DEBATE
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On the alleged anticancer efficacy of the phosphoethanolamine pill, weakness of scientific evidence and ethical concerns

Sobre a alegada eficácia anti-câncer da pílula de fosfoetanolamina, fragilidade da evidência científica e preocupações éticas

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ABSTRACT

Anecdotal reports say that cancer patients improved after taking "synthetic phosphoethanolamine" (*syn*-PEA), anticancer pills produced and distributed by chemists from a Brazilian university. Notwithstanding the fact that *syn*-PEA pill inventors disseminated in the lay press the information that their drug is effective against different types of malignant tumors, they showed no clinical documentation or case reports to corroborate this statement. Moreover, *syn*-PEA failed to exhibit a consistent anticancer response in *in vitro* assays with human and murine cancer cell lines, and in *in vivo* xenograft tumor rodent assays. Despite the lack of nonclinical and clinical evidence of drug efficacy and safety, a bill authorizing production, prescription and consumption of *syn*-PEA pill passed the Congress and the president signed it into law (Law 13269/2016) on April 13, 2016. Astonishingly, the National Committee for Ethics in Research approved (April 19, 2016) *syn*-PEA trials in cancer patients in the absence of scientifically valid indications of a probable efficacy and without an adequate preclinical safety evaluation. It is unlikely that *syn*-PEA will eventually play a role in cancer therapy. Nonetheless, s*yn*-PEA sad story unavoidably damaged country's reputation as far as drug regulation and human research ethical standards are concerned.

KEYWORDS: Preclinical Studies; Clinical Research Ethics; Anticancer Drug; Oncologic Drugs; Cancer

RESUMO

Tem sido informalmente relatado que pacientes com câncer melhoraram após tomar pílulas de fosfoetanolamina sintética (*sin*-FEA) produzidas e distribuídas por químicos de uma universidade brasileira. Embora os inventores da *sin*-FEA divulguem na imprensa leiga que o seu medicamento é eficaz contra diferentes tipos de tumores malignos, eles não apresentaram documentação clínica e relatos de caso que corroborem esta afirmação. Além disso, a *sin*-FEA não mostrou uma resposta anticarcinogênica consistente em ensaios *in vitro* com células neoplásicas humanas e murinas, e em testes *in vivo* em roedores com tumores transplantados. Apesar da falta de evidência não clínica e clínica de eficácia e segurança deste medicamento, uma lei autorizando a produção, prescrição e consumo da *sin*-FEA foi aprovada pelo Congresso e sancionada sem vetos pela presidente (Lei nº 13.269/2016) em 13 de abril de 2016. Surpreendentemente, a Comissão Nacional de Ética em Pesquisa aprovou (em 19 de abril de 2016) testes da *sin*-FEA em pacientes, apesar da ausência de indícios cientificamente válidos de provável eficácia e de adequada avaliação pré-clínica de segurança. É improvável que a *sin*-FEA seja útil no tratamento do câncer. Entretanto, a triste história da *sin*-FEA inevitavelmente maculou a reputação do país com respeito à regulação de medicamentos e padrões éticos de pesquisa clínica.

PALAVRAS-CHAVE: Estudos Pré-clínicos; Ética em Pesquisa Clínica; Medicamentos Antineoplásicos; Medicamentos Oncológicos; Câncer

> "*As to diseases, make a habit of two things—to help, or at least to do no harm*". Hippocrates 460-370 BC (*Epidemics; Book I, Chapter XI*)[1]

INTRODUCTION

Despite anecdotal reports that cancer patients improved after taking phosphoetanolamine (PEA) pills, it remains obscure whether PEA has in fact any influence on the tumorigenesis process. Present in literally every animal tissue, PEA is formed by phosphorylation of ethanolamine (through an ethanolamine kinase-catalyzed reaction) and acts as an intermediate in the biosynthesis of phosphoglycerides and sphingomyelin that serve as components of cell membranes (Figure 1).

As early as in 1936, Edgar Outhouse[2,3] found substantial amounts of PEA in bovine tumors and speculated that this primary amine would be "specific" to malignant tissues. Four decades or so later, Kano-Sueoka et al[4] described that PEA acted as a growth factor of a rat mammary carcinoma cell line. In the last 10 years, six studies tested a PEA synthesized by Gilberto Chierice and co-workers (i.e., "synthetic" PEA) in *in vitro* (cytotoxic effects in some cancer cell lines) and *in vivo* (inhibition of xenograft tumor growth in rodent models) assays[5,6,7,8,9,10]. A tentative rationale for these experiments is the speculation that a massive presence of PEA in some malignant tumors (shown by Outhouse[2,3]) would indicate that PEA is overproduced to hamper neoplastic cell proliferation. In other words, an excess of PEA would be a kind of defense mechanism of the organism against uncontrolled cell proliferation and tumor growth. A corollary to this hypothesis would be that an additional supply of "synthetic" PEA (*syn*-PEA) could help patients to eliminate malignant cells or at least to control their proliferation. Nonetheless, except for the foregoing studies, no other scientific-based report supports - whether directly or indirectly - the notion that PEA would play a role in the process of carcinogenesis.

Reported anticancer effects of "synthetic" phosphoethanolamine

Gilberto Chierice and coworkers' experiments showed that *syn*-PEA in the mM (10^{-3}) concentration range was toxic to some cancer cell lines (Table 1). Actually, these findings revealed that *syn*-PEA is not a particularly cytotoxic compound because virtually all substances kill *in vitro* cultivated cells at such very high levels. Most antineoplastic agents used in clinical practice (e.g., sunitinib, cisplatin, doxorubicin, and others) are cytotoxic to a variety of cancer cell lines in the µM (10^{-6}) or even in the nM (10^{-9}) concentration range, that is, *syn*-PEA was at least 3 orders of magnitude less potent than most cytotoxic oncologic drugs on the tested cancer cells (Table 1)[10,11]. The effects of *syn*-PEA on malignant cells reported by its inventors[6,7,8,9,10], therefore, resulted from nonspecific cytotoxic effects rather than from a specific anticancer activity.

An additional problem with these experiments is the low degree of purity of *syn*-PEA. An analysis conducted by an independent laboratory found that PEA accounted for only 32.2% of *syn*-PEA. The remaining constituents (impurities) were phosphates of Ca, Mg, Fe, Mn, Al, Zn and Ba (34.9%), monoethanolamine (18.2%), pyrophosphates (3.6%) and phosphobisethanolamine (3.9%)[12]. The findings by Chierice and coworkers, therefore, cannot be ascribed to PEA alone[6,9,10].

As shown in Table 2, the effects of *syn*-PEA on xenograft tumor rodent models were modest and inconsistent across experiments. Moreover, administration of *syn*-PEA by intraperitoneal injection (an unlikely route of administration for clinical use in humans) and implantation of tumors on non-immuno-deficient mice led to a flawed interpretation of assay results[7,9,10]. A possible immunostimulation triggered by *syn*-PEA injected into peritoneal cavity might have impaired xenograft tumor growth, thereby eliciting a false positive anticancer response. Further xenograft tumor experiments (conducted by MCTI (Ministry of Science, Technology and Innovation)-contracted laboratories) with immunocompetent mice and rats as well as with nude (athymic) mice treated orally with *syn*-PEA (or PEA) yielded largely negative results (Table 2) [5,6,7,13,14,15].

Overall, these pre-clinical *in vitro* and *in vivo* assays with *syn*-PEA clearly failed to identify an anticancer activity potentially useful in oncologic therapy.

Current anticancer compounds screening paradigm

It is of note that the US National Cancer Institute (NCI) tiered approach for screening novel anticancer drugs begins with a pre-selection based on chemical structure and *in silico* and other relevant data[16,17,18,19]. The subsequent steps of NCI-screening include a panel of 60 cancer cell lines (i.e., the "NCI-*60 Human Tumor Cell Lines Screen*") starting with a set of the most sensitive ones, and *in vivo* hollow fiber[a,20,21,22] and xenograft tumor assays at the final steps[16,17,18,19,23]. Depending on the previous tier test results, a substance goes to the next testing step or undertakes no further testing (see diagram in Figure 2). If *syn*-PEA had undertaken the NCI-tiered screening paradigm, it would have certainly failed to pass the first tier.

In recent years, identification of new anticancer drugs has moved more and more from an empirical screening of cytotoxic compounds against cancer cell lines and uncharacterized tumor models, to a target-orientated screening of compounds with defined mechanisms of action. Inhibitors of enzymes playing a key role in the sustained proliferative activity, such as cyclin dependent kinases (CDK), for instance, are potentially new anticancer agents[24]. PEA and *syn*-PEA, however, have not undergone any target-orientated screening of anticancer drugs.

[a] The hollow fiber assay was developed to bridge the gap between in vitro cell line tests and in vivo xenograft tumor assays in immunodeficient mice. Inert hollow fibers containing human tumor cell lines are transplanted into the peritoneal cavity or implanted under the skin of the host mice. The hollow fiber pores are small enough to retain the propagating cancer cells and large enough to allow the entry of potential anticancer compounds. After the in vivo treatment hollow fibers are retrieved for analysis of the viable cell mass.[20,21,22].

Drug research and development process

Drug research and development (R&D) is a long, costly and complex multi-step process[25,26,27,28]. In the first step (drug discovery), a number of natural or synthetic compounds are screened to select those with a pharmacological activity potentially useful in therapeutics. The subsequent step is a preclinical safety research (including a set of *in vitro* assays and *in vivo* animal tests) to decide whether the compound is reasonably safe for a first-in-man (phase 0) study and/or a phase 1 clinical trial[b]. If investigators and regulators agreed upon that the compound would not expose healthy volunteers and/or patients to unacceptable risks of harm, a sequence of phase 1, 2 and 3 clinical trials (the final R&D step) takes place. Phase 3 trials provide the decisive evidence that a drug is effective and safe for the intended therapeutic use. R&D requires large capital expenditures (from hundreds of millions to billions of US dollars) and takes a long time (7–12 years). It also involves high attrition rates. (Figure 3)[27,28,29]. It was estimated that

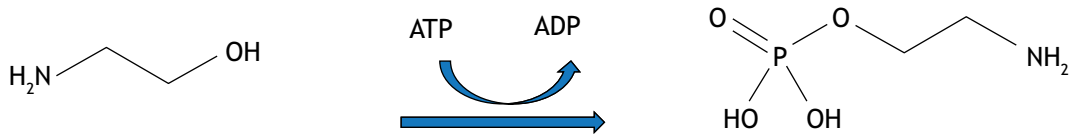

Figure 1. Phosphoethanolamine (PEA) also known as phosphorylethanolamine or *O*-phosphoethanolamine (CAS Nr 1071-23-4, $C_2H_8NO_4P$, Molecular mass = 141.063 g/mol) is an intermediate in the endogenous synthesis of phospholipids, components of cell membranes. PEA and ADP are the products of an ethanolamine kinase (EC 2.7.1.82)-catalyzed reaction the substrates of which are ATP (donor of phosphate group) and ethanolamine (alcohol group acceptor).

Table 1. Cytotoxicity of synthetic phosphoethanolamine (*syn*-PEA) to cancer and non-cancer cell lines.

Study	Cell line	Assay	Cytotoxic concentration range or IC_{50}		Remarks
			syn-PEA	Oncologic drug	
Ferreira et al, 2012 [6]	B16-F10	MTT	12.5-100 mM	-	Mouse melanoma
Ferreira et al, 2012 [7]	MCF-7	MTT	1.82 mg/ml (16 mM)	-	Human breast cancer
	Skmel-28	MTT	1.2 mg/ml (8.5mM)	-	Human melanoma
	Mewo	MTT	2.4 mg/ml (17.1 mM)	-	Human melanoma
	H292	MTT	1.32 mg/ml (9.4mM)	-	Human mucoepidermoidlung carcinoma
	Huvec-CRL1730	MTT	>5 mg/ml (>35.7mM)	-	Human umbilical vein endothelial cell
	FN1	MTT	>5 mg/ml (>35.7mM)	-	Human normal fibroblast
	Lymphocyte	MTT	>5 mg/ml (>35.7mM)	-	Mouse lymph node
	EAT	MTT	2.3 mg/ml (16.4 mM)	-	Mouse Erlich AscitesTumor
	B16-F10	MTT	1.4 mg/ml (10mM)	-	Mouse melanoma
Ferreira et al, 2013 [8]	KG-1	MTT	9 mM	-	Human myeloid leukemia
	KG562	MTT	6 mM	-	Human erythromyeloblastoid leukemia
	Jurkat	MTT	12 mM	-	Human T cell leukemia
Ferreira et al, 2013 [9]	MCF-7	MTT	20 mM	-	Human breast cancer
	MCF-10A	MTT	100 mM	-	Human mammary epithelial cells
Ferreira et al, 2013 [10]	Renca	MTT	90 mM	5 μM[+]	Mouse renal carcinoma
	IRPTC	MTT	134 mM	0.05 μM[+]	Rat Immortalized proximal tubule cells
	Huvec CRL1730	MTT	73 mM	9 μM[+]	Human umbilical vein endothelial cell
LOE-UFC, MCTI- 2016 [11]	HCT-116	MTT	25.9 mM	0.15 μM[++]	Human colorectal carcinoma
	PC 3	MTT	19.7 mM	1.6 μM[++]	Human prostate adenocarcinoma
	SF-295	MTT	43.4 mM	0.38 μM[++]	Human glioblastoma tumor
	L929	MTT	8.6 mM	1.6 μM[++]	Mouse fibroblast
	CMSP		42.4 mM	1.8 μM[++]	Human peripheral blood mononucleated cells - Primary culture

[+]Sunitinib. [++] Doxorubicin. Molar mass of PEA ($C_2H_8NO_4P$) is 141.063 g/mol. If purity of PEA were >95%, then 1mM = 0.14 mg/ml. However, since *syn*-PEA is in fact a mixture containing a great amount of impurities, real molar concentrations of PEA in *syn*-PEA are possibly at least 30 to 40% lower than estimates listed above. LOE-UFC, MCTI – contracted laboratory.

[b] Phase 0 clinical study or a "first-in-man" trial is a test of a compound previously assessed through in vitro, animal assays and/or in silico modelling on human subjects for the first time. It involves a very small group of subjects and a very small dose of a drug candidate. The purpose of Phase 0 trials is to find out whether the drug behaves in the way researchers expect from their previous laboratory tests. Phase 1 also involves a few healthy volunteers or patients and test higher doses of the drug. The aim of phase 1 trials is to investigate for the first time drug safety in humans and to look at doses and side effects. In drug R&D a phase 1 test often skips a previous phase 0 trial.

Table 2. Effects of synthetic phosphoethanolamine (*syn*-PEA) on *in vivo* rodent xenograft tumor assays. The anticancer effects of *syn*-PEA were modest and inconsistent across different studies.

Study	Tumor-bearing rodent		Transplanted tumors	Treatment	Outcome
	Strain-species	Immune function			
Ferreira et al, 2012 [6]	C57BL/6J mice	Unaltered	Mouse melanoma B16-F10 cells	*syn*-PEA 50-100 mg/kg/ d,15 d, ip	Reduction in tumor volume, increase in tumor doubling time and survival rate.
Ferreira et al, 2012 [7]	BALB/c mice	Unaltered	Mouse Ehrlich ascites tumor	*syn*-PEA 35-70 mg/kg/d,15d, ip	Reduction in body wt gain (tumor growth), increase in survival rate.
Ferreira et al, 2013 [8]	NOD/SCID *spf* mice	Immuno-deficient (sublethal Co irradiation : 250 cGy)	Leukaemic cells from hCG-PLM-RARα transgenic mice	*syn*-PEA* 40-80 mg/kg/ d,15 d, ip All-*trans*-retinoic acid 1 mg/kg/d,15 d, ip daunorubicin 10 mg/kg/ d,15 d, ip	Reduction in the % of White blood and immature cells, impairment of expansion of malignant clones of CD34+/ CD117+, CD34+ and Gr-1+ cells. Effects of all-trans retinoic acid and *syn*-PEA were more marked than those of daunorubicin
CIEnP-MCTI, 2016 [15]	Athymic nude mice (NU(NCr)-Foxn1^{nu})	Immuno-deficient - Athymic mice	Human melanoma A-375 cell line	*syn*-PEA 200-500 mg/kg/d, 24d, oral PEA (pure) 500mg/kg/d 24d, oral Cisplatin 2 mg/kg,ip,#	*Syn*-PEA (500 mg/kg) reduced tumor volume. No effect at the lower dose (200 mg/kg). PEA (pure) did not inhibit tumor growth. Cisplatin caused a much more marked reduction of tumor growth.
LOE-UFC-MCTI, 2016[13]	Rat	Unaltered	Rat Walker 256 carcino-sarcoma	*syn*-PEA 1000 mg/kg/d, 10d, oral Cyclophosphamide 25 mg/kg/d, 10d, ip	*Syn*-PEA did not inhibit tumor growth. However, it increased the number of lung metastases Cyclophosphamide inhibited tumor growth.
LOE-UFC, MCTI, 2016[14]	Swiss mice	Unaltered	Mouse sarcoma 180 cells	*syn*-PEA 1000 mg/kg/ d, 10d, oral Cyclophosphamide 25 mg/kg/d, 10d, ip	*Syn*-PEA caused no change in tumor volume Cyclophosphamide inhibited tumor growth.

* According to Ferreira el al, 2013 *syn*-PEA purity was >99%. A MCTI-contracted laboratory, however, found a purity of 40% or less for a sample of *syn*-PEA synthesized by the same laboratory (USP-São Carlos). # cisplatin was injected 3 times a week from day 12 to 21 and once a week from day 21 to 36.

of 5-10,000 compounds that were initially screened for potential therapeutic activity only 250 prove to be sufficiently promising to undertake pre-clinical evaluation, and of those only 10 are eventually tested on humans. Moreover, only 9.6% of all drug candidates that start a phase 1 trial successfully pass a phase 3 trial and receive a marketing authorization (data for 2006-15) [29]. Taking into account this extremely high attrition rate and the poor performance of *syn*-PEA on the initial screening tests, it seems fair to think that MCTI bet heavily on a substance fated to fail a properly conducted oncologic drug R&D[30,31,32].

Brazilian government-sponsored development of syn-PEA anticancer pill

Notwithstanding the weakness of scientific evidence for a *syn*-PEA-mediated anticancer activity, the MCTI allocated a substantial amount of taxpayers' money to develop a *syn*-PEA-based oncologic drug[30,31,32]. Amazingly, MCTI-sponsored studies on the safety of *syn*-PEA are in progress and a phase 1 test on humans is in preparation, while some basic studies are still looking for some pre-clinical evidence of anticancer activity[30,31,32]. Apparently, there was an *a priori* decision to proceed R&D studies of *syn*-PEA up to the clinical phase irrespective of the previous nonclinical efficacy and safety investigation results.

In other words, MCTI-sponsored plan to develop *syn*-PEA as an oncologic medicine is a disarranged version of the conventional tiered approach to drug R&D in which the decision to pass to the next step of tests is based on the outcome of previous step studies (the logic of which is to save money, time and resources in drug development).

Syn-PEA anticancer pill law

A bill that authorizes production, prescription and consumption of *syn*-PEA as an oncologic drug passed the Congress, and the Brazilian president signed it (with no veto) into law (Federal Law 13269/2016) on April 13th, 2016[33]. The *syn*-PEA law was challenged by a lawsuit (Direct Unconstitutionality Action - ADIN) filed by the Brazilian Medical Association (AMB) and the full board of the Federal Supreme Court (STF) - by a 6 to 4 vote - suspended temporarily its effectiveness until a court final decision. The six STF ministers who voted for a temporary suspension of Law 13269/2016 cited the lack of clinical studies of *syn*-PEA in their declaration of vote[34].

Ethical clearance for clinical trials of syn-PEA in Brazil

Astonishingly, the Brazilian National Committee for Ethics in Research (CONEP) authorized (in April 19, 2016) a São Paulo State Secretary of Health-sponsored study of *syn*-PEA

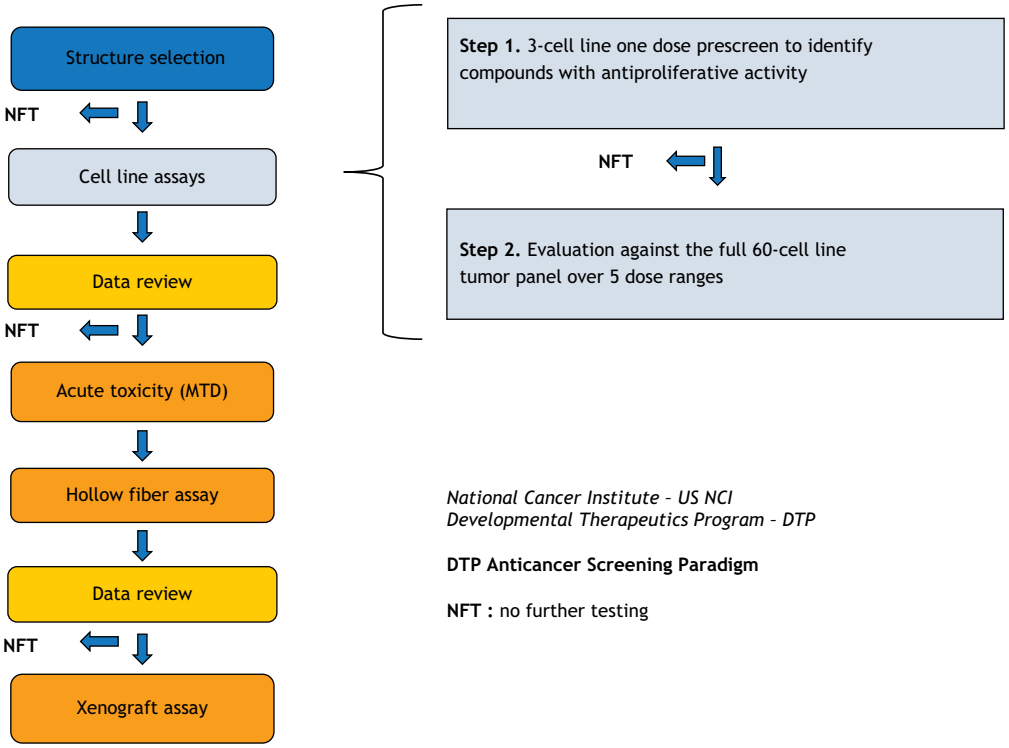

Figure 2. The US National Cancer Institute drug-screening paradigm. The Developmental Therapeutics Program (DTP) Anticancer Screening Paradigm is a tiered multi-step approach. Compounds are pre-selected based on their chemical structures and other data relevant for potential novel anticancer activity. In a second tier, preselected compounds undergo cellular assay (60 different human tumor cell lines) screening in two steps. The first cellular assay step is a 3-cell line / one concentration (dose) prescreen to select compounds with anti-proliferative activity to be further tested against the full 60-tumor cell line panel over 5 concentrations (doses). After a preliminary review of data, novel compounds with identified growth inhibition or killing of tumor cell lines activity undergo acute toxicity testing (to determine maximum tolerated doses) and the hollow fiber assay on rodents. Based on a review of available data, investigators then decide whether a compound should further undergo rodent xenograft tumor assays. As shown in the diagram (adapted from DTP flow chart and information available on https:// dtp.cancer.gov/ discovery_development/ default.htm), compounds undergo "No Further Testing" (NFT) if they fail to pass a previous tier testing.

efficacy and safety in cancer patients[35]. As aforementioned, Chierice and coworkers statement that *syn*-PEA has therapeutic usefulness in oncology is not supported by robust experimental evidence. Notwithstanding the fact that *syn*-PEA inventors have repeatedly said and disseminated in the lay press that cancer patients improved – or even cured - after taking the anticancer pill, they have not shown any clinical documentation (patient records) or published any case report to corroborate their statements.

Moreover, CONEP permitted the onset of clinical trials in the absence of a comprehensive (or even a minimum) preclinical evaluation of PEA safety. It is of note that CONEP neglected a possible harm to cancer patients. Data by Kano-Sueoka et al[4]. suggested that PEA could be a tumor growth factor and one of the MCTI-contracted laboratories reported an apparent *syn*-PEA-caused enhancement of metastatic tumors in a rat xenograft tumor assay[c] [31].

Approval of clinical studies of compounds for which sponsors provided no scientifically valid and convincing evidence of a potential therapeutic usefulness breaks a cornerstone rule of clinical investigation ethics. The CIOMS-WHO ethical guidance for research involving human subjects states explicitly that "*.. scientifically invalid research is unethical..*" and that sponsors and investigators must ensure that "*..studies involving human subjects....are based on adequate knowledge of the pertinent scientific literature*"[d,36]. Moreover, risks and benefits for the individual subject (*i.e.*, the cancer patient) must be reasonably balanced and risks minimized (CIOMS guideline 8)[36]. According to CIOMS-WHO guidance (comments to guideline 8) and to the Declaration of Helsinki (paragraph 11), "*..clinical testing must be preceded by adequate laboratory or animal experimentation to demonstrate a reasonable probability of success without undue risk*".[36] As far as the approved clinical trials of *syn*-PEA are concerned, a crucial question remains

[c] National Cancer Institute - Brazil (INCa) and MCTI. Seminar on phosphoethanolamine (Seminário sobre fosfoetanolamina) held in May 17, 2016.[31] The one-day INCa meeting was recorded and videos can be watched at: www.youtube. com/ watch?v=q6Es2vn3lAw (morning session) and www.youtube. com/ watch?v=fIP_cesJlnY (afternoon session).

[d] CIOMS and WHO ethical guidelines state that (Guideline 1) "... *because scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit, investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles and are based on adequate knowledge of the pertinent scientific literature.*"[36].

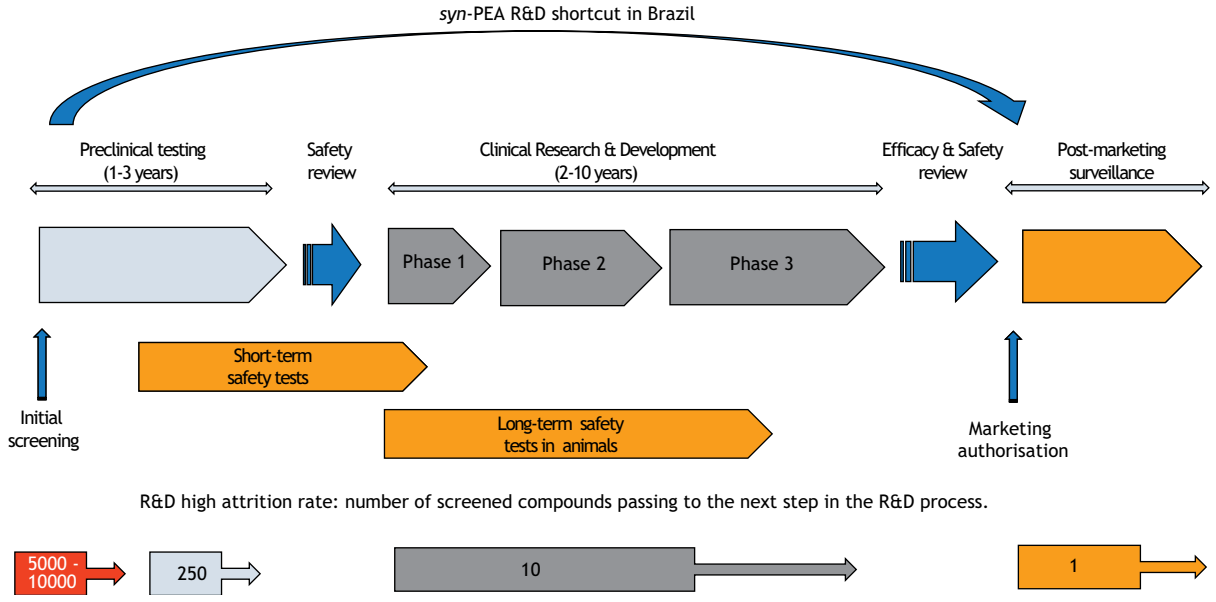

Figure 3. Drug Research and Development (R&D) process. R&D begins with a screening for pharmacological effect of therapeutic interest (compounds generally obtained by prospecting natural products or chemical synthesis) and preclinical toxicity evaluation through in silico, in vitro, and/or short-term in vivo assays. A review of data on genotoxic potential, pharmacokinetics, safety pharmacology and repeated dose toxicity in at least two species (one non-rodent) and all relevant information available (and clinical trial protocols) precedes the beginning of the clinical research and development phase. Clinical R&D is a three-step investigation process involving a sequence of phase 1 (involving a small number of healthy volunteers or patients, focus placed on safety), phase 2 (controlled trial involving a larger number of patients diagnosed with the medical condition the compound is intended to treat, focus placed on safety and efficacy; it is a pilot dose-ranging trial), and the final phase 3 study. Phase 3 trial is a decisive research step to demonstrate drug efficacy and safety to treat the disease of interest. The clinical trial should be controlled, double-blinded, randomized, statistically robust (adequate number of subjects enrolled), and to assess valid clinical outcomes of efficacy. Nonclinical long-term safety studies (reproductive toxicity, carcinogenic potential, long-term repeated dose toxicity) are performed in parallel with the clinical phase. A comprehensive review of all R&D data with emphasis on phase 3 trial results precedes a drug marketing authorization. Post-marketing surveillance is necessary to reveal drug problems of effectiveness under real (marketing) conditions of use and rare adverse events that escape detection in phase 3 trials. Attrition rate of R&D is extremely high and of 5-10,000 compounds that apparently have a pharmacological activity of therapeutic interest only 1 eventually succeeds in achieving a marketing approval. In Brazil, the *syn*-PEA law (Law 13269/2016) authorizing the manufacture, prescription and dispensing of this putative anticancer pill is a radical shortcut to this normally lengthy, costly and highly selective way to approve a drug for marketing.

unanswered: Based on available preclinical scientific data, what are the prospects of benefits for the individual subject (cancer patient)? Needless to say it again: *syn*-PEA (and PEA) did not undergo a properly conducted screening for anti-cancer activity, and initial tests (cytotoxicity and xenograft assays) yielded disappointing results which according to US NCI-screening paradigm would not support further testing (Tables 1 and 2, Figure 2).

The potential risks of *syn*-PEA to clinical research subjects were not adequately investigated either. As stated by ICH guidelines (e.g. ICH guidelines for non-clinical safety studies to conduct clinical trials)[37], "*nonclinical safety studies ..... should be adequate to characterise potential adverse effects that might occur under the conditions of the clinical trial to be supported*". Moreover, nonclinical safety evaluation must include repeated-dose studies in two species (one non-rodent) the duration of which should be at least equivalent to that of the clinical trial to be supported (*e.g.*, to support a 6-month clinical trial, durations of nonclinical repeated dose assays must be 6-month or longer)[37]. It is of note that CONEP approved the onset of São Paulo State Secretary of Health-sponsored clinical studies of *syn*-PEA before the results of the MCTI-contracted preclinical studies (*i.e.*, cytotoxicity assays, acute toxicity and 30-day repeated dose study in rodents) were available. At any rate, the limited set of preclinical studies contracted by MCTI is far from being sufficient to support a clinical study of *syn*-PEA in cancer patients[e].

The current approval of *syn*-PEA clinical study by CONEP without an adequate preclinical evidence of anticancer efficacy and safety may suggest that Brazilian ethical review system allows desperately ill patients (a particularly vulnerable group of people) to volunteer to be "guinea pigs" for poorly tested or even untested drugs. This was certainly the most worrisome consequence of *syn*-PEA sad story: it made a case law for further approval of

[e] The Brazilian Clinical Trial register ("Plataforma Brasil", http:/aplicação.saude.gov.br/ plataformabrasil/ login.jsf) informed that two research protocols with a common title ("Evaluation of safety and efficacy of synthetic phosphoethanolime in patients with advanced solid tumors") were approved by CONEP on March 16, 2016 (FM-USP) and April 4, 2016 (Fundação Doutor Amaral Carvalho, Jau, SP). Malignant tumors from different sites and tissues were listed (11 International Classification of Diseases -ICD codes) but no other details on the study design were provided (e.g., are these studies controlled and randomized trials? What are the efficacy outcomes and the inclusion and exclusion criteria?). It is also unclear whether only "patients without therapeutic possibility" will be enrolled in the *syn*-PEA study.

clinical investigations of drug candidates insufficiently evaluated by preclinical studies.

Concluding remarks

It is very unlikely that *syn*-PEA or PEA-based medicines will eventually play a role in cancer treatment. The *syn*-PEA anticancer pill story, however, is unique in several aspects. Manufacture, prescription, dispensing and consumption of *syn*-PEA was authorized by a Federal Law (the effectiveness of which was suspended by a STF temporary decision). The Congress overwhelmingly passed the *syn*-PEA bill and the president signed it into law despite the fact that the Anvisa, the Brazilian Society for Advancement of Science (SBPC) and the country's physician association (AMB) strongly recommended Congress members and the president not to do it[38]. The MCTI also allocated substantial public funds to support R&D of an unlikely new anticancer drug. Furthermore, CONEP, the highest-level and most influential committee on human research ethics in Brazil, authorized the onset of *syn*-PEA trials in cancer patients in the absence of convincing evidence of anticancer activity and without an adequate and comprehensive set of preclinical safety data. Damages to the country international reputation regarding national drug regulation policies and human research ethical standards are unavoidable. The anticancer pill story, however, taught us an important lesson: the strength of popular beliefs in unsubstantiated allegations, whenever unethical politicians capture and endorse them, should not be underestimated. Incumbent politicians' ambitions, depending on a well-orchestrated lobby and other circumstances, eventually take precedence over general public interests, ethical principles and scientifically based decisions on drug regulatory affairs, thereby misleading decisions on scientific research support and on the approval of clinical study protocols.

REFERÊNCIAS

1. Smith CM. Origin and uses of primum non nocere: above all, do no harm! J Clin Pharmacol. 2005;45(4):371-7. doi:10.1177/0091270004273680
2. Outhouse EL. Amino-ethyl phosphoric ester from tumours. Biochem J. 1936;30(2):197-201. doi:10.1042/bj0300197
3. Outhouse EL. Further studies of amino-ethyl phosphoric ester-a compound apparently specific to malignant tumours. Biochem J. 1937;31(9):1459-63. doi:10.1042/bj0311459
4. Kano-Sueoka T, Cohen DM, Yamaizumi Z, Nishimura S, Mori M, Fujiki H. Phosphoethanolamine as a growth factor of a mammary carcinoma cell line of rat. Proc Natl Acad Sci USA. 1979;76(11):5741-4. doi:10.1073/pnas.76.11.5741
5. Arruda MSP, Correa MA, Venturini J, Félix MC, De Rosis AMB, Galhiane MS et al. The effect of phosphoethanolamine intake on mortality and macrophage activity in mice with solid Ehrlich tumors. Braz Arch Biol Technol. 2011;54(6):1203-10. doi:10.1590/S1516-89132011000600016
6. Ferreira AK, Meneguelo R, Marques FL, Radin A, Mendonça Filho O, Claro Neto S et al. Synthetic phosphoethanolamine a precursor of membrane phospholipids reduce tumor growth in mice bearing melanoma B16-F10 and in vitro induce apoptosis and arrest in G2/M phase. Biomed Pharmacother. 2012;66(7):541-8. doi:10.1016/j.biopha.2012.04.008
7. Ferreira AK, Meneguelo R, Pereira A, Mendonça Filho O, Chierice GO, Maria DA. Anticancer effects of synthetic phosphoethanolamine on Ehrlich ascites tumor: an experimental study. Anticancer Res. 2012;32(1):95-104.
8. Ferreira AK, Santana-Lemos BA, Rego EM, Mendonça Filho O, Chierice GO, Maria DA. Synthetic phosphoethanolamine has in vitro and in vivo anti-leukemia effects. Br J Cancer. 2013;109(11):2819-28. doi:10.1038/bjc.2013.510
9. Ferreira AK, Meneguelo R, Pereira A, Mendonça Filho O, Chierice GO, Maria DA. Synthetic phosphoethanolamine induces cell cycle arrest and apoptosis in human breast cancer MCF-7 cells through the mitochondrial pathway. Biomed Pharmacother. 2013;67(6):481-7. doi:10.1016/j.biopha.2013.01.012
10. Ferreira AK, Freitas VM, Levy D, Ruiz JL, Bydlowski SP, Rici RE et al. Anti-angiogenic and anti-metastatic activity of synthetic phosphoethanolamine. PLoS One. 2013;8(3):e57937. doi:10.1371/journal.pone.0057937
11. Universidade Federal do Ceará (UFC), Laboratório de Oncologia Experimental, Núcleo de Pesquisa e Desenvolvimento de Medicamentos. Avaliação do potencial citotóxico in vitro da fosfoetanolamina sintética (FS) e da fosfoetanolamina sintética nanoencapsulada (FSNE). Fortaleza: Núcleo de Pesquisa e Desenvolvimento de Medicamentos; [2016][access 2016 Jul 12]. Available from: http://www.mcti.gov.br/documents/10179/1274125/Relat%C3%B3rio+CI50_Fosfoetanolamina.pdf/c42404cc-3980-4c63-8200-3263a19cd5db
12. Dias LC, Dessoy MA, Barreiro EJ. Caracterização do conteúdo das cápsulas de fosfoetanolamina (FOS) para o MCTI. 2016[access 2016 Jul 12]. Available from: http://www.mcti.gov.br/ documents/ 10179/1274125/Relat%C3%B3rio+ Completo+de+S%C3% ADntese+e+Caracteriza%C3%A7%C3%A3o/4973d883-9782-4832-873a-b5069d702b24
13. Universidade Federal do Ceará - UFC, Faculdade de Medicina, Núcleo de Pesquisa e Desenvolvimento de Medicamentos – NPDM. Laudo técnico do estudo da fosfoetanolamina sintética: avaliação da possível atividade anticâncer da fosfoetanolamina sintética (FS) no carcinossarcoma 256 de Walker. Fortaleza: Laboratório de Oncologia Experimental; 2016[access 2016 Jul 12]. Available from: http://www.mcti.gov.br/documents/10179/1274125/Relatorio+2+Fosfoetanolamina+Carcinossarcoma+de+Walker+v01+de+15-05-2016/6e3083ce-2a1a-44f0-ba72-f80700e4aa86

14. Universidade Federal do Ceará - UFC, Faculdade de Medicina, Núcleo de Pesquisa e Desenvolvimento de Medicamentos – NPDM. Laudo técnico do estudo da fosfoetanolamina sintética: avaliação da possível atividade anticâncer da fosfoetanolamina sintética (FS) no sarcoma 18. Fortaleza: Laboratório de Oncologia Experimental; 2016[access 2016 Jul 12]. Available from: http://www.mcti.gov.br/documents/10179/1274125/Relatorio+3+Fosfoetanolamina+no+SARCOMA+180+v01+de+15-05-2016/8df7f867-048d-482e-b3f2-0c3749da106b

15. Centro de Inovação e Ensaios Pré-clínicos - CIEnP. Avaliação da atividade antitumoral da fosfoetanolamina sintética (USP- São Carlos) em modelo de tumor xenográfico de melanoma humano em camundongos: relatório final. Brasília, DF: Ministério da Ciência, Tecnologia e Inovação; 2016[access 2016 Jul 12]. Available from: http://www.mcti.gov.br/documents/10179/1274125/Relatorio+Tumor+Xenografico/415ff3fa-59b3-4e63-8d42-d258f3265235

16. Boyd MR. The NCI in vitro anticancer drug discovery screen: concept, implementation, and operation, 1985-1995. In: Teicher B. (Ed.). Anticancer drug development guide: preclinical screening, clinical trials, and approval. Totowa, NJ: Humana; 1997. p. 23-42.

17. Monga M, Sausville EA. Developmental therapeutics program at the NCI: molecular target and drug discovery process. Leukemia. 2002;16(4):520-6. doi:10.1038/sj.leu.2402464

18. Suggitt M, Bibby MC. 50 years of preclinical anticancer drug screening: empirical to target-driven approaches. Clin Cancer Res. 2005;11(3):971-81.

19. National Institutes of Health - NIH, National Cancer Institute. Developmental Therapeutics Program. Anti-cancer screening paradigm. Bethesda: National Cancer Institute; 2015[access 2016 Jul 15]. Available from: https://dtp.cancer.gov/ organization/dscb/ compoundSubmission/ decision.htm

20. Suggitt M, Cooper PA, Shnyder SD, Bibby MC. The hollow fibre model: facilitating anti-cancer pre-clinical pharmacodynamics and improving animal welfare. Int J Oncol. 2006;29(6):1493-9. doi:10.3892/ijo.29.6.1493

21. Temmink OH, Prins HJ, Gelderop E, Peters GJ. The hollow fibre assay as a model for in vivo pharmacodynamics of fluoropyrimidines in colon cancer cells. Br J Cancer. 2007;96(1):61-6. doi:10.1038/sj.bjc.6603507

22. Mi Q, Pezzuto JM, Farnsworth NR, Wani MC, Kinghorn AD, Swanson SM. Use of the in vivo hollow fiber assay in natural products anticancer drug discovery. J Nat Prod. 2009;72(3):573-80. doi:10.1021/np800767a

23. National Institutes of Health - NIH, National Cancer Institute. Developmental Therapeutics Program. DTP anti-cancer screening paradigm: flow chart. Bethesda: National Cancer Institute; 2015[access 2016 Jul 15]. Available from: https://dtp.cancer.gov/organization/dscb/ compoundSubmission/ ACSP_FlowChart.pdf

24. Sánchez-Martínez C, Gelbert LM, Lallena MJ, Dios A. Cyclin dependent kinase (CDK) inhibitors as anticancer drugs. Bioorg Med Chem Lett. 2015;25(17):3420-35. doi:10.1016/j.bmcl.2015.05.100

25. Williams CT. Food and drug administration drug approval process: a history and overview. Nurs Clin North Am. 2016;51(1):1-11. doi:10.1016/j.cnur.2015.10.007

26. Ciociola AA, Cohen LB, Kulkarni P, Kefalas C, Buchman A, Burke C. How drugs are developed and approved by the FDA: current process and future directions. Am J Gastroenterol. 2014;109(5):620-3. doi:10.1038/ajg.2013.407

27. Dickson M, Gagnon JP. Key factors in the rising cost of new drug discovery and development. Nat Rev Drug Discov. 2004;3(5):417-29. doi:10.1038/nrd1382

28. Roses AD. Pharmacogenetics in drug discovery and development: a translational perspective. Nat Rev Drug Discov. 2008;7(10):807-17. doi:10.1038/nrd2593

29. Thomas DW, Burns J, Audette J, Carrol A, Dow-Hygelund C, Hay M. Clinical development success rates 2006-2015. San Diego:Biomedtracker/Washington, DC: BIO/Bend: Amplion; 2016.

30. Ministério da Saúde (BR), Secretaria de Ciência Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia. Relatório de atividades do grupo de trabalho sobre a fosfoetanolamina. Brasília, DF: Ministério da Saúde; 2015[access 2016 Jul 15]. Available from: http://www.mcti.gov.br/documents/10179/1274125/22-12-2015+-+Relat%C3%B3rio+de+Atividades+do+Grupo+de+Trabalho+sobre+a+Fosfoetanolamina/d73d9f0f-16e8-4983-bce9-b5e57dfa2164

31. Instituto Nacional de Câncer José Alencar Gomes da Silva – INCA. Relatório do seminário sobre estudos preliminares da fosfoetanolamina sintética (FOS). Brasília, DF: Instituto Nacional de Câncer José Alencar Gomes da Silva; 2016[access 2016 May 17]. Available from: http://www.mcti.gov.br/documents/10179/1274125/Relat%C3%B3rio+do+Semin%C3%A1rio+sobre+estudos+preliminares+da+Fosfoetanolamina+Sint%C3%A9tica+%28FOS%29/2ca3e868-e3be-491f-9301-ff7bb3ccb99d

32. Escobar H. Governo vai investir R$ 10 milhões em estudo da fosfoetanolamina. Estadão, 12 nov 2015[access 2016 Apr 4];Ciência: 1. Available from: http://ciencia.estadao.com.br/blogs/herton-escobar/governo-vai-investir-r-10-milhoes-em-estudo-da-fosfoetanolamina/hml

33. Brasil. Lei nº 13.269, de 13 de abril de 2016. Autoriza o uso da fosfoetanolamina sintérica por pacientes diagnosticados com neoplasia maligna. Diário Oficial União. 14 abr 2016.

34. Supremo Tribunal Federal – STF. STF suspende eficácia da lei que autoriza uso da fosfoetanolamina. Notícias STF, 19 maio 2016[access 2016 Jun 27]. Available from: http://stf.jus.br/portal/geral/verImpressao.asp

35. Conselho Nacional de Saúde – CNS. Conselho aprova estudos sobre a fosfoetanolamina. 8 mar 2016[access 2016 Jul 12]. Available from: http://conselho.saude.gov.br/ultimas_noticias/2016/03mar08_conselho_aprova_estudos_sobre_fosfoetanolamina.html

36. Council for International Organizations of Medical Sciences – CIOMS. International ethical guidelines for biomedical research involving human subjects. Geneva: Council for International Organizations of Medical Science; 2002.

37. European Medicines Agency, Science Medicines Health. M3 (R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. London: European Medicines Agency; 2013. (EMA/CPMP/ICH/ 286/1995).

38. Escobar H. Brazil bill would legalize renegade cancer pill. Science. 2016;352(6281):18. doi:10.1126/science.352.6281.18

Conflito de Interesse

Os autores informam não haver qualquer potencial conflito de interesse com pares e instituições, políticos ou financeiros deste estudo.