

TECHNOLOGY STRENGTHS
Sterile APIs
High performance microfiltration technology

Archimica is a leading provider of bulk sterile APIs for the pharmaceutical market, offering state-of-the-art technology, broad synthesis capability and a full range of developmental and manufacturing options to meet the specialized needs of a sterile drug commercialization project. In June 2007, our Tonneins site has been successfully inspected by the FDA.

Today, we manufacture bulk sterile APIs to cGMP standards using high performance microfiltration technology at two facilities in southwest France. This capability is complemented by a range of ancillary technologies that ensure aseptic processing of finished pharmaceuticals and offer a range of options for finished product form. Over the past five years, we have delivered thousands of batches of bulk sterile APIs on time without a single quality complaint.

At Archimica, we offer a complete range of synthesis capabilities for sterile API projects – from raw materials through regulated early and late stage intermediates to bulk APIs. We also offer advanced building blocks based on proprietary, leading technologies that can be used in all of these synthesis situations. Our sterilization capability can be integrated with API production or operate as a separate outsourced step for companies that do not have bulk sterile facilities or who may need additional capacity.

State-of-the-art facilities

Archimica produces sterile APIs from kilo to commercial scale at facilities in Bon Encontre and Tonneins, France. These locations operate under full cGMP conditions and ICHQ7A/1A compliance, including all requirements for aseptic processing of finished pharmaceuticals. The Tonneins facili-

Archimica sterile API facilities

Design	Dissolution, sterilization (filtration), crystallization, drying
Reactors	Glass lined and Hastelloy (from 160 l up to 1800 l)
Capacity	Several kilos to 100 mt/year
Clean room	Class A or 100
cGMP	Yes (Tonnes: FDA-inspection June 2007)
Experience	More than 15 years

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Both facilities are capable of manufacturing bulk liquid or solid APIs. The facilities feature multi-purpose equipment as well as a validated cleaning process approved in numerous audits. These facilities have the ability of handling highly corrosive materials, such as hydrochlorides, hydrobromides or mesylates.

Our Bon Encontre location offers small scale production for both process development and regulatory issues. Our Tonneins location was expanded in 2002 to include a sterile pilot plant and a Class A cleanroom handling facility.

These isolated facilities are located on sites with a range of chemistry capabilities that are flexible in size and scope and even allow the handling

of hazardous reagents in chemical syntheses. This allows Archimica to integrate API synthesis, whereby the overall synthesis and process chain can be made more efficient, such as final purification during the sterilization process.

Both facilities are readily expandable and adaptable to match new production requirements. This allows Archimica to manufacture sterile APIs in the smaller quantities that may not allow for an economical investment by a pharmaceutical manufacturer.

Microfiltration offers important advantages

At Archimica, sterilization is accomplished by high performance microfiltration, also called 'aseptic filtration' by the FDA, meaning that biological materials are filtered off. This technology is often used with powder, which is dissolved, filtered and crystallized. In the process, Archimica selects very specific solvents and then passes the mixture through a specialized membrane, which removes biological contaminants from the dissolved product. Once sterilized, the product is recrystallized. This 2-in-1 process offers excellent impurity profile control compared to the other technologies.

In addition, it is a highly efficient and hence economical approach to the manufacturing of bulk sterilized APIs.

Microfiltration is fundamentally different from traditional sterilization methods in that it is non-destructive. Sterilization by steam heat, dry heat and irradiation (γ -ray) function via destruction of biological contaminations. This physically invasive approach has several critical drawbacks.

First, there is the possibility that the API itself will be destroyed to varying degrees along with the biological impurities. This is especially the case with compounds that are sensitive to water, heat and irradiation. As drugs become more specific and more complex, they also become more sensitive and require a gentler approach to sterilization.

Secondly, with the destruction of molecules, there is the possibility of creating new impurities of unknown identities and concentrations. This is particularly the case with irradiation and complex molecules. These molecules may contain functional groups (e.g. heterocycles) that can be activated by irradiation leading to fragmentation. Thus for example, irradiation has the potential to introduce

unwanted color into a drug, which can only be removed through very expensive methods. In addition, as regulatory requirements become stricter, the formation of impurities of a previously biological origin becomes less desired and in some cases will be prohibited.

The Archimica microfiltration process can deliver dry powders – with control of polymorphs – as well as aqueous sterile solutions. Archimica has experience in precisely controlling the physical properties of the final product, with many options available.

Quality is assured

Archimica's sterile API teams have more than a decade of experience with creating the appropriate conditions for the media fill (aseptic process simulation) and process validation even for very difficult to handle or sensitive products. Our QA follows strictest FDA, ICHQ7A and ICHQ1A guidelines and our QC is able to determine all relevant parameters (bio-assay). The plant – especially in the aseptic processing area – uses a system of airlocks and cleanroom zones from class 100000 through to class 100 in the product zone. Thus we ensure the highest standard for the product.

Sterilization technology	Moist heat	Dry heat	Irradiation	Aseptic filtration
Principle	Autoclave 121°C 15 min	160°C 120 min	γ -Ray/electron beam >25kGy	Dissolution/filtration Crystallization
Form	Aqueous product	Dry powder <i>Non-aqueous liquid</i>	Dry Powder <i>Non-aqueous liquid</i>	Dry Powder <i>Non-aqueous liquid</i>
Strength	Closed vessel Cost-efficient	Closed vessel Cost-efficient	Closed vessel	2 in 1 step stability of API Impurities control
Weakness	New impurities	New impurities Time consuming	New impurities Apparatus cost Dark packaging	Manipulation Packaging Step
Destructive sterilization			Chemical purification and sterilization	