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Bioequivalence Criteria for Transdermal Fentanyl Generics

Do These Need a Relook?

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Abstract

With the increasing appearance of transdermal fentanyl generics since 2004 when patent protection of the reference Duragesic® expired, opportunities to switch between different generics have arisen. Transdermal fentanyl is subject to bioequivalence regulation because only approximately 92% of the dose is absorbed as a result of the need to maintain a diffusion gradient from plaster to skin. Considering the high potency of fentanyl and the potential dangerous adverse effects of full μ opioid receptor agonists, we assessed evidence suggesting a revision of the confidence limits of bioequivalence of 80–125%. A few cases have been reported where a prescribed ascension in transdermal fentanyl dosing triggered respiratory depression. Values of concentration that produce a 50% effective response for decreasing the ventilatory volume lie within the plasma concentration range of 1.4–2.5 ng/mL during transdermal fentanyl analgesia. However, an exchange of the reference with a generic with higher bioavailability would trigger respiratory depression only in extreme situations and is clinically supported by only a single case report. Experimental or clinical evidence is required to provide the necessary database for final judgement of bioequivalent limits of fentanyl generics. At present, the evidence is not sufficient to advise other bioequivalence criteria than those previously applied to transdermal fentanyl.

One-fifth of adults in Europe have moderate or severe chronic pain,[1] and successful analgesia is still one of the main healthcare issues. Potent opioids such as morphine, hydromorphone, oxycodone, piritramide, pethidine (meperidine) or the members of the fentanyl group are the basis of step three of the WHO ladder for (cancer) pain treatment. However, adverse effects limit the use of opioids.[2] Respiratory depression, as the most dangerous adverse effect, has an incidence of 0.3% when using naloxone requirement and 17% when using oxygen desaturation as the indicator,[3] and can end fatally even under controlled conditions.[4-10]

Opioid therapy must therefore maintain a balance between adequate pain relief and an acceptably low degree of adverse effects. Rapid changes in the opioid maintenance dose may jeopardize this balance. The more potent the opioid, the greater may be the clinical consequences of changes in absolute doses. With a 100 times greater potency than morphine,[11,12] the μ receptor agonist fentanyl is the most potent opioid routinely administered during chronic pain therapy. Although until the 1980s fentanyl was used mainly during anaesthesia, controlled-release preparations (patches) of fentanyl have been increasingly used since the early 1990s for the treatment of chronic severe pain.[13] Particularly in outpatient settings the development of transdermal therapeutic systems is perceived as an achievement, considering its non-invasive administration and the long dosing interval of usually 3 days. Fentanyl has become one of the most often prescribed strong opioid analgesics, with 15.1 million defined daily doses (DDDs) of transdermal fentanyl prescribed in 2007 in the UK, compared with 35.34 million DDDs of orally and rectally administered morphine.[14] Respective data from Germany are 53.5 million DDDs of transdermal fentanyl in 2007, even exceeding morphine prescriptions of 17.5 million DDDs.[15]

With the increasing appearance of transdermal fentanyl generics since 2004 when patent protection of Duragesic® (Ortho-McNeil-Janssen-Pharmaceuticals, Raritan, NJ, USA) expired, opportunities to switch between different brands have increased. This raises the problem of bioequivalence and its

consequences for the patients' safety. Considering the high potency of fentanyl and the potential dangerous adverse effects of full agonists at μ opioid receptors, we analysed whether the accepted limits of bioequivalence for transdermal fentanyl 80–125% for main pharmacokinetic parameters provide sufficient therapeutic safety. Because the problem has not been directly addressed in a study, available information about toxicity of transdermal fentanyl and concentration dependency of fentanyl effects had to be applied.

1. Evidence for Inadequate Clinical Effects Associated with Transdermal Fentanyl

A PubMed search was carried out during September and October 2008 for reported toxicity of transdermal fentanyl using the following key words: 'transdermal fentanyl', 'respiratory depression', 'generics', 'bioequivalence', 'toxicity' and 'overdosing'. Mostly intentional or accidental intoxications were found, which are not subject to bioequivalence contemplations.[16-18] Primary causes of unwanted inadequate clinical effects observed with routine prescriptions are improper use by the patient or careless prescription by clinicians (table I).

A 44-year-old woman with metastatic breast cancer needed hospital admission after increasing her transdermal fentanyl dose from 175 μg/h to 225 μg/h.[19] Until that incident, she had been tolerating 175 μg/h well for 16 days. Her condition deteriorated gradually during the 5 days following her change in dosage until she was found to need hospice admission. Known concomitant medications were diazepam 2 mg at night, and morphine as breakthrough medication. After admission she recovered well with titrated intravenous naloxone. Her pain medication was converted to a subcutaneous infusion of fentanyl 200 μg/h, which kept her pain free until she died 3 days later of her underlying disease. Similarly, an 80-year-old woman with metastatic pulmonary cancer developed respiratory depression 1 week after increasing her transdermal fentanyl dose from 25 μg/h to 50 μg/h.[19] She had initially been receiving 25 μg/h without any sign of respiratory depression. She recovered quickly after naloxone administration, and her opioid medication was switched to a subcutaneous diamorphine infusion of 15 mg/24 h. She did not show any further signs of respiratory depression. However, she died 1 week later from her underlying condition.

Concomitant diseases seem to increase the risk of adverse effects of transdermal fentanyl. For example, a patient became hospitalized with respiratory depression after developing fever associated with signs of chest infection.[19] The fentanyl dose of 25 μg/h had not been changed. A mechanistic explanation of the relative fentanyl overdosing is vasodilatation as a result of fever, leading to increased transdermal absorption of fentanyl. In addition, toxicity as a result of the effect of a raised body temperature or external heat, applied directly or indirectly to the site of application, is documented by several case reports.[20-22] The manufacturer of Duragesic® warns that a rise in the body temperature to 40°C can lead to an increase in fentanyl plasma concentration by approximately one-third.[23]

2. Concentration Dependency of Fentanyl Effects

The reported cases of opioid toxicity after increasing the fentanyl dose[19] hint at a concentration dependency of the effects of fentanyl within therapeutically administered dosages. This is also indicated by the availability of different strengths of fentanyl patches. Numerical information about the dose or concentration dependency of fentanyl effects has been gathered repeatedly. By assessing in eight healthy young subjects plateau plasma concentrations of 0.1, 0.16, 0.25, 0.4, 0.63, 1, 1.6, 2.5, 4, 6.3 and 10 ng/mL, achieved by computerized infusion with STANPUMP[24] (freely available from Dr Steven L. Shafer at http://anesthesia.stanford.edu/pkpd), respiratory parameters such as ventilatory volumes, respiratory rate, and arterial oxygen (PaO_2) and carbon dioxide partial pressures ($PaCO_2$) changed concentration as expected.[25] Calculated values of concentration that produce a 50% effective response (EC_{50}) ranged from 3.5 ± 1.4 ng/mL for respiratory rate to 6.1 ± 1.4 ng/mL for ventilatory volumes.[25] Concentration-dependent respiratory fentanyl effects were again modelled in 24 healthy subjects having received fentanyl 0.075–0.5 mg/70 kg bodyweight intravenously.[26] By employing a population pharmacokinetic-pharmacodynamic modelling approach, an EC_{50} of 1.14 ng/mL for the decrease in ventilatory volume was obtained. Central nervous effects of fentanyl were also concentration dependent by applying pharmacokinetic-pharmacodynamic modelling to fentanyl plasma concentrations and EEG effects obtained in six healthy young men. They had received an intravenous infusion of fentanyl 150 μg/min until a specific level of EEG depression (delta waves) occurred.[27] The EC_{50} for maximal EEG slowing was calculated to be 6.9 ± 1.5 ng/mL.[27] Pain relief by 50% was seen at concentrations of 1.35 and 1.9 ng/mL for pain-related cortical potentials and subjective pain intensity ratings after dental electrical stimulation in healthy subjects at fentanyl concentrations of 0, 0.75, 1.5 and 3 ng/mL.[28]

For clinical analgesia, such comparatively precise values obtained in healthy subjects under controlled conditions are

Table I. Reported cases of accidental opioid toxicity associated with transdermal (TD) fentanyl

Population	Fentanyl dose	Blood concentration (ng/mL)	Co-medication	Effects	Action	Outcome	Reference
44-year-old woman with T12 paraplegia from metastatic breast carcinoma	175 μg/h TD for 16 days; dose was increased by 50–225 μg/h for 3 days	NA	Morphine 130 mg solution 24 h prior to admission	After 3 days drowsiness, confusion, not cyanosed, hospitalization 2 days later; in hospital respiratory rate <6/min, SaO_2 of 56%	Titrated dose of naloxone IV, further infusion for 24 h; later she was started on fentanyl subcutaneously (200 μg/h)	Died 3 days after admission, likely related to underlying disease; SaO_2 stayed normal throughout her last days	19
70-year-old man with metastatic colonic carcinoma	In the morning before admission he was switched to fentanyl 25 μ/h TD	NA	Controlled-release morphine 50 mg 12-hourly	Pinpoint pupils, central cyanosis, respiratory rate <6/min	Several doses of naloxone IV	Continued to deteriorate and died without further episodes of respiratory repression, most likely related to underlying disease	19
65-year-old man with lung metastases from a renal carcinoma	25 μg/h TD for 3 mo	NA	Temazepam 20 mg at night	Glasgow coma scale of 5, respiratory rate of 6/min, SaO_2 of 94%; additionally, pyrexia and signs of chest infection	Titrated naloxone 350 μg IV, naloxone infusion for 30 h	Since admission, comfortable with paracetamol (acetaminophen) 1 g/day; died 2 mo later, most likely related to underlying disease	19
80-year-old woman with pulmonary and spinal metastases from a squamous cell carcinoma of the lung	25 μg/h TD; dose was increased to 50 μg/h 1 wk before admission	NA	None	Glasgow coma scale of 6, respiratory rate of 7/min, pinpoint pupils, SaO_2 of 93%, marked cutaneous vasodilatation	Titrated naloxone 120 μg IV	Was started on subcutaneous diamorphine, pain free and no further episodes of respiratory depression, died 1 wk after admission, most likely related to underlying disease	19
53-year-old man	Family noted that dose had been increased recently	38 (post-mortem)	Not described	Found dead as a result of drug poisoning with fentanyl TD patch on upper chest		Fatal	17

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Table I. Contd

Population	Fentanyl dose	Blood concentration (ng/mL)	Co-medication	Effects	Action	Outcome	Reference
37-year-old woman with multiple medical problems and excessive prescription medicine use in the past		36 (post-mortem)	Other drugs detected were diazepam, diphenhydramine, nordiazepam, promethazine, citalopram	Fatal fentanyl poisoning, after three patches had been used in 3 days		Fatal	17
44-year-old Latino male with painful HIV neuropathy	75 μg/h TD every 3 days	NA	Oxycodone with paracetamol for breakthrough pain	During a summer camp with outdoor activities he became very tired and could not be woken. He was taken to hospital where pinpoint pupils were assessed	Naloxone IV firstly, later naloxone infusion	After naloxone IV he showed signs of opioid withdrawal; later he returned to a stuporous state, which disappeared after removing the patch	20

IV = intravenous; **NA** = not available; **SaO_2** = oxygen saturation.

not available. The minimum effective analgesic concentrations in opioid-naïve patients range between 0.3 and 1.5 ng/mL. The frequency of adverse effects starts to increase significantly beyond plasma concentrations of 2 ng/mL.[29] However, plasma concentrations up to 6.75 ng/mL have been tolerated without life-threatening adverse effects.[30] Even a dose of 178 ng/mL has been survived in a single case without the patient showing any signs of toxicity.[31] Nevertheless, the therapeutic range of fentanyl is not narrowly defined and varies widely among patients. Modulating factors of the clinically desired fentanyl concentrations include pain intensity, μ opioid receptor regulation, enhancing or inhibiting mechanisms of the nociceptive system, and psychological factors.[29,32]

3. Pharmacokinetics and Bioavailability of Transdermal Fentanyl

Fentanyl (*N*-phenyl-*N*-[1-2-phenyl-ethyl-4-piperidyl]propanamide) is a highly lipid-soluble drug with a low molecular weight, making it suitable for transdermal delivery.[32] The currently available transdermal fentanyl patches consist of a matrix in which fentanyl-containing dipropylene glycol droplets are dispersed, thereby minimizing the risk of accidental drug leakage and intentional intravenous abuse when compared with the original patches with a reservoir design.[33,34] Transdermal fentanyl patches are available delivering 12.5, 25, 50, 75 and 100 μg/h constantly over a period of 72 hours. The release of fentanyl is a rate-controlled process, whereas the amount delivered is proportional to the surface of the absorption area.[23,35] The concentration gradient between the transdermal therapeutic system (high concentration) and the skin (low concentration) necessary to maintain diffusion is provided by a higher loading of the patch system than the released portion. This explains why transdermal patch systems reach a bioavailability of only 92%.[36] The drug is absorbed by the skin and forms a depot in the upper layers of skin, which constantly releases fentanyl into the bloodstream.[12] Although low fentanyl concentrations (approximately 0.2 ng/mL) can be detected after 1–2 hours,[35] the onset of the full analgesic effect can vary between 12 and 24 hours.[23]

Mean peak plasma concentrations after transdermal delivery of 12.5, 25, 50, 75 and 100 μg/h are proportional to the patch's delivery rate, namely 0.3, 0.6, 1.4, 1.7 and 2.5 ng/mL, respectively. After repeated patch administration for several 72-hour periods these plasma concentrations are maintained, achieving a steady state.[23] As a highly lipophilic substance, fentanyl quickly equilibrates between plasma and CNS with

a first-order transfer half-life of 6.6 minutes for effects on EEG,[37] and with 16.4 minutes calculated slightly longer for respiratory effects.[26] Both numerical values are small enough to consider fentanyl equilibrated under conditions of transdermal application, which allows simulating respiratory effects as those of major concern for fentanyl safety.

The relative bioavailability of different matrix fentanyl plasters has not yet been published. The only scientific reports compared a classical reservoir with a more recently introduced matrix formulation, and found bioequivalence within the range of 80–125%. Specifically, in 20 healthy men the point estimate (90% CI) of area under the (plasma/serum) concentration-time curve from time zero to infinity (AUC_∞) was 95.4% (87.2, 104.3), and that of maximum concentration (C_{max}) was 94% (83.1–106.3%).[33] In a similar study, in 24 healthy men aged 23–45 years, point estimates (95% CI) of AUC_∞ of 105.3% (99.3, 111.6) and of C_{max} of 111.4% (100.4, 123.6) were calculated.[38] This agrees with the bioavailability differences of various drugs as generally observed by the US FDA of ±3.25% for AUC_∞ and ±4.29% for C_{max}[39] or ±3.12% for AUC_∞ and ±4.5% for C_{max}.[40]

From the sparse published transdermal fentanyl bioequivalence data,[38] intrasubject coefficients of variation of 11.82% for AUC_∞ and 21.2% for C_{max} can be calculated. With a statistical power of 80%, the resulting maximum allowed deviations to show bioequivalence in 24 subjects are 13.8% (AUC) and 7.1% (C_{max}). This may serve as a basis for simulations of respiratory depressive effects in the case of switches between generics at the opposite limits of the accepted bioequivalence range. Specifically, the effects of fentanyl on the respiratory volume follow a simple sigmoid model[26] (equation 1):

$$E = E_0 \times \left(1 - \frac{\alpha \bullet C_e^n}{C_e^n + EC_{50}^n}\right) \qquad \text{(Eq. 1)}$$

where E denotes the actual ventilatory volume, E_0 the baseline ventilatory volume that has a value of 20.2 L/min,[26] C_e the actual fentanyl concentration at effect site, EC_{50} the fentanyl concentration at half the maximum change in respiratory volume from baseline with a value of 1.14 ng/mL, n is the shape factor of the effect versus concentration relationship with a value of 2.68,[26] and α is the intrinsic activity of fentanyl theoretically varying between 0 and 1, calculated as 0.91.[26] The resulting changes of the ventilatory volume follow a sigmoid course along increasing fentanyl plasma concentrations (figure 1). These can be considered as identical to the actual value of C_e because of the short equilibration time with the CNS and the slow changes, compared with intravenous injection, in fentanyl plasma concentrations following transdermal application. When the reference formulation is exchanged with a generic brand delivering 1.14 times higher fentanyl concentrations, changes in respiratory rate are largest during the almost linear concentration versus effect relationship between 20% and 80% of the maximum effect, i.e. between fentanyl 0.85 and 2.6 ng/mL (figure 1c). This encompasses the range of fentanyl plasma concentrations observed in 38 cancer patients after 2 weeks of treatment with transdermal fentanyl 100 μg/h achieving plasma concentrations of 2.5 ± 1.2 ng/mL.[12,23] The change by a factor of 1.14 in fentanyl dosing is lower than the increase in fentanyl dosing from 175 to 225 μg/h reportedly followed by respiratory depression in a single case.[19] However, changes in fentanyl concentration from a fentanyl brand of 87.7% bioavailability to one of 114% relative bioavailability, both under the assumption by the physician that 100% is administered, may result in differences in ventilation (figure 1b and 1d) with a maximum relative decrease in ventilatory volume by almost one-third. The increase in fentanyl exposure would be by 1.3 and thus similar to that reportedly followed by respiratory adverse effects.[19] In a worst-case scenario, bioavailability could be shown in 200 subjects, which would exceed the largest sample size of 127 observed by the FDA in such studies between 1996 and 2005.[40] Because of this larger sample size, the highest possible point estimate compatible with bioequivalence in the ranges of 80–125% would be 121% for AUC and 117% for C_{max}, with more pronounced consequences than above.

The pharmacokinetics of fentanyl have been repeatedly assessed by (population) modelling approaches.[24,41,42] Its terminal elimination half-life estimates range from about 1.5 to 6 hours, and 15 hours in geriatric patients.[43] However, with transdermal delivery fentanyl disappears from plasma at a much longer apparent half-life of 17.0 ± 2.3 hours after administration,[36] because the absorption continues from the skin reservoir not removed with plaster removal. In addition, the effects of fentanyl are subject to a context sensitivity, i.e. their disappearance also depends on the duration of fentanyl administration.[44] Special populations may be subject to modified pharmacokinetics and require dosing adaptations. Fentanyl is mainly metabolised in the liver via cytochrome P450 (CYP) 3A4/5[45] into the non-toxic norfentanyl without relevant pharmacodynamic activity. CYP3A4/5 metabolism is prone to drug interactions as a result of enzyme inhibition or induction[46] (for inductors and inhibitors, see also http://medicine.iupui.edu/flockhart/table.htm). In contrast, fentanyl pharmacokinetics may be affected only to a minor degree by liver functional loss and not differ significantly between patients with cirrhosis (elimination half-life 304 min, total body clearance 11.3 mL/min/kg and volume of distribution 4.41 L/kg) and

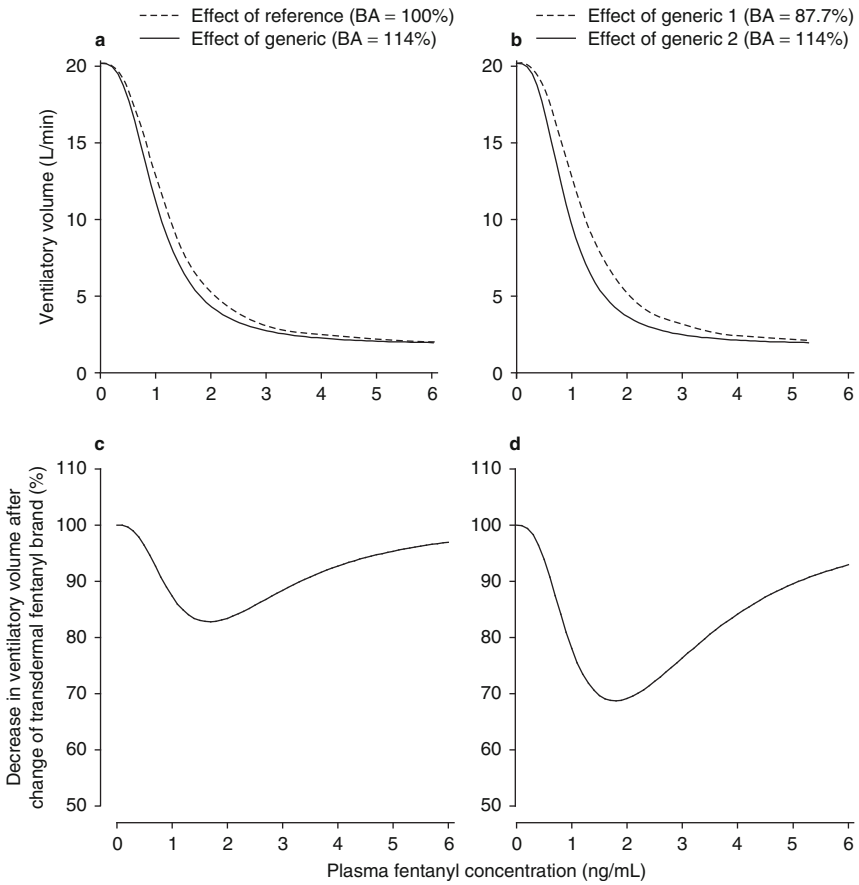

Fig. 1. (**a, b**) Simulations of changes in ventilatory volume along raising fentanyl plasma concentrations when one brand of transdermal fentanyl is exchanged by another under the assumption of the same dosage but in fact delivering a larger dose within bioequivalence confidence limits. (**c, d**) Percentage difference between respiratory effects when two different brands of different absolute bioavailability (BA) are administered. Figures (**a**) and (**c**): when the reference formulation with BA = 100% is exchanged by a generic with BA = 114%; and figures (**b**) and (**d**): when one generic with BA = 87.7% is exchanged with another generic with BA = 114%. Simulations with the numerical values from[26] obtained in healthy subjects.

healthy controls (elimination half-life 263 min, total body clearance 10.8 mL/min/kg and volume of distribution 3.81 L/kg).[47] However, fentanyl clearance decreases proportionally with increasing blood urea nitrogen in renal failure.[48] Elderly patients (aged >60 years) need to be administered transdermal fentanyl patches carefully, as their dose requirement can be lowered as a result of the age-related decrease in clearance prolonging the elimination half-life to up to 15 hours.[49]

4. Discussion

Bioavailability issues with fentanyl generics may theoretically cause insufficient pain relief on the one hand, and toxicity on the other hand. Systematic reports of pain therapy failure after changing the fentanyl generic are not available. The same applies for adverse effects restricted to reports of single cases or small case series (table I). They are often not supported by fentanyl blood concentration values. In fatal cases, post-mortem fentanyl concentrations may substantially vary between individuals because of a considerable redistribution of fentanyl after death, which results in significant anatomical site-to-site variation of drug concentrations.[50] This makes identification of a particular fentanyl plasma concentration obtained post-mortem as the cause of death difficult or impossible.

The sparseness of data might be for several reasons. First, generics of transdermal fentanyl preparations did not exist until 2004, when patent protection of Duragesic® ran out, impeding long-term experience at this point. Second, not all incidents have been published or might have been recognised as opioid intoxications, because fentanyl patches are often administered to terminally ill patients and therefore deaths might have been attributed to metastatic cancer rather than to analgesic treatment. On the other hand, fentanyl may have been causally connected falsely with death when the terminally ill patient had died of the underlying disease. Lastly, the sparseness of toxicity

reports of transdermal fentanyl may be taken as a hint of the satisfactory safety of transdermal fentanyl under the current regulatory demands.

Nevertheless, evidence from single cases suggests that respiratory depression can be triggered by a dose increase of approximately 30%.[19] With the current generics that follow a narrower confidence interval (table II), it is unlikely that such a dose increase will be obtained even when a generic brand with low bioavailability is exchanged for one with high bioavailability, relative to the reference product. Although simulations showed a danger of respiratory depression in this setting, this should not be overestimated. Simulations had to be based on data obtained in subjects not regularly taking opioids, which limits their predictive value for the clinical situation where the use of fentanyl plasters is restricted to opioid-tolerant patients under chronic opioid pain therapy.

With cases of toxicity of transdermal fentanyl during regular pain therapy being very rare, transdermal fentanyl cannot be labelled as unsafe. On the other hand, the worst consequence of too low fentanyl dosing because of brand changes would be inadequate analgesia. This would probably be noted and corrected quickly and does not bear severe consequences such as with sub-therapeutic drug concentrations of antiepileptics or antiretrovirals. Therefore, fentanyl is not considered a narrow therapeutic index drug in current regulatory practice. Canada lists ciclosporin, digoxin, flecainide, lithium, phenytoin, sirolimus, tacrolimus, theophylline and warfarin as narrow therapeutic index drugs.[51] Denmark lists aminophylline/theophylline, lithium, thyroxine, warfarin, antiepileptics apart from benzodiazepines, immunosuppressants, antiarrhythmics, centrally acting anorectics and tricyclic antidepressants as narrow therapeutic index drugs.[52] The present literature survey and simulations do not change this view. However, another approach to reduce the risk of fentanyl overdose as a result of a generics switch has been adopted recently by the German Federal Institute for Drugs and Medical Devices. It restricted the exchangeability of pain relief patches to preparations having equal delivery rates, application intervals and total amount of drug.[53]

Taken together, transdermal fentanyl is subject to bioequivalence regulation because the whole dose cannot be absorbed because of the need to maintain a diffusion gradient from plaster to skin. A bioequivalence limit of 80–125% is currently required for transdermal fentanyl generics. Limited evidence of major fentanyl toxicity is available from just a few single cases or small case series. A narrower confidence limit is therefore not an immediate clinical need. Systematic experimental or clinical evidence is required to provide the necessary database for final judgement of bioequivalent limits of fentanyl generics. This and inclusion of toxicity of upcoming transdermal fentanyl generics into pharmacovigilance programmes will probably provide enough safety in light of the increasing appearance of those formulations on the market.

Table II. Relative bioavailability parameters of German generics of transdermal fentanyl patches, compared with the original reference

Brand name	Dose			Test/reference ratio (%)	Drug delivery system	Manufacturer	Approval year
	release rate (μg/h)	total amount of fentanyl (mg)	area (cm^2)				
Durogesic® SMAT	100	16.5	42.5	Reference product	Matrix	Janssen-Cilag	1995
Fentadolon®	100	19.2	60	AUC: 116.3 C_{max}: 114.5	Matrix	mibe GmbH	2006
Fentanyl esparma®	100	19.2	60	AUC: 116.3 C_{max}: 114.5	Matrix	esparma GmbH	2006
Fentanyl Heumann®	100	19.2	60	AUC: 116.3 C_{max}: 114.5	Matrix	Heumann Pharma	2007
Fentanyl Krewel®	100	19.2	60	AUC: 116.3 C_{max}: 114.5	Matrix	Krewel Meuselbach GmbH	2006
Fentanyl ratiopharm®	100	16.5	30	AUC: 100.56 C_{max}: 96.91	Matrix	Ratiopharm GmbH	2005
Fentanyl Sandoz®	100	23.12	42	AUC: 107.5 C_{max}: 105.3	Matrix	Sandoz Pharmaceuticals GmbH	2005

AUC = area under the (plasma/serum) concentration-time curve; **C_{max}** = maximum concentration.

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