

Modern Wastewater Treatment Solutions in a State-of-the-Art Pharmaceutical Production Environment

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From traditional wastewater treatment to zero-discharge strategy

Traditional end-of-pipe solutions for dealing with effluents coming out of the production plant have been gradually substituted for an increasingly decentralised approach to treat selected wastewater streams in the most effective and economically sound way. Moreover, additional goals like reducing overall effluent emissions by reusing treated wastewater towards zero-discharge strategies or minimising waste generation and disposal costs have been gradually incorporated to a growingly holistic water and wastewater management approach. The future of industrial wastewater treatment has mainly two:

- Both the monitoring and abatement of trace pollutants, as prioritised in the Annex X of the EU directive 2000/60/EC [EU 2000], and additional dangerous trace contaminants [LANUV 2007].
- Further development of existing and new wastewater treatment technologies in order to minimise costs and optimise resource consumption. [Krause et al. 2011] [Rosenwinkel et al. 2011]

As in many other industrial branches, production managers at the pharmaceutical industry are adopting an increasingly decentralised approach when dealing with well characterised wastewater streams.

The removal efficiency of PPCPs (Pharmaceuticals and Personal Care Products), PhACs (Pharmaceutical Active Components) and EDCs (Endocrine Disruptive Components) has been tested for many different technologies which are available for the last decades. Results vary from zero abatement effectivity as shown by traditional coagulation and flocculation processes (alum & ferric chloride) to high and very high removal rates as those achieved by active carbon filtration, biological degradation, membrane filtration technology (e.g. reverse osmosis, ultrafiltration at membrane biological reactors, etc.), oxidation technologies combining different available AOPs (Advanced Oxidation Processes) like ozonation¹, hydrogen peroxide with radiation from UV light, etc. [Khiari 2007] [Ternes et al. 2004]

This article aims to present some examples of modern effluent treatment solutions which have been realised at research-based pharmaceutical companies, where effluents could be specifically treated in order to:

¹ NOTE: In this article the term „ozonation“ will be applied for “the treatment or combination of a substance or compound with ozone”, whereas the term “ozonisation” will be used for defining “the production of ozone in an ozonizer” [Source: Merriam Webster Online / <http://www.merriam-webster.com/>]

- reduce the overall footprint of the wastewater treatment plant by implementing state-of-the-art MBR technology and/or a modular design approach;
- abate trace elements by separating and concentrating them to minimise costs of external disposal (e.g. reverse osmosis and vacuum distillation);
- inactivate streams containing biologically active ingredients (e.g. hormones, antigens, etc.) by means of thermal sterilisation technology;
- eliminate pharmaceuticals implementing advanced oxidation processes (e.g. ozonation);
- or generate green energy (biogas) from digested organic matter (COD) implementing anaerobic treatment technology.

Implementing a modular design approach to reduce the footprint of CAS (Conventional Activated Sludge) wastewater treatment plants

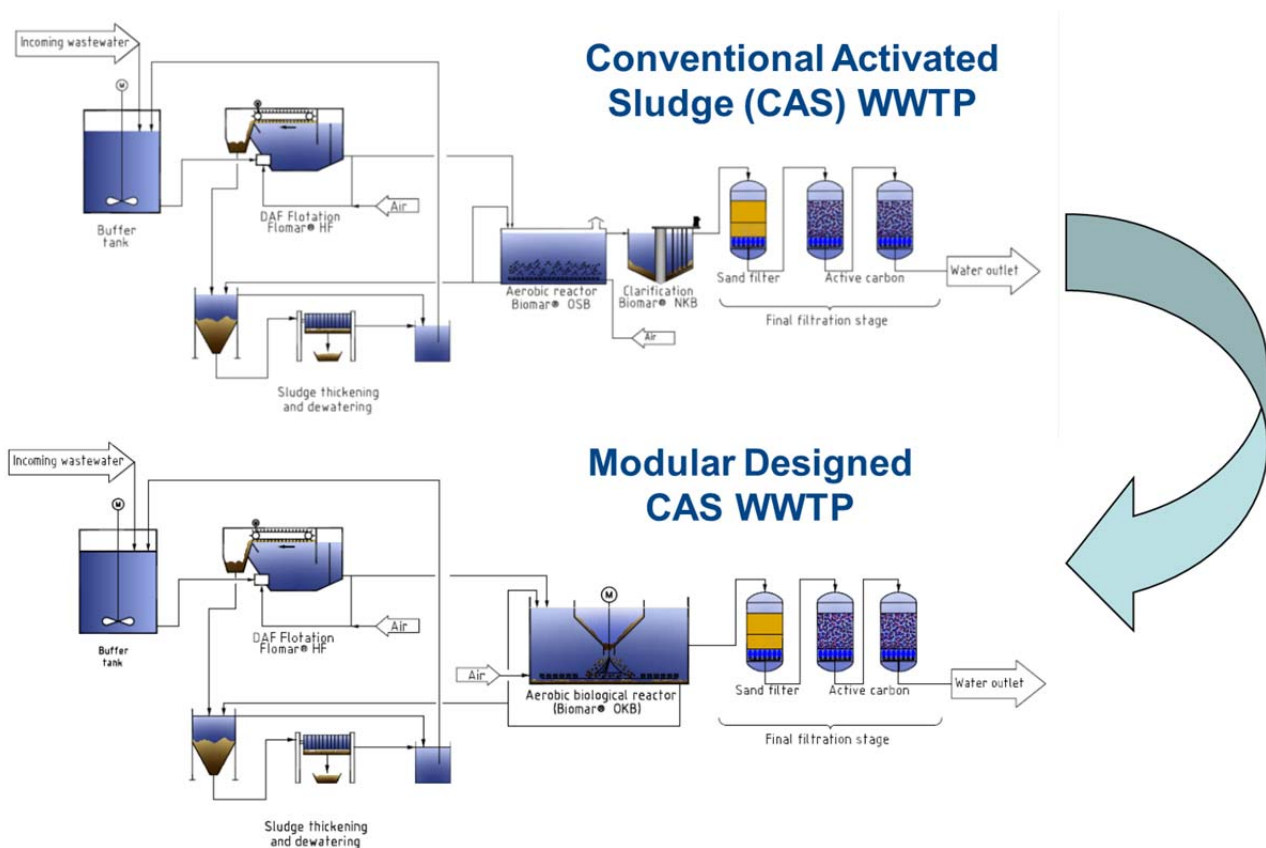


Figure 1. Example of reducing the footprint of a WWTP by integrating of the clarifier within a "conventional" aerated biological reactor. [Source: EnviroChemie GmbH]

Traditional design of CAS wastewater treatment plants has been proven through the years and is based on a selection of robust and reliable technologies including a chemical-physical pre-treatment stage, an activated sludge bio-reactor (aerobic biological treatment) and a final conditioning stage combining chemical-physical processes (e.g. flotation) and filtration units (e.g. sand and active carbon filters). Main drawbacks of CAS wastewater treatment plants are their specific high energy consumption, rather big waste (i.e. sludge) generation and relatively low

selectivity to abate trace pollutants in an efficient way.[Krause et al. 2011] [Rosenwinkel et al. 2011]

Taking a first step to reduce the footprint of CAS wastewater treatment plants, there is the possibility to do so by implementing a modular design approach. For instance, the clarifier can be integrated within the main aeration basin in medium size plants (with an effluent flow not exceeding 15 m³/h). This preliminary measure towards a minimised overall footprint is shown in Figure 1.

In a modular designed wastewater treatment plant, all main technological components (e.g. blowers for the biological reactor, chemical dosing units, the sludge dewatering line, etc.) are pre-assembled and installed in modules which will be attached to the buffer and aeration basins (made of concrete) as depicted in Figure 2 and Figure 3.



Figure 2. General overview of a modular wastewater treatment plant. [Source: EnviroChemie GmbH]



Figure 3. Detail pictures of equipment installed in modules. [Source: EnviroChemie GmbH]

By implementing a modular design approach, the resulting wastewater treatment plant will have a minimal footprint. More advantages from modular design are a high assembly quality (since all modules are pre-assembled at the supplier's workshop) and a reduced on site erection time. Big volumetric units (such as buffer tanks, aeration basins, etc.) can be built in concrete on site

(parallel to workshop pre-assembly of modules). An additional positive aspect of modular design is the potential for standardisation of processes and technology.

Implementing MBR (Membran Biological Reactor) technology to minimise the footprint of CAS (Conventional Activated Sludge) wastewater treatment plants

In order to further minimise their footprint, wastewater treatment plants have been gradually incorporating state-of-the-art technologies like membrane biological reactors (MBR) for the main COD (Chemical Oxygen Demand) abatement stage in order to increase the quality of the final effluent at minimal room requirements (approx. 50% of those of CAS based wastewater treatment plants), which is one of the main advantages of this technology together with the high quality of the permeate.

Energy consumption of MBR based wastewater treatment plants is somewhat higher than that of CAS based plants (0.5 to 1.5 kWh/m³ with submersed ultrafiltration modules, while traditional aerated reactors consume 0.5 to 1.0 kWh/m³), whereas the lower waste generation rates (surplus sludge processing and disposal can account for up to 50-60% of the total wastewater treatment cost) make MBR technology again more attractive [DWA 2002b] [Radjenović et al. 2008].

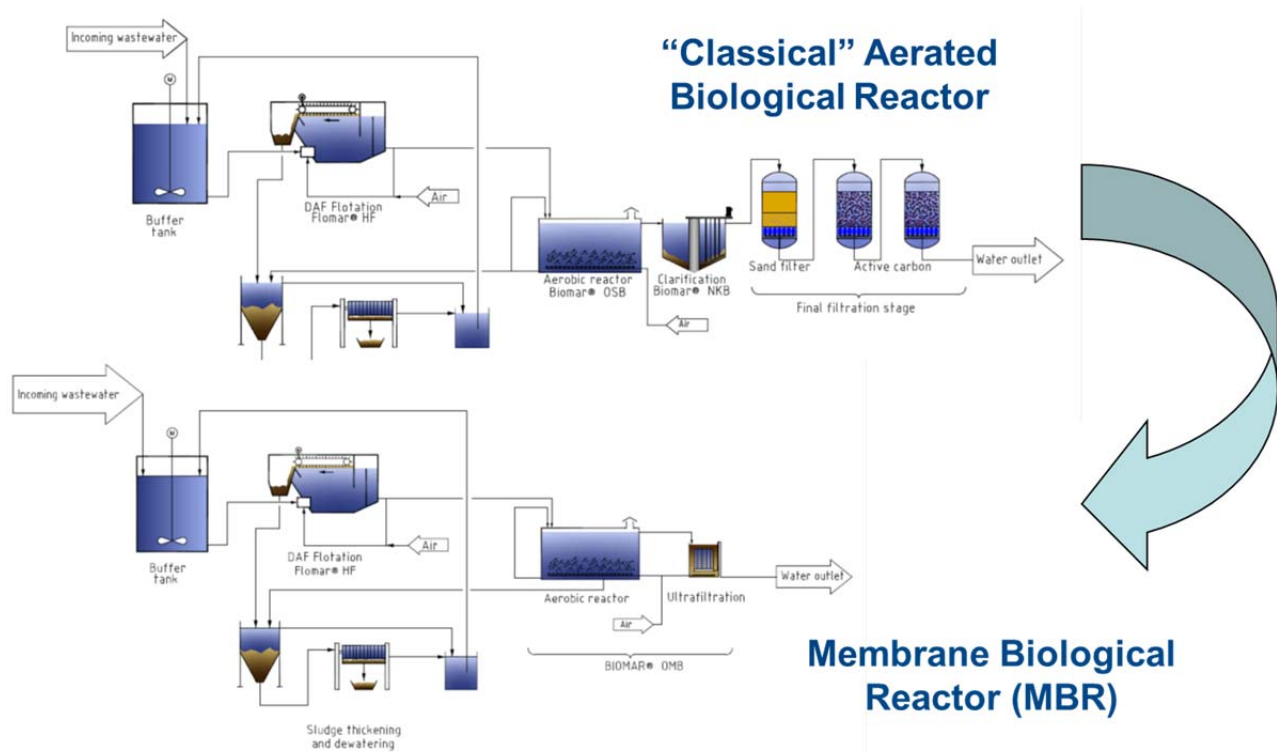


Figure 4. Comparison between a "classical" aerated biological reactor and a membrane biological reactor. [Source: EnviroChemie GmbH]

Industrial wastewater can be treated by means of MBR technology in the most effective way to even meet the requirements for reuse at different production steps if combined with tertiary treatment stages [DWA 2002b] [DWA 2005] [Radjenović et al. 2008] [Drews 2006].

All in all, MBR technology presents many advantages, which can be summarised as follows:

- Overall smaller footprint, since both secondary clarifiers and tertiary filtration processes are not needed.

- Stable quality of clarified water (suspended solids) regardless of mixed liquor suspended solids (MLSS) concentration or characteristics.
- High mixed liquor concentrations possible, therefore less aeration needed (reducing plant footprint).
- Long sludge age, hence low sludge production (solid waste).
- MF/UF quality effluent, which can be suitable for reuse and is optimal for further treatment steps.



Figure 5. View of ultrafiltration modules (left) and MBR reactor in operation (right). [Source: EnviroChemie GmbH]

Most PhACs are characterised by their hydrophilic behaviour. This is important so that the human body can absorb them easily. EDCs (like oestrogens) are on the other hand quite hydrophobic. What are common to both PhACs and EDCs are their biological activity and their somewhat high persistency in order to avoid their degradation before having any effects on the patients taking them [Radjenović et al. 2008].

All this has a very important effect on their biodegradability and results in rather high biological degradation rates (e.g. Estradiol and Paracetamol) or elimination rates tending to zero (e.g. Carbamazepine and Diatrizoate) [Ternes et al. 2004]. According to most of the researchers in this field, the degradation of PhACs and EDCs can be described as an abatement reaction of pseudo first order:

$$\frac{dC_i}{dt} = k_{i,biol.} \cdot SS \cdot C_i$$

C_i : soluble substance concentration of the compound i inside the reactor
 $\left[\frac{\text{g}}{\text{L}} \right]$
 $k_{i,biol.}$: kinetic constant for pseudo first order degradation $\left[\text{L gSS}^{-1} \text{d}^{-1} \right]$
 SS : suspended solids concentration $\left[\text{gSS L}^{-1} \right]$

This formula expresses the very important role of the sludge age in biological abatement kinetics. A higher sludge age (of at least 10 days) will promote a higher degree of biodiversity in the sludge biocenosis with specialist microorganisms in eliminating micro-pollutants such as PhACs and EDCs. Moreover, higher sludge ages present the advantage of lower specific sludge generation rates (i.e. less surplus sludge to be disposed). The only drawback here is the increasing ratio of inorganic (stabilised and inert) sludge. However the positive effects of high sludge ages overcome the negative ones and make MBR technology a more preferable option as CAS technology [Ternes et al. 2004] [Rosenwinkel et al. 2011] [Drews et al. 2006]

Another very important factor for the effective abatement of EDCs and PhACs from effluents is the sorption effect on activated sludge. According to current research results (like those from the POSEIDON Project) only hydrophobic compounds (e.g. oestrogens and Diclofenac) and positively charged ionic substances (e.g. Norfloxacin) show sorption coefficients high enough so that sorption phenomena play a relevant role for elimination of micro-pollutants. Two mechanisms are assumed to be relevant for sorption onto activated sludge particles [Ternes et al. 2004]:

- Absorption based on the hydrophobic interactions of aliphatic and aromatic groups present in EDCs and PhACs with the lipophilic cell membrane of the micro-organisms and the lipid fractions of the bio-sludge.
- Adsorption as result of the electrostatic interactions of positively charged groups of the pollutants to be removed with the negatively charged surface of the activated sludge biocenosis.

Modern wastewater treatment at a pharmaceutical production environment.

Modular design of wastewater treatment plants and MBR technology play a very important role while developing solutions to abate PhACs and EDCs industrial effluents. However they are not the only technological approaches available for production managers in the pharmaceutical and life science industry.

For instance, membrane technology is more broadly implemented than only as ultrafiltration modules in MBRs. One very interesting application is that of reverse osmosis modules as tertiary treatment after a biological treatment stage (most likely based on MBR technology).

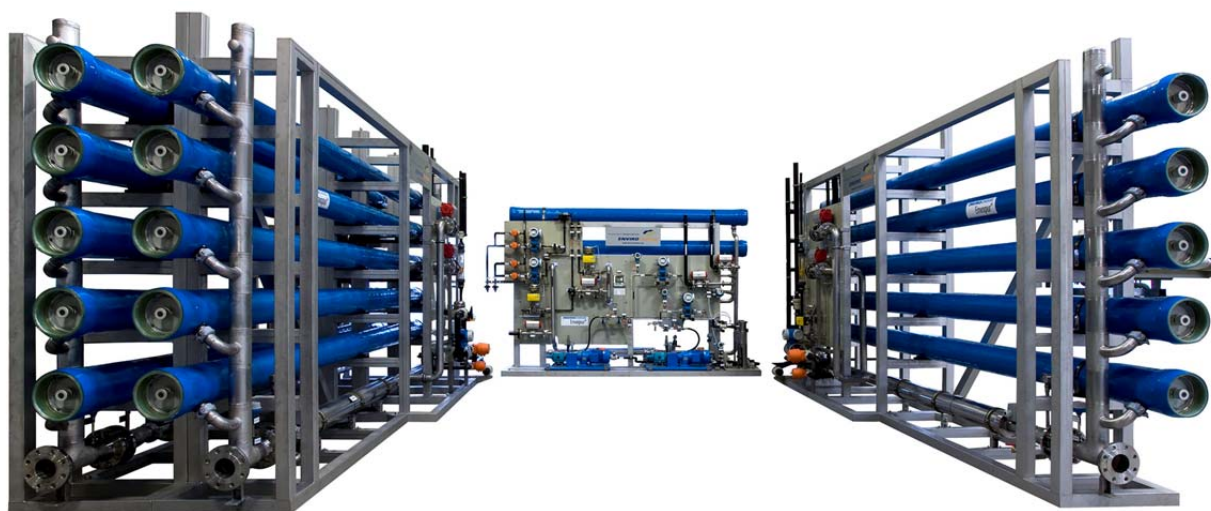


Figure 6. Reverse osmosis modules built in racks. [Source: EnviroChemie GmbH]

The potential of reverse osmosis membranes to retain in their concentrate phase almost every dissolved substance (including monovalent ions), makes this technology a very suitable solution for final treatment of industrial effluents containing micro-pollutants (see Figure 7) [DWA 2002a] [Rosenwinkel et al. 2011]. The main advantage of membrane technology is its wide field of application. As a technology based in a physical principle (filtration) it can be applied to separate many different substances from wastewater. Moreover, the optimal quality achieved by reverse osmosis permeate, makes this technology the keystone of every zero-discharge approach [Jawad et al. 2011]. Therefore permeate can be reused (e.g. as CIP water) and thus contribute to reduce the overall water consumption (water footprint).

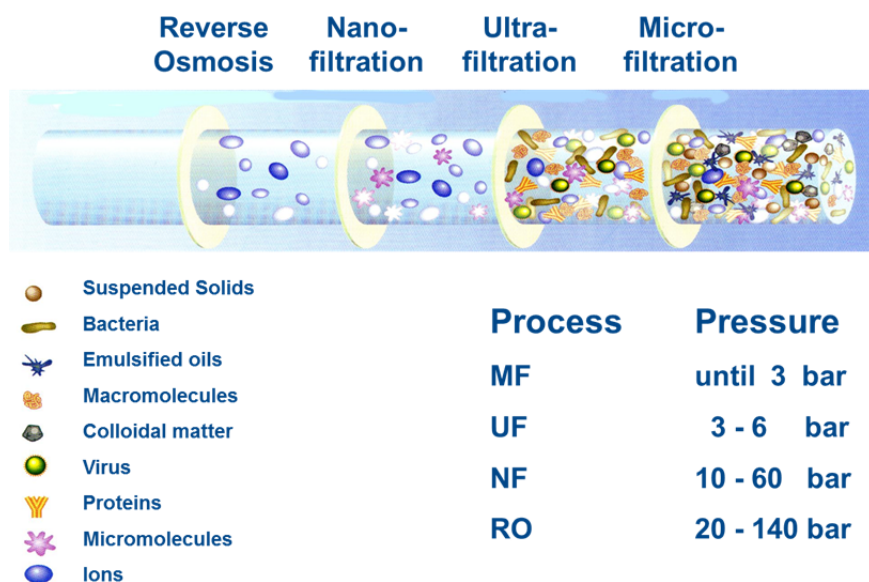


Figure 7. Overview of retentate membrane filtration technologies. [Source: EnviroChemie GmbH]

Apart from the aforementioned wastewater treatment technologies, there is a broad palette of additional technologies to abate micro-pollutants in a very specific and efficient way.

AOPs are for instance a very good option to remove PhACs and EDCs present in wastewater. The oxidation of these organic micro-pollutants is a very effective method to break their complex structures by “attacking” their active groups and thereby reducing their biological activity, i.e. their biodegradability is thus increased [Ikehata et al. 2006]. However, it is very important to take into account that these oxidation reactions can yield by-products which can still have some eco-toxic behaviour. Anyway, it can be stated that most of the by-products and transformation products from oxidised PhACs and EDCs are less critical to the environment as the parent compounds [Huber et al.. 2003] [Ikehata et al. 2008] [Ning et al. 2007]. For instance, when treating EDCs with ozone, by-products resulting from the ozonation are expected to not have any estrogenic activity, since both ozone and hydroxyl radicals will attack the phenolic functional groups responsible for the high estrogenic activity of these micro-pollutants [Snyder et al. 2006] [Ikehata et al. 2006].

Other options available to eliminate micro-pollutants from effluents generated at a pharmaceutical production site are active carbon adsorption, anaerobic treatment and thermal inactivation.

Divide et impera – Effluent segregation for higher efficiency removal rates.

Regardless of which industrial branch are we working in, the most important step to be taken at the very first moment while designing a modern industrial wastewater plant is a proper analysis of the different effluents generated at the production process. By characterising each individual wastewater stream, we will have the information necessary to apply the most efficient technology in each case.

The following examples will show how very specifically efficient technologies such as ozonation could be applied to a very well defined effluent containing Capecitabin and Mycophenolat Mofetil or how wastewater could be segregated in different streams according to their eco-toxicity or suitability for specific technologies such as anaerobic digestion.

Example of bringing MBR technology and both reverse osmosis and active carbon adsorption stages together.

As a matter of fact, MBR technology has become the standard keystone in almost every state-of-the-art wastewater treatment plant in the pharmaceutical industry. Thus MBR played a major role in the following example: a project developed for a world-market leader that produces the active ingredients for its multiple sclerosis treatment and cancer therapy medicines, among other biotech products for clinical trials and commercial phases at one its main production sites in central Europe (name of site and customer cannot be disclosed). Wastewater was analysed and segregated into three main effluents which are treated in two parallel line based basically on MBR and reverse osmosis technologies.

Effluent III comes from MTX production and is eco-toxic. Therefore it has to be pre-treated separately in a biological reactor based on the MBR technology. Permeate is filtrated through activate carbon, where the hazardous MTX is adsorbed. After a reverse osmosis filtration, concentrate is collected for external disposal. The final filtrate of Effluent III is mixed with Effluent I (highly loaded non eco-toxic wastewater from production processes) and Effluent II (wastewater from different utilities with a low COD load). All three effluents are jointly treated at a second line of membrane biological reactors. Permeate is further filtrated at a reverse osmosis stage. Concentrate can be discharged to the municipal sewer (indirect discharge), whereas the permeate can either be disposed to a nearby river (direct discharge) or reused on site.

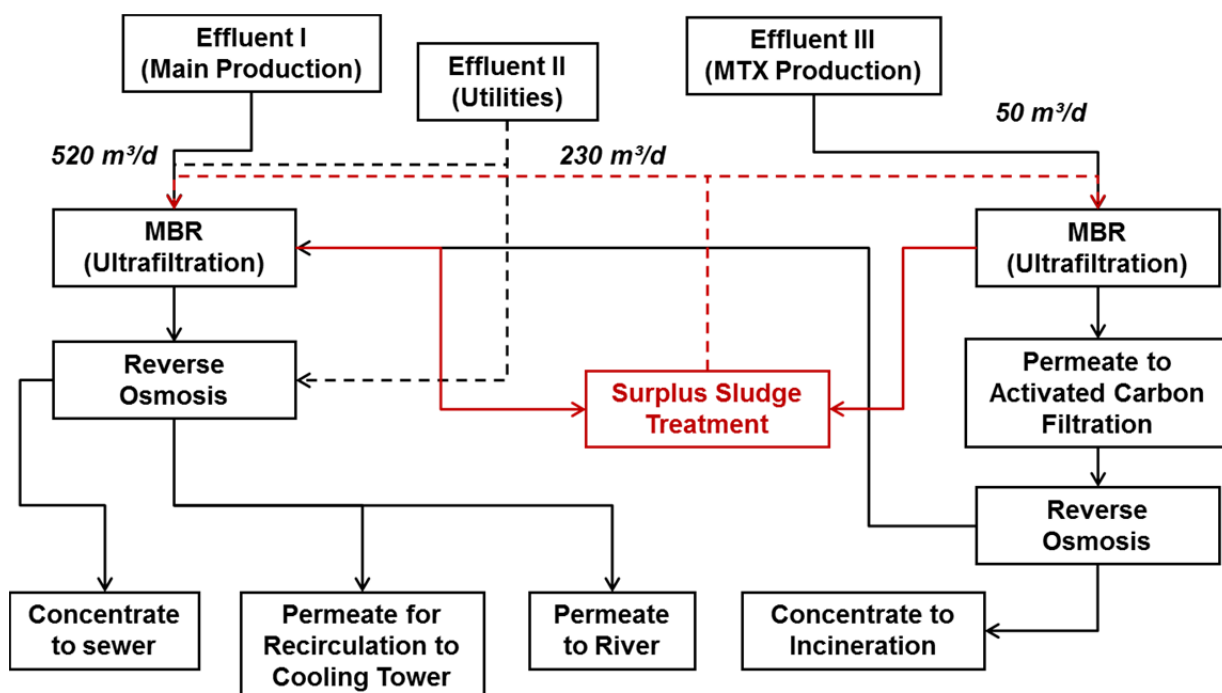


Figure 8. Flow diagram of a WWTP including to parallel lines with MBR and reverse osmosis. [Source: EnviroChemie GmbH]

Example of implementing anaerobic treatment technology at an insulin production facility

Bioton S.A. is a Polish biotechnical company which focuses in the production of recombinant human insulin for diabetes treatment. Other drugs produced by Bioton S.A. are Glimepiride and Metfomin (both anti-diabetic drugs). At its main production site in Poland, wastewater was

separated into three main effluents (see Table 1), which have to be treated prior to discharge into the Ożarowski Channel.

	Effluent I (High Load)	Effluent II (Triton X-100)	Effluent III (Sanitary)
Flow	220 m ³ /d	37 m ³ /d	350 m ³ /d
COD	20.000 mg/l	20.000 mg/l	500 mg/l
Total N	300 mg/l	670 mg/l	50 mg/l
Total P	230 mg/l	690 mg/l	20 mg/l
Chloride	1.700 mg/l	800 mg/l	150 mg/l

Table 1. Composition of wastewater

Highly organic loaded wastewater (Effluent I) is undergoes anaerobic treatment at a first stage. This is done so because the high COD load which can be turned into valuable biogas while reducing the energy consumption at the following aerobic treatment stage. Moreover, biogas is a green energy source that reduces the overall environmental impact of the production.

A part of the wastewater containing Triton X-100 is hardly biodegradable and toxic. Therefore it has to be treated in a vacuum distillation stage. The concentrate resulting from the distillation has to be disposed externally.

Effluent I after anaerobic treatment, permeate from “distilled” Effluent II and Effluent III (sanitary wastewater with a low COD load) are treated jointly at a CAS reactor before being discharged to the environment.

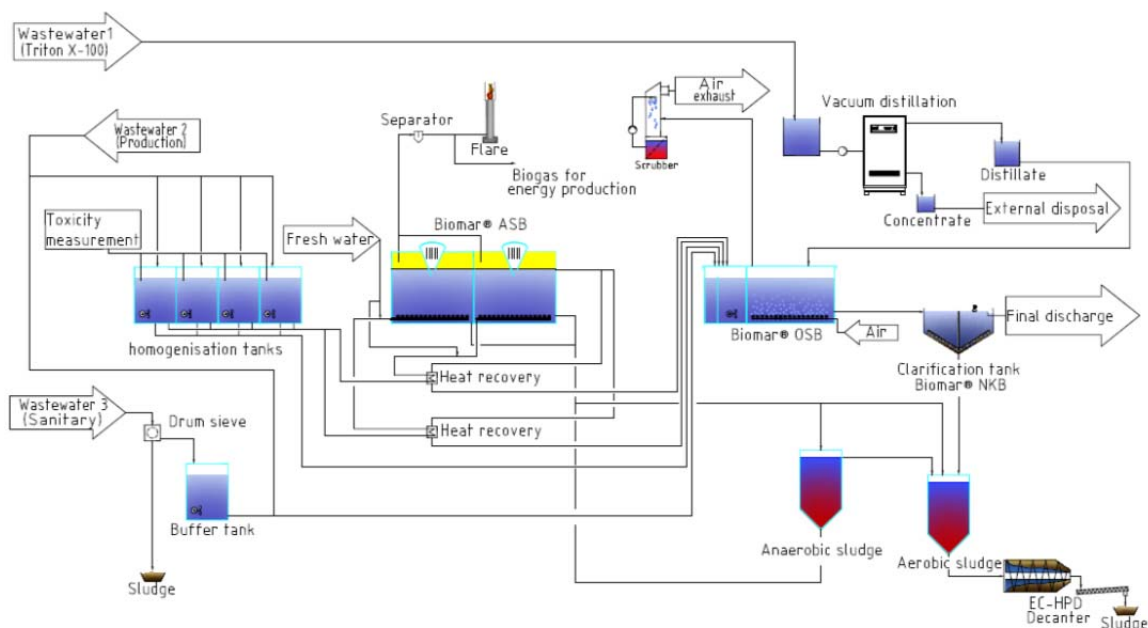


Figure 9. Flow diagram of the WWTP implemented for Bioton S.A. (including anaerobic treatment technology). [Source: EnviroChemie GmbH]



Figure 10. Overview of the WWTP implemented for Bioton S.A. (including detail of biogas flare).
[Source: EnviroChemie GmbH]

Example of decentralised ozonation of selected wastewater streams containing active ingredients.

Two highly effective medicaments for the treatment of cancer are formulated at Roche's facility in Toluca (Mexico). These two agents (Capecitabin and Mycophenolat Mofetil) were proven to be ecologically critical. Approx. 10,000 litres of wastewater containing these PhACs are generated daily and needs to be processed prior final discharge.

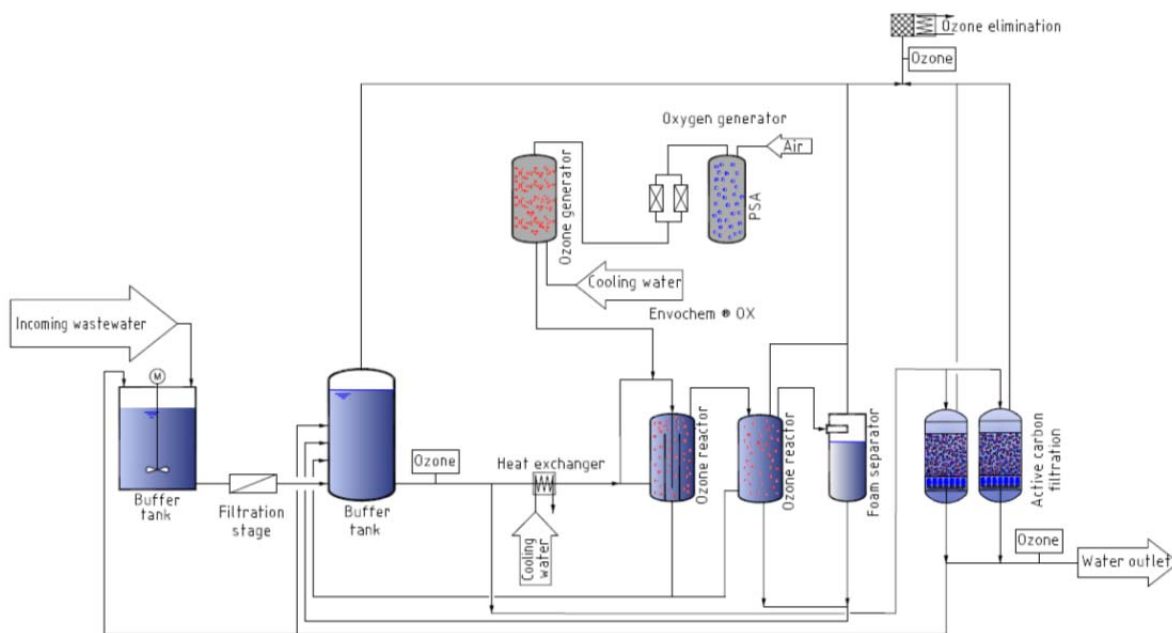


Figure 11. Flow diagram of an ozonation WWTP. [Source: EnviroChemie GmbH]

Roche listed a very ambitious set of specifications for the treatment technology, which should be reliable, ensure very high operational safety with minimal handling of chemicals, have a high degree of automation, be based on a modular design and generate as less waste as possible.

Studies comparing active carbon adsorption, UV/H₂O₂ oxidation and ozonation at lab scale showed that the latter was the most efficient technology. In the designed wastewater treatment plant (see Figure 11) ozone is produced by an ozone generator (ozonisation), which does not draw the

oxygen directly from the ambient air, but from an upstream PSA system. This makes the plant completely autonomous and independent of external supplies.



Figure 12. View of the modular ozonation plant during FAT before its installation. [Source: EnviroChemie GmbH]

An injection system mixes the ozone with the wastewater, which is located in two reactors. There is a slight excess pressure, which ensures an effective reaction of the ozone with the PhACs which have to be oxidised. Foam, which may be produced at the oxidation reaction, is separated in a second reactor. As the ozone requirement depends on the chemical properties and the concentration of the respective drugs in the wastewater, the plant is equipped with sensors for measuring the dissolved remaining ozone concentrations after treatment. The system controls the performance of the ozone generator fully automatically, so that there is always a defined ozone concentration of e.g. 2 mg/l. If the ozone requirement increases, the generator automatically produces more, if it decreases, ozone production is also reduced. A final activated carbon filtration stage removes residual ozone from the effluent.

Example of thermal inactivation of bio-hazardous wastewater

The Germany vaccine producer Dessau-Tornau GmbH focuses its work in developing vaccines for animals (e.g. rabies vaccines). At its main production site in Dessau (Germany) a thermal inactivation plant was installed for a safe disposal of the wastewater resulting from the research and development facilities. The plant (shown in Figure 13) collects and sterilises 2,500 L/d of effluent coming from the laboratories at 121°C during 20 minutes. Batch thermal sterilisation is known to be a reliable technology to inactivate infectious effluents in a safe way.



Figure 13. Batch thermal inactivation plant at Dessau-Tornau GmbH in Dessau (Germany). [Source: EnviroChemie GmbH]

A more energetically efficient way to inactivate bio-hazardous wastewater is to implement a continuous plant as Roche did at its production site in Penzberg (Germany), where the company focuses on cancer research as well as therapeutic protein agents. Due to its nature, wastewater at Penzberg needs to be thermally sterilised before it may be discharged to the sewage system. A continuous flow of 1.2 m³/h is inactivated at 90°C during 2 minutes. Incoming wastewater (cold) is heated up by sterilised outgoing effluent (hot) in a heat exchanger. Thanks to this heat recovery effect, operating costs can be dramatically reduced in comparison to those of batch plants (see Table 2).

Batch thermal sterilisation	Continuous thermal sterilisation
Variable sterilisation time	High treatment capacity (effluent volume per day)
Variable sterilization temperature	Very compact plant design
Easy validation	Due to reduced size, equipment is easy to assembly inside buildings
Highest safety level (like S4 containment level laboratories)	Low running costs due to heat recovery
Redundancy possible (e.g. plants with two sterilisators)	On-line validation possible due to special proprietary validation system
Also suitable for effluent containing solids	Lower investment costs for high effluent flows (than batch systems)
Rather suitable for smaller effluent flows	

Table 2. Comparison batch vs. continuous thermal sterilisation processes

Conclusion

Few production environments are as exigent and challenging as that of the pharmaceutical industry. Highest quality and performance levels are demanded at all levels of the manufacturing process, including also wastewater treatment technologies. In order to be able to tackle the complexity posed by these effluents, an array of modern and innovative technologies is currently available. However the right know-how and practical experience are still critical for a successful implementation of these very effective technologies in the most efficient way. The future will bring the development of growingly sophisticated wastewater treatment solutions for a safer elimination of PhACs and EDCs while clarified water reaches quality levels high enough for recirculation and concentrates are rendered innocuous following a zero-discharge strategy.

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