WHO Collaborating Centre for Pharmaceutical Policy and Regulation

UIPS Utrecht Institute for Pharmaceutical Sciences

How much data is needed?

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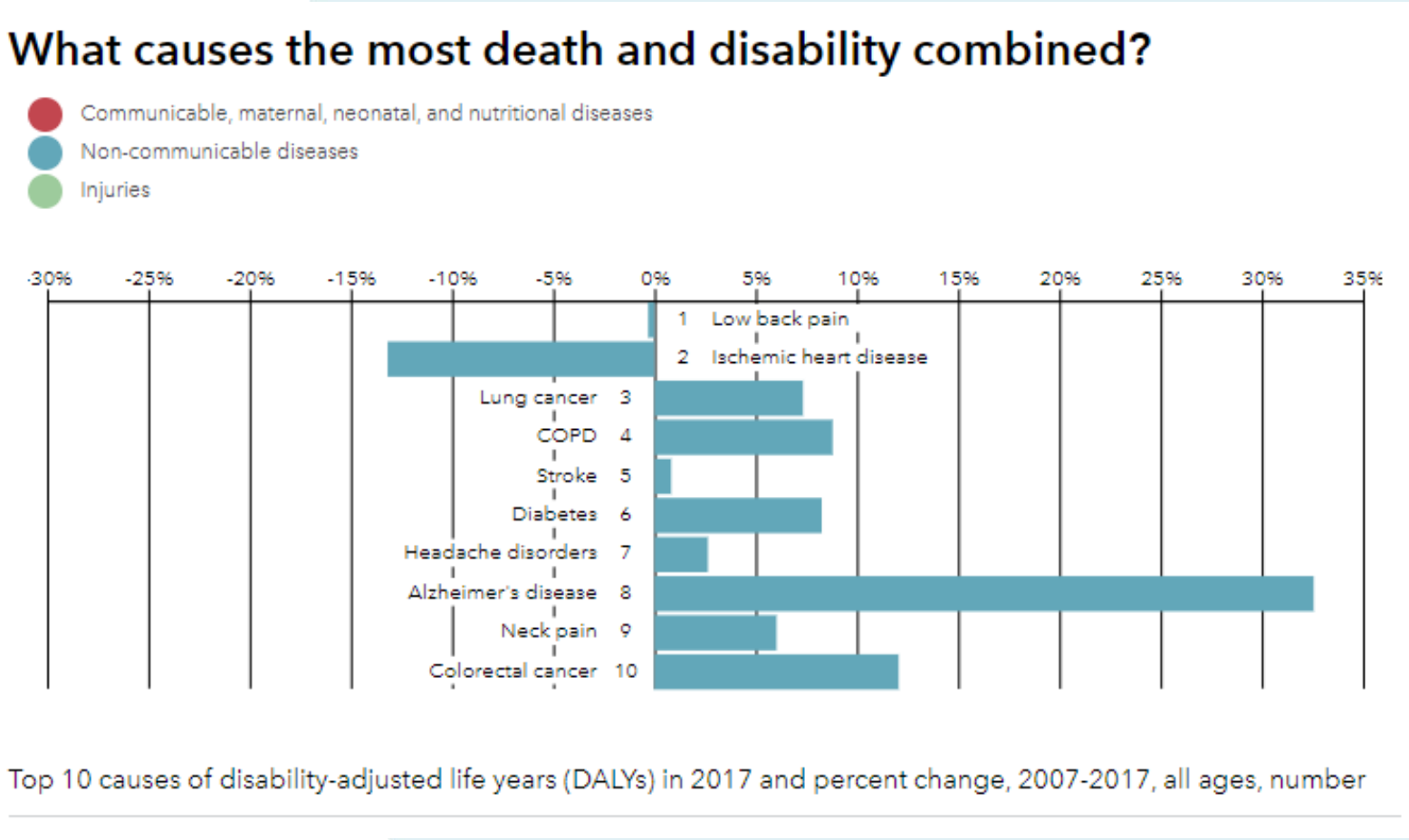
Declaration of interests

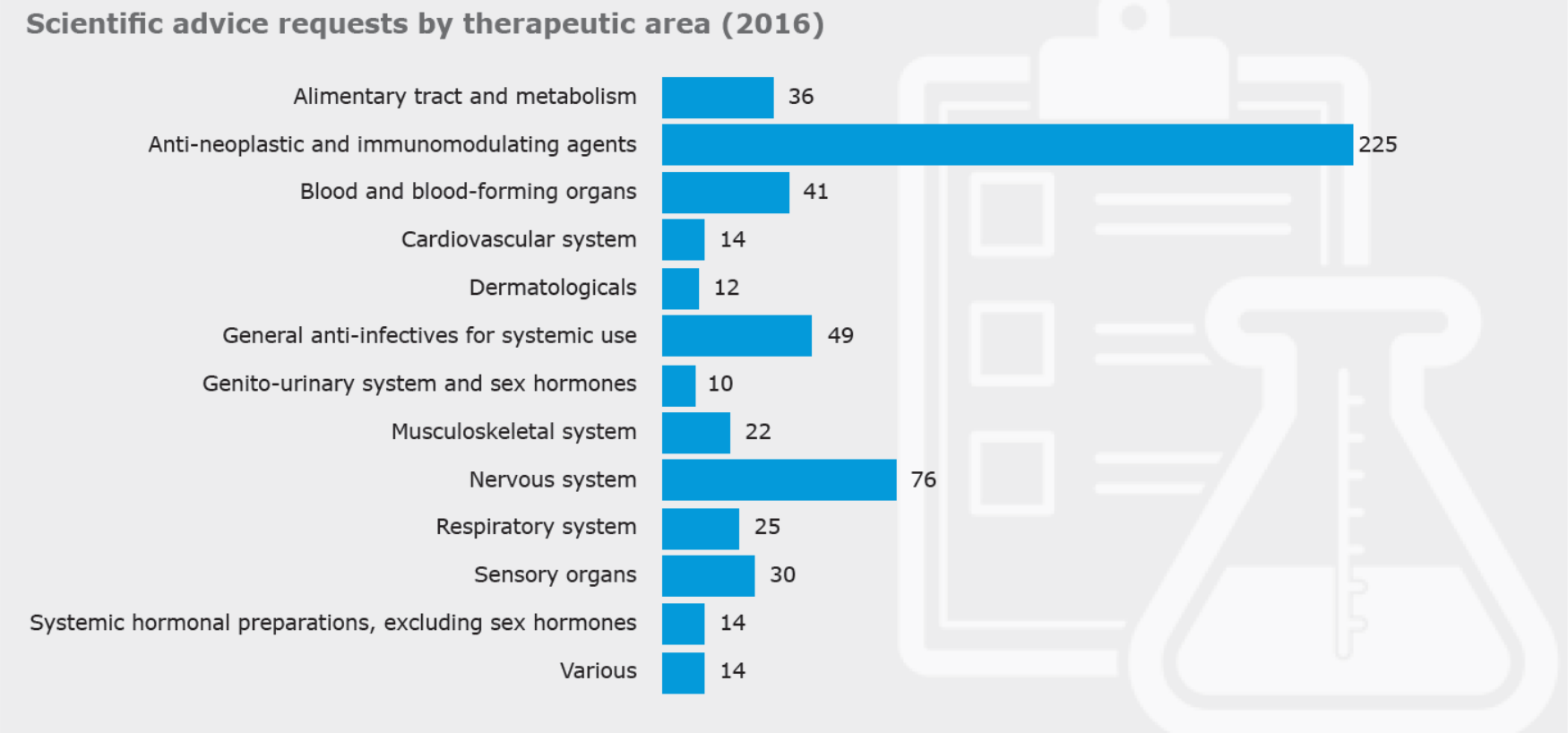
- Professor Pharmaceutical Policy and Regulatory Science, Utrecht Institute of Pharmaceutical Sciences (UIPS).
- Scientific director WHO-Utrecht Collaborating Centre for Pharmaceutical Policy and Regulation.
- Member Scientific Leadership Team Lygature.
- Visiting professor at the Faculdade de Farmácia, Universidade de Lisboa, Portugal and the Copenhagen Centre for Regulatory Science (CORS).
- Chairman of the Dutch Medicines Evaluation Board (MEB), 2007-2017; member of EMA CHMP PhVWP, 2006-2009; member of EMA CHMP 2009-2015.
- No other interests to declare.

Burden of disease Netherlands



http://www.healthdata.org/

What's hot in pharma R&D?



EMA Annual Report, 2016

Bert Leufkens, toezichthouder geneesmiddelen „We moeten nog scherper zijn bij de toelating van nieuwe medicijnen", zegt de voorzitter van het College ter Beoordeling van Geneesmiddelen.

Karel Berkhout 20 april 2016

Er zitten tientallen veelbelovende geneesmiddelen voor onder meer kanker en chronische ziekten aan te komen. Ook al zullen zeker niet alle patiënten er baat bij hebben, een aantal kan mogelijk worden geholpen. Daarom moeten nieuwe middelen zo snel mogelijk aan patiënten worden gegeven, zeggen nogal wat patiënten, artsen én farmaceutische fabrikanten. Ook steeds meer politici en sponsors van biomedisch onderzoek zijn die n

Wete
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'Groot deel medicijnstudies **deugt niet'**

Interview Bert Leufkens, toezichthouder geneesmiddelen

„We moeten nog scherper zijn bij de toelating van nieuwe medicijnen", zegt de voorzitter van het College ter Beoordeling van Geneesmiddelen.

Key questions when regulating a medicine

Question	Today's challenges
Robust definition and diagnosis of disease?	Stratification of cancers, psychiatric morbidities
Clinically relevant endpoints to evaluate drug effects?	PFS/OS/RR in cancer, 6-MWT in PAH, HbA1C in diabetes
Identifiable target population (indication) that may benefit?	First line/second line, biomarkers responders/non-responders
What kind of comparison is useful, needed and feasible?	Placebo, active controls and natural course of disease

European CP products 2016

- 27 NCE/NME
- 10/27 OMP
- 8/27 oncology

- 8/27 NL Rap or Co-Rap.

	NL position
	B/R negative
	Still objections
	B/R positive

	Round 1	Round 2	> 2
Afstyla			
Alecensa			
Alprolix			
Cinqaero			
Darzalex			
Empliciti			
Epclusa			
Galafold			
Ibrance			
Idelvion			
Lartruvo			
Lonsurf			
Ninlaro			
Ocaliva			
Olumiant			
Ongentys			
MedImmune			
Parsabiv			
Strimvelis			
Taltz			
Truberzi			
Uptravi			
Venclyxto			
Zalmoxis			
Zavicefta			
Zepatier			
Zinplava			

The classic clash of type I and II errors in regulatory decision making

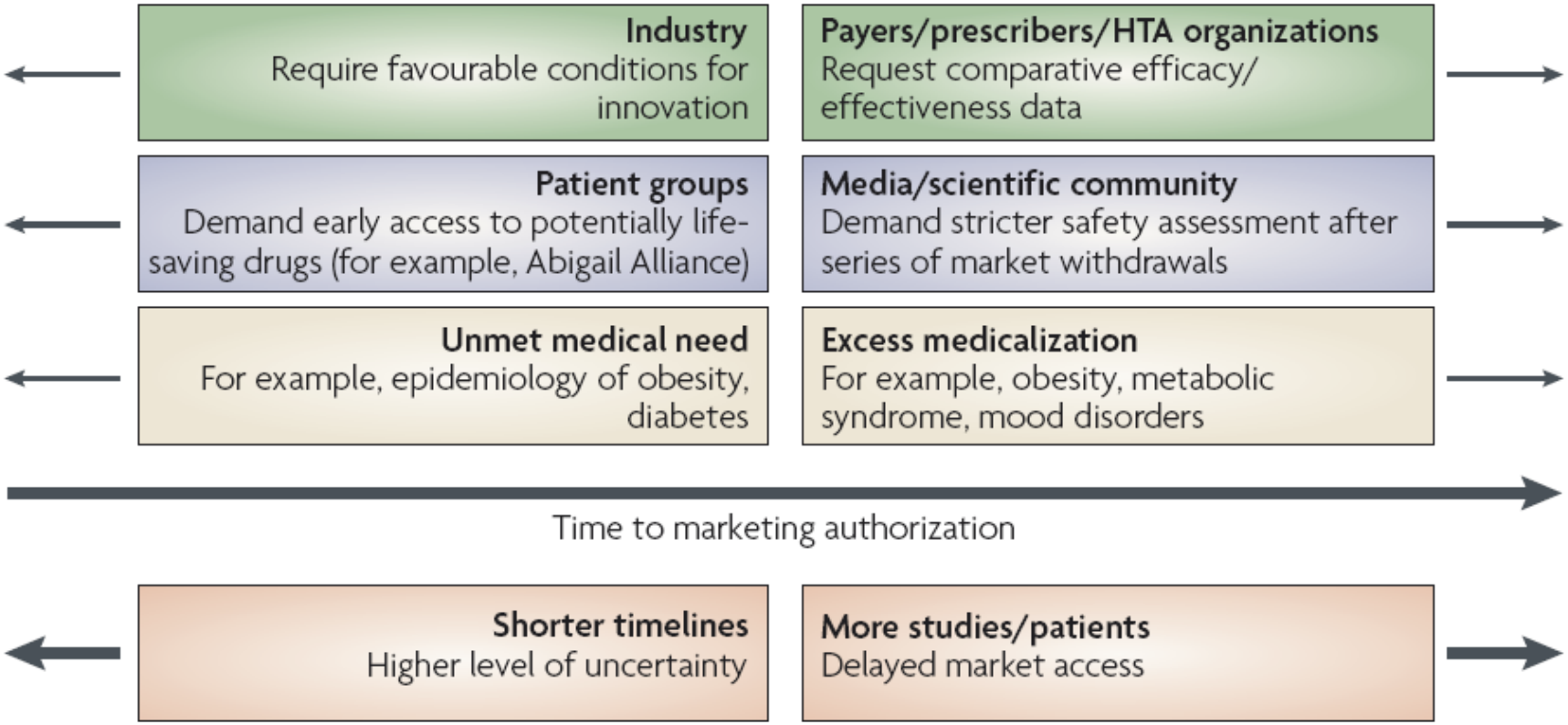
- Type I error: a decision to approve a product is made, but turns out to be wrong, too risky, too many uncertainties, or …….
- Type II error: a decision to approve a product is not made, and turns out to be too precautionary, based on wrong data, too risk averse, or …..

How to come to a decision?

to do. Moving from the least to most restrictive options, 3 members voted to allow continued marketing with no changes to the label; 7 voted that the FDA should adjust the label to account for the new concerns but take no additional action; 10 members voted for the FDA to both increase warnings and limit access to rosiglitazone; and 12 voted that the medication should be removed from the market altogether. The FDA decided to increase warnings and limit access to rosiglitazone substantially.

New Eng J Med 2010; Sept 16.

The best moment to bring a product to the clinic?



Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit-risk data. Nat Drug Discov 2008; 7: 818-26.

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The Large Pharmaceutical Company Perspective

Michael Rosenblatt, M.D.

LARGE PHARMACEUTICAL COMPANIES CO
uate efficacy and identify safety issues f
efficiently, and expeditiously as possible,
the requirements of regulatory authorities ac
people at risk and to learn the most, these tria
evidence for health care providers, regulatory a
health agencies. Because there are so many un
and development is a high-risk business with
product candidates of any industry.

Table 1. Increasing Complexity of a Typical Phase 3 Clinical Trial.*

Trial Design Characteristic	2002	2012
Total no. of end points	7	13
Total no. of procedures	106	167
Total no. of eligibility criteria	31	50
Total no. of countries	11	34
Total no. of investigative sites	124	196
Total no. of patients undergoing randomization	729	597
Total no. of data points collected	NA	929,203

N Engl J Med 2017; 376: 52-60.

Costs of clinical trials FDA approved drugs 2015-2016

Trial Characteristic	Agents, No.[a]	Trials, No. (%) (n = 138)[b]	Mean (95% CI), US$ in millions[a]
Type of end point			
Surrogate outcome	32	73 (52.9)	24.0 (17.7-30.4)
Clinical scale	15	38 (27.5)	20.5 (14.7-26.3)
Clinical outcome	17	27 (19.6)	64.7 (46.6-82.9)
Trial design			
No control group	18	26 (18.8)	13.5 (10.1-16.9)
Placebo-controlled	33	77 (55.8)	28.8 (21.0-36.7)
Active drug	21	35 (25.4)	48.9 (35.0-62.7)
Patient enrollment, No.			
1-100	6	8 (5.8)	5.9 (4.8-7.0)
101-250	25	32 (23.2)	16.2 (12.2-20.3)
251-500	14	33 (23.9)	18.6 (14.1-23.2)
501-1000	27	44 (31.9)	33.6 (23.6-43.6)
>1000	16	21 (15.2)	77.2 (55.8-98.6)

Moore TJ et a. JAMA Intern Med doi:10. 1001/jamainternmed.2018.3931

Addressing the regulatory and scientific challenges in multiple sclerosis – a statement from the EU regulators

Multiple Sclerosis Journal
2014, Vol. 20(10) 1282–1287
DOI: 10.1177/1352458514546876

Pavel Balabanov, Manuel Haas, Andre Elferink, Serge Bakchine and Karl Broich

Abstract: Improving and facilitating the process of making new drugs available to patients with multiple sclerosis (MS) requires cooperation among the regulators and other stakeholders. This cooperation will also positively contribute towards developing guidelines of the highest quality in medical, regulatory and scientific aspects. This would be beneficial both in areas that require further guideline development, but also in fields where existing guidance should be adapted to take into account evolution in science. Considering the input from all stakeholders, the European Medicines Agency confirmed its intention to update the relevant guideline and apply a flexible approach towards new drug development strategies in MS. This article is the first official position from the EU regulators, presenting the main changes to be expected in the guidance document.

Keywords: Multiple sclerosis, drug development, regulatory requirements

Weighing of evidence by HTA bodies for conditionally approved drugs in EU (9/27 controlled, until June 2016)

1999-2014 approvals without controlled data

EMA 35/415
FDA 54/403

Hatswell AJ et al. BMJ Open 2016; 6:e011666.

Vreman RA et al. Clin Pharmacol Ther. 2018 Oct 9. doi: 10.1002/cpt.1251

Pivotal data contrasts in drug development

- More data points from clinical trials than ever before.
  …… Still decisions on B/R under high levels of uncertainty.

- Big cry out for RWE, Big Data, registries, etc.
  …… Impact on regulatory decision making rather limited.

- Advancements in observational methods (e.g. inception cohorts, prevalent new user design, propensity scores).
  …. Not always good for external validity, RW extrapolation.

- Data space for industry and authorities heavily regulated.
  ..... Hardly any regulation social media/academia/NGOs.

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Ten recommendations to unlock the potential of big data for public health in the EU

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Press release 20/01/2020

The joint Big Data Task Force of EMA and the Heads of Medicines Agencies (HMA) proposes ten priority actions for the European medicines regulatory network to evolve its approach to data use and evidence generation, in order to make best use of big data to support innovation and public health, in a report published today .

Big data are extremely large, rapidly accumulating datasets captured across multiple settings and devices, for example through wearable devices, electronic health records, clinical trials or spontaneous adverse reaction reports. Coupled to rapidly developing technology, big data can complement the evidence from clinical trials and fill knowledge gaps on a medicine, and help to better characterise diseases, treatments and the performance of medicines in individual healthcare systems.

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EDITORIAL

Regulatory science: Regulation is too important to leave it to the regulators

Leufkens HG. Br J Clin Pharmacol. 2019 Apr 10. doi: 10.1111/bcp.13917.

On 19 December 2018, the European Medicines Agency (EMA) published its draft "Regulatory Science to 2025" strategy for a 6-month public consultation. In this EMA publication, regulatory science has been defined as "the range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine …." Earlier in 2011, the US Food and Drug Administration of being too risk averse in the interest of giving patients access to new promising therapeutic options.[3]

Reality of regulatory decision making shows that this is not always a straightforward yes or no. Scanning the EMA website for European public assessment reports (EPARs) makes this very visible in situations where products are approved on the basis of majority votes and not on consensus view. Obviously, individual members of the CHMP come

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Two key developments in regulatory innovation, i.e. opportunities for informed impact …..

RSNN Regulatory Science Netwerk Nederland

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Our Network

The Regulatory Science Network Netherlands (RSNN) is a network of regulatory science experts from industry, academia, governmental bodies and the broader regulatory science field. The RSNN is an inclusive organization, with activities open to anyone interested in Regulatory Science. Such inclusiveness helps us to set agendas for future research, and to act as a breeding ground for new research initiatives.

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Shaping regulatory science to 2025

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News 17/10/2018

EMA is hosting a workshop on Wednesday, 24 October to gather insight from stakeholders on the key areas in human medicines to be covered in its 'Regulatory Science Strategy to 2025', a proposed new high-level plan for advancing its engagement with regulatory science.

The workshop will offer an opportunity to reflect on the scientific and technological advances in the pharmaceutical arena, the challenges that the Agency's scientific committees and working parties will face in the future and to look at initial proposals to address them. It will also highlight areas relevant to various stakeholder groups in advance of a six-month public consultation on the proposed strategy to be launched in December 2018.