Market withdrawal and suspension of marketing authorisation of medicinal product due to good manufacturing practice noncompliance in India

C-269/13 Acino AG vs. European Commission, LS&R 885

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INTRODUCTION (AND SUMMARY)

On the 10th of April 2014[1], the Court of Justice of the European Union (hereinafter: "***CJEU***") has clarified that upon establishment of breach of the rules of Good Manufacturing Practice ("***GMP***"), the Commission is entitled to suspend the marketing authorisation and to impose withdrawal of the medicinal product from the distribution network, including pharmacies - even when there is no evidence that the medicinal products at stake were harmful to patients.

To our knowledge, this is the first ruling of the CJEU pertaining to noncompliance with GMP and subsequent suspension of the marketing authorisation for a medicinal product and imposed withdrawal from the distribution network of the medicinal product concerned.

The conditions for suspension, withdrawal or variation of a marketing authorisation are limitatively listed in the Medicines Directive[2]. However, noncompliance with the rules of GMP is not listed as one of those conditions, whereas the fact that the qualitative and quantitative composition of the medicinal product not being as declared, is mentioned as such a condition. The CJEU ruled that the General Court correctly applied the precautionary principle when stating that the grounds laid down in the Medicines Directive aim to prevent certain risks to health, the fact remains that those risks need not be specific but only potential. The Commission was entitled to restrict itself to supplying solid and persuasive evidence which could give rise to reasonable doubt as to their qualitative and quantitative composition, as declared, of the medicinal products at issue. Where it proves to be impossible to determine with certainty the existence or extent of the alleged risk, the precautionary principle justifies the adoption of restrictive measures.

With respect to the withdrawal of the product from the distribution network, the CJEU ruled that non-compliance with GMP may constitute such a potential risk of impairment of the qualitative composition and therefore of detriment to public health, the General Court was justified in holding that the conditions for the application of the relevant provision[3] of the Medicines Directive were met.

This case is highly relevant for marketing authorisation holders whose active pharmaceutical ingredients or medicinal products are manufactured in a factory in India or China, as it has recently been published that relatively more GMP noncompliance has been established in those countries[4].

BACKGROUND

Acino Pharma (hereinafter: "***Acino***") has obtained a centralised authorisation for eight medicinal products containing clopidogrel[5]. The marketing authorisations applications indicated that the active substance, clopidogrel, was (among others)

[1] C-269/13 Acino AG *v.* European Commission.

[2] Article 116 Directive 2001/83/EC (as amended).

[3] Article 117(1)(e) Directive 2001/83/EC (as amended).

[4] See: http://www.gmp-compliance.org/ecanl_0_0_news_4110_8344,S-WKS_n.html. Last accessed: June 16, 2014.

[5] An antiplatelet agent.

manufactured in a factory in Visakhapatnam, India.

In 2010, the Committee for Medicinal Products for Human Use (hereinafter: "***CHMP***") requested the competent authority of Oberbayern (Germany) to inspect the factory whether the manufacturing of medicinal was in compliance with the principles and guidelines of Good Manufacturing Practice (hereinafter: "***GMP***"). Article 46(f) of Directive 2001/83/EC (as amended) stipulates that the holder of a manufacturing authorisation is obliged to comply with the principles and guidelines of GMP for medicinal products and to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on GMP.

The inspection resulted in a report which established that manufacturing at the factory in Visakhapatnam, India did not comply with the rules on GMP. Such inspection reports generally categorize the established breaches into *critical*, *serious* or *minor*. The fact that 70 manufacturing standards had been re-written and that certain initial indications were amended, was considered a critical breach.

Please note that it had been mentioned in the inspection report that the quality of the products was *not* affected as a result of the re-writing of the data relating of quality and that there was no evidence that that breach affected the health of patients.

Furthermore, eight other serious breached were revealed. In an amended version of the inspection report, the withdrawal of medicinal products supplied was found to be unnecessary in the absence of any evidence that the products at issue were harmful to patients.

After the hearing before the CHMP, the Commission initiated an article 20 procedure[6] and finally the Commission[7] adopted provisional decisions entailing that (1) the marketing of consignments of medicinal products containing the active ingredient clopidogrel manufactured on that site was suspended, and that (2) all consignments of medicinal products containing the active ingredient clopidogrel manufactured by that factory were to be withdrawn from the distribution network, including pharmacies.

Afterwards, Acino sent to the Commission a report including a (among others) risk assessment, which concluded that there was no risk to patients' health. Therefore, Acino requested a new examination.

Nevertheless, the Agency (EMA) informed the Commission that it maintained the conclusions of the initial opinion of the CHMP and the final decisions were adopted[8]: Firstly, the authorisations to market medicinal products containing the active ingredient clopidogrel were varied to the effect that the Visakhapatnam site was removed from the list of production sites authorised to supply that active ingredient; and, secondly the consignments of medicinal products containing clopidogrel manufactured at that site may not be placed on the European Union market.

Acino lodged an application with the General Court seeking the annulment of both the provisional and the final decisions. However, the General Court dismissed the action brought by Acino entirely.

The appeal

In essence, the appeal with the CJEU seeks the General Court's assessment of the conditions for application of articles 116 and 117 of Directive 2001/83/EC, in the light of the precautionary principle, as derived from the Court's case-law.

Article 116 of Directive 2001/83/EC provides that the competent authorities shall suspend, revoke,

[6] Article 20 Regulation (EC) No 726/2004 (as amended).

[7] The decisions were adopted in accordance with the first subparagraph of Article 20(3) of Regulation No 726/2004 (as amended).

[8] The decisions were adopted in accordance with the second subparagraph of Article 20(3) of Regulation No 726/2004 (as amended).

withdraw or vary a marketing authorisation if the view is taken that the product is harmful under normal conditions of use, or that it lacks therapeutic efficacy, or that the risk-benefit balance is not positive under the normal conditions of use, or that its qualitative and quantitative composition is not as declared. The provision furthermore stipulates that therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

The following article 117(1) of that directive provides that Member States shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:

(a) the medicinal product is harmful under normal conditions of use; or

(b) it lacks therapeutic efficacy; or

(c) the risk-benefit balance is not favourable under the authorised conditions of use; or

(d) its qualitative and quantitative composition is not as declared; or

(e) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.

Further to the precautionary principle; article 8 of the European Convention on Human Rights on the right to respect for private and family life implies respect for the precautionary principle. The precautionary principle has been developed in the case law of the CJEU and comprises the management of the risk exceeding the level deemed acceptable for society through measures designed to contain it at that level. The General Court therefore concluded that the relaxation of preventive measures adopted previously had to be justified by new elements changing the assessment of the risk in question.

The grounds of appeal and the ruling of the CJEU

Among its first ground of appeal[9], pertaining to disregard for the precautionary principle, Acino holds that breach of rules of GMP cannot automatically lead to a change in the qualitative and quantitative composition of the medicinal product in question, and therefore the conditions for the application of article 116(1) of the Directive were not met.

Furthermore, Acino holds that the correct application of the precautionary principle presupposes that there is a probability of actual harm to public health. Moreover, the evidence furnished by Acino that the medicinal products at issue were not harmful, was not taken into account by the General Court.

The CJEU ruled that since the manufacturing process is a factor capable of varying the qualitative composition of a medicinal product, the non-compliance with that process could lead to a change in the qualitative composition and therefore the Commission was entitled to take account of the manufacturing process declared by Acino. Moreover, the present case entailed a critical breach, in conjunction with eight other serious breaches.

Regarding the alleged disregard for the precautionary principle, the CJEU states that protective measures may be taken without having to wait until the reality and seriousness of those risks become fully apparent.[10]

The General Court has also added that where it proves to be impossible to determine with certainty the existence or extent of the alleged risk because of the insufficiency, inconclusiveness or imprecision of the results of the results of the

[9] Acino put five grounds of appeal forward. As some have been rejected as unfounded or inadmissible, only a selection will be discussed within the scope of this article.

[10] C-236/01 Monsanto Agricoltura Italia and Others [2003], par 111.

studies conducted, but the likelihood of real harm to public health persists should the risk materialise, the precautionary principle justifies the adoption of restrictive measures.[11] The General Court therefore correctly applied the precautionary principle when stating that the grounds set out in the first paragraph of article 116 of Directive 2001/83/EC aim to prevent certain risks to health, the fact remains that those risks need not be specific but only potential.

Acino also claimed that the conditions set out in article 117(1)(e) of Directive 2001/83/EC were not satisfied. However, given that the General Court observed that non-compliance with GMP may constitute such a potential risk of impairment of the qualitative composition and therefore of detriment to public health, it was justified in holding that the conditions for the application of article 117(1)(e) of Directive 2001/83/EC were met in the present case.

With regard to the burden of evidence, the CJEU confirmed that it is not the holder of an authorisation for a medicinal product who is required to adduce evidence of the effectiveness or safety of that medicinal product, but rather it is the competent authority, in the present case the Commission, that is required to establish that one of the conditions set out in Articles 116 and 117 of Directive 2001/83 has been satisfied. In that context, the General Court stated that the Commission may, nevertheless restrict itself to providing solid and persuasive evidence on the basis of which, while not dispelling scientific uncertainty, there can be reasonable doubt as to the declared qualitative and quantitative composition of the medicinal products at issue and as to compliance with one of the obligations connected with the grant of the manufacturing authorisation. It would seem that, in response, the holder should then be allowed to produce evidence of the effectiveness and safety of the medicinal product, but that was not at issue in this case before the CJEU.

Furthermore, Acino holds that contested decisions exceed the Commission's power of discretion.

The CJEU remarks that in so far as it has been established that the obligations connected with the manufacturing process are essential for the purpose of ensuring the quality of medicinal products, the Commission was entitled to conclude that the medicinal products at issue did not have the declared qualitative and quantitative composition and that an obligation pertaining to the grant of manufacturing authorisations for medicinal products had not been complied with. Therefore, the contested decisions are not infringed by any manifest error of assessment and the Commission also clearly did *not* exceed the limits of its discretion.

On *inter alia* these grounds, the Court dismisses the appeal and Acino is ordered to pay to costs.

CONCLUSION

This judgment reveals that when a breach of GMP rules is being established, no evidence of harm due to noncompliance with GMP is required in order to 1) vary the marketing authorisation for the medicinal product at issue and/or 2) to order the medicinal products concerned be withdrawn from the distribution network, including pharmacies. However, the burden of proof of the breach and of its potential harm initially is on the authorities.

This judgment of the CJEU underlines that where subsequently it proves to be impossible to determine with certainty the existence or extent of the alleged risk (for which the burden of proof then shifts to the manufacturer), the precautionary principle justifies the adoption of restrictive measures.

With respect to the withdrawal of the product from the distribution network, the CJEU ruled that non-compliance with GMP may constitute such a potential risk of impairment of the qualitative composition and therefore of detriment to public health, the General Court was justified in holding that the conditions for

[11] C-129/01 Commission v. Denmark, par. 52; C-333/08 Commission v. France [2010], par. 93.

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the application of the article 117(1)(e) of Directive 2001/83/EC were met.

This ruling seems therefore to broaden the margin of appreciation of the Commission when imposing measures following established noncompliance with the rules of GMP.

Pharmaceutical companies should be well aware of the status of GMP compliance in the factories where their medicinal products and/or active ingredients for their medicinal products are being manufactured. Increasing the frequency of GMP audits and mock-inspections at factories at-risk may be worthwhile, considering that *e.g.* a suspended marketing authorisation and a withdrawal of the medicinal products due to noncompliance with GMP will result in more serious economic loss – apart from the possible impact on the quality of the medicinal products concerned.

Furthermore, it should be realised that the CHMP would recommend - upon establishment of GMP noncompliance - that the factory concerned be removed from the list of sites authorised to manufacture the pharmaceutical ingredient or product, this could, in case of dependency on one of the manufacturing factories, even lead to acute or chronic shortages of certain medicinal products. In such case, the marketing authorisation holder should notify the Agency and inform the Agency of the reasons of temporary cessation of placing the medicinal product concerned on the market.[12]

By way of closing remark, it should be noted that it cannot be excluded that the abovementioned way of reasoning will also be followed upon breach of *for instance* the rules on Good Pharmacovigilance Practice ("***GVP***"). Therefore, Qualified Persons should also be well aware of the above case law and assure that all medicinal products are manufactured in a GXP compliant manner: the risk on direct economic loss due to such noncompliance seems to have increased.

[12] For centrally authorised products: article 13(4) and article 14b of Regulation (EC) No 726/2004 (as amended).