CR Competence, Lund, Sweden

Value proposition for pharmaceutical companies

Business model

Our business model is straight forward B2B where you as our client own the rights to the results of our collaboration. Our work can lead to new patents and when it does we assign all rights to you. As a knowledge-based company, what we want to keep is only the right to use new understandings of a general nature in contexts that are not competitive with your field of use.

We treat everything we are told in confidence as long as we have not received a written confirmation that it is not. It is however our expectation that our client shares our intention to phrase certain case stories based on our work for future references and that this can be agreed upon in a collaborative manner.

The CR corporate claim: *Adding Value Through Science*

Through our combination of industrial experience and scientific approach we aim to take our clients further by providing additional fundaments for decision in the format of scientifically sound data in its applicable context. In many ways, CR is a fully equipped research institution, with access to the extensive resources at the Chemical Center in Lund and elsewhere. While operating close to academic researchers brings added value to our services, we are privately owned to 100%, act and function as a private institute.

Global personal care company: "*CR has brought great insights and value to real world problems in our product development cycle. They have a great balance of being focused on the end product and also bring best in class scientific thinking and approaches*"

We engage through diploma projects and post-docs to ensure a consistently high scientific level, which is the foundation of our ability to provide our clients with extraordinary services. Our core scientific fields are colloid- and surface chemistry, proven truly valuable for the pharmaceutical industry.

Our industrial expertise comes not only from the vast number of projects carried out at CR and our joint projects for the pharmaceutical industry through the Medicon Valley Inhalation Consortium, MVIC. It also stems from many years of experience in the pharmaceutical industry for several of our team members.

CR way of working

Already in the design phase of a project we will invest time in understanding our client's need not only from a scientific point of view but also from an industrial perspective as communicated to us. Throughout the project we will adhere to changes applicable to this need, whether these changes have come about because of results we have found or because of information our clients gather in parallel pursuits with internal capacities. Thus, while keeping the goal of a project the same, the content may change, but these changes are always swiftly communicated and in mutual agreement. We take responsibility for our professional ways, and you as our customer certifies in the end that you are pleased. We are not done until you can take the project further internally. At the end of the day we want you to know that we helped you to develop what is yours.

Science is a good handle to hold on to

Project team set-up

All projects are equipped with a project manager, a scientific responsible and the specific experts needed. The roles are transparent and with our defined team we deliver on time, on budget and with the right added value catering to your need and expectations. We have put a lot of emphasis on how our project teams work and are very proud of how capable we have proven ourselves to be in demanding situations.

Pharma company: *"CR impressed by being on time, on budget in a very demanding situation"*

Project Manager, Scientific Responsible and Expert

Applied science is what we do – with an eye open for serendipity

Our business areas are ***Scientific Consulting***, ***Applied Research*** and ***Education***. In the projects, we tackle problems from all phases in the product development chain, from early stage concept generation and method development through process- and formulation development to patent enforcement of commercial products. We are no strangers to trouble shooting, optimizing for improvement or line extensions, and assisting the marketing department with scientific arguments. We have a portfolio of methodological and instrumental tools that we can use in combination to address our challenges.

Our strategy of working within several business disciplines generates cross-business learnings with several synergies between cases. The main problem in one project is clearly the solution for someone else. After closer to 900 projects from 100+ customers in fields as far apart as solar cells and shampoo, we enjoy the *Eureka* moments on a regular basis.

Our goal is to provide our clients with the means required to take the next step. This could be results that are the basis for sound decisions or understanding as the basis for our client's Best Practices. Consequently, new findings can lead to changes in the project plans and this is never a problem for us. This is highly appreciated by our clients, in particular in the pharmaceutical industry where coordination with other key partners (GLP labs, CROs etc.) are crucial.

Personal care company *"I think that the key difference vs. other contract research organizations is the flexibility, I have really appreciated your ability to change plans in order to meet new needs and findings"*

What CR can do within Pharma - finding the answer to the right question

Product- and process development within the field of pharmaceuticals in many ways boils down to the following question. ***How do the substances in the formulation interact, with each other and with the surroundings?*** This single question captures the essence of the product and the answer can be used to predict both performance and stability. The formulation is the context of the actives and as such will determine solubility, bioavailability, chemical and physical stability. Proper understanding of the formulation will also pave the way to line extension possibilities.

Within the area of pharma, we are proud to offer services such as the following:

- Study: Adsorption to surfaces as characterized by QCM-D, AFM and Ellipsometry.
- Study: Characterization: Solid-state evaluation, rational form- and salt selection, based on experimental solubility data, calculations and phase behavior
- Study: Particle size (distribution) and evolution with time or other parameters.
- Strategies: Formulation of poorly-solubles and more. New concepts.
- Process: Milling and micronization of "difficult" compounds for research purposes.
- Seminar: "Effect of Surfactants on Peptide and Protein Stability"
- Seminar: "pH-solubility and the usefulness of pH solubility diagrams in the work with poorly soluble drug substances"

Global Chemical Company: "*The seminar that you gave at our premises and the follow up discussions were a success: based on this activity, we are currently running preliminary experiments, which are showing promising results."*

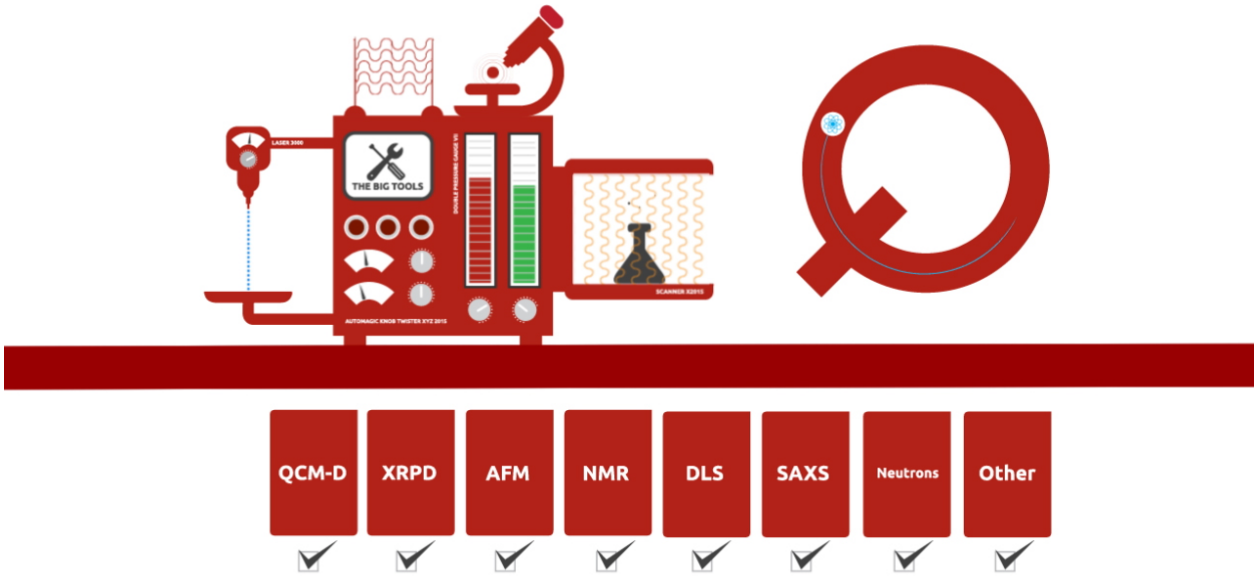
Techniques we have access to and use on a regular basis include the following:

- XRPD for polymorph investigations
- DLS for aggregation studies (here we have access to standard DLS as well as 3DDLS for turbid systems)[1]
- SAXS for aggregation studies and studies of formulation phases (lamellar, vesicles, other liquid crystalline phases etc)[1]
- NMR diffusion for studies of aggregation and interactions with excipients
- NMR spectroscopy for non-destructive stability studies
- HPLC for stability studies
- Viscometry, tensiometry, turbidimetry, FT-IR etc

In addition to the small- and mid-sized equipment mentioned above, we are also a good partner for projects the require access to synchrotron or neutron sources.

In pharma, material supply is sometimes scarce, and we are used to having this in mind. In the words of one of our major clients:

Pharma company: *"When deviations are made due to e.g. availability of materials, the solutions are pragmatic, proactive and well communicated.*



References

A selection of assignments relevant for the pharmaceutical industry are listed below. The list also includes selected Personal Care projects, since they are in many ways overlapping in character.

2017	Med. Device company	Optimization of a liquid formulation with several key ingredients displaying significantly different stability profiles. Theory combined with stab using HPLC.
2017	Pharmaceutical company	Aggregation study (NMR and DLS) of formulations under various conditions.
2016	Pharmaceutical company	Generation of formulation concepts and thereafter, upscaling, characterization and manufacturing of material for rat studies.
2015	Pharmaceutical company	Physicochemical characterization of a novel excipient of natural origin.
2015	Pharmaceutical company	Investigating the root cause of batch variations of a peptide formulation, using DLS and NMR (^{13}C, ^{1}H, solid state)
2015	Pharmaceutical company	Leading a TPP workshop and subsequent release studies for a high dose combination product.
2014	Global Personal Care Company	Studying key ingredient stability non-destructively, and suggesting formulations to improve chemical stability.
2013	Global Personal Care Company	Prediction of fragrance release based on calculations and theoretical modeling
2013	Pharmaceutical Company	Revision and adjustment of manufacturing process, in order to inhibit detrimental precipitation
2013	Pharmaceutical company	Risk evaluation of API salt-selection strategy
2013	Pharmaceutical Company	Reaching in-depth understanding of the API and its self-aggregating characteristics
2012	Global Personal Care Company	Comparing lubricating effects of different formulations and educating the client about adsorption effects
2012	Global Personal Care Company	Innovation of a new product formulation (IP owned by client)

The team at CR has an extensive publication history mainly based on academic collaborations in parallel with our client-based projects. For the extensive list of >100 papers we refer to our homepage.

Example 1: Excipient characterization for QbD

In a QbD setting, there is no such thing as a "generic critical attribute" of an excipient. Rather, the criticality of any given attribute depends on the exact role of the excipient in the final product, together with the manufacturing protocol of the product, its regulatory framework (for instance, post-approval flexibility) and other factors that are unique for the product at hand. We therefore approach excipient characterization in a case-by-case fashion and work closely with the client to arrive at a tailored and optimized package.

We have experience of characterization of a wide range of excipients, including ethoxylated surfactants, polysaccharides (xanthan gum; cellulose and its derivatives), alkylpolyglucosides, carbohydrates (lactose, dextrose) and polyacrylate microgels (Carbopol and Pemulen). Whatever the excipient, we always ensure that we put the characterization into context in order to maximize that value from a QbD perspective. Our modus operandi is firmly based in science, not in statistics. This means that we build scientific understanding about your excipients and their interactions in the formulation, rather than to use multivariate analysis and other indirect statistical methods. However, we are used to working together with statisticians and appreciate the need to combine science and DoE-type statistics in order to build a robust design space for your product.

A specific case study is provided by our work with a complex polysaccharide. The polysaccharide is being developed as a new excipient for tablet formulations, and our contribution consisted of physical and chemical characterization aimed to establish the correlation between function and parameters like molecular mass, degree of branching, substitution pattern and impurity levels. The project necessitated application of a wide variety of techniques combined with creative development of novel methods – in other words, a project perfect for our way of working!

Pharma company: *"What I love with you guys is that you talk about very complex matters in a way that I can follow so I know I can make use of the results."*

Example 2: Root cause investigation of a batch to batch variation related to peptide aggregation

Peptides and proteins are prone to aggregation, both during manufacture and over shelf life. Aggregation impacts not only the potency, but also the safety of the product, since aggregates may cause adverse effects based on undesired immune-response. Identification and quantification of aggregation, as well as determination of its root cause, are therefore critical for biopharmaceutical products.

We have worked in a number of projects devoted to peptide aggregation. Here, our ability to combine state-of-the-art scattering techniques with spectroscopy (primarily NMR) has proved extremely valuable. In contrast to many specialized lab active in this field, our competencies cover not only aggregation in solution, but also the solid state. A case in point is our application of solid state NMR (ssNMR) in the optimization of the process conditions pertaining to the manufacture of aggregating peptides. The unique advantage of ssNMR is its ability to pinpoint, with molecular resolution, the structure *and* dynamics of the solid material and its dependence on process conditions. This, in turn, makes it possible to understand the intermolecular interactions and hence aggregation.

Example 3: Line extension through formulation

Approval of novel APIs become increasingly challenging, which fuels an increasing interest in line extensions of existing ones. Identification and development of line extensions are far from being a run-of-the-mill-exercise. On the contrary, it requires a combination of creative product development and in-depth formulation knowledge. We provide both. Our combined experience covers solid oral dosage forms (tables, capsules and pellets), inhaled formulations (nasal and pulmonary solutions, suspensions and solids), subcutaneous depos, formulations for topical and parenteral administration, and it includes both small organic molecules and peptides.

One assignment was focused on nasal delivery of the active substance. We assisted the client with initial work-shops directed towards concept generation and risk assessment, performed formulation screening and developed the necessary analytical methods.

Another assignment was focused on finding a formulation with a different release pattern. We assisted the client with a number of potential new concepts, for several of which we later also developed and characterized formulations for evaluation in animal studies. One of the formulation ideas are now evaluated based on the performance in an animal study to which we produced the formulations. The work has also led to several new findings regarding the API that we are sharing in parallel through seminars and in written comprehensive reports.

Pharma company: *CR has been pivotal for the scientific strategy.*

The benefits of the small company collaborator

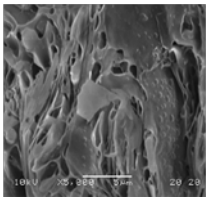
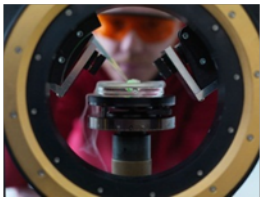
The small size of our team has always been one of our most attractive qualities. We take advantage of the short lead times, the possibility to engage fast and develop a creative environment in which our clients often want to stay. Our team is also characterized by personal commitment and a pronounced willingness to discuss data and results in the appropriate industrial context, also after projects have been finalized.

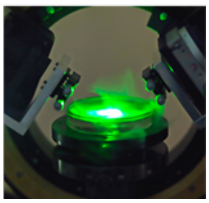
Health Care Company: *"We have found their willingness to discuss data with us very useful"*

But our team is also part of a larger eco-system, which makes it possible to take on projects where more complex coordination is needed, or where complementary capabilities are necessary. We have our offices and lab in a private part within the Chemical Centre of Lund University. The Chemical Centre is one of Europe's largest institutions for Chemistry and Chemical engineering and this is also our environment. We have close collaboration with the departments of Physical Chemistry, Food technology (including pharmaceutical sciences) and Biotechnology. We are collaborating with the synchrotron research facility MAXIV in Lund and several complementary high-end service companies in the area of Medicon Valley.

Personal Care Company: *"The collaboration with CR has been very positive; we have really appreciated their ability to propose and carry out experiments able to provide important learning on product application on top of the theoretical model. We have really appreciated their flexibility, which has allowed us to change plans in a timely way and to match project needs that have changed based on new learnings and/or a new business direction"*

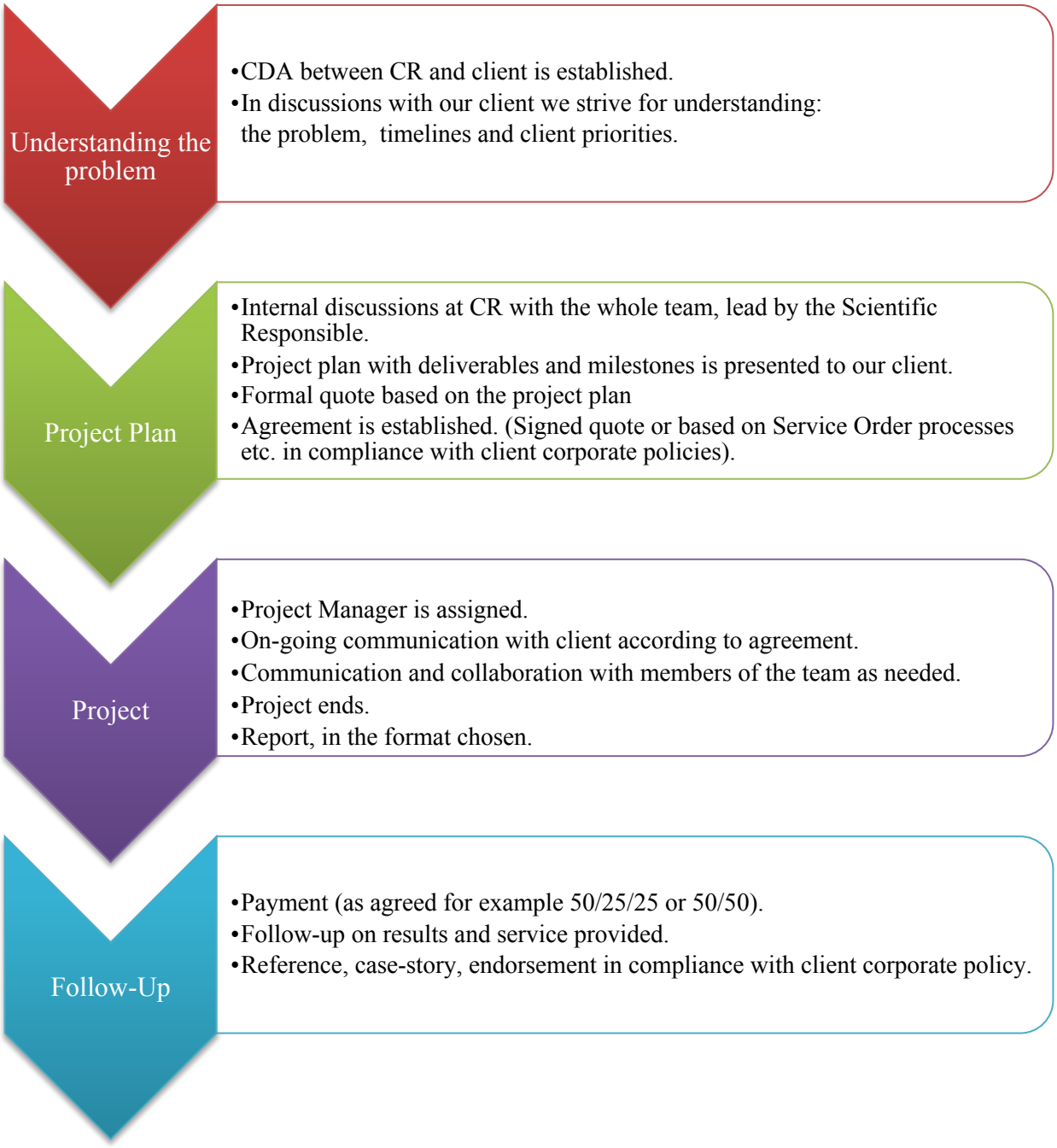
Our business idea is to function well and efficiently in this eco-system and one of the main purposes is to use the nearly unlimited instrumental possibilities of the academic institutions. Thus, we have access to and use instruments for the different projects on an as-needed basis, which is of great value to our clients and our creativity. For pharma this is very often instruments such as Ellipsometry, QCM-D, and AFM for adsorption and surface characterization studies, NMR spectroscopy for chemical stability and NMR diffusion methods for physical stability, SAXS (Small angle x-ray scattering) and different light scattering methods for solubility and other phase behavior studies. HPLC is run on our own instrumentation.

The CR Competence work flow:

At CR, we show our strength in our commitment to understand our client's need. We put *your need* into a scientific context and *our results* into *your business context*.



In addition to the project manager, one of our seniors are assigned the scientific responsibility of the project to make sure we do not only deliver in time and within budget but with high scientific standards.

:CR: ADDING VALUE THROUGH SCIENCE

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We sit down with you