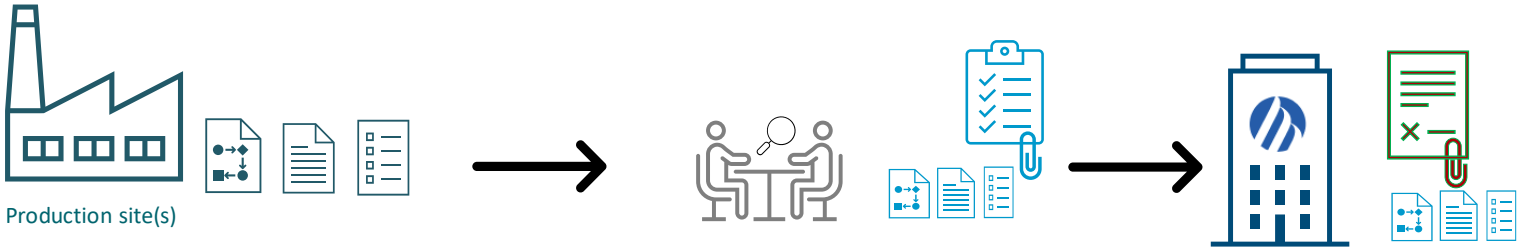
* Based on Environmental Quality Standards (EQS)

ELVs - brief background

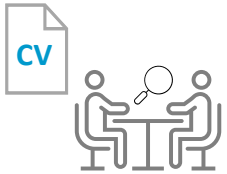
- Antibiotics
  - PNEC-MIC recalculated with modifications (Bengtsson-Palme & Larsson 2016)
  - Ciprofloxacin based on EQS (resistance selection)
  - No dilution factor included in emission limit value
- NSAIDs
  - PNEC based on statistics for around 200 NOEC values
  - Diclofenac based on EQS
  - Dilution factor 10 or 100 included depending on recipient
- Sex hormones
  - Estrogens and progesterones based on chronic NOEC data from fish
  - Ethinylestradiol and estradiol based on EQS
  - Other sex-hormones fit into the “200 NOEC statistics”
  - Dilution factor 10 or 100 included depending on recipient

Verification

- A third-party auditor engaged by the applicant should confirm:
  - That sampling and analysis is done in accordance with requirements
  - That concentration of API is below the limit value
  - That all documentation requested is in accordance with the conditions at the production site/s



Audit



- A qualified auditor linked to a company with a certified quality management system
- Carried out in accordance with good auditing practice and follow relevant international auditing standards and methods
- The auditor or a group of auditors needs to have:
  - relevant education – technology or natural sciences
  - good knowledge from the production of pharmaceuticals or organic fine chemicals
  - experience from previous relevant audit assignments
  - experience from handling and purification of wastewater

Application

- The plan is to start from mid 2025 – *depending on the regulation*
  - *Remittance/referral of the regulations by the government and the agencies*
- E-portal will be set up
- Application should contain:
  - Administrative information
  - Documentation including third party verification