THE ITALIAN 648/96 LIST: APPROVALS, REJECTIONS AND METHOD IN AIFA'S EVALUATION PROCESS BETWEEN JANUARY 2013 AND OCTOBER 2015

Authors: Prada M[1], Bertozzi C[1], Proietti B[1], Urbinati D[2]

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Introduction

The Italian Law 648/96 allows, on the costs of the National Health Service, the use of three types of medical products: innovative drugs for which the sale is authorized abroad, but not in Italy; drugs which have not yet received an authorization, but have undergone clinical trials; and drugs to be used for a therapeutic indication different from the one which had been authorized (off-label). The original art. 1, sub. 4, Law 648/1996 allowed the prescription (paid by the producer) of these drugs, provided that phase II or III clinical trials with favourable evaluation in terms of efficacy and safety were published, but only if any other therapeutic alternative is available. It was a derogation to Legislative Decree 219/06, art. 6, sub 1: "no medicinal product can be put on the market without either an AIFA authorization (Autorizzazione all'Immissione in Commercio) (AIC), which may be national, by mutual recognition or by decentralized procedures or an EU authorization granted in accordance with the EMEA Regulation".

By the amendment published on May 2014 (law 79/2014, art 4bis), the Technical Committee of AIFA can include a given medication in the official list even if there is a therapeutic choice. This is an important change: by this new law, AIFA can grant an authorization for a new indication, based only on scientific evidences, granting to Italian patents the access to innovative drugs.

According 648/96 Law, health operators or patients associations can request early access to medications by submitting a written request to AIFA, listing the evidence of efficacy available in the scientific literature. The request is discussed by the Technical and Scientific Committee (CTS) of AIFA and approved for clinical use if deemed appropriate. Thus, the medication becomes available to patients with inclusion and exclusion criteria set by AIFA. In addition, the medication is subjected to a program of surveillance and should be reported in a list which is periodically updated.

Objectives

This study aimed to assess AIFA's approach, by reviewing approvals, rejections and methods followed by AIFA for its decisions and to analyze their temporal evolution.

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In order to ensure transparency in the decision process, AIFA makes electronic files available through an online system of transparency. The most important information are published online, after each CTS meeting.

By connecting to the dedicated page, we systematically performed a review of each single document (Verbali CTS - "Esiti Ufficio Ricerca e Sperimentazioni Cliniche"), and collected all the available information.

Reports of CTS meetings from January 2013 to October 2015 were reviewed, checking number and characteristics of drugs under evaluation, and analyzing each single decision taken by CTS.

In order to complete the analysis, we also checked all the Determine and Gazzette Ufficiali published in the timeframe considered and related to 648. As an example, in 2013 and 2014 some specific 648 lists have been published, containing all the 648-approved products for Neurology (4), Transplantation (5), Antivirals (7) or Cardiology (8). All these information are public and available on a dedicated section of the official AIFA site (information http://www.agenziafarmaco.gov.it/it/content/normativa-di-riferimento-sperimentazione-clinic).

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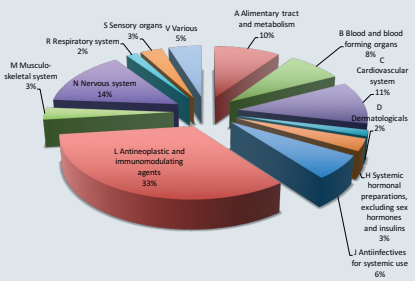

The main represented ATC-1 for products under AIFA's evaluation (Figure 2) were: L (antineoplastic and immunomodulants agents) 33%, N (nervous system) 14%, C (cardiovascular system) 11% and A (alimentary tract and metabolism) 10%.

Results

- Out of 113 applications evaluated (some products gained different approvals for different indications), 55 received a positive evaluation, 37 a negative evaluation, 2 are waiting for EMA's decision, and 5 have been referred to the Law 326/2003 (Fondo AIFA 5%) and to the Law 94/98 (Legge Di Bella). Other 14 requests are still waiting for an in depth examination, have been delayed because of lack of time or have been addressed directly to other competent offices, when 648 law was not applicable.
- In the timeframe under analysis, further 25 drugs have been approved and insert in cumulative disease specific lists (i.e. cardiology, transplantation, neurology).
- Of the 55 approved products/indications, 3 have obtained a full registration for the "648 authorized indication" (see Table 2), and other 14 recently obtained an EU Marketing Authorization.
- Analysis indicated that the drivers for the inclusion in the 648 List were the presence of strong clinical data, the lack of therapeutics alternatives on the Italian market, the rare disease condition and a specific paediatric indication.

Conclusions

In the observed period (January 2013-October 2015), thanks to 648 law, several safe and efficacious therapeutic options have been made available to Italian patients.

This analysis shows the important role of the Italian Law 648/96, a precious tool for patients to be treated with a drug, with strong clinical and safety data, waiting for the whole Italian regulatory process to be completed. Law 648/2006, together with Fondo AIFA 5% and Law 94/98, demonstrates the strong AIFA's commitments to allow early access to orphan drugs for Italian patients

References

- Law 648/96
- Legislative Decree 219/06
- Law 79/2014, art 4bis
- http://www.agenziafarmaco.gov.it/it/commissioni
- http://www.agenziafarmaco.gov.it/it/content/normativa-di-riferimento-sperimentazione-clinic
- Patient Access Monitor Portal
- Ministerial Decree 8 May 2003
- Law 94/1998 and Law 326/2003 (Fondo AIFA 5%)
- http://www.whocc.no/atc_ddd_index/

FOR FURTHER INFORMATION: Please contact – Mariangela Prada

Intexo Srl - via del Tritone, 169 – 00186 Rome Italy – *mariangela.prada@intexo.it*

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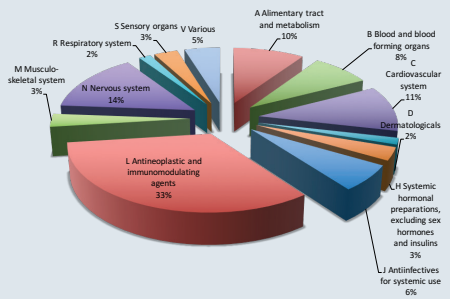

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Conclusions

In the observed period (January 2013-October 2015), thanks to 648 law, several safe and efficacious therapeutic options have been made available to Italian patients.

This analysis shows the important role of the Italian Law 648/96, a precious tool for patients to be treated with a drug, with strong clinical and safety data, waiting for the whole Italian regulatory process to be completed. Law 648/2006, together with Fondo AIFA 5% and Law 94/98, demonstrates the strong AIFA's commitments to allow early access to orphan drugs for Italian patients.

References

- Law 648/96
- Legislative Decree 219/06
- Law 79/2014, art 4bis
- http://www.agenziafarmaco.gov.it/it/commissioni
- http://www.agenziafarmaco.gov.it/it/content/normativa-di-riferimento-sperimentazione-clinic
- Patient Access Monitor Portal
- Ministerial Decree 8 May 2003
- Law 94/1998 and Law 326/2003 (Fondo AIFA 5%)
- http://www.whocc.no/atc_ddd_index/

FOR FURTHER INFORMATION: Please contact – Mariangela Prada
Intexo Srl - via del Tritone, 169 – 00186 Rome Italy – *mariangela.prada@intexo.it*