

WHITEPAPER



FROM EVIDENCE TO CONSEQUENCE



INTRODUCTION

A new reality is emerging in the Danish healthcare sector. Perhaps the clearest indication of this is the establishment this year of the priority institute Medicinrådet. In the new reality, more than ever before, public funding bodies and medical authorities will prioritise medicines on the basis not just of clinical evidence and real world outcomes, but also social norms.

In this new reality Market Access will play a vital role in aligning evidence with norm-based arguments that funding bodies and decision-makers for medical treatment will accept. Evidence, in other words, will no longer be enough.

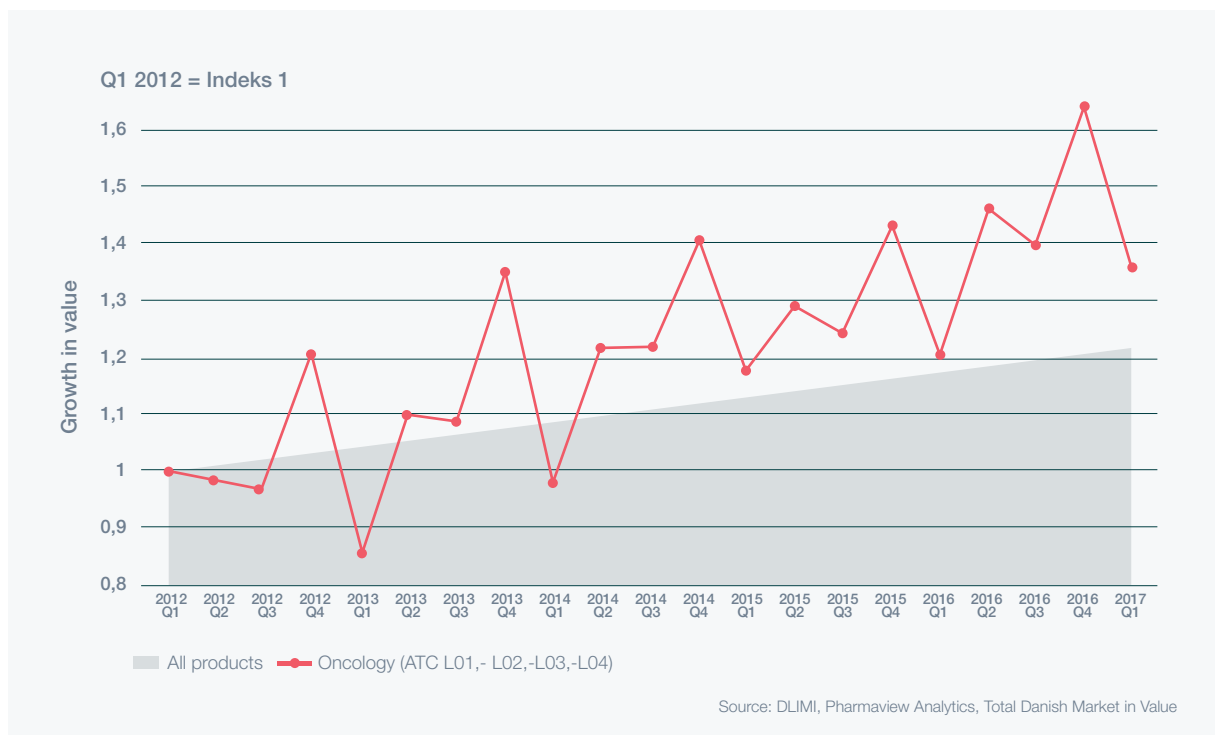
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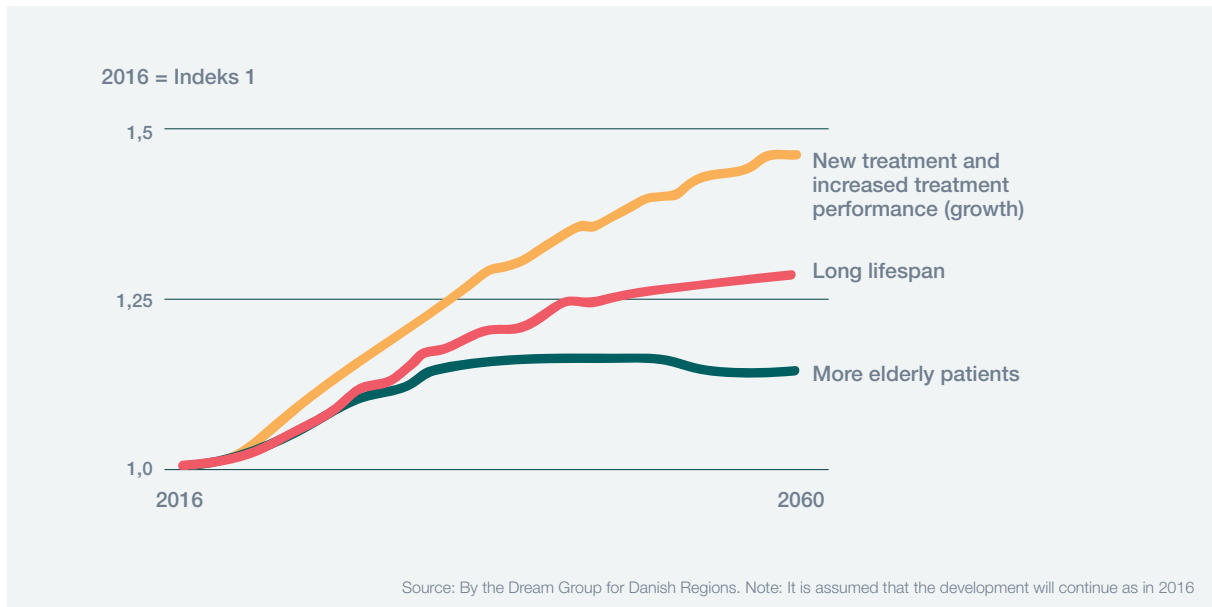
THE NEW REALITY

Until now the political bodies at national and regional level responsible for the delivery of medical treatment have been largely successful in controlling costs. However, they know this cannot continue. It is already clear that the collective cost of oncology will soon mean that the total cost of medical treatment in the Danish healthcare system may spin out of control (see Fig 1).

Fig 1: Growth in medical costs for oncology and total market¹



On top of this, economic forecasters predict that a massive increase in health spending will result from longer life spans, increased numbers of elderly citizens, and the introduction of costly new healthcare treatments.

Fig 2: Economic forecast of health expenses²

Obviously, economic resources are limited. Already, they are reducing spending on medicine by a billion kroner a year, and further reductions in medical spending are factored into their planning.

The Danish regions are not underestimating this challenge. With medical spending heading towards unsustainable levels if it is not contained, they required an instrument that ensured optimal treatment for an optimal price. To this end, the regions established the priority institution Medicinrådet (Danish Medicines Council) in 2017. The creation of Medicinrådet signalled a new reality for the Danish healthcare market in general – a reality in which the prioritisation of medical treatments is not based on evidence alone.

” *Value based management will be a paradigm shift in the healthcare system. We will have growing focus on monitoring the outcome for the patient, the entire patient journey and reducing healthcare costs per capita. This is a change in culture“*

Danish Regions, 2017³

In this paper, we describe this new reality and underline the important role Market Access plays in bridging clinical evidence and market authorisation with treatment in daily practice. We also show how real world data can be used in dealing with the less objective elements in the prioritisation of medicines.

To understand how this new reality changes decision-makers' choice of medicines, and how – consequently – this will affect pharmaceutical organisations, we need to take a step back in time.

The selection of medicines to be used

It was not too long ago that decisions to use – or not use – newly introduced medicines were made by individual doctors. Based on the evidence at hand, each doctor could make his or her own assessment of the optimal treatment for a patient. Thus, via a trial and error approach, doctors built their own experience of how well new medicines performed in a real world setting.

However, with the rise of evidence-based medicine in the 1970s, medical communities focused increasingly on the need for an evidence-based consensus within their medical specialities. This resulted in the development of, among other things, the national recommendations which now govern choice in medicines more than ever.

In practice, national recommendations invariably involve an evaluation of the consequences of a medical treatment in terms of implications and wider impacts for both patients, for the healthcare system, and even for healthcare resources. This evaluation is unavoidable, because the recommendations need to be operationally feasible. Thus, there is always an element of consequence assessment underlying recommendations – even if that part of the assessment is, in most cases, hidden behind medical evidence.

With the establishment of Medicinrådet, 'cost of treatment' will affect the final recommendation as to which medical treatment is to be prioritised. Likewise, economic implications are factored into the Reimbursement Committee's recommendations and are taken into account in the Rational Pharmacotherapy's National Recommendation List, underlining that the cost of treatment is a cornerstone in the new reality.

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The price for expensive medicines, still, is a pivotal element in budgeting for the hospitals in Denmark's largest region”

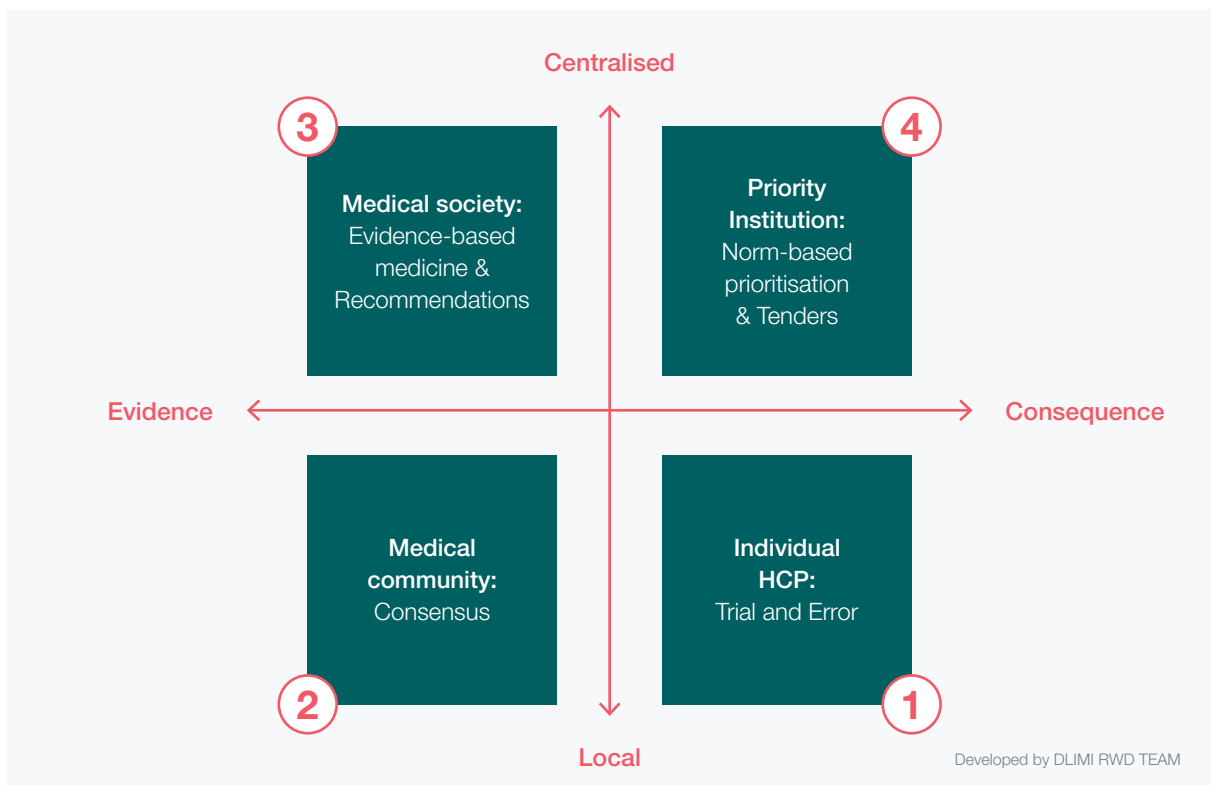
Sophie Hæstorp Andersen, Chairman Regional Council, Hovedstaden (Capitol Region)

Politicians in Denmark have decided not to use QALYs, which are a quantified measure of a medical treatment's effect on disease burden, when prioritising the use of medicines. Consequently, we have no clear measuring stick for assessing medical treatments beyond their purely clinical outcomes. This, in turn, leaves room for less formalised criteria for assessing the societal benefits of treatments.

It can be seen, then, that decisions to recommend and use medical treatments are suspended between two axes:

1. An organisational axis for decisions, with 'centralised decisions' represented in national guidelines on the one hand and 'local decisions' best represented by the individual treatment choices doctors make for their patients on the other.
2. An assessment axis of the medical treatment, with the assessment of 'evidence' from scientific studies contrasting with the assessment of real world 'consequences' of the treatment choice based on experience.

Fig 3: Decision-field for choice of medical treatment in public healthcare



In mapping out the two axes, we can identify four decision-fields:

1. Individual HCPs (e.g. doctors) – and their personal assessment of a treatment based on trial and error experience.
2. Medical communities (e.g. groups of specialists) – and the disciplinary consensus that communities of doctors build.
3. Medical societies – and the Evidence-based recommendations developed in order to implement rational choice in treatment.
4. Priority institutes – and the assessment of the treatment based on social norms in the society.

The point is that a choice of medicine will in fact involve all four decision-fields. However, with different decision-makers, one field may have more weight than the others – and fields may even come into direct conflict. Doctors' choices and medical treatment recommendations are of course based on evidence. Yet, it should also be obvious that individual doctors as well as collective groups of decision-makers reflect on the consequences of their choices and recommendations in relation to the patient (population) and the use of healthcare resources. To emphasise the point, treatment decisions do not stand on evidence alone. They also reflect social norms against which issues such as cost of treatment versus treatment outcome versus patients' quality of life are balanced.

So there will always be some level of assessment of the societal, ethical and budgetary consequences of recommendations as well as the individual choice of the doctor.

When moving from evidence to consequence, decision-makers will include norm-based factors that allow them to assess the consequences of recommending or choosing one medicine rather than another. The reason for this is simple: medical evidence alone has nothing to offer when it comes to ethical considerations, decisions about optimal treatment or the use of health resources in a real world setting.

” *Values and political decisions frame how we prioritise. We may, however, forget or try to hide these values behind the clinical knowledge when prioritising. But, medical recommendations are always also value-based... political – and should therefore be an object for ethical and political debate*”

Mickey Gjerris, Associate Professor in Bioethics, former member of The Danish Council on Ethics

Norm-based decisions are tied up with different social values, moral categories, cultural norms, and even political agendas, that decision-makers use in order to assess the consequences of recommending or choosing medicines. This makes the decision-makers susceptible to the norm-based arguments of, for example, patient advocacy organisations, HCP organisations, funding bodies and public media.

We predict that the norm-based decision-field will become increasingly important in the future, since:

1. Treatment choices will continue to be centralised with the growing importance of national guidelines
2. National health budgets are under pressure, motivating the prioritisation of medical treatment
3. Prioritisation, i.e. the move from evidence to consequence, has now been fully realised in Denmark with the introduction of Medicinrådet

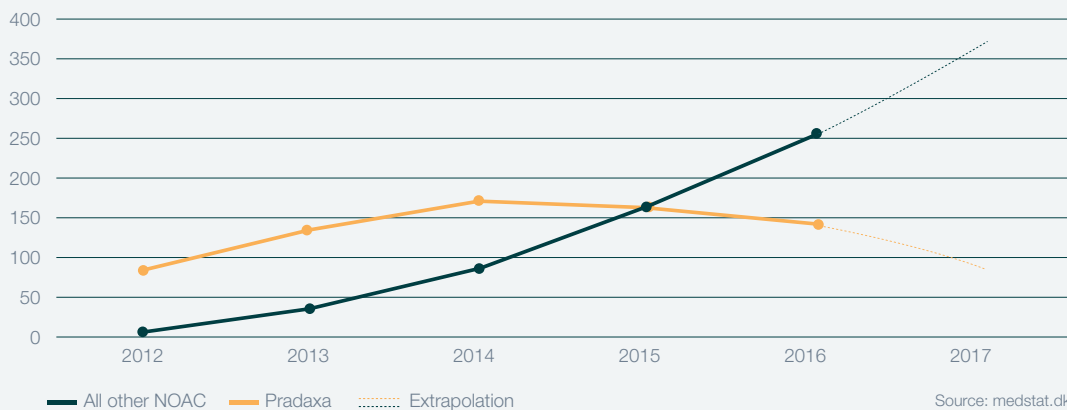
Given this, we shall now look at how the pharmaceutical industry currently produces knowledge and evidence. This will enable us to highlight the challenges facing the industry in the new reality of norm-based prioritisation.

CASE 1:

New Anticoagulants: Review committee rates patient safety high and concludes, having reviewed concerns, that Pradaxa, in collective judgement, cannot be the first Line treatment⁴

Background: In preventing malign clot-formation the new class of drugs, factor Xa-inhibitors NOAC, has almost replaced vitamin k-antagonists (warfarin). Companies have developed four types of NOAC, but so far nobody has published a direct comparison of them. To prevent thrombosis in patients with non-valvular atrial fibrillation, a Danish evaluation committee (RADS) conducted an appraisal of the NOACs and issued recommendations for use in 2016. They concluded by issuing a strong recommendation for (use) three NOACs, while giving Pradaxa only a weak recommendation (consider). In comparison with warfarin, the RADS' evaluation committee did not find evidence that any of the four NOACs differed in terms of mortality or bleeding rate (evidence was downgraded due to risk of bias). A recommendation that affected usage of Pradaxa (see Graph 1).⁵

Graph 1: Market development of Pradaxa versus All other NOAC (Sold packs (1000) in primary sector (all doses))/Denmark



For Pradaxa, the committee found renal elimination, frequency of gastrointestinal side-effects, more cardiovascular drug interactions and limited opportunities for automatic dose dispensing. RADS emphasised the importance of the drug fitting into clinical handling practice. Hence, the committee did not find Pradaxa equal to the three other NOACS in a collective judgement. In press communications, RADS explained that experience from the clinic has raised concerns about patient safety related to the specifics of Pradaxa, and that they had found it relevant to include the daily clinical problems in the final decision.

Decision-files	Stakeholder	Consideration	Consequence
1	Individual clinician	In meeting the patient, the clinician needs to consider the specific situation. Would the patient be medically fit and capable of following an anti-coagulant treatment using factor Xa inhibitors?	The clinician will tailor a treatment, monitor and adjust for undesired effects (e.g. poor bleeding control, side-effects like gastrointestinal complications). The patient may change treatment several times.
2	Medical communities	What is the collective experience in the community of medical prevention by the available drugs?	The clinician will choose the most commonly used treatment, monitor and adjust for undesired effects.
3	Medical society	After considering evidence, which drugs can clinicians choose?	the clinician will prescribe from among the drugs listed on the formulary, which is set by a consensus decision among a group of experts who have studied the evidence.
4	Priority bodies	Which specific drug will best contribute to the management of clinics and maximise patient safety?	One drug is routinely used in most cases for every patient covered by the priority body.

Discussion: We identify a specific dilemma (situation) for decision-makers in each of the four quadrants of Figure 1. Moving from quadrant one to quadrant four gradually shifts the choice from a personal dialogue between doctor and patient to a predefined treatment based on a collective understanding of clinical efficacy, costs and patient safety, all of which are balanced by underlying norms in order to make a recommendation.

The organisation of knowledge in pharmaceutical organisations

As the case with Pradaxa illustrates, the pharmaceutical industry is not only in the business of selling medicines. It needs equally to develop argumentation of a kind that can be presented persuasively to public funding bodies, medical authorities and others about the effects, safety, and benefits of the technology it sells. The question is whether the industry's traditional methods of handling evidence will meet decision-makers' needs now that medical treatments are being chosen and recommended in the new reality of norm-based prioritisation.

In our white paper 'Beyond Real World Evidence'⁶ we introduced a novel model for exploring the use and benefits of 'Real World Data' in relation to the main data-driven knowledge domains in the pharmaceutical industry – i.e. 'Research and Development' (R&D), 'Randomised Clinical Trials' (RCT), and 'Big Data' (BD).

Fig. 4: Data-driven knowledge domains in the pharmaceutical industry

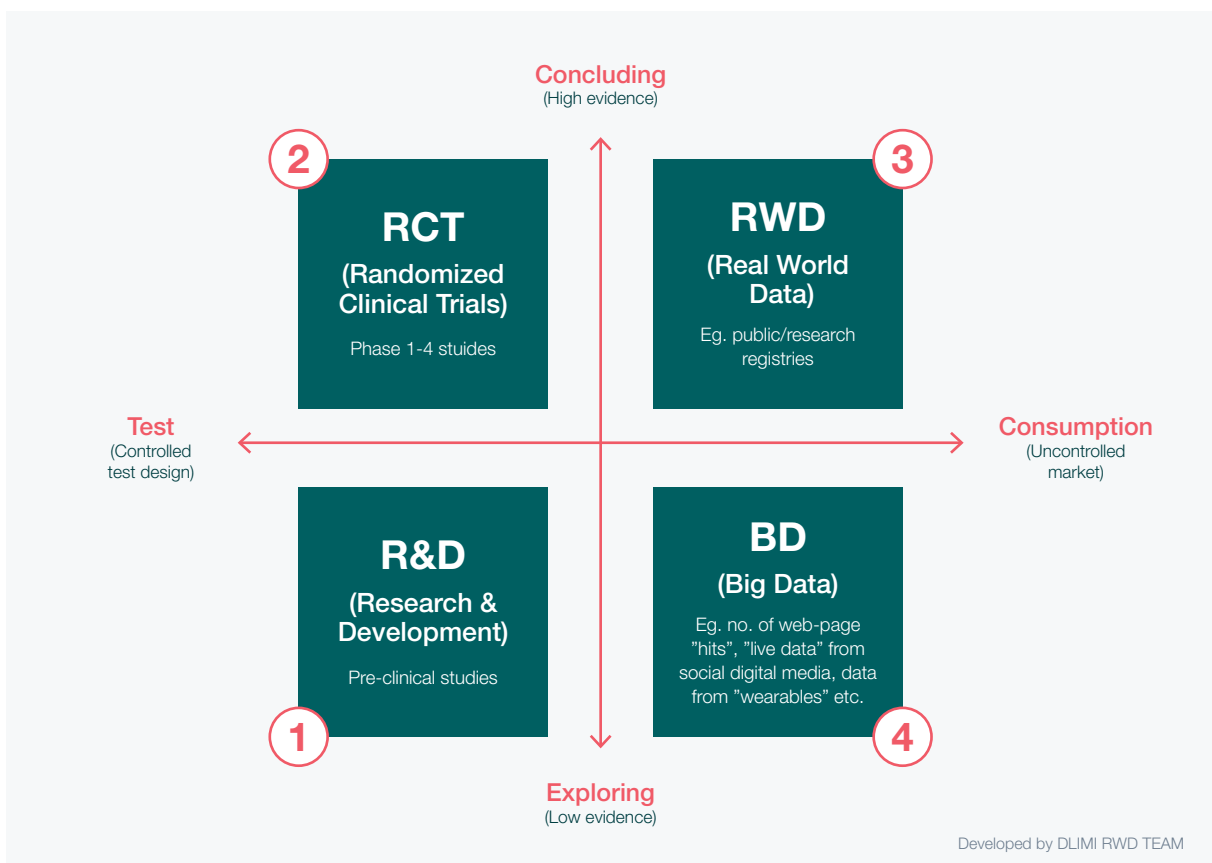
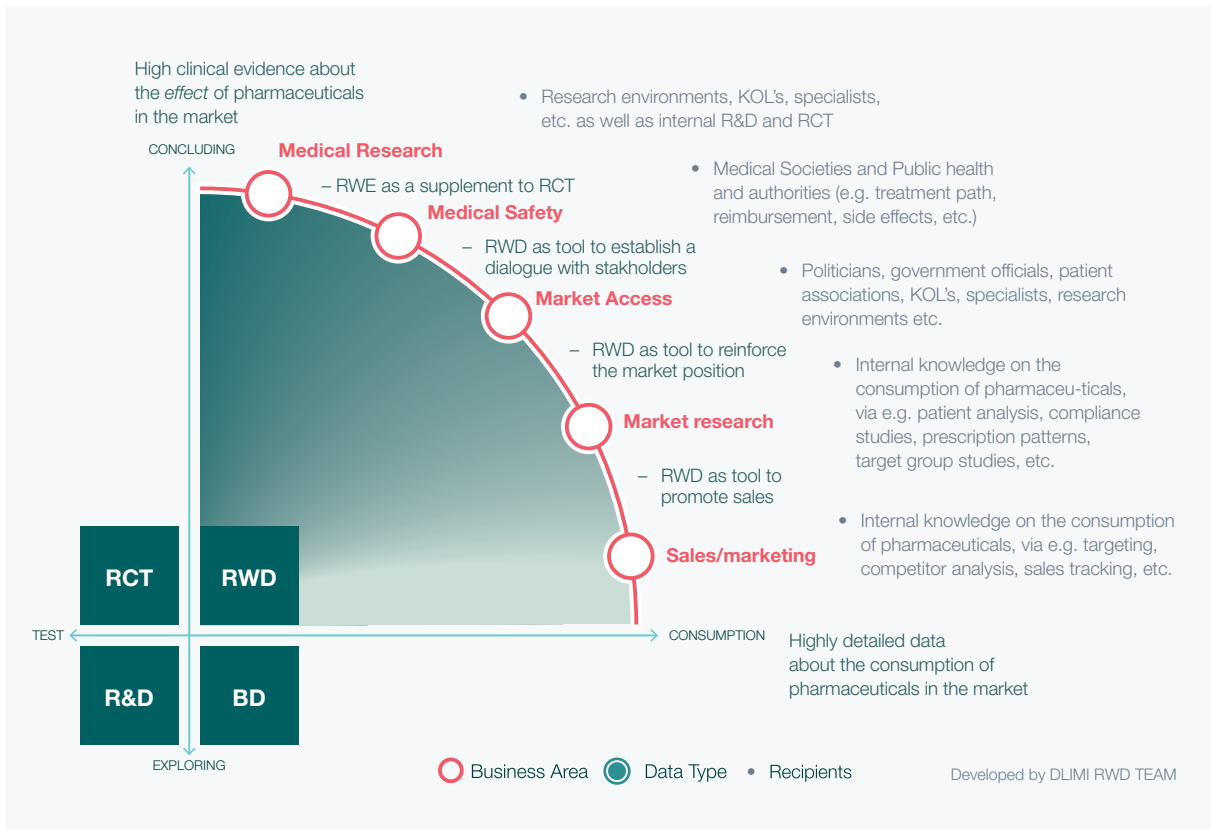


Figure 4 shows how knowledge production within the pharmaceutical industry is suspended between two fundamental axes: 'exploration' versus 'conclusion', and 'test' in a control setting versus 'consumption' in the uncontrolled market.

Fig. 5: Knowledge production and complimentary competences



If we focus for a moment on the market-facing side of the industry (Figure 5), we see that sales/marketing is located closest to the sales data which, within the sales process, are used as the main business intelligence source.

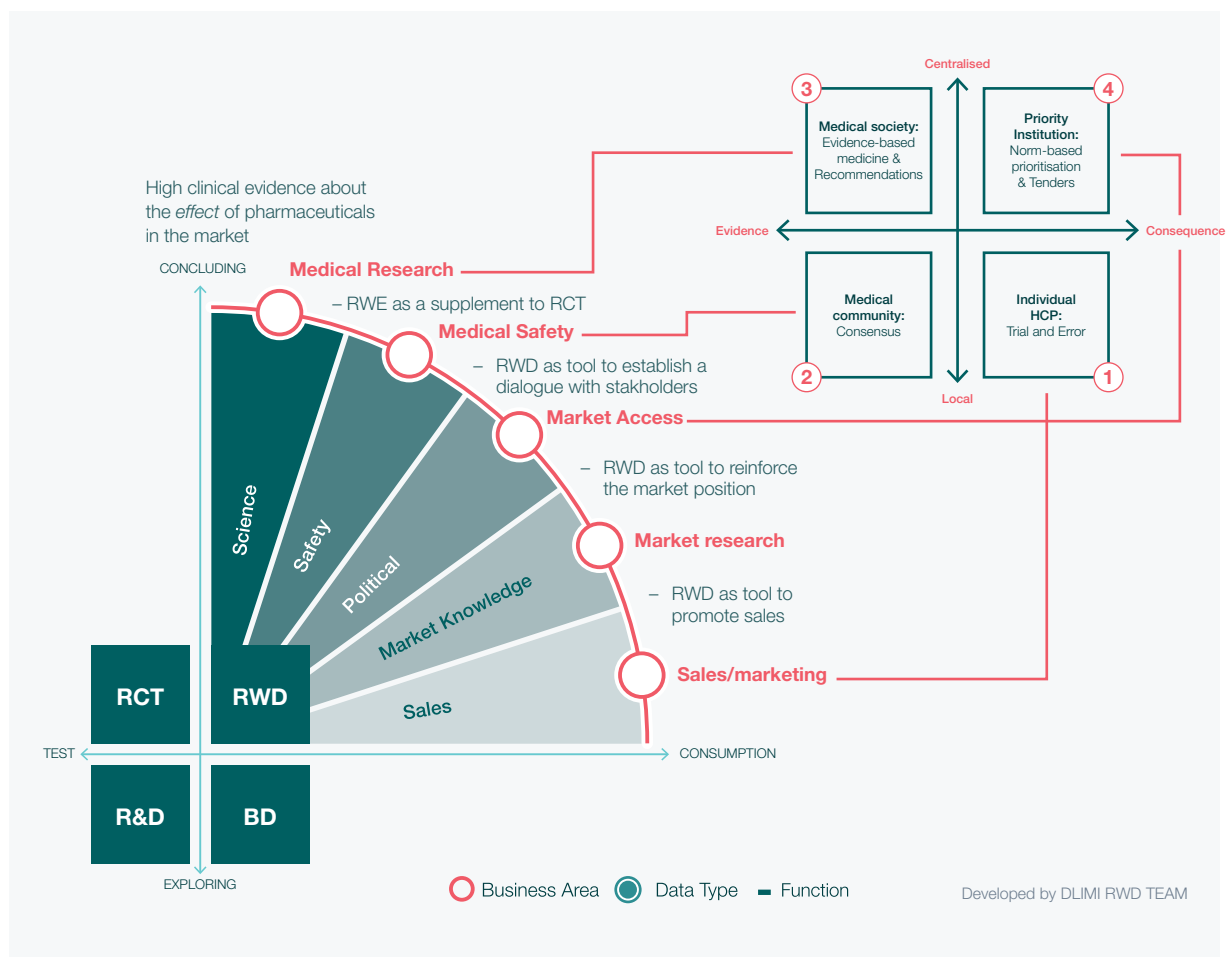
By contrast, medical research and safety are located at the top of the model, since these typically use high quality medical sources, most often mirroring the method and thinking of RCT in a real world setting. In short, the market-facing business units within a single organisation utilise RWD very differently, because they have different business aims, different disciplinary backgrounds for knowledge production, and different stakeholders.

The increasing importance of Market Access

It is no secret that Market Access has come to have a more dominant role because medical treatment has become more centralised via guidelines, and because the norm-based field for the choice and recommendation of medicines has grown in importance.

When a case is being made for a medicine’s superior cost-effectiveness and treatment benefits in a real world context, Market Access often spearheads interactions with stakeholders and decision-makers. Consequently, Market Access often drives the utilisation of RWD studies, since such studies can document real world outcomes. Safety and medical research personnel primarily seek to deliver documentation of safety and evidence-based outcomes to medical societies and regulators that is derived from RCT. And sales representatives still seek to engage the individual doctor and HCP in order to promote sales. Thus, in many cases, interactions between industry competences and decision-fields in healthcare run the risk of being siloed.

Fig. 6: Interactions between industry competences and decision-fields in healthcare



A decision-maker’s choice or recommendation of a medicine will always be made in relation to other decision-fields. This creates a potential challenge for pharmaceutical organisations: to engage a specific decision-field successfully the industry must orchestrate evidence and arguments from the surrounding decision-fields into one argument that departs from the decision-maker’s point of view. Thus, very different knowledge domains within the pharmaceutical organisation must now collaborate. The question is how to do this.

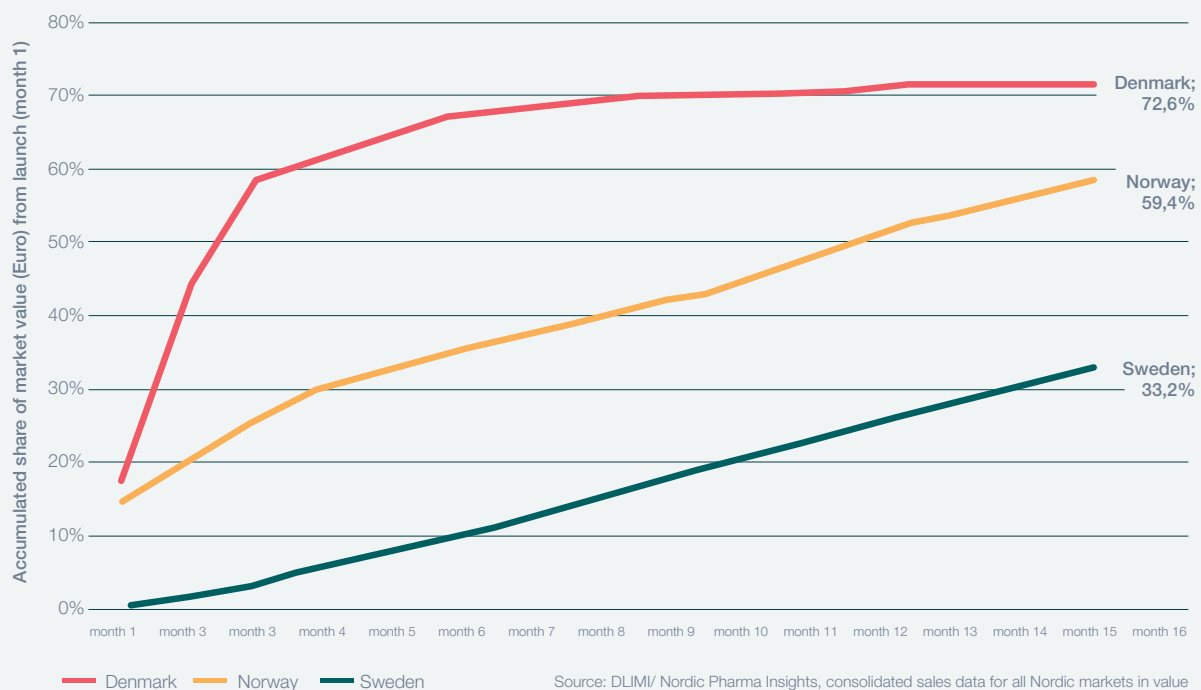
CASE 2:**Biosimilar drug interchangeability: A successful new drug launch**

Background: Even with biological drugs, patents expire and one morning the original drug manufacturer wakes up to a new reality. Infliximab, a monoclonal antibody designed for immunological diseases like rheumatoid arthritis, is a good example of this. In just three months, an alternative medicine took over the Danish market completely (see Graph 2).

The original product is defined as the reference product. The European Medical Agency (EMA) appraise new biosimilar drugs by comparing the non-clinical part of the EMA assessment report for the reference product and running some kind of bioequivalence study. Thus EMA manage biosimilar drugs very much in the way that generic drugs would be managed, and usually register a new biosimilar by using the ATC code of the reference product.

The Danish Appraisal Committee (RADS) made a bold statement about how to make biosimilars available: “if the EMA judges the biosimilar drugs to be equivalent to the reference-product, full interchangeability will exist for patients to be treated for the first time and for patients who were previously or are currently being treated. This will be the position unless the committee finds clinical contraindications” (present authors’ translation). However, recommendations based on the same evidence were quite different in neighbouring markets (see Graph 2).

Graph 2: Development of market share of a selected biosimilar from launch (month 1) to month 16



With infliximab the biosimilarity issues arose in April 2015 and were reinforced in March 2016. No communications from RADS’ Appraisal Committee contained any reference to evidence supporting full interchangeability. On the contrary, RADS stated: “The Danish Medical Agency has pointed out that no switch studies exist, but the regulatory requirements for biosimilarity, as well as a growing clinical experience, supports interchangeability” (present authors’ translation).⁷

Discussion: The RADS Appraisal Committee acted as a Priority Institute, as fully illustrated in quadrant 4 of Figure 1. For medical societies this was a paradigm shift: when they are writing consensus-based recommendations, experts seek evidence, rate it and draw conclusions. In this example, the appraisers acknowledged that no evidence existed and that if something were deducted from experience the experts would not rate it very high. However, the appraisal turned the arguments 180 degrees when balancing costs versus patient safety and stressing that there was no evidence against switching.

In the case of biosimilar infliximab (see Case 2), its manufacturer had elegantly orchestrated a balance between the medical evidence (the required bioequivalence study), the sales value proposition (comparable to reference product) and an attractive market access position (price). All of this apparently harmonised with the core values of the decision-makers, ensuring, for example, that ethical issues such as patient's right to safe and efficient treatment, responsible usage of public resources, and scientific soundness of treatment choice, were not at risk.

Are you asking the right question?

Navigating in the new reality requires pharmaceutical organisations to include the norm-based decision-field in their argumentation for the relevance of their medical product when engaging decision-makers. This, in turn, means that the pharmaceutical industry must re-think how they produce knowledge and build arguments that support their product claims. Competences, methods of knowledge production, and aims, must all be aligned across different disciplinary silos, just as different disciplinary silos have to be able to collaborate and, on a very practical level, deliver together.

To meet this challenge, we recommend that you ask three simple questions. These will guide you when you are navigating in the new reality.

1. The knowledge challenge: Are you asking the same question?

Pharmaceutical organisations continue to have difficulties in meeting centralised decision-makers' requirements, since the industry's arguments and logic depart from medical evidence thinking, which is often regarded as the gold standard for knowledge within pharmaceutical organisations.

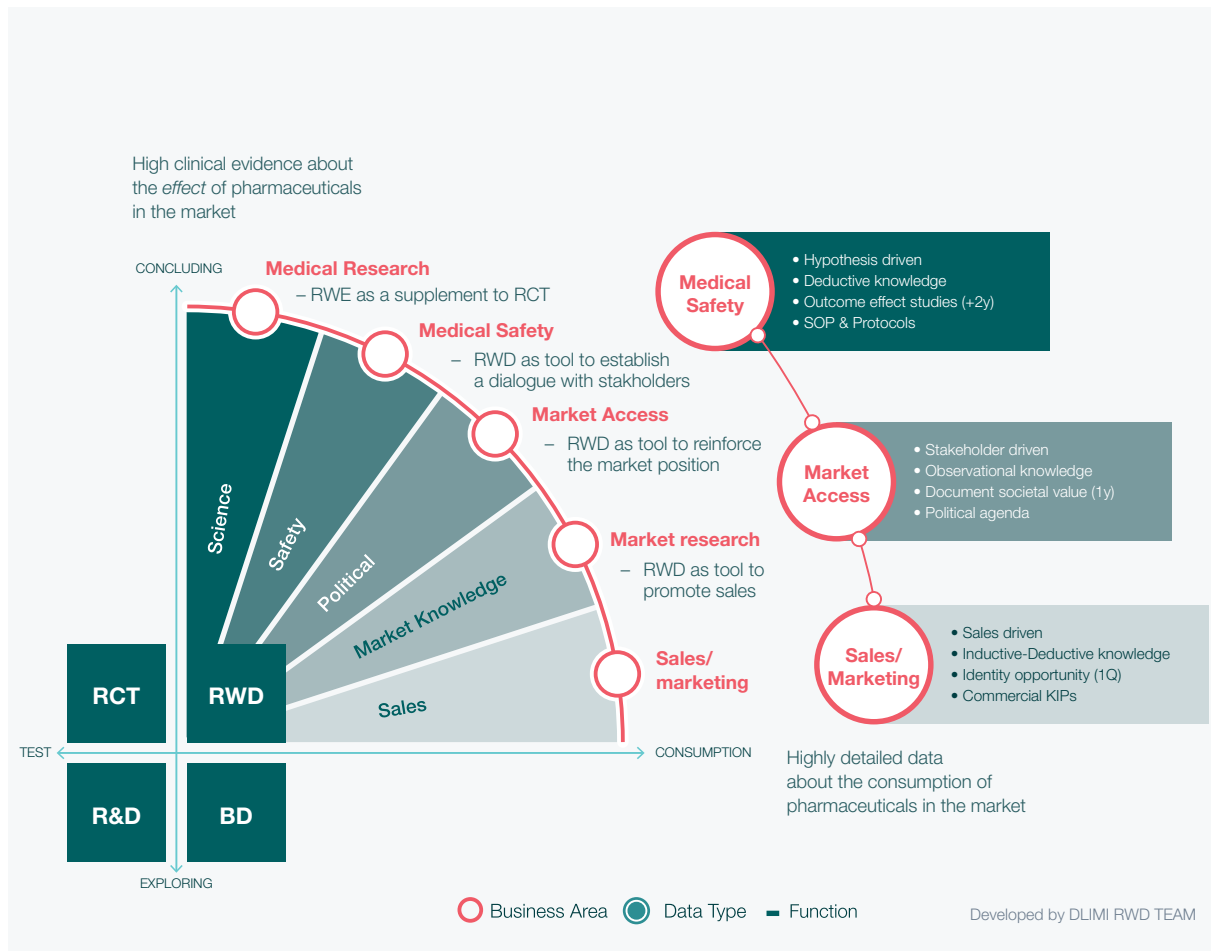
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In the future, the elegantly conducted RCT will provide admission to the market, data collected afterwards (RWE) will decide on continuous presence...”

*Jørgen Schøler Kristensen, Chairman Medicinrådet,
Chief Physician Hospitalsenheden Horsens*

Thus, the first step is to accept – throughout the organisation – that scientific evidence alone is not enough anymore if you wish to engage the norm-based decision field successfully. In its engagement efforts, your organisation must reflect the fact that other means of knowledge production will be needed in building the case for products in which very different teams, with different disciplinary outlooks, methods, aims and criteria of legitimate knowledge, collaborate.

Fig. 7: Different knowledge paradigms in pharmaceutical organisations



Medical and safety units’ disciplinary training inclines them to view evidence as the strongest type of knowledge. Their methods often aim to falsify hypotheses via deductive reasoning governed by scientific as well as regulatory thinking, with an emphasis on the observance of protocol and Standard Operational Procedures (SOPs).

Marketing and sales people seek to identify sources of business and short-term commercial opportunities, and Market Access operatives are often driven by external stakeholders’ agendas, aiming to build strong arguments that support product claims in a societal context. To this end, Market Access increasingly utilises RWD in order to document the value of a product in a real world setting – in turn, making it easier for decision-makers to assess the consequences of recommending their medicine when prioritising treatment.

The point is that each knowledge domain – medical, safety, market access, sales, marketing, etc. – builds its arguments differently by asking different questions.

2. The collaboration challenge: Are you answering the same questions?

In the new reality, different units must learn that they are all aiming to answer the same question: What is our medicine's value proposition in society? In other words, from the perspective of the decision-makers, what justifies the use of our medical treatment?

TEAMS		MEDICAL	EPIDEMIOLOGY	HEALTH ECONOMICS	MARKET ACCESS
QUESTIONS	SOCIAL NORMS	How does societal justification align with clinical evidence?	How does societal justification align with real world findings?	How does societal justification align with cost of treatment?	What is the ethical/political/societal justification for this treatment?
	COST OF TREATMENT	How does cost of treatment align with clinical evidence?	How does cost of treatment align with real world findings?	What is the cost of treatment?	How does cost of treatment align with the societal justification of the treatment?
	REAL WORLD OUTCOME	How does real world outcome align with clinical evidence?	What is the real world outcome?	How does real world outcome align with cost of treatment?	How does real world outcome align with the societal justification of the treatment?
	CLINICAL EVIDENCE	What is the efficacy & Safety?	How does clinical evidence align with real world findings?	How does clinical evidence align with cost of treatment?	How does clinical evidence align with the societal justification of the treatment?

Table 1: Cross-organisational collaboration

When we are designing and conducting real world studies we need to communicate the same messages based on these questions. It is precisely then strong arguments are built.

3. The norm-based challenge: Have you identified the right question?

But how do we get inside the decision-makers' perspective and work out what they take to be the reasons, or justification, for using a medical treatment?

The approach we propose is to explore and map the norm-based field, looking at relevant stakeholders and their non-evidence based criteria for assessing medical treatment. The aim here is to explore the fundamental norm-based opinions that stakeholders rely on to move from evidence to consequence when assessing and choosing medical treatment. There are different methods for this, depending on the specific case:

- **Desk research to map discursive formations determining the final norm-based assessment of medical treatment**
- **Qualitative interviews of key HCPs to explore perceptions and fundamental non-evidence criteria of treatment choice**
- **Workshops to utilise embedded knowledge within relevant teams**

However, the best results will be obtained when external insight is integrated into the process so that silent assumptions, taken-for-granted understandings, and “inside-out” perceptions in the organisation, are challenged.

Using the initial stakeholder mapping together with the exploratory analysis of the case at hand, a deep lying conflict axis can be identified. This axis will show the normative terrain in which the product must be assessed. It will offer a vivid picture of the answers that need to be provided if the medicine is to be prioritised.

CONCLUSION

The founding of Medicinrådet this year signalled a new reality in which evidence alone is at most a prerequisite of market introduction. From now on the assessment of medical treatments will be unavoidably norm-based. Decisions reflecting priorities will go beyond clinical evidence and assess the societal consequences of treatments in a real world setting.

To ensure continued success, pharmaceutical companies must deliver strong documentation that covers:

- **clinical evidence**
- **real world outcomes**
- **social benefits**

And this documentation will need to meet the criteria decision-makers apply in their assessments of the evidence and consequences for any given medical treatment.

REFERENCES

1. Costs for new technology grows faster than total market: For the total market (all products), we observe a steady average quarterly grow of 0.989 % (from 1st quarter 2012/Index 1). This results in a growth of the total market value from 3.900 Million DKK to a total market value of 4.800 Million DKK (1st quarter 2017) (numbers not shown in graph). In the same period, oncology (ATC L01, -02, -03 and -04) rose from a total market value of 943 Million DKK to a total market value of 1.281 Million DKK (numbers not shown in graph). We observe that the quarterly growth rate of oncology in the period went from 5 % (2012 range: -3%; +20%) to 10% (2016 range: +20%; +64%)
2. Danske Regioner. Prioritering. Available at: <http://www.regioner.dk/sundhed/medi-cin/prioritering> Accessed August, 2017
3. REGIO #15 (2017) p. 3, <http://www.e-pages.dk/regioner/109/2> Accessed August, 2017
4. RADS. Available at: <http://www.rads.dk/media/4092/artrieflymmer-24.pdf> Accessed August, 2017
5. Dagens Pharma. Available at: <http://dagenspharma.dk/hjerteforeningens-forskningschef-kritiserer-ny-rads-vejledning/> Accessed August, 2017
6. Micheelsen (2016): Beyond Real World Evidence: How to improve utilisation of Real World Data throughout an organisation. DLIMI Denmark, Available at: https://www.dli-mi.dk/SiteCollectionDocuments/DLIMI_RealWorld_endelig%2028042016.pdf Accessed August, 2017
7. RADS. Available at: <http://www.rads.dk/media/3488/rads-notat-om-anvendelsen-af-biosimilaere-juni-2016.pdf> Accessed August, 2017

ABOUT DLIMI

DLI Market Intelligence (DLIMI) is a leading provider of business intelligence and Real-World insight to pharmaceutical and health-related companies operating in the Nordic region. We offer pharmaceutical sales statistics on a variety of platforms as well as market research, market access support, real world studies, and consultancy services covering Denmark, Sweden, Norway and Finland.

Reference

Hirsch et. al. (2017): From Evidence to consequence – the new reality for prioritisation of medicines in Denmark. DLIMI, Denmark

Disclaimer

This white paper contains no information gained from client-projects. All cases are available by public sources.

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