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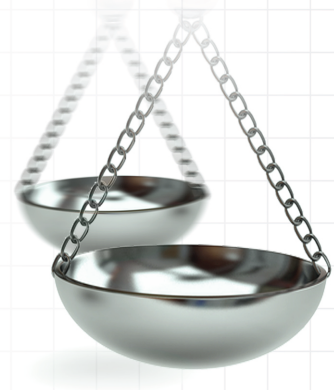

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# Access in all areas? A round up of developments in market access and health technology assessment: part 8

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**In this update, we discuss the pricing paradox of combination therapies in health technology assessment; examine the Inflation Reduction Act's impact on pharmaceutical innovation and analyze the revised Dutch economic evaluation guidelines.**

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Combination therapies involve the use of multiple therapeutic agents, often structured around a well-established backbone treatment paired with an add-on drug that enhances efficacy or addresses resistance [1]. Timely access to these innovative combinations is critical for patients, notably in oncology. The combination therapy pricing paradox represents one of the most complex challenges in health technology assessment (HTA) today. As highlighted by NICE, the 'not cost-effective at zero price' phenomenon occurs when an add-on treatment to an existing backbone therapy cannot demonstrate cost–effectiveness even if offered for free. This seemingly illogical situation arises when a backbone therapy is already priced close to a cost–effectiveness threshold, and the combination's extended treatment duration increases the backbone therapy costs without proportional health gains. A key challenge in value assessment of combination treatments is that they undergo HTA as a single technology despite component therapies being priced independently. This complexity intensifies when these components are patented and manufactured by different companies. Each manufacturer controls only their product's price, not the overall combination cost. Determining how to divide the combined value between component drugs lacks a standardized mechanism that satisfies all stakeholders. Recent publications propose technical solutions to this value attribution challenge [2,3]. Both solutions share the core principle that value attribution should be based on each component's relative contribution to health gain, although they differ in specific approaches. Both frameworks require a price adjustment mechanism for the backbone (and potentially add-on) therapy, highlighting the need for indication-based pricing to implement these solutions. They also acknowledge competition law challenges when different manufacturers must negotiate component prices and suggest that payers or HTA bodies should mediate this process. A recent editorial by the authors of these technical solutions highlight that HTA bodies and pricing authorities have predominantly adopted one of three approaches to combination pricing [4]: doing nothing and assessing combinations as presented; implementing simplistic approaches like Germany's mandatory 20% price 'haircut' for combination products; or 'passing the parcel' to manufacturers and competition authorities to develop solutions. The authors highlight that even with recent developments like the UK Competition and Markets Authority's 'safe harbor' for negotiation frameworks, significant obstacles remain. Towse, Briggs and Steuten make a compelling case that HTA bodies must actively participate in value attribution. Leaving manufacturers to resolve these issues independently is unlikely to produce efficient outcomes due to a number of factors, including extreme bargaining power imbalances favoring backbone product manufacturers, and the need for indication-based pricing mechanisms that only payers can implement. For manufacturers, the technical solutions developed provide a foundation for approaching combination pricing negotiations and companies should advocate for HTA body involvement in

establishing attribution principles. As combination therapies continue to represent a growing proportion of the pharmaceutical pipeline, particularly in oncology, resolution of this value attribution challenge is increasingly urgent to ensure patient access to clinically beneficial treatments.

While combination therapy pricing challenges HTA frameworks in Europe, significant policy changes in the USA are creating different but equally consequential market access hurdles with implications for global drug development priorities. The Inflation Reduction Act (IRA), signed into law in August 2022, introduced Medicare drug price negotiation for the first time [5–7]. The Congressional Budget Office initially projected minimal impact on innovation, estimating that only about two fewer drugs would be introduced in to the US market during 2023–2032 as a result of the IRA. A key feature of the IRA is that it creates different timeframes for Medicare price negotiation based on molecule type: small molecules and large molecules (biologics) face price setting beginning in year 9 and year 13 after approval, respectively, creating divergent financial incentives by molecule type, particularly for diseases prevalent in the Medicare-aged population. In order to see if the IRA is already influencing drug development, Schulthess and colleagues conducted an analysis of biotech companies with valuations $\leq$\$2 billion [8]. They observed a 35% reduction in clinical trials being started after the IRA's introduction. Aggregate investments in small molecules decreased dramatically by 68% from their pre-IRA peak, leading to ten-times larger investment in large molecules than those in small molecules for the first three-quarters of 2024. When examining Medicare exposure impact, the study found that investments in lead assets with high Medicare exposure (prevalence in those over 65 years old) showed a statistically significant 51% decline after the IRA's introduction. For small molecules specifically, investments declined by 57% as Medicare exposure increased. Interestingly, no statistically significant change was observed in large molecule investments. The study contradicts earlier claims that the IRA will have minimal impact on biopharmaceutical innovation. Instead, it reveals significant shifts in early-stage investment patterns that will likely reshape drug development priorities, with decreased focus on small molecules targeting age-related conditions. It remains to be seen if the Trump administration will reverse this 'pill penalty', but currently as venture funding shifts toward large molecules, biotech companies may need to adjust their development priorities to remain competitive in securing investment.

Beyond these market-specific challenges in the US and combination therapy assessments, evolution in HTA methodologies continues to reshape the evidence requirements for manufacturers, as exemplified by recent updates to the Dutch economic evaluation guidelines. The National Health Care Institute in The Netherlands updated its guideline for economic evaluations in healthcare and published the fourth version in January 2024 [9]. The Dutch guideline has historically promoted the societal perspective, which has been further strengthened in this latest version. The many changes to the Dutch guideline include a lower discount rate for costs (reduced from 4 to 3%, while maintaining 1.5% for effects), additional guidance on expert opinion and expert elicitation, inclusion of health-related quality of life of informal caregivers, requirement for probabilistic analysis for main results, inclusion of indirect medical costs in life years gained in the base case analysis, additional guidance on empirical (trial-based) economic evaluations, and mandatory value of information analyses. The costing manual was also updated – notably, two cost categories outside the healthcare sector were added: education-related costs and justice-related costs, reinforcing the societal perspective. The committee identified areas requiring further research. Most prominently, they highlighted the need to re-examine the appropriateness of current willingness-to-pay thresholds (€20,000, €50,000, and €80,000 per quality-adjusted life year (QALY) gained based on severity of illness), which have remained unchanged since 2015. Additionally, they emphasized developing and validating a generic outcome measure of well-being, acknowledging that the EQ-5D-5L may not adequately capture benefits of noncurative interventions like care for older adults. For pharmaceutical manufacturers, the revised Dutch guideline introduces several important implications. First, the requirement to include indirect medical costs in life years gained in the base case analysis will likely increase incremental cost–effectiveness ratios for life-prolonging interventions, potentially making them appear less cost-effective. However, conversely, the lowered discount rate for costs (from 4 to 3%) may make interventions with upfront costs and long-term benefits appear somewhat more favorable in economic evaluations. The mandatory inclusion of value of information analyses (EVPI [expected value of perfect information] and EVPPI [expected value of partial perfect information]) in reimbursement submissions represents another significant change. This provides decision makers with information about the consequences of uncertainty related to decisions given current information, potentially identifying areas where additional research would be valuable (although it is unclear what the ask to a manufacturer would be if this was the case). The inclusion of health-related quality of life of informal caregivers in scenario analyses (though not in the base case) represents a step toward more comprehensive assessment of societal impacts, particularly relevant for therapies that reduce caregiver

burden. Similarly, the addition of educational and judicial cost reference prices expands the scope of intersectoral impacts that manufacturers can consider in their submissions, particularly for mental health interventions. Overall, the revised Dutch guideline further reinforces The Netherlands' unique position in requiring a broad societal perspective for economic evaluations.

As we navigate these complex developments in market access and HTA, manufacturers face a rapidly evolving landscape requiring adaptive strategies. From addressing combination therapy value attribution challenges and responding to policy-driven investment shifts to meeting increasingly sophisticated economic evaluation requirements, successful market access now demands earlier planning, cross-functional collaboration and innovative approaches to demonstrating value.

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