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China: Assessing inventive step for pharmaceutical combination formulations

Wu Xiaohui, 10 June 2025, first published by MIP

A ‘combination formulation’ refers to a pharmaceutical formulation containing two or more active ingredients. Leveraging synergistic effects, a combination formulation often exhibits better efficacy and fewer adverse reactions than single-component drugs. The inventive step assessment of a combination formulation has been closely watched by practitioners in the pharmaceutical industry. A recent invalidation decision – No. 580332, made by the CNIPA on September 30 2024 – provides some guidance in this regard.

Case summary

Egis Pharmaceuticals plc owns invention patent No. 200980138060.7 (the Subject Patent), which relates to a pharmaceutical composition containing amlodipine besylate and bisoprolol fumarate.

On March 15 2024, a Chinese biopharma company launched an invalidation action against the Subject Patent, challenging its inventive step and citing multiple combinations of prior art, using Evidence 2 and Evidence 3 as the closest prior art.

Claim 1 of the Subject Patent protects a tablet prepared by direct compression. The tablet contains amlodipine besylate and bisoprolol fumarate packaged in cold-formed blisters with aluminium foil-covered OPA AL PVC composite foil, along with pharmaceutically acceptable excipients, as well as a compound of formula (3), which weighs less than 0.5% of the active ingredients. The tablet does not require separate processing of amlodipine besylate and bisoprolol fumarate during its preparation.

Evidence 2 discloses a direct compressing tablet of amlodipine maleate prepared by the wet granulation method. The resulting tablets contained below 0.5% of impurity 6 (i.e., the compound of formula (3) in the Subject Patent) in the initial phase and after one month when the temperature is controlled at 40°C and the relative humidity 75%.

Evidence 3 discloses that conventional approaches fail in combining the two drugs, either by mixing amlodipine besylate and bisoprolol fumarate with diluents such as lactose and microcrystalline cellulose and then granulating the mixture with starch paste, or by separately granulating and drying the two drugs, and subsequently compressing the mixture into tablets. That is because, as acid addition salts, amlodipine besylate and bisoprolol fumarate may react with each other, leading to chemical instability, thus making the traditional methods of making tablets unviable, unless there is a method to avoid harmful chemical reactions between the two drugs.

The CNIPA’s reasoning

The CNIPA’s panel identified the following differences between Claim 1 and Evidence 2:

- The active ingredients in the Subject Patent are amlodipine besylate and bisoprolol fumarate, whereas Evidence 2 uses amlodipine maleate;
- The Subject Patent specifies that the two active ingredients do not require separate processing; and
- The Subject Patent selects cold-formed blisters with aluminium foil-covered OPA AL PVC composite foil as packaging.

The patent specification dictates that amlodipine besylate and bisoprolol fumarate exhibit chemical

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incompatibility, leading to the formation of impurity compound (3) upon contact. The invention aims to prepare a stable pharmaceutical composition of the two drugs without separate processing by selecting specific packaging and conditions. Data included in the specification indicates that the two active ingredients are not sensitive to temperature to such an extent that mere contact would induce reactions. When prepared by direct compression and packaged in cold-formed OPA AL PVC composite foil blisters with aluminium foil coverage, the composition could achieve a favourable impurity control effect. Based on these distinguishing technical features and the described effects, Claim 1 addresses the technical problem of providing a stable pharmaceutical product containing bisoprolol fumarate and amlodipine besylate through specific preparation methods and packaging.

The panel found that Evidence 3 neither identifies the impurity formed by the reaction of the two active ingredients nor provides the teaching to avoid separate processing of the ingredients. On the contrary, it explicitly instructs separate processing of each active ingredient with excipients before combining them into the final formulation.

Although Evidence 2 suggests that an amlodipine base reacts to form the compound of formula (3), it attributes the impurity formation to the presence of water or moisture during preparation. Evidence 3, however, attributes the instability to the potential chemical reaction between the two acid addition salts, without specifying that the impurity is definitely the compound of formula (3). Even considering the structural relationship between fumaric acid and maleic acid, which suggests that bisoprolol fumarate may react with amlodipine besylate, Evidence 3 teaches that the two active ingredients must first be separately mixed with excipients before being combined for tableting or encapsulation. Thus, combining Evidence 2 and 3 would result in a technical solution requiring separate processing of the active ingredients.

The panel specifically noted that although the active ingredients, impurities, packaging materials, and even preparation methods used in the Subject Patent are taught in the prior art or conventional in the field, this does not make any pharmaceutical formulation obvious relative to the prior art. The development of pharmaceutical formulations typically begins with selecting appropriate formulation strategies to overcome any identified bioavailability issues of active ingredients, meaning the technical problem is usually the starting point for formulation development.

The key issue in this case is whether a person skilled in the art, being aware of the reaction between amlodipine besylate and bisoprolol fumarate from the prior art, would still seek to prepare a formulation without separate processing. However, given the known reactivity upon contact, the most conventional approach, as demonstrated by Evidence 3 and other prior art, would be to process the two ingredients separately or minimise their contact. Therefore, the prior art not only lacks motivation to combine Evidence 2 and 3 but also shows that solving the stability issue of combining two easily reactive ingredients without separate processing is inherently non-obvious.

Ultimately, the panel concluded that Claim 1 possesses an inventive step over each and every closest prior art and therefore issued invalidation decision No. 580332, maintaining the validity of the Subject Patent.

Commentary on the CNIPA panel’s findings

In this case, the panel took a holistic approach in analysing Evidence 2 and 3, dissecting the technical teaching by combining the two prior arts, and concluded that the mere replacement of the active ingredients in Evidence 2 with those in Evidence 3 would contradict the teaching of Evidence 3.

In assessing the technical teaching for an inventive step, it is essential to evaluate the prior art as a whole, by taking into account the technical facts disclosed in the prior art and identifying the technical teaching provided, from the perspective of a person skilled in the art. When the prior art contains both supporting and contradictory information, an assessment should be made within the boundary of the prior art, benchmarking against the technical know-how of a skilled person.

The decision also affirms that whether the raw materials, excipients, or preparation methods used in a formulation are conventional shall have no bearing on the assessment of their contribution to inventiveness. This finding underpins the significance of adopting a holistic approach in the inventiveness assessment as it would be pivotal to reach a sound conclusion on whether there is a teaching leading to the claimed technical solution, and solving the technical problem. Otherwise, the assessment would become moot, as when a technical solution is broken down into isolated technical features, the chances are that most, if not all, the features will be covered by the prior art.

This decision also underscores that in drafting patent applications, applicants need to articulate the uniqueness of the technical problem, highlight the synergistic effects of technical features, and validate these through experimental data.