BILAG 36

46

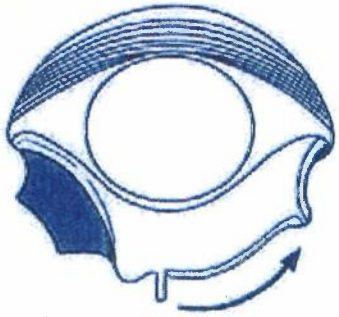
Queen Elizabeth Hospital Birmingham NHS
Part of University Hospitals Birmingham NHS Foundation Trust

About your Accuhaler

It is important you use the inhaler correctly to make sure you have the full dose of the medication you need.

How does it work?

The accuhaler can be used to deliver different types of medication (different colours indicate different medication) depending on your problem and how severe it is. It is likely to be either: Salmeterol/Serevent (green), Fluticasone/Flixotide (orange), Seretide (purple) or Salbutamol (blue) and may include a steroid component (Fluticasone and Seretide include a steroid). These inhalers work by relaxing the muscles of the large airways and/or reducing the inflammation of the airways.



How do I use it?

1. Push the outer cover round with your thumb.
2. Push the dial round until you hear a 'click'.
3. Breathe out as far as is comfortable (without the device in your mouth).
4. Place lips tightly around mouthpiece and breath in quickly and deeply.
5. Remove your Accuhaler from your mouth and hold your breath for 10 seconds or as long as is comfortable and then breathe out slowly and calmly.

Repeat the above process as your prescription indicates. If you have an inhaler that contains a steroid you must rinse your mouth out with water to prevent developing a sore mouth, husky voice or oral thrush.

UHB is a no smoking Trust

To see all of our current patient information leaflets please visit
www.uhb.nhs.uk/patient-information-leaflets.htm

P14/0878/03 UHB/PI/06/8 Authors: Sharon Rees and Dee Curry
Date: December 2014 Review: date: December 2016

INDEX

API MICRONISATION

Micronisation

The objective is to reduce to the appropriate particle size the active ingredient to enable the right product performance. Micronized actives are used in respiratory products, ophthalmic ointments, tablets...

Evreux site is in charge of micronising the API for GSK manufacturing network. This stage requires a specific knowledge and a complex technology.

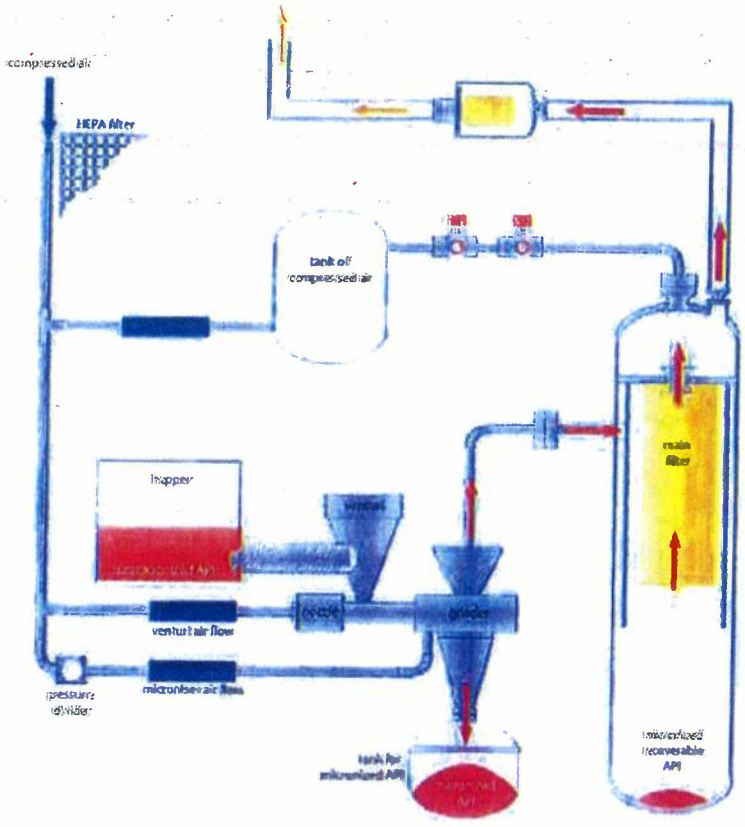
Equipements / Technologies:

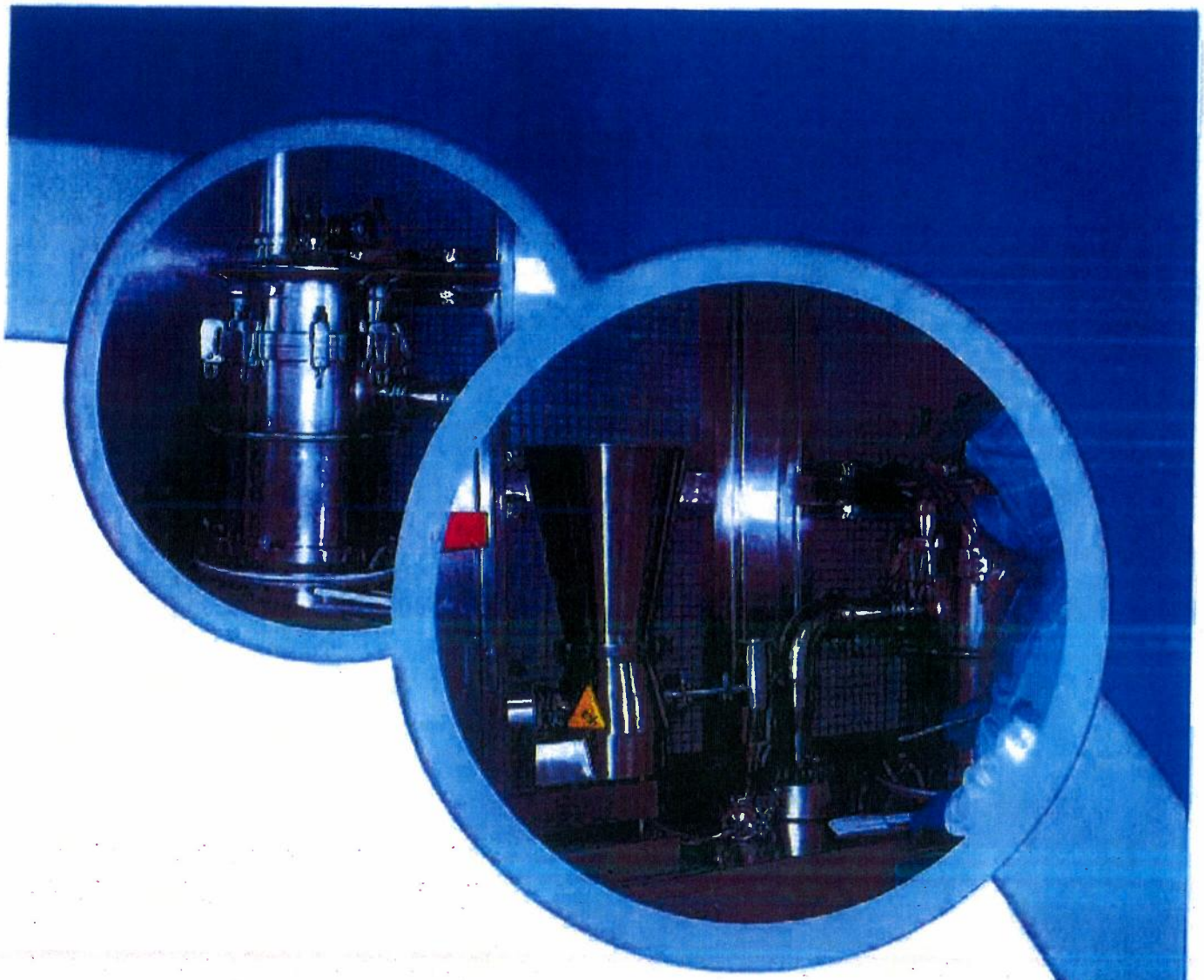
- 4 micronisers of 8 inches technology
- Feeder: gravimetric system
- Nitrogen or air grind techno
- Compressed air with dew point – 70°c
- Respiratory free
- HVAC
- Capacity: from 3 to typically 10 kgs/hour
- Batch size: from 300 g to typically 7 kgs

Process flow

Key Features:

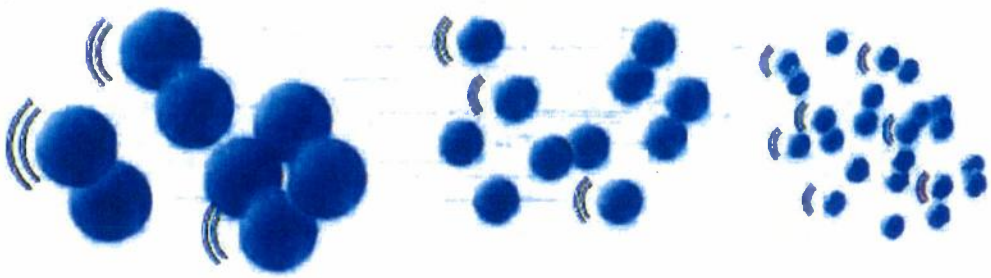
- Particle Size Distribution: from ultra fine (<0.1 µm) to fine (100 µm) particles
- Real time data acquisition system





Overview

The active ingredient is introduced into a hopper and is fed to the venturi. The process air reaches a speed of Mach 2.5. At this speed, particles will collide with each other and their size will be reduced to meet required specifications. The micronised active ingredient is recovered in the vessel.



Aerosols PRODUCTS
Features

Aerosol specifications

A Metered Dose Inhaler is composed of 5 main components: active ingredient, propellant, can, valve and actuator. The combination of these components results in a product with high degrees of technology and technical complexity requiring a committed team of technical masters to produce.

Each year, about 80 million aerosol packs are produced for 120 customers around the world. Our main customers are the United Kingdom, France, Australia, the US and Japan.

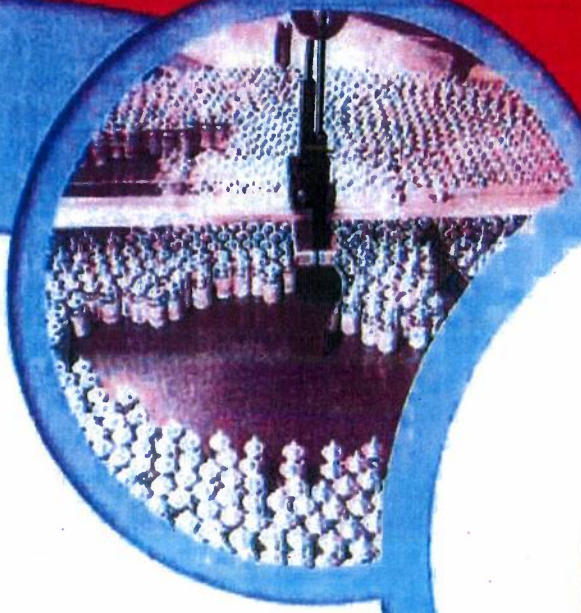
Key Features:

- Aluminum can filled with a suspension or solution of API in a gas
- 60, 120 or 200 doses typically
- Colored actuator
- Dose counter available

Main technical characteristics:

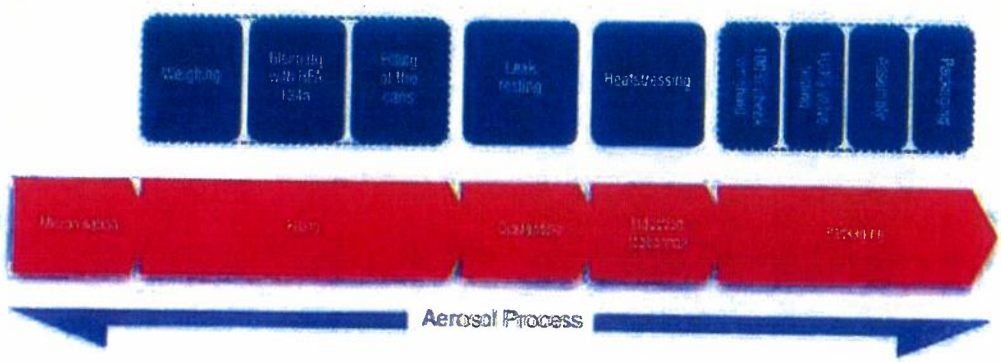
- Standard can design
- Recyclable components
- Color per API and darkness of color depending on strength
- Tamper evidence
- CFC Free - Environmentally friendly
- API full protection (no conservative)
- Constant pressure during all aerosol life
- Could be filled with different API
- Valve down use
- Easy to clean
- Decremental dose counter : feed back to patient
- Auto power pack
- No patient age constraints
- 3 Steps use: open, breathe, close
- Alternative to DPI/MDPI devices
- Cost competitive
- High level dose accuracy

AEROSOLS PRODUCTS



The active ingredient went previously through the micronisation process.

Production process



Aerosols PRODUCTS

Blending & filling

Filling operation

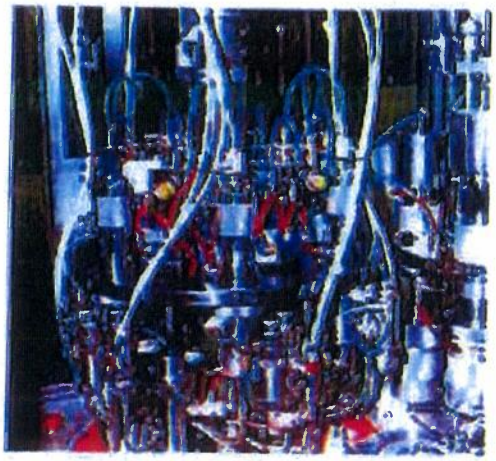
The micronized drug is weighed and blended with a defined amount of propellant HFA134a and transfered to a specific tank which then feeds this suspension to the filling line. First the valve is placed on the can. The can is purged with propellant to remove remaining air within the can and the valve is crimped on. Afterwards, the can is filled with the propellant and the suspension directly through the valve. Finally, the canister is weighed and printed with an identification code.

Key Features:

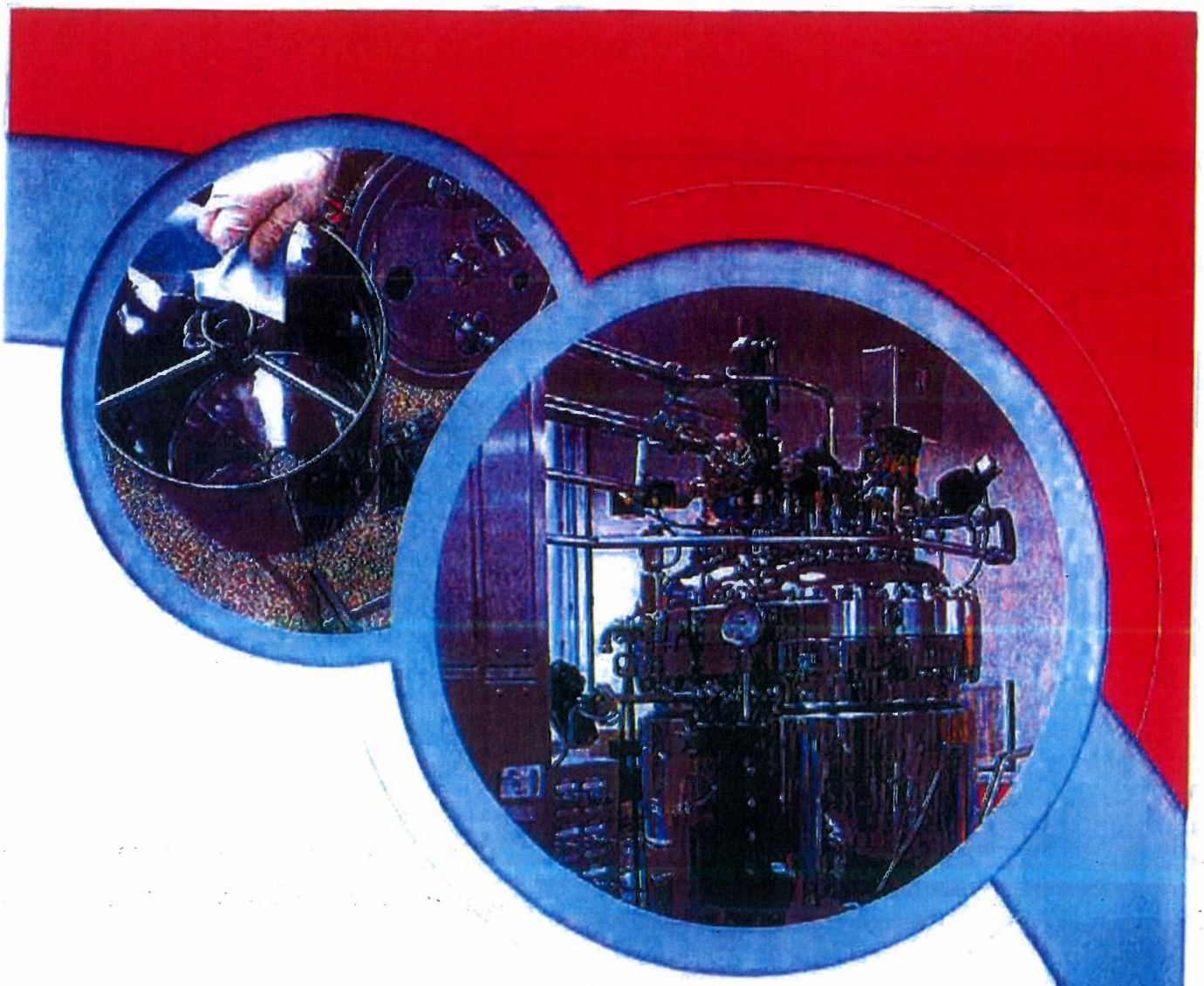
- 5 production HFA manufacturing lines
- 1 pilot line
- 1 line with double technology (solution or suspension)
- Dedicated dispensing room per line
- Dedicated pharmaceutical manufacturing facility
- ATEX (flam proof) environment
- Electronic Batch Record
- Air environment control
- Waste treatment
- Canisters are 100% check weighed

Equipements / Technologies:

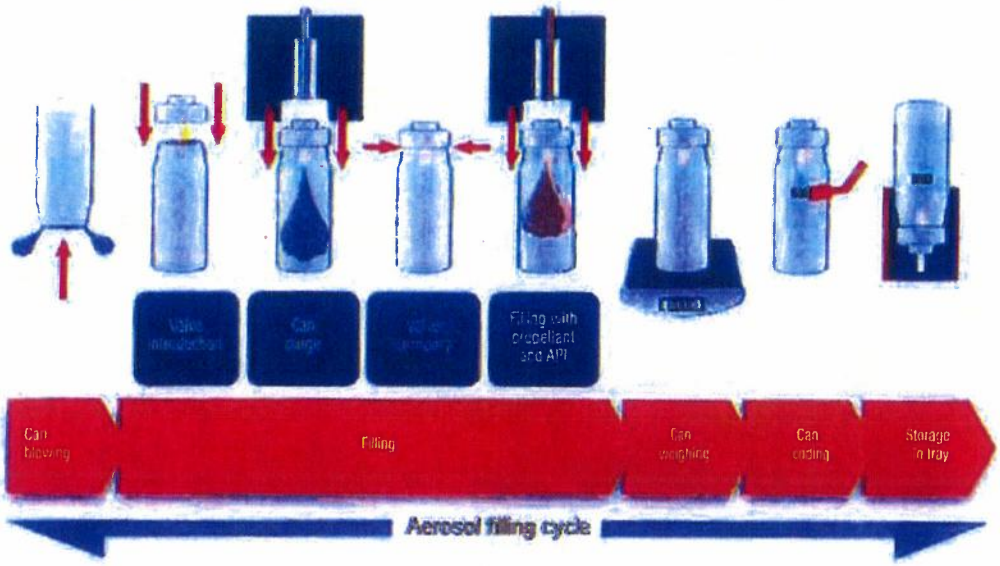
- Drug Additionnal Volume capacity: 20 liters
- 400 L stainless steel vessel capacity
- Double jacket and heater/chiller system
- CIP (clean in place) water or ethanol
- 100 % filled weight checked
- Supervisory control and data acquisition system
- Coding station
- 1 pilot line: 45 cans/min and 20 L capacity
- Batch size: from 15 000 to 75 000 or from 90 kg to 405 kg
- Can of 5, 8 and 12.5 ml
- Can sizes 22 mm to 61 mm width and 55 mm to 165 mm height
- Valve sizes including 15 mm, 20 mm
- HFA 134a propellant



AEROSOLS PRODUCTS



Filling process



Aerosols PRODUCTS

Packaging

Packaging operation

8 packaging lines are dedicated to aerosols. After the quarantine period, each canister is identified, checkweighed and spray tested to ensure proper valve operation and to detect potential leakage.

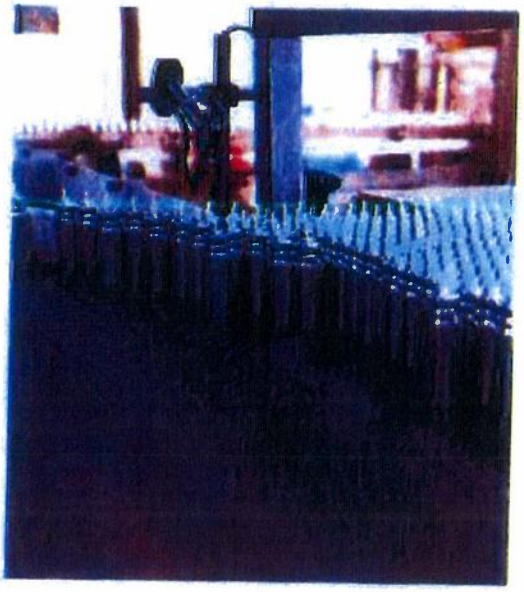
All the packaging components are controlled before use by identification code. The canister is labelled, coupled with an actuator, fitted with or without a dose counter and inserted into cartons with the patient leaflet.

Key Features:

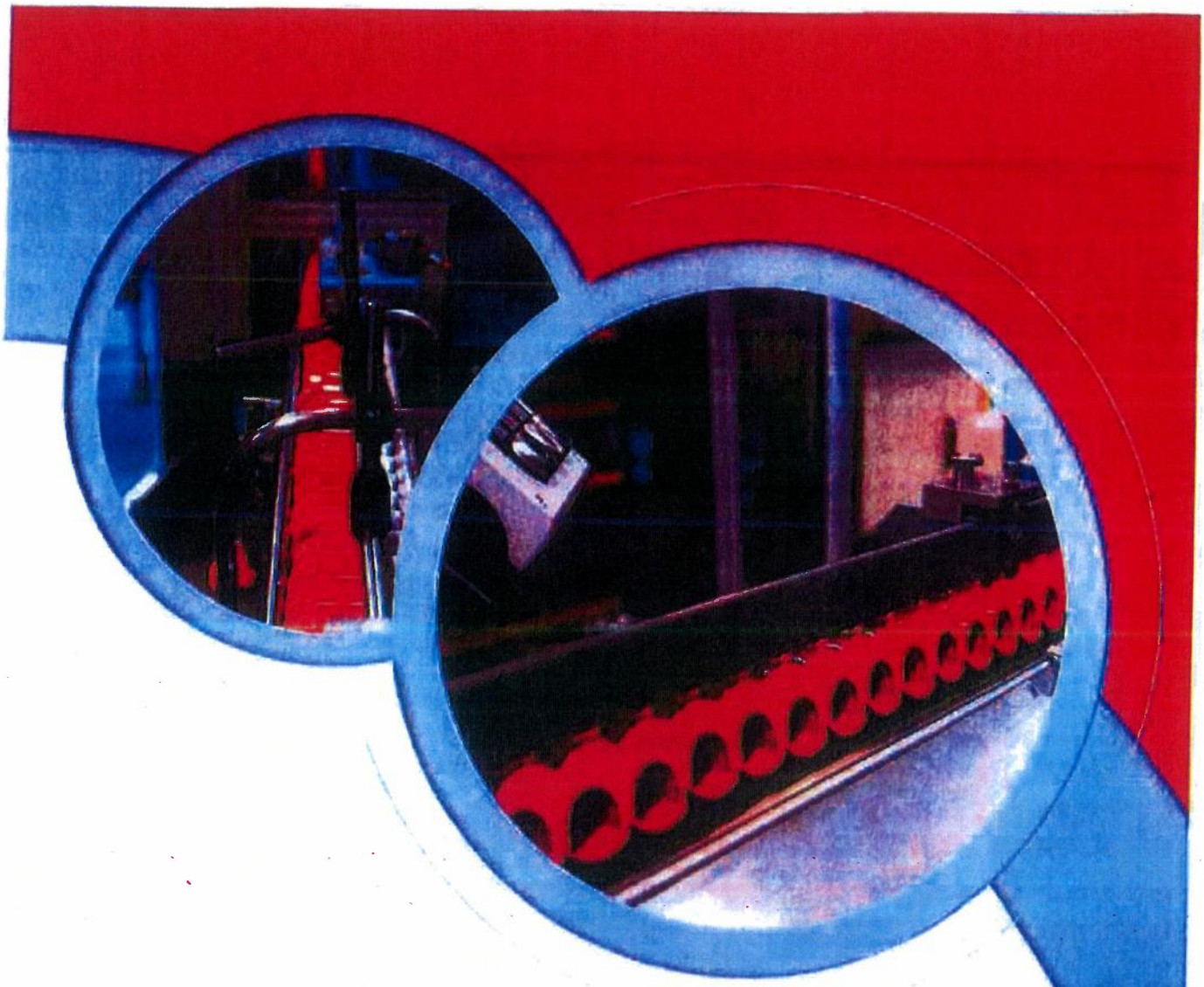
- 6 automatic packaging lines including 1 line with overwrap capacity
- 2 manual packaging lines US/Japan/ Standard
- Assembling machine dedicated to Dose Counter
- Heat stress capacity
- Electronic Batch Record
- Automatic vision checking system

Equipements / Technologies:

- Induction technology
- Laser or ink printer
- Check weighing, spray testing, labeling equipments
- Cartoner equipment
- Automatic check weighers
- Labellers
- Labeller case packer equipments
- Typical can size : 5 ml, 8 ml, 12.5 ml



AEROSOLS PRODUCTS



Packaging process

DPI PRODUCTS

Features

Rotadisks® and Diskus® specifications

Rotadisk® is an aluminium circular blister of 4 pockets. The associated device is the Diskhaler®, which is a multi-dose dry powder reusable device. At each use, the device pierces one pocket of the blister. The powder is released to be breathed by the patient.

Diskus® is a multi-dose dry powder disposable device. Inside this discoid shape device comprising of 14 plastic moulded components, the inhaled dry powder is sealed in an aluminium blister, which is inserted into the Diskus®.

Typically, there are 28 or 60 doses in the blister. A dose counter indicates the remaining doses. The Diskus® device peels the base foil and the lid foil. The individual drug product is then released to be breathed by the patient.

Rotadisk® key Features:

- The Rotadisk® is made of blister foil containing powder inside the 4 pockets.
- Reusable device with refill pack

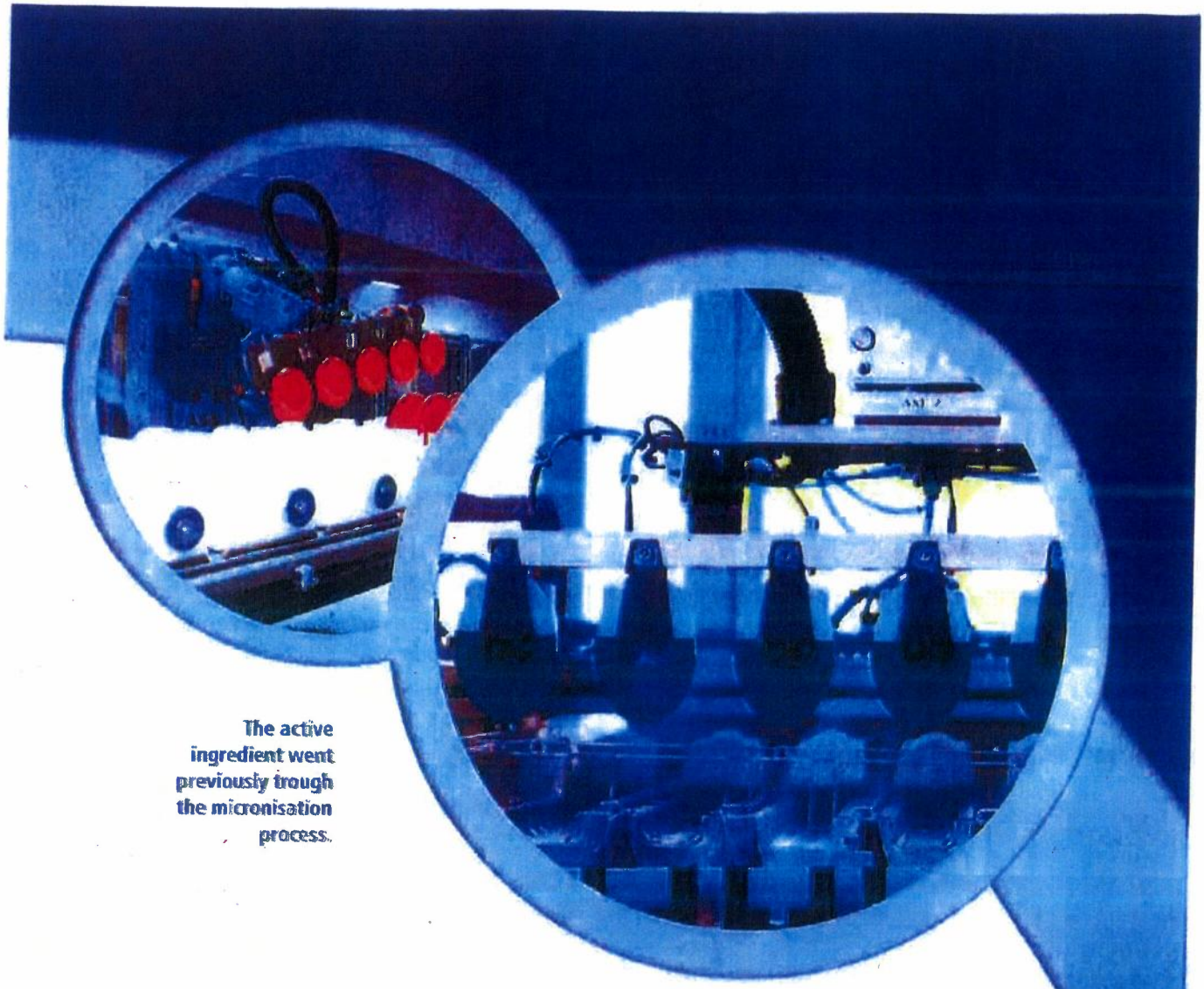
Diskus® key Features:

- The Diskus® contains an aluminium strip
- Dose counter, high technology assembly process

Commun main characteristics:

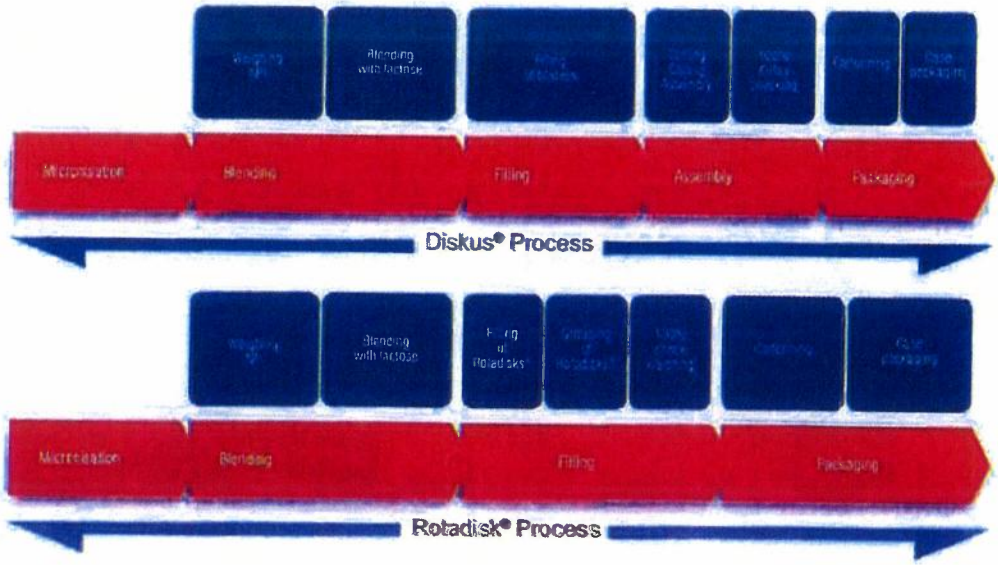
- Multi-dose device
- Easy & quick to use/learn/teach
- No coordination hand/breatlne required (user independent)
- Compact, easy to carry
- Easy to grip
- Low force to operate
- Robust
- Distinctive image
- Tamper resistant and evident
- Color distinctive per API
- Discreet and safe
- Filled with blend of lactose and active

DPI PRODUCTS



The active ingredient went previously trough the micronisation process.

Production process



DPI PRODUCTS

Blending & filling & packaging

Blending operation: Rotadisks® & Diskus®

Micronised API and excipient are blended together.

The blending step follows a very rigorous process : time, speed, temperature and humidity are strictly controlled. GSK has developed a specific know how to blend small quantity of API in a large amount of excipient (less than 1%).

Key Features:

- 6 blending areas
- Wastes treatment
- Electronic Batch Record
- Air environment control
- Dedicated pharmaceutical manufacturing facility

Equipments and Technologies:

- 4 low shear blenders:
  Speed: 250rpm / Energy: 18kW/m3
  Flat blad
- 2 high shear blenders:
  Speed: 470rpm - 600rpm
  Energy: 132kW/m3 / Double propeller
- 1 Sieve with batch size: from 12kg to 75kg
- Dedicated HVAC

Rotadisks® filling operation

The base foil is formed with pockets. Pockets are filled through a dosator with a very accurate low weigh of dry powder (typically 25mg). Each pockets are checked for the absence of powder by an automated vision system. The batch number and expiry date are embossed or printed on the lid foil.

Key Features:

- 5 filling lines
- Dosage accuracy: from 13 to 25 mg per pockets
- Packaging in plastic tubes or in carton of 5 to 15 disks
- 1 automatic high speed and accuracy checkweigher
- Cold formed blister technic
- Air environment control
- Electronic Batch Record
- Filling technic powder compaction

Equipments and Technologies:

- Filling lines with vision system
- Automatic tubing equipment
- Automatic high speed checkweigher
  2 mg (speed = 60 cpc)

- 100% checking vision system for powder absence and disk printing
- 100% laser detection for micro crack

DPI PRODUCTS

The diskhaler® is loaded with a blister by the patient. No assembly step is requested before packaging activity.

Rotadisks® packaging operation

The Rotadisks® are inserted by group of 5 into tubes or grouped with a leaflet in small cartons. These are packed in larger cartons with a Diskhaler® device and a patient information leaflet. If required by market, the tube is overwrapped and an outsert is applied to the back of the box. The batch number and expiry date are printed on carton boxes.

Key Features:

- 3 automatic packaging lines
- 1 semi-automated packaging line, for pandemic preparation

Equipments and Technologies:

- Automatic packaging lines
- Flowwrap equipments
- Hybrid flexible printing systems (electronic cliche)
- Tamper evidence system by sticking equipment or labeling equipment
- Labellers
- Cartonners
- Tubing equipments

DPI PRODUCTS

Filling & assembly & packaging

Diskus® filling operation

The base foil is formed with pockets into a double strip with the appropriate number of blister pockets. Pockets are filled, by immersion, with a accurate low weigh of inhaled dry powder (typically 13 mg).

The drug is sealed into an individual pocket with a lid foil. Traceability is ensured by printing key information on every strip.

Key Features:

- 6 filling areas
- Waste treatment
- Electronic Batch Record
- Air environment control
- Dedicated pharmaceutical manufacturing facility
- 100% checking vision system for powder failure
- 100% laser detection for micro crack

Equipments and Technologies:

- Typical filled weight : 13 mg
- 4 lines dedicated to 60 Doses
- 2 lines dedicated to 28 and 60 Doses
- Automatic checkweigher on each line

Diskus® assembly operation

Assembly step consists in inserting the strip inside the device. All the different steps are fully automated on specific manufacturing lines. The filled strips are fed into the unit and cut and coiled to the appropriate length.

The machine places the cut coiled strip into the device sub assembly. The assembly station assembles the top onto the body base. The mouth piece and the cover are then assembled onto the device. 23 critical quality parameters are checked on all devices through a X-Ray checking system. Devices which do not meet specifications are automatically rejected.

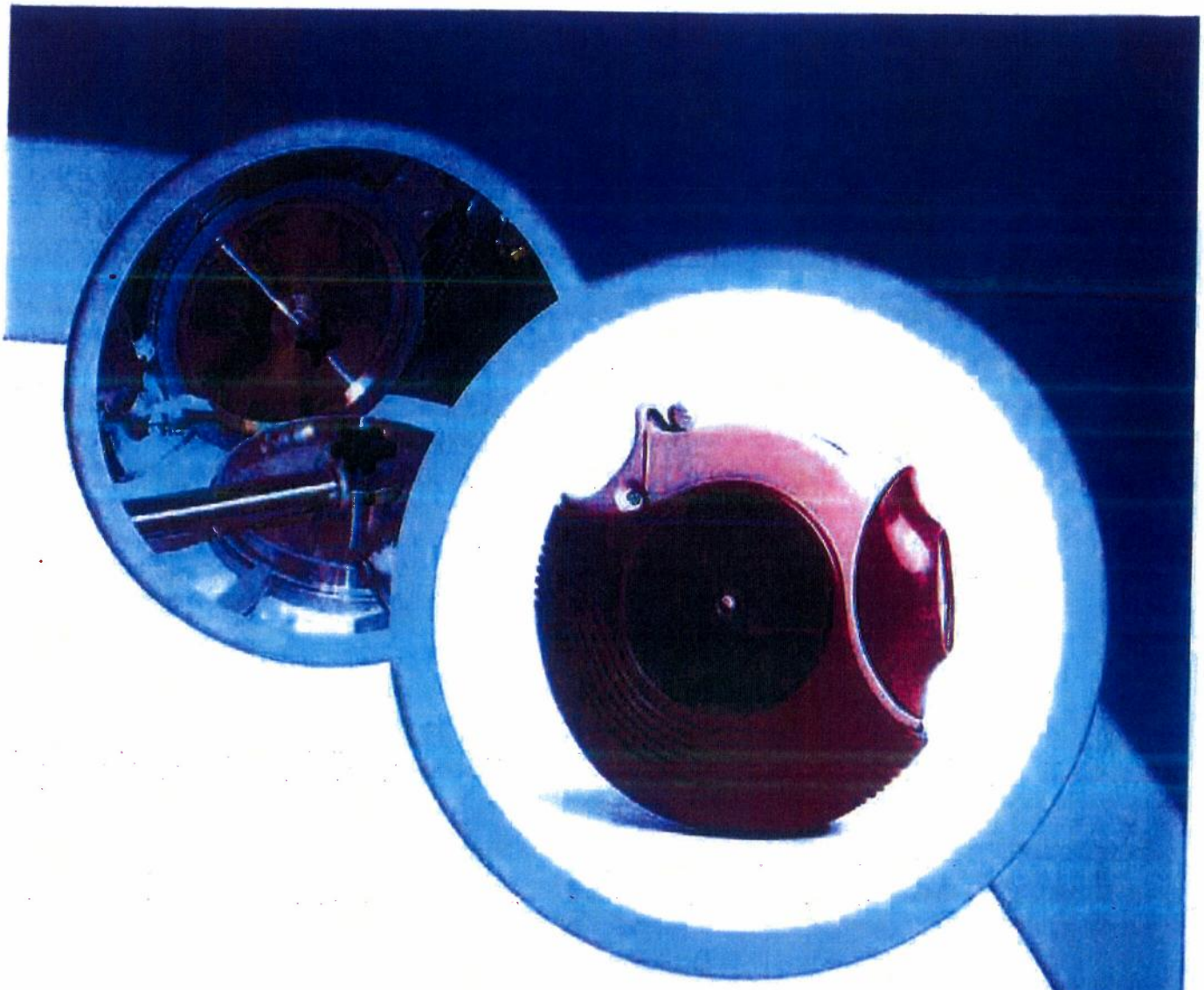
Key Features:

- 5 assembly lines (28 and 60 Doses)
- Automated X-Ray checking station (23 non destructive tests)
- 5 in process control indexing robots
- 4 palletizer automated lines
- Electronic Batch Record
- Waste treatment

Equipments and Technologies:

- Assembly lines in cells concept
- Rollcutting equipment

DPI PRODUCTS



Diskus® packaging operation

The product is finally packed according to customer requirements. The Diskus® device is labelled on its two sides with Commercial name, batch number and expiry date and then packed, with a leaflet into a carton.

Tamper proof labels are placed on the carton. In process controls are performed at each step of the packaging process.

Key Features:

- 5 packaging lines (including 2 for Japan)
- Pack of 1, 3 or 10 units
- Top loading packaging equipment
- 1 line equipped with overwrap equipment
- Electronic Batch Record

Equipments and Technologies:

- Tray unloader robot
- Labeller with data matrix control available
- Labeller
- Vision system
- Continuous process cartonner
- Packaging line
- Overwrap equipment
- Ultrasoning system for overwrap welding
- Laser printing
- Case packer
- Robot for pallet unloading

Development

pilot and industrialisation

Pilot and industrialisation

The pilot unit contains equipment, facilities and competencies for the development of inhaled drugs. It allows to carry out many different studies:

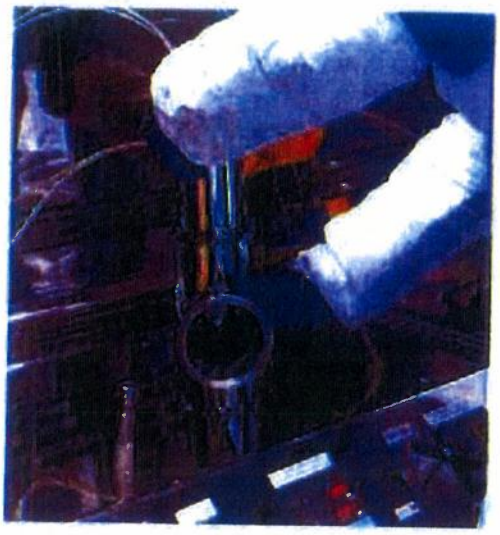
- small scale or exploratory batches
- formulation & process development
- clinical studies phase I to III
- commercial process development

Key Features:

- 500 m² of 9 GMS flexible and multi-purpose work zones
- Controlled environment (35/55% RH, < 15% RH) with a central weighing station, and a dedicated warehouse
- GMP qualified pilot plan, from lab development to large-scale.
- Mecanic grinder
- Microfluidiser (2 batch scales)
- Spray-dryer

Equipments and Technologies:

- 500m² + 2,200m² Technical Plant Area
- Manufacturing and Packaging from a few grams up to 30 kg
- Full GMP conditions for exploratory to clinical
- Micronization
- Blending: rotary blenders, planetary blenders, high shear mixers
- Coating: perforated pan, fluid bed dryer, spray dryer
- Capsule Filling: laboratory scale, pilot scale
- Automated Dose Delivery (ADD)
- Automatic Sample Recovery System (ASRS)
- Andersen Cascade Shake Fine (ACSF)
- Tomography
- Particle sizing by laser diffraction



DEVELOPMENT

An industrialisation knowledge to meet your business challenges

The Evreux site is fully dedicated to respiratory products. The site has developped a recognized knowlekdge and a specific know-how around respiratory business: process, components and devices, technology.

Respiratory high skills are covering:

- Process expertise with a dedicated team managing process, improvements, new product introduction and technical mastery.
- Device expertise with a dedicated team highly skilled in respiratory packaging components, devices and packaging.
- Equipment Expertise with a dedicated team in charge of maintenance, improvement of current equipments and introduction new technology.
- Qualification and validation team experienced in Pharmaceutical national and international references and guidelines.
- Regulatory registration expertise who can support registration of product from full filing to post approval changes.

Key Features:

- **Changes introduction, with an impact on existing products:**
  - **Primary (API)**
  - **Manufacturing process and new technologies**
- **Process improvement implementation**
- **Support to technical investigation**
- **Development of primary and secondary components**
- **Development and implementation of devices and packaging components**
- **Management of packaging components changes (specifications, suppliers' equipment,...)**
- **Management of data related to technical specifications of packaging components**
- **Knowledge Management**

Equipments and Technologies:

- Tomography
- Automatic data collection system on equipment
- High speed camera
- Statistical softwares
- Lean sigma tools
- Product data base

Development

pilot and industrialisation

Expertise in Tomography

2D X-ray image

Section issued from 3D volume

X. Ray Technology: Understanding the science

We identify all the quality critical parameters and design the optimum manufacturing processes and control these parameters. Working this way will allow us to launch products more quickly, operate our processes more effectively, with higher yields, fewer batch refusal and ultimately, lower cost of goods.

The X.Ray objectives

- X-ray technologies can provide relevant and detailed information about our products in a way to:
- Improve our control and measurement on components and product at reception or during manufacturing process.
- Reduce the investigation time (ap. 30%) and the potential re-test in QC labs.
- Validate process component.
- Support new product development.

DEVELOPMENT

GSK EVREUX