US compounding law changes put European system under spotlight

New legislation in the US brings significant changes to the way compounding operations are regulated there. All eyes are now on Europe and, in particular, on Germany where a ruling that is due soon will have important implications for reprocessing and compounding. ***Philippe Bradley*** reports.

The US has now signed into law the Drug Quality and Security Act, which brings significant changes to the way compounding operations are regulated in the US[1]. Attention is now turning back to Europe. Here, observers await a ruling by German courts on whether European requirements to hold a manufacturing authorization should apply to the reprocessing of blockbuster cancer and ophthalmology drugs into ready-to-use syringes by Apozyt, a German manufacturer of compounded medicines.

New US rules on compounding

The DQSA clears the way for enforcement by the Food and Drug Administration of Section 503A of the Federal Food, Drug and Cosmetic Act[2], and creates a voluntary regulatory framework for direct FDA oversight of large interstate compounding manufacturers. The DQSA therefore represents a step towards addressing long-standing concerns over the manufacturing standards being followed by compounding pharmacies in the US.

The implementation of the DQSA follows a fatal meningitis outbreak in October 2012 that killed 64 people and injured hundreds more. The infected patients had received mould-contaminated injections prepared by a large compounding pharmacy, the New England Compounding Center.

Until the passage of the DQSA, US compounding pharmacies such as the NECC operated under what US senators called a "regulatory black hole"[3] that gave compounding pharmacies "relative immunity from standards of safety and effectiveness"[4].

Under current FDA policy, acceptable compounding is that which is conducted in the course of traditional pharmacy practice, ie the compounding of drugs in limited quantities on the basis of individual prescriptions. The FDA does not tolerate compounding practices akin to drug manufacturing, ie large-scale compounding without individual patient prescriptions. By excusing manufacturers of compounded medicines from federal oversight if their activities meet certain conditions, the US system is in some respects similar to the one in Europe.

EU rules and the Apozyt case

In the EU, the Community code on human medicinal products (as embodied by Directive 2001/83/EC) generally prohibits the placing on the market of medicinal products unless they have received prior marketing authorization[5].

Nevertheless, Article 5(1) of Directive 2001/83/EC allows European countries to make an exception for medicinal products supplied in response to a bona fide unsolicited order in order to fulfil special needs, formulated in accordance with the specifications of an authorized healthcare professional and for use by an individual patient under his or her direct personal responsibility.

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This provision has been the subject of a number of rulings by the Court of Justice of the European Union[6].

In particular, the CJEU has held that only purely therapeutic considerations can be taken into consideration when assessing whether there is a "special need" for reliance on an Article 5(1) exemption[7]. A key case is that of Case C-185/10, *Commission v Poland* [2012], where the CJEU held that:

> *(…) the power, which arises from Article 5(1) of Directive 2001/83, to exclude the application of the directive's provisions can be exercised only if that is necessary, taking account of the specific needs of patients.*[8]

Article 5(1) therefore cannot exempt the supply of unlicensed medicinal products having the same active substances, the same dosage and the same form as existing licensed medicinal products[9]. Such supplies, which would not cater to special needs, would require a new marketing authorization.

Two other types of pharmacy preparation are excluded from the EU Community code on medicines for human use:

- medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient – commonly known as the "magistral formula" (per Article 3(1) of Directive 2001/83/EC); and
- medicinal products which are prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question – commonly known as the "officinal formula" (per Article 3(2) of Directive 2001/83/EC).

Because Directive 2001/83/EC does not apply to such preparations, they are regulated in a piecemeal manner at national or regional level. The CJEU, meanwhile, has yet to issue any rulings on the scope or application of these two provisions.

In respect of manufacturing, Directive 2001/83/EC requires that most medicines cannot be manufactured, divided up, packaged or presented unless the manufacturer is specifically licensed by a national authority for that purpose[10]. However, there is an exemption in Article 40(2) of Directive 2001/83/EC in respect of the

> *preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.*[11]

Articles 5(1) and 40 of Directive 2001/83/EC are therefore being relied upon by Apozyt, a German manufacturer of compounded medicines, to avoid having to obtain marketing and manufacturing authorization for its production and sale of medicines for treating wet age-related macular degeneration (AMD). Apozyt purchases vials of Lucentis (ranibizumab), Novartis's wet AMD medication, only to then distribute the contents of those vials into ready-to-use syringes, which are then sold to doctors.

Apozyt also does this with Avastin (bevacizumab), a blockbuster cancer medication marketed by Roche in Europe. Some doctors are prescribing Avastin in small doses (for example, the smaller doses made available by Apozyt in the form of pre-filled syringes) on an off-label basis to treat wet AMD, instead of using approved medicines such as Lucentis and Eylea (aflibercept).

The key questions in the ongoing legal dispute between Novartis and Apozyt are whether Apozyt is required by European law to hold marketing and manufacturing authorizations for the preparation of its pre-filled syringes.

The CJEU held in April 2013 that the selling of pre-filled Avastin syringes did not need a

marketing authorization, so long as certain conditions are met, including that such syringes are ordered by prescribers on the basis of purely therapeutic considerations. Following the same logic, the CJEU held that those conditions could not be satisfied in respect of Lucentis, which was already widely available in appropriate dosages for wet AMD[12].

A remaining question is whether Apozyt requires a manufacturing authorization in order to prepare the syringes, or whether Apozyt's activities fall within the scope of the Article 40(2) exemption described above. The CJEU referred the question back to the national court in Hamburg[13]. It remains to be seen whether the Hamburg courts will recognize that a lack of tight regulation over compounding manufacturers, particularly those preparing pre-filled syringes, is precisely what led to fatal outcomes for patients in the NECC fungal meningitis outbreak in 2012. The decision of the Hamburg Landgericht is expected in the first half of 2014.

France

As proceedings in the *Apozyt* case continue, the head of the French medicines regulatory authority, the ANSM, has warned French senators of the risks associated with the off-label use of Avastin as a Lucentis substitute. Compounding – for example the preparation of ready-to-use syringes by Apozyt – is a key step in the repurposing of Avastin for use instead of Lucentis.

When asked by a French senator why the ANSM was not lending its backing to the off-label use of Avastin for wet AMD[14], Dominique Maraninchi explained that:

> *Firstly, no country in the world authorizes the substitution of Avastin for Lucentis (…) no government has taken that responsibility. Secondly (…) we haven't forbidden it, but nobody has authorized it because they are two different products.*

Professor Maraninchi later added:

> *Thirdly (…), these are radically different products (…) we don't consider them to be equivalent and substitutable; what they are, is another subject. (…) people who do that must take responsibility in case of any accidents; for now, that's the state of play in France and in the rest of the world.*

Despite acknowledging the "great quality" of both Lucentis and Avastin, Professor Maraninchi warned against off-label use of compounded Avastin preparations for economic reasons, saying:

> *When it's cheaper to use a product, it needs to be equivalent and it must not present greater risk. Pharmacovigilance data shows that there is greater toxicity when using Avastin compared to Lucentis. Now, that data is publicly available worldwide. If some people can accept that increased toxicity isn't a problem, I won't comment on that; but we need to be transparent on the subject.*

Professor Maraninchi added that:

> *[W]e must be cautious on substitutions, on the swapping of treatments for purely economic reasons despite increased toxicity.*

Meanwhile, the French government is moving ahead with social security cost-cutting reforms designed to permit pharmacists to substitute cheaper biosimilars when given prescriptions for biologics[15,16]. These will be included in the "*Projet de loi de financement de la Sécurité sociale*" (PLFSS) for 2014, which received its final reading in parliament on 3 December 2013[17].

References

1. *Obama signs US compounding/track & trace bill, Scrip Regulatory Affairs, 28 November 2013*
2. *Section 503A of the FD&C Act has historically contained a range of federal regulatory powers over compounding pharmacies. However, a series of rulings had held that a number of Section 503A's provisions were unconstitutional. Faced with the resulting uncertainty, the FDA has historically not aggressively exercised its Section 503A powers. The DQSA removes the unconstitutional provisions that created uncertainty.*
3. *US Pharmacist, 17 October 2012, http://bit.ly/KIUyxP*
4. *Senator Richard Blumenthal press release, 8 October 2012, http://1.usa.gov/1ktpp1O*
5. *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, Article 6*
6. *See, inter alia, Case C-143/06, Ludwigs-Apotheke München Internationale Apotheke v Juers Pharma Import-Export GmbH [2007]; Case T-301/12, Laboratoires CTRS v Commission [2013]; Case C-535/11, Novartis Pharma GmbH v Apozyt GmbH [2013]; Case C-185/10, Commission v Poland [2012]*
7. *Case C-185/10, Commission v Poland [2012]; Case C-535/11, Novartis Pharma GmbH v Apozyt GmbH [2013]; Case T-301/12, Laboratoires CTRS v Commission [2013]*
8. *Case C-185/10, Commission v Poland [2012], paragraph 33*
9. *Case C-185/10, Commission v Poland [2012], paragraph 37*
10. *Directive 2001/83/EC, Article 40*
11. *Directive 2001/83/EC, Article 40(2)*
12. *Case C-535/11, Novartis v Apozyt*
13. *Novartis v Aposan – case pending before the Hamburg Landgericht, ref 416 HKO 78/11*
14. *Question asked by Senator Gilbert Barbier to Professor Maraninchi during the 19 July 2013 session of the French Senate Commission on the Evaluation and Control of Laws on Finance and Social Security (MECSS). Video available at http://videos.senat.fr/video/videos/2013/video18749.html (question at 14:10; answer at 30:41). The full transcript of that part of the discussion reads as follows: "Sur Avastin, sur Avastin versus Lucentis, je voudrais simplement dire une chose. Premièrement, il n'y a aucun pays au monde qui autorise la substitution de l'Avastin au Lucentis. Aucun pays au monde, enfin en tant de responsable, c'est-à-dire aucune agence ni aucun gouvernement n'a pris cette responsabilité. Deuxièmement – étant exposé, excusez-moi, je suis obligé d'avoir fait le tour de tous mes collègues de toutes les agences – on ne l'a pas interdit mais personne ne l'a autorisé puisque, par nature, c'est deux produits différents. Deuxièmement, nous avons des données de pharmacovigilance, puisque il faut savoir ce qu'on veut, faut que ce soit moins cher et moins dangereux [… note de transc. : inaudible]. Là, on a parlé de génériques, quand c'est moins cher, il faut que ce soit équivalent et que ce ne soit pas plus risqué. Donc, les données de pharmacovigilance, montrent qu'il y a plus de toxicité lorsqu'on utilise l'Avastin que le Lucentis. Bon, elles sont rendues publiques à l'échelle mondiale, maintenant, bon, certains peuvent accepter que ce n'est pas grave si c'est plus toxique parce que c'est moins cher, moi je ne ferais pas de commentaires, mais il faut être transparent sur ce type de sujet. Troisième et dernière remarque là-dessus, c'est que ce sont des produits radicalement différents. C'est comme si on comparait l'aspirine et le paracétamol. Les deux principes actifs sont intéressants, diminuent le mal de tête, ont des effets inflammatoires, mais une molécule mutée sur un Fab, c'est un petit morceau, n'a rien à voir et ne touche pas la même partie du principe actif qui est le VEGF. Mais pourquoi pas, il arrive qu'on prenne, soit du paracétamol soit de [… note de transc. : inaudible] le mal de tête, par contre on ne les considère pas comme équivalentes et substituables ; ce que c'est, c'est un autre sujet. Voilà, donc, il y a une étude clinique qui a été faite en France, il y a une méta-analyse, donc ce n'est pas interdit et par contre les personnes qui le font doivent assumer leur responsabilité en cas d'accident, pour l'instant c'est ça la situation en France et partout dans le monde. Je voudrais rappeler que ça a été très popularisé aux États-Unis puisque les patients paient de leurs poches et que, pour eux, ça change beaucoup de choses. Mais il n'est pas, il est anormal effectivement que la collectivité paie beaucoup d'argent pour le Lucentis, mais soyons prudents sur les substitutions, sur les changements de traitements pour des raisons purement économiques s'il y a plus de toxicité. En tous les cas, ce sont des produits différents et tous de grande qualité. Vous aurez à arbitrer prochainement les substitutions possibles sur les biosimilaires qui vont arriver de façon très nombreuse."*
15. *Biosimilar substitution gets the all-clear in France, Scrip Regulatory Affairs, 20 December 2013*
16. *French give go-ahead to biosimilar substitution, Scrip Regulatory Affairs, 11 December 2013*
17. *Article 47 of the definitive text of the "Projet de loi de financement de la sécurité sociale pour 2014", TA no 250 (copy – in French – is available at www.assemblee-nationale.fr/14/ta/ta0250.asp)*

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