Medicaid's Proposed "Line Extension" Redefinition Imperils Innovation and Patient Access

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In June, the Centers for Medicare & Medicaid Services (CMS) released a proposed rule that would, among other changes, introduce a vastly expanded redefinition of "new formulation" to include any change to a drug, provided that the new formulation contains at least 1 active ingredient in common with the initial brand-name listed drug.[1] This expansion directly contravenes Congress' stated interests over the last 10 years since the Affordable Care Act introduced the alternative unit rebate amount (Alternative URA) for line extensions. Legislative history documents that Congress was focused exclusively on minor chemical alterations to brand drugs (eg, extended-release versions and other "slight" alternations) that could provide manufacturers an easy means to avoid the inflation penalty via the Alternative URA.

CMS proposes to treat as line extensions "any new formulation that contains at least 1 active ingredient in common with [a previously approved drug]" including "a drug that is a combination of 2 or more drugs" and "changes in indication accompanied by marketing as a separately identifiable drug (for example, a different NDC [National Drug Code])." That interpretation would cause many new products to be categorized as "line extensions" and tie their rebate obligations to the inflation penalties of their predecessor products. As a result, the proposal has the potential to increase manufacturer Medicaid rebate liability and 340B exposure.

Combination therapies are important to the successful treatment of infectious diseases, cancer, mental health, and many rare disorders; the Food and Drug Administration (FDA) has long encouraged manufacturers to submit for approval fixed-dose combination (FDC) products.[2] This broad interpretation could dampen the life-changing innovation and may also create a new financial incentive for manufacturers to bring any new molecule to market separately. Ultimately, regulations that discourage their development could result in worse outcomes for patients.

To determine the breadth of combination products being studied in clinical trials that might be considered line extensions under the Medicaid proposal, Xcenda conducted an analysis and found that 17 clinical trials include FDC combination therapies that CMS might newly classify as line extensions under the proposed rule. This included trials that are exploring combination therapies to treat some of the most persistent and troublesome indications facing us today:

- Amyotrophic lateral sclerosis
- Bipolar depression and suicidal ideation
- Cystic fibrosis
- HIV infection
- Opioid abuse and dependence
- Parkinson's disease
- Pulmonary arterial hypertension

Given the wide-sweeping breadth of the proposed line-extension definition, these make up only a small subset of the drugs currently being studied that could be affected. Line-extension drugs are subject to increased Medicaid rebate obligations, potentially leading manufacturers to reprioritize their development efforts. This would be an unfortunate unintended consequence of this expansion of the line-extension definition, despite the profuse evidence that combination products are well outside Congress' intent to only include drugs with "slight alterations."

Should CMS finalize its proposals for line extensions and new formulations, there is a very real possibility that manufacturers will change their development plans for future combination therapies, potentially bringing medicines to market as separate products or canceling development plans altogether. The disincentives inculcated by its proposals threaten patient health and outcomes, which should concern CMS, especially in these times.

Current Clinical Trials Where the Studied Compound Would be Newly Considered a Line Extension Under the Medicaid Proposed Rule

Manufacturer	Study Title	Combination Products	Rationale for Line Extension	Indication	Trial URL
NeuroRx	NRX-101 for Maintenance of Remission From Severe Bipolar Depression in Patients With Suicidal Ideation (SBD-ASIB)	Oral NRX-101 (fixed dose combination of D-cycloserine and lurasidone)	Latuda (lurasidone) manufacturered by Sunovion	Depression and suicidal ideation	https://www.clinicaltrials.gov/ct2/show/NCT04223791
NeuroRx	NRX101 Glx Biomarker Validation Study (NRX-GLX)	D-cycloserine and lurasidone	Latuda (lurasidone) manufacturered by Sunovion	Bipolar Depression and Suicidal Ideation	https://www.clinicaltrials.gov/ct2/show/NCT04223778
NeuroRx	NRX100 vs. Placebo for Rapid Stabilization of Acute Suicidal Ideation and Behavior in Bipolar Depression (SevereBD)	D-cycloserine and lurasidone	Latuda (lurasidone) manufacturered by Sunovion	Bipolar Depression and Suicidal Ideation	https://www.clinicaltrials.gov/ct2/show/NCT04233216
Actelion	Clinical Study to Compare the Efficacy and Safety of Macitentan and Tadalafil Monotherapies With the Corresponding Fixed-dose Combination Therapy in Subjects With Pulmonary Arterial Hypertension (PAH) (A DUE)	Macitentan and Tadalafil fixed dose combination	Monotherapies are FDA approved and marketed	Pulmonary Arterial Hypertension	https://www.clinicaltrials.gov/ct2/show/NCT04233879
Janssen	A Study of Macitentan and Tadalafil as a Fixed Dose Combination and the Free Combination in Healthy Adult Participants	Macitentan and Tadalafil	Monotherapies are FDA approved and marketed	Phase 1 study in health adults	https://www.clinicaltrials.gov/ct2/show/NCT03904693
Janssen	A Study of Macitentan and Tadalafil as a Fixed Dose Combination and the Free Combination in Healthy Adult Participants	Fixed dose combination (FDC) of 1 film-coated tablet containing 10 mg of macitentan and 40 mg of tadalafil will be administered orally.	Monotherapies are FDA approved and marketed	Healthy	https://www.clinicaltrials.gov/ct2/show/NCT04235270
Merck Sharp & Dohme	Switch to Doravirine/Islatravir (DOR/ISL) in Human Immunodeficiency Virus 1 (HIV-1) Participants Treated With Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF) (MK-8591A-018)	Fixed dose combination of doravirine and islatravir	Doravirine is FDA approved and marketed	Human Immunodeficiency Virus	https://www.clinicaltrials.gov/ct2/show/NCT04223791
Merck Sharp & Dohme	Safety and Efficacy of a Switch to Doravirine/Islatravir in Participants With HIV-1 (MK-8591A-017))	Fixed dose combination of doravirine and islatravir	Doravirine is FDA approved and marketed	Human Immunodeficiency Virus	https://www.clinicaltrials.gov/ct2/show/NCT04223778
Merck Sharp & Dohme	Doravirine/Islatravir (DOR/ISL) in Heavily Treatment-Experienced (HTE) Participants for Human Immunodeficiency Virus Type 1 (HIV-1) Infection (MK-8591A-019)	Fixed dose combination of doravirine and islatravir	Doravirine is FDA approved and marketed	Human Immunodeficiency Virus	https://www.clinicaltrials.gov/ct2/show/NCT04233216
Merck Sharp & Dohme	Randomized, Double-blind, Efficacy, and Safety Study of Doravirine/Islatravir (DOR/ISL) in Treatment-naïve Participants With Human Immunodeficiency Virus Type 1 (HIV-1) Infection (MK-8591A-020)	Fixed dose combination of doravirine and islatravir	Doravirine is FDA approved and marketed	Human Immunodeficiency Virus	https://www.clinicaltrials.gov/ct2/show/NCT04233879

Manufacturer	Study Title	Combination Products	Rationale for Line Extension	Indication	Trial URL
Merck Sharp & Dohme	Doravirine/Islatravir (DOR/ISL) in Heavily Treatment-Experienced (HTE) Participants for Human Immunodeficiency Virus Type 1 (HIV-1) Infection (MK-8591A-019)	Fixed dose combination of doravirine and islatravir	Doravirine is FDA approved and marketed	Human Immunodeficiency Virus	https://www.clinicaltrials.gov/ct2/show/NCT04233216
Merck Sharp & Dohme	Islatravir (MK-8591) With Doravirine and Lamivudine in Participants Infected With Human Immunodeficiency Virus Type 1 (MK-8591-011)	Fixed dose combination of doravirine and islatravir	Doravirine is FDA approved and marketed	Human Immunodeficiency Virus	https://www.clinicaltrials.gov/ct2/show/NCT03272347
Pharma Two B	A Phase 3 Study With P2B001 in Subjects With Early Parkinson's	Fixed dose combination of pramipexole and rasagiline	Monotherapies are FDA approved and marketed	Early untreated Parkinson's disease	https://www.clinicaltrials.gov/ct2/show/NCT03329508
Vertex	A Study Evaluating the Long Term Safety and Efficacy of VX-659 Combination Therapy	VX-659 in triple combination with tezacaftor and ivacaftor	tezacaftor and ivacaftor are FDA approved as SYMDEKO	Cystic fibrosis	https://www.clinicaltrials.gov/ct2/show/NCT03447262
NeuroSense Therapeutics	Ciprofloxacin/Celecoxib Combination in Patients With ALS	Fixed dose Ciprofloxacin and Celecoxib capsule to be taken twice daily, total dose 748 mg/day	Monotherapies are FDA approved and marketed	ALS	https://www.clinicaltrials.gov/ct2/show/NCT04090684
The University of Texas Health Science Center at San Antonio	Reducing the Abuse of Opioids in Drug Users	The study team hypothesize that this can be accomplished by administering a fixed-dose-combination of an opioid with an atypical antipsychotic drug, in the same pill or capsule. Oxycodone (20mg) plus Risperidone (2 mg) Oxycodone (20mg) plus Ziprasidone (80 mg)	Monotherapies are FDA approved and marketed	Opioid Abuse, Unspecified	https://www.clinicaltrials.gov/ct2/show/NCT03837860
Gilead	B/F/TAF FDC in HIV-1 Infected Virologically Suppressed Adolescents and Children	bictegravir/ emtricitabine/tenofovir alafenamide 30/120/15 mg fixed dose combination	New dosage for FDA-approved drug combination	HIV-1 Infection	https://www.clinicaltrials.gov/ct2/show/NCT02881320

References

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