Bronkhorst®

布琅轲锶特

制药行业低流量流体处理解决方案

29-03-2018 | China

Bronkhorst® SHANGHAI

Bronkhorst® HONG KONG

PharmaTEC 制药业

38 years

experience - innovation - responsibility

Bronkhorst®

Performance for Life

PharmaTEC 制药业

Headlines of Bronkhorst®

- Thought leader in micro to low flow fluidics handling technology.

  微、小流量流体处理技术专家

- Headquarters located in Ruurlo, the Netherlands
- Market leader in Europe, Top 5 worldwide
- 24/7 world wide support：+31 859 02 1866； China hotline: 400 110 7259
- 超过24个全球服务中心提供本地化服务：全球60%以上的服务是本地化进行，中国更达到90%以上。

  More than 24 satisfied Global Service Office for local Customer service. 60% of total global customer service is done locally, for China is higher to above 85%.

- ISO 17025:2005国际标准的检测和校验中心

  全球唯一：热质式和科氏质量流量计都达到检测和校准实验室能力

  Bronkhorst Calibration Center, ISO 17025:2005 for both Thermal Mass Flow and Coriolis Mass Flow.

- Above 20% of employees active in R&D and Engineering

Pharma-TEC 制药业

Bronkhorst Service China

- 本地化经验丰富的服务团队专门服务于中国客户
  Experienced Service team in China to serve our customers in China
- 设施齐全的全球服务中心，提供全天候的本地化服务
  Fully equipped Global Service Office, fast local service
- 10000级洁净室 Class 10.000 cleanroom
  100级流量测试台 Class 100 flow benches
- 全球统一标准技术培训，全球统一的服务标准
  Well-educated, multilingual technicians, same level service standard worldwide

CERTIFICATE

Bronkhorst Global Service Office

Certificate no: GSO207-2018-A

awarded to

Bronkhorst (Shanghai) Instrumentation Trading Co., Ltd

No. 99, Tianzhou Road, 200233, Shanghai, Peoples Republic of China

Bronkhorst (Shanghai) Instrumentation Trading Co., Ltd is entitled by Bronkhorst® for general customer **support** and **local repair** and **calibration** of the following series:

EL-FLOW | LOW-ΔP-FLOW | IN-FLOW | FLOW-SMS | VAPOUR

COMBI-FLOW | Production | Clean Room | CORIOLIS

This certification guarantees best quality and has been proven against Bronkhorst® standard procedures (summary: QA-S-001).
This certificate is issued on 3rd January 2018
and
is valid until 31st December 2018 and endorsed by:

G.J. Gossink
Customer Service Manager

Bronkhorst® GSO
GLOBAL SERVICE OFFICE

P. van der Hall
Sales Management

Bronkhorst Global Service Office Shanghai

PharmaTEC 制药业

Bronkhorst Service China

- 全天候快速服务响应 Fast response on Support and Service
- 协助调试及试运行服务 Start-up service
- 定期性检验及校准服务 Periodical inspection/calibration service
- 产品及服务培训 Product and service training
- 全球服务热线 WORLDWIDE SUPPORT LINE： +31(0)859 02 1866
- 中国本地化销售服务热线CHINA LOCAL HOTLINE: 400 110 7259

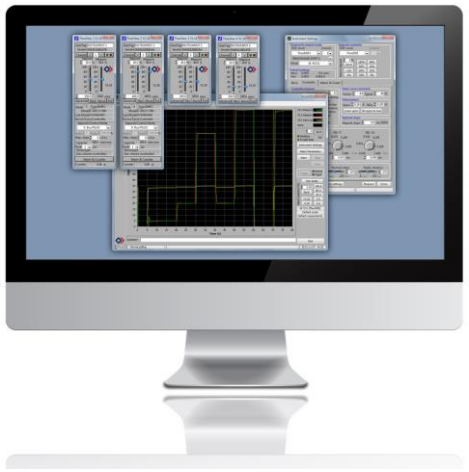
Bronkhorst Products

Bronkhorst®

Thought leader in micro to low flow fluidics handling technology

Expertise in MASS FLOW and PRESSURE meters and controllers

微、小流量流体处理技术专家，专业提供质量流量及压力测量与控制产品方案



Pharma·TEC 制药业

EL-FLOW Prestige

The Latest

Bronkhorst®

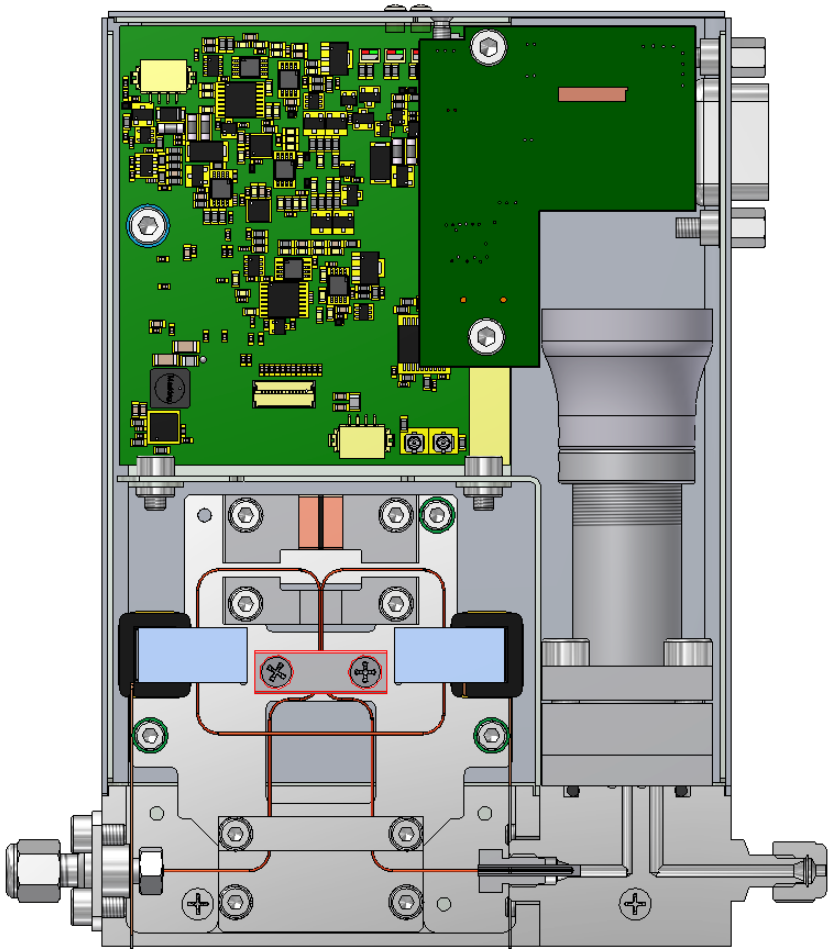
- **Extremely accurate and stable**
  Improved linearity, improved gas conversion, active temperature compensation
- **Adaptable to the customer's process**
  Embedded intelligence, flexible I/O options
- **Cost reduction**
  Reduced stock due to (expanded) MFMR, longer life time
- **Increased yield**
  Outstanding behavior/performance
- 25 available (selectable) gases + mixtures up to 5 components via FlowTune software
- Fluid capacity rangeable between 40% and 120% of nominal capacity (1:150 rangeability)

Pharma-TEC
制药业

The Latest

Bronkhorst®

- **Low internal volume**
  - Construction
  - Piezo valve压电阀
- **Excellent long term stability**
- **Excellent repeatability**
- **世界上最小的（超）低流量科里奥利流量计、控制器**
  WORLD'S SMALLEST (Ultra)LOW FLOW CORIOLIS INSTRUMENTS



PharmaTEC 制药业

ES-FLOW™

Revolutionary Ultrasonic Flow Meter

- Innovative non-intrusive flow measurement technology
- Designed to measure low flow rates: 4…1500 ml/min
- Liquid independent (actual speed of sound is measured)
- Hygienic design
- Integrated PID controller
- Low pressure drop
- CIP cleanable
- Straight sensor tube with zero dead volume
  - ID = 1.3 mm
  - Length = 11 cm
  - Surface roughness = < 0.8µm
- Ability to measure temperature

Five Key Features of the ES-FLOW

- One sensor for multiple liquids
- Hygienic design
- Vibration insensitive
- Integrated PID controller and fast response
- Installation in any direction and user friendly, ‘plug-and play’ device

PharmaTEC 制药业

Markets & Applications

Miscellaneous

- Automotive
- Aerospace
- Defence
- Pulp & Paper

Stability in pharmaceutical process 制药过程稳定性问题解决方案

需求：优化药物中生物活性成分API的新型生产线。
这条新型生产线非常独特，前所未有，未来可能成为业内引领。

关键点：该生产线要实现对不同成份含量的甚至含有固体颗粒的反应混合物进行精准、平稳地给料。这家医疗保健公司的研发人员开始用配备一台隔膜泵的小型装置进行各种化合物的配料试验。然而，这种装置既不能实现所期望的高流速，隔膜泵产生的高脉动还导致工艺流程中的严重问题。此外，没有流量控制-仅有流量测量-导致给配料非常不准确。

Bronkhorst作为低流量流体处理专家受邀加入该项目开发。

案例：一家欧洲领先的医疗保健公司

Stability in pharmaceutical process制药过程稳定性问题解决方案

Bronkhorst's mini CORI-FLOW M15 Coriolis Mass Flow Meter in combination with LEWA's PID-controlled LDB3 three head pump.

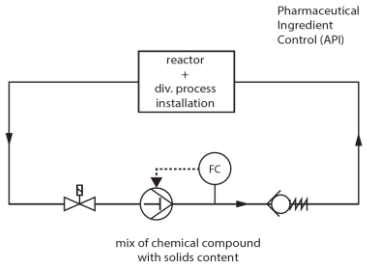
应用需求: 由于是创新型生产线，精准配料对药物品质至关重要，工艺过程的重复性和稳定性成为关键的要求。还必须同时满足所需要的高流速和高度精准的配料。为此，既要能改变加药剂量，又必须对加药过程进行良好的控制。同时，不能破坏生产线重要环节-化学反应过程，加药设备不能产生太多的脉动。

重点:

- 加药过程的稳定和更好的监控
- 精准给料（加药）
- 降低加药物质的成本
- 提高工艺过程灵活性

案例：一家欧洲领先的医疗保健公司

Stability in pharmaceutical process制药过程稳定性问题解决方案



Bronkhorst's mini CORI-FLOW M15 Coriolis Mass Flow Meter in combination with LEWA's PID-controlled LDB3 three head pump.

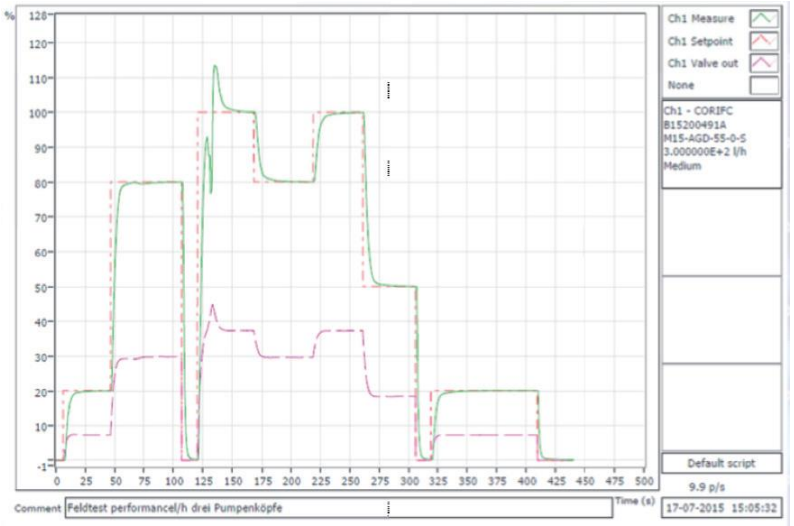
工艺解决方案: 结合里瓦LEWA PID控制的LDB3 三头隔膜泵与Bronkhorst mini CORI-FLOW M15 质量流量计。 mini CORI-FLOW 配备PID控制键盘，直接实现泵的控制。三个泵头受流量计控制，一起平稳工作，实现最佳的剂量加药，脉动大大减小，流量精准而稳定。

降低药物化合物的消耗就会降低成本。工艺流体及其原料极其昂贵，处理过程中所涉及的化学反应也至关重要，准确计量和更好地监控所使用的配料药物成份对生产成本产生非常积极的影响。

由于该医疗保健公司希望生产广泛的活性药物成分，目前配置的三个泵头控制设备方案，其灵活性足以满足此要求。

案例：一家欧洲领先的医疗保健公司

远程监控与数据记录留档: 这种泵和mini CORI-FLOW 结合的装置可以在医疗保健公司内其它电脑系统，通过软件工具进行远程控制和监测。此外，控制过程中的所有参数、测量数据均可记录并存档。



Field test performance of the setup with three pump heads

Configuration settings of the mini CORI-FLOW M15

案例：一家欧洲领先的医疗保健公司

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具体需求:

- 通过流量控制在1分钟之内实现混合配比，若流量跨度太大的话，流量要求大的场合可以考虑降低流速来减少流量计的数量（5分钟以内），总的累积误差控制在0.5ml以内即可。
- 若一组无法实现的话，最多考虑2组。
- 常温，压力2bar以下，不需防爆，要求耐轻微腐蚀---316L不锈钢可以，脉冲或者模拟输出均可。
- 若有显示功能可以推荐。

配比批次	异丙醇累计	去离子水累计	Qz3289累计	总累计量	总累计误差要求
1	85.5ml	4.5ml	10ml	100ml	+-0.5ml
2	256.5ml	13.5ml	30ml	300ml	+-0.5ml
3	427.5ml	22.5ml	50ml	500ml	+-0.5ml
4	855ml	45ml	100ml	1000ml	+-0.5ml

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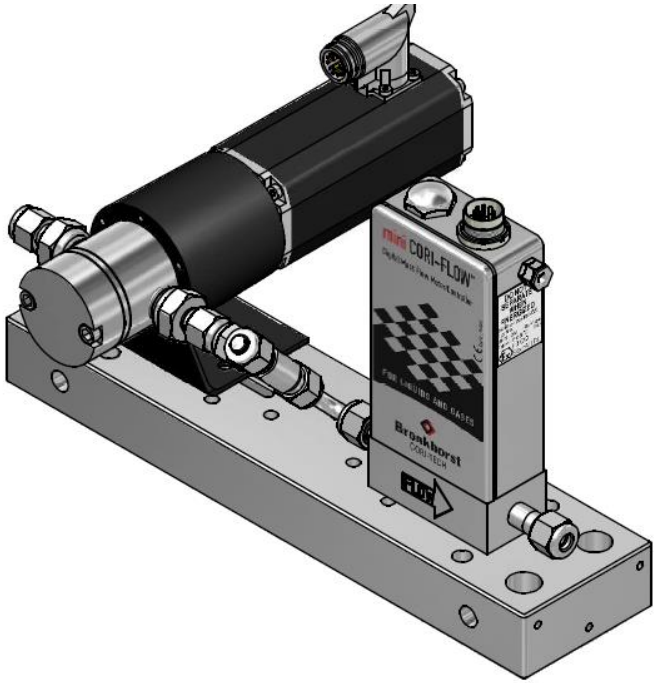
Mixture of Medicine Liquid药液混合



Bronkhorst Solution:

使用科氏质量流量控制器来实现药液混合系统，最佳的配置是采用一组（共3台，异丙醇一台，去离子水一台，qz3289一台）就实现要求

重点：

- 使用方便
- 无需压力源
- 直接质量流量控制
- PID调节
- 配料快而准.

PharmaTEC 制药业

CORI-FILL™: Compact Fluid Dosing Assemblies

CORI-FILL™:紧凑型流体配料组件:

CORI-FLOW™ 系列MFM搭配控制阀或（齿轮）泵即可实现紧凑型流体定量配料系统。只需组装好流体组件并上电，MFM内置的PID控制器将优化阀或（齿轮）泵的控制，配料剂量即刻开始。在操控模块（或遥控PC）输入目标流量或批量即可实现质量定量给料，不受环境温度、背压影响。集成CORI-FILL™技术，科里奥利MFM的累加器能够高精准地批次剂量，确保执行器基于批量达成即刻响应。配备以下组件即可:

- 流量计
- 阀/泵
- 批量计数模块/PLC
- 相关软件

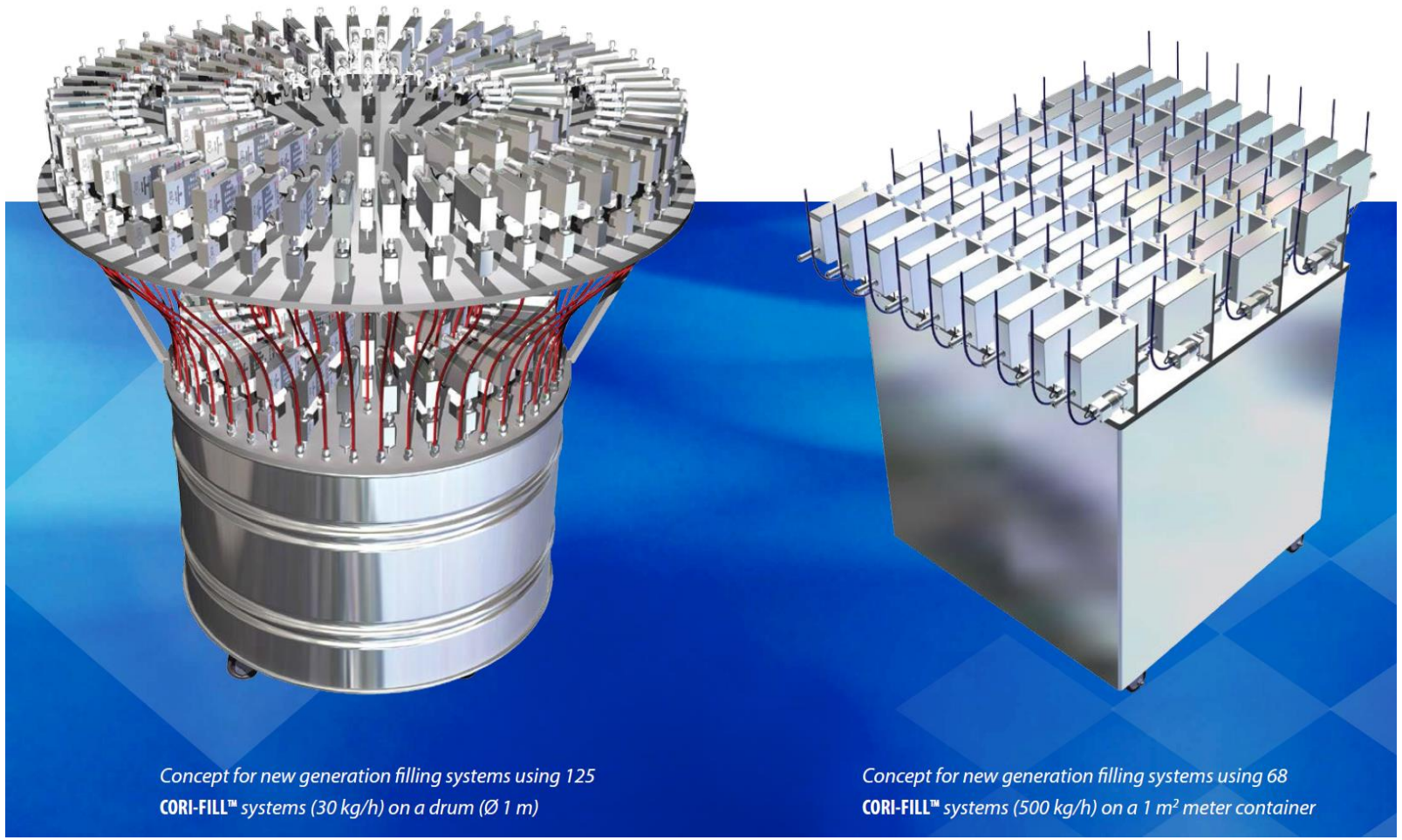
CORI-FILL™一个简单系统就可实现上述所有功能，无需对硬件进行复杂的编程。

典型应用:

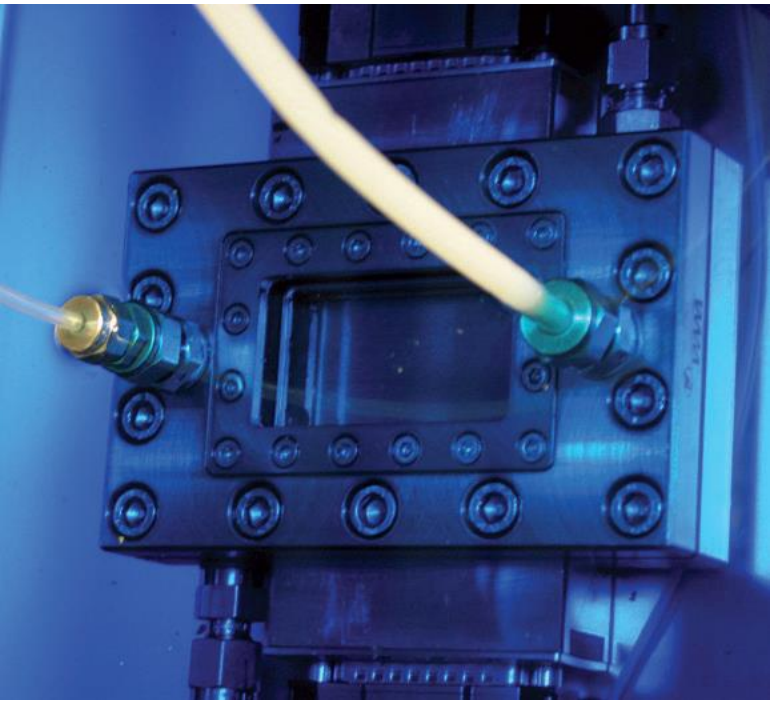
添加剂如芳香剂、调味剂、色素及消毒液(H2O2)的配料与剂量
各种生物及化学反应器
各种装瓶罐装过程

CORI-FILL™: Compact Fluid Dosing Assemblies

CORI-FILL™:紧凑型罐装系统



Micro Reactor Technology



需求: 出于更高产量、更高效率、更高安全性和环境风险最小化需求，如今的制药行业寻求传统批次反应器的替代方案；因此，行业趋势是采用微型反应器作为替代方案，特别适用于极端放热（非）混相流体的有机合成。

应用需求: 试验过程的研究需要新一代液体定量给料系统，即直接质量流量测量与控制。这种系统必须要非常准确和稳定（极低的流量脉动）。给配料装置最好是即插即用型部件(如由质量流量仪表来控制泵)，还可以集成PID设置与调整最为方便。

重点:

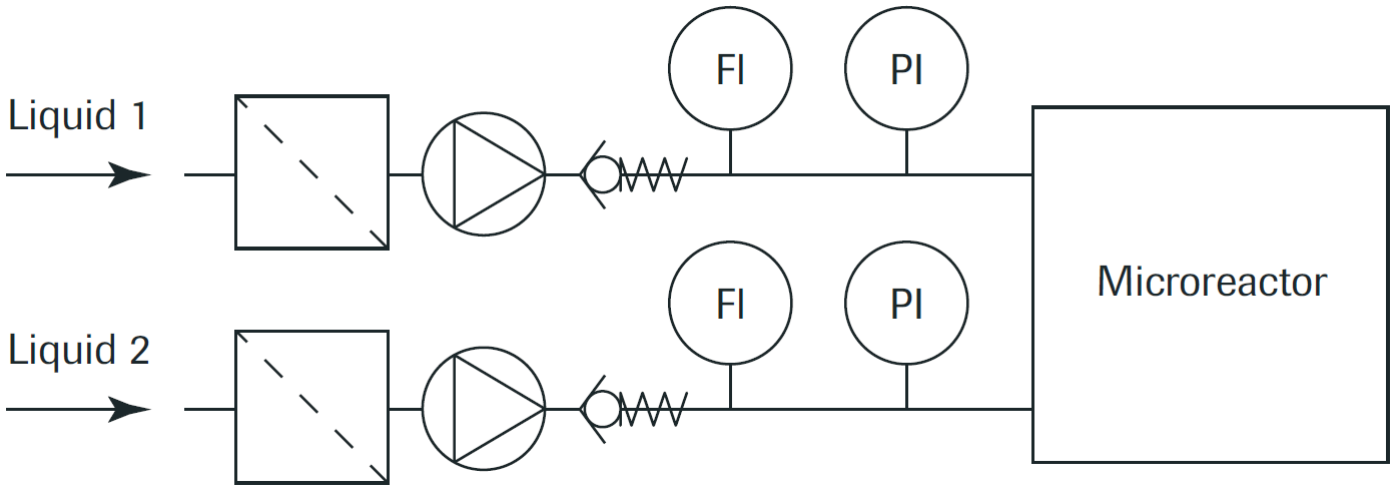
- 使用方便
- 无需压力源
- 直接质量流量测量与控制
- 集成PID控制
- 质量与体积配料剂量均可能

Bronkhorst®

工艺解决方案要求:

微型反应器是体积非常小的连续反应器。这种尺寸适用于中试反应，但也可以通过组合多个平行运行的反应器，将这种解决方案转变为具有生产规模的能力。

由于其上述特点，这种替代反应器非常方便，可以实现卓越的控制和试剂的最佳使用。由于所有过程都是在封闭的系统中进行，因此可以使用有毒、危险或爆炸性化学品，而不会引起严重的安全和环境问题。鉴于微反应器尺寸非常小，涉及到非常低的流体流动。为达到最佳工艺，适合的外围流量控制器和计量系统非常重要。



PharmaTEC 制药业

Bronkhorst开发的解决方案之一是使用我们独特的带控制功能的LIQUI-FLOW或CORI-FLOW系列流量传感器、齿轮泵、过滤器、止回阀和所有配套连接材料。

这种装置的优点是可以实现稳定而准确的液体流量而不产生气泡。此外，得益于科里奥利测量原理，该系统可使用于多种不同的液体。

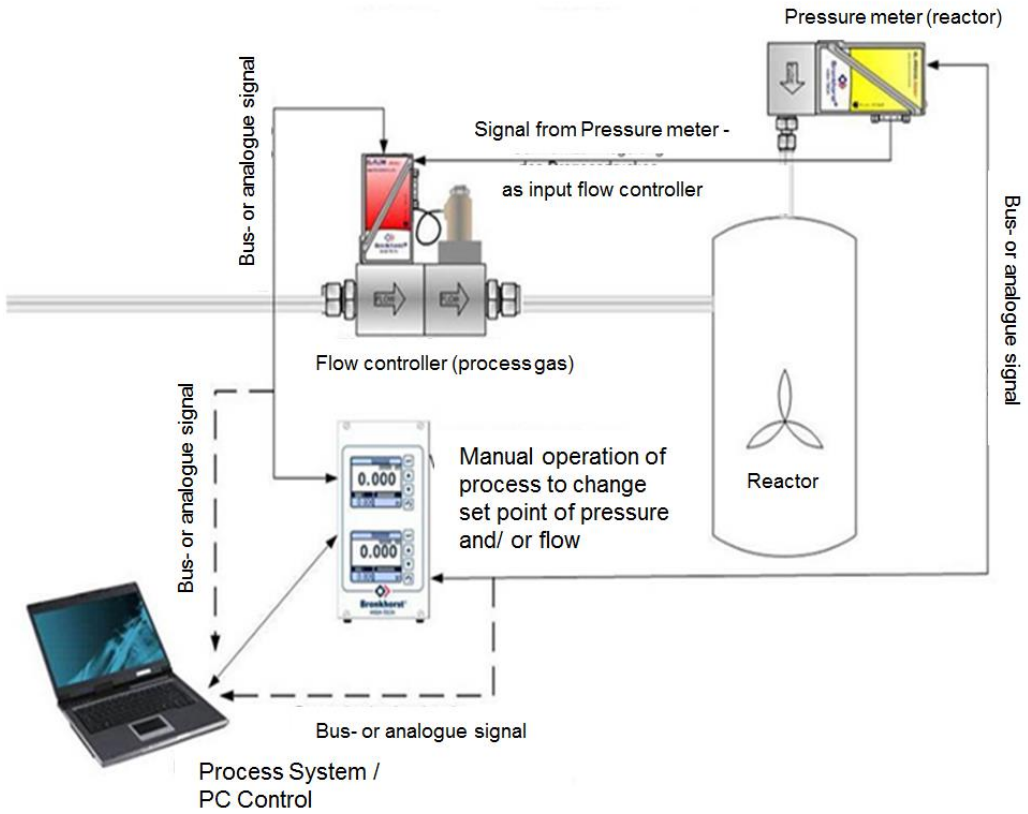
结果非常令人满意，解决了专注于微反应的化学家们在普通系统中发现的众多令人尴尬的困扰。

PharmaTEC 制药业

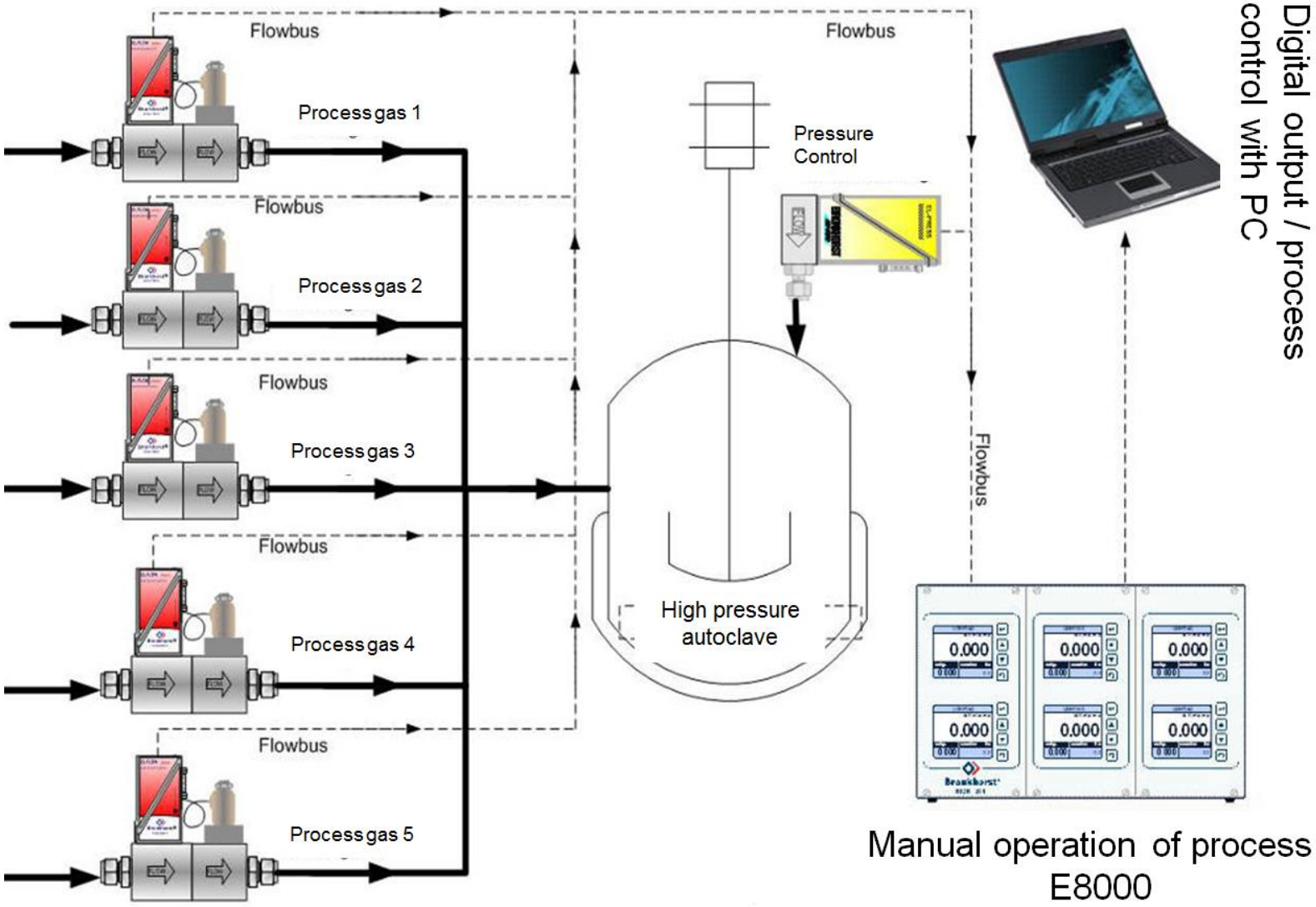
Bioreactors

- Flow Pressure Control 流量压力组合系统

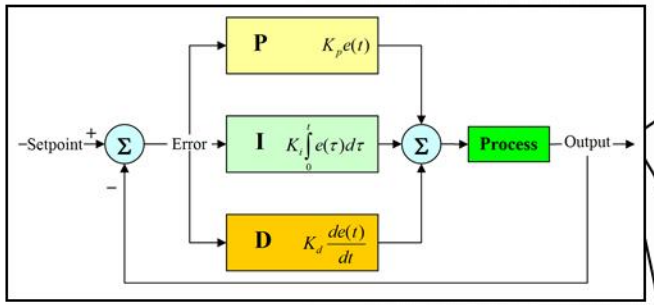
- 流量和压力是两个直接相邻的物理量。但在某些应用中，这两个变量的组合相干系统是非常必要的。通过压力测量和流量控制的耦合，可以获得显著的优势。 通常过程/反应器的压力应可调节，这是最重要的变量。但同时，所提供的流量（气体）应可记录/跟踪或限制在一定范围内。
- 为此，我们将质量流量控制器与压力控制器组合起来，质量流量控制器用作压力控制的执行机构。质量流量控制器的控制阀用来限定最大流量， 传感器检测流量。
- 这两种仪器的自动耦合， 其中一个控制器作为主控制器（MASTER CONTROLLER），使极快的控制成为可能。



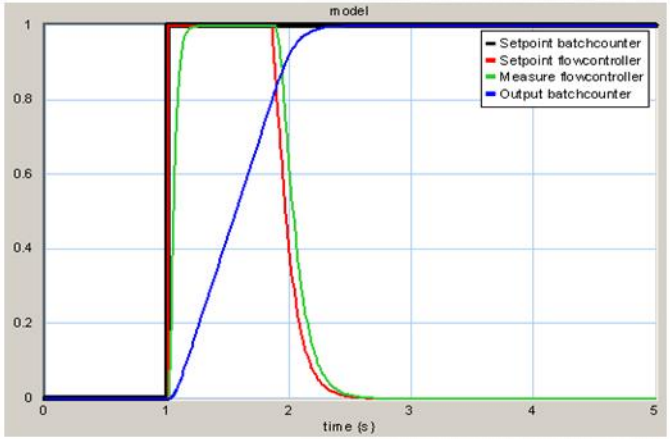
Bioreactors



CORI-FILL®



Integrated PID-controller



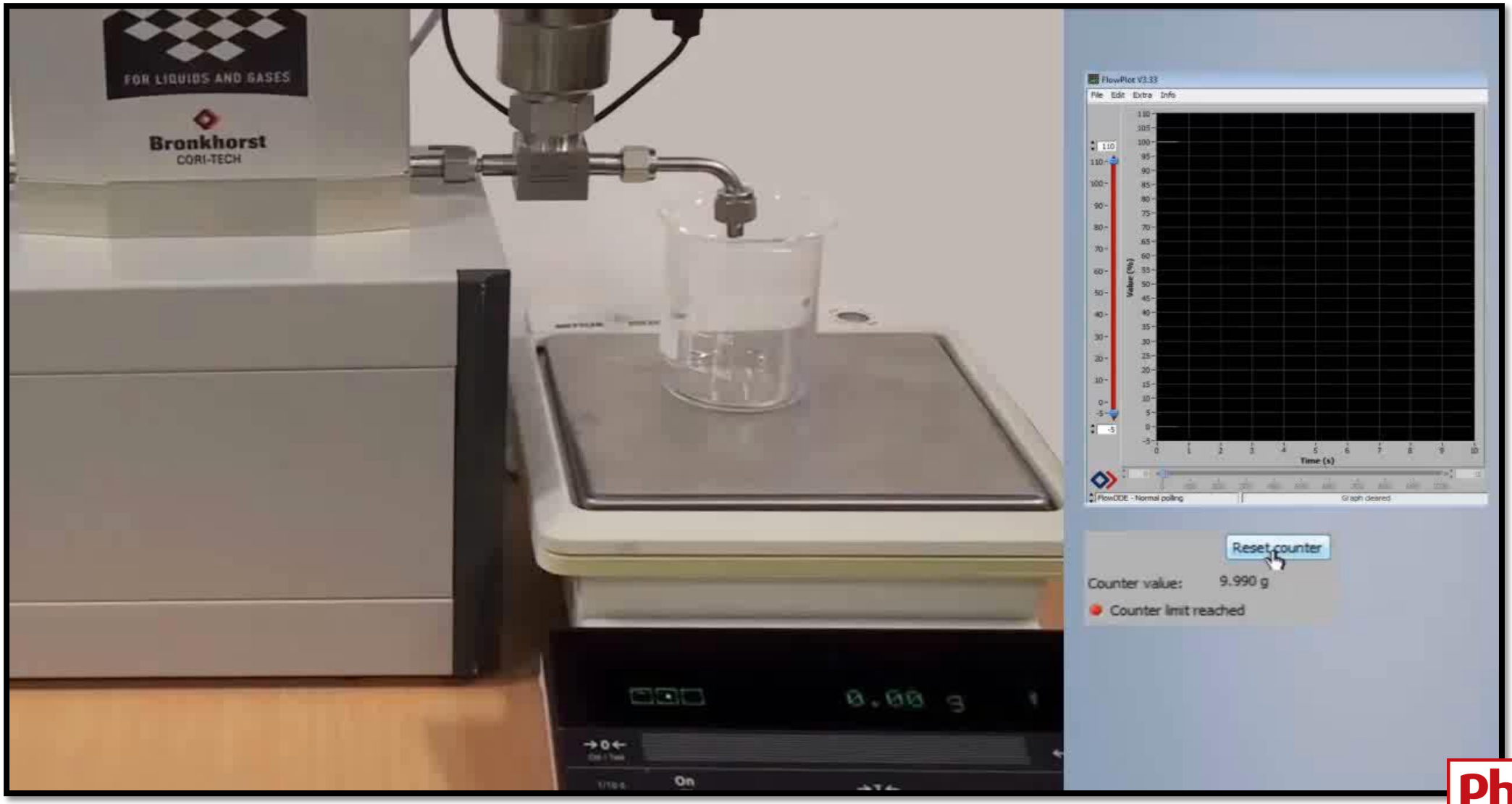
Integrated batch counter

Shut-off valve

Poportional valve

Pump

CORI-FILL®


FOR LIQUIDS AND GASES
Bronkhorst
CORI-TECH
FlowPlot V3.33
File Edit Extra Info
Value (%)
Time (s)
FlowDDE - Normal polling
Graph cleared
Reset counter
Counter value: 9.990 g
Counter limit reached
On

Bio-technology

Bio-reactor : 40L, 200L,1000L,5000L

Fluid: Air, N2, CO2, O2

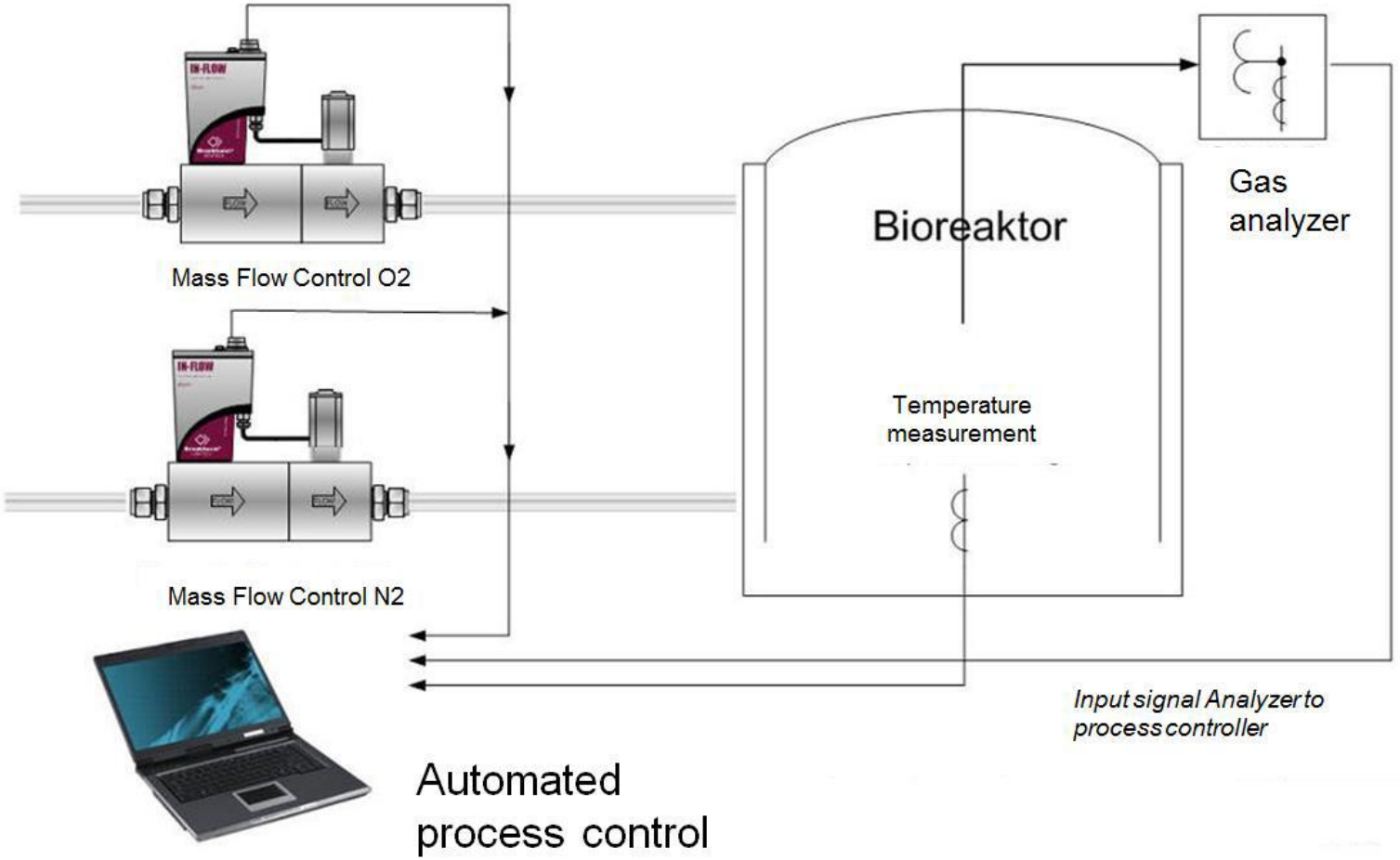
Bronkhorst instrument: Thermal MFC

Benefits: high accuracy control, compact size
Flexible solution

Reference: Applikon, Sartorius, T&J Bio-engineering, BIO-YD….

Bio-technology

Control of oxygen and nitrogen based on output of gas analyzer in reactor

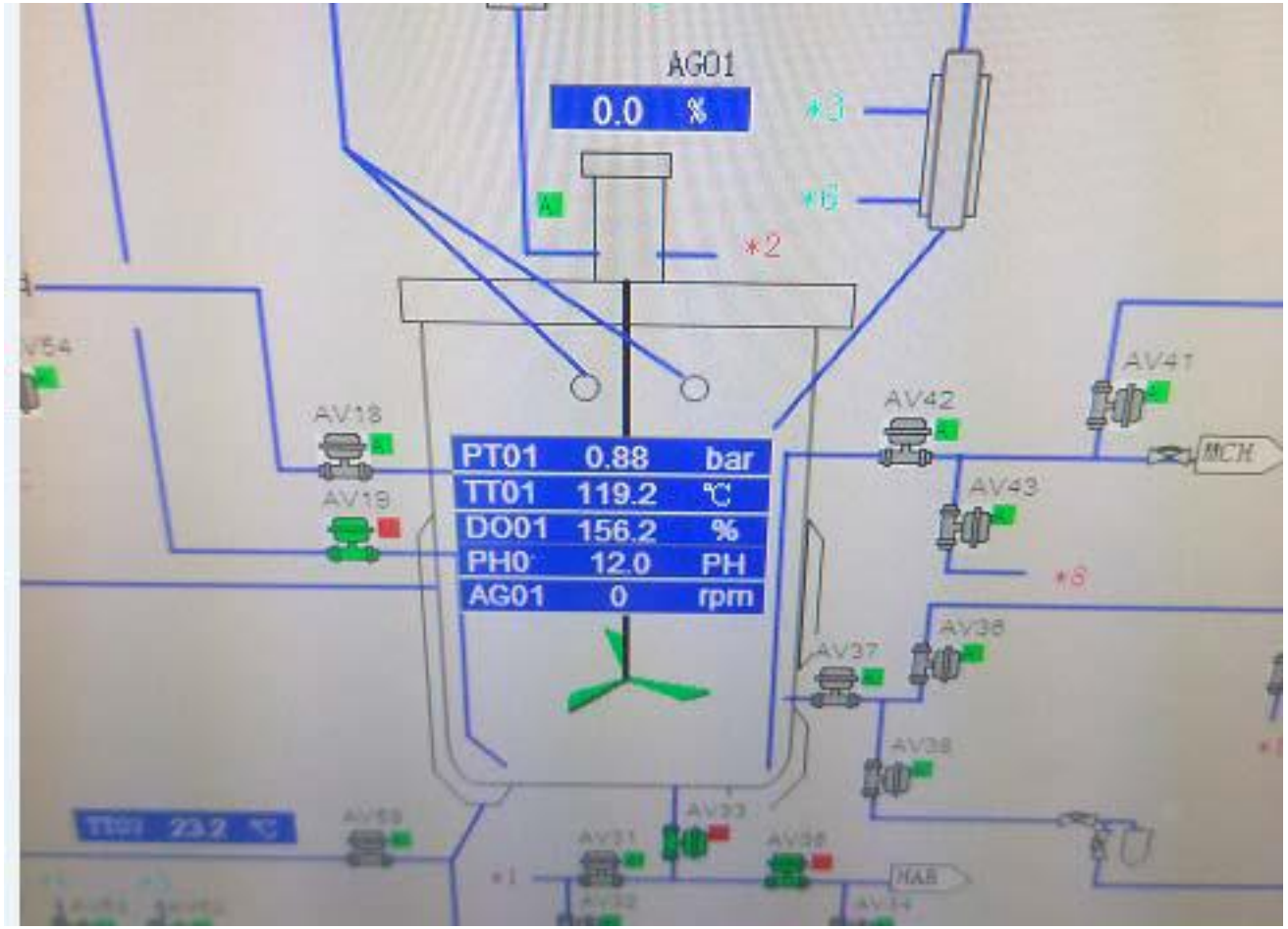


Pharmaceutical-M15 test

- Instrument：Bronkhorst Coriolis M15 flow meter（0~500kg/h）
- Fluid: water(inlet :0.8barg)
- Vapor pressure(1barg)
- SIP: 110~120℃ , 25min
- Result：tested with water , 0.8barg inlet and the totalize flow is 3kg which the same as balance
- verdict：recommend to use on pharmaceutical project

Pharmaceutical-M15 test

- M15 SIP test



Pharmaceutical-Blood project

- Fluid: ethylic PH4 ethylic acid, ethanol,Blood mixture
- Flow range:　500ml/min to 3L/min
- SIP : 120 ℃，25min
- Connector: Tri-clamp
- surface roughness: less than0.8μm
- Material certificate EN10204 2.1/2.2 or EN10204 3.1/3.2
- No dead volume in sensor tube design and thus easy clean ability

- Reference: Morimatsu, Bio-YD, GEA…

Pharmaceutical- Protein chromatography 蛋白质层析

- Fluid: Protein and others
- SIP : 120 ℃，30min
- Connector: Tri-clamp
- surface roughness: less than 0.8μm
- Material certificate EN10204 2.1/2.2 or EN10204 3.1/3.2
- No dead volume in sensor tube design and thus easy clean ability

Pharmaceutical

- Bronkhorst In-flow MFC
- Used for gases control on pharmaceutical projects to achieve the automatic, continuously, safe purpose.

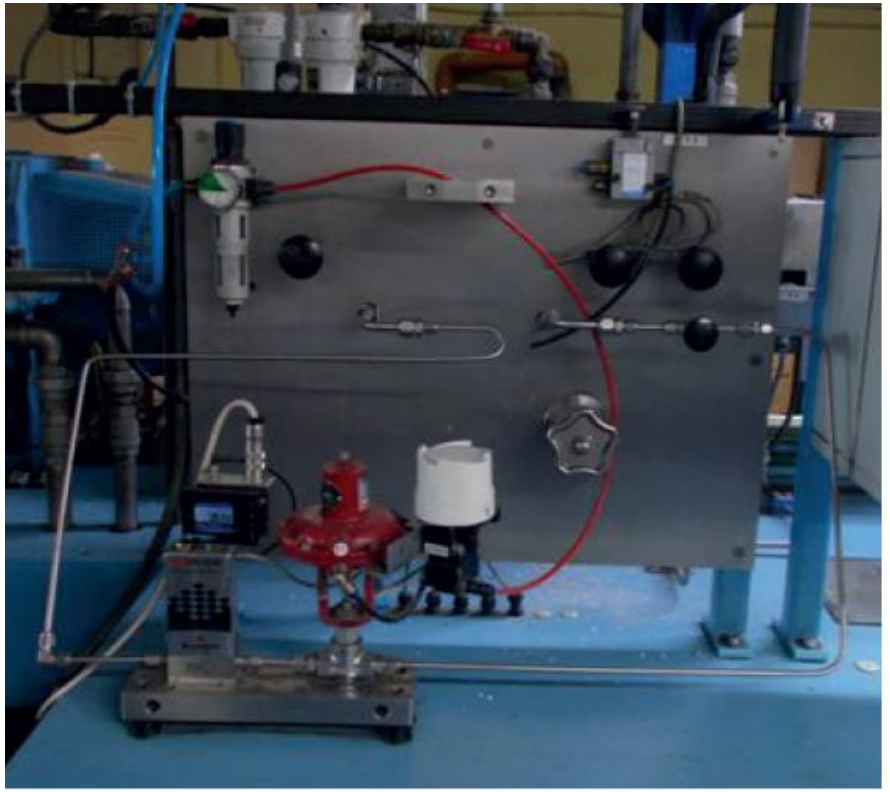
- IP 65 classification and option Zone 2
- Suitble for large size equipment duo to high flow range
- Flexible field bus communication
- Accuracy,astablility and compactable

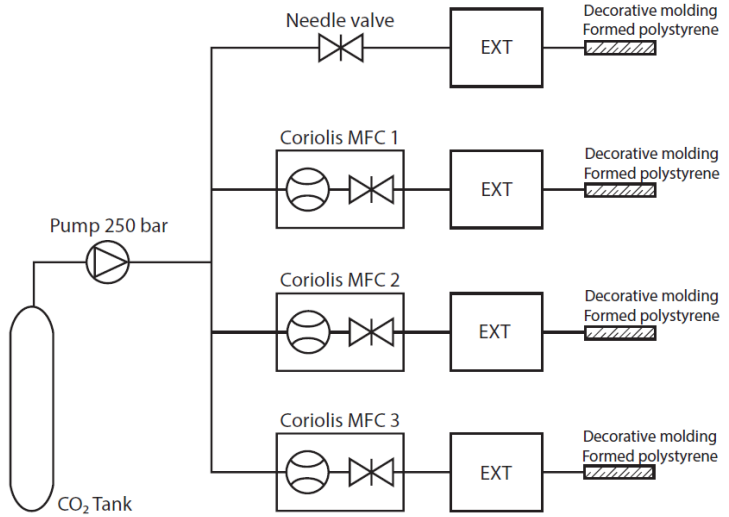
PharmaTEC
制药业

Pharmaceutical-Supercritical CO2

- Traditional extraction methods, such as water decoction, alcohol regurgitation and maceration, are time-consuming and inefficient.
- Therefore, this industry has adopted several new techniques such as supercritical fluid extraction and forced circulation extraction in recent years to improve efficiency and save energy

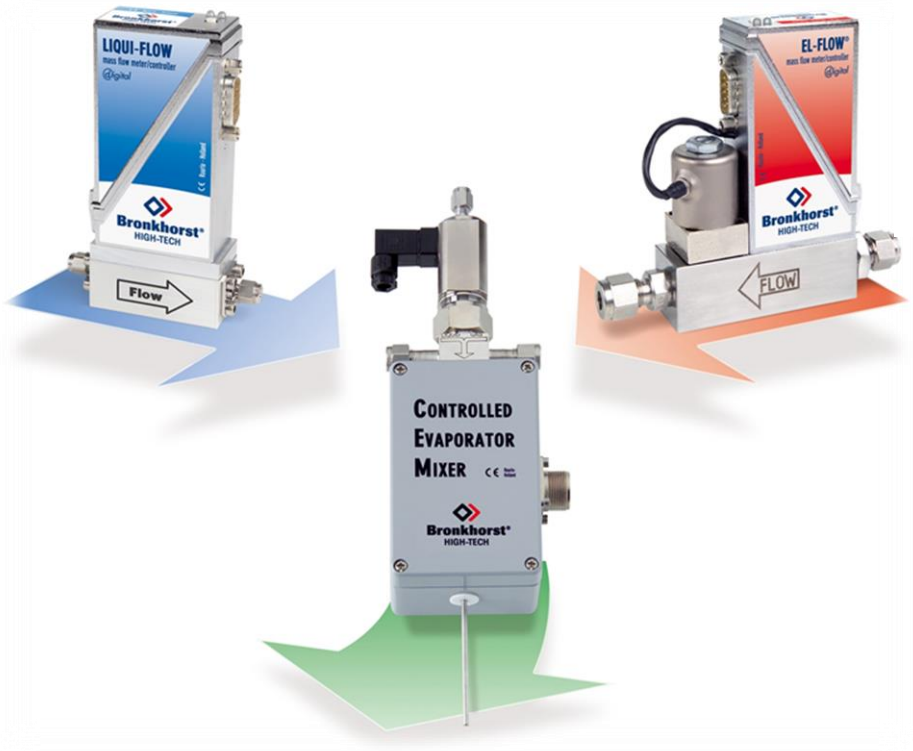
- 传统的提取方法，如水煎剂、乙醇回流、浸渍等耗时、低效。
- 因此，近年来超临界流体萃取和强制循环萃取等新技术越来越被采纳，以提高效率，节约能源。





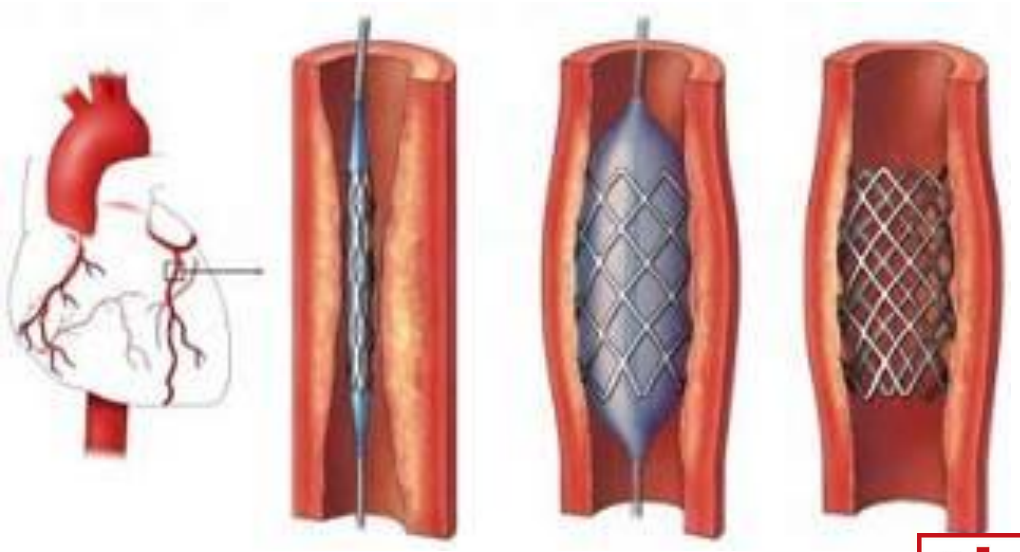
Applications

- H_2O_2 for sterilizing packaging 过氧化氢灭菌包装
  - Hydrogen peroxide



Applications

- Drug coating on medicinal stents
  - Precise dosing
  - Reproducibility
  - Stable control



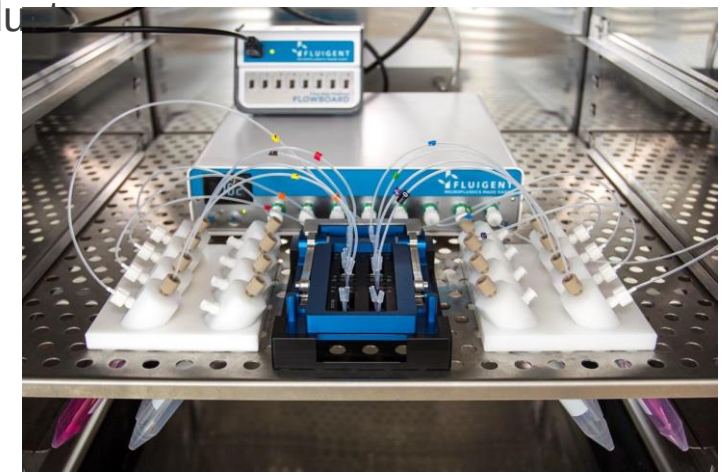
Applications

- MEMS Bronkhorst Markets for liquid µCoriolis

What is Organ on a Chip?

- Simulation of human organs on a fluidic plate
  流体板上人体器官的模拟
- Cell tissue is grown and kept alive on the fluidic plate
  细胞组织在流体板上生长并保持活力
- Continuous flow control of nutrients and medicines
  营养和药物的连续流动控制
- Application: medicine testing, cosmetics testing
  药品检测，化妆品检测
  - Pharma and cosmetics indu

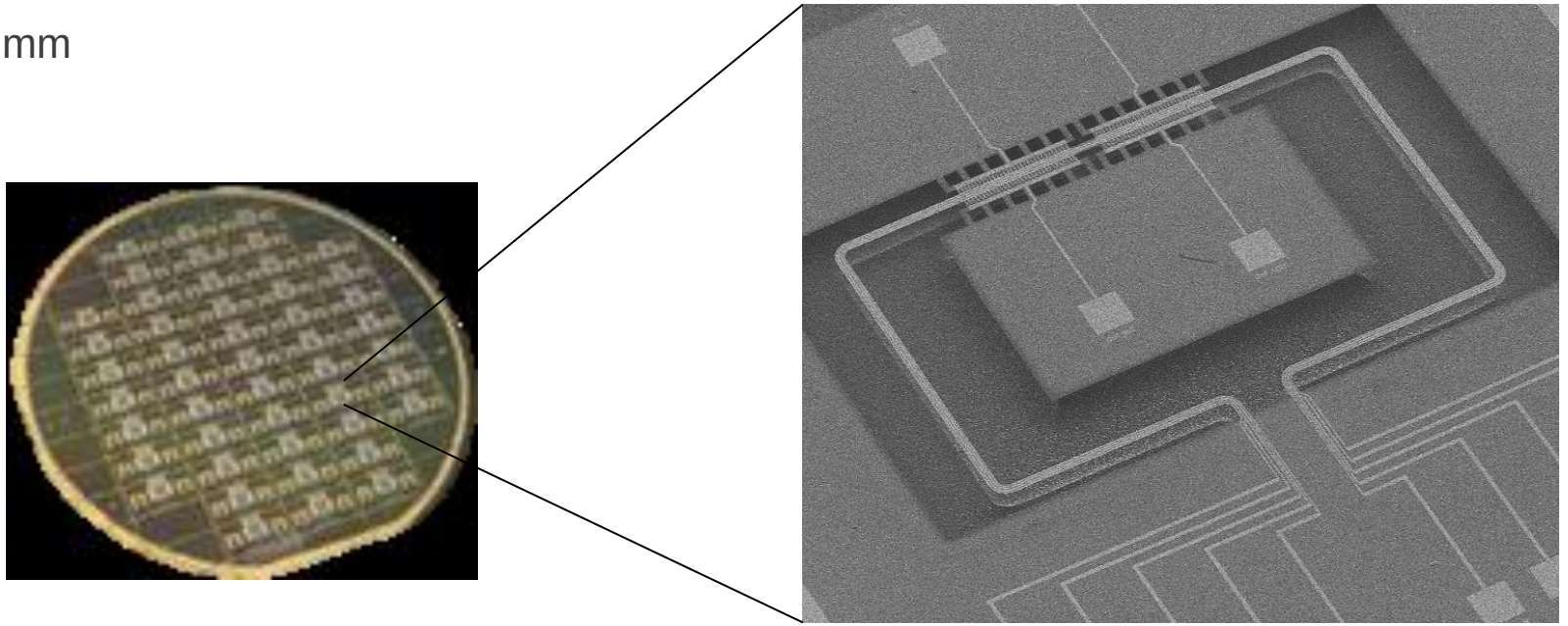
Organ on a Chip fluidic plate



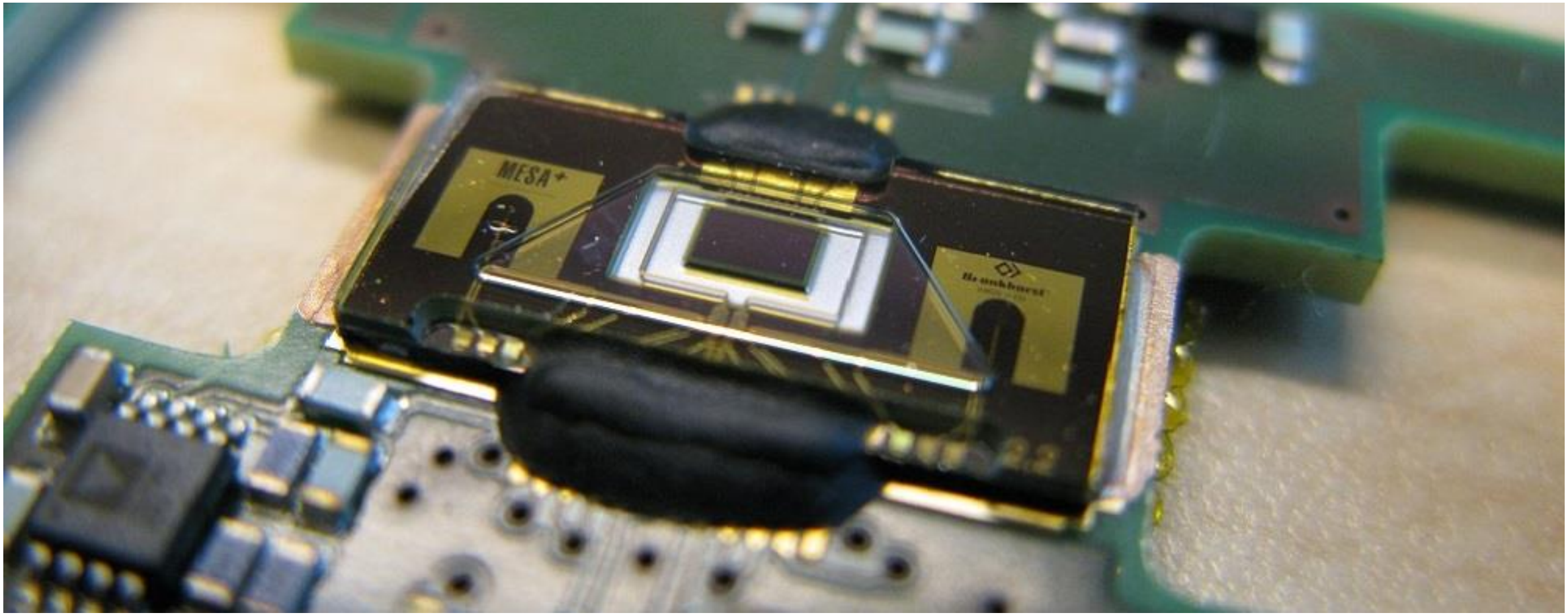
Organ on a Chip flow set-up in an incubator
培养皿里芯片上器官的流量设置

Product Development BL100

- MEMS (Micro Electro Mechanical System)
- Diameter: 0.055 mm



Product Development BL100



Product Development BL100

Ultra-Low Flow Coriolis Mass Flow Meter / Controller

- Range 0.01…4 g/h
- Control valve: Piezoelectric + metal plunger
- Internal volume:
  - MFM +/- 10 µL
  - MFC +/- 560 µL
- Vibration insensitive
- Bi-directional measurement

WORLD'S SMALLEST LOW FLOW CORIOLIS INSTRUMENTS

Markets & Applications

Website

- Bronkhorst website Applications

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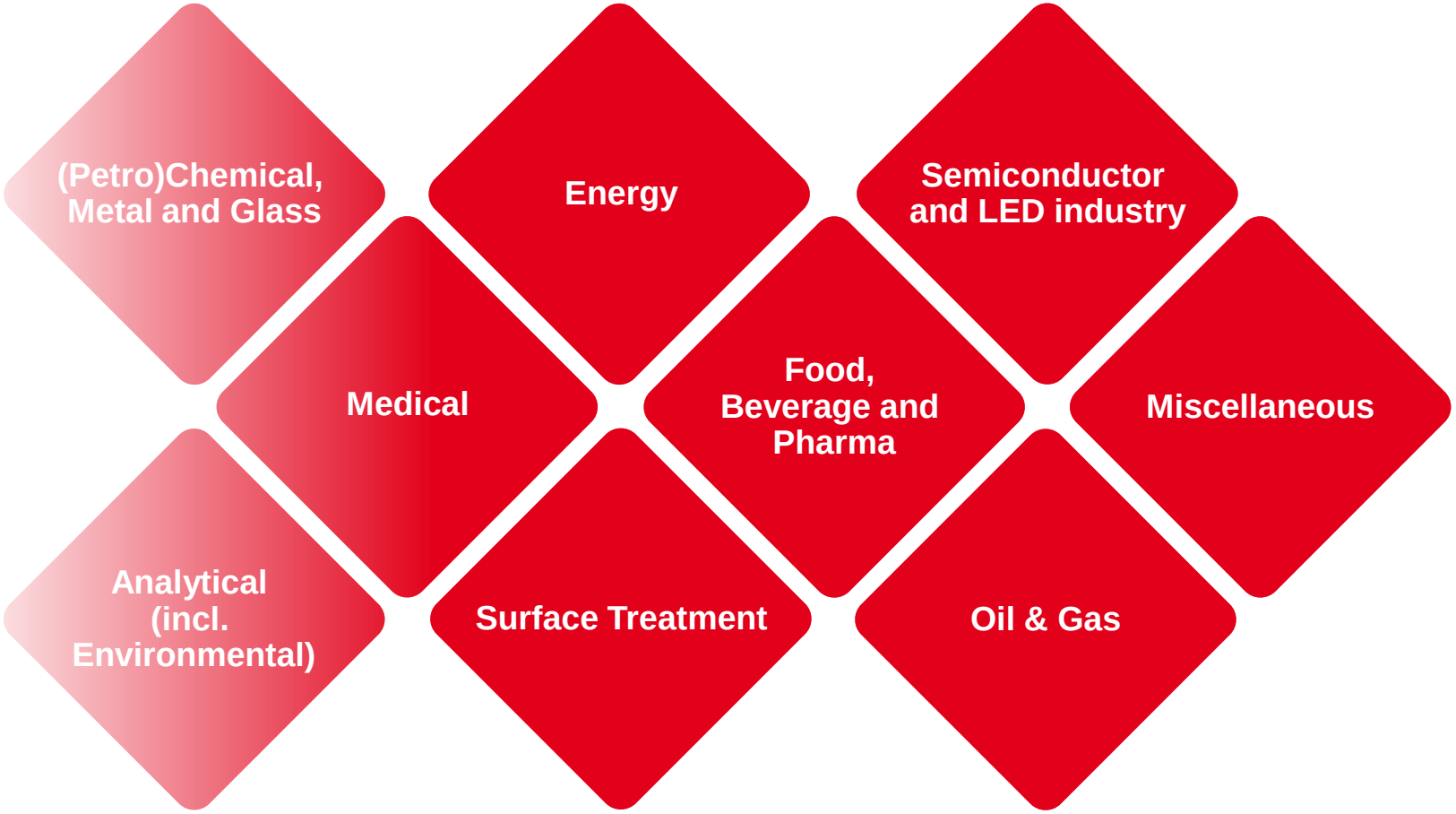
BRONKHORST® 微信二维码



Conclusion

Bronkhorst®

Thank you for your attention

PharmaTEC 制药业