Health technology assessment requirements: Sensitive to bacteriophage products or too resistant to change?

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Acceptance code HTA3

Background and Objective

- Antimicrobial resistance is a global threat. PTMPs can help address this crisis by providing an effective treatment against antimicrobial-resistant pathogenic bacteria, but a clear regulatory and market access framework is lacking
- PTMPs can be either *prêt-à-porter* (FPPs) or *sur-mesure* (personalised magistral preparations). *Sur-mesure* PTMPs consist of monophages or multiphage "cocktails" whose composition is regularly adapted to the specific targeted bacterial host to maintain efficacy and prevent resistance (1)
- The aim is to determine if current HTA processes are suitable to deal with both types

Methods

- Methods and process guides by HAS, the G-BA, and NICE were reviewed along with national and EU policy documents, and a search conducted for any antimicrobial-specific processes (2-9). Information was extracted on regulatory classification, HTA processes, and related funding pathways. Eligibility to all of these were mapped to PTMP characteristics to determine fitness for purpose
- Two analogues (LDT for chronic, necrotic wounds and FMT for recurrent or refractory Clostridioides difficile infections) were selected to analyse HTA processes and the funding of drug products made from living organisms

Results

Regulatory classification and requirements:

Under current European law, PTMPs for human use are considered medicinal products and must be regulated as such with no specific provisions or requirements (10,11). Thus, as for a chemical drug, access to a PTMP would require standard MA. This would be the relevant regulatory pathway for *prêt-à-porter* PTMPs, but it is not suitable for *sur-mesure* PTMPs; for the latter, the exact composition of the phage cocktail is tailored to the individual patient's pathogenic bacteria, and it is not feasible for the vast variety of phages that could qualify as active substances to each obtain MA.

A potential solution can be found in magistral formulae (medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient), which are exempt from MA requirements (10). This is the approach that has been adopted in Belgium since 2016 (12). In other European countries, *sur-mesure* PTMPs would only be available to patients for compassionate use under the Declaration of Helsinki (13).

HTA classification and processes:

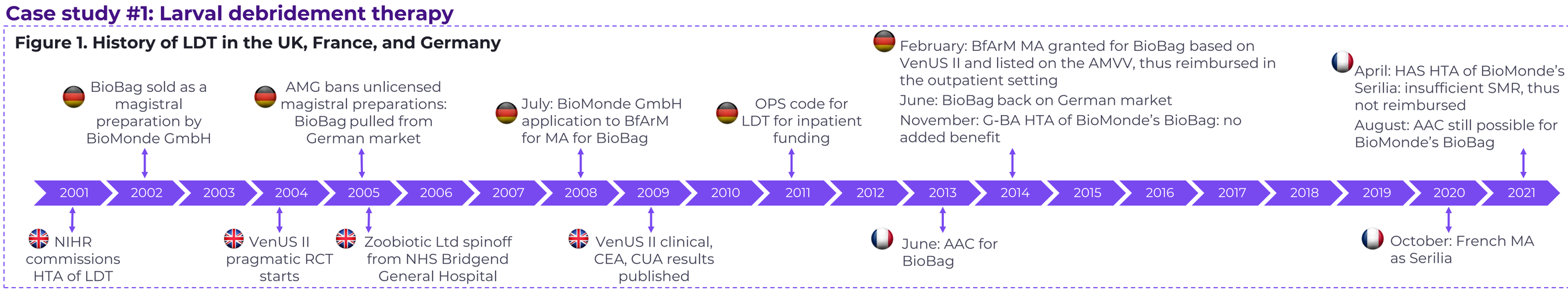
All 3 HTABs have established processes for medicinal products that are distinct from their HTA processes for non-drug interventions. These processes are only applied to medicinal products with MA (2,4-6). In their medicinal products processes, all 3 HTABs make special provision for antimicrobial products that meet specific criteria (See Table 1). However, although NICE makes these available to all antimicrobials, HAS and the G-BA restrict these to antibiotics, excluding other types of antimicrobials. Existing HTA processes therefore cannot be applied to PTMPs based solely on formal grounds.

Table 1. Antimicrobial-specific HTA processes

Country	HTA process	Process advantages	Eligibility criteria				Suitable for PTMP?	
			Product type	WHO priority	MA	Other	Prêt-à-porter	Sur-mesure
France (2,3)	Standard drug HTA	• Antibiotics-specific evidence requirements • More weight given to unmet need in determining the ISP and ASMR	Last-resort antibiotics	Yes	Yes	N/A	✗	✗
Germany (4,7,8)	None exempted	• No HTA • Free pricing	Last-resort antibiotics	Yes	Yes	• Few/no alternatives	✗	✗
UK (9)	Antimicrobial-specific HTA	• HTA includes broader STEDI values • Subscription model payment	Antimicrobials	Yes	Yes	• Relative effectiveness • Unmet clinical need • Pharmacological benefit • Health system benefit	✓	✗

Case study #1: Larval debridement therapy

Figure 1. History of LDT in the UK, France, and Germany



LDT is classified as a medicinal product in all three countries. In the UK, LDT is considered an *unlicensed medicine* and has thus not been appraised by NICE. However, the NIHR had funded primary research via the NHS R&D HTA Programme demonstrating its efficacy and cost-effectiveness. Thus, LDT is funded on the NHS as either free larvae or the FPP BioBag (living larvae of lucilia sericata). In Germany, the 2005 AMG banned magistral formulae using unlicensed substances, so LDT can only be marketed as an authorised FPP. In France, LDT is also only marketable as an FPP, not as a magistral preparation. Both the G-BA and HAS have assessed an LDT FPP manufactured by BioMonde but under different brand names (BioBag and Serilia, respectively). In Germany, BioBag is reimbursed in both the inpatient and outpatient setting; in France, Serilia is not reimbursed at all following the HAS decision, yet BioBag is still available via AAC. BioMonde was acquired in 2005 by Zoobiotic, a spin-out of an NHS Trust, which underlines the long history of use of LDT on the NHS.

Case study #2: Faecal microbiota transplantation

FMT is also classified as a medicinal product in all three countries. Despite this, NICE recommended it for recurrent Clostridioides difficile infection via non-drug pathways (Interventional Procedures Guidance in 2014 and Medical technologies guidance in 2022). The United Kingdom is the only country where FMT is routinely funded (✓) (See Table 2).

HAS and the G-BA have not assessed FMT, as there is no authorised FMT drug product in Europe, nor have they assessed it via a non-drug pathway. Consequently, FMT is not routinely funded (✗). Although there are several treatment centres where FMT is regularly performed in both countries, funding is on a named-patient basis only (≈).

Table 2. Comparison of regulation, HTA, and funding in the UK, France, and Germany

Product	LDT			FMT		
Country	**UK**	**FR**	**DE**	**UK**	**FR**	**DE**
Regulatory classification	Medicinal product			Medicinal product		
HTA conducted?	NICE: ✗	HAS: ✓	G-BA: ✓	NICE: ✓	HAS: ✗	G-BA: ✗
Funded?	✓	≈	✓	✓	≈	≈

Conclusions

EMA has recognised that a flexible regulatory framework is needed due to the specific nature of PTMPs where a variable composition of the final product is expected (13,15). However, the enacted regulation and guidance only apply to veterinary medicinal products and leaves the regulatory position of PTMPs for human use uncertain.

Currently, there is inconsistency between the regulation and the HTA of products consisting of living organisms. Although HTA bodies recognise the need to incentivise the development of novel antimicrobials, their rules of procedure will exclude PTMPs from standard appraisal. Consequently, there is no clear pathway towards stable reimbursement and patient access.

Overall, a similarly flexible HTA framework is also needed to support the development of PTMPs for human use and tackle the antibiotic resistance crisis. Ideally, the regulatory and HTA frameworks should be aligned and consistent across borders.

Abbreviations: AAC, autorisation d'accès compassionnel; AMG, Arzneimittelgesetz; AMVV, Arzneimittelverschreibungsverordnung ASMR, amélioration du service médical rendu; BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DE, Germany; EMA, European Medicines Agency; FR, France; FMT, faecal microbiota transplantation; FPP, finished pharmaceutical product; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; HTA, health technology assessment; HTAB, health technology assessment body; ISP, intérêt de santé publique; LDT, larval debridement therapy; MA, marketing authorisation; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NIHR, National Institute of Health and Care Research; OPS, Operationen- und Prozedurenschlüssel; PTMP, phage therapy medicinal product; RCT, randomised controlled trial; STEDI, spectrum, transmission, enablement, diversity, and insurance value; UK, United Kingdom; WHO, World Health Organization

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