
CPME
克雷格工程技术（北京）有限公司
CPME CHINA
Bonfiglioli
Engineering

THE COMPANY 公司简介

- Since it was founded in **F**errara ITALY 1974, Bonfiglioli **E**ngineering has continuously invested, innovated and evolved, becoming a Global Leader in CCIT
  1974年成立于意大利费拉拉，BE不断投入，创新并进化成为包装密封完整性检测（CCIT）的世界领军企业。

- Bonfiglioli Engineering provides its clients with solutions customized to their product and needs, giving us an edge over the competition.
  BE为客户的产品和需求提供定制化的解决方案并赢得市场竞争。

50 Years of Experience
50年检测技术和设备行业经验

We Export 90% Of Production
出口产品占90%

70% Of Machines Destined to Pharma
70%的设备用于制药行业

€ 25 + Mln Turnover
年营业额2500万欧元

100 Employees
员工约100人

BONFIGLIOLI ENGINEERING 公司简介

- More Than 5000 Machines Worldwide
  全球销售5000多台设备
- Over A Decade Of Experience In Combin of CCIT, HGA & VI
  密封完整性，激光顶空分析和视觉检查组合设备10余年经验
- Expansive Pharma Portfolio, From Vials To IV Bags
  不断扩充制药产品系列，从西林瓶到输液袋
- Evolving Expertise And Continuing Innovation
  专业进化和持续创新
- Innovation Is Our Driving Force
  以创新为驱动力

Your Challenge
Our Solution
Your Success

COMPANY HISTORY 历史沿革

1974
Company Foundation with first ingenious leak testing machine for plastic containers.

1985
Bonfiglioli begins producing package integrity equipment for the cans and aerosol market.

1988
Bonfiglioli, engineered and manufactured its first patented pharmaceutical package testing in-line rotary equipment.

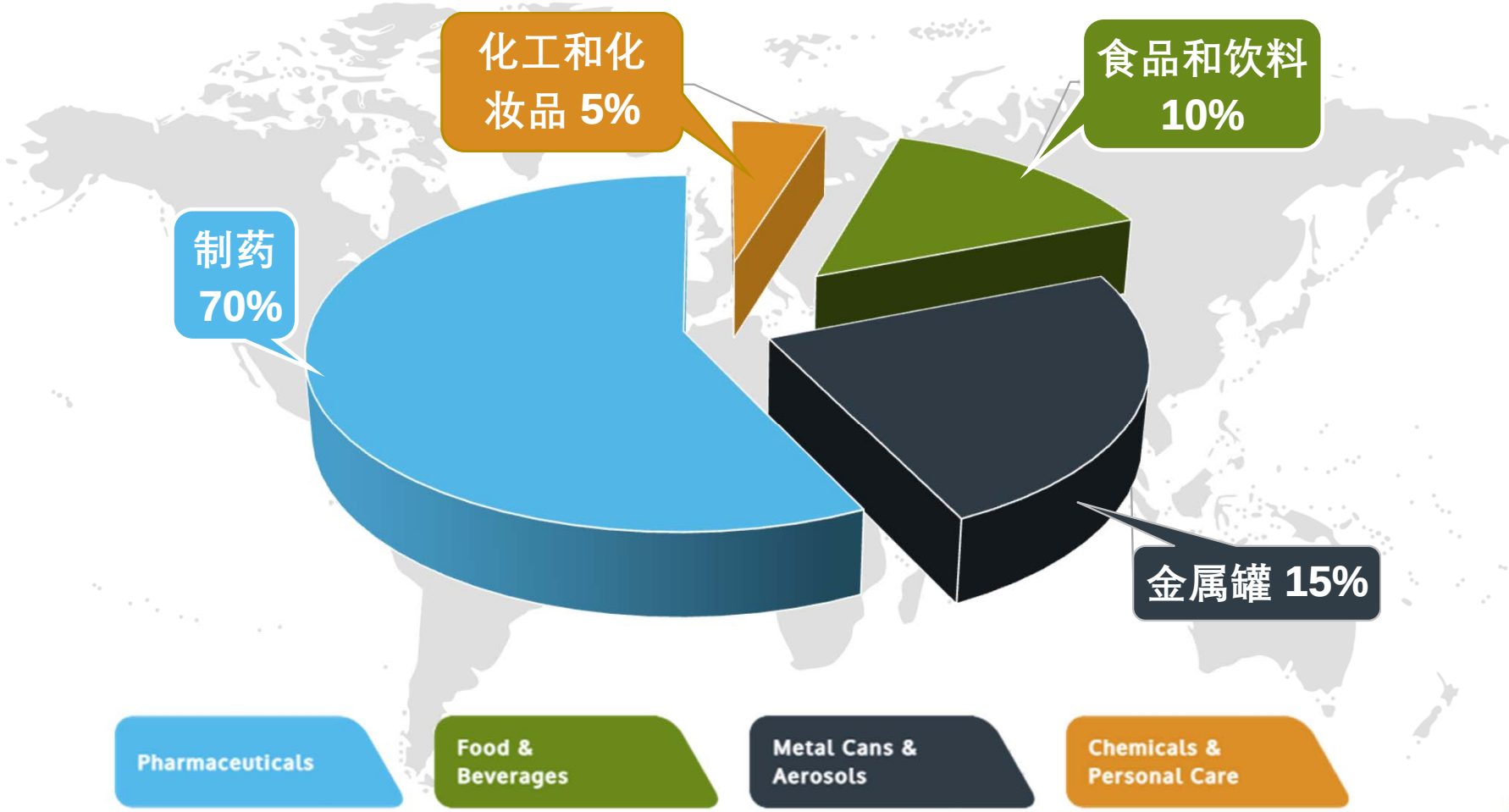
2012
Acquisition by Tasi Group

2013
Innovation into Visual Inspection Technology with the launch of PK-VIS in-line rotary series.

2014
Breakthrough in all-in-one solutions combining Headspace Gas Analysis with Vacuum Decay Method.

2019
New premise and manufacturing area (11,000 sq. meters) with optimized lean approach.

SALES DISTRIBUTION 市场应用



TECHNOLOGIES 技术

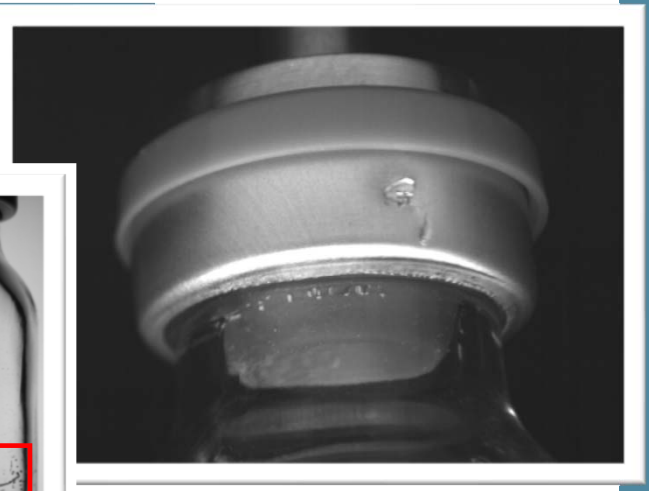
Leak Detection/CCIT 泄漏检查/CCIT

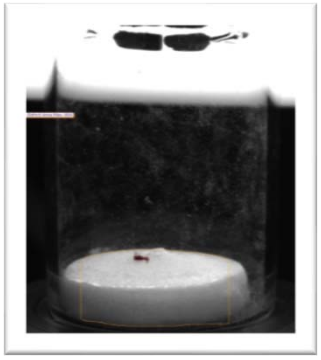
- Recognized in USP 1207 USP 1207 认可
- Customized for each product 定制化设备
- Vacuum Decay mode F2338-09 真空衰减测试方法遵循 F2338-09
- Pressure Decay mode E2390-13 压力衰减测试方法遵循 E2309-13
- Extensive machine portfolio 产品系列众多
- Unique innovations such as lid displacement or dual testing cycle 独特创新例如软盖位移检测和双测试系统
- Feasibility test for special products 特殊产品的可行性研究
- Scalable LAB application 可放大的实验室应用

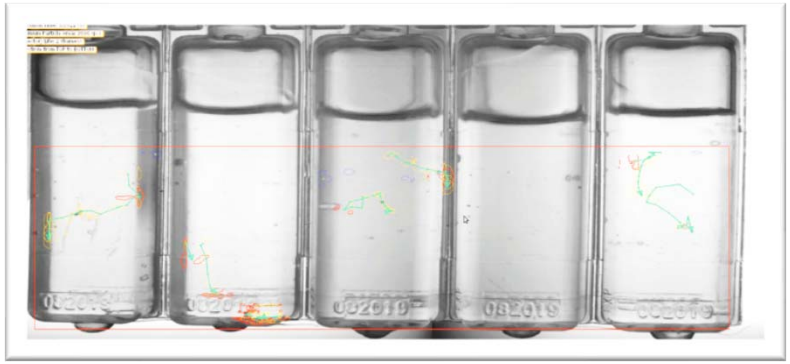
TECHNOLOGIES 技术

Visual Inspection AVI 视觉检测

- Recognized in USP-790 / USP-1790 USP-790/USP-1790认可
- Customized for each product 定制化设备
- Performed via camera acquisition 基于摄像及图像分析技术
- Multiple inspections can be done simultaneously 可同时多项检测
- Possible design for inspect both lyo & liquid in the same mc可能使用同一台设备检测冻干和液体产品
- KNAPP test Validation Approach KNAPP验证方法



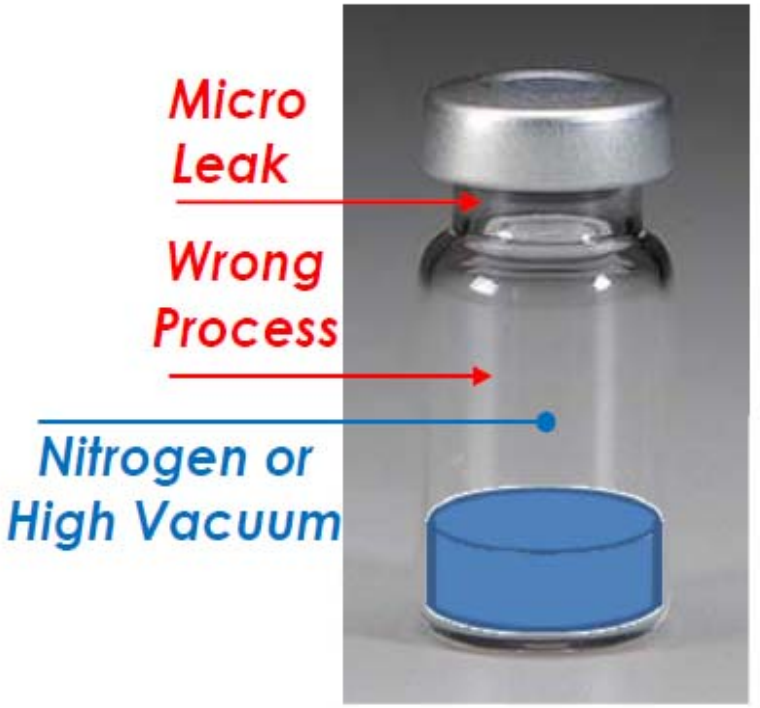




TECHNOLOGIES技术

Head Space Gas Analysis (TDLAS) 顶空分析法

- Recognized in USP 1207 as CCIT (in special conditions)
  USP1207认可，在一些特殊情况下作为CCIT方法
- Process control for 100% safe parenteral devices
  100%安全的注射剂过程控制设备
- Based in Oxigen or Moisture absorption
  基于氧气或水气光谱吸收技术
- No Nitrogen purging required
  无需氮气吹扫
- Applicable for not completely transparent products
  适用于半透明产品



PRODUCT PORTFOLIO 产品系列

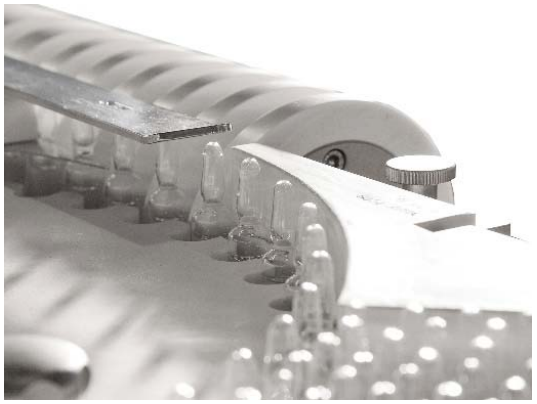
LAB CCIT

LAB HGA

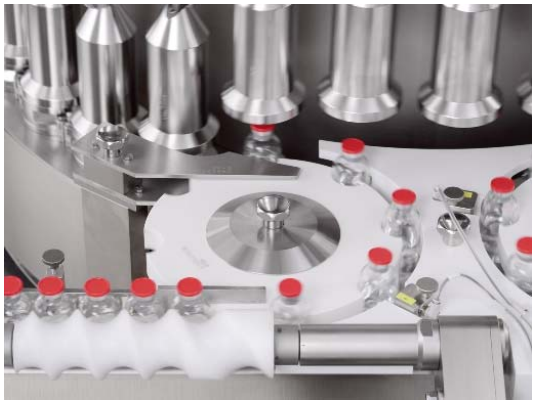
IN-LINE / OFF-LINE
CCIT, HGA, VI

IN PROCESS
CONTROL

COMBINED SOLUTIONS CCIT/HGA/VI





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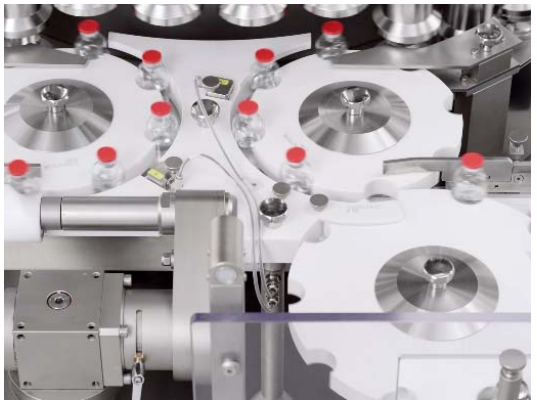


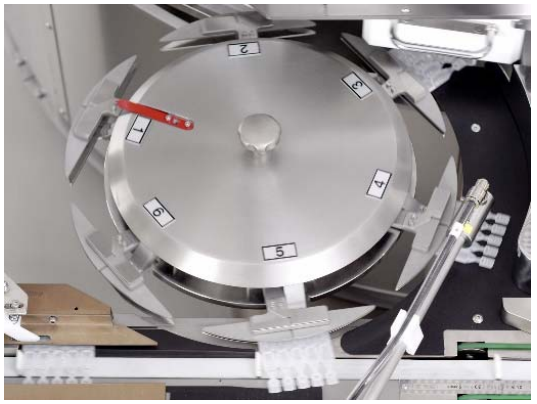
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HEADSPACE GAS ANALYSIS
顶空分析法

Directory 主题

Background技术背景

- Sterile drugs无菌药物:
  - Oxygen sensitive liquid products 氧敏感液体产品
  - Lyophilized or powdered products 冻干或粉剂
- Any modification in headspace pressure, moisture or O_2 level may result in
  顶空中的湿度，氧气水平的改变会导致:
  - Degradation of the active drug 活性成分降解
  - Reduction of drug potency药效降低
  - Decrease in product shelf life 货架期缩短
  - …

Regulatory Overview 法规要求

Specific requirements for sterile drugs packaged under full or partial vacuum are covered by EU GMP Annex 1 欧盟GMP 附件1中对采用全真空或部分真空包装的无菌药品的特别要求:

- § 123 – “Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period”
  真空封装的产品需要在一个合适的，预定的期限内检测真空度的保持性。

- New regulations are expected to enter into force including measures to demonstrate the micro biological integrity over time
  新的法规会增加限定包括显示产品包装随时间无菌完整性保持水平的方法。

- USP <1207> Sterile Product Package Integrity Evaluation, Proposed Rev
  无菌药品包装完整性评估，建议版:
  - $ 10 Leak Test Selection Criteria: “*Headspace gas or pressure must be preserved ensuring product sterility and stability*”
    检漏方法选择标准 推荐：顶空气体或者压力必须保持以维持产品的无菌性和稳定性。

Regulatory Overview 法规要求

国家药品监督管理局
National Medical Products Administration

药品生产质量管理规范（2010 年修订） 无菌药品附录

第七十七条 无菌药品包装容器的密封性应当经过验证，避免产品遭受污染。熔封的产品（如玻璃安瓿或塑料安瓿）应当作 100% 的检漏试验，其他包装容器的密封性应当根据操作规程进行抽样检查。

第七十八条 在抽真空状态下密封的产品包装容器，应当在预先确定的适当时间后，检查其真空度。

第七十九条 应当逐一对无菌药品的外部污染或其他缺陷进行检查。如采用灯检法，应当在符合要求的条件下进行检查，灯检人员连续灯检时间不宜过长。应当定期检查灯检人员的视力。如果采用其他检查方法，该方法应当经过验证，定期检查设备的性能并记录。

Regulatory Overview 法规要求

USP 41 <1207.2> PACKAGE INTEGRITY LEAK TEST TECHNOLOGIES

2.2 Laser-Based Gas Headspace

Rigid or flexible packages made of nonporous components (transparent or semi-transparent material, either amber or color-less) that allow transmission of near-IR diode laser light may be tested....Test samples that may be analyzed fall into these categories:

- *Products that require low-oxygen or low-carbon-dioxide headspace content*
  需要低氧或低二氧化碳顶空含量的产品
- *Products that require low water vapor content (e.g., lyophilized or powdered products)*
  需要低水蒸气含量的产品（例如冻干或粉状产品）
- *Products that require low internal package pressure (e.g., lyophilized products)*
  内部包装压力低的产品（例如冻干产品）

9650 无菌药品包装系统密封性指导原则（公示版）

附3 激光顶空分析试验法

本方法可实现离线或在线检测，适用于允许透射激光且具有一定顶空高度的包装系统密封完整性检测。例如：

（1）需要低氧或低二氧化碳顶空环境的产品

（2）需要低水蒸气顶空环境的产品（例如，冻干或粉状产品）

（3）需要低内部包装压力的产品（例如，真空封装的冻干产品）

Headspace Gas Analysis “HGA” 顶空气体分析

- 100% In-Line and Off-line Laser-Based Non destructive measurement of oxygen level, residual moisture content and absolute pressure
  基于TDLAS激光技术对氧气含量，残余水分含量和绝对压力进行100% 在线或离线无损检测的方法。
- Applications 应用的产品包装:
  - Glass Packages (tubing, molded, clear, amber)
    玻璃材料包装（管制瓶，模制瓶，透明，深色）
  - Plastic Packages optically non transparent to a NIR laser radiation
    对近红外激光辐射光学不透明的塑料材质包装
  - Sterile products as O_2 sensitive / Lyo under modified atmosphere or vacuum
    包装内充氮的氧敏感产品/或真空或气调的包装的冻干产品。
- Target: to confirm sterility and stability in filled and finished packages
  目的: 确认灌装后的产品包装的无菌稳定性:
  - Verification of Container Closure Integrity
    验证包装容器密闭完整性
  - Monitoring the sterile manufacturing process (filling + stoppering)
    监测无菌生产工艺 （灌装+加塞）

1. Oxygen Level Analysis 氧含量分析

- Oxygen-sensitive products 氧敏感产品
- The exposure of such products to oxygen may determine此类产品暴露于氧气可能导致:
  - Drug potency decrease 药效降低
  - Shelf life reduction 货架期缩短
  - Chemical degradation 化学成分降解
  - Photo-degradation 光降解
  - Toxicity 产生毒性
  - Negative side effects 其它负面效果

2. Moisture Level Analysis 水份分析

- Lyophilized products 冻干产品
- Measure the vacuum level in the headspace测量顶空的真空度:
  - A loss of vacuum indicates a leak in the Package真空度降低说明产品包装有泄漏
- Traditional inspection methods: time consuming / destructive传统检测方法：耗时/破坏性
  - Sample Inspection 样品检测
  - Disposal of destroyed product 破坏样品处理
  - No timely feedback on filling process 对灌装工艺没有实时反馈

Why Laser-Based Headspace Inspection?

- Need for non destructive and reliable automated analysis

  非破坏性，可靠且自动执行的分析方法需要:

  - Inspecting all Packages in a reference batch 按批次对所有产品进行检测
  - Quickly determining the target headspace gas level 快速确定顶空气体的目标限度

will show if the issue is可以发现:

I. Systematic process unwanted deviation 系统工艺的非期望偏差

II. Random Package closure integrity failure随机发生的产品包装的密闭完整性失效

Prevent Possible Failures e.g. 防止可能的失效:

1. Lyophilized product冻干产品:

- Targeted to be maintained under a vacuum of 50 mbar
  设定目标顶空维持压力低于50mbar
- Headspace Moisture analysis measures 200 mbar
  顶空水份分析实测压力200mbar
- What has occurred原因:
  - The Package has been stoppered at incorrect pressure
    产品加塞时的压力不正确
  - The Package has leaked
    产品包装有泄漏

2. O_2 Sensitive product氧敏感产品:

- Targeted to be maintained under 2% headspace oxygen
  目标顶空氧气浓度设定维持低于2%
- Headspace Oxygen analysis measures 5%
  顶空氧分析测得浓度为5%
- What has occurred原因:
  - The Package has been improperly purged (with N2)
    产品未正确充氮
  - The Package has leaked (some amount of oxygen is entered)
    产品包装泄漏（氧气进入）

Directory 主题

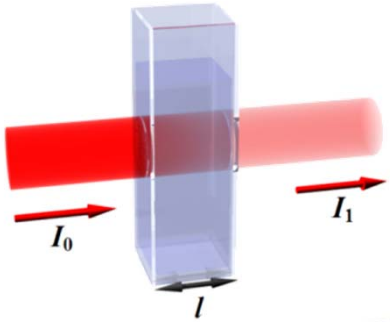
Technology 技术说明

Tunable Diode Laser Absorption Spectroscopy调谐二极管激光吸收光谱（TDLAS）：

- ✓ Laser Beams are passed through headspace region of the container
  激光束穿过容器顶部区域
- ✓ Absorption of energy by the gas molecules at one specific wavelength λ
  特定气体分子吸收特定波长的光的能量
  - Oxygen level氧气: λ = 760 nm
  - Residual Moisture Level残余水气: λ = 1854 nm

Absorption $A = \log_{10}(I_0/I_1)$

- ✓ If λ matches the vibrational frequency of target gas molecule, energy is absorbed
  如果波长与气体分子振动频率一致，能量被吸收。
- ✓ Beam intensity is reduced according to the Lambert – Beer law
  光强度减弱遵循比尔-兰伯定律



Modulation Technique 调制光谱技术

- Wavelength Modulation Spectroscopy (WMS)波长调制光谱技术:
  - Improved sensitivity and noise-rejection capabilities over direct absorption
    提高吸收信号的精度和抑制噪声的能力
  - No need for extremely fast detection electronics, as required by Frequency Modulation Spectroscopy (FMS) 使用频率调制光谱，不需要高速探测电子元件
  - Non-Invasive 非侵入检测
  - Compatible with all glass types 适用于所有玻璃类型

- System Worldwide Patent 国际专利:
  - 专利号 WO 001633

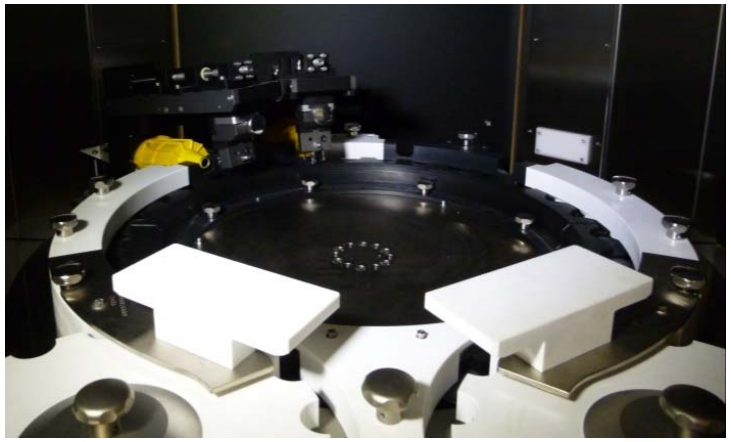
Bonfiglioli™ Engineering

Directory

CPME

Portfolio产品系列

- HGA Laser Systems顶空激光系统:
  a) Oxygen Level Analysis 氧气含量分析
  b) Moisture Level Analysis 水气含量分析
- Our Systems offer a wide range of flexible solutions to suit 设备提供灵活的解决方案提高:
  - Performances 性能
  - Resolution and accuracy精度和准确度
  - Usage 使用便利性
  - Every environment and requirement 各种环境和需求



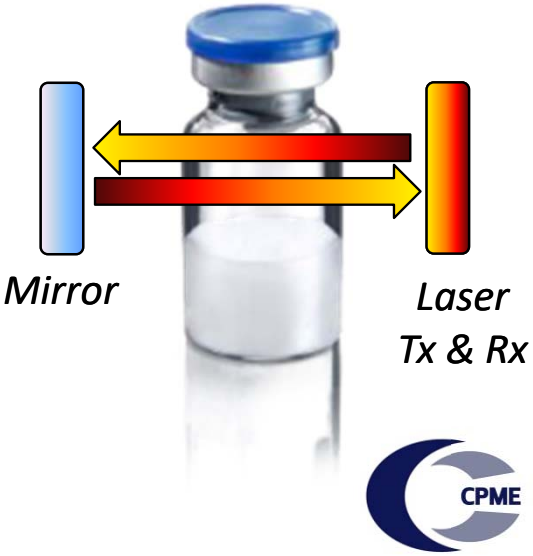
HGA: Product Range 顶空分析设备范围

Equipment设备	Details介绍
Lab-Scale 实验室级 **100% Off-line 离线设备** **100% In-line 在线设备** **Combined HGA 组合机** **Combined Technologies** 技术组合机 **Headspace Generator** 顶空标准品制作设备	

Directory 主题

Strong Points of our System (1) 优势

1. O_2 Level Analysis: Nitrogen Purging not require
   氧气含量分析无需氮气吹扫
   - 4th generation laser` unit used. Oxygen does not interfere with the measurement
     使用第4代激光检测单元，容器外环境氧气不影响测量
   - Accuracy and robustness without the need for purging the Package surroundings
     足够高的精度和可靠性，无需氮气吹扫。
2. Single PathVS Double Path System
   单路径对比双路径
   - As the 4th generation laser` unit being used. Double path system no longer used.
     由于使用第4代激光检测单元，双路径系统不再需要
   - Increase accuracy and decrease test time.
     提高精度，缩短测试时间



Strong Points of our System (2) 优势

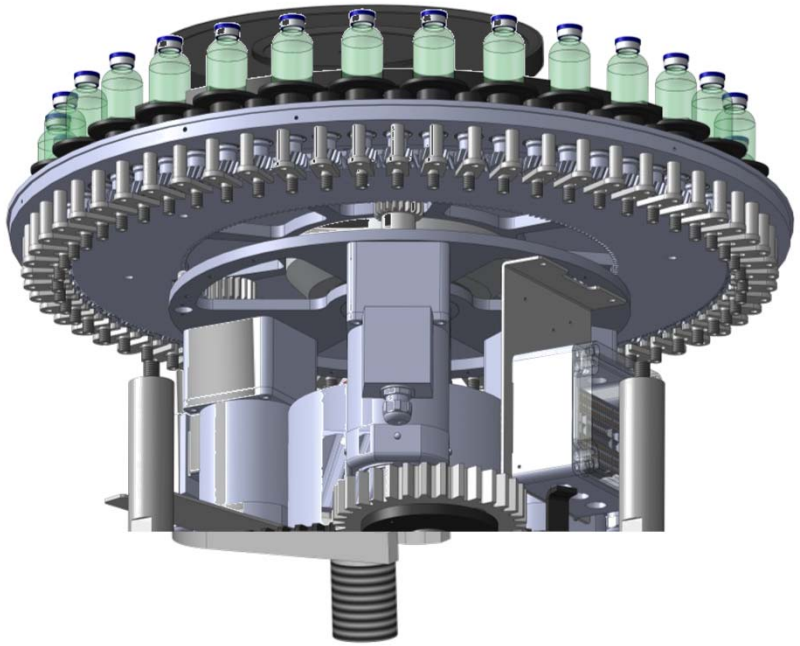
3. Standard Container(s) not required
无需标准样品

- In LH Headspace Gas Analysis System HGA 系统:
  - ✓ Height & width of laser absorption signal are measured and compared to preset values (Standard Container) during each cycle
    在每个测试循环中测量激光吸收信号的特征并与预存的（标准品）值进行比较
  - ✓ If the measured parameters are not within acceptable ranges, an “out of Calibration” failure occurs
    如果测量的参数不在接受范围内，给出“校准失效”的故障报警

Strong Points of our System (3) 优势

4. Etalon Effect is made negligible
   Etalon效应可以忽略不计

   - Etalon effect is a major source of signal distortion
     Etalon效应是信号失真的主要来源
   - Laser beam through molded glass introduces distortion
     激光束通过模制瓶产生信号失真
   - Old type: Package is spun during inspection (360° along its vertical axis)
     旧机型：检测时360°旋转产品消除Etalon效应
   - New Type：Multiple Laser beam.No need rotation.
     多束激光检测，产品无需旋转。



Strong Points of our System (4) 优势

5. Inspection of non-transparent containers
可检测非透明容器

- A different set-up is required: Laser beam power must be higher than HGA inspections of glass packages
需要不同的配置：激光功率比玻璃容器检测更高
- Other potential packages: IV Bags, BFS, plastic Vials and Bottles
可测试包装：输液袋，BFS，塑料瓶

6. No warm-up time

- No warm-up time needed for the 4th generation laser unit.
第四代激光检测设备开机测试前无需通过试测产品来进行预热。

Old type 旧型号:
- **Inspection time = 400ms**
- **Warm-up time = ~ 3 min**

Old type 新型号:
- **Inspection time = 20ms**
- **Warm-up time = 0**

Bonfiglioli™ Engineering

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