# FDA Proposes Policy Change Concerning 5-Year NCE Exclusivity for Certain Fixed-Combination Drugs

Prompted by citizen petitions filed by Ropes & Gray and by two other companies, FDA issued draft guidance proposed a change in the Agency's interpretation of 5-year new chemical entity ("NCE") exclusivity as applied to certain fixed-combination drug products ("fixed-combinations"). Fixed-combinations are drug products that generally include two or more drug substances (i.e., active ingredients) in a fixed ratio, synthetically combined in a single dosage form. Historically, FDA interpreted the relevant statutory and regulatory provisions to preclude 5-year NCE exclusivity for a fixed-combination that included both a new active moiety a previously approved active moiety. Under FDA's new interpretation, such a fixed-combination will be eligible for 5-year NCE exclusivity so long as it contains at least one drug substance, no active moiety of which has been previously approved.

## Historical Approach

FDA's long-standing position has been that fixed-combinations are eligible for 5-year NCE exclusivity only if every active moiety in the combination is new – if just one of the active moieties has been approved previously, the fixed-combination is not eligible for 5-year NCE exclusivity. This approach was based on FDA's interpretation of the 5-year NCE exclusivity provision, which states:

> If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved . . . no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of approval of the application under subsection (b) of this section…[1]

The statute thus includes clauses describing both eligibility for 5-year NCE exclusivity (the "eligibility clause") and the parameters of this exclusivity once it attaches (the "bar clause"). Historically, FDA interpreted the term "drug" in the eligibility clause to mean "drug product," while it interpreted the term "drug" in the bar clause to mean "drug substance." Because FDA interpreted "drug" to mean "drug product" in the eligibility clause, a drug product could only be eligible for 5-year NCE exclusivity if "no active ingredient" in the drug product had previously been approved. This led to FDA's conclusion that fixed-combinations including both a new active ingredient and a previously approved active ingredient were not eligible for 5-year NCE exclusivity.

## Citizen Petitions

In 2013, three companies each petitioned FDA to revise its interpretation of 5-year NCE exclusivity with respect to certain fixed-combinations. The petitioners argued that FDA's interpretation of the word "drug" to mean two different things in the 5-year NCE exclusivity provision was contrary to the statutory language, Congressional intent, and FDA's own implementing regulations. In addition, the petitioners argued that FDA's historical approach leads to illogical and arbitrary results by putting undue weight on the order in which a sponsor's applications are approved in determining their eligibility for 5-year NCE exclusivity.[2] The petitioners also pointed out that FDA's policy favors the development of a new active ingredient in a single-entity drug product that is cross-labeled for use with another drug product that contains a previously approved active ingredient, as opposed to development of the new active ingredient in a fixed-combination.

## Response to Petitions and New Interpretation

In its consolidated response to the three petitions, FDA concluded that the petitioners articulated a reasonable alternative interpretation of the statute and regulations that would be beneficial to the public health. FDA recognized that a change in policy was warranted given recent changes in the field of fixed-combinations. FDA also acknowledged that its historical approach to fixed-combinations could result in suboptimal development strategies.

Accordingly, FDA announced that it is proposing to change its interpretation of 5-year NCE exclusivity to align the exclusivity incentives more closely with FDA's public health goals. Under this interpretation, the term "drug" in the eligibility clause (and in the regulatory definition of "new chemical entity") will refer to "drug substance," not "drug product." If FDA adopts this interpretation, a 5-year NCE exclusivity determination will be made for each drug substance in a drug product, not for the drug product as a whole. As a result, a fixed-combination drug product that contains a drug substance with a single, new active moiety would be eligible for 5-year NCE exclusivity, even if the fixed-combination also contains a drug substance with a previously approved active moiety.

## New Draft Guidance

On the same day that FDA responded to the petitions, it issued new draft guidance proposing and seeking public comment on the new interpretation that would recognize 5-year NCE exclusivity for certain fixed-combinations. FDA stated that if, at the conclusion of the comment period, it is convinced that the proposed new interpretation is appropriate, it will issue final guidance and will adopt the new interpretation. The draft guidance also states that the new interpretation will not apply to fixed-combinations that are approved "prior to adopting the new interpretation."

FDA will be accepting comments on the draft guidance until April 25, 2014.

If you would like to discuss the foregoing or any related matter, please contact any member of Ropes & Gray's FDA regulatory practice or your usual Ropes & Gray advisor.