



Good Experience with SYGEF HP BCF at Eprova

The Eprova company in Schaffhausen has invested in the most modern of systems for the manufacture of pharmaceutical substances. The old water treatment system was replaced with a state-of-the-art and efficient pharma water system. SYGEF HP BCF was a perfect fit for their requirements.

The Eprova company is a subsidiary of Merck KGaA (Darmstadt, Germany) and was founded in 1952 as a chemical research institute. Eprova provides a range of services from chemical synthesis, analysis, and product manufacturing to microbiological and biochemical testing.

The second sector focuses on the manufacture of their own pharmaceutical substances. For example, Eprova is a market leader in the manufacture of pure diastereoisomer derivatives of tetrahydrofolic acids (folates). The most important product (Levoleucovorin) is used as an antidote and modulator in chemotherapy. Currently, a new compound is being developed which can be used in the treatment of heart and circulatory illnesses.

Project work 97/98

The assignment was to replace the old water treatment system with a new, state-of-the-art and efficient pharma water system.

The Eprova project team had the following goals:

- meeting legal requirements for pure water (cGMP)
- fulfilling customer expectations
- rational and efficient internal procedures
- care given to the use of resources (drinking water, energy, chemicals)

The entire project had to pass the very stringent requirements of the FDA (Food and Drug Administration, a federal agency in the USA responsible for testing the legal conformity of pharmaceutical plants). In the course of establishing the specifications and designing the new system, our SYGEF HP BCF (PVDF) piping system and the SIGNET HPV Vortex were selected for conveying the pure water. Why?

Piping system

The standard for the distribution of pure water, especially in the USA is a hot (> 70 °C) circulation pipeline made of stainless steel. PVDF systems are rare and still subject to prejudice (in regard to resistance, extracts). The decision to go with SYGEF HP BCF was made on the basis of the following plus points:

- data available regarding corrosion and extracts
- easy handling (installation during

ongoing chemicals production)

- expansion possibilities

SYGEF HP BCF (PVDF) is a very pure piping system with bead/crevice-free fusion jointing. It is used to convey water in its cleaned state, which is subsequently used for pharmaceutical purposes. It is clear to see that pharmaceutical medicines which are administered must remain pure and free of microbiological contamination. Consequently, enormous value is placed on permanent adherence to the water quality, which is often stipulated legally. The essential features of SYGEF HP BCF are the following:

- very pure (manufactured, controlled, washed, and packaged in cleanrooms) and free of additives, stabilizing agents, pigments, or other fillers
- inert, no tendency to corrode
- lowest extraction values organically and metallic
- excellent surface quality of 0.20 µm Ra without pre or post-treatment
- not susceptible to biofilm growth
- ozone-resistant and can be steam-sterilized (135 °C)
- FDA-approval
- easy handling.

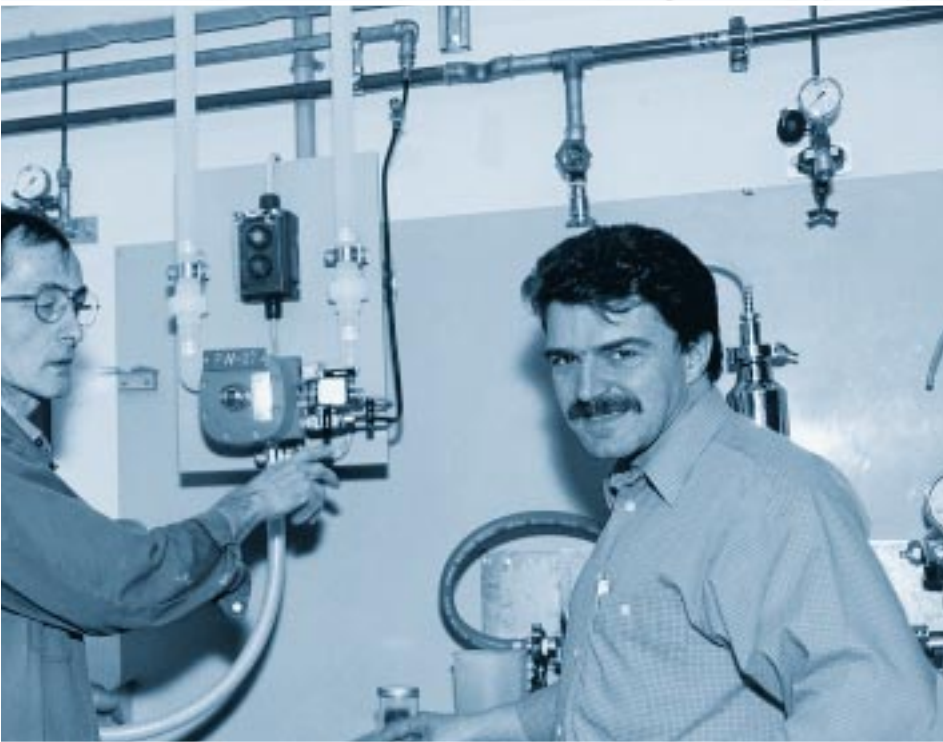
Vortex measurement system

Normally, pure water needs to be drawn at a tapping point and weighed. Only after this process, may it be introduced into the reactor.

In view of their rational processes, Eprova was interested in a measurement system integrated in the circulation pipeline, which would permit direct tapping of a defined amount of water. Inquiries and, more importantly, testing revealed however that despite grand promises on the part of suppliers, the results were disappointing.

By then, under pressure to meet a deadline, the project team decided on the SIGNET HPV Vortex (from the pilot lot) because





Rolf Bollinger (left), technical manager and Martin Ullmann, assistant manager at Eprova AG standing in front of the finished SYGEF HP BCF ring mains.



With our new SIGNET HP Vortex, the measurement system could be integrated in the circulation pipeline.

- the water quality does not become impaired (all-PVDF material, no moving parts)
- test runs demonstrated the required precision
- support from the GF development team was warranted.

Exact dosing (accurate to ± 0.5 lt) into the reactors was realized at Eprova by means of the newly introduced Vortex HPV flow meters. Two sensors in this flow meter allow measurement of the difference between the flow volume before and after the tapping valve. The quantities dosed in this way are accurate to ± 0.1 lt which means they are below the required limit value. This precise measurement is achieved by oscillating a sensor bag with an integrated piezo crystal; the pulses thus created are emitted as a measurable electronic signal. The pulsation is created by a bluff body integrated in the system, which swirls the medium in relation to the flow velocity, thereby causing the sensor bag to oscillate. The Vortex installation also met with the approval of the customer and a special permit was issued by the SEV (Swiss Electrotechnical Association) for Ex Zone 1. The ring mains for the pure water at the Eprova plant has been in operation

since February 1998. In November 1998 the complete system was inspected by their most important American customer according to FDA regulations and was very positively evaluated. The microbiological values, which are the most important parameter for water quality, are excellent and have remained consistently good in the production of folates since official approval. We would like to take this opportunity to thank the project team at Eprova for their open-mindedness and pragmatism which we admired and greatly appreciated in working with them. We wouldn't mind having more of these kinds of customers!

More expansion at Eprova

The future trend of the folate product line is considered to be very positive. With this foresight, a building near the Eprova headquarters was purchased so that a new plant for the manufacture of folates could begin installation by the year 2000 and be in operation by 2001. We look forward to working together with Eprova team and hope that the good experience with the existing SYGEF HP BCF ring mains and with the Vortex HPV flow meter can be brought into the new project.