PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Building responsible supply chains

# Indian Case Study on Controlling API Releases

JON PEERS

ENVIRONMENTAL DIRECTOR

TEVA API & BIOLOGICS

# Speaker Bio

Jon Peers – Environmental Director, Teva api & Biologics

- Located: Madrid, Spain
  - Joined Teva: 2015
  - B.Sc. in Environmental Science;
  - Business Sustainability Management
  - 20+ Years experience in EHS
    - Ciba SC
    - GSK
    - Abbott Laboratories
- Fields of expertise:
  - Safe handling of: powders/solvents/hazardous chemicals
  - Emergency response
  - Waste management
  - Wastewater treatment
  - Air pollution
  - Industrial Hygiene

# Serving around 200 million people every day

# Our Mission

To be a **global leader** in **generics** and **biopharmaceuticals**, improving the **lives of patients**

# Teva's history

## 1901-1940

### A new pharmaceutical industry is founded

1901: Established in Jerusalem by Chaim Salomon, Moshe Levin and Yitschak Elstein

## 1960-1980

### Consolidation of the local pharmaceutical industry

1976: Eli Hurvitz forms Teva Pharmaceutical Industries Ltd.

## 1980-1990

### Global expansion

1984: Hatch-Waxman Act paves way for U.S. generic entry

## 1990-present

### A global leader in generics/ establishes specialty

1996: Teva launches COPAXONE® in the US
2017-2018: Teva launches AJOVY(R) and AUSTEDO (R) in the US

# Teva today

A strong specialty medicines portfolio

2019 **revenues**:

**$16.9B**

**40,000**

**employees**

The leading global generic company

**68**

**Manufacturing** sites

**60**

**Markets**

**Over the counter medicines & active** pharmaceutical Ingredients (API)

# Leveraging scale and enhancing our competitiveness

**68**
**Manufacturing Sites** in 33 countries

**80B**
**Tablets / Capsules**

**20,000**
**Employees** in Operations

**3,500**
**Products**

**35,000**
**SKUs**

# Teva's Sustainability position

- Teva environmental sustainability position includes our approach to reduce API emissions from our manufacturing sites: https://www.tevapharm.com/globalassets/tevapharm-vision-files/teva_environmental_sustainability_position_statement2018.pdf
- Teva EHSMS establishes a global standard for emissions including our approach to reduce API emission from our sites
- AMR is Teva's current priority and by YE2020, we will have completed AMR assessments of 93% of drug products and 100% of drug substances; our AMR position is at: https://www.tevapharm.com/globalassets/tevapharm-vision-files/teva_amr_position_statement2018.pdf

# Teva api & biologics by numbers

teva | api

**400+**
High-quality API products

**1,100**
Customers

**100+**
Countries

**5,000**
Employees

**16**
Sites worldwide

**85**
Years

## GAJRAULA SITE

Manufacturing

**Address**
Plot. Nos. A-1, A-1/1 & A-1/2
UPIDC Industrial Area.
Bijnor Road,
Distt.J.P.Nagar
1444235 Gajraula (Uttar Pradesh)
India

**Tel** 05924252591-92-93
**Fax** 05924252590
**Established** 1994 (JK Pharmaceutical)
**Acquired by Teva api** 2003

## MALANPUR SITE

Manufacturing

**Address**
Plot Nos. Q1 - Q4
Industrial Area, Ghirongi,
District-Bhind, Malanpur
477 117 (Madhya Pradesh)
India

**Tel** 07539 - 283942
**Established** 2008

## TEVA API INDIA PRIVATE LIMITED

R&D

**Address**
2-G, 2-H, 2-I Eco Tech – II, Udyog Vihar
Greater Noida
201 306 (Uttar Pradesh)
India

**Tel** +91-120-4073300
**Fax** +91-120-4073275

# Antibiotic Mass Balance Summary

*Common Antibiotic Manufacturing Framework*

- Framework includes commitment to quantify antibiotics in effluent by mass balance.

**Water Management Program**

**Principle:** Compliance with all applicable regulations. All required environmental permits, licenses, information registrations and restrictions are in place, available for review, and their operational and reporting requirements are followed. Systems are in place for the management of water discharges. Any wastewater or wastewater sludge from on-site wastewater treatment operations with the potential to adversely impact human or environmental health is managed, controlled, and treated prior to release to the environment. Systems are in place to prevent and mitigate accidental spills and releases to the environment.

1) Site possesses a valid authorization/license/permit for water intake (i.e. from groundwater, river or public system) and discharge. Compliance with each condition in the authorization/ license/ permit is demonstrated.
2) Levels of antibiotic in process wastewater are quantified e.g. mass balance.
3) Wastewater sources from operations are characterized and evaluated for treatability and control.
4) Effective wastewater treatment is provided (e.g., neutralization, clarification, settling, inactivation, biological or chemical treatment).
5) Water/wastewater monitoring devices and treatment systems are in good operating condition and appropriately maintained (e.g. in accordance with manufacturer's recommendations).

**83%** of manufacturing company members have assessed all of their own antibiotics manufacturing sites against the Alliance's new manufacturing **framework**

**82%** of owned sites **meet the framework's requirements** wholly or in part

**56%** of products made at member-owned sites are expected to be made in accordance with discharge targets **within the next 3 years** and **88% within the next 7 years**

**24%** of products made at supplier sites are expected to be made in accordance with discharge targets **within 3 years** and a further **70%** of products made at supplier sites are expected to be made in accordance with these targets **within 4-7 years**.

- It's a Journey…
  - Industry led initiative. Not "compliance" vs "non-compliance"
  - All members at different points of journey but committed to meeting safe discharge targets.

# Antibiotic Mass Balance Summary

***Common Antibiotic Manufacturing Framework***

## Background

- AMR Industry Alliance released Common Antibiotic Manufacturing Framework in January 2018.
  - Framework includes commitment to quantify antibiotics in effluent by mass balance.

- AMR Industry Alliance released discharge concentration targets for antibiotics in September 2018 (Predicted No Effect Concentrations - PNECs) and updated January 2020.
  - Target based on lower of PNEC for resistance (PNEC-MIC) or PNEC for ecotoxicity (PNEC-ENV).
  - Target applied at point of entry into environment after mixing.

- PNEC = Concentration of API in environment that is believed (predicted) to not have an impact on the environment demonstrated by testing certain species.

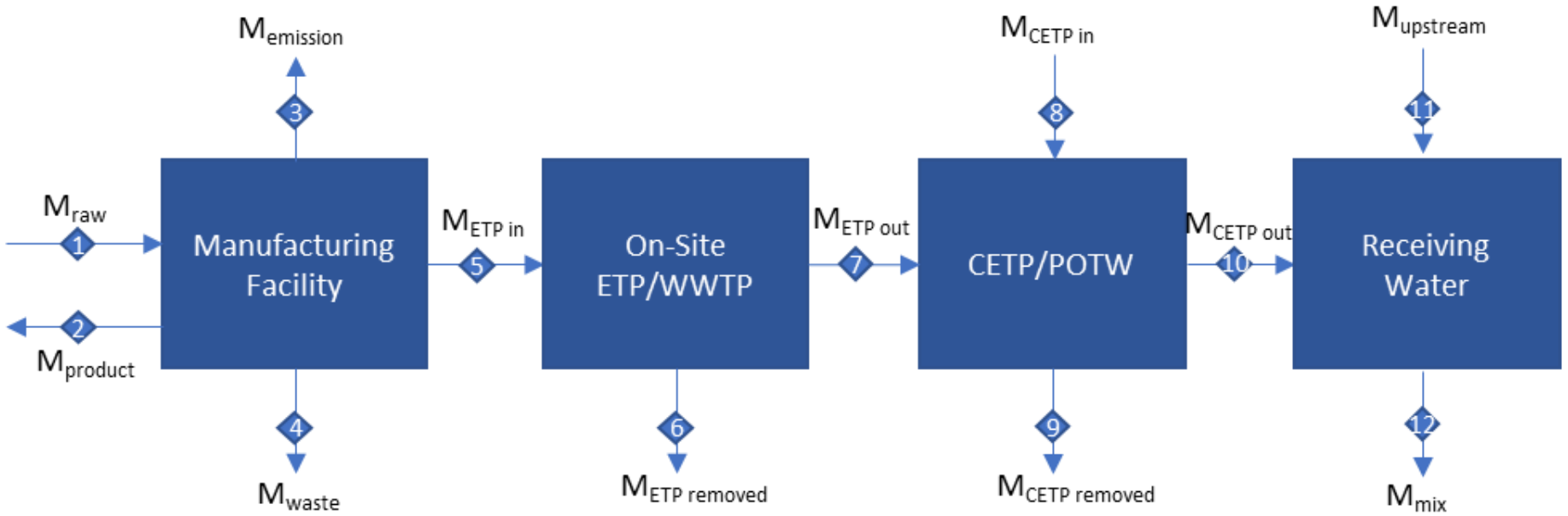
| Source for Publication | API | $EC_{10}$ (µg/L) | Species | Test Guideline / Reference | $PNEC_{ENV}$ (µg/L) | $PNEC_{MIC}$ (µg/L) | Lowest Value (µg/L) | $PNEC_{ENV}$ Rationale | Revisions Since Last Version |
|---|---|---|---|---|---|---|---|---|---|
| Bengtsson-Palme & Larsson, 2016 | Amikacin | | | | N/A | 16.00 | 16.00 | No industry data | No change |
| Industry Data | Amoxicillin | 5.7 | *Anabaena flos-aquae* | OECD 201 | 0.57 | 0.25 | 0.25 | *Anabaena flos-aquae* $EC_{10} \div 10^{a}$ | Industry testing completed |
| Gonzalez-Pleiter, et al., 2013 | | 6160 | *Anabaena sp. CPB4337* | OECD 201 | | | | | |
| Industry Data | | 530000 | *Raphidocelis subcapitata* | OECD 201 | | | | | |
| Gonzalez-Pleiter, et al., 2013 | | 1500000 | *Raphidocelis subcapitata* | OECD 201 | | | | | |
| Bengtsson-Palme & Larsson, 2016 | Amphotericin B | | | | N/A | 0.02 | 0.02 | No industry data | No change |
| Industry Data | Ampicillin | 44.6 | *Anabaena cylindrica* | OECD 201 | 0.60 | 0.25 | 0.25 | *Cyanobium gracile* $EC_{10} \div 10$ | Industry testing completed & new literature data added ($PNEC_{ENV}$ originally 0.87 µg/L) |
| Le Page et al., 2019 | | 8.3[h] | *Anabaena flos-aquae* | OECD 201 | | | | | |
| Industry Data | | 13 | *Anabaena flos-aquae* | OECD 201 | | | | | |
| Le Page et al., 2019 | | 18.7 | *Anabaena flos-aquae* | OECD 201 | | | | | |
| Le Page et al., 2019 | | 5.9 | *Cyanobium gracile* | OECD 201 | | | | | |
| Industry Data | | 91500 | *Daphnia magna* | OECD 211 | | | | | |
| Industry Data | | 94300 | *Desmodesmus subspicatus* | OECD 201 | | | | | |
| Le Page et al., 2019 | | 34.3 | *Geminocystis herdmanii* | OECD 201 | | | | | |
| Industry Data | | 100000 | *Raphidocelis subcapitata* | OECD 201 | | | | | |
| Le Page et al., 2019 | | 36.5[h] | *Synechocystis sp.* | OECD 201 | | | | | |
| Le Page et al., 2019 | | 38.8[g] | *Synechococcus elongates* | OECD 201 | | | | | |
| Le Page et al., 2019 | | 16.2[g] | *Synechococcus leopoliensis* | OECD 201 | | | | | |
| Industry Data | | 19 | *Synechococcus leopoliensis* | OECD 201 | | | | | |
| Le Page et al., 2019 | | 38[g] | *Synechococcus sp.* | OECD 201 | | | | | |
| Bengtsson-Palme & Larsson, 2016 | Anidulafungin | | | | N/A | 0.02 | 0.02 | No industry data | No change |
| Industry Data | Avilamycin | 1250[b] | *Synechococcus leopoliensis* | OECD 201 | 125.00 | 8.00 | 8.00 | *Synechococcus leopolensis* NOEC ÷ 10 | Industry data added |
| Le Page et al., 2019 | Azithromycin | 5 | *Anabaena cylindrica* | OECD 201 | 0.03 | 0.25 | 0.03 | *Microcystis aeruginosa* $EC_{10} \div 10$ | Original $PNEC_{ENV}$ (0.02 µg/L) based off NOEC, $EC_{10}$ used preferentially |
| Le Page et al., 2019 | | 10.5[h] | *Anabaena flos-aquae* | OECD 201 | | | | | |
| Industry Data | | 4.4 | *Ceriodaphnia dubia* | OECD 201 | | | | | |
| Le Page et al., 2019 | | 4.8 | *Cyanobium gracile* | OECD 201 | | | | | |
| Le Page et al., 2019 | | 3.2 | *Geminocystis herdmanii* | OECD 201 | | | | | |
| Industry Data | | 0.33 | *Microcystis aeruginosa* | EPA 1002.0 | | | | | |
| Industry Data | | 4600 | *Pimephales promelas* | OECD 210 | | | | | |
| Industry Data | | 1.8 | *Raphidocelis subcapitata* | OECD 201 | | | | | |

Revision Date: 24 January 2020

# Antibiotic Mass Balances

## Methodology

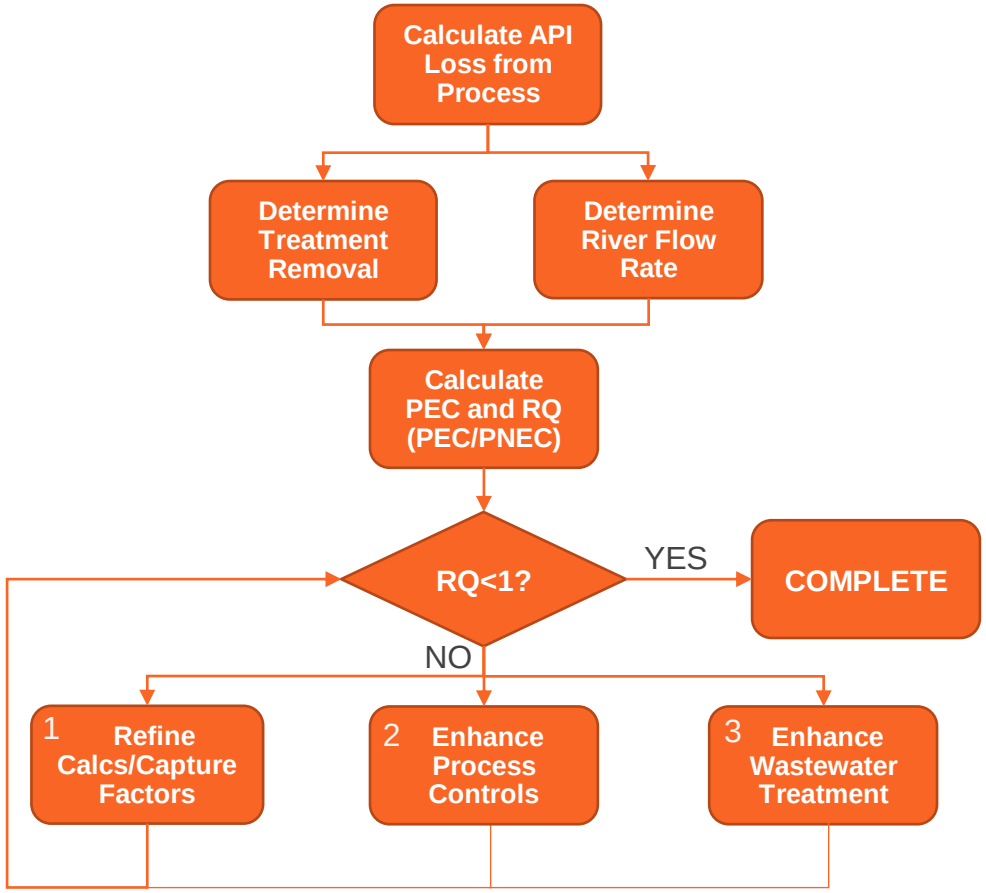
- Methodology outlined by PSCI
- Average daily loss of API from batch based on batch records.
- Removal efficiencies applied for wastewater treatment based on published literature.
- Flow of receiving stream used to calculate antibiotic concentration in environment (Predicted Environmental Concentration - PEC).
- Risk Quotient (RQ) calculated as ratio PEC / PNEC. Target is RQ of 1 or less (i.e. PEC < PNEC).



# Antibiotic Mass Balance Summary

***Common Antibiotic Manufacturing Framework***

- Mass Balance Approach
  - Determine quantity of "unaccounted" API from process
  - Apply "Capture Factors" and assumptions
  - Apply removal efficiencies for wastewater treatment plant(s)
  - Determine mass and concentration in final receiving water
- Impact Assessment
  - RQ<1 (Meets PNEC): No Further Action Required
  - RQ>1 (Does Not Meet PNEC): Additional Assessment/Risk Reduction & Action Plan Required
- Risk Reduction Hierarchy – RQ>1
  - Calculation Refinement: Refine assumptions, conduct additional studies, repeat mass balance/RQ.
  - Process Controls: Implement additional controls, procedures, etc. to reduce quantity of API discharged.
  - Wastewater Treatment: New/enhanced wastewater treatment to reduce quantity of API in effluent.



# Teva api & biologics - Malanpur

**MALANPUR SITE**

Manufacturing

**Address**
Plot Nos. Q1 - Q4
Industrial Area, Ghirongi,
District-Bhind, Malanpur
477 117 (Madhya
Pradesh)
India

**Tel** 07539 - 283942

**Established** 2008


Teva Malanpur manufactures antibiotic products for distribution in the US, Canada and Europe.

The site employs approximately 260 people and creates products from a total of 22 different APIs. Of these APIs, Clarithromycin was selected to be the subject of the PiE assessment, since Clarithromycin is the highest production volume antibiotic at Malanpur.

The Malanpur PiE Assessment was performed in July –December 2019 as a part of a Global Teva PiE Assessment initiative. This initiative aims at estimating the effect of antibiotics emissions to surface water.

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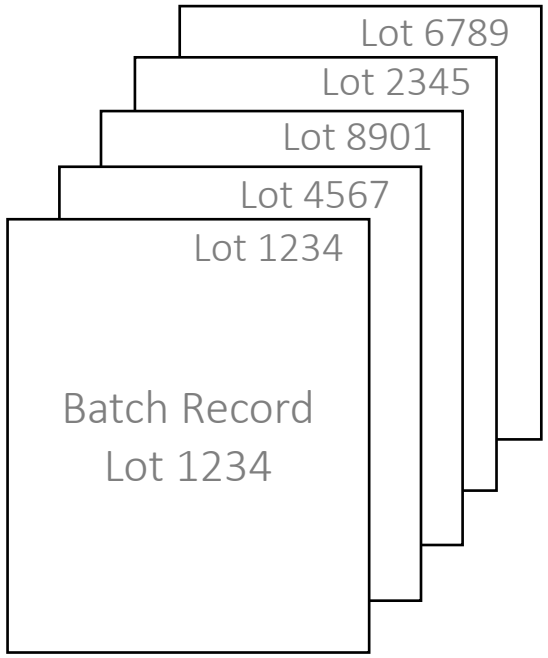
The site is a zero liquid discharge facility. Process water is treated in an on site wastewater treatment plant (WWTP), in which both biological and physical-chemical treatment processes are taking place. WWTP effluent is reused as cooling water and for gardening purposes.

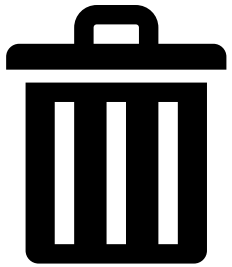
As a result, there is no discharge of WWTP effluent to surface water. Re-use for gardening purposes is currently allowed, but new legislation (currently in draft) might limit or prohibit this in future

# Mass Balance Summary

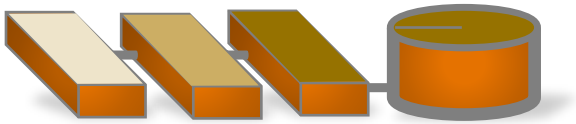
Getting Started: What you need




Completed Batch Records (Mandatory)



Capture Factors (May Be Optional)

Treatment Removal (May Be Optional)

Stream Flow Data (Mandatory)

ZLD

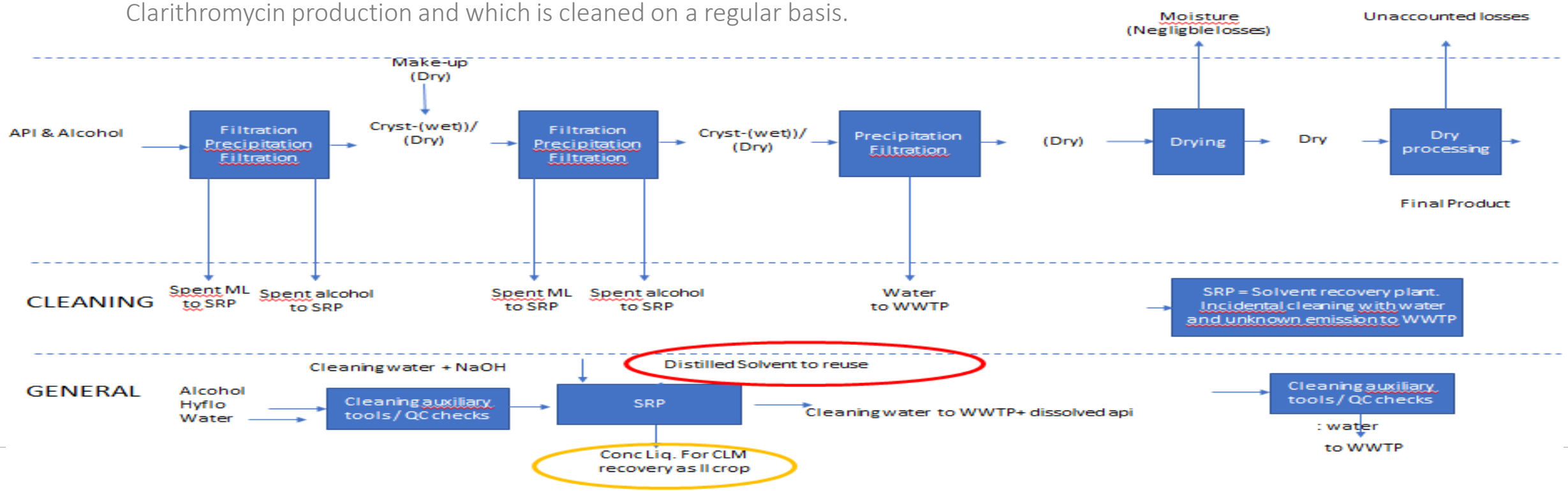
AMR Alliance Recommended PNECs for Risk Assessments

| Active Pharmaceutical Ingredient | PNEC-ENV (µg/L) | PNEC-MIC (µg/L) | Lowest Value (µg/L) |
|---|---|---|---|
| Amikacin | N/A | 16 | 16 |
| Amoxicillin | Testing On-Going | 0.25 | 0.25 |
| Amphotericin B | N/A | 0.02 | 0.02 |
| Ampicillin | 0.87 | 0.25 | 0.25 |
| Anidulafungin | N/A | 0.02 | 0.02 |
| Avilamycin | N/A | 8.0 | 8.0 |
| Azithromycin | 0.02 | 0.25 | 0.02 |
| Aztreonam | N/A | 0.50 | 0.50 |
| Bacitracin | 100 | 8.0 | 8.0 |
| Bedaquiline | 0.08 | N/A | 0.08 |
| Benzylpenicillin | N/A | 0.25 | 0.25 |
| Capreomycin | N/A | 2.0 | 2.0 |
| Cefaclor | N/A | 0.50 | 0.50 |
| Cefadroxil | Testing On-Going | 2.0 | 2.0 |
| Cefalonium | 21 | N/A | 21 |
| Cefaloridine | N/A | 4.0 | 4.0 |
| Cefalothin | N/A | 2.0 | 2.0 |
| Cefazolin | N/A | 1.0 | 1.0 |
| Cefdinir | N/A | 0.25 | 0.25 |
| Cefepime | N/A | 0.50 | 0.50 |
| Cefixime | 0.18 | 0.06 | 0.06 |
| Cefoperazone | N/A | 0.50 | 0.50 |

PNECs (Mandatory)

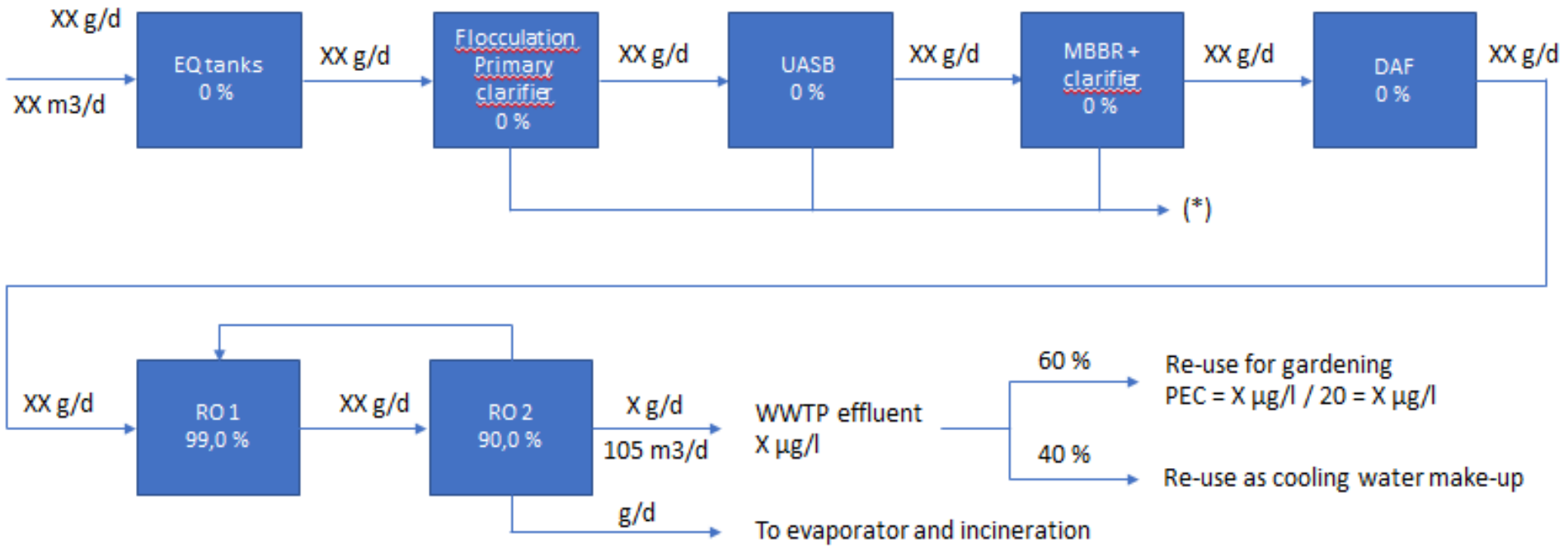
# What was our approach? Mass Balance

1. Mass balance estimates were calculated using batch records from previous campaigns.
   - From these batch records, a flow scheme for Clarithromycin production was established indicating possible routes of Clarithromycin loss to water, dust and cleaning solvent (ethanol).
   - The flow scheme was adjusted to accurately represent the actual production process (including losses to water, dust and ethanol). Subsequently the Clarithromycin loss to wastewater was established by compiling a mass balance, for which typical mass data from Production were used.
   - Special attention was paid to the Solvent Recovery Plant (SRP), which receives all ethanol-based washing liquids from Clarithromycin production and which is cleaned on a regular basis.



# What was our approach? WWTP

2. After that, the on-site wastewater treatment plant was studied in more detail. There was no data available about Clarithromycin removal in the on site WWTP, neither reliable data on Clarithromycin removal available in literature.
   - Assuming no Clarithromycin removal in the on site WWTP, except for the RO units, a worst case Clarithromycin effluent concentration was calculated.



# What was our approach? WWTP

3. WWTP effluent is partially reused as cooling water make up, and partially for gardening purposes.
    - To quantify the ecological impact of WWTP effluent that is reused for gardening, a predicted environmental concentration for groundwater may be calculated based on irrigation rate, the area of concern, the infiltration rate of the soil, hydraulic conductivity and the aquifer thickness.
    - In the Malanpur case, in the absence of site-specific data, a default dilution-attenuation factor of 20 was used to account for contaminant dilution and attenuation during transport through the saturated zone to a receptor.
    - The outcome is then divided by the Clarithromycin PNEC-ENV to yield the Risk Quotient (RQ).

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(*) Sludges are send to on site sludge drying beds. After drying, sludges are transported for off-site incineration at the CHWTSDF Facility (Madhya Pradesh Waste Management Projects, Pithampur , Distt- Dhar (M.P.), India).

The on-site sludge drying beds have a concrete lining to prevent groundwater pollution. Leachate is collected and fed to the WWTP. Because of low water solubility, the leachate Clarithromycin load from the sludge drying bed leachate to the WWTP is considered negligible.
(**) Residuals from the evaporator are also transported to CHWTSDF for inceration.

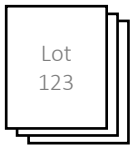
# Next Steps

- Investigate alternative effluent disposal, since re-use for gardening might be prohibited in future
- Further evaluate the risk of WWTP effluent infiltration (e.g. what is the environmental impact?
    - Is PNEC-ENV the appropriate reference?
- Quantify losses and/or WWTP removal efficiency and/or effluent concentration during the next Clarithromycin run.
    - Clarithromycin is poorly soluble (0.23 mg/l) which might indicate that the bulk of the API is not present in a dissolved form, meaning that physical/chemical treatment steps might reduce the Clarithromycin more than assumed during the PiE assessment.

# Challenges & Considerations

**Resources**
- Internal
- Third party/consultant

**Products**
- Multiple strengths
- Different formulations

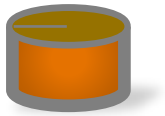



**Batch Records**
- Adequate representation
- Outliers, gains, campaigns, high yields, etc.

**Cleaning**
- Method (dry cleaning vs wet cleaning)
- Entire process vs step-by-step

**Capture Factors**
- Filters (washed vs disposed/wet vs dry)
- Waste (offsite vs onsite treatment)

**Flow Data (Not ZLD)**
- Location (upstream vs downstream)
- Low flow calculation



**Wastewater Treatment**
- Availability of “good” data
- Third party reliability

**PNECs**
- Availability
- Default value?

**Suppliers**
- Resources
- Understanding/Accuracy

# CONTACT

pscinitiative.org

info@pscinitiative.org

Annabel Buchan:
+44 (0) 7794 557524

PSCI

@PSCInitiative

## For more information about the PSCI please contact:

**PSCI Secretariat**
Carnstone Partners Ltd
Durham House
Durham House Street
London
WC2N 6HG

info@pscinitiative.org

+44 (0) 7794 557 524

**About the Secretariat**
Carnstone Partners Ltd is an independent management consultancy, specialising in corporate responsibility and sustainability, with a long track record in running industry groups.

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