EU HTA Assessment Outcome of Same Drug – an Industry Perspective

26. May 2014

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A little bit about me…

Selected Professional Experience:

- 2013- Manager, Public Health Evidence & Insights, Corporate Public Affairs, Novo Nordisk A/S
  - 2012 Principal Health Economist, Novo Nordisk Inc., Princeton, US
  - 2011 Principal Health Economist, Health Economics & HTA, Global Development, Novo Nordisk A/S
  - 2008-10 Health Economist/Health Economics Specialist, Medical & Science Haemophilia, Global Development Novo Nordisk A/S
  - 2007 Trainee, Organisation for Economic Co-operation & Development (OECD), Health Division, Paris, France
  - 2004 Medical Orderly, Danish Armed Forces Health Services
  - Pre-graduate (2000-04) National Board of Health, Denmark
- 2009- External Lecturer, Department of Public Health, University of Copenhagen

Education:

- MSc Public Health (2004), PhD Health Sciences (2008) (University of Copenhagen), MMPI (2012) (CBS-SIMI Executive)

Agenda

1. New hurdles in Drug Development
2. Changing to Meet Market Demands
3. Between Agency Variability: The Case of Type 2 Diabetes
4. Playing the Hand You're Dealt
5. Implications for Drug Development
6. Take Home Messages
7. Q&A

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New Hurdles
In Drug Development

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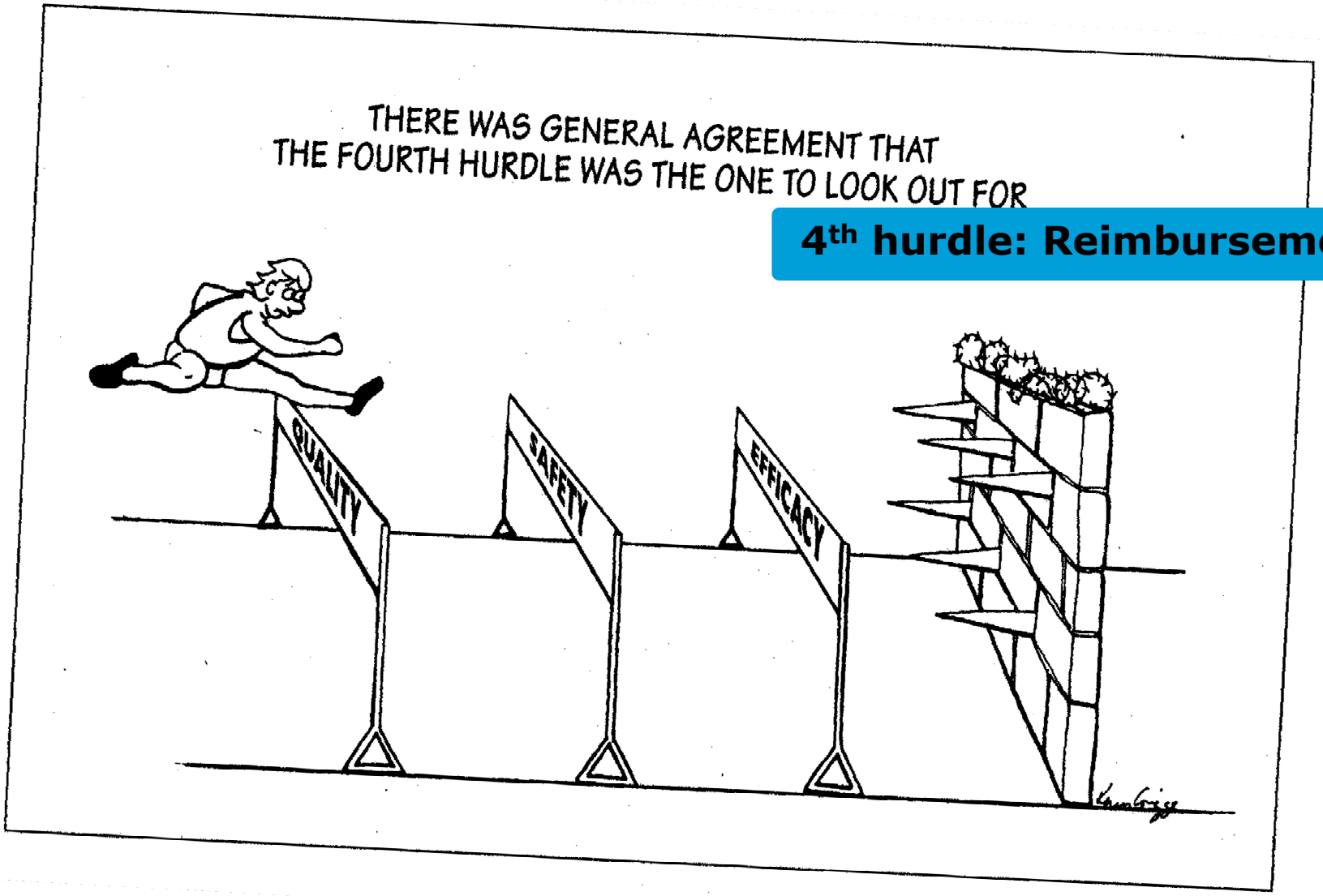
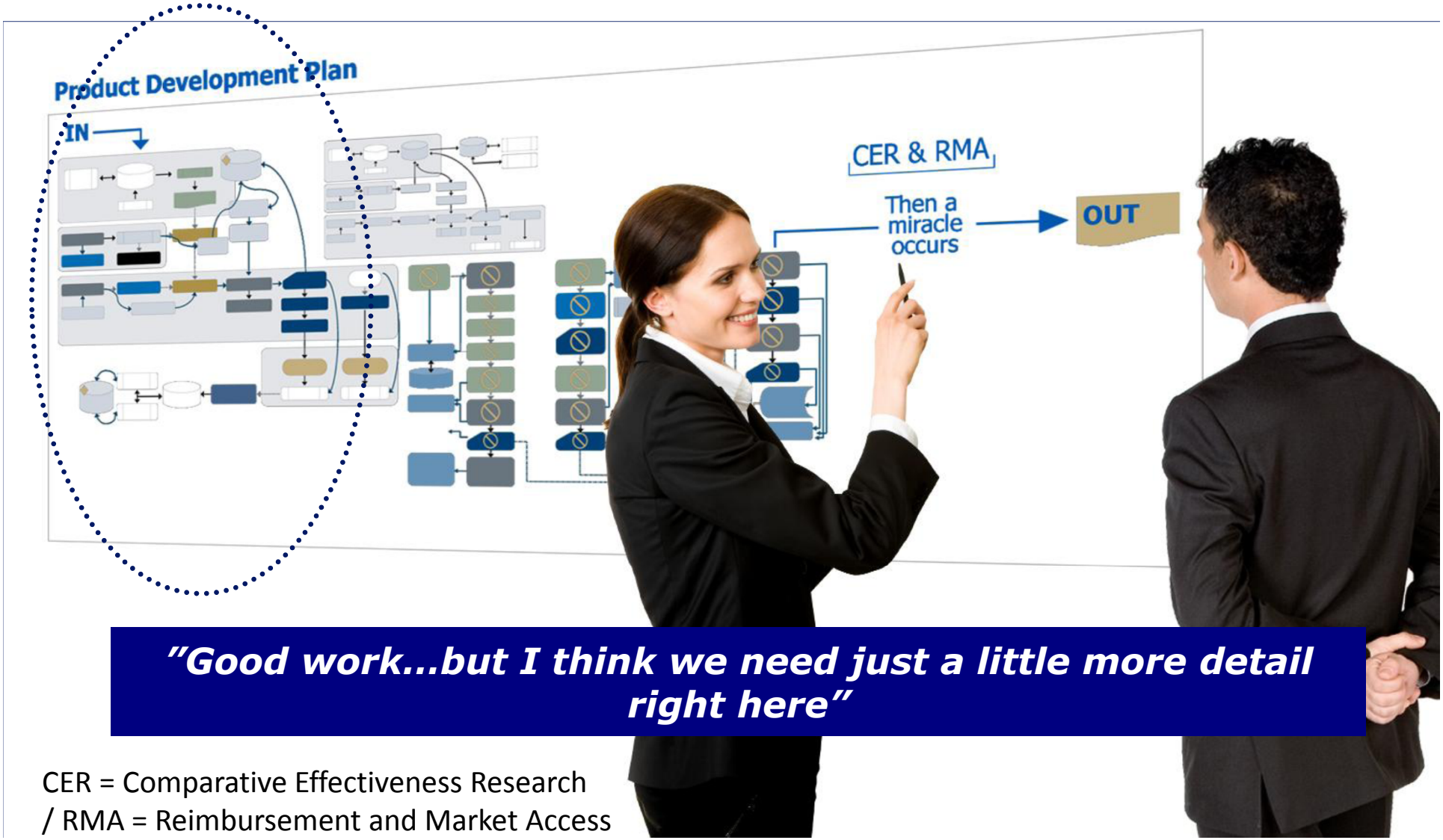
The 4th hurdle in Drug Development



4th hurdle: Reimbursement

Changing to Meet Market Demands:
The HTA perspective should be included early!



"Good work…but I think we need just a little more detail right here"

CER = Comparative Effectiveness Research
/ RMA = Reimbursement and Market Access

Between Agency Variability
The Case of Type 2 Diabetes

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Study Objective and Scope

- **Objective :** Identify "between HTA agency" variability (intra-drug, intra/inter-class in disease area) in drug assessment and key drivers of a successful HTA outcome

- **Scope:** HTA review of products (2007 – 2011)
  - Type 2 Diabetes (37 reviews)
  - England, Scotland, Sweden, France, Spain (Catalonia), Netherlands
  - Canada (Ontario, Quebec) included as reference

- **Disclaimer:** Novo Nordisk makes no representation about the content and suitability of this information for any purpose.

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Different Approved Indications Impact Access and Success

Compound	Byetta	Victoza	Januvia	Galvus	Onglyza
INN	Exenatide	Liraglutide	Sitagliptin	Vildagliptin	Saxagliptin
Class	GLP-1 agonist	GLP-1 agonist	DPP-4 inhibitor	DPP-4 inhibitor	DPP-4 inhibitor
Manufacturer	Elli Lily	Novo Nordisk	MSD	Novartis	BMS / AZ
Monotherapy	-	-	x	-	-
+ MET	x	x	x	x	x
+ SU	x	x	x	x	x
+ TZD	x	-	x	x	x
+ MET + SU	x	x	x	-	-
+ MET + TZD	x	x	x	-	-
Add-on insulin	-	-	x	-	-

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MET = metformin / SU = sulphonylureas / TZD = thiazolidinediones

Overview of HTA Assessments: Significant "between HTA agency" variability

Compound/HTA body	Exenatide	Liraglutide	Sitagliptin	Vildagliptin	Saxagliptin
UK - NICE	-	RST	-	-	-
Scotland – SMC	RST 2nd RST	RST	RST 2nd RST 3rd RST	RST 2nd REC	RST
France - HAS	RST	REC	RST 2nd RCT	REC	REC
Netherlands – CVZ	NR 2nd RST	REC	RST 2nd RST 3rd RST 4th REST	RST	REC
Sweden – TLV	REC 2nd RST	RST	REC 2nd RST	REC 2nd RST	RST
Spain* - CANM	RST	-	1st RST	NR	-
Canada - CADTH	-	-	NR 2nd RST	-	NR
Ontario - MoH	-	-	RST (General Benefit Scheme)	-	RST
Quebec - INESS	-	NR	RST 2nd RST	-	-

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NR – not recommended, REC – recommended, RST – restricted
* CANM: institution within the Catalan Institute of health

Mapping Access Performance

Compound	Exenatide	Liraglutide	Sitagliptin	Vildagliptin	Saxagliptin
Time to market average months across all countries (min. / max.)	21 (7/34)	6.75 (0/11)	7.8 (3/11)	2.25 (0/10)	5.5 (1/10)
Date of marketing Authorization	Nov 20, 2006	Jun 30, 2009	Mar 21, 2007	Nov 19, 2008	Oct 1, 2009
Indications approved	++	++	+++	+	+
HTA - Restricted	5	3	7	2	3
HTA - Recommended	0	2	1	2	2
HTA – Not recommended	0	1	0	1	1
Total HTAs (RST%/REC%)	8 (75/0)	6 (50/33)	17 (82/12)	7 (43/43)	6 (50/33)
Total number of trials (Label)	6	5	5	6	6

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Summary Conclusion

- HTA restrictions and non-recommendations is widespread
- Significant "between HTA Agency" variability can be observed
  - Between country variability
  - Within Class variability
  - Within Disease area variability
- Access performance and sales uptake is linked to a combination of strong product features and to the strategic HTA approach rather than to the number of trials and size of the clinical program

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Playing the hand you're dealt
An example of a "poor" and of a "successful" HTA Strategy

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Poor HTA Outcome: Exenatide 1/2

- The strategy for Exenatide appeared to be:
  - Achieve approval for second add-on with only placebo-controlled studies
  - Gain recognition by being as good as insulin, which is the reference rescue treatment after oral combination fails.
- The strategy raised substantial HTA hurdles due to:
  - No active comparator in second add-on
  - Comparator for third add-on inappropriate
- The weight loss benefit was underestimated
- Health economics models were not robust

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Poor HTA Outcome: Exenatide 2/2

- It seems like the new mode of action, high level of unmet need and comparable efficacy to insulin were thought to be adequate
- HTA bodies' reactions were mixed:
  - Pragmatic ones gave it a chance in third add-on and requested coverage with evidence development (CED)
  - Less pragmatic ones niched it in third add-on as an alternative to insulin or for patients with BMI > 35 also with coverage with evidence development (CED)
- The company had to resubmit in many countries before reaching a reasonable access level
- The delay in access between countries jeopardized the company's global strategy

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Successful HTA Outcome: Sitagliptin

- Indication in second add-on only allowed fast access with a large market potential
- Better study designs (separate second add-on and third add-on trials rather than use stratification)
- HTA extension after 1-2 year
  - The step by step progression with H2H trials paid off
  - Limited risk was taken on the clinical development strategy which was smartly coupled with the regulatory and HTA strategy
  - Strategy was country-specific in order to accommodate "between HTA agency" variability
- Robust Health Economic Model

Summary Learnings

- For Exanatide 2 of the 3 insulin-controlled studies was useless
  - Could have been replaced with a third add-on TZD-controlled trial
  - Include active-controlled arm in second add-on trials
    - Show non inferiority and focus on weight loss (pre-planned subgroup analyses in high BMI/show benefit of weight loss on diabetes equilibrium)
- Strategic regulatory/HTA integration & interaction is becoming critical
  - Separate indications to gain quicker access
- Provide stronger health economics models

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TZD = thiazolidinediones

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Implications for Drug Development

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Better Practice HTA Strategies

- Realistic definition of
  - Target indication
  - Target (sub-) population
  - Differentiation strategy
  - Price anchor
  - Launch sequence
  - Life cycle strategy
- Will set right expectations related to HTA outcome
- Increase likelihood of successful HTA outcome

Integrating HTA Strategy in Development

•Input to Target Product profile (TPP) requirement •Input to development plan for costing •HTA recommendation and implication for pricing	•Landscape study to inform HTA requirements: outcome, duration, comparator, country sites for RCTs etc.	•Power for secondary endpoints (20%) •Introduce patient focused endpoints (PRO's) •Follow-up on drop-outs •Long-term open label follow-up with valuable endpoints •Active comparator arm	•Study design •Identify right comparators •Piggy back •Duration •Expend inclusion criteria and sample size •Adaptive design combined endpoints	•Ad-hoc study with combined end point, adaptive design etc.
			•Indirect comparisons •Test and simulation on subgroups	

Early modelling

Cost			+ 5-20%	+ 5-20%	+ 10 millions €
Benefit			•Appropriate phase II with predefined endpoints and power	•Increased differentiation •Prevent useless and/or dangerous studies •Favourable HTA recommendation	

Take home messages
From Industry Site

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Take Home Messages

- Without reimbursement product fails
- Expectation and Requirement from HTA bodies are changing fast
  - Need to anticipate
- Integrating the HTA perspective from early clinical development is becoming critical and will de-risk investment and optimize development
- It is not about doing more…
  - But about doing the right things, in the right order at the right time

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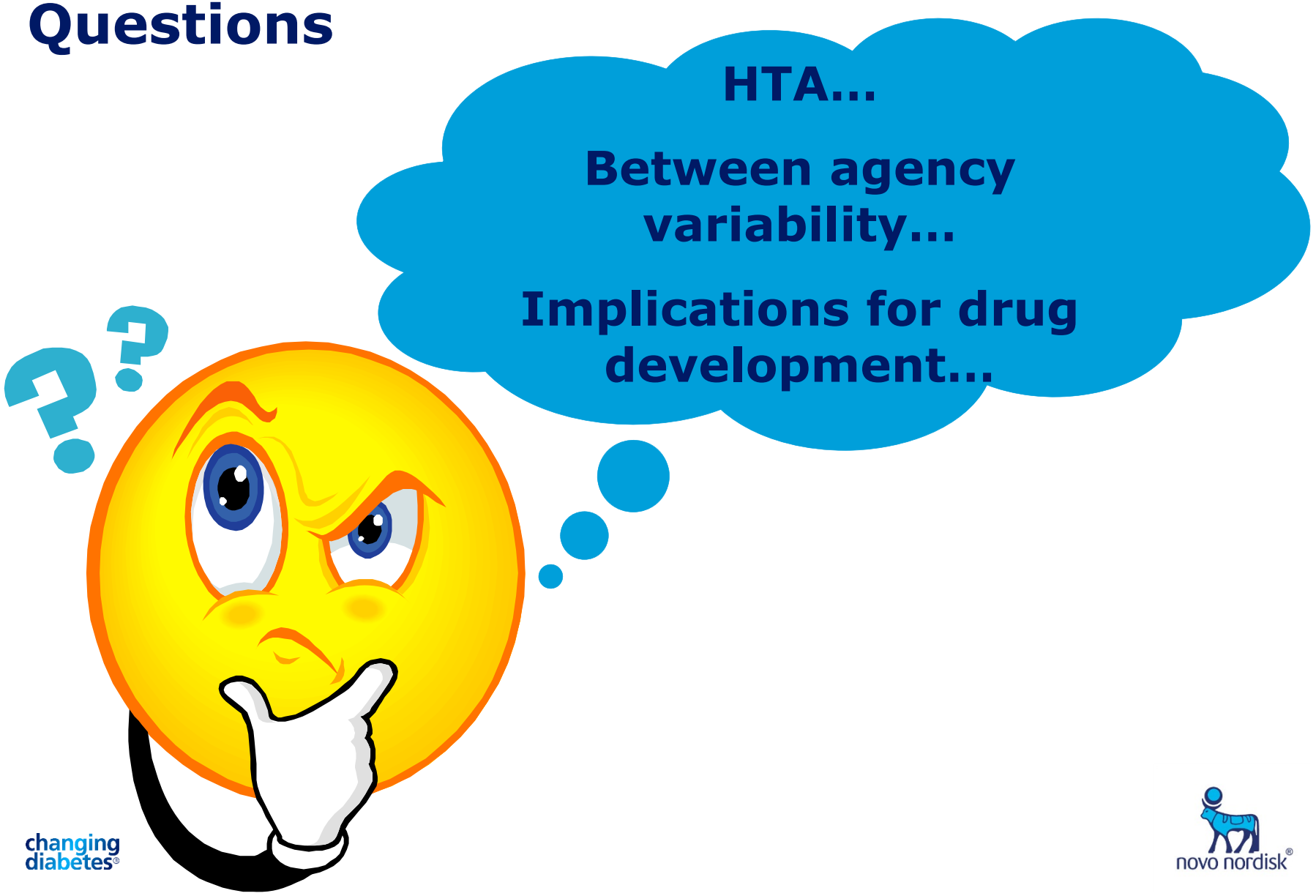
Questions



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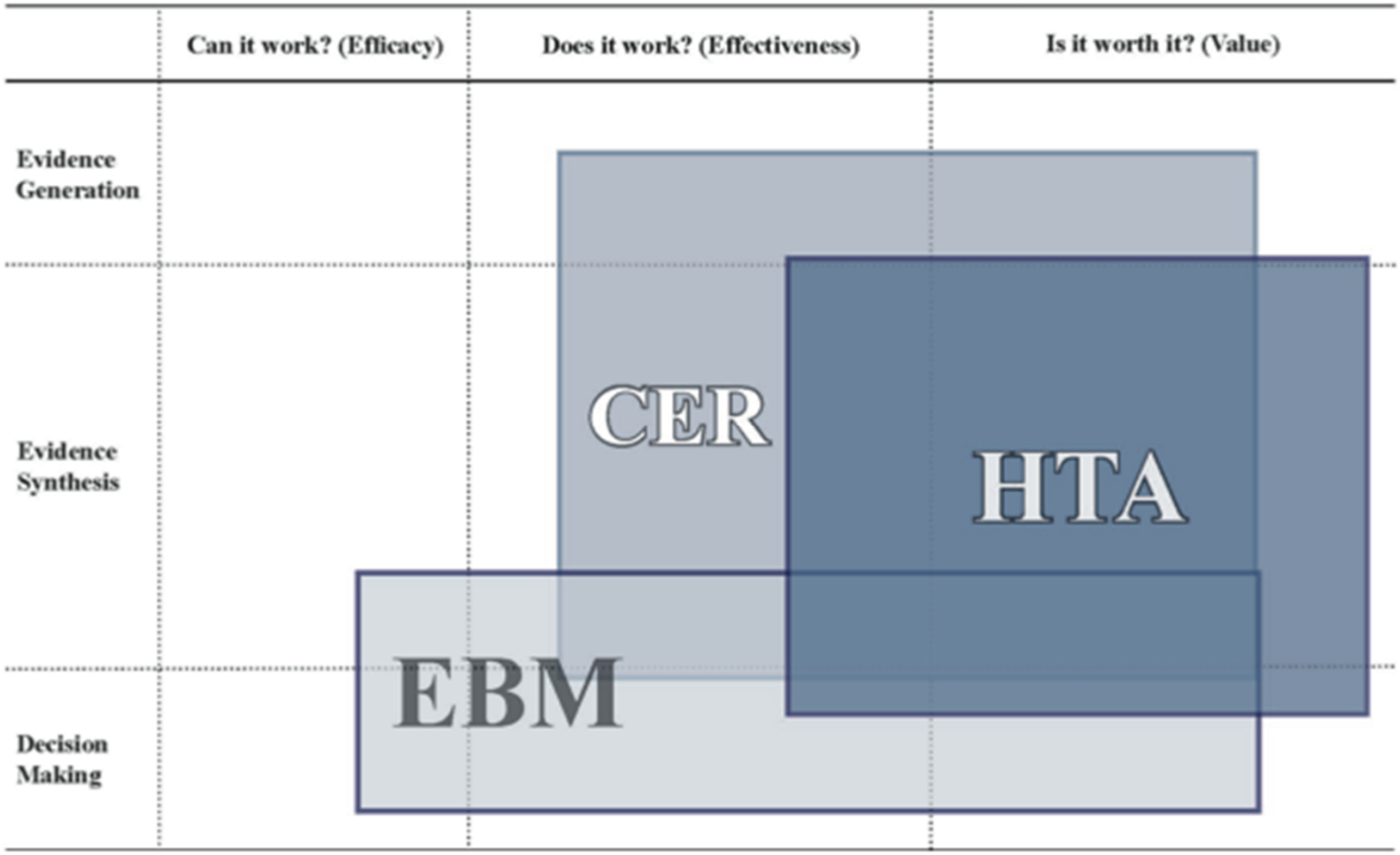
Relationships of Evidence Processes: EBM, CER, and HTA



International Working Group for HTA Advancement. Luce BR, Drummond MF, Jonsson B, Neumann PJ, Schwartz JS, Siebert U, Sullivan SD. EBM, HTA, and CER: Clearing the Confusion. *Milbank Memorial Fund Quarterly. In press.*