GERRESHEIMER

# UPDATE

## Development and large series production of the Respimat® re-useable inhaler housing module

### Boehringer Ingelheim trusts in the competence of Gerresheimer for the Respimat® re-useable inhaler housing module

Our customer Boehringer Ingelheim has set a new standard for sustainable drug delivery devices with the re-useable Respimat® inhaler. The environmentally-friendly successor model to the established Respimat® inhaler can be successively loaded with up to six active agent cartridges, thus ensuring less waste and a considerably reduced $CO_2$ footprint during the product life cycle. We have developed the housing module for the new inhaler and developed and built the pre-series and series molds, as well as the pre-series and series special-purpose machines in the Technical Competence Center (TCC) in Wackersdorf, Germany. Large series production is in the meantime also taking place in our production facility in Pfreimd, Germany. Challenging for this project was the necessity the new inhaler be immediately available in large numbers for its market launch in order to replace the established Respimat® in defined markets. We, therefore, had to immediately transition from the development phase to a robust, high-volume series production. The most challenging technical change for the new inhaler was the development of a reversible blocking mechanism without changing the exterior design of the product with its high recognition value.

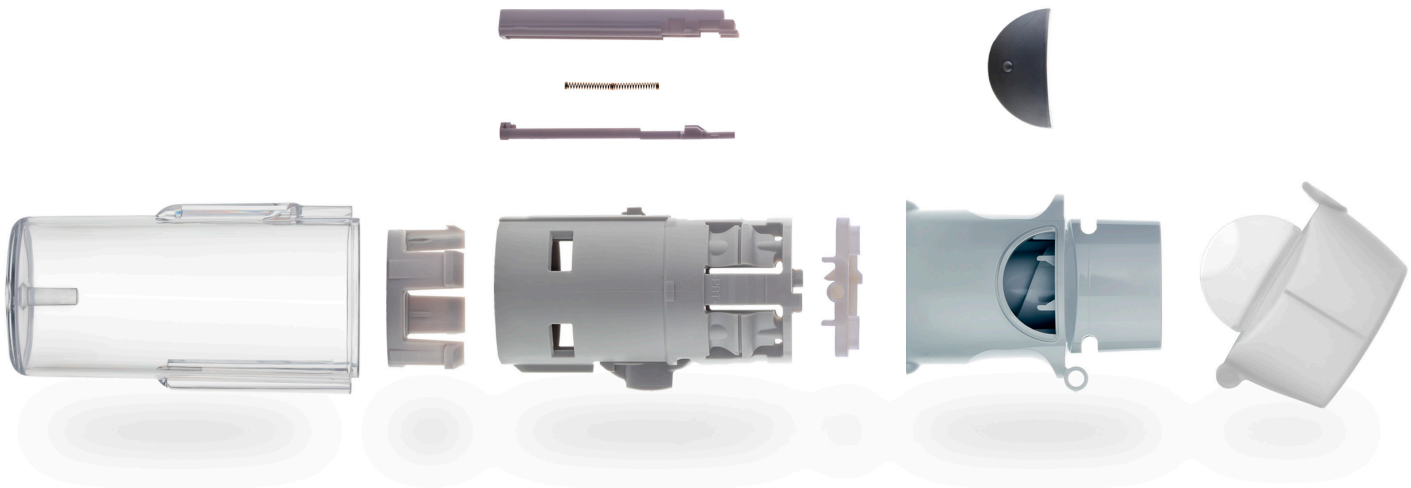
The Respimat® from Boehringer is an inhaler for the treatment of respiratory diseases that is firmly established in the market. Patients with chronic lung diseases like COPD use bronchodilation drugs on a daily basis to relieve their illnesses.

Correspondingly high is the consumption of inhalers, which are usually designed such that the inhaler needs to be replaced when the active agent has been exhausted. Boehringer Ingelheim therefore decided to develop a sustainable version of the Respimat®, into which up to six active agent cartridges can be inserted successively. "Sustainable action is a very important matter for us," says Dr. Sabine Nikolaus, Manager for Germany at Boehringer Ingelheim. "We are thus very pleased at the re-useable Respimat® being awarded with the Pharmapack Eco-Design Award. We will also consider principles of recycling management for future product developments." The latest packaging innovations of companies in the fields of drugs, medical technology, health products, and veterinary drugs are honored with the Pharmapack Award.

The Respimat® was already an environmentally-friendly product, because it works without propellant. The Respimat® has a $CO_2$-footprint that is 20 times smaller than dosage aerosols that use hydrofluoralkane (HFA) as a propellant. Thanks to the inhaler, which can be reused multiple times, the Respimat® now contributes even more to avoiding waste. The further development of the inhaler takes the feedback of patients into account. Thus, with a view to the ergonomics of the Respimat®, the grip has been further improved by an extension of the housing. The readability of the dosage display has also been made easier.

The re-useable Respimat®
from Boehringer Ingelheim

Gerresheimer develops and produces the Respimat® re-useable inhaler housing module



# Robust development for the leap to large series production

The task posed by Boehringer Ingelheim was to completely replace the established Respimat®, which is produced in large numbers, in select markets with the Respimat® re-useable by the time of the market launch. A transition thus had to be made immediately from the development phase to a robust large series production, with which the demand in the existing markets can be met. We developed a concept for this task, with which we were able to assert ourselves with the customer against all competitors.

The basis of our approach was the proven 5-phase development model, the qualification steps of which we have carried out in their entirety. The special feature of the Respimat® project was that the development phase and the creation of the equipment for large series production had to be pursued parallel in order to enable a quick market launch. We first established foundations with low-cavity molds and semi-automated processes, on the basis of which the development of high-cavity molds and completely automated processes for high-volume, large series production were immediately commenced with. In this way, the development of the series equipment could be initiated 10 months prior to the planned design verification. The creation of the second set of high-cavity series molds also already began during the creation of the first mold set and of the series automatic machines in order to be able to ensure the immediate supply of the market for the product launch.

Our robust development approach proved itself for the prescribed functional density of the device throughout the entire development process. Thus, despite these challenges, all functional tests for the design verification of the low-cavity molds and later for the implementation of the high-cavity series molds were passed immediately.

The fact that we also have our own clean room production for small series was a decisive competitive advantage for development. Small Batch Production enabled us to test samples under real conditions and to immediately consider test results in development. Start-up problems could be identified more quickly through in-house production and the experience gathered could be transferred to large series production in order to assure series start-up without disruptions. In addition to the parallelization of the development phases, this procedure contributed considerably to keeping to the ambitious schedule of the project.


Clean room production in our Small Batch Production in Wackersdorf, Germany

# Reliable product quality through a risk-based approach

For the jump to the robust large series production of a fundamentally altered product, it is of decisive importance to design the production process in such a way that all risks are reliably mastered and it becomes highly unlikely that defective products are even created. The prerequisite for this is to recognize all relevant risks in the life cycle of the product from development to series production, to classify them according to their severity, and to develop appropriate strategies for mastering them. With the risk-based approach, the risks for each stage of the product life cycle are determined in a systematic failure mode and effects analysis (FMEA). The risk assessments in an FMEA are thereby adopted respectively as input into the FMEA of the following phase, so that a complete picture of the risk profile is ultimately provided. A reliable basis for the appropriate robustness of the functions (Sigma level) is created through the determination, evaluation, and prioritizing of the risks.

Among other things, plastic/elastic key data of the materials used, as well as the friction coefficients of the planned material pairings were determined for our development. We were able to carry out highly realistic simulations of the functions on the basis of these project-specific input factors. We also created 2D and 3D tolerance analyses.

In order to quickly secure our results, we produced partial function samples with 3D printing. We used CT scans, high-speed cameras and scanning electron microscopy to optimize individual functions. Partly through tolerance samples, we have tested critical functions for the low-cavitiy molds of the development phase in function tests using traction/compression torsion test machines from ZwickRoell. We used statistical processes for the evaluation of the test series. In addition to with real time aging, we secured the long-term stability of the functions through computer-aided simulation and accelerated aging.

Quality lab in the Technical Competence Center in Wackersdorf, Germany

# Molds of extraordinary complexity

The molds for the development phase and series production were developed, produced, and optimized in the Technical Competence Center in Wackersdorf with its own mold-making facility. A special challenge here was presented by the size and complexity of the high-cavity molds for large series production, which weigh up to 3 tons.

We used mold flow and FEM calculations during mold development, as well as for the continuous improvement and securing of the long life fatigue strength of the mold design.

Verification of the results took place on the basis of real long life fatigue strength experiments through the creation of Gerresheimer-specific fatigue curves of select types of steel. Techniques of reverse engineering were also used during the optimization phase. We also used 3D print masks for the targeted final processing of critical long life fatigue strength ranges. We used scans from our CT systems for measurement and analysis.

We secured the start-up management of the molds with the help of Kepner Tregoe analyses for the methodological, continuous improvement process. Using the KT method, complex processes are systematically analyzed in order to reliably determine the causes of potential problems and to develop sustainable solutions for these. High-volume series production with our tools has commenced successfully. We are currently working on the creation and qualification of the third generation of successor molds.

# Automation with best practices model

In order to master automation in the context of a tight schedule, we established the high-volume assembly line parallel with development. The first SAT run was immediately successful. We also implemented 100% testing of the complex test procedures with data recording pursuant to 21 CFR Part 11 of the FDA for statistical quality assurance.

We used the innovative XTS system from Beckhoff for the automation of the module assembly for the re-useable Respimat®. Here, products are transported on movers, which are moved over the transport area by electromagnetic forces that can be freely configured.

As a decisive function of the re-useable inhaler, the device block requires a complex assembly process. We used the following best practice procedure for the transition from development to series production. We first developed several promising approaches to solutions and evaluated these with a concept rating. We checked the solution determined in this selection process with a preliminary test (proof of principle). The confirmed assembly process was realized in a semi-automatic assembly system and then transferred dually to a high-volume series automated machine. The immediately successful SAT run confirmed the selected procedure for this complex assembly process of the device block.

High-volume line for the assembly of the Respimat® re-useable inhaler housing module in a clean room ISO class 8 in Pfreimd, Germany

## Challenges

- Development of a reversible blocking mechanism without changing the exterior design of the product with its high recognition value.
- Transition from the development phase to a robust, high-volume series production.

## Our services at a glance

- Development of the housing module
- Development and construction of the pre-series and series molds
- Development and construction of the pre-series and series special-purpose machines
- Simulations / tests
- Production of partial function samples with 3D-printing
- Production of samples in our Small Batch Production
- Injection molding of nine partly complex plastic parts
- Procurement of purchased parts
- Product-specific production steps:
  Vaseline metering to improve gliding properties
- Fully automatic assembly of plastic and metal parts (springs)
- 100% testing of critical functions with data recording

# The project team of the Respimat® re-useable

## The core team Wackersdorf

from left: Florian Schönberger, Siegfried Winter, Josef Schmid, Nina Zielonka, Markus Müller, Melanie Braun, Rainer Lingl, Sandra Frieser, Andreas Schmidbauer

## The core team Pfreimd

from left: Roland Messer, Martina Friedrich, Christoph Hüther

## The team in detail

| | |
|---|---|
| • **Project Manager:** | Josef Schmid |
| • **Project Engineer Development:** | Markus Müller |
| • **Project Engineer Molds:** | Rainer Lingl (low-/high-volume)<br>Nina Zielonka (low-volume/series) |
| • **Project Engineer Automation:** | Siegfried Winter (low-volume)<br>Mathias Vielberth (high-volume) [not in the picture] |
| • **Quality Representative:** | Melanie Braun (low-volume)<br>Sandra Frieser (high-volume)<br>Andreas Schmidbauer (series) |
| • **Project Lead Production Small Batch Production:** | Florian Schönberger |
| • **Customer Support Engineer Pfreimd:** | Roland Messer (high-volume)<br>Benjamin Danner (high-volume) [not in the picture]<br>Michael Preiss (series) [not in the picture] |
| • **Customer Quality Engineer Pfreimd:** | Martina Friedrich |
| • **Process Engineer Assembly Pfreimd:** | Christoph Hüther |

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