MANAGEMENT OF UNCERTAINTY IN HTA RECOMMENDATIONS ON DRUGS FOR RARE DISEASES

A study of CADTH recommendations for drugs for rare diseases

Alexandra Kourkounakis[1], Bonnie Macfarlane[1], Purva Barot[2], Shoghag Khoudigian-Sinani[2], Brad Millson[3], Maureen Hazel[1]

1 Janssen Inc, Toronto, ON, Canada; 2 IQVIA, Mississauga, ON, Canada; 3 IQVIA, Kanata, ON, Canada

BACKGROUND

- A rare disease (RD) is a life-threatening, seriously debilitating, or serious chronic condition that affects a very small number of patients (typically less than 5 in 10,000 persons)[1,2].
- Drugs for rare diseases (DRDs) are often lifesaving, but costly medications that present unique challenges for traditional HTA approaches.
- For example, clinical trials for DRDs face challenges such as adequate study design, power, and validity, due to small populations, limited disease information and difficulty defining endpoints[3,4].
- Many international HTA agencies have developed DRD-specific approaches, including greater acceptance of evidence uncertainty and higher willingness-to-pay (WTP) thresholds[5,6].
- While CADTH lacks a DRD-specific approach, its procedures include special considerations for uncertain evidence in cases of high unmet need and practical challenges in conducting robust clinical trials and pharmacoeconomic (PE) evaluations[6]. There is limited research assessing how these considerations are applied in reimbursement recommendations for DRDs[7].

OBJECTIVE

This study sought to understand how CADTH applies considerations for significant unmet need outlined in its procedures in recommendations for DRDs, with the objective of informing future policy.

METHODS

- CADTH recommendations for DRDs issued between January 2017 – March 2021 were identified based on the following selection criteria. Recommendations must have been:
  - for a non-oncology pharmaceutical
  - for a drug and indication designated as orphan by USFDA or EMA*
  - the first recommendation for the molecule and indication
  - the latest recommendation for the drug and indication, if resubmitted
  - for a drug review initiated by drug sponsor
- Predefined variables (unmet need, clinical uncertainty, economic evidence, and clinical expert and patient input) were assessed in final recommendations

***Acronyms:** USFDA, United States Food and Drug Administration; EMA, European Medicines Agency

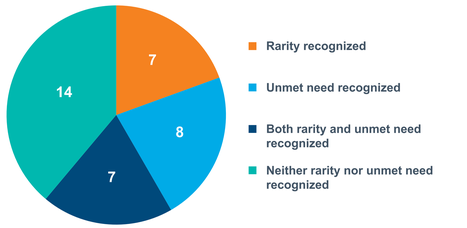
RESULTS AND DISCUSSION

- Of the 244 CADTH recommendations issued during the study period, 36 met the inclusion criteria and were assessed based on predefined variables.
- 89% (n=32) were 'reimburse with conditions/criteria' while 11% (n=4) were 'do not reimburse' recommendations.

RECOGNITION OF RARITY AND UNMET NEED

- 7 (19%) of recommendations only recognized 'rarity' of the indication in the recommendation and reasons; 1 among these was recognized as 'ultra-rare'.
- 8 (22%) of recommendations only recognized 'unmet need' of the indication in the recommendation and reasons. The magnitude of unmet need was not characterized in the recommendations and reasons.
- Only 7 (19%) of recommendations explicitly recognized both 'rarity' and 'unmet need' of the indication in the recommendations and reasons; 1 among these was recognized as 'very rare'.
- 14 (39%) recommendations did not recognize the indication's 'rarity' or 'unmet need' of the indication in the recommendations and reasons.

Figure 1. Recognition of rarity and unmet need(n=36)



CLINICAL UNCERTAINTY

- The most common clinical limitations recognized in reasons for recommendations, in order of frequency, were small sample size (n=30), lack of comparator or inappropriate comparator (n=29), short study duration or follow-up (n=21), insufficient evidence on meaningful endpoints (n=21), and non-validated clinical endpoints (n=22).
- No single type of uncertainty appeared to drive a positive vs. a negative recommendation.

APPROACH TO ADDRESSING CLINICAL UNCERTAINTY

- Recommendations were assessed to determine if CADTH addressed the clinical uncertainties by:
  a. Recognizing practical challenges in generating robust evidence
  b. Indicating need for additional evidence generation
  c. Recommending clinical criteria

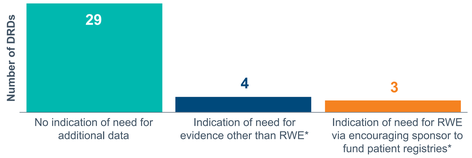
a. Recognizing challenges of DRD

- The majority (n=30, 83%) of recommendations did not recognize practical challenges of RD indications. While 6 (17%) recognized challenges of RD indications, no explicit link with the ultimate recommendation was made.

b. Indicating need for additional evidence generation

- Additional data generation as a condition for reimbursement was not found in any recommendations.
- However, 3 recommendations encouraged generation of real world evidence and 4 recommendations indicated need for another form of additional data.
- The Majority (n=29, 81%) of recommendations did not indicate need for any form of additional data.

Figure 2. Indication of need for evidence

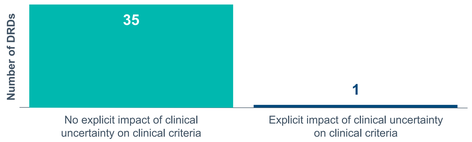


** Although additional evidence need was indicated in 7 recommendations, feasibility of generating such evidence for rare diseases was not elaborated.*

c. Recommending clinical criteria

- Only 1 recommendation explicitly noted impact of clinical uncertainty on clinical criteria. Due to lack of evidence in a certain group of patients, CDEC recommended against use in that group.

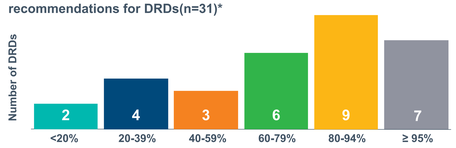
Figure 3. Impact on clinical criteria



ECONOMIC EVIDENCE AND PRICE CONDITIONS

- Economic evidence was considered among the reasons for all 'reimburse with conditions/criteria' recommendations (n=32), all of which included a price reduction condition. However, economic evidence was not cited as a reason for 'do not reimburse' recommendations.
- 30 out of 32 'reimburse with conditions/criteria' recommendations indicated economic uncertainty as a result of clinical uncertainty.
- Price reductions were recommended in all 32 cases, with 31 DRD recommendations including a percentage price reduction, with a mean of 70%.
- More than 74% (23 out of 31) of recommendations required a price reduction of 50% or greater.

Figure 4. Percentage price reduction in 'reimburse with conditions/criteria' recommendations for DRDs(n=31)*



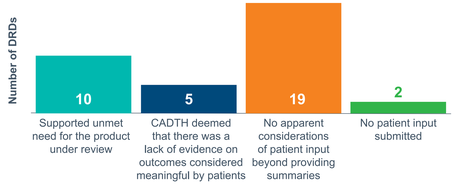
** Percentage reduction was not indicated for one DRD with a 'reimburse with conditions/criteria' recommendation*

- Over 75% of all recommendations, and 100% of recommendations issued in the past year, referenced an ICER of $50,000 per QALY, which is the WTP threshold typically used for non-RD drugs[8].

PATIENT GROUP AND CLINICAL EXPERT INPUT

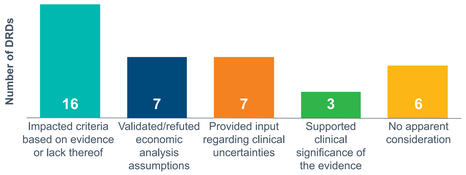
- Patient input was included for all DRD recommendations except for two. In the majority (n=19) CADTH did not clearly state whether or how the input directly impacted the recommendation.
- In one instance, it was explicitly stated that patient input confirmed the meaningfulness of the outcome measure.

Figure 5. Impact of patient group input on DRD recommendations



- Clinical experts were consulted for all DRD recommendations, with 7 including more than one expert opinion. In the majority (n=30), CADTH noted clearly how clinical experts impacted the recommendation.

Figure 6. Stated Impact of clinical expert input on DRD recommendations



CONCLUSION

- There was inconsistent recognition of rarity and unmet need, and challenges in evidence generation across reviews. This created uncertainty in terms of whether a DRD was eligible for special consideration.
- A high proportion of DRDs received a positive recommendation with conditions (89%) despite uncertain evidence, suggesting special considerations may have been applied. However, how these considerations were applied was not explicitly stated and remains unclear.
- While CADTH reviews effectively identified and described clinical deficiencies within the DRD submissions, there was no clear evidence of clinically-based considerations or allowances based on unmet need or feasibility of evidence generation.
- Price reduction recommendations were the primary method identified across reviews to address uncertainty, with no accommodations in willingness to pay threshold, often resulting in prohibitively large discount recommendations.
- While the impact of physician input on recommendations was clearly illustrated, the link between patient input and final recommendations was less defined and difficult to ascertain.
- This analysis highlights the opportunity for a dedicated and transparent rare disease approach to incorporate clinical or value-based tools to address uncertainty, rather than relying on a one-size fits all discounting strategy that can be counterproductive in improving value for money and sustaining innovation in these underserved populations.
- A robust DRD framework has the potential to help reviewers systematically define and transparently apply special considerations for rare diseases in a manner relevant to all stakeholders.

REFERENCES

1. Richter et al. Rare disease terminology and definitions—a systematic global review: report of the ISPOR rare disease special interest group. Value Health 2015;18.
2. Government of Canada. Archived - Minister Ambrose Announces Patient Involvement Pilot for Orphan Drugs - Canada News Centre.
3. Canadian Cancer Statistics: A 2018 special report.
4. Shah et al. Challenges in Evaluating Safety and Efficacy in Drug Development for Rare Diseases: A Review for Pharmacists. Journal of pharmacy practice 2021;34:472-9.
5. CADTH Health Technology review. Drugs for Rare Diseases: A Review of National and International Health Technology Assessment Agencies and Public Payers' Decision-Making Processes. Environmental scan. CADTH Journal of Health Technologies May 2021.
6. Procedures for CADTH Reimbursement Reviews. June 2021.
7. Janoudi et al. Health technology assessment of drugs for rare diseases: insights, trends, and reasons for negative recommendations from the CADTH common drug review. Orphanet journal of rare diseases 2016;11:164.
8. Griffiths et al. CADTH's $50,000 cost-effectiveness threshold: fact or fiction? Value in Health 2016;19:A488-A9.

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson