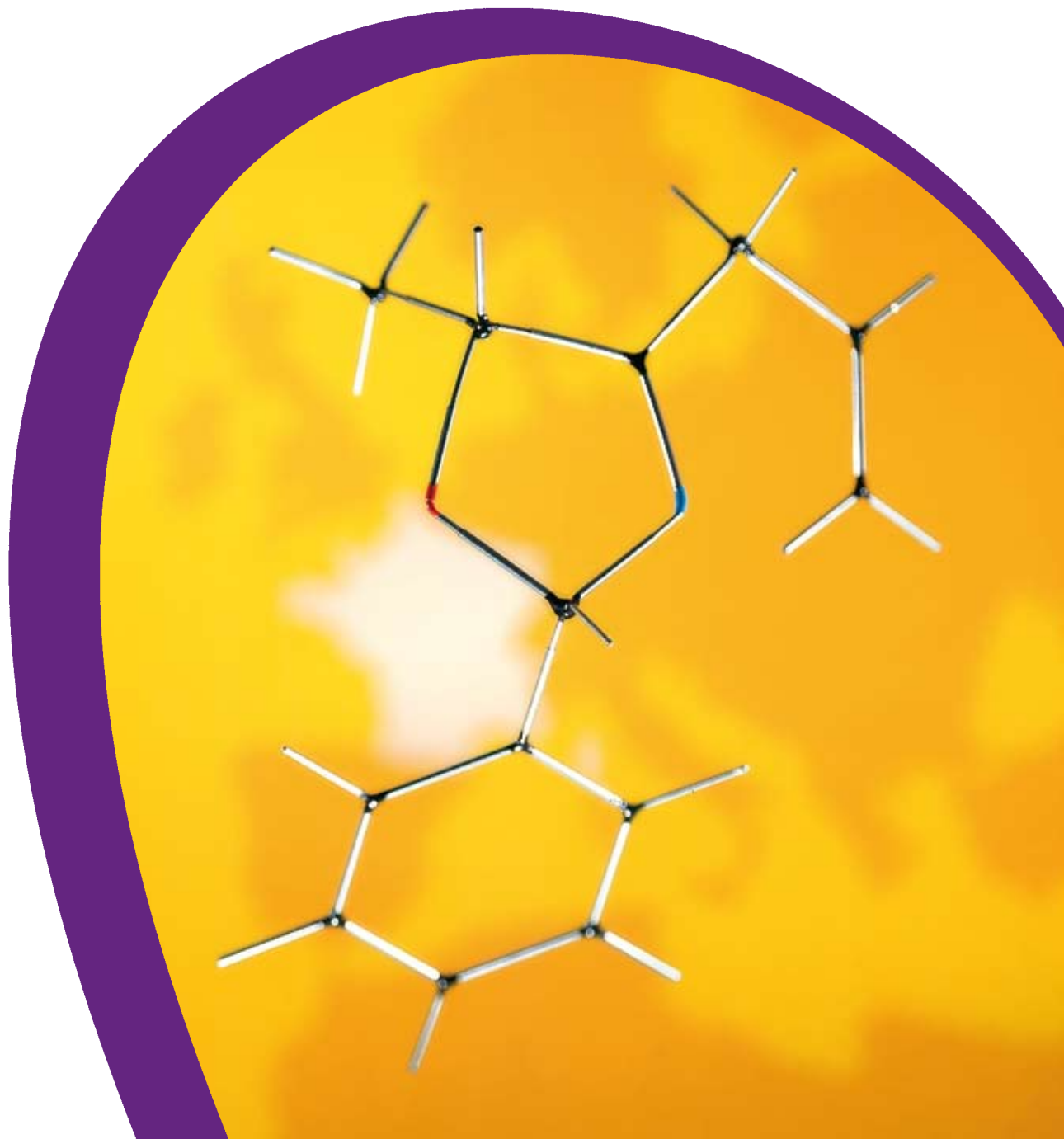


***Pharma Services & Manufacturing
Bon-Encontre & Tonneins/France***

cGMP Solutions from Drug Discovery to Full Scale Production





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Our Pharmaceutical Services

Archimica is a leader in developing and outsourcing some of the industry's most important – and most difficult to manufacture – active pharmaceutical ingredients (APIs) and intermediates. The activities of our French sites Bon-Encontre and Tonneins focus on process development and production. The sites are equipped for cGMP chemical manufacture on any scale.

Experienced in Process Optimization

Unique expertise in process optimization is at the heart of Archimica's corporate culture, which gives our customers a decisive advantage over their competitors.

The Bon-Encontre site possesses highly specialized laboratories coupled with a broad plat-

form for efficient analytical development. Based on this equipment, the development team can react quickly to improve existing technical packages or to propose alternative solutions that are more economical for customers.

Scale-up Services: from Kilograms to Metric Tons

We usually start custom synthesis work on APIs in the laboratory on a kilo scale and accompany our customers throughout the entire scaling-up process as the project proceeds through the clinical phases. With this procedure, we aim to identify processes that are competitive in the long term and to implement them as quickly as possible. As

the impurity profile is highly important, we always strive to develop processes that will remain stable through the entire scaling-up process. In addition, our flexibility allows us to quickly deliver substances by choosing the best process options available with respect to access to raw materials.

New Chemical Entities or End-of-Lifecycle Products

Whatever your asset management strategy is, Archimica is always glad to help you explore your outsourcing options. In today's rapidly changing

world, Archimica's commitment to confidentiality, reliability and excellence in service is something our customers can rely on.



Active Pharmaceutical Ingredients Manufacturing

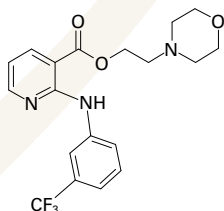
Archimica's sites are developing APIs under exclusive synthesis contracts and strict confidentiality. Generic APIs are manufactured to support our customers in the late stage of their drug's lifecycle and in new applications that offer economic advantages.

Broad Active Pharmaceutical Ingredients Portfolio

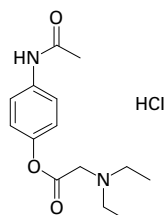
Archimica's sites in France offer a wide-ranging portfolio of small- to large-volume APIs. It all started in 1963 with the first samples of Niflumic Acid. In 1993, a turn was taken with the launch of propacetamol, an injectable analgesic, manufactured in a class A workshop. Due to our 40

years of experience, we have great expertise in managing Good Manufacturing Practices and their recent evolution, as well as in manufacturing active pharmaceutical ingredients. We have mastered a wide range of chemical routes requiring various assets.

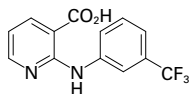
Morniflumate
Anti-inflammatory



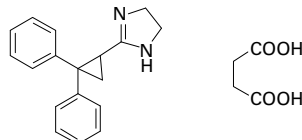
Sterile Propacetamol
Analgesic



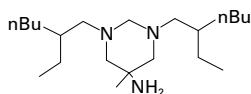
Niflumic Acid
Anti-inflammatory



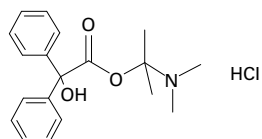
Cibenzoline Succinate
Anti-arythmic



Hexetidine
Antiseptic



Difemerine
Anti-spasmodic





Sterile Bulk Active Pharmaceutical Ingredients

In the last 15 years Archimica's sites have developed unique expertise in the sterilization of bulk active pharmaceutical ingredients (APIs) using high-performance aseptic filtration technology conforming to cGMP standards (ICH Q7A and ICH Q1A compliance). Clean rooms with a 100 or A classification are readily available for your projects.

Aseptic Filtration Technology

This technology is generally used in situations where other technologies (e.g. heating, irradiation) do not guarantee the stability of the API and a good impurity profile. To remove biological materials, the API (often in solid form) is dissolved in a suitable solvent, filtered and crystallized. The choice of solvent is crucial for properly dissolving the API, controlling polymorphism and avoiding problems created by residual solvent. Archimica is able to work with water and

most organic solvents, among others: methanol, ethanol and acetone.

Archimica's ability to work with this demanding technology is also based on strong in-house expertise in process validation, including media fill trials (simulation of aseptic manufacturing). This know-how has been continuously improved and updated as a result of major investments made in 1998, 2002, 2003, 2006 and 2007.

State-of-the-art Facilities

The two sites have dedicated facilities for sterile production on a small or large scale. Operating and management personnel receive constant training to keep them abreast of the current developments.

The sterile bulk unit in Bon-Encontre is used as a pilot plant or production facility for APIs with a high dissolving rate. The plant was modernized in 2002 and now contains two 160-liter glass-lined vessels. The Tonneins facility is used as a

production plant for two sterile APIs. Glass-lined Hastelloy reactors with a capacity ranging from 650 liters to 2,000 liters are used to manufacture several tens of metric tons a year. Over the past five years, we have delivered several hundred batches without receiving a single quality complaint.

Its state-of-the-art facilities give Archimica the flexibility it needs to offer pharmaceutical manufacturers economical alternatives.

Continuous Technology Improvements

In recent years, a series of investments have been realized at Tonneins to achieve even higher performance levels in the continuous improvement process.

Examples of improvements realized are:

- Set-up of a water for injection system used for equipment cleaning and process solvent
- Implementation of septic seeding equipment to control the crystallization step

- Insuring a high sterility level up to the filling operation through extensive use of glove boxes
- QC labs

Archimica also has extensive experience in the use of organic solvents such as methanol, ethanol and acetone in this sterilization step.

Sterilization Outsourcing or Back-integration Solution

Pharmaceutical companies thinking about outsourcing the sterilization step to avoid capital investments have two options with Archimica: to outsource only the sterilization step or to benefit from the advantages of outsourcing the synthesis of APIs as well. Usually the process integration,

which includes the active pharmaceutical ingredient manufacturing and the aseptic filtration step, benefits our customers significantly. Regardless of the option you choose, our team will tailor its offer to your specific requirements, including your quality and purchasing policies.

Safeguarding the Consumer

Our staff are trained for several years to work within a sterile environment, limiting any risk of contamination. This know-how is reinforced by a quality control department that is able to test the

sterility of the product and the absence of pathogenic bacteria. We regularly perform these tests throughout the entire production chain as well as in the manufacturing environment.

Sterilization Technology

<i>Sterilization Technology</i>	Moist Heat	Dry Heat	Irradiation	Aseptic Filtration
<i>Principle</i>	Autoclave 121°C 15 min	160°C 120 min	γ -Ray/ Electron Beam > 25kGy	Dissolution/ Filtration Crystallization
<i>Form</i>	Aqueous Product	Dry Powder Non-aqueous Liquid	Dry Powder Non-aqueous Liquid	Dry Powder Non-aqueous Liquid
<i>Strengths</i>	Closed Vessel Cost-efficient	Closed Vessel Cost-efficient	Closed Vessel	2 in 1 Step Stability of API Impurities Control
<i>Weaknesses</i>	New Impurities	New Impurities Time Consuming	New Impurities Apparatus Cost Dark Packaging	Manipulation Packaging Step
	Destructive Sterilization			Chemical Purification and Sterilization



Large-scale Nitrogen Heterocyclic Chemistry

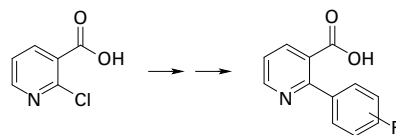
The chemical expertise concentrated at Bon-Encontre and Tonneins has one of its focuses on 2- and 6-chloronicotinic acid and their derivatives and aryl piperazines. Consequently, our employees are used to handling hazardous reactants – such as hydrogen peroxide, phosphorous oxychloride, hydrazines, chlorosulfonic acid, triphosgene and bis(chloro-ethyl)amine – and to control and optimize related processes on a large industrial scale.

2- and 6-Chloronicotinic Derivatives

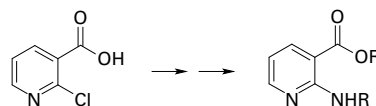
Building blocks like 2- and 6-chloronicotinic derivatives, industrially manufactured on a large scale, are widely used in the pharmaceutical and crop science industries to build complex structures. We can back integrate our customers' APIs into our heterocycles expertise and production. This enables us to offer significant advantages.

Moreover, our expertise with these materials makes Archimica's sites in France very well-suited to solve similar synthesis problems even in other fields of heterocyclic chemistry.

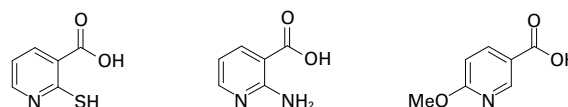
Due to the close cooperation in our global sites network, we can always offer the most suitable and economical solution. For example, we possess several highly active catalyst systems for the Suzuki coupling of pyridines, developed in our worldwide centers of excellence.



We additionally offer aminonicotinic acid derivatives...

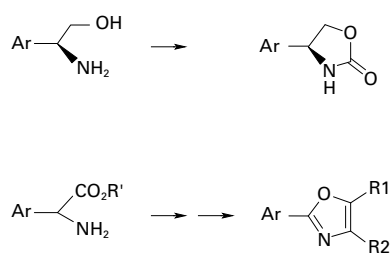


... and a broad range of esters and substitution derivatives, which are available on a commercial scale.



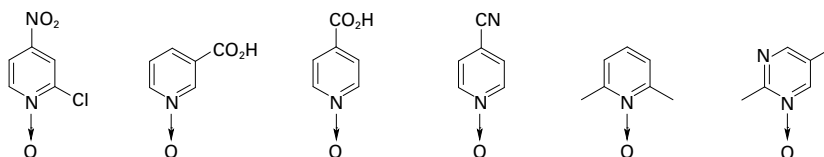
Chiral Oxazoles and Oxazolidinones

The reagent bis(trichloromethyl)carbonate is the key to chiral oxazolidinone compounds. These processes have to be managed carefully, with close monitoring of pH, temperature and solvent. In addition, Archimica has developed an original process for the production of specific oxazole compounds.



Amine N-Oxides

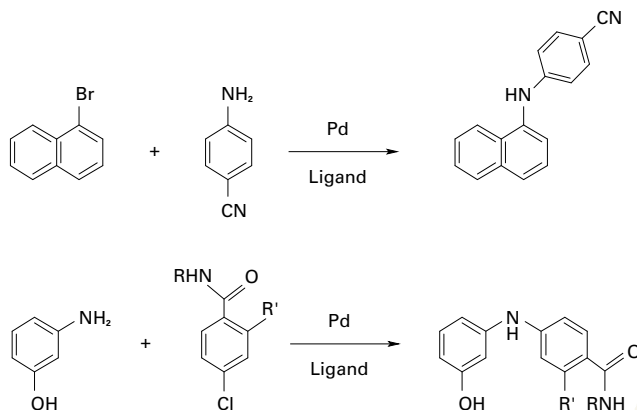
At Archimica we use large volumes of high concentration hydrogen peroxide under our standard safety conditions to access a broad range of pyridine N-oxides and other fused heteroaromatic compounds.



C,N-coupling – A New General Method

C,N-couplings can be used in producing a broad range of substituted amines. Several catalytic systems have been developed, often characterized by high loadings of expensive catalysts, which is not ideal for commercial scale manufacture. Expensive tertiary alcoholate bases, inflexibility of solvents utilized and, most importantly, the diffi-

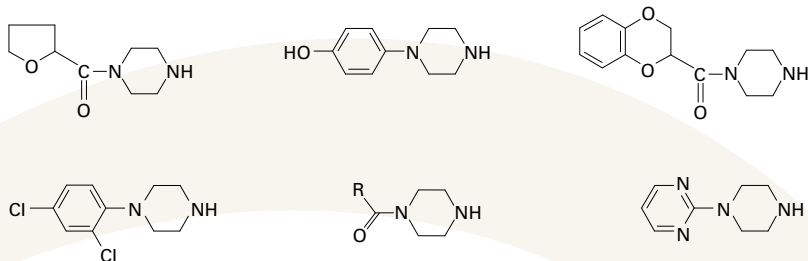
culties of removing catalyst and metal traces from the final product – since these final products are often very efficient in binding catalysts such as palladium – have now been solved by what can be considered an important breakthrough in the field of C,N-coupling technology.



Archimica has developed sulfonated hydroxy-biphenyl phosphane ligands that yield highly polar ligand/catalyst systems while using non-expensive bases. These systems show very high catalytic activities at very low concentration. They allow work with a broad range of solvents, and thanks to their specific properties allow the easy removal of the catalyst/ligand system.

Aryl and Alkyl Piperazines

Archimica has some 30 years of experience in producing aryl piperazines on commercial scale, starting either from free piperazine or from bis-chloroethylamine. Our expertise enables us to select the best and most economical method and to manufacture these materials, some of which are highly sensitive, self-reactive and difficult to purify materials in excellent quality.



Based on this know-how, Archimica is continuously working on more complex piperazine structures.



Handling of Hazardous Reactants

Archimica is used to handling hazardous chemicals requiring stringent safety procedures. Based on our experience, we operate globally under the highest safety standards and continually train our staff in safe handling of substances and processes.

Hydrogen Peroxide (H₂O₂) and Hydrazines

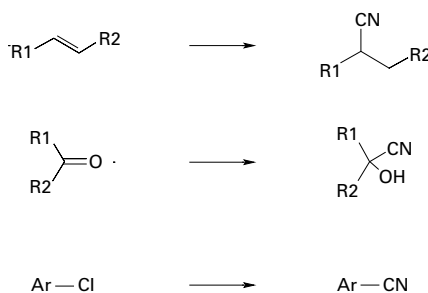
Hydrogen peroxide is one of the most important reactants used at Bon-Encontre and Tonneins. Oxidations and pyridine N-oxides can be obtained easily.

Hydrazines are used to manufacture some of our end-use products. They give access to a broad range of nitrogen compounds, including acyl hydrazides and polyazoles.

Acetone Cyanohydrin

Acetone cyanohydrin is used to generate cyanide ions. Thus, we avoid using hydrogen cyanide (HCN) gas and satisfy the related safety requirements. For safety reasons, this reactant is

stored in a bulk tank. It gives us access to hydrocyanation and cyanide substitution chemistry as described below. This multi-ton process is run also under cGMP conditions.



Phosphorous Oxychloride (POCl₃) and Phosphorous Oxybromide (POBr₃)

Many chlorination processes use phosphorous oxychloride (POCl₃). At Archimica's French sites, we are able to handle this material even on a large scale, including the recycling of phosphorous side-streams.

Since 2008, we are also handling phosphorous oxybromide (POBr₃) for brominations at a multi-metric ton scale.



Quality Standards and ESH

Archimica's sites have more than 40 years of experience in producing APIs and intermediates, and a long tradition of maintaining top-notch standards in pharmaceutical quality control and assurance. Archimica has taken up the challenge of continuously adapting and improving its quality systems to meet the ever-increasing expectations of the regulatory authorities, such as the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA).

Certification and cGMP Standards

Regulatory requirements are constantly adjusted. We anticipate changes by continuously improving our quality systems to always reflect the best practices in the industry.

Both sites comply with the highest international standards and have been certified in accordance with ISO 9000, ISO 14000, OSHAS 18000 and SEVESO II. Pharmaceutical materials are manufactured in compliance with cGMP and ICH Q7A.

Sterile production requires the performance of media fill trials (simulation of aseptic manufacturing), inspected by the French Medical Agency (AFSSAPS). In addition, we continuously use audits by customers and authorities as an opportunity to update our expertise.

Our Tonneins site has been successfully inspected by the FDA in 2007.

Quality Audits

The French Medical Agency (AFSSAPS) audited the plants in 1999 and 2004. Additionally, our customers frequently audit the sites, providing

additional control of our quality management procedures by third parties.

Environment, Safety and Health

Environmental protection is an ever-present issue and is taken into consideration from the earliest stages of product development. Thus, we constantly contribute to sustainable development. Moreover, process-integrated environmental protection permits us to optimize our processes by

reducing the volume of effluents and ensures more economical production for our customers. Both sites were certified according to ISO 14000 in 2003. Archimica's Corporate Principles for Environment, Safety and Health are available at www.archimica.com.

Equipment

The site layout reflects the fact that the plant is flexible enough to handle most of the reactants to perform multi-step synthesis. The broad range of reactor sizes enables the economically viable production of volumes of materials ranging from one kilogram to tens of tons.

Production Facilities

Bon-Encontre has 4,775 m² of non-sterile production area and 130 m² of clean room area. Three facilities are devoted to chemical production in A1, A3 and A4 categories.

<i>Production facility</i>	<i>cGMP</i>	<i>Reactors</i>	<i>Centrifuges</i>	<i>Dryers</i>
A3	Comply	9 glass lined 1.6 – 5.5 m ³ Cryogenic stainless steel reactor, 3 m ³ , -100°C	1.2 m in diameter: 1	1 hastelloy vacuum filter dryer
A4	Comply	4 glass lined 4 m ³ 7 stainless steel 4 – 6 m ³	1.2 m in diameter: 3	1 stainless steel filter dryer
A1	Regulatory Starting Material Quality	13 glass lined 1.6 – 3 m ³ 6 stainless steel 2 – 4 m ³ (1 hastelloy)	1 – 1.2 m in diameter: 8	See A5/A7

Multi-purpose Pilot Plant

Owing to its outstanding flexibility and efficiency, this multi-purpose pilot plant is a perfect platform for starting early-phase projects prior to the scaling-up phases.

<i>Production facility</i>	<i>cGMP</i>	<i>Reactors</i>	<i>Centrifuges</i>	<i>Dryers</i>
A2	Regulatory Starting Material Quality	10 glass lined 0.25 – 2 m ³ 5 stainless steel 0.003 – 2.2 m ³ Hydrogenator 250 L, 50 bar 17 liters glass	0.5 – 1 m in diameter: 4	See A5/A7

Drying Department

Both sites specialize in powder management either for sterile APIs or intermediates. Crystallization, achieved in a large range of solvents, is a key technology for Archimica. Efficient drying equipment is thus required to handle most of the chemicals developed and produced. The drying departments supply dedicated dryers or filter dryers from 150 liters to 2.5 m³ in volume, made of hastelloy or stainless steel, most of them in dedicated rooms, partially classified in class 100 000.

<i>Production facility</i>	<i>cGMP</i>	<i>Dryers</i>	<i>Environment</i>
A5	Comply	3 vacuum dryers (stainless steel, hastelloy) 4 tray dryers	Class D environment
A7	Comply	5 vacuum dryers (stainless steel, hastelloy)	

Analytical Department

This department has access to almost all modern analytical equipment. It includes, among others, HPLC, GC, 200 MHz NMR, DSC, etc. For specific studies, GC/MS and 400 MHz NMR are also available.

It enables the quality control department to guarantee reliable service, to ensure high-quality raw materials and finished goods, and to support the R&D department in new developments.

Sterile Equipment

Archimica has two production units dedicated to aseptic filtration of bulk APIs.

<i>Production facility</i>	<i>Investments</i>	<i>Technical data</i>	<i>Environment</i>
L1, Bon-Encontre	1973/1992/2002	2 vessels of 160 L, hastelloy filter dryer, organic solvent handling	Class D to A rooms
A2, Tonneins	1993/2003/2006	7 vessels: from 50 to 2,000 L (stainless steel and glass lined), 2 hastelloy filter dryers, organic solvent handling and water for injection	Water for injection, Isolator class A, class C and D rooms

Storage Areas

The Bon-Encontre site has 2,580 m² of pallet storage space, including 650 m² in a temperature-controlled environment, as well as static tank storage areas for solvents, aqueous acids and bases.

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