LACDR

Evaluation report for the research review of the

Leiden Academic Centre for Drug Research (LACDR)

at

Leiden University

for the period 2016-2021

Research review according to the

Strategy Evaluation Protocol 2021-2027

March 2023

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This report was finalized on 17 March 2023

I. Introduction

Scope of the assessment

In 2021, the Executive Board of Leiden University commissioned a review of the research conducted in the Leiden Academic Centre for Drug Research (LACDR). The review is part of the regular six-year quality assurance cycle of the university; it is intended to monitor and improve the quality of the research and fulfil the duty of accountability towards government and society. The quality assessment in this report is based on the assessment system in the Strategy Evaluation Protocol for Public Research Organizations 2021-2027 (SEP, appendix 1), drawn up by the Universities of the Netherlands, the Netherlands Organization for Scientific Research (NWO) and the Royal Netherlands Academy of Arts and Sciences (KNAW).

The review committee

The Executive Board of Leiden University appointed a review committee (hereafter: committee) of external peers, including a mid-career researcher, a (recently graduated) PhD candidate and a representative from industry. The committee consisted of:

- Prof. dr. Ton de Boer (chair), emeritus professor in Foundations of Pharmacotherapy, Utrecht University, Dutch Medicines Evaluation Board;
- Dr. Thomas Steger-Hartmann, Head of Investigational Toxicology, Bayer AG, Pharmaceuticals, Germany;
- Dr. Christophe Junot, Head of the Medicines and Healthcare Technologies Department at CEA, Université Paris-Saclay, France;
- Prof. dr. Tanja Weil, Director of the Max Planck Institute for Polymer Research, Germany.
- Dr. Francesca Grisoni, Assistant professor at the Biomedical Engineering Department, TU Eindhoven;
- Carin Biel MSc, PhD candidate at the department of Pharmaceutical Technology and Bio pharmacy, University of Groningen.

Dr. Meg van Bogaert was appointed as independent secretary to the committee. Members of the committee signed a declaration and disclosure form to the effect that they would judge without bias, personal preference, or personal interest, and their judgment would be made without undue influence from the centre, the divisions, or other stakeholders. Any existing professional relationships between committee members and programs under review were disclosed. The committee concluded that there was no risk in terms of bias or undue influence.

Assessment criteria

The Strategy Evaluation Protocol 2021-2027 ('SEP') was the starting point for the committee's review. This protocol describes the aims and methods used to assess publicly funded research in the Netherlands.

SEP 2021-2027 identifies three main assessment criteria: (1) research quality, (2) relevance to society and (3) viability. Furthermore, SEP asks committees to take four specific aspects into account when assessing the three central criteria, see figure 1. These are: (1) Open Science, (2) PhD Policy and Training, (3) Academic Culture and (4) Human Resources Policy.

In addition to the guidelines and criteria suggested by the Strategy Evaluation Protocol, the committee

Figure 1: SEP-criteria and aspects

considered the Terms of Reference issued by the Executive Board of the university. LACDR posed four questions to the committee:

1. LACDR's average PhD duration is comparably long, the main causes being delays due to the involvement of PhD candidates in our education program and the negative effects of the Corona pandemic. What (additional) measures can we take to limit the duration of our PhD graduation times?
2. LACDR's divisions were created in 2016 as a result of decreasing income and group size in the years before. In the last six years, however, LACDR has seen strong growth mainly initiated due to the increased student enrolment and an external funding increase. Is the current internal structure, i.e., a clustering in divisions and a rather flat hierarchical structure of principal investigators still adequate?
3. LACDR is an institute with a strong education program. The career perspective of academic staff with a focus on education (mainly assistant professors) is perceived to be unclear. What measures can we take to further improve the position of academic staff based on teaching performance?
4. LACDR has the ambition to be at the forefront of both fundamental research and the translation of our research outcome into tangible products to be used e.g., by start-up companies or other collaboration partners. Do we have the proper instruments to stimulate the valorisation of our research?

The report addresses these questions provided the committee has sufficient information and knowledge to advise the LACDR on them.

Documentation

The committee received detailed documentation consisting of:

- Self-evaluation report 2016-2021, including appendices;
- Standard Evaluation Protocol 2021-2027;
- Sectorplan Pharmaceutical Sciences.

Working method

The site visit took place in Leiden on 1 and 2 December 2022. Before the site visit, the committee members were asked to read the documents provided above and formulate questions for the interviews. In an online kick-off meeting, one week prior to the site visit, the committee agreed upon procedural matters and discussed potential conflicts of interests. At the start of the site visit the committee discussed its preliminary findings. Professor Weil was unable to come to Leiden for the site visit, she attended several interviews online.

During the site visit, the committee met with representatives of the faculty and LACDR and discussed its findings. To conclude the site visit, the committee chair presented the main preliminary conclusions. The schedule for the site visit is included in appendix 2.

After the site visit, the chair and the secretary drafted a first version of the committee report, based on the assessments drawn up by the committee members. It describes the findings, conclusions, and recommendations of the committee. This draft report was circulated to the committee for all members to comment on. Subsequently, the draft report was presented to the LACDR and university for factual corrections and comments. After considering this feedback in close consultation with the chair and other committee members, the secretary finalized the report. The final report was presented to the Executive Board of the university and the board of the LACDR. The report was completed on 17 March 2023.

II. LACDR

Introduction

The Leiden Academic Centre for Drug Research (LACDR) is responsible for the research and education in Bio-Pharmaceutical Sciences and jointly with LUMC for the Master Pharmacy program, both conducted at Leiden University. The LACDR participates in the university-wide research profile area of *Collaborative and effective drug development*. The research is clustered within three divisions and one centre. The divisions are BioTherapeutics, Drug Discovery & Safety, Systems Pharmacology and Pharmacy. In addition, the Metabolomics & Analytics Centre is part of LACDR.

Strategy and mission

LACDR has the mission to be at the leading edge in developing novel scientific concepts and technologies in drug research. It has the ambition to perform fundamental, curiosity-driven and translational research at the highest possible level to set the stage for innovation that makes a difference, both in academia and industry. In the period 2016-2021, LACDR had five strategic objectives:

- Build a strong research and education environment in pharmaceutical sciences;
- Build a top-class pharmaceutical ecosystem in collaboration with strategic partners
- create and maintain an engaging internal culture
- Maintain strong links between academic research and teaching programs
- stimulate valorisation of research outcome

The committee appreciates the objectives that emphasize the starting point of concepts and technologies in the research of LACDR. Furthermore, the committee notes that LACDR took adequate action on the recommendations by the previous peer review committee (2016). One of these previous observations, however, remains according to the present committee: "…*LACDR wants to position itself as an institute with an almost industrial drug-discovery development program*." According to the self-evaluation report, the profile was sharpened though the committee has the impression that aspects of the LACDR strategy and mission remain focused on an industry-style ambition. The committee is of the opinion that LACDR's strategy could be further sharpened to differentiate more clearly from industrial pharmaceutical R&D and emphasize the unique strengths of the public status of LACDR. This may make the institute even more attractive as a collaborative partner for industry. The committee recommends a LACDR-wide discussion on its unique selling points (USPs). On this basis, a strategy for the coming years can be developed in which the LACDR explicitly profiles itself against both industry and other academic institutions. This strategic focus could be guided by the question: "Drug Research: what can LACDR contribute to society, what pharmaceutical companies cannot deliver?"

Organizational structure

LACDR is one of eight research institutes of the Faculty of Science at Leiden University. After the previous research review, the institute underwent a substantial change in its internal structure. The divisions represent the core research environment of LACDR and comprise their own management team. The division chairs, together with the scientific director, education director(s) and institute manager, form the LACDR management team (MT).

The description of the organizational structure as provided in the self-evaluation report was insufficiently detailed to allow an adequate evaluation. For example, the task and focus of the individual sub-functions of each division did not become entirely clear, particularly since some functions seem to have scientific and technological overlaps between divisions. For example, pharmacology functions exist in Drug Discovery and Safety (DDS) as Molecular Pharmacology but also in System Pharmacology & Pharmacy (SPP) as Predictive or Quantitative Pharmacology. However, the presentations of the three divisions and the centre (MAC) during the

site visit provided valuable additional information, resulting in a better understanding and clarification of the organizational set-up. Specifically, the LACDR management was able to convincingly explain the motivation for the departure of the Analytical BioSciences group from the SPP Division into a separate centre (MAC). This strategic step allowed MAC to obtain a higher degree of independence and increased external visibility. For the remaining SPP division, this departure of the Analytical BioSciences group means that the profile needs to be adjusted and sharpened.

LACDR went from discipline-focused departments to multidisciplinary divisions, each with 6-7 principal investigators (PIs). Overall, the flat hierarchy of the LACDR and division structure represent a meaningful organizational set-up. The rather independent PI role with less teaching and administrative tasks assures the high scientific standard of LACDR. This is evidenced by the numerous industrial collaborations and the successful acquisition of large national and international grants. The committee did notice that the three divisions and the MAC seem to exist rather independently, i.e., the cross-divisional activities and collaborations seemed to be limited and are evidently mainly based on personal contacts.

The committee believes that LACDR could be more strongly established as an umbrella above the divisions. At the moment, mainly the divisions, centre and PIs are in the lead while steering by the MT of LACDR seems limited. This leads to differences between the divisions/centre in the implementation of policies. Positive examples of LACDR corporate visibility are initiatives, such as spring and fall symposia, which are organized for the entire LACDR. Another positive example being the jointly used technical facilities such as the microscopy labs. In several interviews, LACDR researchers made it clear that this collectivity may be more prominent, both scientifically and socially. The committee encourages LACDR to provide more guidance - without restricting academic freedom within divisions - and to pursue a joint strategy.

HR policy and academic culture

In the review period, LACDR saw significant growth in its research staff. The hiring of new research staff involves the instalment of diverse appointment committees, open advertisement procedures and clear job profiles. The final decisive voice in the appointment lies with the scientific director, division chair and one of the education directors, safeguarding the embedding of the new staff member in research and education.

All tenure track assistant professors, associate professors and full professors have the status of PI, which includes the freedom and responsibility to design their own independent research lines within the mission and vision of their division. The institute is satisfied with the development towards the PI system, although there are still some areas for improvement. Criteria for becoming a PI are drawn up for internal promotions but seem not known to all candidates. Furthermore, unclarity has increased as a result of the tenure track PIs. The committee also notes that there are differences between the divisions regarding PI status. The assistant professors' immediate colleagues and supervisors have a lot of influence, resulting in different approaches that can in turn lead to friction (such as different starting packages).

LACDR is a flat and bottom-up organization, in which PIs exist already at the tenure-track level. This approach is valuable in the changing land-scape of Dutch – and even European - academia and might constitute an example for other universities. Also, the fact that new PIs are allowed to make their own research choices and receive a start-up package is very stimulating and probably attracts high potentials. The downside might be that the freedom reduces research focus within the division or cross-divisional research approaches. This could be detrimental for enough critical mass in specific research topics. The committee recommends to regularly organize a ‘fleet review’ (in Dutch: vlootschouw) of its PIs at LACDR level. By assessing all PIs on a set of four (self-formulated) criteria, the total of researchers can be evaluated in context and across divisions. It

furthermore makes clear to the research staff what is being considered important.

Talent management

The interviews during the site visit helped the committee to paint a more detailed picture of the talent management strategy at LACDR, and complemented the information from the self-evaluation report. As mentioned earlier in the report, the committee appreciates the introduction of the PI system. However, not all tenured research staff is PI. There are two options at the assistant professor level: PI-positions or with a 50:50 research/ education profile. Currently, new assistant professors receive a permanent position after 12-18 months.

Career perspectives are important for junior and mid-career researchers and similar to LACDR, the committee considers the Recognition & Reward initiative as a positive development. According to the LACDR-management, guidelines exist on expectations and career perspectives at LACDR. The committee has not seen these documents and cannot express an opinion on their content. However, the committee does understand that these documents do not seem to be widely used – or even known – by the staff members who should be using them. It was expressed that it is not always clear what situation the candidates are in and what their possibilities and opportunities are. The committee recommends that LACDR works on this.

Another concern that was mentioned was that, although it was stated that various positions receive similar appreciation within LACDR, e.g., tenure-track assistant professors vs teaching-oriented assistant professors, career perspectives for teaching-oriented positions are not similar to those in the PI-group. Importantly, although the promotion of teaching-oriented staff is under discussion at LACDR, it seems to be restricted by university wide policy. The committee would like to emphasize that the diversification of positions with equal valuation is important for a healthy future for the LACDR.

Workload

One major challenge that emerged during the site visit is the high teaching load at LACDR, involving all staff members, from PhD candidates to full professors. In the interview with LACDR management, it was mentioned to be a balancing act. According to the committee, the high teaching load significantly contributes to the substantial lengths of PhD thesis time, which will be more extensively covered in the chapter on the PhD Education and supervision program. The educational programs are popular, and the large student population demands a lot from staff members. This is often at the expense of research time. The previously introduced *numerus fixus* to moderate undergraduate intake has been lifted. From next year onwards, different intake requirements will apply (vwo-profile), so the expectation is that the intake will remain manageable. To address the teaching load, LACDR devoted several positions to 50% teaching alongside research, in particular for some of the PhD candidates and assistant professors. Even though it is clear to this group of assistant professors that they have 50% teaching duties, they also report that the teaching load exceeds the agreed time which might comprise their research time. Differences in the overall teaching load seem to exist on a case-by-case basis and differs between divisions.

In conclusion, despite various measures taken, the teaching load remains very high, in particular for some groups of staff. The committee has insufficient insight and information on this problem to offer concrete solutions, although it stresses the importance of continuing and evaluating measures. It is important here that differences in teaching load between different groups of staff (e.g. PIs, non-PIs and PhD candidates) do not become too large.

Diversity and integrity

A good gender balance is observed across all levels of the staff. Furthermore, the effort by LACDR to educate its staff members on diversity and inclusion is appreciated. By establishing a top-to-bottom (by LACDR management team) as well as bottom-to-top (by institute council) approach the LACDR manages to represent, hear, and discuss with all employees. This approach is

valuable and allows people at different levels to express their opinions. From bachelor's students to PhD candidates, courses are organized to educate students in scientific integrity and ethics.

Research quality LACDR

The committee is impressed with the quality of research across LADCR. All divisions have a good track record, very good publications, and an international network for collaboration. In Part IV of this report, the committee gives its findings on the divisions and centre.

The case studies presented in the self-evaluation report were largely division-specific and did not clearly demonstrate interactions across the divisions. This observation was partly confirmed by statements of the PhD candidates, who expressed that cross-divisional activities are largely dependent on their own initiatives or if the group heads, division heads or PIs already have standing cross-divisional relationships for a specific topic. There might be opportunities to further institutionalize the existing collaborations and thus leverage synergies and joint expertise. A more organized and structured way of collaboration between the divisions could further strengthen the LACDR as an institute. Especially since the committee sees an overlap between different divisions. At the same time, LACDR provides technological platforms (as demonstrated at the microscopy facilities and the metabolomics labs), which already serve as basis for a cross-divisional collaboration. Furthermore, MACs leading role in data science & management could also represent an topic for a stronger cross-divisional collaboration.

In the self-evaluation report and in interviews, translational research and the pipeline approach were emphasized. The divisions also mentioned this aspect, although the committee does not see it reflected sufficiently clear in the joint LACDR perspective. From the interview with LACDR management, the committee understood that the institute does not cover the entire pipeline, but works on parts of the process with specific focus on knowledge, risky fields and slightly ahead of industry. With this, they spark the interest of industry and clinics, and in collaboration they are able to take developments to the next stage. Currently, about a third of publications are set up in collaboration with industry.

Facilities and infrastructure

During the site visit the committee visited part of the facilities and infrastructure. The committee was impressed by the state-of-the-art facilities which are well fitting with the fundamental and curiosity-driven research ambitions of LACDR. The committee acknowledges the threat that was mentioned by the LACDR management on the fact that lack of lab and office space might deter recruitment opportunities and retaining of top scientists. Furthermore, expensive research technologies are not acquired or maintained from direct funding but from highly competitive research grants. This challenge is not unique to LACDR, but entails a potential threat to keeping facilities state-of -the-art. The committee is positive about the fact that part of the sectorplan funding will be dedicated to keeping infrastructure updated.

The committee furthermore commends the excellent surrounding in which LACDR finds itself in: the bioscience park and in close proximity to CHDR and LUMC. There are many links and collaborations with these institutes and organizations.

LACDR is looking forward to moving to a new building in 2023/2024, part of this building is already in use. LACDR will then benefit from having all researchers working in the same building.

Funding

Total funding has increased significantly over the period of this review, from 15 m€ to over 22 m€. This is mainly due to the increase in direct funding. At the same time, LACDR shows that second and third streams also provide a stable source of income. The approval of the Pharmaceutical Sciences sector plan will ensure further increases in the total budget, making the financial future of LACDR look bright.

Relevance to society

Similar to the quality of research, the committee provides its findings on the societal relevance of the divisions and centre in Part IV of this report. Based on the interviews and cases in the self-evaluation report, it is clear that the impact on society is impressive. However, the committee has the impression that LACDR is underselling itself on this criterion. At the institute level, the committee suggests that LACDR should reflect on its definition of impact and relevance. This does not need to be always quantitative, or valorisation. Specifically for an academic institute, other impact factors are also important and valuable. LACDR seems to undervalue its results and impact, e.g., on patient engagement, contribution to 3R, development and qualification of new approach methods (NAMs), drug target identification and target safety assessment as well as regulatory training (see also the comments regarding the LACDR mission and strategy). This could also be more strongly present on LACDR's website.

According to the committee it is important to convey knowledge of relevant regulatory guidelines to ensure that the research results can be used in a later phase for regulatory assessments and decision making. This knowledge on regulatory guidelines is also relevant in educating PhD candidates and undergraduate students in Bio-Pharmaceutical Sciences and Pharmacy. In addition, LACDR has the possibility of influencing such regulatory frameworks through its own research (e.g., in the field of NAMs).

Open Science

Open science is pursued in several ways by LACDR. Open access publications is one aspect of open science. The percentage of open access publications has steadily increased from 66% up to 94% publications being open access (gold, hybrid, bronze or green).

Another aspect is data management and data access. A working group has been established with representatives from each division, dealing with both technical and policy topics related to good data management practices. One of the outcomes was the recruitment of a dedicated data steward who will train LACDR researchers in FAIR practices. According to the LACDR management, a lot of developments have taken place over the past years, although there are differences between divisions to what level FAIR principles are internalized.

The committee is of the opinion that LACDR is doing very well regarding open science and it commends the institute for the achievements in the evaluation period, with a leadership role by MAC. However, further progress on implementation is possible, in particular in some divisions. LACDR would benefit from a joint approach and central steering. This particularly pertains to research activities covering aspects of data science, where new databases or IT applications are developed, which require sustainable storage or handling. Specifically, a clear plan and timeline would help the divisions and PIs to do their parts.

Viability LACDR

According to the committee, LACDR has many strengths that led to high-quality research in the period of evaluation, like the quality of the research staff and PhD candidates, the new, flat organizational structure, societal relevant research topics, facilities and sectorplan funds. If LACDR takes into account its recommendations, the committee is confident that a bright future lies ahead.

III. PhD Education and supervision program

PhD training

PhD candidates of LACDR are formally embedded in the Graduate School of Science (GS) of Leiden University. In addition, LACDR established a comprehensive PhD Education & Supervision program to support PhD candidates in their daily activities. At the start of a PhD-trajectory, an education and supervision plan (ESP) is prepared. PhD candidates should at least spend 140 hours on academic training activities and another 140 hours on transferable skills. For this, LACDR offers mandatory and optional courses. According to the committee, the overall rules and training opportunities are sufficient.

PhD guidance and supervision

The amount and frequency of supervision, daily, weekly, or monthly of PhD-candidates differs strongly and is highly dependent of the specific promotor. Some PhD candidates are satisfied with the level of supervision while others would have liked more regular and frequent meetings.

PhD candidates are guided by a PhD-advisory committee (PAC), that consists of the program director, (co)supervisors and an advisor. Annual meetings with the PhD-candidate and the PAC are organized to provide guidance in the PhD trajectory. The involvement of an advisor, in the committee's opinion, is a good addition of the PAC. The advisor must be independent and not be involved in the PhD-candidates PhD trajectory, so they can provide advise and guide unbiased. There is not a clear way in how this advisor is invited for a specific PAC. According to the committee, to be independent, this advisor should not be chosen by the (co)-promotor but rather by the PhD-candidate.

Duration of PhD trajectories

The graduation time of the current and previous cohorts of PhD-candidates is far too long. The committee concurs with the statement in the self-evaluation report that teaching load of nearly all PhD-candidates is (too) high and should be lowered. This is also important to assure international competitiveness of graduates.

Other, smaller factors also might play a role, like the corona crisis, the move to a new building and overambitious PhD candidates wanting to publish more than requested. However, the main reason for the long duration of PhDs is the high teaching load. For some of the PhD-candidates, teaching load is unexpectedly high and impacts the amount of time that can be spend on research. The committee is of the opinion that teaching load should be clearly clarified (in the contract) before hiring a new PhD candidate, the agreed teaching load may not be exceeded and should be evaluated in the Education and Supervision Plan (ESP) and/or PAC during the PhD-trajectory.

During the site visit, the committee learned that the teaching load for PhD candidates seems to differ significantly between divisions. Although the committee understands that teaching load differs between divisions, this should not impact the teaching load of individual PhD candidates. There should be better regulation and clarification on the teaching duties of PhD-candidates, for example by setting a maximum on teaching hours/number of BSc/MSc students that PhD-candidates can supervise.

To help managing the teaching load, LACDR developed a 'new' PhD position, the educational PhD. This group of PhD-candidates is hired for an additional one or two years, will get more extensive teaching training and more 'compulsory' teaching duties as well as a teacher-diploma (BKO). Such positions are certainly an opportunity to strengthen the educational skills of those PhD candidates who are interested. In the committee's opinion, this is a good development, although the discrepancy between a 'normal' and an 'educational' PhD candidate is not sufficiently clear within the LACDR.

Wellbeing of PhD candidates

During the site visit, it was mentioned that well-

being of the PhD-candidates will get specific attention in the upcoming period. It seems that the high work-load, especially due to teaching duties is a burden to the candidates. According to the committee, the high work-load, burn-outs and well-being issues might be reasons for delayed or no graduation. It therefore might indeed be good to further increase attention to these issues. The committee got the impression that not all PhD candidates feel free to speak openly about mental health issues in their PI group. Moreover, not all PhD-candidates are aware of the availability of confidentiality persons and/or PhD-psychologists at the university.

Future career perspectives

Career perspectives seem to be good for LACDR graduates, often graduates move to industry in the surrounding bioscience park Leiden. During their trajectory, PhD-candidates follow courses in transferable skills, for example entrepreneurship. Career opportunities are not a standard point of discussion in the annual interview (with the PAC), this could be a good addition.

IV. Divisions and Centre

Drug Discovery and Safety

The Drug Discovery and Safety (DDS) division has the mission to resolve the unmet medical need for novel drug targets to establish or improve the treatment of life-threatening diseases. By employing novel innovative technologies for drug target and drug lead identification and optimization, as well as test methods to uncover pharmacological and toxicological mode of action, DDS contributes to developing efficient and effective drug discovery process.

Research quality

DDS has achieved a high international reputation in the field of toxicology, which is evidenced by the number of publications, the successful acquisition of national and international grants over a longer period of time (e.g., IMI projects, European FP7 and Horizon 2020 grants) and a high level of valorization (licenses to OcellO, later Crown BioScience, Hello Science and Toxys). Some of the DDS developments have found entry in industry use (e.g., ToxProfiler of Toxys). Some of the *in-silico* developments of DDS would require attention with regard to sustainability of the valuable assets (e.g., Tox-MAPR). The self-evaluation report quotes funding acquired by DDS of > € 30 million in the evaluation period. Although comparative figures were not reported for the other divisions, and it was not possible to calculate the percentage to the overall research budget, the number it is estimated to be substantial.

Facilities are outstanding, DDS is well equipped with cutting-edge technologies like tempoSeq, CRISPR and computational tools.

As depicted in the self-evaluation report, DDS claims to cover the early phases of drug discovery and developments from hit over lead to early safety assessment. During the hit-to-lead phase of drug discovery the major scientific and technological contributions are provided by Medicinal Chemistry (synthesis of candidates) and Pharmacokinetics (evaluation of key phys-chem and metabolic parameters. Some of these activities can certainly be performed with *in silico* approaches, but eventually a confirmation of a new candidate would require compound synthesis and experimental evaluation. One of the experts in Medicinal Chemistry retired in 2021 and from the self-evaluation report and the subsequent presentation during the site visit, it did not become entirely clear where these activities are currently situated.

Relevance to society

In two international projects DDS has delivered remarkable contributions to the field of 3R, namely “New approach methods” (NAMs) and Next Generation Risk Assessment (NGRA). Particularly the latter aspect (NGRA) is of high societal relevance, since NAMs will only find their entry into future regulations, if current regulation is revised accordingly.

In its projects, DDS has always strived for an active involvement of regulatory experts and agencies profiting inter alia from its contacts to RIVM. DDS should further build and develop this societal contribution by e.g., providing lectures on regulatory aspects of safety assessment and drug development (which could also be run in a cross-divisional set-up) and training courses for regulators in the field of NAM and NGRA, thus shaping and impacting future drug and chemical regulation in Europe.

Viability

DDS might consider to further develop its interaction with industry. During the site visit a cross-divisional project on adenosine receptor antagonists was presented. Such drug target projects could allure the interest of industry, if an appropriate platform for presentation of such target discovery projects and potential drug candidates can be identified.

BioTherapeutics

The BioTherapeutics (BT) division focuses on advancing innovative biopharmaceutical concepts, such as biologicals, small molecules and nanomedicines, to control disease progression and enable novel therapies against diseases with a strong (auto-)immune component. According to the committee, this division has a very broad scope (vaccine development, cardiovascular diseases, oncology and immunotherapies) and a strong immunological focus. These focus points are not necessarily reflected in the division's name. The committee considers a name change appropriate, e.g., Immunotherapies.

Research quality

The committee thinks that the BT division has been doing very well in the evaluation period. The research output is impressive, which is reflected in the very good publications in leading journals. BT has also done very well in attracting external funding both national and international, in particular for PhD and postdoc positions. BT is involved in the national nanomedical research network to further improve the position of the Netherlands in nanomedicine research. BT is actively working on improving the nanomedicine skillset, for example by computational methods.

Notwithstanding the impressive quality of the research by the division, the committee is of the opinion that the focus might be too broad and scattered to maintain the present level of quality. This challenge is reflected in the lack of common understanding of what the division aims for, the committee did not encounter a common view. This may be due to the origins of the division, in which two groups were merged. Currently, BT has several vacancies at the senior level, according to the committee this to be a major opportunity to increase coherency within the division.

BT oversees the facilities for nanoparticle characterization and the animal research facility. This gives the opportunity for collaboration between PIs and divisions within LACDR. However, at this moment, this does not seem to be used at its maximum potential. Furthermore, there is currently no clear focus on the development or use of translational models without using laboratory animals. Here, there should be room for collaborations between surrounding hospitals and industry.

Relevance to society

BT aims at bridging fundamental and translational research and engages with society by close interactions with patient organizations, foundations and stakeholders in research consortia, for example, by fulfilling a leadership role in a consortium on dermatology, connecting all UMC's. In line with the vision of LACDR, the division aims to intensify collaborations with pharmaceutical industry, start-up companies and has the intention to establish a spin-out company. Increasingly the translational research structure is taking shape, and the BT division has started collaborations. The zebrafish model is ideal as an *in vivo* translational model in vaccinology or nanomedicine and could partly replace the use of mice, however, there should be more focus on *ex vivo* and *in vivo* translational models, to eliminate the use of animals. *Strong* output is not yet visible, but longstanding collaborations are important to achieve societal impact.

An interesting and emerging direction to connect to hospitals and other industrial partners, according to the committee, might be to shift attention towards emerging AI and machine learning approaches.

Viability

With the departure and/or prolonged absence of several researchers, the division will have to consider its future activities and strategy. The different PIs collectively have a heterogenous profile, leading to a lack of consistency and seniority within the division. During the site-visit it became clear that the division is very much aware of this, and that due to the recent changes this is not entirely resolved yet. To the committee it is not entirely clear whether the focus of the BT division is on disease-understanding or on development of therapies. The committee questions whether available resources are adequate to follow both objectives.

Systems Pharmacology and Pharmacy

The division of Systems Pharmacology and Pharmacy (SPP) is structured according to five PI-groups. In the context of organizational change within the division (separation of MAC and addition of Pharmacy), SPP has maintained its activities in the fields of clinical pharmacology, systems pharmacology, and population PK-PD modelling, while new PIs (or those who recently joined LACDR) initiated new themes such as organ-on-chip models and developed new application fields such as infectious diseases.

Research quality

Over the evaluation period, SPP has been successful in terms of European and national funding. The scientific output is of outstanding quality, with an impressive average of scientific articles produced by the PIs over the evaluation period. Some members of the SPP-division are involved in national research networks and also in national and European academic foundations and review committees.

The research activities are conducted in a strong collaborative context with other institutes of the Faculty of Science at Leiden University, e.g., the institutes of biology, mathematics, physics and chemistry. Local collaborations with other Leiden institutes were formalized through appointments of two full professors from LUMC Pharmacy and the CHDR.

Relevance to society

In terms of relevance to society, the SPP-division has established many collaborations with clinical partners, both within and outside Leiden University. The committee stresses furthermore that SPP researchers received funding from patient/disease organizations in several projects, and from the Gates foundation. Also, in the period of this review, research staff has been involved in a number of projects in collaboration with industry, such as IMI projects. Clinical collaborations are logically based on the expertise of SPP-members in the field of pharmacokinetics, with input aiming at optimizing drug treatments in special patient populations. Finally, the collaboration with the Department of Clinical Pharmacy and Toxicology (LUMC) is noteworthy, especially in the context of the recent reorganization.

Viability

In terms of viability, it was unclear from the self-evaluation report how SPP plans to embed the new staff members - involved in Pharmacy – in the division. The strategy on how the division will further diversify from the activities of the previous division, Systems Pharmacology and Biomedicine and to which extend the organizational change impacted research activities remained unclear from the self-evaluation report.

These aspects were clarified during the site visit, during the discussion with the PIs. This led the committee to believe that the merger with the research staff involved in the Master's program of Pharmacy makes sense. It provides a good opportunity to continue the development of expertise in the division in the fields of PK-PD and quantitative systems pharmacology, while strengthening the link with clinical data and artificial intelligence approaches. The committee encourages the SPP - members to continue in this direction. The committee does recommend to this division to sharpen its profile towards including the current research activities and expertise.

Metabolomics & Analytics Centre

The Metabolomics & Analytics Centre (MAC) was created after the reorganization of the former Systems Pharmacology and Biomedicine division in 2021.

Research quality

The centre performs active and successful methodological research for metabolomic applications in the field of health, from sample preparation to data interpretation. Research activities are performed in the context of national and international consortia and through the obtaining of important national, EU and NIH fundings. It must be stressed that MAC has developed expertise and knowledge for handling large-scale clinical studies in terms of data production, processing and interpretation. The committee was impressed by the level of automation. MAC is clearly one of the leading groups in the field of metabolomics applied to personalized medicine at an international level, with pioneering activities for connecting FAIR metabolomic data to clinical metadata of patients in order to obtain metabolomic signatures of diseases and response to therapies. Scientific staff from MAC organized and chaired two congresses: “Metabolomics 2019” and “Microscale separation and bioanalysis 2017”.

During the site visit, questions by the committee were clarified regarding the internal organization of MAC and balance between methodological research activities and collaborative projects in the field of personalized medicine. The committee is satisfied with the way MAC monitors and prioritizes this balance.

Relevance to society

In terms of relevance to society, five patents were filed on miniaturization and high throughput technologies for handling small volume biological samples. Furthermore, research activities contributed to the creation of two spin-off companies. The committee was impressed by the effectiveness in obtaining external funding for structuring and large-scale projects and initiatives, involving industrial and hospital partners. Also the willingness to apply tools developed to public health (COVID-19 project) and economic and ethical issues, e.g., metabolomics for determining the sex of chicken eggs. Although not explicitly discussed during the site visit, the committee concludes from the SWOT-analysis that university-imposed rules limit the creation of and participation in companies.

Viability

With respect to viability, the initial questions by the committee on creating a separate centre with only one PI were clarified in the discussions with MAC staff. The multi-disciplinary research activities are carried out by senior scientists who are leading independent research lines, and by PhD candidates and post-docs. The research is funded by collaborative networks with industrial and hospital partners, with data production and analyses performed by Biomedical Metabolomics Facility Leiden (BMFL). The strategy is based on methodological research for data production and analysis, and on application of the developed tools to analyses of biological samples coming from personalized medicine projects.

In conclusion, the committee found MAC's organizational structure to be efficient, effective and sustainable. The ambition of coupling FAIR metabolomic data to FAIR clinical metadata, or even *real world* data by developing artificial intelligence-based approach should be supported, especially in the frame of collaborations between LACDR and LUMC. Furthermore, the committee also recommends to continue supporting upstream methodological research for FAIR data production, processing and interpretation, which should help MAC maintain its position as an international leader in the field.

V. Conclusion and recommendations

The committee commends LACDR with the excellent research that was performed in the period of the evaluation, this is a clear sign that the institute is successful. Furthermore, the committee appreciated the openness by LACDR staff in the meetings during the site visit. This provided the opportunity for an open conversation in which the committee was able to ask questions with the goal of seeking opportunities to further strengthen the LACDR. The committee has the following recommendations:

- Relating to the strategy and mission, the committee recommends that LACDR organizes an institute-wide discussion on its unique selling points (USPs). These can subsequently be translated into a strategy for the upcoming period in which LACDR explicitly profiles itself complementary to both industry and other academic institutions.
- The flat, bottom-up PI structure that is introduced is valuable with respect to academic freedom of the PIs. At the same time, LACDR would benefit from more central guidance or steering to pursue a joint strategy. One of the measures that could be used is a regular fleet review at LACDR level.
- More transparency is required regarding career opportunities for academic staff, in particular in the education area. Furthermore, support by the faculty and university is required to allow for career development opportunities based on education and teaching performances.
- The workload is high, partly due to the success of the educational programs. Despite various measures being taken, the teaching load remains very high, in particular for some groups of staff. The committee stresses the importance of continuing to take and evaluate measures. It is important that differences in teaching load between different groups of staff (e.g., PIs, non-PIs and PhD candidates) is transparent and does not become too large.
- LACDR is doing well in terms of open science, further implementation is stimulated by the committee, specifically in some divisions.
- It is important to convey knowledge of relevant regulatory guidelines to ensure that research results can be used in a later phase for regulatory assessments and decision making.
- Increasing attention is given to PhD training and supervision. Nevertheless, the duration of PhD trajectories is often too long, and the teaching load of most PhD candidates is very high. The committee has several recommendations to further improve the position and wellbeing of PhD candidates:
    - PhD candidates strongly depend on their supervisor. If issues occur, this is problematic for the candidate. The LACDR PhD office could work on introducing safety measures, PhD candidates can find support if issues arise.
    - The teaching load of nearly all PhD candidates exceeds what is acceptable and should be reduced. PhD candidates teach a significant amount of their time that cannot be spent on research. This is the major reason for the long duration of PhD projects. There are furthermore differences between divisions in teaching load for PhD candidates. It is important to be transparent on the expectations at the start of a PhD project. LACDR should furthermore regularly check/evaluate if the amount of time spent on teaching is in line with this agreement.
    - The committee is positive about the PhD Advisory Committee (PAC), which is a valuable tool to support PhD candidates. It is important, however, to let the PhD candidate choose his/her own advisor. The PAC might furthermore include future career opportunities of the PhD candidate in its meetings.
    - In the period of evaluation, the LACDR PhD office has worked on structure and procedures for PhD candidates. The next step is to enforce this policy and clearly communicate expectations to both PhD candidates and supervisors.

VI. Appendices

Appendix 1: The SEP 2021-2027 Criteria and Categories

The committee was requested to assess the quality of research conducted by the UHS as well as to offer recommendations to improve the quality of research and the strategy of the UHS. The committee was requested to carry out the assessment according to the guidelines specified in the Strategy Evaluation Protocol. The evaluation included a backward-looking and a forward-looking component. Specifically, the committee was asked to judge the performance of the unit on the main assessment criteria and offer its written conclusions as well as recommendations based on considerations and arguments. The main assessment criteria are:

1) Research Quality: the quality of the unit's research over the past six-year period is assessed in its international, national or – where appropriate – regional context. The assessment committee does so by assessing a research unit in light of its own aims and strategy. Central in this assessment are the contributions to the body of scientific knowledge. The assessment committee reflects on the quality and scientific relevance of the research. Moreover, the academic reputation and leadership within the field is assessed. The committee's assessment is grounded in a narrative argument and supported by evidence of the scientific achievements of the unit in the context of the national or international research field, as appropriate to the specific claims made in the narrative.

2) Societal Relevance: the societal relevance of the unit's research in terms of impact, public engagement and uptake of the unit's research is assessed in economic, social, cultural, educational or any other terms that may be relevant. Societal impact may often take longer to become apparent. Societal impact that became evident in the past six years may therefore well be due to research done by the unit long before. The assessment committee reflects on societal relevance by assessing a research unit's accomplishments in light of its own aims and strategy. The assessment committee also reflects, where applicable, on the teaching-research nexus. The assessment is grounded in a narrative argument that describes the key research findings and their implications, while it also includes evidence for the societal relevance in terms of impact and engagement of the research unit.

3) Viability of the Unit: the extent to which the research unit's goals for the coming six-year period remain scientifically and societally relevant is assessed. It is also assessed whether its aims and strategy as well as the foresight of its leadership and its overall management are optimal to attain these goals. Finally, it is assessed whether the plans and resources are adequate to implement this strategy. The assessment committee also reflects on the viability of the research unit in relation to the expected developments in the field and societal developments as well as on the wider institutional context of the research unit.

During the evaluation of these criteria, the assessment committee was asked to incorporate four specific aspects. These aspects were included, as they are becoming increasingly important in the current scientific context and help to shape the past as well as future quality of the research unit. These four aspects relate to how the unit organizes and actually performs its research, how it is composed in terms of leadership and personnel, and how the unit is being run on a daily basis. These aspects are as follows:

4) Open Science: availability of research output, reuse of data, involvement of societal stakeholders.

5) PhD Policy and Training: supervision and instruction of PhD candidates.

6) Academic Culture: openness, (social) safety and inclusivity; and research integrity.

7) Human Resources Policy: diversity and talent management.

Appendix 2: Program of the site visit

Thursday 1 December 2022	
9.00 - 10.15	Arrival and preparatory meeting committee
10.15 - 11.15	Management meeting
11.15 - 11.30	break
11.30 - 12.15	Division Drug Discovery and Safety (DDS)
12.15 - 13.00	Lunch
13.00 - 13.45	Division BioTherapeutics (BT)
13.45 - 14.00	Break
14.00 - 14.45	Division Systems Pharmacology and Pharmacy (SPP)
14.45 - 15.00	break
15.00 - 15.45	Metabolics & Analytics Centre (MAC)
15.45 - 16.30	Break and committee meeting
16.30 - 17.30	Lab tour
Friday 2 December 2022	
9.00 - 9.45	PhD candidates
9.45 - 10. 00	break
10.00 - 10.45	Postdocs and mid-career scientists
10.45 - 11.00	break
11.00 - 12.00	management
12.00 - 13.00	Committee meeting and lunch
13.00 - 13.30	Feedback – oral presentation chair

Appendix 3: Quantitative data

Table 1: Research staff in FTE

	2016		2017		2018		2019		2020		2021	
	FTE	#	FTE	#	FTE	#	FTE	#	FTE	#	FTE	#
Scientific staff	21.6	31	24.2	28	26.3	30	29.7	32	30.2	34	32.9	36
Postdocs	26.8	38	23.5	35	21.0	34	26.2	39	32.5	44	33.0	43
PhD candidates	57.1	68	54.7	70	56.0	73	57.3	75	65.1	91	78.5	94
PhD Candidates external	14.0	14	17.0	17	20.0	20	24.0	24	24.0	24	28.0	28
PhD Candidates independent	23.0	23	21.0	21	19.0	19	18.0	18	19.0	19	17.0	17
Total research staff	**142.5**	**174**	**140.**	**171**	**142.3**	**176**	**155.2**	**188**	**170.8**	**212**	**189.4**	**218**
Support staff	23.5	32	25.7	37	22.9	29	21.4	29	24.7	35	27.5	37

Table 2: Main categories in research output

categories	2016	2017	2018	2019	2020	2021
Journal articles (refereed)	147	156	151	182	161	144
Books			1			1
Book chapter	3	3	4	2	2	7
PhD thesis	13	24	13	15	15	16
Datasets, digital infrastructures and databases	0	16	10	23	26	8
Software			4	1	7	12

Table 3: funding in M€

	2016		2017		2018		2019		2020		2021	
	M€	%	M€	%	M€	%	M€	%	M€	%	M€	%
Total direct funding*	6.8	44	7.7	49	8.0	63	9.0	50	9.6	47	13	57
Research	*3.2*		*3.2*		*3.0*		*3.4*		*2.2*		*3.3*	
Education	*2.9*		*3.8*		*4.4*		*5.5*		*5.9*		*6.7*	
Special funding	*0.7*		*0.6*		*0.6*		*0.1*		*1.5*		*3.1*	
Research grants	4.9	31	4.7	30	5.2	34	6.6	37	7.6	38	5.9	26
Contract research	4.0	25	3.3	21	2.0	13	2.5	14	3.0	15	3.9	17
Total funding	**15.6**	**100**	**15.6**	**100**	**15.2**	**100**	**18.1**	**100**	**20.3**	**100**	**22.8**	**100**

* Direct funding is divided into three categories