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IMPLICATIONS OF DISCARDED WEIGHT-BASED DRUGS

Global Approaches & Considerations in Weight-based Pharmaceutical Pricing

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Galapagos NV

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We are

A pioneering biotechnology company, developing innovative medicines that will improve people's lives.

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We discover
Our unique target discovery platform
is transforming how medicines are discovered. Today our pipeline ranges from inflammation to fibrosis candidate drugs.
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Our drug development

78%
OPERATING EXPENSES TO R&D

40+
DRUG CANDIDATES

45
PATENT FAMILIES

>50%
IN THE CLINIC

Values as per 31-12-2019

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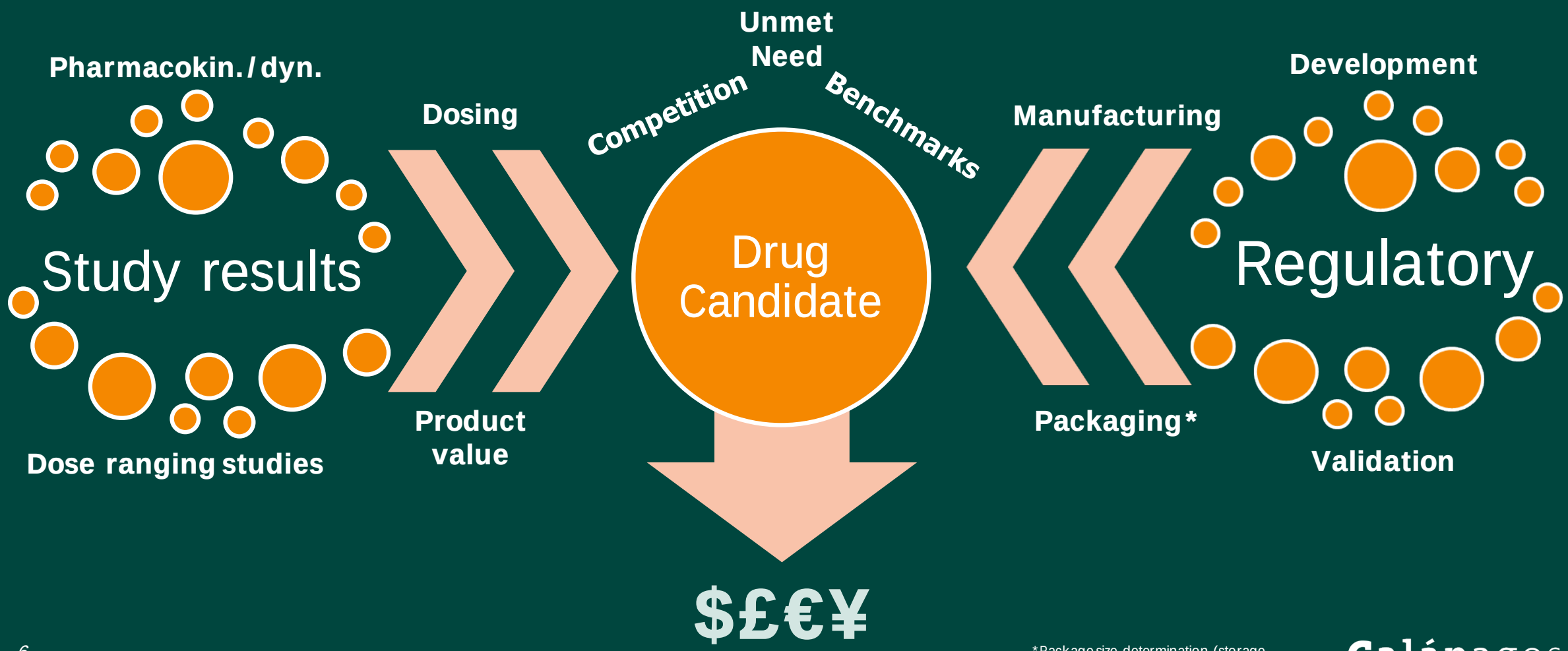
Approaches to Weight-based Pricing

What we can do is bound by regulatory demands and scientific results



*Package size determination (storage, customer feedback, patient epidemiology, etc)

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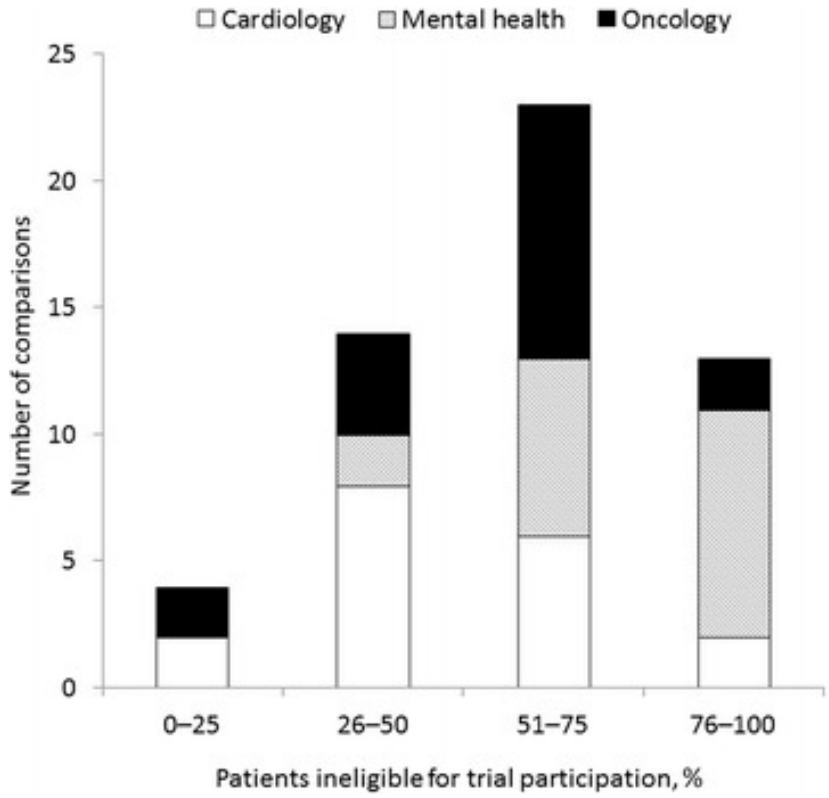
Phase III trials are often our initial source of patient characteristics

- In one analysis, 71.2% of RCT samples were not representative of patients encountered in clinical practice
- Differences in demographics, clinical characteristics, and treatments and procedures were reported between RCT and real-world patients

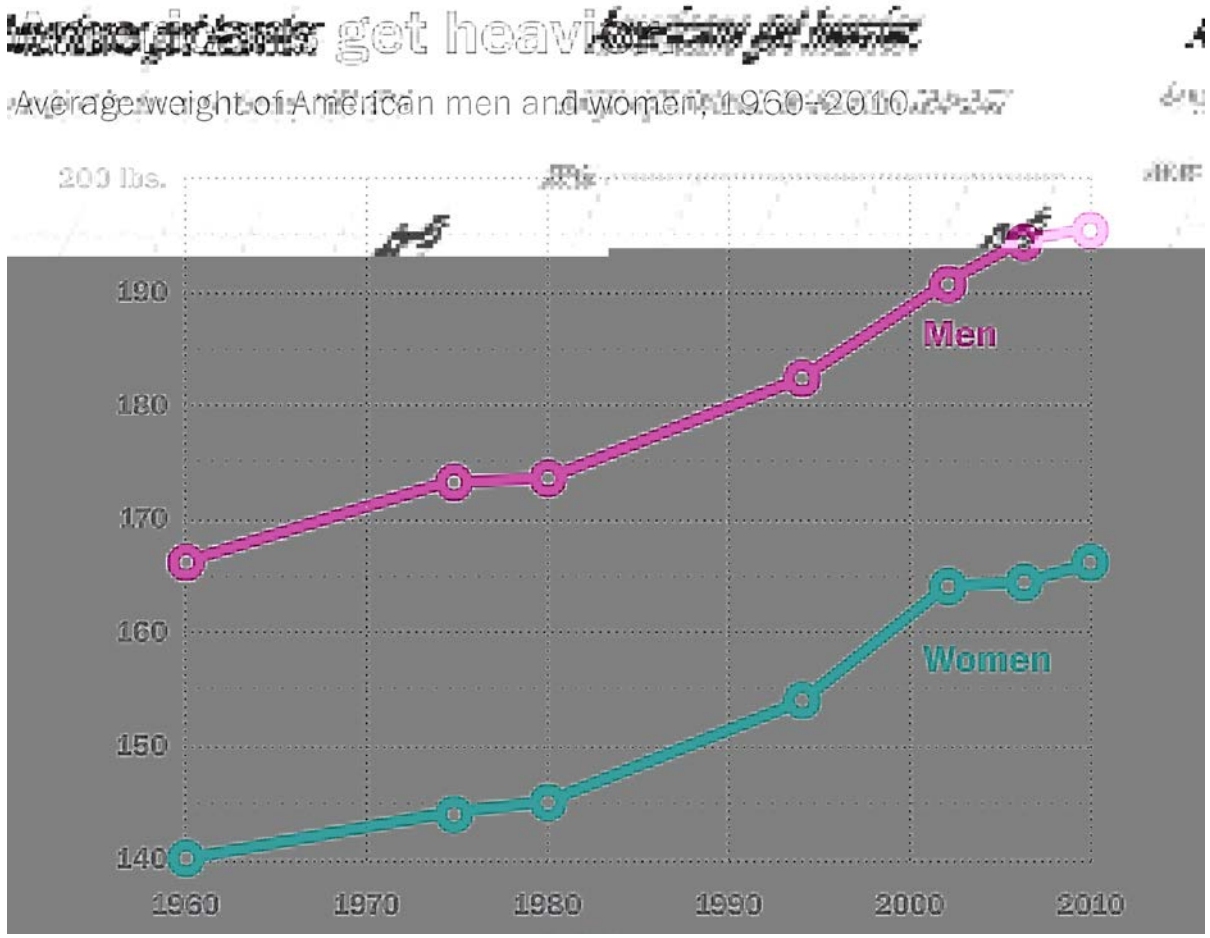
Proportion of real-world patients ineligible in randomized controlled trials (RCTs) after application of inclusion/exclusion criteria



Source: A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results, Kennedy-Martin et al. Trials (2015) 16:495 DOI 10.1186/s13063-015-1023-4

Issues and challenges in determining real-world dosing

- Hindsight is always 20/20 but these decisions are made early and rapidly
- The “average 70 kg adult” is based off of the consensus from the 1976 International consortium for Radiation Protection document
  - In 2012, the average US adult male was 86.8 kg; female 74.7 kg
  - The average adult in the USA has gained 11 kg (~25 lbs) over that time
  - Standards updated to at least 81 kg



Source: Data from CDC National Health and Nutrition Examination Survey, 1999–2010. Washington Post (link)

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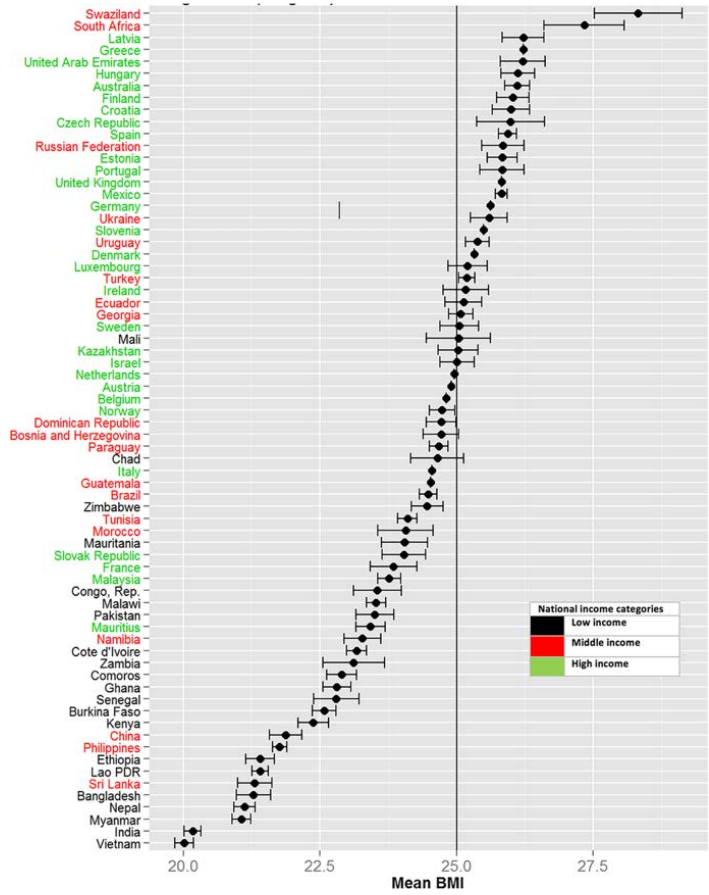
Which country is the base case?

- Weights of patients differ around the world
- Assumptions and ranges impact administration needs for individual patients
- Pricing often based on mean estimates, rather than specific populations

Design-based mean BMI (weighted) and confidence interval for each country



Source: Effect of national culture on BMI: a multilevel analysis of 53 countries, Mohd Masood, BMC Public Health volume, September 2019, DOI: 10.1186/s12889-019-7536-0

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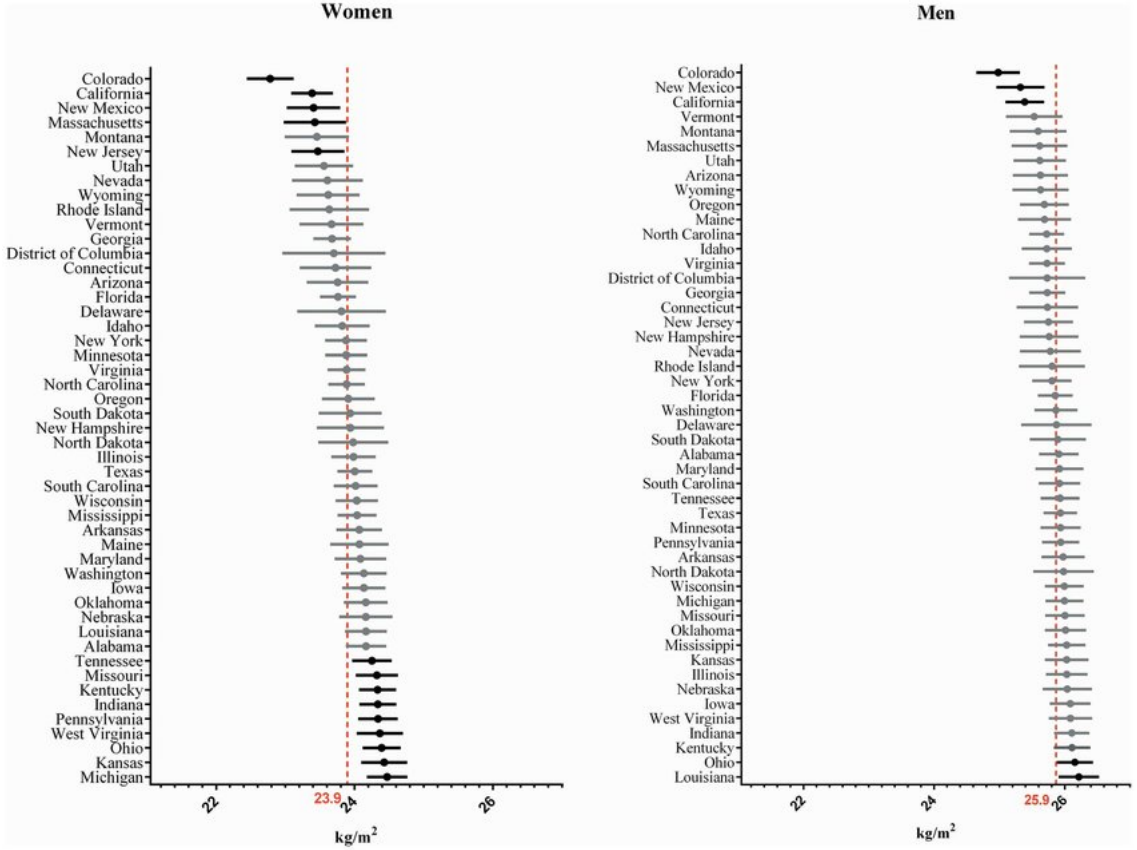
Does that meet everyone's needs?

- Even within countries these may differ by Region or State
- Community versus Academic, Rural versus Urban, etc. may skew your reference patient

"For any dosing strategy, wastage and cost savings may vary from site to site based on patient numbers, sterile compounding procedures, and purchasing practices."

The Canadian Agency for Drugs and Technologies in Health (CADTH)

BMI mean and 95% confidence interval for US states, 2009 Reference group: young adult, White, highest household income and college graduated



Source: Geographic Variability in the Association between Socioeconomic Status and BMI in the USA and Canada; 10.1371/journal.pone.0099158

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Weight assumptions differ, along with wastage impact

Weight Assumptions Used by Global Health Assessment Bodies

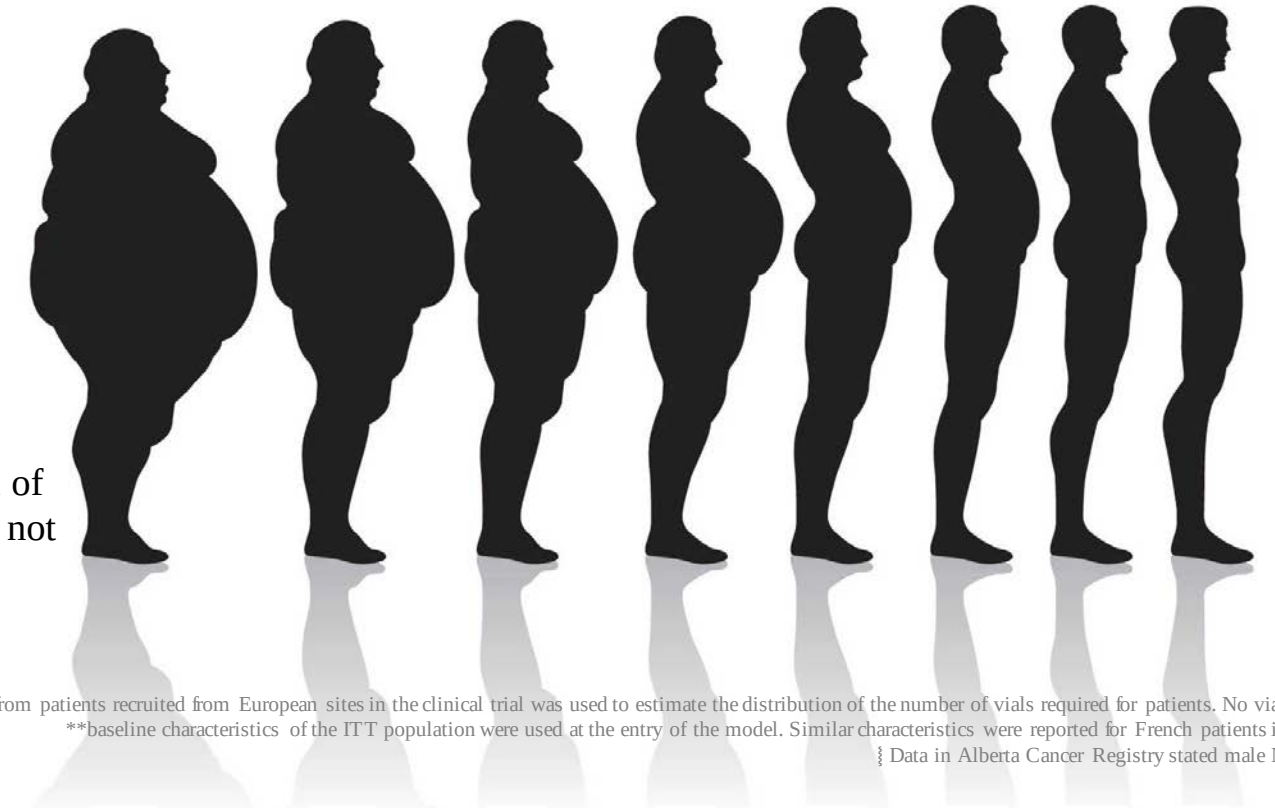
Germany
average body weight of **77.0 kg** and an average height of 1.72 m according to the 2017 microcensus

USA (ICER)
Mean weight: **74.13 kg** based on clinical trial in second-line NSCLC cohort

Canada
Range from **64.0 kg – 77 kg** for female to male NSCLC patients, respectively ⁞

UK (SMC)
Estimated assuming a patient weight of **78.66kg** based on the Scottish Health Survey

France
70.0 kg the number of French patients included in the trial was insufficient (11 out of 305) to be considered as country-representative



UK (NICE)
84.8 kg Data on the typical weight distribution of patients with NSCLC was not available for the UK*

Spain
70.0 kg teniendo en cuenta el número de viales utilizados para cada día de tratamiento con aprovechamiento de estos y utilizando la presentación más económica

*the weight distribution from patients recruited from European sites in the clinical trial was used to estimate the distribution of the number of vials required for patients. No vial sharing is assumed within the model.
**baseline characteristics of the ITT population were used at the entry of the model. Similar characteristics were reported for French patients in two observational studies in NSCLC
⁞ Data in Alberta Cancer Registry stated male NSCLC patients 77.0kg, female 64.0kg

Various Sources: See notes

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Weight impacts our calculation of price in many ways

If a condition is much more prevalent in one sex, is linked to weight, or affects children, general population data may need to be further stratified

e.g. trastuzumab in Breast vs Gastric

A relatively small costing error per dose could amount to considerable inaccuracy if administration is frequent or continuous. This is magnified over longer durations of time

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Disincentives for Drug Waste

Wastage is already acted upon globally through a variety of mechanisms

- Dose rounding
- Dose banding
- Dose ceilings
- Vial sharing
- Multi-dose injections

Wastage negatively impacts payer reviews in HTAs

- According to a review of submissions to payers, drug wastage was considered in:
  - Wastage was considered in two of three HTAs (67%)
  - Primary or base-case analysis in one third of all publications reviewed (12 of 38; 32%).
  - 10 of 35 peer-reviewed reports (29%)
- The consideration of wastage changes the calculated ICER significantly
  - Range from 2.6%-48.2% worse

Source: The Impact of Cancer Drug Wastage on Economic Evaluations, Judy Truong, BSc, Cancer 2017; DOI: 10.1002/cncr.30807; Adjusting for Drug Wastage in Economic Evaluations of New Therapies for Hematologic Malignancies: A Systematic Review, Karen Lien, MD(C), 2016 n Journal of Oncology Practice, DOI: 10.1200/JOP.2015.005876

Two-Thirds

...of models include wastage assumptions

Half

...incorporate wastage into their base-case or sensitivity analysis

15-24%

...worse cost-effectiveness results when wastage included

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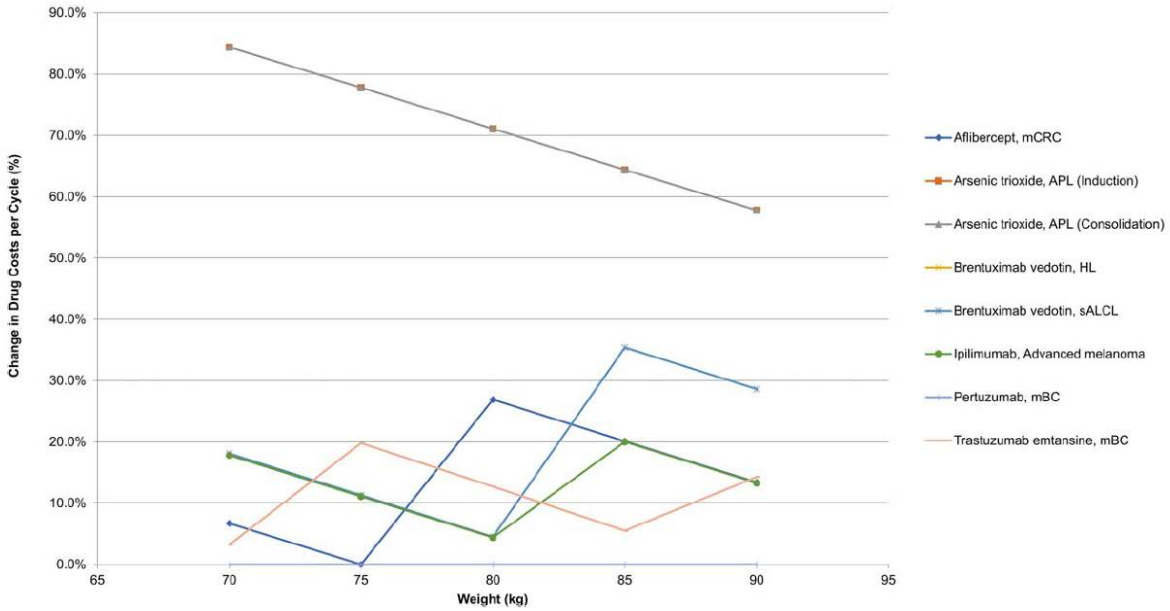
Effect of changing the body weight on drug costs per cycle when maximum-wastage and no-wastage scenarios are compared



... and weight assumptions matter

- The percentage increase in drug costs over body weight ranges (from 70 kg to 90 kg) accounted for up to...

84.4%

...variation in drug cost

Source: The Impact of Cancer Drug Wastage on Economic Evaluations, Judy Truong, BSc, Cancer 2017; DOI: 10.1002/cncr.30807; Adjusting for Drug Wastage in Economic Evaluations of New Therapies for Hematologic Malignancies: A Systematic Review, Karen Lien, MD(C), 2016 n Journal of Oncology Practice, DOI: 10.1200/JOP.2015.005876

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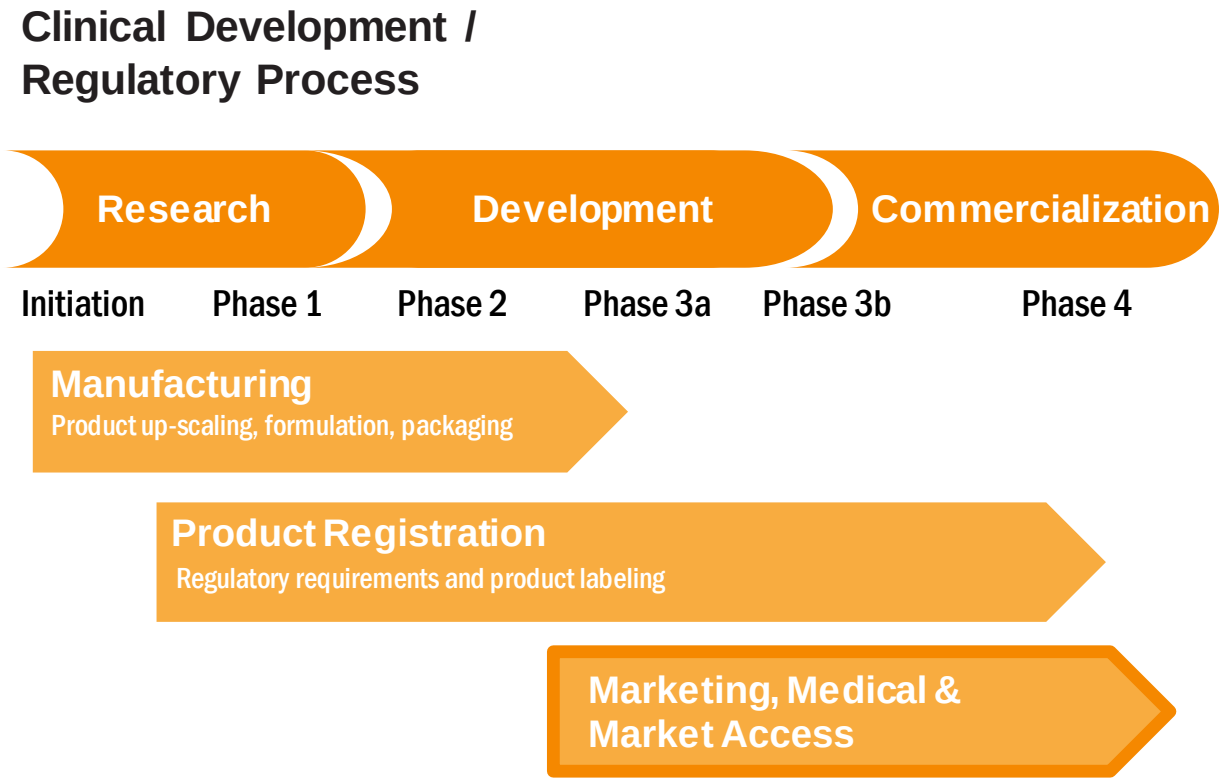
Potential Solutions

Understanding real world patient populations earlier in drug development

- Market Access involvement early in R&D appears to be underimplemented
- This impact is likely larger at smaller companies where planning comes late and internal market access expertise does not yet exist
  - Half (24 of 49) of drug approvals in 2018 came from small companies with <4 registered products
  - 75% of those (18 of 24) were from companies with no prior products
- There is a need to improve early understanding of real-world settings to ensure effective dosing formulations



Source: Pharmaceutical Market Access: current state of affairs and key challenges–results of the Market Access Launch Excellence Inventory (MALEI), J Mark Access Health Policy. 2015; 3(1): 29679., doi: 10.3402/jmahp.v3.29679

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Lifecycle strategies for flat dosed formulations

- Within oncology, there has been a shift from traditional weight-based dosing with cytotoxic agents to the use of a flat dose with monoclonal antibodies
  - **Herceptin SC** is given as an injection under the skin at a fixed dose of 600 mg. In contrast to IV Herceptin, a loading dose and weight-adjusted dosing (2012)
  - Rituxan Hycela / MabThera SC contains the exact same antibody as the IV-administered MabThera
  - Anti–PD-1 antibodies nivolumab and pembrolizumab were initially approved with weight-based dosing, but the dosing was changed to flat dosing
  - Other examples include Obinutuzumab, Ofatumumab, and Pertuzumab
- These are developed despite the fact that new SKUs retrigger negotiations ex-US with most payers

Potential Benefits flat dosed formulations

- Patient convenience
- Provider convenience & efficiency
- Less room for error
- Reduced drug spillage
- Efficiency in supply chain
- Scale for manufacturing
- Reduced financial & product wastage

Reducing spillage examples (a) the complete content of a vial can be used for preparation and (b) prepared infusions can be used for other patients when treatment is canceled at the last moment. However, costs can be further reduced by fixed dosing since patients with a body weight above average are relatively overdosed at a body weight-based schedule /

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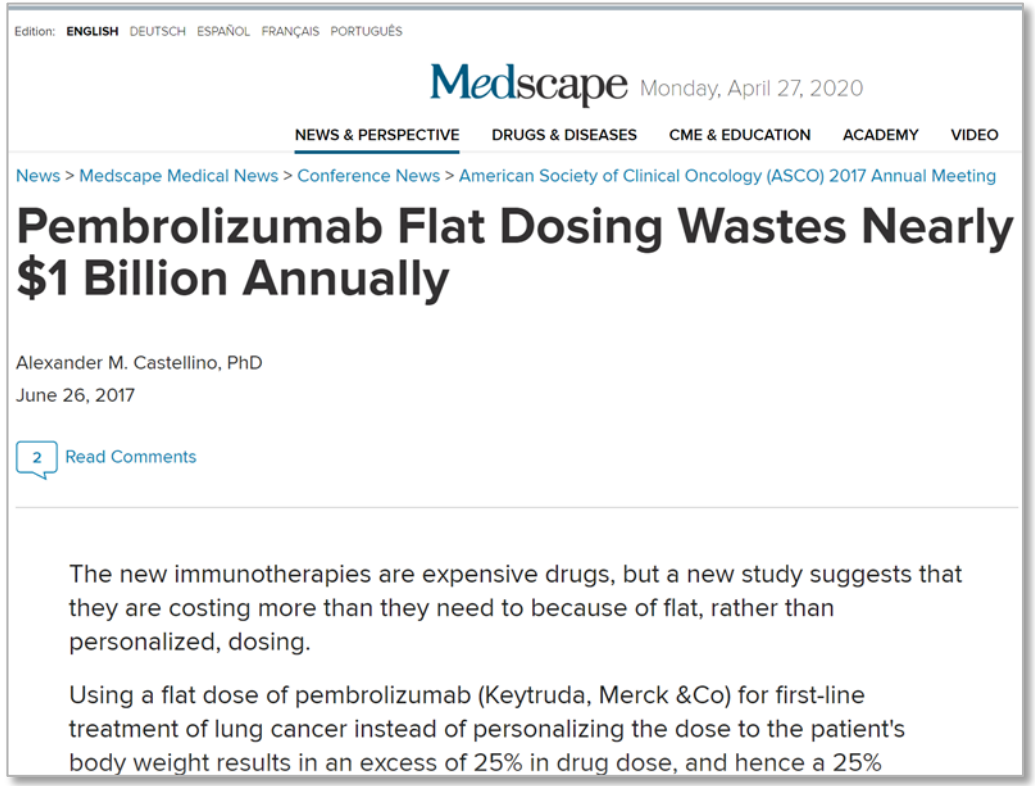
But do you really want to reduce waste or just for some patients?



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News > Medscape Medical News > Conference News > American Society of Clinical Oncology (ASCO) 2017 Annual Meeting

Pembrolizumab Flat Dosing Wastes Nearly $1 Billion Annually

Alexander M. Castellino, PhD

June 26, 2017

2 Read Comments

The new immunotherapies are expensive drugs, but a new study suggests that they are costing more than they need to because of flat, rather than personalized, dosing.

Using a flat dose of pembrolizumab (Keytruda, Merck &Co) for first-line treatment of lung cancer instead of personalizing the dose to the patient's body weight results in an excess of 25% in drug dose, and hence a 25%

Source: Pembrolizumab Flat Dosing Wastes Nearly $1 Billion Annually, A Castellino, Medscape article, 2017

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Companies have collaborated within the health system to improve care efficiency

- Pfizer & University of Leicester Hospitals collaboration
- EPIFFANY project (effective performance insight for the future)
- Reduce errors in prescribing

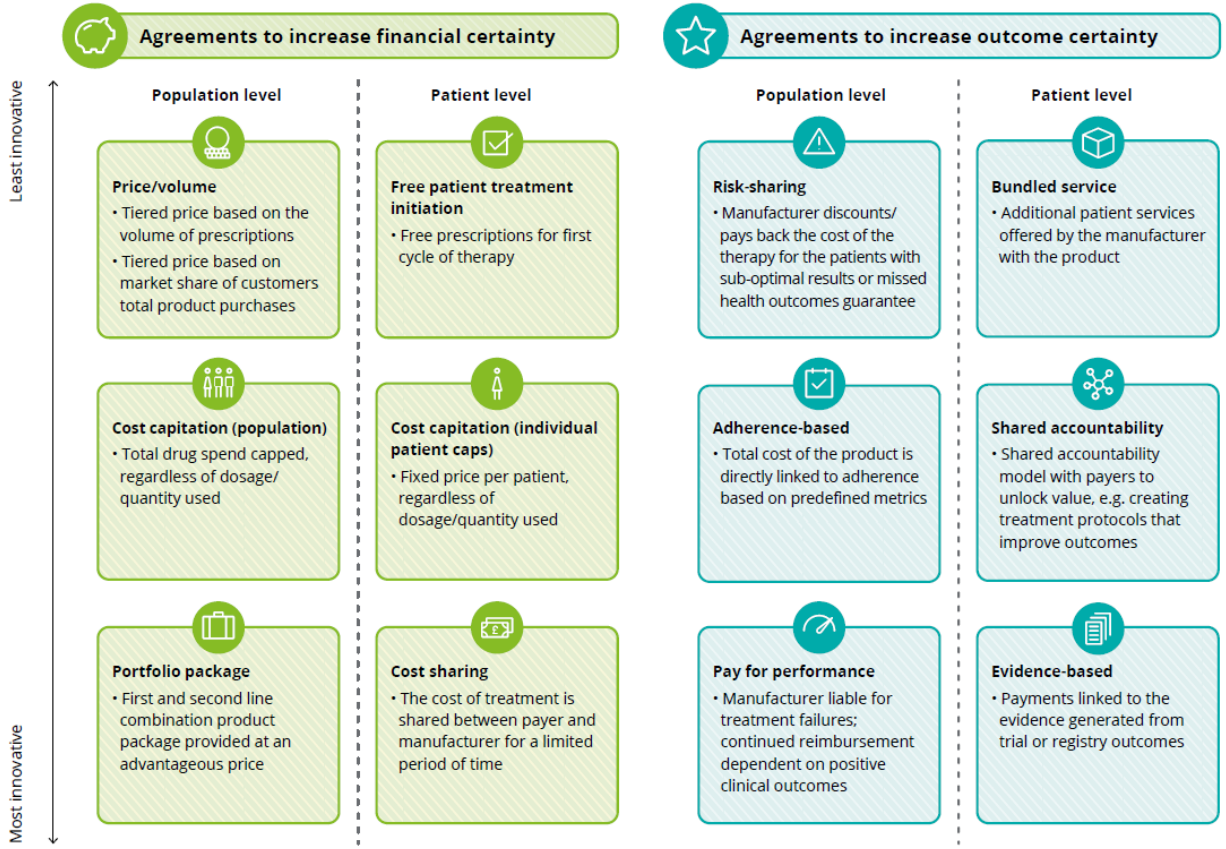
The **approach leads to a large improvement in performance on complex workplace tasks**, such as prescribing complex medicines

> *"EPIFFANY is a fantastic example of supporting and enhancing junior doctors' education and training. It's been demonstrated to improve prescribing behaviour, wellbeing and keep patients safer while in hospital through a safety culture. We're thrilled that something supported by HEE across the East Midlands is now being rolled out to more areas and would like to see it taken up further and across the whole of England."*
>
> **Jill Guild, Head of Quality and Education for Health Education England, East Midlands**

Source: UK NHS Academic Health Science Networks (AHSNs) website

Risk sharing models

Types of innovative value-based contracts



Source: Patient Access to Innovative Medicines in Europe: A collaborative and value based approach, Deloitte Center for Health Solutions, January 2019

- Several models have been implemented to reduce waste and cap risk of cost exposure
- Examples of dose capping risk-sharing models have been implemented
  - NICE (UK) entered into individual patient based scheme over ranibizumab (Lucentis) for macular degeneration
  - NICE (UK) recommended ustekinumab (Stelara) for severe plaque psoriasis on the condition that Janssen-Cilag ensures that the costs of treating patients weighing more than 100 kg will be no more than those of patients weighing less than 100 kg

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