Rentschler Biopharma

LEUKOCARE BIOTECHNOLOGY

Strategic Alliance

BEST-IN-CLASS FORMULATIONS PROVIDE SIGNIFICANT COMPETITIVE ADVANTAGES

Through the integration of Leukocare's unique SPS® formulation platform and Rentschler Biopharma's proven development and manufacturing process, clients gain exciting new opportunities to realize the full potential of their biopharmaceuticals in the market.

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Advancing the quality of biopharmaceutical product development and manufacturing

Formulation development in the current manufacturing process is suboptimal

- **Current standards do not leverage the strategic opportunities of formulation development**
- **Current standards focus on formulation development of the commercial product much too late in product development**
- **This can delay development programs if product opportunities are not maximized prior to phase II trials**
  - Changes of formulations after phase II may require additional studies, costs, and delays of the overall development programs
  - Not considering competitor developments and needs of physicians, patients, and payors early enough may result in a less competitive product

Standard commercial formulation development often starts in Phase III

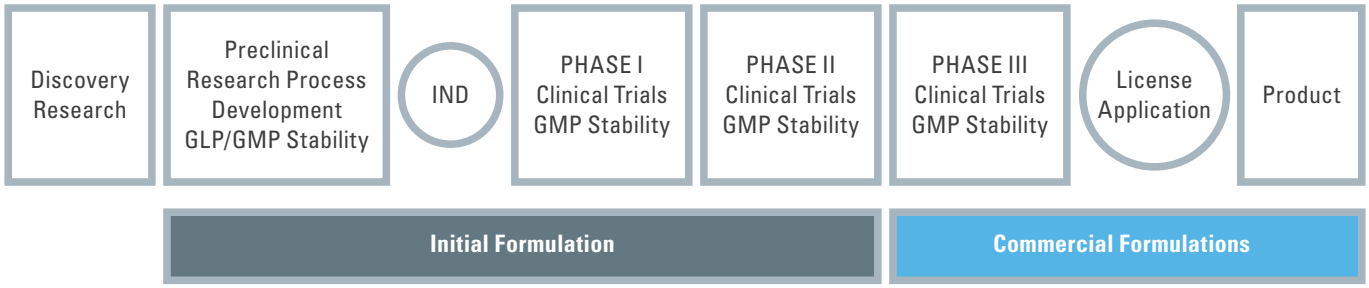


Figure (adepted): Chang, B.S. and Hershenson, S. 2002. Practical approaches to protein formulation development. in "Rationale Design of stable protein formulations-theory and practice" (J.F. Carpenter and M.C. Manning eds.) Kluwer Academic/Plenum publishers, New York, pp. 1-25

Product stability remains a challenge

- **Even with quality manufacturing procedures firmly established, product stability during purification, sterilization, filling, shipping, and storage remains a challenge**
- **Breakdown as a result of thermal changes, agitation, and/or oxidation impacts product quality (including efficacy and safety) and cost**

Formulation stability impacts costs in ways that may not be obvious

- **Direct costs:** typically visible to the supply chain of the organization
- **Indirect costs:** may be difficult to identify and consolidate because siloed departments in the organization track and account for them
  - Business and client risk must also include these real costs of supply chain failure

THE IMPACT OF STABILITY

Direct costs:
- Invoice value

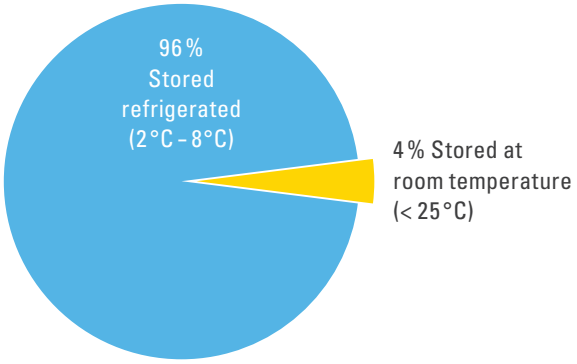
Indirect costs:
- Regulatory issues
- Brand risk
- Loss of product efficacy
- Back office invoicing
- Cost of packaging
- Product losses
- Management time
- Patient safety
- Cost of monitors
- Recovery of product

Data show many missed opportunities in formulation development

- **We analyzed 51 recently approved biopharmaceuticals**
- **The analysis demonstrates that a majority might have benefited from more strategic formulation development**

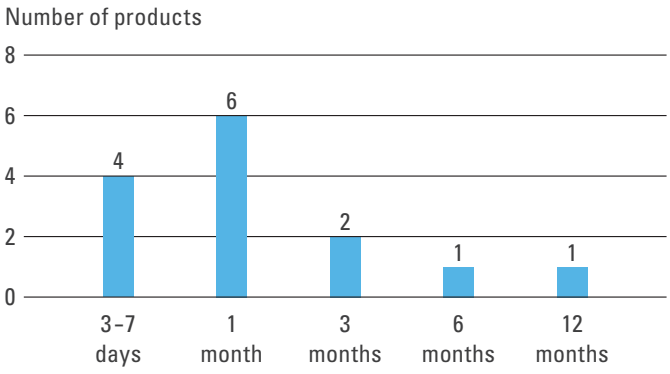
Most products do not allow even brief room-temperature storage

GENERAL STORAGE TEMPERATURE



- 96 % required refrigerated storage (< 2 °C – 8 °C)
- Only 4 % (N = 2, both lyophilized) could be stored at room temperature (< 25 °C)

PRODUCTS WITH LIMITED STORAGE AT ROOM TEMPERATURE



- Of the products stored refrigerated, only 28 % could be stored at room temperature for a defined period of time
- Only 8 % could be stored at room temperature for > 1 month

The importance of advanced formulation in product development

Why is it important to improve formulation development?

- **Advanced formulation maximizes product potential**
  - Provides optimal direct benefit to patients, physicians, payers (e.g. subcutaneous administration at home vs. IV administration in a clinic)
  - Supports maintenance of efficacy and safety of products during shelf life
  - Increases competitive advantage and maximizes market share
  - Provides LCM planning opportunities early in the process
  - Extends patent lifespan
  - Increases sales
- **Improves cost efficiency in product planning and development**
  - Optimizes planning (especially timing the start) of clinical trial programs
  - Early adoption of an advanced formulation in clinical trials can avoid the need to repeat them and simplify compliance with regulatory agencies
- **Improves market implementation logistics**
  - Container systems, packaging, transportation, storing, and handling by pharmacists, physicians, and patients

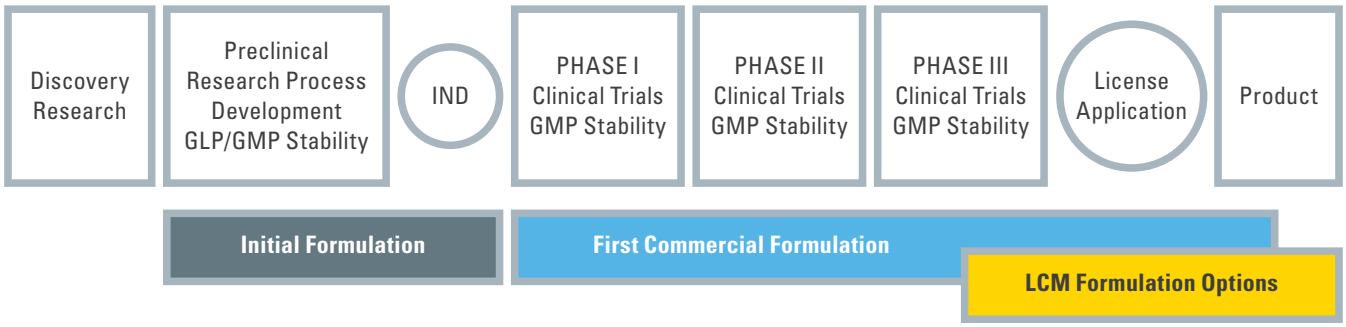
The Rentschler Biopharma/Leukocare Alliance

- **The Alliance of Rentschler Bioharma and Leukocare** offers contract development and manufacturing with proven excellence including best-in-class formulation that enables clients to realize the full medical and commercial potential of their products.
  Advanced formulation development is considered at every step of the manufacturing process to capitalize on the full product potential.
- **The Alliance offers full-service development and manufacturing** from gene to vial and full integration of patented SPS® (Stabilizing and Protecting Solutions) formulation technology at every relevant step of development and manufacturing.
- **Leukocare is the specialized technology partner** and the exclusive formulation developer for Rentschler Biopharma's biopharmaceuticals business. Rentschler Biopharma is the first and only contract development and manufacturing organization to use Leukocare´s patented SPS® formulation technology.

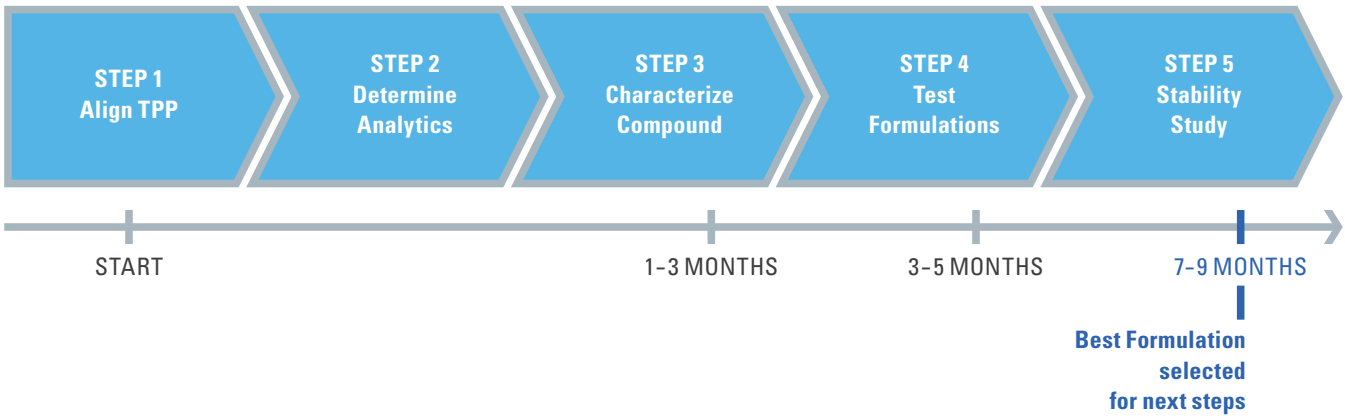
The difference catalyst – the SPS® formulation technology platform

- **The SPS® formulation technology development platform is a best-in-class formulation platform for the protection of proteins like biopharmaceuticals to facilitate the development of better products. This approach to product improvement investigates the possibility of:**
  - Liquid instead of lyophilized formulations
  - High-concentration products allowing for subcutaneous vs. IV administration
  - Products that can be distributed and stored unrefrigerated
  - Appropriate – even prolonged – shelf life
- **The SPS® technology platform is based on an SPS® library of 100 different well-known excipients, all listed in pharmacopoeias in the US, Europe, and Japan. Many are listed as inactive ingredients by the FDA.**
- **The SPS® technology platform combines this proprietary database of excipients with an advanced formulation development process to:**
  - Identify the most appropriate excipients
  - Create a compact theoretical design space focused on quality – not quantity – of potential formulations
  - Test the identified formulations to determine the best-performing formulation

SPS®-based formulation approach ensures shorter timelines and a much greater probability of success



SPS® formulation development process has 5 key steps



The Rentschler Biopharma/Leukocare Alliance – specialized technology partners

Over 40 years of exceptional quality manufacturing combined with best-in-class SPS® formulation technology platform

- **Advanced formulation development is the central part of our manufacturing process**
- **Improves cost efficiency in product planning and development**
  - Optimizes planning (especially timing) of clinical trial programs
  - Early adoption of an advanced formulation in clinical trials can avoid the need to repeat them and simplify compliance with governmental regulations
  - Improved market implementation logistics (transportation, packaging, storage)
- **Initial investment costs to generate better stability provide significant financial payback**
  - A stable, reliable product with optimal formulation (e.g. liquid instead of lyophilized), limited aggregation, reduced immunogenicity, longer shelf-life, increased convenience for physicians and patients, and/or other competitive advantages
- **Our state-of-the-art manufacturing process is flexible and customizable to your needs**
- **We can engage and partner with you at any stage of product development**

Contact us

Rentschler Biopharma

Rentschler Biopharma SE
Erwin-Rentschler-Str. 21
88471 Laupheim, Germany
www.rentschler-biopharma.com

LEUKOCARE BIOTECHNOLOGY

LEUKOCARE AG
Am Klopferspitz 19
82152 Martinsried/Munich, Germany
www.leukocare.com

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