Substitutability of inhaler fixed combination medicinal products in the Italian Case Law

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63° EMACOLEX Meeting – Warsaw 3-4 April 2025

Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	x	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	x	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	x	☐	☐	☐ optional
2. Consultancy for a company	x	☐	☐	☐ optional
3. Strategic advisory role for a company	x	☐	☐	☐ optional
4. Financial interests	x	☐	☐	☐ optional
5. Ownership of a patent	x	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	x	☐	☐	☐ optional
7. Investigator	x	☐	☐	☐ optional
8. Grant or other funding	x	☐	☐	☐ optional
9. Family members interests	x	☐	☐	☐ optional

*Carla Cantelmo, in accordance with the Conflict of Interest Regulation approved by AIFA Board of Directors (Resolution n. 37 dated 13/10/2020)
N.B. < I am not receiving any compensation>

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Italian regulation/Background

- According to art. 7, par. 1, of Law Decree no. 347/2001, conv. by Law no. 405/2001: *"Medicines, having equal composition in active ingredients, as well as pharmaceutical form, route of administration, mode of release, number of posological units and equal unit doses, shall be reimbursed to the pharmacist by the National Health Service up to the lowest price of the corresponding product available in the normal regional distribution cycle, on the basis of special guidelines defined by the Region".*
- This definition is expression of the principle of therapeutic equivalence of medicinal products as interpreted by national administrative jurisprudence.
- On 10th February 2021 AIFA adopted the Directorial Determination no. 166/2021, for the purpose to clarify and explicit the criteria for the inclusion of equivalent medicinal products, generic products or MPs whose patent protection had expired, in the so called "Transparency List", monthly published.

Italian regulation/Background

- According to Annex to Det. no. 166/2021, art.3, "*When **further investigation** of the actual substitutability of MPs **for the purpose of inclusion on the Transparency List are required**, the Scientific Technical Committee(CTS) will be consulted and **will take into account the following criteria** in its evaluation, by way of example:*

- *in vivo and/or in vitro comparison studies or possibility of exemption from such studies;*
- *therapeutic index of the active ingredient;*
- *characteristics of the active ingredient (such as chemical/physical characteristics, active ingredient with complex structure, method of production);*
- *characteristics of the MP delivery device (e.g., inhalation powders)*
- *Any other elements relevant to the evaluation*"

Italian regulation/Background

- AIFA carried out a reassessment of certain therapeutic classes of medicinal products that, until then, had not been included within the Transparency List, as inhaler MPs.
- In September 2022, CTS adopted a general opinion on the inclusion of budesonide+formoterol (fixed dose combination) inhaler MPs in the Transparency List.
- Following the assessment on the substitutability of such devices and the existence of all legal requirements, it was concluded that the whole class of inhaler MPs, based on the said active principles, could have been included in the Transparency list taking into account their interchangeability .
- On November 2022, AIFA included in the Transparency List some budesonide+formoterol MPs.

Italian regulation/Background

- Taking into account that those kind of MPs are fully reimbursed by the National Healthcare System, the inclusion of a new therapeutic class in the transparency list allows, as a direct consequence, a **substantial saving for public spending**, since the total price of each MP is no longer covered by the NHS.

- The NHS only provides for the so-called "reference price," i.e., the lowest price within each class, unless the physician appose the not-substitutability clause to the prescription issued.

The lawsuits against AIFA's position

- Four lawsuits were issued in front of the National Administrative Court by MAHs of budesonide+formoterol MPs, claiming:

➢ Infringement and erroneous application of art.7 L.D. 347/2001 - Lack of assessment as the device constitutes an integral part of inhalation therapy and as a result the MPs cannot be automatically substituted by the pharmacist;

➢ Although the inhaler MPs had been on the market for several years, AIFA had never included them within the Transparency List;

➢ Economic damage resulting from lower sales of MPs, due to the mechanism of reimbursement by the NHS related to their inclusion in the Transparency List.

Plaintiffs' position

- Inhaler MP consists of a device/pharmaceutical combination (powder for inhalation + device for administration) and is entirely reimbursed by NHS.

- The reason for the previous not-inclusion of Budesonide + Formoterol inhaler MPs in the Transparency List was that these products, although similar in composition, have each one a completely different device (Turbohaler vs. Easyhaler vs. Spiromax).

- The device is a relevant part of the inhalation therapy, making it so that the drugs in question isn't automatically interchangeable according to the substitution mechanism.

AIFA's position

- "*on the basis of the results obtained in vitro and in vivo, it was possible to conclude that the therapeutic equivalence of the drug in application to the reference drug was demonstrated*"
- MPs belong to the type of "Dry Powder Inhalers"
- Legal basis of authorization (art. 8, 10 b) and 10 §3, of Directive 2001/83/CE)
- Legal requirements (art. 7, § 1, Law Decree. No. 347/2001)

The judgement of the Administrative Court

- Although a link between an incorrect use of the inhaler and COPD symptom control has been demonstrated, none of the RCTs conducted have established the superiority of one device/formulation vs. another, as moreover pointed out in the 2020 update of the Gold Guidelines.
- The assessment, as set out by AIFA, was articulated and punctual and also took into account the procedures to be followed for the use of the concerned MPs, deeming them "*in any case as interchangeable*."
- The judgment of the AIFA' Commission was expression of its technical discretion and did not present any profile of illogicality and/or unreasonableness, being the outcome of a series of detailed and thorough assessments.

The judgement of the Administrative Court

- The plaintiffs appealed for the reformation of the decision of the first instance administrative Court.

- All the previous complaints were reiterated in appeal.

The Judgment of Court of Appeal

- "**The peculiarity of this case is the fact that all the parties peacefully acknowledge the existence of the requirements of Art. 7**";
- Failed the appellant's contention that incorrect use of the device is potentially capable of compromising the efficacy of the therapy;
- Substitutability has been proved by AIFA and also clearly derives from the preliminary investigation;
- Specificity of the device can be relevant for the purpose of art. 7 only when related to "*modalities of use that assume a particular, objective and unfungible impact on therapeutic efficacy*."
- This hypothesis is residual but should always be substantiated;
- The act of dispensing a MPs is a **medical act.**

Conclusion

- The right to health is also guaranteed in its declination of **immediacy of protection**, without any prejudice connected to the lack of a therapeutic alternative, such as the delay in the administration of the therapy prescribed in case of shortage.
- **Budesonide+Formoterol (ATC V Level R03AK07) represents one of the molecules in the broader category of respiratory drugs for the treatment of COPD that contributes, together with the other active substances included in the same class, to savings for the NHS spending.**
- There is an optimization of NHS resources while ensuring the same, if not greater, availability of MPs.

Thank you for your attention!