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By Email

Office of Pharmaceuticals Management Strategies
Strategic Policy Branch
Health Canada
Brooke Claxton Building
70 Colombine Driveway
Ottawa, ON K1A 0K9

Re: National Strategy for High-Cost Drugs for Rare Diseases

I write on behalf of the Agora Open Science Trust (https://www.agoraopensciencetrust.org/) in response to Health Canada's consultation process regarding a National Strategy for High-Cost Drugs for Rare Diseases. Agora, a spin out initiative of the Structural Genomics Consortium (https://www.thesgc.org/), is a Canadian charity whose mission is to accelerate the discovery and development of affordable new medicines through open science.

Rather than addressing issues of access to currently existing therapies in the short term, my comments focus on the underlying causes of ever-escalating prices for new rare disease drugs and how these might be addressed in the long term through innovation policy.

1. Current Systemic Pathologies in Drug Discovery and Development

The innovation system for the discovery and development of new medicines is suffering globally from a number of pathologies:

- Pharmaceutical R&D is inherently risk averse, with too much investment into incremental innovation on the same previously validated targets and too little investment into truly novel areas of the human genome with breakthrough potential.
- The costs of pharmaceutical R&D have been increasing steadily over many decades and, when R&D does take place for novel therapeutic hypotheses, it is increasingly inefficient and redundant. Multiple parallel programs pursue the same failed therapeutic hypotheses in proprietary silos well into late-stage clinical development, magnifying many times over the aggregate costs of failure.
- Little innovation is occurring for medical indications with patient populations that are too small or impecunious or with other underlying market failure dynamics.
- New drugs that do arise from this system are increasingly priced at levels unaffordable to even the most affluent countries, including Canada.

There are a range of complex factors driving the above pathologies, but the problem at its most fundamental is that we rely almost exclusively on profit-maximization to drive the entire cycle of discovery, development, registration, manufacturing, and distribution of new drugs, and largely leave it to private businesses with exclusive rights to set prices, even for groundbreaking therapies for rare diseases with no available substitutes (where demand is almost completely inelastic). Individually rational actors driven by profit-maximization will of course choose (1) to invest in programs that are lower-risk or offer the largest potential future financial reward, (2) to keep results and data secret for competitive advantage, (3) to appropriate as much intellectual property to themselves as possible to exclude would-be competitors, and (4) to set prices at whatever the market will bear. These individually rational choices in pharmaceutical R&D lead in the aggregate, however, to the socially deleterious pathologies above.

The pricing problem is certainly at its most acute with rare diseases, where the same cost basis of drug development must be amortized over smaller patient populations. It is not limited to rare diseases, however, and will only become more widespread over time, as larger indications become segmented into genetically well-characterized sub-populations better treated with targeted therapeutic modalities.

Because we allocate research priorities and decision-making to profit-maximizing organizations, the only way to incentivize capital investment into a proposed early-stage, preclinical drug development project for a rare disease is for a drug company executive or investor to be able to envision charging extremely high prices once a drug is on the market, many years down the road. Otherwise, the investment opportunity will not be financially rational at this stage. The reason is that the following underlying features must be taken into account when generating a financial model for a potential drug development project investment:

- Each stage of drug discovery and development has a very high risk of failure
- There is a long lag time between upfront expenditures on R&D and downstream revenues
- The patient population is small

The net effect is that, after appropriate discounting to account for the high risk of failure and long lag time to market, the only opportunities with a positive net present value (NPV) will be those for which anticipated future cash flows are enormous. And, of course, the smaller the patient population, the higher the requisite price per patient. This result is not a byproduct of evil pharmaceutical executives manipulating financial analysis to justify high drug costs; it is an inescapable consequence of allocating to corporations legally required to maximize shareholder value the task of determining which early drug development projects to pursue. Under this regime, some rare diseases have and will continue to garner private investment if investors can envision how to achieve sufficient future profits through exorbitant pricing. However, many others have been and will continue to be ignored.

2. <u>Overcoming the Pathologies: A Way Forward</u>

How do we move beyond this broken paradigm to create an innovation system that generates truly novel and affordable medicines, including for rare diseases? Three fundamental shifts are necessary.

First, we need to reimagine drug discovery and development in many areas, including rare diseases, as pre-competitive, publicly financed, mission-oriented, hypothesis-driven scientific discovery, and uncouple it from commercial decision-making around manufacturing, marketing, and distribution.

We can do this through adequate public and philanthropic funding entrusted to mission-driven non-profit organizations and social enterprises with mandates: (1) to coordinate partnerships that conduct preclinical and clinical discovery and development in riskier, unexplored areas of the human genome for publicly determined therapeutic priorities, (2) to assemble regulatory dossiers for successful candidates that emerge and use these dossiers as assets for commercial licensing and partnerships, and (3) to ensure affordability of marketed products.

There is no inherent reason that drug discovery and development must be undertaken by profit-maximizing corporations. Most of what occurs during preclinical and clinical testing of a novel drug candidate is hypothesis-driven, discovery science of the sort particularly well-suited to academic and other public institutions. Moreover, expertise and functions that were long ago limited to big pharmaceutical companies – medicinal chemistry, structure-activity relationship profiling, assay screening in *in vitro* and animal models, formulation science, clinical trials, and even regulatory expertise – now abundantly reside in universities, public research institutions, hospitals, contract research organizations (CROs), and consultancies. In fact, pharmaceutical corporations often sponsor and coordinate drug discovery and development research at these various types of external organizations in order to 'own' the outputs of this work and assemble a regulatory dossier for marketing authorization. These same outsourcing, coordination, and project ownership functions can be done well by publicly-funded, mission-driven organizational forms. This is not merely hypothetical. Evidence that this approach can work already exists in the successes of the Drugs for Neglected Diseases Initiative (DNDi) and the Medicines for Malaria Venture (MMV) in tropical diseases, the Global Antibiotic Research & Development Partnership (GARDP) in antimicrobials, the Structural Genomics Consortium (SGC) in early-stage drug discovery, and M4K Pharma in pediatric oncology.

To make this model work on a larger scale, we need to envision well-designed, mission-driven programs as worthy of significant public investment and to stop relying entirely on the private sector to provide capital to finance drug discovery and development in areas of public priority. Public and philanthropic funders would need to align around providing meaningful funding to drive forward therapeutic needs-based drug discovery and development programs from the early stages onward – not only for basic biology science, but also for hypothesis-driven preclinical and

clinical testing of drug candidates against novel therapeutic targets, along with formulation and chemistry, manufacturing, and controls (CMC) work. Much of this work could then be outsourced, including to for-profit businesses such as CROs, AI companies, and the like, in the same way that a pharmaceutical company does currently. The difference would be that ultimate control of the drug candidate asset and the accumulating regulatory dossier in support of its potential marketing authorization would reside with a mission-driven organization instead of a profit-maximizing entity, at least until the point at which a for-profit corporation would rationally invest under affordable pricing constraints.

Next, we should eliminate the substantial inefficiencies and redundancies in, and reduce the aggregate costs of, drug discovery and development by encouraging mission-oriented partnerships to adopt open science practices at all preclinical and clinical stages.

Open science refers to early and widespread dissemination of results, data, and tools to the research community without patents or other restrictive intellectual property. Open science: (1) minimizes transactional barriers to collaboration and knowledge flow, (2) prevents redundant investigation of the same failed avenues, freeing resources for other areas of inquiry, (3) better distributes project risks, (4) creates a public commons of knowledge to spur more innovation, (5) enhances reproducibility and public trust in scientific data, and (6) enables secondary analysis, meta-analysis, and new hypothesis generation. Applied to drug discovery and development, open science can also (1) enable better decision-making by health regulators, prescribers, health technology assessment (HTA) agencies, and drug purchasers, (2) provide the necessary data inputs for artificial intelligence (AI) applications aimed at accelerating new drug discovery, and (3) better respect the contributions of clinical trial participants by maximizing the scientific benefits of their contributions while minimizing their exposure to risk in duplicative studies.

Though they forego early-stage restrictive IP, publicly mandated drug discovery and development initiatives that deploy open science can still generate powerful intellectual property assets in the form of regulatory data and marketing exclusivities. For example, new chemical entities are entitled to 8 years of protection from generic competition in Canada as "innovative drugs" under C.08.004.1 of the *Food and Drug Regulations*, whether or not they are patented. Similar protections exist in other major pharmaceutical markets and additional market exclusivity incentives exist for "orphan drugs" for rare diseases in the US, EU, and other jurisdictions. Contrary to popular conception, there are many examples of new drugs that have been launched and marketed without patents, instead relying solely on data exclusivity or orphan drug status for market protection. These assets provide attractive licensing opportunities for potential commercial partners.

The benefits of open science partnerships and strategic considerations around the use of regulatory exclusivity protections for drug candidates developed through open science are explored further in the following publications:

- Gold ER. The fall of the innovation empire and its possible rise through open science. *Research Policy* 2021, 50 (https://doi.org/10.1016/j.respol.2021.104226)
- Morgan MR, Roberts OG and Edwards AM. Ideation and implementation of an open science drug discovery business model – M4K Pharma. *Wellcome Open Res* 2018, 3:154 (https://doi.org/10.12688/wellcomeopenres.14947.1)

Finally, we need a rational approach to partnering with commercial actors to ensure manufacturing, distribution, and affordable pricing of new drugs emerging from the above-discussed open science partnerships.

Applying a financial analysis lens, if we want an affordable rare disease drug, we should not seek to leverage private capital investment until a point in the drug development cycle when future cash flows from affordable pricing are sufficiently proximate and de-risked to produce an attractive positive NPV at the desired affordable price. It is only at this point that a profit-maximizing corporation could rationally decide to invest in marketing and distribution of the drug at the affordable price. In many cases, this inflection point is unlikely to occur until after Phase II clinical proof of concept has occurred, at the earliest. Of course, the more proximate the marketing revenues and the more de-risked the drug candidate, the better the negotiating position of a publicly financed, mission-oriented organization to secure affordable pricing commitments from a commercial partner. In the event that such a mission-oriented organization is able to bring a drug candidate all the way through marketing authorization without private capital, depending on the particular market dynamics, this further opens the possibility of non-exclusively licensing generic manufacturers to enable competitive supply and pricing.

Either way, publicly funded programs should impose contractual conditionalities in licensing with commercial partners that ensure resulting products are marketed at prices capped at a reasonable mark-up over costs. The "costs" calculation should only be permitted to amortize R&D expenditures directly attributable to the commercial partner itself. Contractual frameworks for this type of cost-plus pricing commitment already exist and have been implemented by DNDi in its partnerships with pharmaceutical companies, for example. There is no reason they cannot be applied more broadly.

3. Canada Can Lead by Creating the Right Funding and Policy Environment

Though the pathologies outlined above are global in nature and so must be the solutions, Canada's economy, global reputation, and health care system can benefit greatly by Canada being a first mover. Three policy initiatives in particular could place Canada at the forefront of a more efficient, more equitable, therapeutic needs-based drug discovery ecosystem grounded in open science.

First, the federal government should provide substantial and sustainable public funding for mission-oriented, open science partnerships seeking to discover and develop innovative new medicines in areas of therapeutic priority for Canada, including rare diseases.

Such public funding should come with stringent conditionalities around open science practices (including disclosure of negative trial results) and affordable pricing of resulting products. Approaches to contracting and licensing that have been implemented by organizations like DNDi, and structures for open science-based partnerships pioneered by organizations like the SGC, can be readily adapted for these purposes.

Next, the federal government should invest in creating infrastructure to catalyze open science drug development partnerships.

For example, Health Canada should create and host an open drug development data repository that enables new drug sponsors to register and deposit their preclinical and clinical datasets during the development process. The depositing sponsor could assemble its full regulatory dossier within the repository and ultimately submit it to Health Canada as a new drug submission (NDS). Datasets that are registered and deposited into the repository would be made immediately publicly available for non-competitive uses, including for secondary analysis and meta-analysis by other researchers, for early evaluation by Health Canada and HTA agencies such as CADTH to make better-informed approval decisions and funding recommendations, and to improve transparency with physician prescribers, drug purchasers, and patients. At the same time, data depositors should be afforded a period of exclusive regulatory use of their data from the date of deposit to protect them against unfair commercial use.

Finally, the federal government should provide meaningful regulatory incentives to encourage open science development of affordable new medicines.

For example, Health Canada should provide a 4-year extension of data protection for openly-developed innovative drugs under C.08.004.1 of the *Food and Drug Regulations* (from 8 to 12 years) to approximate the average patent life of new medicines developed in proprietary settings. To qualify for this "open science extension" provision, a sponsor would be required to (1) demonstrate upon submission of its NDS that it has diligently made its preclinical and clinical data publicly available via the open drug development data repository advocated above; (2) certify that it has not filed for patents covering the new product or uses thereof, rendering the sponsor ineligible to list patents against its drug in Health Canada's Patent Register; and (3) certify that it will sell the drug at or below an affordable price ceiling determined, for example, through pharmacoeconomic cost-effectiveness analysis or as a reasonable mark-up over costs. The sponsor would need to demonstrate ongoing compliance with the price ceiling requirement to maintain its exclusivity extension.

The benefit of extended data exclusivity for mission-oriented open science drug development programs would be that late-stage, de-risked clinical assets would represent a positive NPV to investors either earlier in development or under even lower pricing constraints, thereby improving the negotiating position with potential commercial partners. The exclusivity extension could even provide incentives for private capital to fund early open science drug development in some contexts. Sample amending language for C.08.004.1 of the *Food and Drug Regulations* is provided at the end of this letter submission.

The three foregoing policy recommendations would not undermine the current drug development ecosystem or involve a public take-over of the pharmaceutical industry. Rather, these policies would simply help to create an alternative, voluntary pathway for mission-oriented, needs-based drug discovery and development, while leaving the current proprietary mechanisms intact. The approach can be adopted for areas of market failure – like rare diseases – where the free market is not functioning properly because it is either not producing new drugs to address therapeutic needs or is only producing new drugs affordable to a tiny segment of the population. Even in these areas, there is a substantial role for the private sector, both in servicing mission-oriented programs (through CROs, AI biotechs, regulatory affairs consultancies, and the like) and in manufacturing and distribution of products produced by such programs (with potential opportunities for both innovator and generic firms). Thus, public investment and a supportive policy environment in Canada for mission-driven, therapeutic needs-based drug discovery have the potential to spur on significant domestic economic activity. The dividends could extend beyond the health system benefits of affordable medicines for rare diseases to job creation and economic growth.

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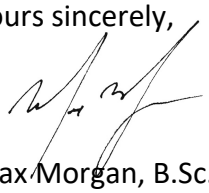
Thank you for considering the comments and suggestions in this submission letter. Please do not hesitate to contact me with any questions.

Yours sincerely,



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An Amendment to Encourage Open Science Development of Affordable Medicines

Food and Drug Regulations (C.R.C., c. 870)

PART C

Drugs (continued)

DIVISION 8 (continued)

New Drugs (continued)

C.08.004.1 (1) The following definitions apply in this section.

abbreviated new drug submission includes an abbreviated extraordinary use new drug submission. (*présentation abrégée de drogue nouvelle*)

affiliate means an entity that controls, is controlled by, or is under common control with an innovator.

Consumer Price Index means the Consumer Price Index published by Statistics Canada under the authority of the *Statistics Act.*

innovative drug means a drug that contains a medicinal ingredient not previously approved in a drug by the Minister and that is not a variation of a previously approved medicinal ingredient such as a salt, ester, enantiomer, solvate or polymorph. (*drogue innovante*)

new drug submission includes an extraordinary use new drug submission. (*présentation de drogue nouvelle*)

pediatric populations means the following groups: premature babies born before the 37th week of gestation; full-term babies from 0 to 27 days of age; and all children from 28 days to 2 years of age, 2 years plus 1 day to 11 years of age and 11 years plus 1 day to 18 years of age. (*population pédiatrique*)

(2) The purpose of this section is to implement Article 1711 of the North American Free Trade Agreement, as defined in the definition ***Agreement*** in subsection 2(1) of the North American Free Trade Agreement Implementation Act, and paragraph 3 of Article 39 of the Agreement on Trade-related Aspects of Intellectual Property Rights set out in Annex 1C to the Agreement Establishing the World Trade Organization, as defined in the definition ***Agreement*** in subsection 2(1) of the World Trade Organization Agreement Implementation Act.

(3) If a manufacturer seeks a notice of compliance for a new drug on the basis of a direct or indirect comparison between the new drug and an innovative drug,

> **(a)** the manufacturer may not file a new drug submission, a supplement to a new drug submission, an abbreviated new drug submission or a supplement to an abbreviated new drug submission in respect of the new drug before the end of a period of six years after the day on which the first notice of compliance was issued to the innovator in respect of the innovative drug; and
>
> **(b)** the Minister shall not approve that submission or supplement and shall not issue a notice of compliance in respect of the new drug before the end of a period of eight years after the day on which the first notice of compliance was issued to the innovator in respect of the innovative drug.

(4) The period specified in paragraph (3)(b) is lengthened to eight years and six months if

> **(a)** the innovator provides the Minister with the description and results of clinical trials relating to the use of the innovative drug in relevant pediatric populations in its first new drug submission for

the innovative drug or in any supplement to that submission that is filed within five years after the issuance of the first notice of compliance for that innovative drug; and

(b) before the end of a period of six years after the day on which the first notice of compliance was issued to the innovator in respect of the innovative drug, the Minister determines that the clinical trials were designed and conducted for the purpose of increasing knowledge of the use of the innovative drug in those pediatric populations and this knowledge would there-by provide a health benefit to members of those populations.

(4.1) The period specified in paragraph (3)(b) is lengthened to twelve years if

(a) before the end of a period of five years after the day on which the first notice of compliance was issued to the innovator in respect of the innovative drug, the innovator provides the Minister with information to establish that digital copies of the following items have been and will continue to be freely accessible to the public via electronic means for research use, in each case since the prescribed date

(i) all information and documents referred to in paragraphs C.05.005(a)–(d) submitted to the Minister in any application for authorization to sell or import the innovative drug for the purposes of a clinical trial and in any amendments thereto, no later than 30 days after the date of submission,

(ii) all information referred to in paragraphs C.05.005(e)(i)–(vi) in respect of the innovative drug and all supporting data relating thereto, in each case no later than six months from the date of completion of each study or test that produced the information,

(iii) all information and material referred to in paragraphs C.08.002(2)(g) and (h) filed with the Minister in the new drug submission for the innovative drug and in any supplements thereto, no later than 30 days after the date of filing,

(iv) sectional reports referred to in paragraph C.08.005.1(1)(b) for each human, animal, and *in vitro* study included in the new drug submission for the innovative drug and in any supplements thereto, and all supporting data in respect thereof redacted of any information that could reasonably be used to identify one or more human study participants, in each case no later than six months from the date of study completion in respect of each animal and *in vitro* study and no later than eighteen months from the date of study completion in respect of each human study,

(v) the comprehensive summary referred to in paragraph C.08.005.1(1)(c) filed with the Minister in the new drug submission for the innovative drug and in any supplements thereto, no later than 30 days after the date of filing;

(b) on or before the day on which the first notice of compliance was issued to the innovator in respect of the innovative drug, the innovator certifies to the Minister that

(i) the innovator has not submitted, and will not submit during the twelve year period applicable under this subsection (4.1), a patent list pursuant to section 4(1) of the *Patented Medicines (Notice of Compliance) Regulations* in relation to the new drug submission in respect of the innovative drug or any supplement thereto,

(ii) the innovator and its affiliates have not been, and will not be at any time during the twelve year period applicable under this subsection (4.1), a "patentee" within the meaning of section 79(1) of the *Patent Act* in relation to any invention "pertaining to" the innovative drug within the meaning of section 79(2) of the *Patent Act*; and

(iii) the innovator irrevocably waives all past, current, and future rights of action under sections 55 and 55.2(4) of the *Patent Act* in relation to any patent pertaining to the innovative drug;

(c) before the end of a period of three months after the day on which the first notice of compliance was issued to the innovator in respect of the innovative drug, the innovator certifies to the Minister that, during the twelve year period applicable under this subsection (4.1), the innovator will exclusively sell the innovative drug in any market in Canada at a maximum price not to exceed a price determined to provide attractive cost-effectiveness in a national health technology assessment process deemed acceptable by the Minister or, in the absence thereof, in an independent pharmacoeconomic analysis deemed acceptable by the Minister, in either case adjusted for changes in the Consumer Price Index; and

(d) before the end of a period that is six years after the day on which the first notice of compliance was issued to the innovator in respect of the innovative drug, the Minister determines that

(i) the digital copies referred to in paragraph (4.1)(a) have been freely accessible to the public via electronic means for research use since the prescribed dates in one or more formats that are adequately findable, accessible, and usable for independent scientific analysis thereof,

(ii) the innovator has not submitted a patent list in contravention of paragraph (4.1)(b)(i), neither the innovator nor its affiliates have been a patentee in contravention of paragraph 4.1(b)(ii), and neither the innovator nor its affiliates have brought a cause of action under sections 55 or 55.2(4) of the *Patent Act* in relation to any patent pertaining to the innovative drug; and

(iii) the innovator has not sold the innovative drug in any market in Canada at a price exceeding the maximum price referred to in paragraph (4.1)(c).

(5) Subsection (3) does not apply if the innovative drug is not being marketed in Canada.

(5.1) An extension granted pursuant to subsection (4.1) shall cease to apply if at any time during the remainder of the applicable twelve year period, the Minister determines that

(a) digital copies referred to in paragraph (4.1)(a) have ceased to be freely accessible to the public via electronic means for research use in one or more formats that are adequately findable, accessible, and usable for independent scientific analysis thereof,

(b) the innovator has submitted a patent list in contravention of paragraph (4.1)(b)(i), the innovator or an affiliate of the innovator has become a patentee in contravention of paragraph 4.1(b)(ii), or the innovator or an affiliate of the innovator has commenced a cause of action in contravention of paragraph 4.1(b)(iii); or

(c) the innovator has sold the innovative drug in any market in Canada at a price exceeding the maximum price referred to in paragraph (4.1)(c).

(5.2) In order to make a determination pursuant to paragraph (4.1)(d) or subsection (5.1), the Minister may require an innovator to provide the Minister with information and documents respecting any of the matters referred to in subsection (4.1).

(6) Paragraph (3)(a) does not apply to a manufacturer if the innovator consents to the filing of a new drug submission, a supplement to a new drug submission, an abbreviated new drug submission or a supplement to an abbreviated new drug submission by the manufacturer before the end of the period of six years specified in that paragraph.

(7) Paragraph (3)(a) does not apply to a manufacturer if the manufacturer files an application for authorization to sell its new drug under section C.07.003.

(8) Paragraph (3)(b) does not apply to a manufacturer if the innovator consents to the issuance of a notice of compliance to the manufacturer before the end of the period of eight years specified in that paragraph or of eight years and six months specified in subsection (4) or of twelve years specified in subsection (4.1).

(9) The Minister shall maintain a register of innovative drugs that includes information relating to the matters specified in subsections (3), (4) and (4.1).