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An update on the first decade of the European centralized procedure: how many innovative drugs?

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What is already known about this subject

- We recently proposed an algorithm to assess the degree of therapeutic innovation of new therapeutic agents. It was based on the disease seriousness, the availability of previous treatments and the extent of the therapeutic effect, and was applied to all therapeutic agents approved by the EMEA in the period 1995–2003.
- A low percentage (32%) of important therapeutic innovation was found. This figure may be an underestimate of the actual level of innovation, because common biotechnological products, such as recombinant human insulins, must follow the centralized procedure.

What this study adds

- Details for each agent, focusing on the comparison of the degree of therapeutic innovation between biotechnological and nonbiotechnological therapeutic agents approved by EMEA during the its first decade of activity (1995–2004). The underlying hypothesis was that the latter have a higher degree of innovation because they followed the centralized procedure on the assumption that they are innovative.
- The percentage of important therapeutic innovation was low not only for biotechnological products (25%), as expected because they include many already known products such as insulins, but also for nonbiotechnological therapeutic agents (29%).

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Aims
In a previous paper, we proposed an algorithm to assess the degree of therapeutic innovation of the agents approved by the European centralized procedure, which must be followed by biotechnological products and is optional for drugs claimed as innovative. A low overall degree of therapeutic innovation (about 30%) was found. This figure may be an underestimate of the actual level of innovation, because common biotechnological products, such as recombinant human insulins, must follow this procedure. To test the hypothesis that therapeutic innovation prevails among nonbiotechnological products, we evaluated separately the degree of therapeutic innovation of biotechnological *vs.* nonbiotechnological agents in the first decade of European Medicines Agency activity, also studying a possible time trend.

Methods
We assessed, for each drug: (i) the seriousness of the target disease, (ii) the availability of previous treatments, and (iii) the extent of therapeutic effect according to the previously proposed algorithm.

Results
Our analysis considered 251 medicinal products corresponding to 198 active substances, classified according to four main areas as therapeutic agents (88.9%), diagnostics (5.5%), vaccines (5.1%) and life-style drugs (0.5%). Among all therapeutic agents, 49 out of 176 agents (28%) were classified as having an important degree of therapeutic innovation. Fifteen out of 60 biotechnological therapeutic agents were considered important therapeutic innovations (25%), whereas this figure was 29% for nonbiotechnological agents.

Conclusions
Among active substances claimed as innovative by the manufacturers, only a minority deserve this definition according to our algorithm.

Introduction

With the Council Regulation (EEC) no. 2309/93 of 22 July 1993 [1], the European Medicines Agency (EMEA) was established and the European Community was provided with procedures for the authorization, supervision and pharmacovigilance of medicinal products for human and veterinary use. Part A of the Regulation annex stated that all marketing authorization applications of medicinal products for human and veterinary use deriving from biotechnology processes (e.g. recombinant DNA technology, controlled expression of genes coding for biologically active proteins, hybridoma and monoclonal antibody methods) must follow the so-called centralized procedure. On the other hand, other nonbiotechnological drugs, if considered potentially innovative (e.g. products administered by means of new delivery systems, products based on radio-isotopes, or products containing a new active substance), may access, at the discretion of the applicant, the EMEA centralized procedure. The latter item introduces a key aspect, i.e. the concept of innovation in pharmacotherapy, which is a matter of debate [2–4].

The aim of this study was to test the hypothesis that therapeutic innovation prevails among nonbiotechnological products, separately evaluating the degree of therapeutic innovation of biotechnological *vs.* nonbiotechnological agents in the first decade of EMEA activity, also studying a possible time trend.

Methods

A preliminary description of the method used to analyse part of the EMEA-approved drugs has already been published [5]. The algorithm described was slightly modified to acknowledge innovation provided by medicinal products with improved kinetics, as suggested by Aronson [6]. In order to have a complete picture of the first phase of the activity of the EMEA, we retrieved the full list of medicinal products authorized from January 1995 through July 2004.

The degree of therapeutic innovation was assessed by evaluating: (i) the seriousness of the disease, (ii) the availability of previous treatments, and (iii) the extent of the therapeutic effect, according to the algorithm presented in Figure 1. For details, refer to the previous paper [5].

The combination of these scores (each therapeutic agent considered in this study received three scores for disease seriousness, availability of previous treatments, and therapeutic effect) yielded the following overall scores of therapeutic innovation: A, important; B, moderate; and C, modest (see Figure 1).

The scores were independently assigned by D.M., F.D.P. and N.Mo. and possible disagreements were resolved by a consensus meeting among all authors, who approved the final scores.

Results

Between January 1995 and July 2004, the EMEA approved 277 medicinal products corresponding to 209 active substances. In the same period, 26 products (six biotechnological and 20 nonbiotechnological products) were withdrawn from the European market and were excluded from the analysis. [Some of these products were voluntarily withdrawn by the manufacturers for commercial reasons, but their active substances are still available in other EMEA-approved products (desloratadine, reteplase, valdecoxib, imiquimod, olanzapine). In other cases, the withdrawal was due to serious public health concern. In particular, trovafloxacin (and its prodrug alatrofloxacin) was withdrawn in 2001 (the drug was authorized in 1998) due to severe hepatotoxicity, involving necrosis and organ failure leading, in a few cases, to transplantation and/or death [7]. Levacetylmethadol, authorized in 1997 for the maintenance treatment of opiate addiction, was followed by spontaneous reports of torsade de pointes soon after its introduction. In 2001, the EMEA reassessed its risk/benefit profile and recommended its withdrawal from the European market (see public statement EMEA/8776/01). Another example is dofetilide, a pure class III antiarrhythmic agent, which was voluntary withdrawn by the manufacturer in 2004, also in the light of the availability of alternatives.] Therefore, our analysis considered 251 medicinal products corresponding to 198 active substances.

Table 1 shows the distribution of the approved products according to the four main areas: therapeutic agents (88.9%), diagnostics (5.5%), vaccines (5.1%) and life-style drugs (0.5%). Overall, 72 active substances (36.4%) were obtained via biotechnological processes.

Figure 2 shows the distribution of the products according to the Anatomic Therapeutic Chemical (ATC) classification (first level) and their source. Most of the products approved in the period under scrutiny belong to the ATC groups J (anti-infectives for systemic use), L (antineoplastic and immunomodulating agents), A (alimentary tract and metabolism) and B (blood and blood-forming organs). Biotechnological products prevailed among ATC groups A, B and L, whereas they were a minority in groups M, J, S and G and were absent in groups C, N and R.

Table 2 shows the distribution of the degree of therapeutic innovation according to biotechnological source and disease seriousness. As far as the latter is concerned,

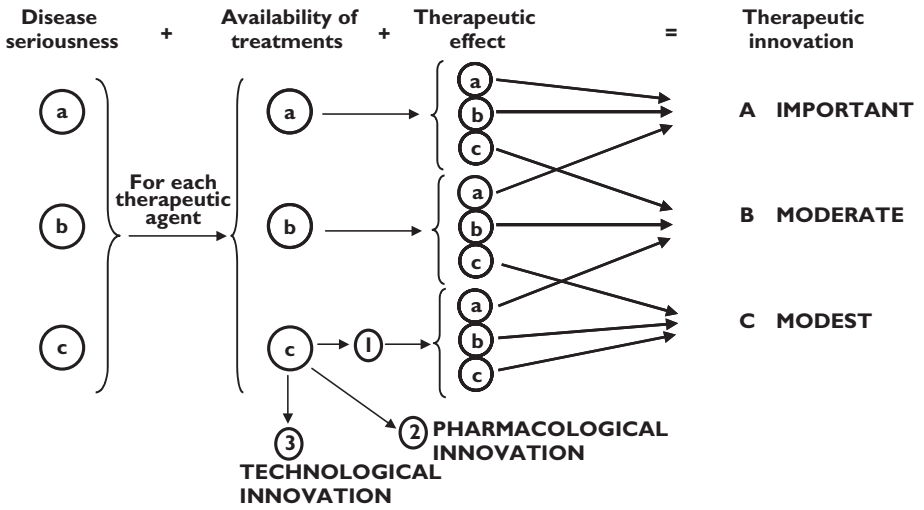


Figure 1

Algorithm used to assign the overall score for innovation. Disease seriousness: a, drugs for serious diseases; b, drugs for risk factors for serious diseases; c, drugs for nonserious diseases. Availability of treatments: a, drugs for diseases without recognized standard treatment; b, drugs for diseases where subsets of patients are less responsive to marketed drugs and/or other medical interventions; c, drugs for diseases responsive to marketed drugs or other medical interventions (c_1, more effective or safer or with a better kinetics than existing drugs; c_2, mere pharmacological innovation, i.e. drugs with a new mechanism of action; c_3, mere technological innovation, i.e. a new chemical or biotechnological product with a therapeutic role similar to already existing ones). Therapeutic effect: a, major benefit on clinical end-points (e.g. increased survival rate and/or quality of life) or validated surrogate end-points; b, partial benefit on the disease (on clinical or validated surrogate end-points) or limited evidence of a major benefit (inconsistent results); c, minor or temporary benefit on some aspects of the disease (e.g. only partial symptomatic relief of a serious disease)

Table 1

Distribution of the European Medicines Agency-approved medicinal products according to main areas (number of active substances in parentheses)

Area	No. of products	Derived via biotechnological processes	Derived via nonbiotechnological processes
Therapeutic agents	225 (176)	74 (60)	151 (116)
Diagnostics	13 (11)	4 (4)	9 (7)
Vaccines	12 (10)	10 (8)	2 (2)
Life-style drugs	1 (1)	0 (0)	1 (1)
Total	251 (198)	88 (72)	163 (126)

80% of the active substances received a score 'a', serious disease, 9% a score 'b', risk factors for serious disease, and 11% 'c', nonserious disease. Concerning the overall degree of therapeutic innovation among the therapeutic agents, 49 out of 176 agents (28%) were considered important therapeutic innovations (A), while over 50% of the drugs represented only a pharmacological or technological innovation (for details, see Table 3).

The degree of important therapeutic innovation was substantially similar between biotechnological and nonbiotechnological products: 25% (15 active substances out of 60) and 29% (34 out of 116), respectively.

Figure 3 shows the time trend of the degree of therapeutic innovation of the EMEA-approved therapeutic agents. Apart from the first year of authorization, no apparent trend was seen, in particular for active substances reaching an important degree of therapeutic innovation, except for a decrease in the last 3 years.

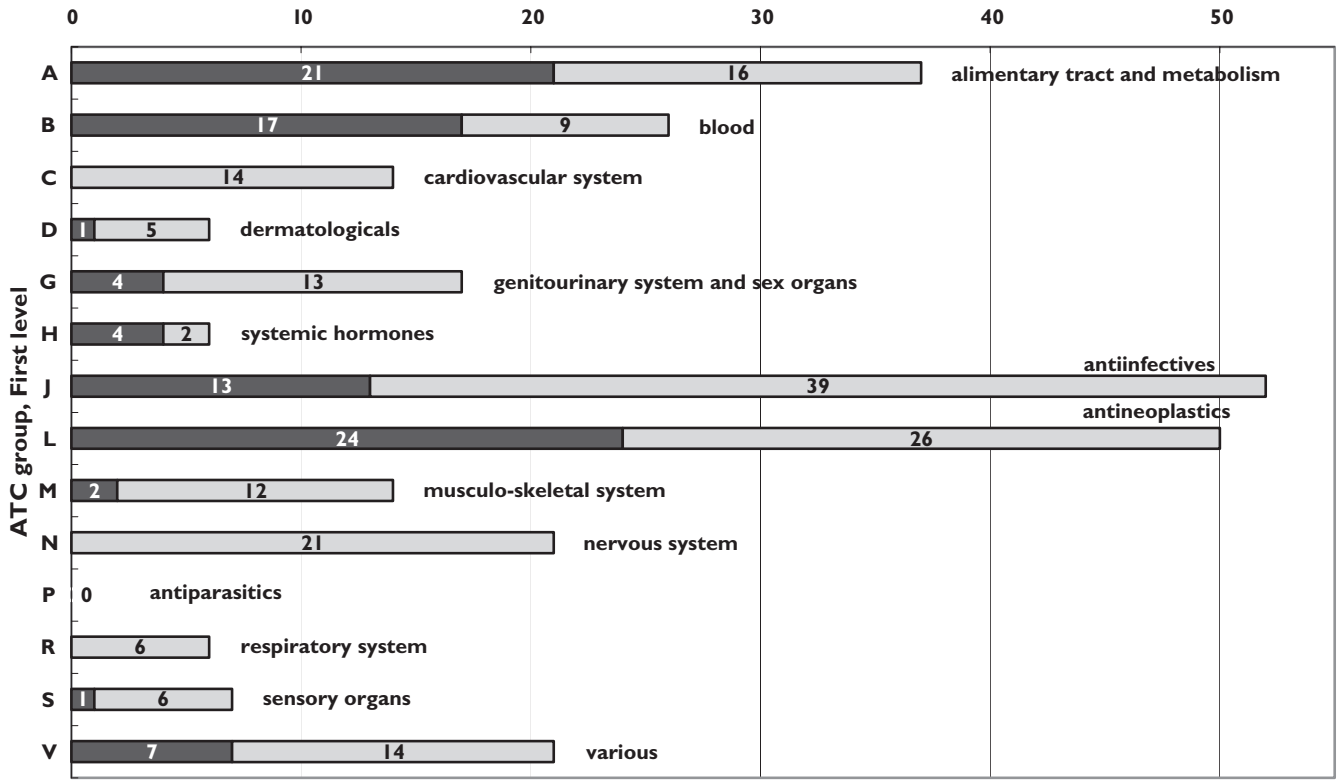
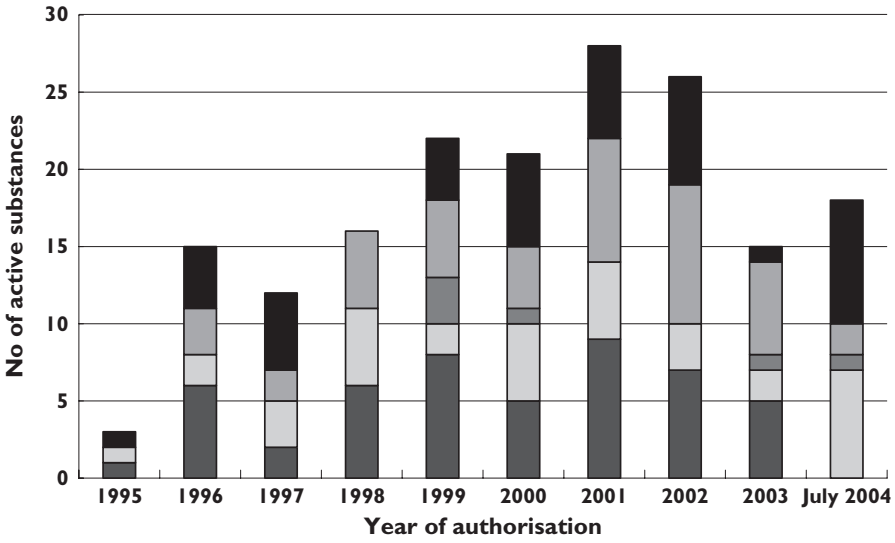


Figure 2
Distribution of the European Medicines Agency approved products according to the Anatomic Therapeutic Chemical classification I level and biotechnological source. Biotechnological (■), nonbiotechnological (□)

Figure 3
Time trend of the degree of therapeutic innovation among therapeutic agents in the period 1995–2004. Important (■), moderate (□), modest (■), pharmacological (■), tecnological (■)



Discussion

According to our algorithm, it emerges that the degree of therapeutic innovation reached by EMEA-approved therapeutic agents is low, since active substances achieving the highest score (A) represented about one-quarter (28%) of all the therapeutic agents considered. This figure becomes even worse when all the active substances are considered (24%, corresponding to 49 active substances out of 198). This is a disappointing result, in light of the economic efforts required in research and development of each new chemical entity [8, 9]. However, we should not overlook the introduction of drugs

Table 2
Distribution of the European Medicines Agency-approved therapeutic agents according to the degree of therapeutic innovation and the biotechnological source

	Disease seriousness							
	Drugs for serious diseases		Drugs for risk factors for serious diseases		Drugs for non-serious diseases		Total	
Therapeutic innovation	*N*	%*	*N*	%*	*N*	%*	*N*	%*
Biotechnological	54		2		4		60	
A	15	27.8	–	–	–	–	15	25.0
B	11	20.4	–	–	–	–	11	18.3
C	1	1.9	–	–	–	–	1	1.7
Pharmacological	9	16.7	2	100	1	25.0	12	20.0
Technological	18	33.3	–	–	3	75.0	21	35.0
Nonbiotechnological	86		14		16		116	
A	32	37.2	–	–	2	12.5	34	29.3
B	21	24.4	2	14.3	1	6.3	24	20.7
C	3	3.5	2	14.3	–	–	5	4.3
Pharmacological	20	23.3	7	50.0	6	37.5	33	28.4
Technological	10	11.6	3	21.4	7	43.8	20	17.2
Total	140	79.5	16	9.1	20	11.4	176	100.0

**The percentages in columns are referred to the subtotals of biotechnological and nonbiotechonological substances within each group of disease seriousness.*

such as anti-HIV agents, monoclonal antibodies against tumour necrosis factor-α, imatinib mesilate and others, which represented significant improvements for thousands of patients worldwide [10].

Concerning the distribution of important therapeutic innovation among biotechnological and nonbiotechnological, the EU Regulation, by establishing that biotechnological substances must compulsorily follow the centralized procedure, introduces a bias since it dilutes the average degree of innovation of these agents, owing to the obliged presence of several me-too compounds (15 out of 60 new biotechnological therapeutic agents, corresponding to 25%, were me-too drugs). On the other hand, the nonbiotechnological drugs may access the EMEA-centralized procedure, if considered potentially innovative, at the discretion of the applicant. A much higher degree of therapeutic innovation was expected in this group, but only 34 out of 116 active substances (29%) reached an important degree of therapeutic innovation, indicating that only a minority of drugs claimed as innovative by manufacturers deserve this definition.

An intrinsic limitation of our approach is the lack of robust data concerning real-life clinical effectiveness and safety at the moment of marketing authorization, since we estimated the degree of therapeutic innovation of drugs on the basis of the European Public Assessment Reports and of the published literature available at the beginning of their life. However, new and up-to-date evidence may become available after a few years of clinical use of a new drug, requiring a re-evaluation of its place in therapy, in either direction (better or worse).

In conclusion, the low percentage of important therapeutic innovation found when considering all approved therapeutic agents (32% in the 1995–2003 period [5] and 28% in the 1995–2004 period as found in the present analysis) is confirmed when biotechnological and nonbiotechnological products are considered separately: 25 and 29%, respectively. Only less than one-third of medicinal products claimed as innovative by the applicant emerged as a therapeutic innovation according to our algorithm.

Competing interests: None declared.

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Table 3
Classification of therapeutic agents according to disease seriousness and degree of therapeutic innovation. As examples of application of algorithm, details are provided in footnotes for a few representative agents

Scores for therapeutic innovation		
Drug for serious diseases 'a'		
Important	aa	Carglumic acid, lepirudin*, sodium phenylbutyrate
	ab	Agalsidase alfa†, agalsidase beta†, botulinum toxin Type B‡
	ba	Adalimumab, alemtuzumab, all anti-HIV drugs, arsenic trioxide, basiliximab, bexarotene, caspofungin, daclizumab, docetaxel, drotrecogin alfa, etanercept, imatinib mesilate, infliximab, miglustat, mycophenolate mofetil, pegvisomant, protein C, rituximab, tasonermin, topotecan, trastuzumab, verteporfin, voriconazole
	ac	Riluzole, rivastigmine§
Moderate	bb	Atazanavir, bimatoprost, bortezomib, brinzolamide, cetuximab, deferiprone, entacapone, eptotermin alfa, fulvestrant, ibritumomab, interferon beta-1a, interferon beta-1b, laronidase, levetiracetam, mitotane, nitric oxide, palivizumab, pramipexole, temoporfin, tolcapone, travoprost
	c1a	Aprepitant, atosiban¶, capecitabine, fosamprenavir**, insulin glargine**, olanzapine, pegfilgrastim, peginterferon alfa-2a, peginterferon alfa-2b
Modest	c1b	None
	c1c	Beclaplermin
	bc	Alitretinoin, paclitaxel, temozolomide††
Pharmacological		Anakinra, aripiprazole, bosentan, busulfan, cladribine, cytarabine, darbepoetin alfa, desirudin, dibotermin alfa, doxorubicin, ertapenem, iloprost, insulin lispro, leflunomide, memantine, nateglinide, pioglitazone, repaglinide, reteplase, rosiglitazone, samarium, sevelamer, telithromycin, tenecteplase
Technological		Calcitonin (salmon), epoetin beta, epoetin delta, factor VIIa, ibandronic acid, ibuprofen, imiglucerase, insulin human (rDNA), interferon alfa-2b, interferon alfacon-1, mercaptamine, moroctocog alfa, nonacog alpha, octocog alfa, pregabalin, sirolimus, somatropin, valdecoxib, zoledronic acid
Drug for risk factors for serious diseases 'b'		
Important	aa	None
	ab	None
	ba	None
Moderate	ac	None
	bb	None
	c1a	Clopidogrel‡‡, raloxifene
Modest	c1b	Porfimer sodium
	c1c	None
	bc	Celecoxib§§
Pharmacological		Eptifibatide, fondaparinux sodium, irbesartan, orlistat, rasburicase, telmisartan, teriparatide
Technological		Colesevelam, ibandronic acid, human fibrinogen/human thrombin
Drug for non serious diseases 'c'		
Important	aa	Sildenafil
	ab	None
	ba	Tacrolimus
Moderate	ac	None
	bb	None
	c1a	Imiquimod
Modest	c1b	None
	c1c	None
	bc	None
Pharmacological		Apomorphine hydrochloride, eflornithine, lutropin alfa, oseltamivir, tadalafil, vardenafil, zaleplon
Technological		Cetrorelix, choriogonadotrophin alfa, desloratadine, emedastine, follitropin-alfa, follitropin-beta, ganirelix, olopatadine, oxybutynin, parecoxib

**Lepirudin is indicated in heparin-associated thrombocytopenia (HAT) type II. Note that desirudine, another hirudin-related compound, was classified as pharmacological innovation, owing to a different therapeutic indication. †Both indicated for replacement therapy in patients with Fabry's disease. We assigned a score 'b' to the therapeutic effect considering that the clinical efficacy of these drugs was assessed by means of surrogate end-points, namely the effect on serious debilitating pain and quality of life [11,12], and that they affect only some aspects of the disease [13,14]. ‡Used for the treatment of cervical dystonia, received a score 'b' for the therapeutic effect because of the variability of its duration, in particular the tendency of the response to fade over time [15]. §Rivastigmine offers only a modest symptomatic benefit in patients with mild to moderately severe Alzheimer's disease, as stated by the CPMP scientific risk/benefit assessment [16]. ¶Atosiban was scored B (a + c1 + a) owing to its better safety profile in terms of reduced cardiovascular side-effects, although the drug addresses a serious condition (imminent pre-term birth) where previous treatments (e.g. ritodrine) were available [17]. **Fosamprenavir and insulin glargine (a + c1 + a) show better kinetics profiles than already existing drugs. ††It is approved for the treatment of malignant glioma showing recurrence or progression after standard therapy. The drug appears better tolerated than other agents, but its therapeutic effect was scored 'c' owing to its palliative benefit in the approved indication [18]. More recently, however, the addition of temozolomide to radiotherapy for newly diagnosed glioblastoma was shown to result in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity [19, 20]. ‡‡Clopidogrel (b + c1 + a) has a safer profile than ticlopidine with respect to haematological adverse effects, such as neutropenia and thrombotic thrombocytopenic purpura (TTP), although a few cases of TTP [21] and leukopenia [22] have been reported with clopidogrel. §§Celecoxib was scored as a modest therapeutic innovation for its indication in the reduction of the number of adenomatous intestinal polyps in familial adenoumatous polyposis, as an adjunct to surgery and further endoscopic surveillance. However, the efficacy of the drug in reducing the risk of intestinal cancer has not been demonstrated and the drug was approved under exceptional circumstances with the commitment of further efficacy studies.*

expressed herein are those of the authors and do not necessarily reflect the views of the European Medicines Agency or the Italian Medicines Agency.

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