

ISO 9001

# Pharmacy and specialty chemicals



*Particular constraints  
for equipment*

# SPECIFIC MATERIALS AND EQUIPMENT



## Specific constraints

for the life sciences industry

**CARBONE LORRAINE equipment** is unequalled for safely and reliably solving temperature resistance and corrosion resistance problems, due to the very good stability of the materials used:

- ◆ **GRAPHILOR 3: ultra-fine graphite impregnated with highly cross-linked resin**
- ◆ **Reactive metals: Titanium, Tantalum, Zirconium, Niobium, Alloy, etc.**
- ◆ **PTFE**
- ◆ **Silicon carbide**

The pharmaceutical industry produces specialties or active constituents according to the Pharmacopoeia, and is controlled by other constraints.

These constraints are identified in the following documents:

- ◆ "Good Manufacturing Practice" (GMP) produced by Food and Drug Administration (FDA)
- and
- ◆ "Good Manufacturing Practices for Active Ingredient Manufacturers" published by the European Chemical Industry Council (CEFIC-EPIC) in cooperation with European Federation of Pharmaceutical Industries Association (EFPIA).

There are two basic criteria for these constraints:

- **Inertness of materials making up the equipment (stability related to corrosion, mechanical and thermal forces, thermal shock, impermeousness and no release of component elements of the material).**

■ The equipment design shall satisfy three main points:

- ◆ impossible for any mixing between the service fluid and the process fluid, by passing through or around the materials.
- ◆ easy cleaning, sterilization if necessary, in line CIP possible if required, no dead areas.
- ◆ maintenance procedure that does not modify the "inertness" of equipment.

The operator's specifications or his engineering specifications vary in different companies, on different sites and depending on the processes, starting from these basic criteria.

1. Guide to Good Manufacturing Practice for Medicinal Products, in "The Rules governing Medicinal Products in the European Community", Volume IV, January 1992.

2. "Guidelines for the Manufacture of Active Pharmaceutical Ingredients (Bulk Drug Substances)", published by the Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products, Document 2/87, (June 1987).

3. "Bonnes Pratiques de Fabrication des produits chimiques à usage pharmaceutiques", SICOS Biochimie, Paris, (May 1989).

4. Good Manufacturing Practices, "Guidelines" for the production and control of Bulk Pharmaceutical Chemicals, 4th Edition, Aschimfarma, Milan, Italy, (March 1991).

5. "Bulk Pharmaceutical Chemicals", Pharmaceutical Quality Group Monograph, The Institute of Quality Assurance, London, 1992, ISBN 0 906810 22 3.

6. "Recommendations for Good Manufacturing Practices for Active Ingredients", VFA Monograph, approved by VFA, Bonn, Germany, March 1995.

7. "Good Manufacturing Practices, Guidance for Bulk Pharmaceutical Chemicals Manufacturers", edited by the BPC Committee, CEFIC, Bruxelles, ("The CEFIC Draft"), (May 1995).

8. "Concepts for the Process Validation of Bulk Pharmaceutical Chemicals" edited by the Pharmaceutical Manufacturers Association, C.C. Section, Bulk Pharmaceuticals Committee, in Pharmaceutical Technology Europe, January 1994.

9. Commission Directive of 13 June 1991 laying down the principles and guidelines of good manufacturing practices for medicinal products for human use, (91/356/EEC) - Official Journal of the European Communities, N° L 193 of 17 July 1991.

10. Commission Directive of 23 July 1991 laying down the principles and guidelines of good manufacturing practices for veterinary medicinal products (91/412/EEC) - Official Journal of the European Communities, N° L 228 of 17 Aug. 1991.

11. "Good Manufacturing Practices for active pharmaceutical ingredients (bulk drug substances) in WHO Expert Committee on Specifications for Pharmaceutical Preparations, 32nd Report", Geneva, 1992, ISB 92 4 1208236.

12. Current Good Manufacturing Practices for Finished Pharmaceutical Products, US Food and Drug Administration, 21 CFR Part 211.

13. "Guides to Inspection of Bulk Pharmaceutical Chemicals", US Food and Drug Administration, Revised Edition, May 1994.

14. "Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients", The International Pharmaceutical Excipients Council, October 1995.

### OTHER LITERATURE

- Good Manufacturing Practices for Pharmaceutical Products, Annex - Guidelines on the Validation of Manufacturing Processes, WHO / Pharm / 93.562 / rev 2.
- FDA Guide to Inspection of Validation of Cleaning Processes, US Food and Drug Administration, July 1993.
- FDA Regulation of Bulk Pharmaceutical Chemical Production, D.B. Barr et al, in Pharmaceutical Technology, September 1993.
- FDA Regulation of Bulk Pharmaceutical Chemicals - An Industrial Commentary, N.C. Franklin et al in Pharmaceutical Technology, Part I, October 1994, Part II November 1994.
- An FDA Perspective on Bulk Pharmaceutical Chemical GMPs, E. Rivera Martinez, in Pharmaceutical Technology, May / June 1994.
- ICH - Harmonized Tripartite Guideline on Stability Testing of New Drug.

This introduction reviews the development of Good Manufacturing Practices (GMPs) for Active Ingredients (A.I.s) and explains the purpose of the present Guideline.

In the USA, although the FDA has not yet issued separate GMP regulations for active ingredients to assist agency personnel, guidelines have been produced entitled "Guidelines to the Inspection of Bulk Pharmaceutical Chemicals". These were last updated in May 1994.

Guidelines have also been developed in the USA by PhRMA (Pharmaceutical Research Manufacturers' Association) entitled "Guidelines for the Production, Packing, Repacking of Holdings of Drug Substances" which were published in September 1995.

A WHO guideline for active pharmaceutical ingredients is included in Chapter 18 of the 32nd report of the World Health Association, Geneva, 1992.

In Japan, standards for the Manufacture of BPCs, mainly emphasizing responsibilities in active ingredient manufacture were issued from the Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare in 1998.

In Europe the Pharmaceutical Inspection Convention (PIC) issued a "Guideline for the Manufacture of Active Pharmaceutical Ingredients" in June 1987. This document has not been revised since its original publication and provided the basis for the WHO guideline cited above.

In the European Union the principles of GMP for medicinal products were laid down in the "Guide to Good Manufacturing Practice for Medicinal Products" in Volume IV of "The Rules governing Medicinal Products in the European Community". This Guide states that, for the manufacture of active ingredients, the PIC document was an appropriate reference. This PIC document therefore is, at present, the only official guidance available to all member states of the European Union.

In several countries manufacturers of active ingredients found that the PIC document did not provide sufficient guidance, and thus several organisations in Europe published more detailed guidelines for GMP of active ingredients. These include the French SICOS, Biochimie, the Italian Aschimfarma, the UK Pharmaceutical Manufacturers' Association, the German VFA (the European Chemical Industry Council) and the German VFA (the Association of Research-based Pharmaceutical Manufacturers) document of February 1995: "Recommendations for Good Manufacturing Practices for Active Ingredient Manufacturers". It is this VFA document that EFPIA, the European Federation of Pharmaceutical Industries Association, adopted as the basis for a European Industry Guideline for Active Ingredients.

The present document has been produced by a joint EFPIA/CEFIC working group and reflects the objectives of both associations to produce and publish one guideline suitable for all active ingredient manufacturers. Its purpose is to serve as a guide, with the intention of ensuring that active ingredients are manufactured under a quality assurance system which is appropriate for their subsequent use. The scope is limited to GMPs for active ingredients; excipients are not covered.

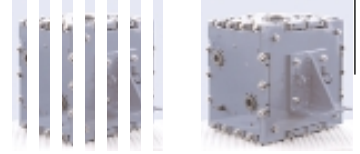
\* Extracts from:

"Good Manufacturing Practices for Active Ingredient Manufacturers"

Published by CEFIC-EPIC (Brussels)

# CARBONE LORRAINE, YOUR PARTNER

CARBONE LORRAINE satisfies your equipment needs for units controlled by GMP



## How ?

Using a range of particularly stable and inert materials in its equipment, namely:

- ◆ GRAPHILOR 3
- ◆ Reactive metals
- ◆ Steel reinforced PTFE ARMYLOR®
- ◆ Silicon carbide

Through the design of appropriate equipment and accessories:

- ◆ Heat exchangers
- ◆ Reactors and columns
- ◆ Pipework and accessories

Through maintenance procedures that do not deteriorate the equipment.



*Cubic heat exchanger type NK*



*PTFE ARMYLOR® column*



*Reactor coated with reactive metals*



*Silicon carbide and PTFE heat exchanger*



*Heat exchanger made of reactive metals*

# STABLE AND INERT MATERIALS



## GRAPHILOR 3

(see documentation GCA 15 F):

The major advantage of GRAPHILOR 3 is that it is extremely stable; this stability is related to the combination of an ultra-fine graphite, highly cross-linked resins and a well-proven impregnation technology.

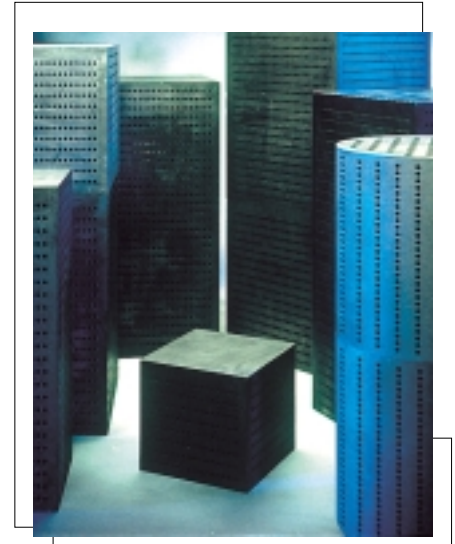
In particular, this excellent stability will satisfy the concerns of the user obliged to respect GMP for his installation, namely:

- ◆ Corrosion resistance
- ◆ Temperature resistance
- ◆ Exceptional mechanical characteristics not influenced by temperature or time.

The reader can refer to documentation GCA 15 and technical data sheets EGC 301, EGC 303 and the corrosion table that describe these problems in detail.

In particular it satisfies three criteria:

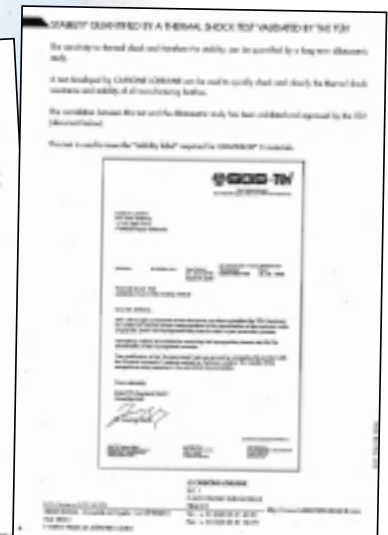
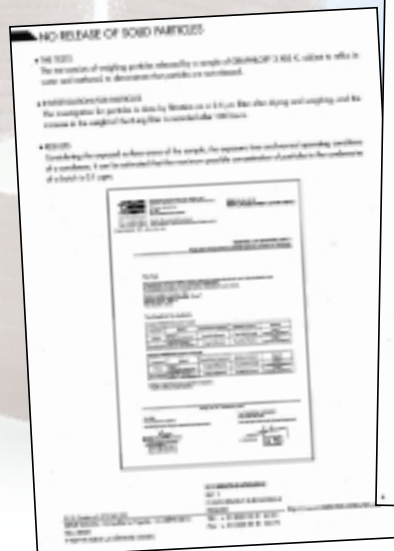
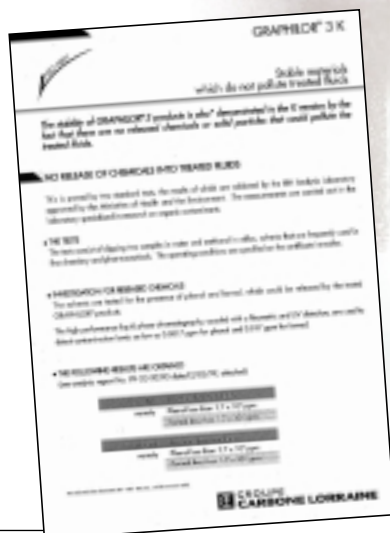
- ◆ No tension in the material due to temperature gradients and/or contact with solvents. This is due to: A resin stabilization treatment (over cross-linking) that makes resin expansions and expansions of the support graphite compatible, and eliminates swelling of this resin in contact with the corrosive fluid.
- ◆ Guaranteed imperviousness in the long-term time even to fluids used in this industry, as shown by tests carried out with the dowtherm.
- ◆ No release of molecules and particles from which the materials are made. Due to our K versions of GRAPHILOR 3 and their corrosion resistance. This is confirmed by a certificate issued by a laboratory approved by the Ministry of Health and the Environment (see inset).



GRAPHILOR 3 K monoblocks

Refer to technical data-sheets EGC 306, EGC 302 and EGC 305 that describe these problems in detail.

The inset shows essential points that ensure that GRAPHILOR 3 materials satisfy the needs of GMP units.





### Reactive metals

Ideal materials for their stability and inertness, and recommended particularly for the final production phases of products.

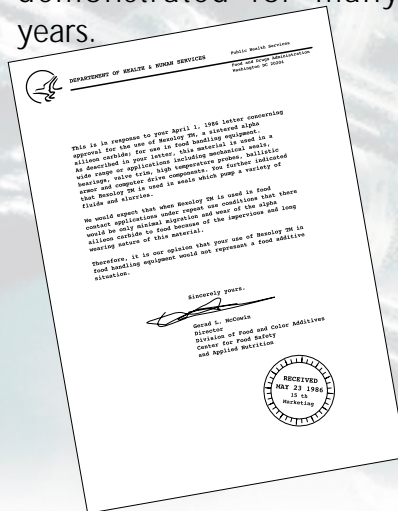
Their characteristics and experience in use make them ideal materials for satisfying constraints imposed by GMP.

Details are given in the AstroCosmos documentation.

### Silicon carbide

The inertness of Hexoloy in the form marketed by CARBONE LORRAINE is sufficient to provide all guarantees necessary for use in the pharmaceutical industry.

The certificate shown in the inset confirms that its advantages have been demonstrated for many years.



### PTFE

PTFE is well known for its inertness, and is widely used in the pharmaceutical industry, in medicine and in food processing.



Tantalum heat exchangers



Silicon carbide and PTFE heat exchangers



ARMYLOR® accessories  
(PTFE lined steel)

# AN APPROPRIATE DESIGN



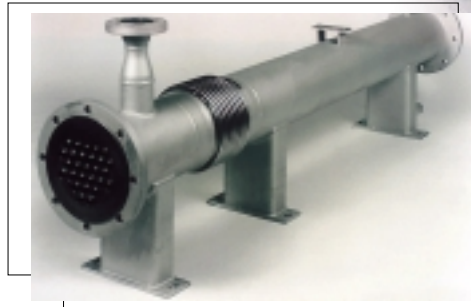
## Sheet metal equipment

Heat exchangers, reactors, columns, pipework

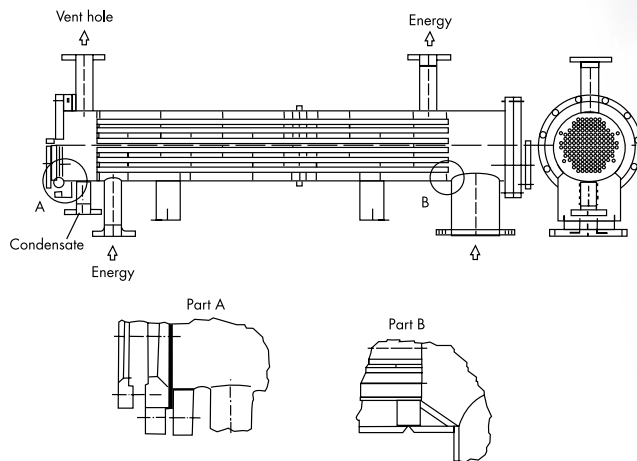
This type of equipment is designed using reactive metals and alloys to satisfy the specifications of each customer. In particular, assemblies are made such that there are no dead volumes and to make cleaning easy.

Obviously, welds make it impossible for the service fluid to mix with the process fluid.

The attached inset gives an example construction layout for an exchanger to be used in a GMP unit.



*Tantalum heat exchanger*



*ARMYLOR® PTFE column*

## ARMYLOR equipment

Pipework - columns

Cladding of sheet metal equipment using a thick unwelded joint free PTFE liner makes these materials quite suitable for use in GMP units.

## GRAPHILOR 3 equipment

Heat exchangers

A special design ensures that GRAPHILOR 3 heat exchangers satisfy design criteria necessary for use in GMP units.

A single-block unit is used without any joint between the process circuit and the service circuit.

NK models of cubic heat exchangers are used.

Refer to the specific documentation for these models.



*Impregnated graphite cubic heat exchanger*

# MANY REFERENCES

In the pharmaceutical and fine chemicals industry



## PHARMACEUTICALS

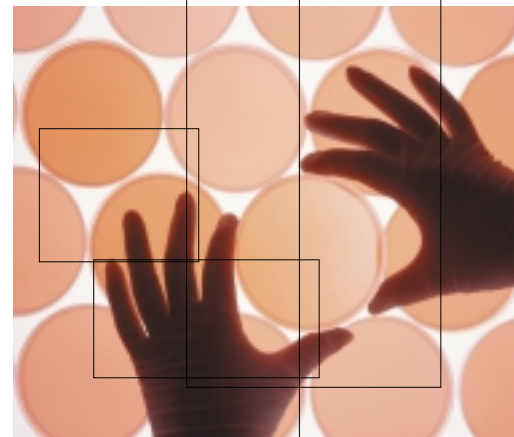
ABBOT LABORATORIES  
BOEHRINGER  
CHIREX  
CILAG  
CLARIANT  
DIOSYNTH  
GENZYME  
GLAXO WELLCOME  
IROTEC LABORATORIES  
KLINGE PHARMA & CO  
KNOLL PHARMACEUTICALS  
MERCCK SHARP & DOHM  
NIPA LABORATORIES  
NOVARTIS  
PFIZER  
PHARMACIA & UPJOHN  
RHONE POULENC RORER  
ROCHE  
SMITHKLINE BEECHAM PHARMACEUTICALS  
SWORDS LABORATORIES  
TARO PHARMACEUTICALS  
YAMANOUCHI IRELAND CO  
ZENECA  
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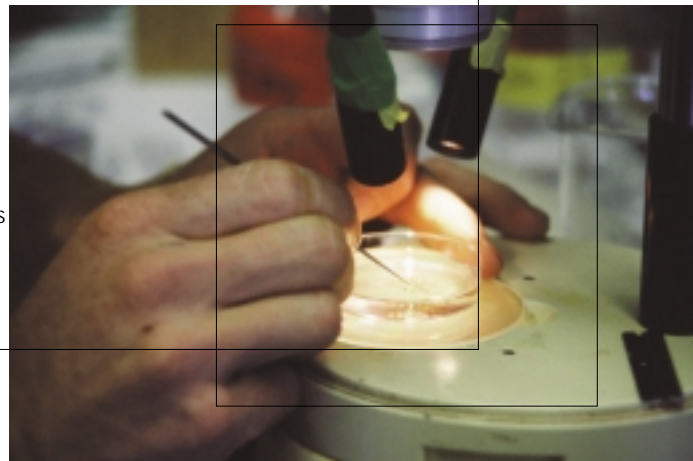
## FINE CHEMICALS

AGREVO  
A H MARKS & CO  
ALBRIGHT & WILSON  
ALLIED COLLOIDS  
ARCHIMICA  
ARRAN CHEMICAL CO  
BUSCH BOAKE ALLEN  
CHESHIRE CHEMICALS  
CHIROSCIENCE  
CIBA  
COALITE CHEMICALS  
CONTRACT CHEMICALS  
CRODA UNIVERSAL  
DOW CORNING  
EASTMAN CHEMICAL  
ELF ATOCHEMETMA SA  
...  
FD COPELAND & SONS  
FMC CORPORATION  
GREAT LAKES FINE CHEMICALS  
HERCULES  
HICKSON & WELCH  
HODGSON CHEMICALS  
HOLIDAY DYES & CHEMICALS  
IFF  
JOHNSON MATTHEY  
LAPORTE FINE ORGANICS  
LAPORTE INSPEC  
MANRO PERFORMANCE CHEMICALS  
MITCHELL COTTS CHEMICALS  
NUFARM LIMITED  
OXFORD ASYMMETRY  
PEBOC DIVISION OF EASTMAN

PUROLITE  
QUEST INTERNATIONAL  
RESOLUTION CHEMICALS  
REVERTEX CHEMICALS  
RHODIA  
RHONE POULENC AGRICULTURE  
ROBINSON BROTHERS  
ROHM & HAAS  
THOMAS SWAN & CO  
UOP LIMITED  
UNITED PHOSPHORUS  
WILLIAM BLYTHE  
WITTON CHEMICALS  
ZENECA  
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## WORLDWIDE SPECIALIST in industrial components

Since its founding in 1892, CARBONE LORRAINE has built an international reputation by creating subsidiaries on all continents. Today with industrial and commercial plants located in more than 30 countries, agencies and representatives in more

than 70 countries and 250 commercial contacts throughout the world, CARBONE LORRAINE offers its customers worldwide reliable, high technology products and the service of its experienced technicians.

## A worldwide organization

