



The intellectual property implications of Open Access drug discovery

A report of a meeting entitled “Pharmaceuticals open access innovation and collaboration – intellectual property issues” organised by the Oxford Academic Health Science Network in collaboration with the Structural Genomics Consortium held at the Saïd Business School, Oxford on 21 January 2015.



About the Structural Genomics Consortium

The Structural Genomics Consortium (SGC) leads an Open Access programme involving industry and academic scientists. Supported by charity, government and industry funding, the SGC brings together pharmaceutical firms – including Novartis and Merck – with several universities including Oxford and Toronto.

The SGC mandate is to accelerate the discovery of new medicines by generating high-quality research tools such as novel human protein and its structure, and small-molecule inhibitors, placing the data and reagents generated as part of the work into the public domain without restriction.

This information is seen as vital to the discovery of new drugs to combat human diseases – common and rare – including cancer, diabetes and inflammation.

About the Oxford Academic Health Science Network

The Oxford Academic Health Science Network unites the regional NHS, universities, businesses, patients and public to achieve two goals – improving health and generating economic growth in our region.

As catalysts of change, we strive to reduce variation in the quality of care. Our aim is that innovative ideas and technologies are rapidly and universally introduced into clinical practice. This will advance patient safety, improve patient outcomes and experience, and ensure the NHS is more sustainable and efficient.

Collaboration underpins the Oxford AHSN concept and change programmes. We work with partners to embed projects into local systems and plans, building acceptance and sustainability.

The report was authored by Dr Hugh Penfold, Oxford AHSN Commercial Development Manager (Berks).

For further information

Email hugh.penfold@oxfordahsn.org or visit our website www.oxfordahsn.org.

Summary

The Open Access approach to drug discovery and development, advocated *inter alia* by the Structural Genomics Consortium (SGC), is a disruptive alternative to circumvent many challenges encountered by the conventional model of drug discovery – but is it compatible with the status quo?

Organised by the Oxford Academic Health Science Network (AHSN) in collaboration with the SGC, a meeting entitled “Pharmaceuticals open access innovation and collaboration – intellectual property issues” held on 21 January 2015 at the Saïd Business School, Oxford posed the question “Is the absence of an all-encompassing patent portfolio, begun before or during the medicinal chemistry phase of a drug discovery programme, incompatible with the ultimate requirement by a pharmaceutical company for a significant degree of market exclusivity?”

Speakers discussed alternative approaches to obtaining the assurance of such market exclusivity, including regulatory data package exclusivity; orphan drug status; a Protected Commons approach; and possible changes in patenting practice which could be advantageously adopted.

The consensus view was that the Open Access approach, with its many advantages over the standard model of drug discovery and development, did not present an insuperable obstacle to subsequent market exclusivity for the resulting therapeutic product. Further explorations of the topic with pharmaceutical companies and investors are fully justified.

Introduction

Open Access, Open Innovation, Open Model, Open Collaboration, Open Data – the use of these and similar terms in the pharmaceutical world has grown rapidly over the past decade or so, but with little consensus as to their precise meaning. For the purposes of this report, Open Access means the prompt release of all research outputs – materials and knowledge – into the public domain without restriction on use. This is the approach adopted by the SGC, based in Oxford, Toronto, São Paulo, Stockholm, Chapel Hill and Frankfurt. The foundation, partners, aims, activities and outputs of the SGC are covered in detail on its website (www.thesgc.org). A brief description of its activities relevant to the question addressed here is given in **Box 1**.

Notwithstanding the pre-competitive argument advanced by the SGC (see Box 1), its Open Access model, and similar initiatives seeking to reduce the costs and inefficiencies of the traditional approach to drug discovery and development, still raises important questions regarding the generation of Intellectual Property (IP) which remains a pre-requisite for investment in later-stage drug development and commercialisation.

The Oxford AHSN organised this meeting to explore the SGC approach, compare it with other similar approaches, and to evaluate the options available to companies who wish to develop prospective drugs deriving from the outputs of Open Access projects for obtaining a degree of exclusivity.

Invited representatives (see Attendee List p. 9) included those from the SGC, pharmaceutical companies, university technology transfer offices, patent agents, IP consultants and academia.

The report summarises conclusions and recommendations, highlights unanswered questions, and proposes next steps.

Box 1

The Structural Genomics Consortium (SGC)

The SGC is a public-private partnership aiming to take pioneer compounds through to clinical phase 2a/b – proof of clinical mechanism (POCM) or “does the drug have the desired effect?” Over 90% of compounds are rejected at this point in product development. The SGC advocates delaying patent filing until positive POCM results have been obtained. It further recommends the immediate publication of all negative studies and the release of positive results once these fulfil pre-defined quality criteria.

The aim is to place into the Public Domain all the data and reagents, enabling quick crowdsourcing to perform open target validation, thus de-risking assets which can be converted into drug discovery programmes with higher chances of success.

Benefits include the pooling of resources; rapid, free data access for global academia; reduced duplication; and fewer patients exposed to new and unproven compounds. In answer to the inevitable questions from pharma about patents, the SGC argues that its activities are pre-competitive, pointing out that securing IP prior to Phase 2a/b is of limited value in cost/benefit terms as most of the chemical compounds will fail to show efficacy, and arguing that more is to be gained from joining efforts to share information and risks. Once the structure has shown POCM, one proposal is to put it and the supporting data up for auction, with specific time lines for patent exclusivity.

The SGC Open Access Model

Prof Chas Bountra (SGC Oxford Chief Scientist) described the work of the SGC and its future plans. He advocated that phase 2a (proof of clinical mechanism) should be the pre-competitive i.e. pre-patent filing boundary. He asserted that “validation happens in patients, not in cells or animal models”. See **Boxes 2** and **3**.

The discussion centred on the threat from subsequent

filing of over-broad, blocking, activity claims. This threat could be countered by prompt publication – in the complete absence of patents – of high-potency, high-specificity chemical entities, mainly inhibitors of specific proteins, identified by the SGC. A requirement for academic and commercial recipients of the inhibitors to sign up to a Code of Conduct was suggested. The enforcement of such a code, and by whom, was not discussed. It was generally agreed that public availability of assays was almost as important as access to the inhibitors themselves.

Box 2

Optimal exploitation of early discovery tools and novel disease associations identified by academics globally

Prof Chas Bountra, Chief Scientist, SGC Oxford identified the challenges and drawbacks of the standard closed drug discovery process based on early patenting, often executed in isolation, as: duplication of effort; wastage of resources; focus on shorter term, lower risk projects; poor understanding of biological basis of disease, disease heterogeneity and drug action; inadequate biomarkers and preclinical assays.

As a consequence: R&D is becoming unsustainable, too slow, risky and expensive. The UK is seeing sector down-sizing as industry seeks to reduce risk/costs. New medicines are becoming unaffordable.

Meanwhile society is desperate for new medicines to treat chronic illnesses such as dementia and diabetes, and rare diseases.

The SGC approach is to focus on novel or intractable proteins and to generate tools to aid early drug discovery including proteins, assays, structures, inhibitors and antibodies. It is identifying pioneer chemical structures as medicine precursors and seeking to reduce duplication and wastage through open access, immediate sharing of data and reagents. This enables pooling of resources, expertise and infrastructure, and risk-sharing.

SGC is currently working with over 10 pharmaceutical companies, more than 250 academics, biotech companies and clinical research organisations.

Box 3

Impact of SGC Open Access model – a case study

2009

SGC Oxford began work on an ‘intractable’ protein family

2010

First novel inhibitor generated and efficacy shown in a rare cancer. Reagents were given to >500 laboratories which demonstrated potential in other areas including cancers, cardiac hypertrophy, fibrosis, chronic obstructive pulmonary disease, sepsis, and male contraception. This work generated over 200 additional publications, and more than 40 proprietary efforts. One collaborator created a new biotech company. In four years, 14 clinical trials on this novel target have been registered by 7 different companies since SGC made the novel inhibitor publicly available. Six compounds from six companies are now in clinical studies.

Current position: 28 novel inhibitors have been identified, and several hundred papers published. Over 150 principal investigators are working on more than 250 rare diseases (Oxford).

Funding has been secured: to investigate novel kinase inhibitors; for “lead-op ready programmes” for novel dementia targets; to work on novel discovery tools for high priority genes and better inflammatory disease targets.

Future plans include: generating further new clinical molecules, studies with Cancer Research UK and Takeda, growing links with patient groups e.g. Huntington’s Disease, increased tissue access and dissemination of reagents.

“This is the only way to generate more novel medicines, more quickly and more cheaply,” concluded Prof Bountra.

IP mechanisms supporting open biomedical innovation

MacKenna Roberts (former IP Consultant to the Oxford/UCL Centre for the Advancement of Sustainable Medical Innovation) opened her presentation by quoting a Lancet report¹ which concludes that the existing system of global governance has “failed to promote or protect health or address health inequities”. The author argues that failures in communication and IP policy have led to the public misperception that IP laws, particularly patents, are a tool to protect corporate domination. Roberts asserted that, on the contrary, IP rights can help to create and defend an open knowledge-sharing economy. She summarised a recent CASMI/Wellcome/Kinapse systemic review² of open innovation adoption in the life sciences which included literature analysis, workshops, surveys of institutions active in Open Access/Innovation, data mining software analysis, and structured interviews for case studies. In addition to the report, the authors have built a tool kit with guidelines for organisations considering engaging in Open Innovation.

Roberts explored various IP strategies and models that have been adopted in the “Open Space” using case studies to illustrate different solutions. See **Box 4**.

The concept of a hybrid Protected Commons model was mooted through which the information is released to a selected expert pool under conditions enabling subsequent patenting.

In discussion, Bountra argued that this approach is unnecessary because the clinically-valuable molecules derived from the SGC’s outputs following further work by pharma companies are likely to be sufficiently distant chemically from those made public to enable patenting. Bountra also suggested that this approach would restrict academic collaborations, which represent a major benefit of SGC’s Open Access strategy. The potential for problems with EU anti-trust law was noted but not explored further.

Participants agreed that over-broad patents, filed too early, represent a major issue for the proposed model of drug development. Such patent applications, coupled with poor examination and low quality decisions by some patent offices, result in poorly defined claims of uncertain scope. They represent a significant burden for drug developers, particularly smaller companies. Patent offices in Australia and US are tightening up their procedures whilst others e.g. Japan, China and Korea have been more focussed for some time. Patent agents will nevertheless continue to be obliged to seek the broadest possible protection for their clients’ inventions.

Box 4

Emerging IP mechanisms supporting open biomedical innovation

MacKenna Roberts (Oxford-UCL Centre for the Advancement of Sustainable Medical Innovation)

Open Innovation: innovating with others; sharing risk and reward to mutual benefit; and creating new products, processes or ideas either not achievable alone, or achievable more affordably or efficiently in concert.

Open Access: openly sharing knowledge and data with the public without creating IP rights and without charge or restriction. It is distinguished by absence of legal rights, relying for compliance on social capital – mainly trust – and broad agreement with leaders not to claim ownership and profit from access to the knowledge.

Open Source: active use of IP to ensure free access e.g. Linux OS.

The human genome and HapMap projects were initiated by the landmark creation of the Bermuda Principles (1996) ensuring prompt release of human DNA sequences into the public domain.

The Biomarkers Consortium

The public-private partnership running the I-SPY 2 gene breast cancer clinical trial which had the potential to generate biomarkers of direct commercial value as companion diagnostics. Open access was achieved using an independent third party to hold IP resulting from the trial. Such third party could offer exclusive licences to the supplying company restricted to the trialled drug, specific biomarker and therapeutic indication, and non-exclusive licences to others for research involving the same biomarker outside that area. <http://www.biomarkersconsortium.org/>

Double-blinded drug discovery

A scheme providing researcher access to industry tools and screening libraries, managed by the Lankenau Institute (USA) acting as key holder to sets of blinded industry compounds. Active compounds identified by academic investigators are reported to the Institute and unblinded to the company. Universities are incentivised by milestone payments for successful screens. Any structures that are not encumbered or of interest to the company may then be revealed for publication. The speaker was not aware of the scheme’s having produced any tangible results since starting two years ago.

<http://www.lgcinc.com/Pages/DBDDiscovery.html>

¹“The political origins of health inequity: prospects for change” *The Lancet*, 383, No. 9917, 630–667, Ole Petter Ottersen, et al.

²“Shaping the Future of Open Innovation” http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtp057218.pdf

Patent strategies for downstream commercialisation

Nick Lee (Partner, Kilburn and Strode Patent Agents) discussed the scenario where a drug has been taken publicly into phase I and options for securing exclusivity. See **Box 5**.

Over-broad claims were again raised during the discussion. It was agreed that a partial solution would be to seek a change in European Patent Office rules so that *in vitro* data are insufficient to secure disease-specific patent claims. The option to file broadly but early and then put in a freely-accessible pot was suggested but the issue of responsibility for, and the costs of, such filings were not discussed.

The desirability, or otherwise, of grace periods was also discussed. A universal grace period is favoured by universities. Praxis-Unico has advocated the change in Europe on behalf of its UK university technology transfer office members. However a word of caution was sounded. Big pharma, particularly in the US, is a strong advocate of grace periods. It was suggested that what is good for them might not be so good for universities³.

Box 5

Patent strategies for downstream commercialisation

Nick Lee, Partner, Kilburn and Strode, Patent Agents

Scenario:

The SGC has taken Drug X into phase I/2 clinical trials for the treatment of a specific disease Y. All the information and data relating to the drug and the trial is in the public domain. Huge sums of money are still needed to complete clinical trials and take the drug to market. Potential partners or funders will require some sort of exclusivity to protect their investment.

What are the options?

Patents:

Patentability requires novelty, inventiveness and industrial applicability. In the above scenario, details of the molecule or compound are already published so cannot be protected.

Method of use

e.g. "Drug X in a method of treating disease Y" or "A method of treating disease Y in a subject comprising administering drug X to the subject" is possible but publication of phase I trials makes this very difficult under current law.

Other patent strategies for consideration are:

dosage regime; structural modifications of the molecule; use of Drug X to treat a different (unpublished) disease; or use of Drug X in combination with another therapy. It is open for debate whether one of these approaches might be sufficient to persuade a third party to pay for the clinical trials.

Grace period:

Normally one year in the US, a grace period allows the inventor to publish details of the molecule or study without prejudicing to subsequent patent filing. Opinions vary as to whether one year is long enough.

In summary:

Patenting of Drug X for the treatment of disease Y is difficult under the current law. Any protection is likely to be narrow and may not be sufficient to encourage third parties to fund clinical trials.

³In the author's view, the adoption of a grace period in Europe is unlikely, particularly in light of the recent changes to the grace period regime in the US pursuant to the America Invents Act (2011).

Data exclusivity

Matthew Frankel, General Counsel, Circassia Pharmaceuticals, outlined the benefits of using data and market exclusivity provisions as means to ensure a fair investment return, even in the absence of patents. See **Box 6**.

Data exclusivity refers to the period during which a second applicant for a marketing authorisation (MA) cannot cross-refer to the pre-clinical and clinical data in the dossier of the originator product (the reference product) to support its own application for an MA. After the protection period has lapsed, second applicants can, instead of producing their own data, refer to the originator's data. The legislation strikes a balance between rewarding originators, limiting unnecessary repetition of pre-clinical and clinical studies on humans and animals, and promoting availability of cheaper generic products. In the EU, data exclusivity is granted for eight years.

Marketing exclusivity in the EU is a further period of two years during which a generic or biosimilar product cannot be placed on the market even if it has already received an MA. Further information about data and marketing exclusivity in various countries can be found in **Box 7**.

Such rights are automatic, once the investment has been made in clinical trials. They cover active substances but not any device used for delivery.

In the biologicals space, contractual means to obtain manufacturing exclusivity are commonly employed.

The discussion concluded that these forms of exclusivity are most likely to be used as adjuncts to the options offered by intellectual property. In the case of products coming to the end of their patent life, data exclusivity can sometimes extend exclusivity in the market at the point where peak sales are to be expected. It is predicted that data exclusivity is likely to be increasingly emphasised to prospective investors.

Box 6

Data exclusivity

Matthew Frankel, General Counsel, Circassia Pharmaceuticals plc.

Data exclusivity, the period during which a second applicant for a marketing authorisation (MA) cannot cross-refer to the pre-clinical and clinical data in the dossier of the originator product (the reference product) to support its own application for an MA, is currently eight years in the EU.

Marketing exclusivity – two years in the EU – is a further period of time during which the generic or biosimilar product cannot be placed on the market even if it has received an MA.

New indications can extend the ten-year total exclusivity period to a maximum 11 years if, during the first eight of those ten years, the MA holder obtains an authorisation for one or more new therapeutic indications which are held to bring a significant clinical benefit in comparison with existing therapies. Significant clinical benefit appears to mean improved efficacy, safety, or mode of administration

and will almost certainly require comparative clinical trials. The extended period of protection applies to the medicinal product to which the authorisation relates, not just the additional indications.

Data submitted to obtain authorisation for additional strengths, pharmaceutical forms, variations or extensions, are protected by the data exclusivity right. The protection period for all products that are part of a Global Marketing Authorisation (EU only, despite the name) ends when the MA protection period for the initial products ends. It applies to products authorised by the same MA holder but does not apply to independently-developed products.

An independent period of data and marketing exclusivity is reserved for New Active Substances. Different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives are considered the same active substance, unless they have significantly different safety and/or efficacy.

Data exclusivity by country

Matthew Frankel, General Counsel, Circassia Pharmaceuticals plc.

Japan: A re-examination system functions in a manner similar to the EU data and marketing exclusivity systems. An MA holder for a newly approved drug may apply for a re-examination of its safety and efficacy study period up to a maximum ten years. A generic developer must file the same or more extensive data than attached to the MA application of the original drug during the study period.

US: Manufacturers receive five years' exclusivity for new chemical entities and three years' for new indications. Biologics receive 12 years' data exclusivity from the date of approval. An additional six months' exclusivity applies to paediatric indications and an additional five years for drugs designated as Qualified Infectious Disease Products i.e. antimicrobials designed to treat serious and life-threatening infections.

China: A six-year exclusivity period for data included in an MA application for a drug containing a new chemical entity.

Brazil: Data package exclusivity is possible for veterinary but not human products. Marketing exclusivity rights are not available.

Russia: Six year data exclusivity as of 2012. Scope uncertain.

India, South Africa: No data or marketing exclusivity provisions.

Orphan drug provisions

Dr Nick Scott-Ram, Commercial Director, Oxford AHSN, outlined orphan drug provisions in Europe and the US, citing examples of drugs which started as orphan products – medicines treating rare diseases of limited prevalence – and have grown into blockbuster products with multi-million sales e.g. Abilify (aripiprazole) – US\$8bn (2013) and Provigil (modafinil) – US\$800m (2007).

Orphan drug designation remains an attractive option as personalised medicine, fragmenting larger indications, opens further opportunities. There is less competition, if any, from branded and generic rivals. A fast-tracked regulatory review process and lower cost late-stage development are compelling commercial arguments. By 2018, the global market for orphan products is projected to be worth US\$127bn and comprise 16% of total prescription drug sales. However, inconsistency between incentives to develop drugs and challenges around market access to such drugs remain.

Discussion

Participants generally agreed that the marketing exclusivity opportunity has been “gamed” by many companies. The system works, up to a point, but it can lead to drug treatments costing tens or hundreds of thousands of dollars. For example, a year's supply of Vimizin A to treat Morquio A syndrome costs US\$380 000. For further details about orphan drugs and marketing exclusivity see **Box 8**.

The general discussion touched on various themes, including over-broad patent drafting (again), the role of universities and the need for more intelligent investment.

The consensus was that the current IP system, although far from perfect, is not incompatible with the Open Access drug discovery and early development approach being followed by the SGC. However, to obtain the significant funds required – £15m was one figure quoted – to develop an SGC structure to the point of validation in patients and generate a prospectively patentable compound, VC or corporate investors need to be persuaded that a raft of all-encompassing and unnecessarily broad patent applications are not required in advance.

Vertinsky⁴ (Emory University School of Law) recently published an alternative approach. She proposed the introduction of a Fair Use exemption into patent law, analogous to, but distinct from, existing fair use provisions in copyright law. In the author's view, strong objections by patentees to such provisions can be guaranteed, and the international adoption of a system mainly addressing the US IP regime seems improbable.

Bountra's view, that there's plenty of headroom in the chemospace to enable proprietary protection of compounds derived from the molecules emerging from the SGC programmes, was not challenged. He pointed out the manifold benefits of taking Open Access up to phase 2a in reducing duplication and saving increasingly scarce resources. Some participants considered the phase 2a goal to be too ambitious and advocated that the pre-patent boundary be after phase 1b.

A university's broader public service role was discussed. The technology transfer function does not exist primarily to make significant money for the university. However, there is a tendency for institutions to see early patent protection as the only way to enable prompt publication and benefit from the fairly rare occasions when an academic discovery proves to have direct commercial applicability. The problems of lawyer paranoia and fears over "the one that got away" were also mentioned⁵.

A follow-on meeting to include both VCs and pharma/biotech companies was agreed to be desirable.

Orphan drug provisions

Dr Nick Scott-Ram, Director of Commercial Development, Oxford AHSN

In the EU:

An estimated 6% of the population is affected by one of 5 000 – 8 000 orphan diseases. To qualify for orphan designation and ten years' marketing exclusivity, a medicine must meet several criteria which include being intended for life threatening or chronically debilitating diseases affecting fewer than 5 in 10 000 citizens.

In the US:

To qualify for orphan designation, a seven year exclusivity period and clinical trial tax incentives, a drug or biological would be intended to treat a disease affecting fewer than 200 000 people in the US, or to treat a disease that affects more than 200 000 people but which is not expected to recover development and marketing costs.

Orphan drugs have been designated in 600 clinical trials to date, over 30% in cancer. Thirty eight orphan drugs were approved before the 1983 Orphan Drug Act since when a further 420 medicines received approval.

Examples:

Cerezyme (imiglucerase) indicated for Gaucher's disease, which affects 1 in 40000, costs US\$200 000 pa, and attracted sales of US\$715m (2014).

Pulmozyme (dornase alfa) for cystic fibrosis with affects c.25 000 people in the US and 20 000 in Europe returned US \$560m in 2013.

Projected 2018 sales of top 3 orphan drugs

Rituxan (rituximab) indicated for chronic lymphocytic leukaemia – Roche US\$6.9bn.

Revlimid (lenalidomide) indicated for multiple myeloma with anaemia – Celgene US\$6.6bn.

Soliris (eculizumab) indicated for paroxysmal nocturnal haemoglobinuria – Alexion US\$3.4bn.

⁴Vertinsky, Liza. *Patents, "Partnerships, and the Pre-Competitive Collaboration Myth in Pharmaceutical Innovation"* (March 27, 2015). *UC Davis Law Review*, Vol. 48. Accessed online 18.08.15 at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2586021.

⁵In the author's view, the perceived "failure" to patent the original monoclonal antibody technology for the UK, over thirty years ago, casts a very long shadow.

Meeting attendees

Dr Paul Ashley, Technology Transfer Team Leader, *Isis Innovation Ltd*

Ian Bingham, Chief Executive, *IP Asset LLP*

Professor Chas Bountra, Chief Scientist, *Structural Genomics Consortium, Oxford*

Dr Phil Clare, Associate Director and Head of *Oxford University Knowledge Exchange*

Tony Dolan, Director of Patents, *BTG plc*

Dr Mark Edwards, Independent Consultant

Dr Nick Edwards, Chairman, *Medinnovate Ltd*

Matthew Frankel, General Counsel, *Circassia Pharmaceuticals plc*

Julie Hart, Associate Director of Networking, *Oxford AHSN*

Dr Mick Hunter, Director of Discovery & Development, *Atopix Therapeutics Ltd*

Nick Lee, Partner, Kilburn and Strobe, *Patent Agents*

Dr Wen Hwa Lee, Strategic Alliances Manager, *Structural Genomics Consortium, Oxford*

Dr Richard Liwicki, Deputy Director, Research Services, *Oxford University*

Dr Hugh Penfold, Commercial Development Manager, *Oxford AHSN*

Dr Carolyn Porter, Deputy Head of Technology Transfer, *Pharma and Biotech, Isis Innovation Ltd*

MacKenna Roberts, Former IP consultant, *Centre for the Advancement of Sustainable Medical Innovation, Oxford University/UCL*

Dr Nick Scott Ram, Director of Commercial Development, *Oxford AHSN*



www.oxfordahsn.org

Magdalen Centre North,
1 Robert Robinson Avenue, Oxford Science Park, OX4 4GA, United Kingdom

t: +44(0)1865 784944 **e:** info@oxfordahsn.org

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