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IMPLEMENTATION PROCEDURE OF AN ADVANCED SUPERVISORY AND CONTROL STRATEGY IN THE PHARMACEUTICAL INDUSTRY

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Abstract: This paper describes the different steps followed during the implementation procedure of a temperature controller and a supervisory controller in a SCADA to control two batch reactors of 60 l and 160 l size of an industrial pharmaceutical plant. These reactors are used to produce the first quantities of drugs needed to perform clinical tests. The chemical reactions involved are often changed (several a week). The different steps of the project will be presented : design of a new heating-cooling system, development of a dynamic simulation model, design of the predictive and supervisory controller (SCA), connection of the SCA to the SCADA, experimental validation according to GMP. This SCA has been daily used as the standard control system for more than one year. *Copyright © 2002 IFAC*

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1. INTRODUCTION

Two particularities are clearly attached to the pharmaceutical industry: the use of batch processes and the necessity to satisfy to strict validation procedures. These two characters are antagonist in the sense that most of the apparatus used in such an industry have been designed not for a specific operation but for their use in a wide range of different operations. Contrarily to classical chemical processes it can be said that the operation has to be adapted to the available apparatus. In the other hand, the authorisation to put a new drug on the market demand to pass successfully validation procedures what implies that all the disturbances have been predicted and their effects on the operation performance minimised. Any development in such an industry has to face to these two concepts.

The heart of a drug manufacturing process is the batch or fed-batch reactor that is still widely used in fine and pharmaceutical industries. It is often characterised as flexible and multipurpose equipment. That means that a same apparatus is used to carry out different reactions and operations under various operating conditions involving chaining of sequences. Nevertheless, in the same time these apparatus are well known to be potentially one of the major causes of lack in the operation reproducibility and of severe damages which can go up to run-away problems. To minimise these causes it is necessary to implement efficient automation and supervisory control. But, all the developed strategies have also to match with the flexible and the multipurpose characters. With the lack of on-line sensors for concentration measurement, the control of batch reactor still remains a problem of temperature control.

In this paper, we want to focus on the different steps followed during the implementation procedure of a temperature controller and a supervisory controller in a SCADA (Fisher Rosemount DeltaV) to control two batch reactors: 60 and 160 litres of an industrial plant

(Sanofi-Synthelabo). These reactors are used to produce the first quantities of drugs needed to perform clinical tests. The chemical reactions involved are often changed (several a week) and as it will be seen, even different operation such as crystallisation or chaining of operations are also carried out in these two apparatus. The different steps of the project were the following:

- Design of a new heating-cooling system, which is a good compromise between the multifluid and the monofluid systems to fit both reactors

- Development of a batch reactor simulation model based on mass and energy balances with a lumped jacket to model changeovers of fluid

- Development of the predictive controller and the supervisory control procedure (based on the control of the thermal flux) and implementation in the SCADA

- Connection of this simulation package to the SCADA (via Microsoft's OPC technology for on-line data exchange) to test the predictive controller and the supervisory controller

- Connection of the predictive controller and the supervisory controller to the real plant and experimental tests

- Tests on behalf validation procedures to get the agreement to produce drugs in these reactors

2. DESIGN OF A NEW HEATING-COOLING SYSTEM

As said previously, the typical batch reactor has not been designed to perform as a good heat exchanger. They are generally fitted out with a surrounding jacket fed with a thermal fluid. The heating-cooling system used is of particular importance since the good performance of the heat transfer lie on it. Several heating-cooling systems are used in industry. The most popular ones are the multifluid and the monofluid systems. These two systems have their respective advantages and disadvantages :

- the multifluid heating/cooling system consists in the direct injection of the required utility into the reactor jacket. This allows for simple design of the heating cooling system at low cost. Furthermore, heat transfer time delays are smaller than in the monofluid case, except if a purge of the reactor jacket is necessary when switching from one utility to another. The main drawback of this approach consists in the abrupt temperature changes and the time delay when changing the utility.
- the monofluid system consists of a thermal fluid circulating in a closed loop through the reactor jacket and a system of heat exchangers. By means of these heat exchangers energy is transferred from the utility (steam, water, glycol water) to the thermal fluid or vice versa. This monofluid system offers smooth and continuous evolution of the temperature of the thermal fluid over a wide temperature range. On the other hand, disadvantages arise from higher investment cost (due to the required heat exchangers) and time delays in heat transfer dynamics.

The industrial plant concerned by the controller implementation is located at Toulouse in the South West of France. This is part of the Chemical Development Department of Sanofi-Synthelabo. On of the tasks of this department is to scale up the production procedures of new drugs from laboratory to industrial scales and to verify the feasibility of the procedures proposed by the chemists. They own pilot batch reactors of different sizes. On this site, two reactors (60 and 160 litres) were available. It was an old plant fitted out with a conventional multifluid system and it suffered of comparison with a new pilot plant recently built in an other site fitted out with a monofluid system. The plant manager had two alternatives :
-either he prove that these reactors could still be used to test any new reaction without restriction of reaction duration, in safe conditions, with reproducibility and without engaging any important investment cost
-either this plant was closed and the planned tests should be carried out in the new one.

These reactors were operated manually but no operator were present on plant during the nights. The first decision taken was to fit the two reactors with a SCADA to face to reproducibility, safety and automation requirements (possibility to have reactions covering several days). Nevertheless, this acquisition did not make disappear the difficulty to control a batch reactor with a multifluid system, at the contrary it rendered the problem more crucial especially dealing with fluid changeovers which had to be automatically managed by the SCADA (the plant operators had a rather long experience and most of the time were able to anticipate). So the second decision was to improve the "operability" of the plant by few adaptations. The requirements were :

- from the existing multifluid system, to find a new system enabling to gather advantages of multifluid and monofluid system
- to establish a safe and easy supervisory control procedure
- this heating-cooling system can be connected either to the 60l either to the 160l reactor and settled in a very narrow place.

The first requirement has been satisfied by adopting the alternative system (named hybrid system) which was proposed in (Louleh, *et al,* 1999, Cabassud, *et al*, 1995). Its main characteristic is the use of an intermediate utility, pressurised water. It is generated at a constant flow rate in the thermal environment of the reactor unit by mixing steam and water (Fig. 1). The ratio of steam and water is adjusted at each sampling period so that the desired – time varying – temperature is reached. Pressurised water circulates in a closed loop through the reactor jacket, a pump and a mixer where the required amount of steam or water are added. At a pressure of 3 bars the pressurised water covers a temperature range from 20 to 120°C. Within this range the heating/cooling system exhibits a monofluid type behaviour. Furthermore, by mixing water and steam which are utilities directly available on the plant, it does not demand to invest in auxiliary costly heat exchangers. In the other hand, if a greater heating / cooling capacity is required, the system switches to a multifluid behaviour and, after a purge of the reactor jacket, steam or a cold utility are directly injected into the reactor jacket. For utilities directly injected into the reactor jacket, the controller acts on the flowrate as manipulated variable. In the case of the intermediate fluid (pressurised water) the flowrate is fixed at a constant value and the ratio of steam and water is adjusted so that the desired temperature of the intermediate fluid is reached.

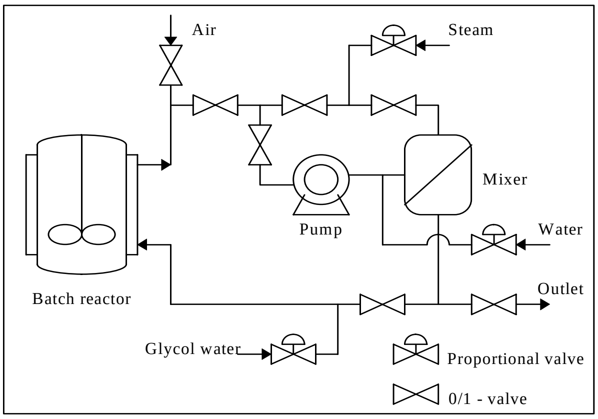

Fig. 1. Hybrid heating-cooling system

The second requirement has been fulfilled by using the thermal flux q that has to be transferred from the thermal fluid in the reactor jacket to the reaction mixture as the manipulated variable (controller output). The controller (a predictive control algorithm) is receiving a setpoint T_c for the temperature of the reaction mixture T_r. At each sampling time the control algorithm computes a value for the manipulated variable q using the current process measurements and the future setpoint. The value of q is then introduced into the supervisory algorithm (Fig. 2). This routine computes - by means of enthalpy balances on the reactor jacket and the reaction mixture - the maximum/minimum thermal flux $q_{i,min}$ / $q_{i,max}$ that can be exchanged by the utility i, for all available utilities. The appropriate utility is chosen by comparing these enthalpy fluxes with the one calculated by the predictive control algorithm. If this enthalpy flux is in the range given by the maximum and minimum thermal flux of the current utility, this utility is kept. Otherwise a utility with a higher/lower maximum/minimum enthalpy flux is chosen respectively. Once the appropriate utility is determined, the required flow F of this utility is calculated by means of enthalpy balances between the reactor jacket, the reaction mixture and - if pressurised water is the current utility - the mixing unit.

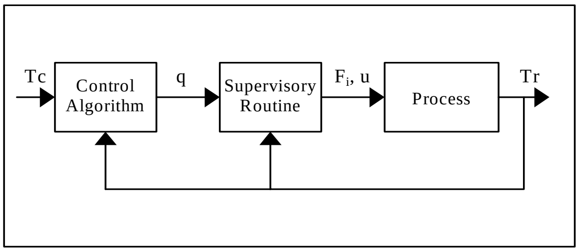

Fig. 2: Supervisory control scheme.

Finally, the value of the required flow is transferred as setpoint to a low level PID control-loop that regulates the flow (measured by a flowmeter) by manipulating the valve opening degree of the respective utility valve. Or, if this control loop is not available, the desired flow is converted into a valve opening degree using a calibration curve of the respective valve.

The last demand has been satisfied by adopting a very compact design of the heating-cooling system (dimension : 2mx1.5mx1.5m(h)). It can be easily moved as it has been built on the concept of a “skid”.

3. DEVELOPMENT OF A BATCH REACTOR SIMULATION MODEL

The critical point to verify before experimental application is the capacity of the set supervisory + predictive controllers to handle various operations involving different sequences and particularly that need changeovers of fluid. Checking these sequences by simulation requires a simulation model that contains the concerned actuators and also comprises the physical effects affected by the actuators (e.g. mass flow and pressure in a tube connected to a valve). Consequently very detailed models are required.

The simulator is described in detail in (Preuss, 2001). The simulation model represents the batch reactor by a set of differential equation derived from mass balances of the reaction mixture and enthalpy balances of the reactor jacket, its inner wall and the reaction mixture. The reactor jacket is modelled by a number of perfectly mixed tanks. Moreover, a filling-up coefficient is defined for each tank. It represents the on-line calculated ratio of utility and air of each tank during the simulation. Hereby precise modelling of the switching from one utility to another, on this occasion the reactor jacket is emptied by pressurised air and then refilled with the new utility, is achieved. Precise modelling of this stage is necessary for a realistic verification of the interactions.

The thermal environment of the batch reactor is modelled by a static mass balance containing all flows entering or leaving the thermal environment. Dynamic behaviour of the thermal environment is not taken into account and it is supposed that changes take place instantaneously.

4. DEVELOPMENT OF THE PREDICTIVE CONTROLLER

During this project, several predictive controllers have been developed, tested in simulation and experimentally on the plant and compared (Preuss, *et al.*, 2000 ; Preuss, 2001). The best one being definitively implemented on the plant and validated by GMP is the : Model Gradient Predictive Controller denoted MGPC with a linear model. The main difference between this controller and a classical model predictive controller (Richalet, 1993) is the objective function minimised which is expressed as function of variable gradient:

$$J° = \| d/dt\, \mathbf{y}_{ref}(k+1) - d/dt\, \mathbf{y}(k+1) \| \qquad (1)$$

In this application the process model of the controller gives a relation between the thermal flux q transferred from the reactor jacket to the reaction mixture (manipulated variable) and the temperature of the reaction mixture T_r. The simple model consists of one differential equation:

$$d/dt\, T_r = b * q \qquad (2)$$

with: $$b = 1 / (m_r * cp_r) \qquad (3)$$

The details of the calculations for obtaining the optimal value of the manipulated variable and the assumptions made can be found in (Preuss, *et al.*, 2000 ; Preuss, 2001). This value is given by :

$$q(k+1) = d/dt\, T_{ref}(k+1) * 1 / b \qquad (4)$$

where the gradient of the reference trajectory is calculated as a function of the future set point , the measurement at time k and the predictive horizon.

In practical applications it is necessary to determine the value of the model parameter b on-line. During the experimental tests it dealt out that the time delay is not constant and that it depends on the utility used and on the value of the manipulated variable as well. Therefore the on-line model parameter estimation described in the following includes the search of the appropriate time delay nr*. Parameter estimation is achieved by minimising the objective:

$$J(nr) = \Sigma\, [T_r(k-He+i) - T_{mes}(k-He+i)]^2 \qquad (5)$$

with $i = 0, 1, ..., He-1$ and $nr = nr_{min}, nr_{min+1}, ..., nr_{max-1}, nr_{max}$ over an receding estimation horizon (length He sample times) of measured temperature of the reaction mixture T_r and the applied thermal flux q. The values of T_r are obtained by discrete integration of equation 2.

The objective is minimised using a least squares optimisation by calculating the optimal value of the model parameter b. This minimisation is carried out for every value of nr in the range defined by nr_{min} and nr_{max}. Their values have to be fixed a priori and can be deduced from existing experimental data. The value of b used in the controller is the one for the time delay nr^* that gives a minimal value for the objective J:

$$J(nr^*) \leq J(nr)\ , nr = nr_{min}, nr_{min+1}, ..., nr_{max-1}, nr_{max}$$
$$nr \neq nr^* \qquad (6)$$

5. CONNECTION OF THIS SIMULATION PACKAGE TO THE SCADA

In the concerned implementation, the sequences for actuator settings and operation/safety routines are implemented in a SCADA (DeltaV, Fisher-Rosemount). The supervisory control algorithm (SCA) is an additional software tool containing the control and supervision algorithm described in the previously. Both software are running under Windows NT and are connected by a software interface for on-line data exchange based on OPC-technology . Information is transferred between SCA and SCADA at each sampling period. The SCA determines the appropriate utility to use and the required flow as well and transfers this information via the OPC interface to DeltaV which then carries out the actuator settings in the thermal environment of the reactor (Fig. 3).

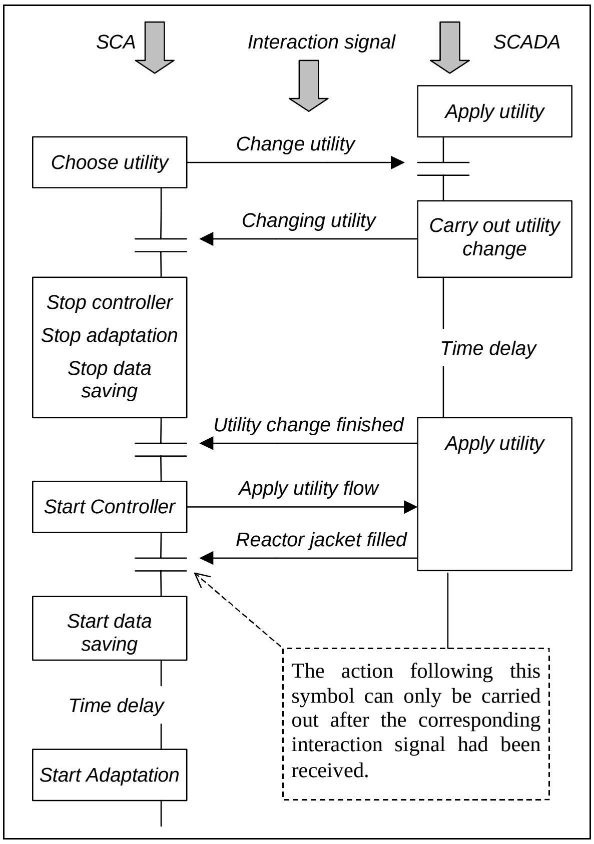

Fig. 3. Interactions between SCADA and SCA when changing utility.

Measurements from the process are taken up by DeltaV and fed back, together with the current values of discrete process states, to the SCA via the OPC interface. The control actions initiated by the SCA are carried out on a lower control level, which is located on the SCADA. They are related to start-up or shut-down of the thermal environment and to switching from one utility to another. In the latter case algorithms implemented in the SCADA and the SCA affect their execution mutually as shown in figure 3 . This simulator was implemented as independent software application. By means of an OPC software interface it can be connected to the SCADA which then receives simulated values instead of the real plant measurements. Either the real plant or its simulator is connected to the SCADA, performing read/write operations on the same variables of its on-line database. This offers the advantage that the tests in simulation can be carried out with exactly the same configuration of SCADA and SCA as it will be in real operation. Several test runs have been performed (Preuss, 2001) such as the one given in figure 4. The imposed set point profile drives the supervisory algorithm to initiate a switchover from pressurised water to glycol water after 1.5 hours, triggering the interactions shown in figure 3 . By means of this test it was verified that, for this type of switchover, the SCADA and SCA interact correctly.

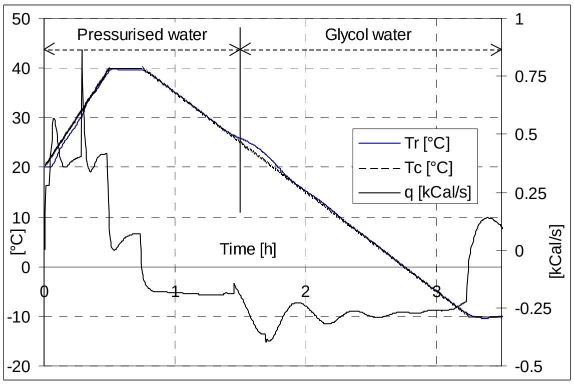

Fig. 4. Test of SCADA and SCA in simulation

6. CONNECTION TO THE REAL PLANT AND EXPERIMENTAL TESTS

Several preliminary tests have been performed by imposing temperature set point profiles to the reactors loaded with various solvents (Preuss, *et al.*; 2000). The fig. 5 shows the results obtained during such an experiment performed in the 160 l - reactor (filled with 100 l of DMF). The changeovers from pressurised water to glycol (i.e. to the monofluid type behaviour to the multifluid type) has been correctly handled and did not affect the excellent performance of the controller : the mean error measurement/set point was 0.2°C when pressurised water was used and 1°C in the case of glycol water.

The SCA has been daily used as a standard routine for more than 1 year. In fig. 6, an example of a classical operation carried out in such reactors is shown. This is a crystallisation performed during 25 hours according to a very precise set point profile. The precision in the temperature was of high importance since it has an incidence on the clinical quality of the obtained product. Similar operations have been carried out in the 60l-reactor using the same heating-cooling system , the same predictive and supervisory controllers. An example of results obtained is shown in fig. 7.

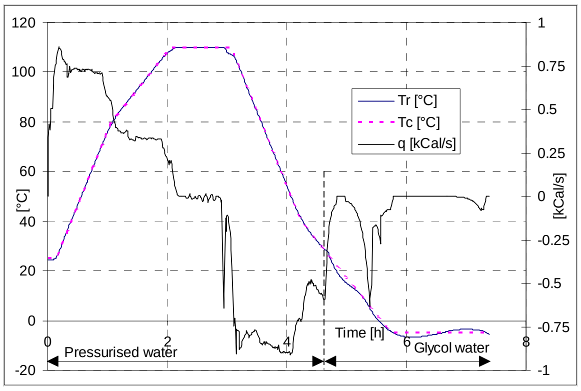

Fig. 5 : Experimental test 160l-reactor filled with 100 l DMF

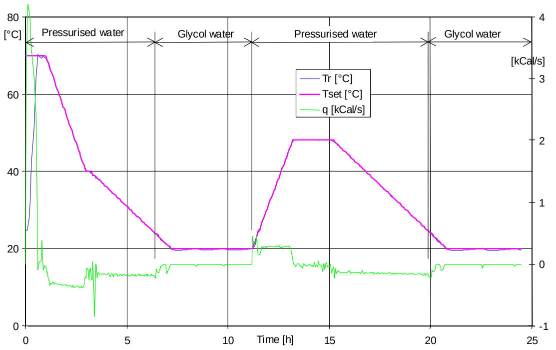

Fig. 6. Production of a specified chemical product by crystallisation

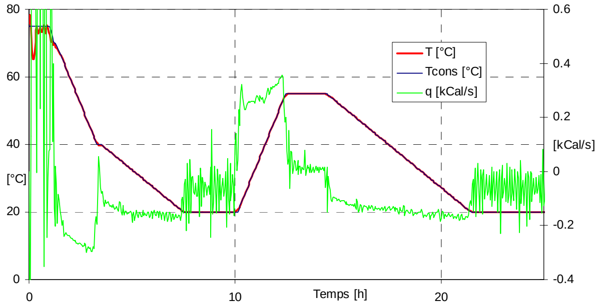

Fig. 7. Experimental results (60 l–reactor)

7. TESTS ON BEHALF VALIDATION PROCEDURES

When the development of an active pharmaceutical ingredient comes to the stage of clinical trials, it has to be proved that its manufacturing process consistently produces a product meeting its predetermined specifications and quality attributes. This is the core intention of regulations like GMP. The first step to achieve compliance to this regulations is that a pharmaceutical company identifies what qualification and validation work is necessary to prove control of the critical aspects of their particular operation. This risk analysis should evaluate direct and indirect effects of all parts of the manufacturing process, including computer systems, with respect to GMP. Common sense and an understanding of the pharmaceutical process go a long way towards determining what aspects of an operation are critical. Any aspect which may affect the quality of the products should be qualified and validated. As temperature has an important impact on the synthesis of pharmaceutical ingredients, it is quite obvious that regulatory compliance must be proved for this sub-system of the manufacturing process.

The Validation Master Plan (VMP) presents an overview of entire validation operation that consists of several steps. The Design Qualification (DQ) proves that the object of a particular validation operation is designed in accordance with GMP requirements. As far as process control software is concerned the GAMP-guide gives guidance on how to achieve DQ. It is for example necessary that for accessing the software three hierarchical levels with certain rights exist (i.e. User, Supervisor and Administrator). In the present case, the controller was designed and implemented as Plug-In to the SCADA system with all accessible parameters of the controller software, that might be subject to changes, hosted by the SCADA. Thus the hierarchical facilities of the SCADA are also applicable to the controller Plug-In. The Installation Qualification (IQ) comprises tests to ensure that the (software-) equipment used in a manufacturing process is correctly installed and works in accordance with established specifications. Hereby it is tested and ensured that the controller can be operated from the SCADA user interface (i.e. set point transfer) or that data logging is correctly performed. During the next step, Operational Qualification (OQ) experimental tests using the pilot plant will be conducted to prove that the considered sub-system performs as intended throughout all anticipated operating ranges. In the present case it had to be proved that the controller keeps the temperature within predetermined ranges for the operation conditions and set point profiles defined in the respective recipe. Finally, Process Validation (PV) leads to a documented verification that the integrated system functions as intended in its normal operating environment.

These steps take place according to a validation protocol, a written plan stating how validation will be conducted, including test parameters and decision points on what constitutes acceptable test results. Theses protocols allow for establishing the validations report, reporting the validation activities and the conclusions drawn.

Qualification and validation should not be considered as once-off exercises: ongoing activities should follow the first implementation to review proposed or actual changes that might affect a validated status. This change control is part of the lifecycle of the control software. Desired changes to functional options, or reported bugs are documented, collected and regrouped in a new update of the software. Every introduction of an update on the plant floor is then examined considering regulatory requirements so that the system is maintained in a validated state.

8. CONCLUSIONS

This paper described which steps concerning control and supervision appeared when temperature control was implemented on an industrial plant. It gave how the tasks were distributed among the intervening software. The proposed SCA for temperature control of batch reactors (16 litres and 60 litres size) is now being daily used for preliminary tests of feasibility production of a new drug. It is used also to produce the first quantity of these new drugs used in the clinical tests. Despite the fact that the initial heating/cooling system was based on the multifluid type, the hybrid system, introduced by the presented approach, allowed for smooth - monofluid type – behaviour of the heating/cooling system in a temperature range from 20°C to 120°C, enabling heating and cooling in this range without the need to switch from one utility to another and without an important investment cost. The SCA has been qualified and validated according drastic GMP rules which have been imposed in pharmaceutical industry. The success of this project led the industrial company to study the implementation of this strategy in another plant composed of 17 reactors from 100 litres to 6000 litres. Preliminary tests have recently been performed on two of these reactors (1000 and 6000 litres) and provided very promising results.

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