Quality generics, copy drugs, counterfeit medicines – how are they different, and where are we in CML?

5 November 2023 • CML Horizons 2023 • Berlin / Germany

Advocacy Session #5: What role do generics play in CML today?

Nicole Schröter

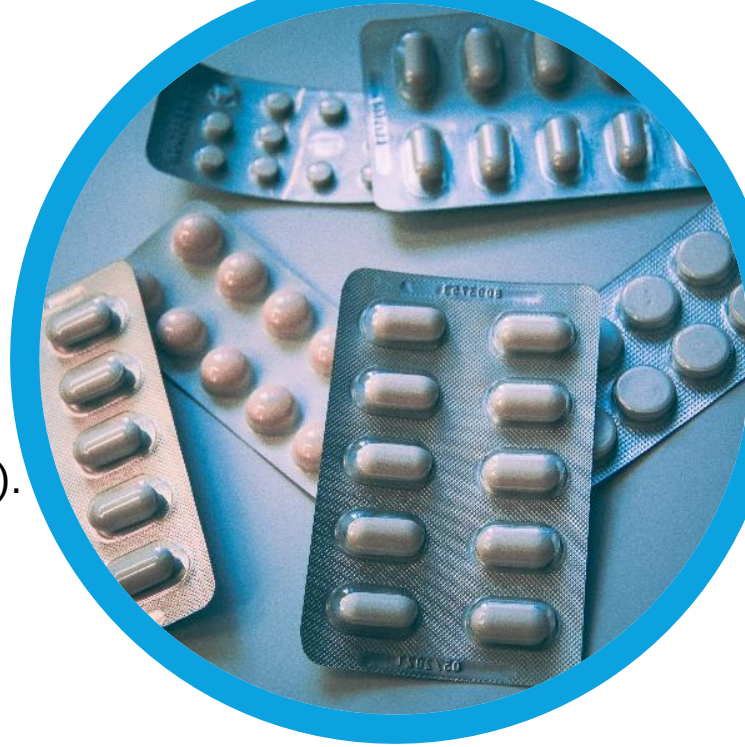
CML-CAB officer

CML Advocates Network

What will be covered

- Definition and distinction of terms
- Generics
  - Regulation
  - Cost & quality
- Generic CML TKIs
  - Switching to a generic CML TKI – what does the literature say?
  - Results from CMLAN´s field trial (2018)
  - What do the ELN guidelines say?
- The economic burden of cancer treatment and the role generics can play
- Falsified drugs & supply chain risks

Definition and distinction of terms (1/2)



Originator drug / innovator product

- **Pioneer** or **first-in-class drug**.
- Temporary **exclusive rights** to sell the medicine (patent protection, market exclusivity).
- Recoup R&D costs as well as the cost of failed drug candidates → high costs.
- **Brand name** (e.g. Glivec®, Sprycel®, etc.).

Generic drug

- **Legal copy** of an innovator drug.
- Interchangeable.
- **Legally marketed** after patent & exclusivity protection ends and **Marketing Authorisation** has been obtained.
- **Generic name** (e.g., imatinib) **or** a **brand name** (e.g. Veenat® by Natco or Imatib® by Cipla).

Definition and distinction of terms (2/2)

* Can pose significant risks to patients' health and safety!

Copy drug

- Sold **despite the drug still being patented** → illegal
- **Not approved** by regulatory authorities such as FDA or EMA.
- **Unknown standards** of quality, safety and efficacy.

Substandard drug

- **“out of specification” drugs** (not meeting the required quality standards or specifications)
- May lead to **lack of therapeutic equivalence** (impurities, degradation products, etc.)

Falsified drug

- Deliberately and **fraudulently mislabled** original or generic drugs.
- Examples: wrong, no or too little active ingredient; false information on origin, identity, or ingredients; fake packaging, etc.
- **Don’t provide the needed therapeutic value**.

*

World Health Organization

In 2017, WHO introduced the terms **"substandard"** and **"falsified medical products"** to replace the general term **“counterfeit drugs”** or **“fake drugs”**. Still, the terms are often used interchangeably in some contexts, which can lead to confusion.

Looking into generic medicines more deeply

Same quality standards and drug safety requirements as for branded drugs apply for generics
(at least in US & EU)

In tightly regulated markets, generic drugs are required to have:

- Same active ingredient, amount of active ingredient, purity
- Same pharmacokinetic & pharmacodynamic properties
- Same stability / shelf life
- Same mechanism of action, safety & efficacy
- Same therapeutic indication & route of administration

What is allowed are…

- Different salts and excipients (pharmacologically inert agents)
- Different manufacturing process
- Different product name & packaging

As long as they do not differ significantly in their safety and/or efficacy properties.

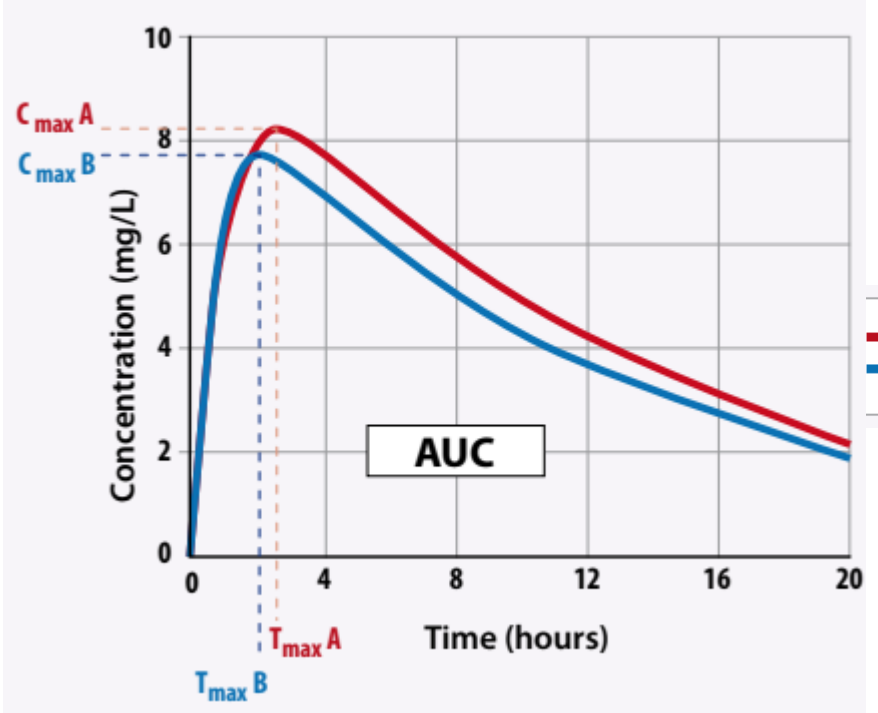
If so, the generic manufacturer must submit further proof of efficacy and safety.

Sources:
https://www.progenerika.de/topics/quality-of-generic-medicines/generic-vs-original-a-comparison/?lang=en – accessed 29.10.2023
https://gabionline.net/reports/Quality-control-for-generic-drugs – accessed 29.10.2023

Bioequivalence studies

Bioequivalence = Therapeutic equivalence

- Comparative studies on healthy volunteers.
- Prove that the generic drug acts in the body in the same way as the innovator drug
- **Same levels of active substance.**
- If **onset of action, plasma concentration** and **duration of action** are comparable, the generic is considered **"bioequivalent"** to the reference drug → it is presumed to be **“therapeutically equivalent”** and therefore interchangeable (regulatory assumption)



C_{max} maximum plasma drug concentration

T_{max} time required to achieve a maximal concentration

AUC total area under the plasma drug concentration-time curve

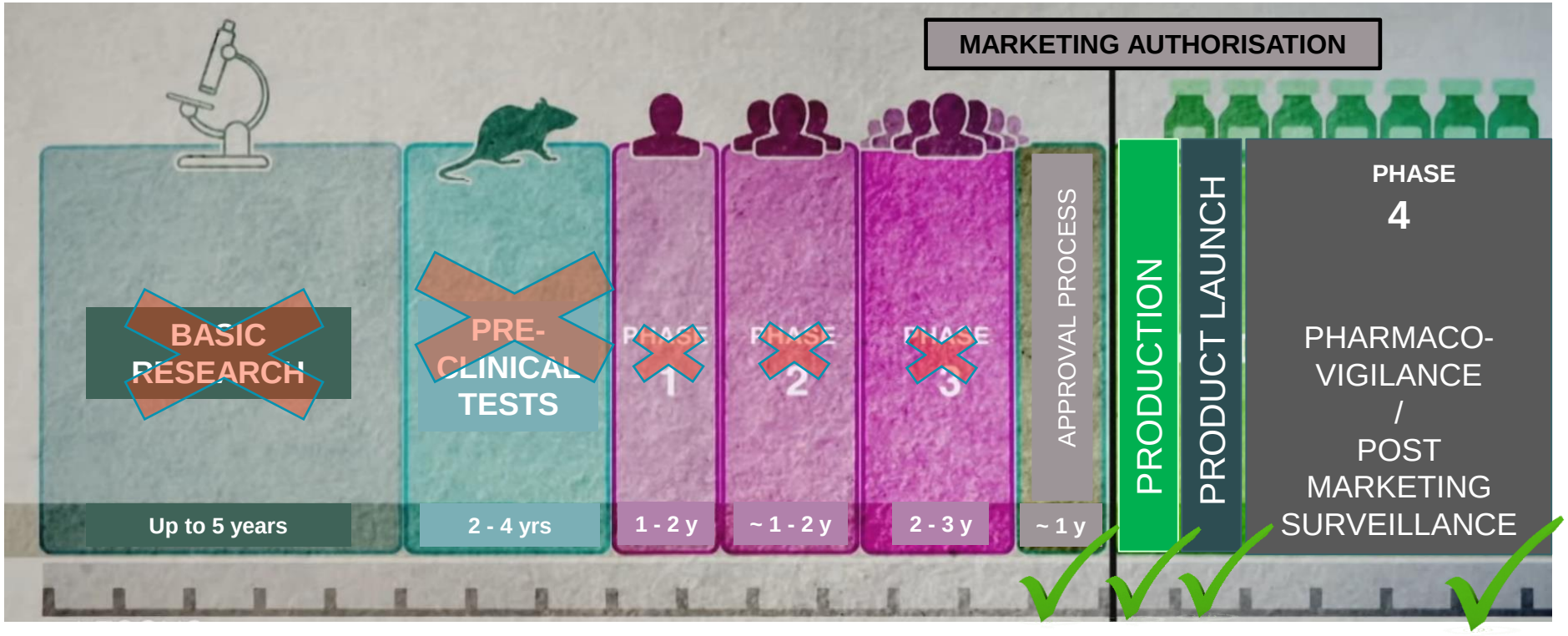
Sources:

EUPATI Toolbox Presentation on Generic Medicines - accessed 29.09.2023

sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/therapeutic-equivalence - accessed 29.09.2023

bpac.org.nz/magazine/2009/generics/docs/bpjse_generics_bio_pages_4-8.pdf - accessed 29.09.2023

Drug development and approval process: generic vs. originator product

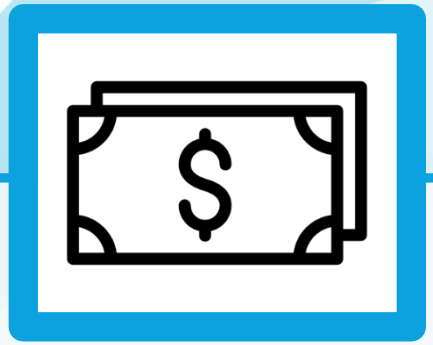


~ 15 years
~ 400 million to 1.5 billion EUR
~ 1-2% success rate

Source: Modified from „Impfen - Wettlauf mit dem Virus – Leschs Kosmos Spezial“, 26 January 2021
https://www.youtube.com/watch?v=UBQeVO6G0gM

Cost and Quality of approved Generic Medicines

- Generics must comply with appropriate **regulatory approval processes** assessing and ensuring quality, safety, and efficacy.
- Approved generics are **regulated** in the same way as the original medicines.
- Manufacturing facilities and conditions must be of high standard (GMP, GDP, etc.) → regular inspections of facilities e.g. by FDA.
- Collection and reporting of additional post-marketing safety data are required as for originators.

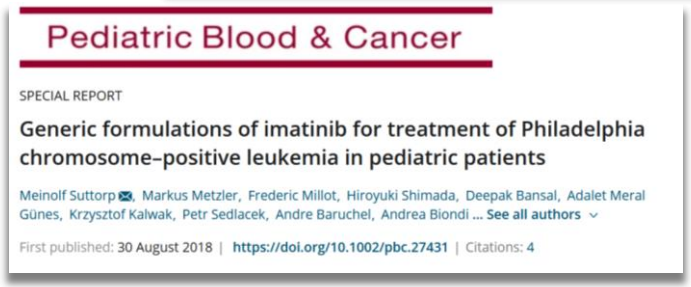


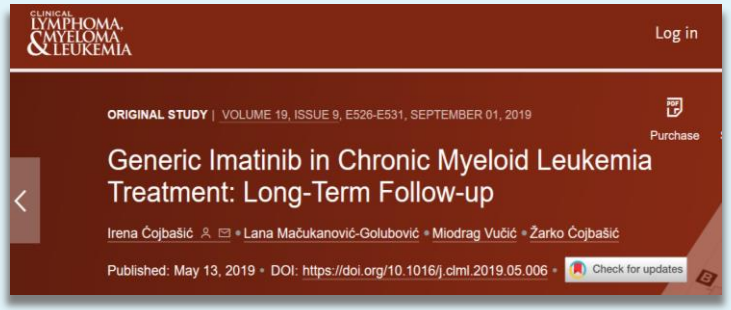
- **Reasons for lower cost option:**
  - ✓ Nearly no development costs (no clinical research)
  - ✓ No clinical studies
  - ✓ Low marketing costs (original drug is known to and used by physicians)
  - ✓ Competition
- Because of their comparatively low cost, the equality of generics and original medicines is **often questioned by patients.**

Source: EUPATI Toolbox Presentation on Generic Medicines - accessed 29.09.2023

Switching from Glivec® to generic imatinib - what does the literature say?

- There are numerous national and international studies and observational studies (USA, Italy, Serbia, Latvia, Poland, India, etc.)
- Efficacy and safety: the available clinical data consistently show that the **generics are at least not inferior to the original**
- Tolerability: New and sometimes more pronounced side effects were reported → psychological effect? → excipients?
- Cases in which generics were even better tolerated than the reference drug have also been reported.





A systematic literature review on generic imatinib use in CML evaluating 36 papers concludes: “Generics not inferior to original imatinib“

- Systematic literature review carried out by three Turkish hematologists through Dec 2020.
- Published in *Blood Adv*. in Sept 2021.
- 91 articles were accessed, 36 full text papers were evaluated.
- Both in vitro and in vivo studies of generic imatinib showed comparable results with branded imatinib in terms of bioequivalence and bioavailability.
- **In most studies, generics were comparable with the original molecule in terms of efficacy and safety, both in newly diagnosed patients and after switching from Gleevec.**
- **3 studies showed failure** of non-originators to maintain response: in 2 cases (Egypt), clearly non-authorized copy drugs! In 12 cases, Copy-drugs? Substandard drugs? Dubious involvement by manufacturer of innovator drug (*“Financial support for medical editorial assistance was provided by Novartis (…).”)* – how seriously can these negative reports be taken?


blood advances ISSUES LATEST ARTICLES GUIDELINES COLLECTIONS AUTHOR CENTER ABOUT

SYSTEMATIC REVIEW | SEPTEMBER 3, 2021

Current evidence on the efficacy and safety of generic imatinib in CML and the impact of generics on health care costs

Abdülkadir Erçalışkan, Duygu Seyhan Erdoğan, Ahmet Emre Eşkazan

Check for updates

Blood Adv (2021) 5 (17): 3344–3353.

https://doi.org/10.1182/bloodadvances.2021004194 Article history

Split-Screen Share Tools PDF

Abstract

Since the introduction of imatinib, the management of chronic myeloid leukemia (CML) has changed considerably. Tyrosine kinase inhibitors (TKIs) are the mainstay of CML treatment; however, the high financial burden of TKIs can be problematic for both the patients and health care systems. After the emergence of generics, reimbursement policies of many countries have changed, and generics offered an alternative treatment option for CML patients. There are many papers published on the use of generics in CML patients with conflicting results regarding both efficacy and safety. In this paper, we systematically reviewed the current literature on generic imatinib use in CML, and 36 papers were evaluated. Both in vitro and in vivo studies of generic imatinib showed comparable results with branded imatinib in terms of bioequivalence and bioavailability. In most studies, generics were comparable with the original molecule in terms of efficacy and safety, both in newly diagnosed patients and after switching from Gleevec. Some generic studies showed contradictory findings regarding efficacy and toxicity, and these

- **Conclusion: “generally favourable efficacy and safety of generics worldwide to date”**, but **more time will be needed “to draw firmer conclusions on the longer-term outcomes of generics.”**

Source: ErçalışkanA, Seyhan ErdoğanD, Eşkazan AE. Current evidence on the efficacy and safety of generic imatinib in CML and the impact of generics on health care costs. *Blood Adv*. 2021;5(17):3344-3353. doi:10.1182/bloodadvances.2021004194 – accessed 29.10.2023

Use of generic imatinib as first-line treatment in patients with CML: the GIMS (Glivec to Imatinib Switch) study

- Observational, retro-prospective, multicenter analysis of patients with CML in chronic phase with stable disease for whom treatment was switched from brand to generic imatinib.
- Carried out in Italy (**12 Italian institutes**) with 5 types of generic drugs according to individual hospital licenses, i.e. all products meeting EU standards.
- 200 patients enrolled between Sept 2017 and June 2019.
- **Conclusions:**
  - **“data indicate that generic imatinib does not have deleterious effects on CML control and present an acceptable safety profile, similar or better than brand imatinib.”**
  - **“useful to clarify doubts and fears among CML patients and doctors about generic safety and effectiveness, provided that strict quality controls be implemented.”**

BLOOD RESEARCH VOLUME 55 · NUMBER 3 September 2020 ORIGINAL ARTICLE

Use of generic imatinib as first-line treatment in patients with chronic myeloid leukemia (CML): the GIMS (Glivec to Imatinib Switch) study

Maria Gemelli[1#], Elena Maria Elli[2#], Chiara Elena[3], Alessandra Iurlo[4], Tamara Intermesoli[5], Margherita Maffioli[6], Ester Pungolino[7], Maria Cristina Carraro[8], Mariella D'Adda[9], Francesca Lunghi[10], Michela Anghileri[11], Nicola Polverelli[12], Marianna Rossi[13], Mattia Bacciocchi[14], Elisa Bono[3], Cristina Bucelli[4], Francesco Passamonti[6], Laura Antolini[15], Carlo Gambacorti-Passerini[2,14]

[1]Oncology Unit, San Gerardo Hospital, ASST-Monza, [2]Hematology Division and Bone Marrow Unit, Ospedale San Gerardo, ASST-Monza, Monza, [3]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, [4]Hematology Division, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, [5]Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII, Bergamo, [6]Hematology Unit, Ospedale di Circolo, Varese, [7]Division of Hematology, ASST Grande Ospedale Metropolitano Niguarda, Milano, [8]Hematology and Transfusional Medicine Unit, ASST Fatebenefratelli Sacco, Milan, [9]Department of Hematology, ASST Spedali Civili di Brescia, Brescia, [10]Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, IRCCS Milano, [11]Oncology Department, ASST Lecco, Lecco, [12]Chair of Hematology, Unit of Blood Diseases and Stem Cell Transplantation, University of Brescia, ASST Spedali Civili di Brescia, Brescia, [13]Department of Hematology, Cancer Center, IRCCS Humanitas Research Hospital/Humanitas University, Rozzano, [14]Department of Medicine and Surgery, University of Milano-Bicocca, [15]Center of Biostatistics for Clinical Epidemiology, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2020.2020130
Blood Res 2020;55:139-145.

Received on June 5, 2020
Revised on July 14, 2020
Accepted on July 24, 2020

*These authors contributed equally to this work.

Background
Generic formulations of imatinib mesylate have been introduced in Western Europe since 2017 to treat patients with chronic myeloid leukemia (CML). However, results on the safety and efficacy of generic formulations are contrasting. The aim of this study was to investigate the safety and efficacy of generic imatinib in CML patients treated in 12 Italian institutes.

Methods
This is an observational, retro-prospective analysis of patients with CML for whom the treatment was switched from brand to generic imatinib. We analyzed and compared the variation in quantitative PCR values before and after the switch, and the proportion of patients who maintained molecular response after changing from brand to generic imatinib. Adverse events (AEs) were also evaluated.

Source: Carlo Gambacorti-Passerini, Ph.D. et al, Blood Res 2020; 55(3): 139-145, Published online September 30, 2020, https://doi.org/10.5045/br.2020.2020130 https://www.bloodresearch.or.kr/journal/view.html?uid=2372&vmd=Full& - accessed 29.10.2023

Switching from Sprycel® to generic dasatinib - what does the literature say?

- Sprycel® will become off-patent for the indication CML in 2025 only. Study data are sparse (**2 studies found in PubMed** only).
- Back in **2014**, CML Advocates Network members reported alternatives to the original Sprycel® even in 32 countries! **Presumably, many of those were of dubious quality…**
- **Observational studies and case studies give no reason to doubt the efficacy, safety or tolerability of the available approved quality generics.**


National Library of Medicine
National Center for Biotechnology Information

PubMed.gov

Search PubMed

Advanced

Save

Multicenter Study > Curr Med Sci. 2018 Dec;38(6):1005-1011. doi: 10.1007/s11596-018-1976-0. Epub 2018 Dec 7.

Efficacy and Safety of Generic Dasatinib as a Second-line Treatment for Patients with Chronic Myeloid Leukemia: a Multicenter Retrospective Study in Hubei Province, China

Li-Feng Chen [1], Guo-Lin Yuan [2], Zhao-Dong Zhong [1], Ping Zou [1], Deng-Ju Li [3], Yin Bao [4], Hong-Bo Ren [5], Li Meng [6], Wei-Ming Li [7]

Affiliations + expand

PMID: 30536062 DOI: 10.1007/s11596-018-1976-0


Multicenter Study Clin Lymphoma Myeloma Leuk. 2022 Sep;22(9):e867-e873. doi: 10.1016/j.clml.2022.05.002. Epub 2022 May 21.

Efficacy and Safety of Generic Dasatinib in Patients With Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase: A Multicenter Prospective Study in China

Wenjuan Yu [1], Xin Du [2], Weiguang Wang [3], Jin Lou [2], Peng Liu [3], Li Meng [4], Jie Jin [5]

Affiliations

PMID: 35842355 DOI: 10.1016/j.clml.2022.05.002

Abstract

Background: Brand-name dasatinib was approved for newly diagnosed chronic myeloid leukemia-chronic phase (CML-CP) patients due to its deeper and faster molecular response than imatinib. Generics, as the alternative, low-cost forms, are much in demand. This study aimed to evaluate the efficacy and safety of generic dasatinib (Yinishu) as a first-line treatment in CML-CP.

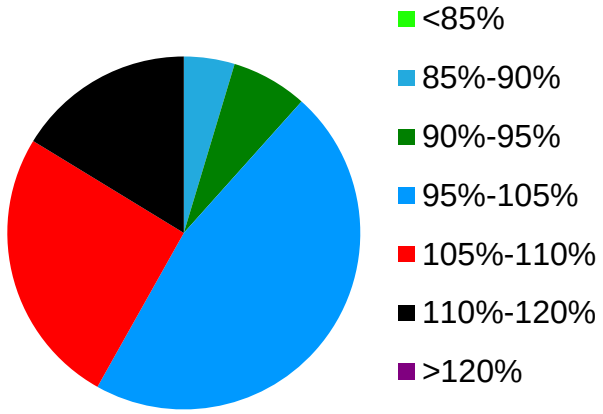
1 multicenter retrospective study from China with Yinishu, a generic dasatinib made in China, administered as a second-line treatment (published 12/2018): „*The results showed that there were no significant differences in the rates of optimal response between Yinishu and SPRYCEL for patients who started second-line treatment because of treatment failure.*"

Prospective, multicenter, single-arm study from May 2016 to October 2018 with a 2-year follow-up analysis carried out in China with Yinishu, a generic dasatinib made in China, administered to newly diagnosed CML patients (published 05/2022): „*Generic dasatinib is an effective option for newly diagnosed CML-CP patients, producing an MMR early in a greater number of patients during their therapy.*"

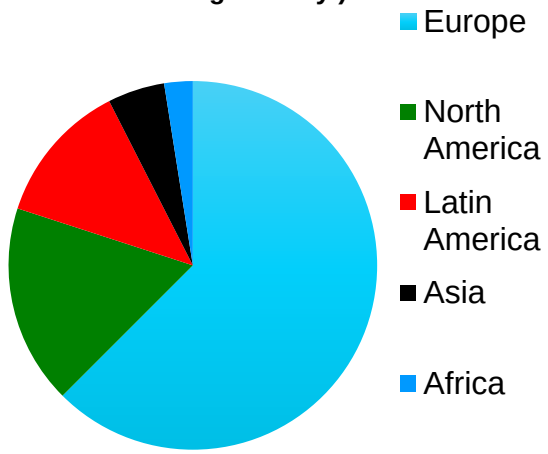
CML Advocates Network initiative: Determination of active ingredient in generic imatinib

- Samples collected at CML Horizons 2017 from CML Advocates Network members attending CML Horizons.
- 43 different Imatinib products from 22 countries were analysed in a laboratory in Israel.

% of active ingredient found vs expected



Countries of sale of samples
(not manufacturing country!)



CML Advocates Network (2018, unpublished) – Source: Jan Geissler, Generic TKIs (in CML): An introduction. CML Horizons 2020.

Determination of Imatinib Mesylate active pharmaceutical ingredient in generic drugs

	NAME	COUNTRY OF SALE	ACTIVE INGREDIENT EXPECTED (mg)	ACTIVE INGREDIENT FOUND 1 PILL (mg)	PERCENTAGE
1	Mesilato de Imatinib	Brazil	400	432	108
2	Matinac	Colombia	100	89	89
3	Meaxin	Slovenia	400	400	100
4	Siotinib	Ecuador	400	432	108
5	Sandoz	Finland	100	104	104
6	Accord	Finland	100	104	104
7	Imatinib Ratiopharm	Finland	100	99	99
8	Imatinib Heumann	Germany	400	418	104
9	Imatinib VMG	Guatemala	400	429	107
10	Nibix	Hungary	400	442	111
11	Imakerbin	Luxemburgo	400	409	102
12	Accord	Malta	400	415	104
13	Imatinib Accord	Malta	400	446	111
14	Imatinib Cooper	Morocco	100	116	116
15	Sandoz	Netherlands	400	372	93
16	Sandoz	Netherlands	100	98	98
17	Teva	Netherlands	100	104	104
18	Imatinib Accord	Palestine	400	440	110
19	Timab	Peru	400	417	104
20	Nibix	Poland	400	434	108
21	Imatinib Accord	Poland	100	112	112
22	Telux	Poland	400	408	102
23	Imatinib	Russia	400	383	96
24	Alvotinib	Serbia	100	119	119
25	Imatinib PharmaSwiss	Serbia	100	95	95
26	Meaxin	Serbia	100	108	108
27	Imatinib Teva	Spain	400	399	100
28	Imatinib Kern Pharma	Spain	400	387	97
29	Alvotinib	Thailand	400	407	102
30	Teva	UK	400	429	107
31	Intrapharm	UK	400	431	108
32	Imatinib Teva	Ukraine	400	399	100
33	Imatinib Grindex	Ukraine	100	106	106
34	Gleevec	USA	100	106	106
35	Gleevec Novartis	USA	100	98	98
36	Gleevec Novartis	USA	400	436	109
37	Imatinib Mesylate	USA	400	443	111
38	Imatinib Mesylate	USA	400	375	94
39	Gleevec (Flat Pack)	USA	400	360	90
40	Gleevec	USA	400	397	99
41	Teva		100	104	104
42	Novartis		400	446	111
43	Novartis		100	109	109

Switching from Glivec® to generic imatinib – what do the ELN guidelines say?

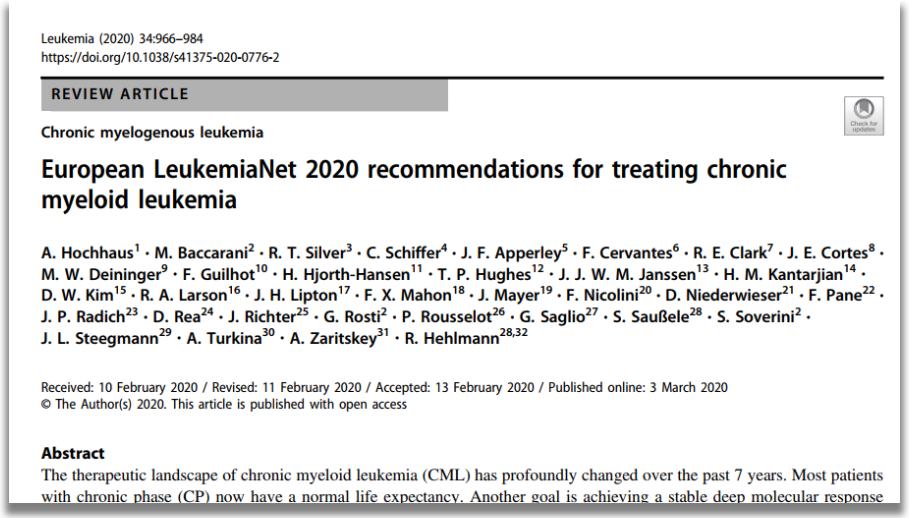
- Generic TKIs are an **acceptable alternative** to the original TKI as long as the **same quality** has been demonstrated and the same dosage is administered.
- **Life-long therapy** for most patients

  → **Cost-effectiveness** of treatment is an important consideration.
- Generic imatinib is a **cost-effective initial treatment for chronic phase CML**.

Recommendations of the Expert Commission:

- **More frequent molecular monitoring and assessment of side effects** for up to 6 months after switching to generic TKI.
- Subsequently: monitoring of response analogous to the original TKI.
- **No switching between different generic preparations** with the same active ingredient.

Source: European LeukemiaNet 2020 recommendations for treating CML - Patient-friendly Summary



Leukemia (2020) 34:966–984
https://doi.org/10.1038/s41375-020-0776-2

REVIEW ARTICLE

Chronic myelogenous leukemia

European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

A. Hochhaus[1] · M. Baccarani[2] · R. T. Silver[3] · C. Schiffer[4] · J. F. Apperley[5] · F. Cervantes[6] · R. E. Clark[7] · J. E. Cortes[8] · M. W. Deininger[9] · F. Guilhot[10] · H. Hjorth-Hansen[11] · T. P. Hughes[12] · J. J. W. M. Janssen[13] · H. M. Kantarjian[14] · D. W. Kim[15] · R. A. Larson[16] · J. H. Lipton[17] · F. X. Mahon[18] · J. Mayer[19] · F. Nicolini[20] · D. Niederwieser[21] · F. Pane[22] · J. P. Radich[23] · D. Rea[24] · J. Richter[25] · G. Rosti[2] · P. Rousselot[26] · G. Saglio[27] · S. Saußele[28] · S. Soverini[2] · J. L. Steegmann[29] · A. Turkina[30] · A. Zaritskey[31] · R. Hehlmann[28,32]

Received: 10 February 2020 / Revised: 11 February 2020 / Accepted: 13 February 2020 / Published online: 3 March 2020

Abstract
The therapeutic landscape of chronic myeloid leukemia (CML) has profoundly changed over the past 7 years. Most patients with chronic phase (CP) now have a normal life expectancy. Another goal is achieving a stable deep molecular response

Patient-friendly summary available in 18 languages!

Recommendations for Treating People Living with CML

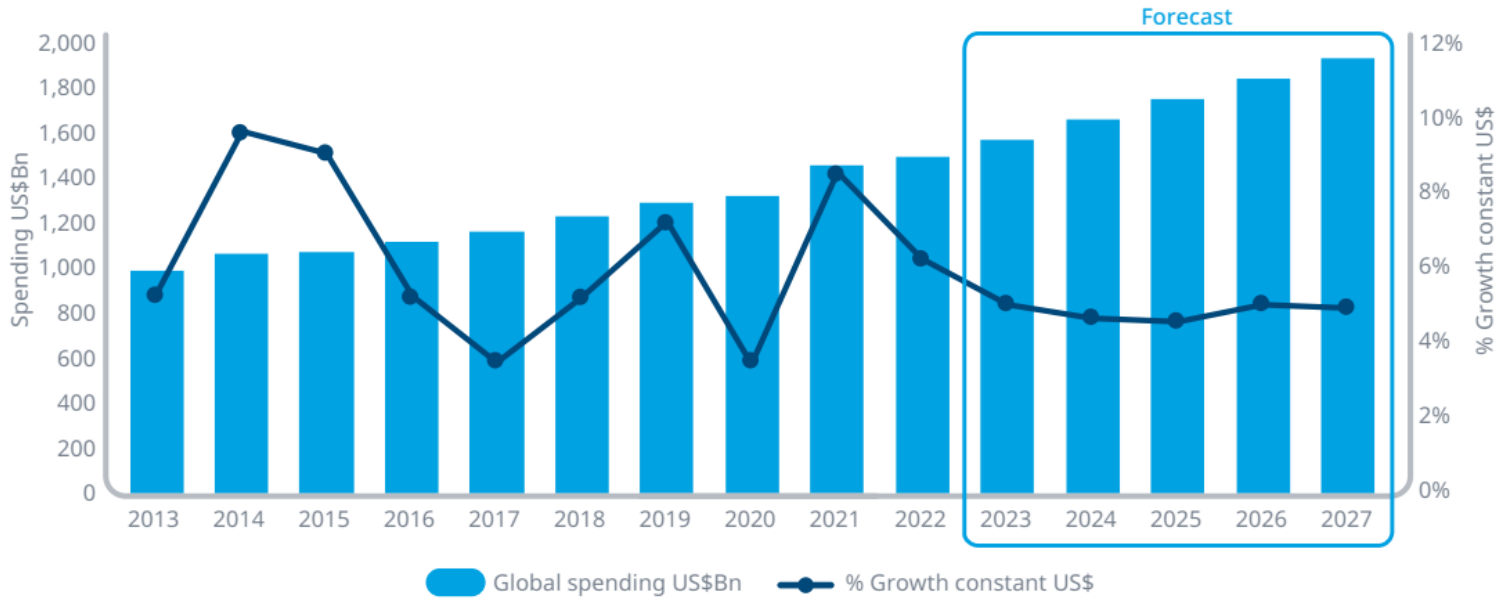
A patient-friendly summary of the European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

Published by the
CML AdvocatesNetwork

“The elephant in the room – the economic adverse event”[1]

The global medicine market — using invoice price levels — is expected to grow at 3–6% CAGR through 2027 to about $1.9Tn

Exhibit 14: Global medicine market size and growth 2013–2027



Source: IQVIA Market Prognosis, Sep 2022; IQVIA Institute, Nov 2022.

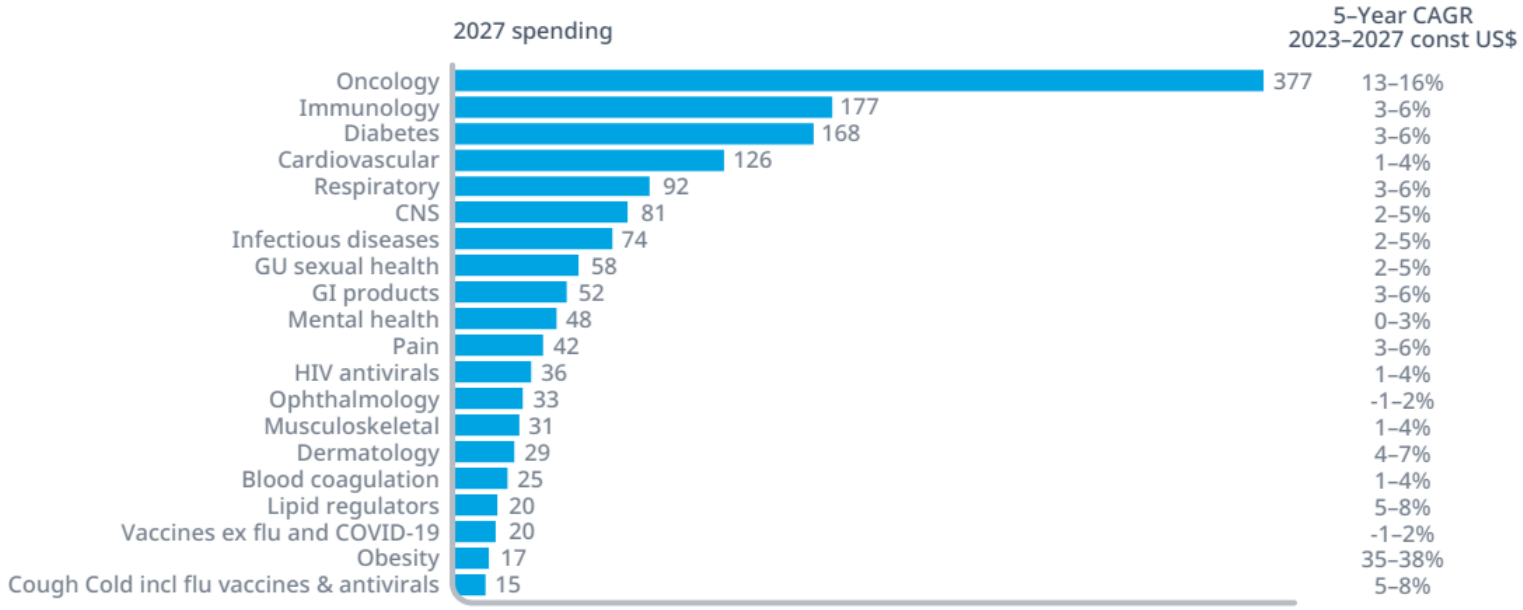
[1] Jeffrey H. Lipton, Leukemia Group, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada.

Source: Global Use of Medicines in 2020. Report by the IQVIA Institute for Human Data Science https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2023

“The elephant in the room – the economic adverse event”[1]

Oncology and obesity lead growth while immunology slows due to biosimilars, many other classes growing in mid-single digits

Exhibit 34: Top 20 therapy areas in 2027 in terms of global spending with forecast 5-year CAGRs, const US$



Source: IQVIA Forecast Link, IQVIA Institute, Nov 2022.

[1] Jeffrey H. Lipton, Leukemia Group, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada. Source: Lipton, J.H. The expanding CML treatment landscape: an introspective commentary. *Blood Cancer J.* **13**, 145 (2023). https://doi.org/10.1038/s41408-023-00918-3 - accessed 30.10.2023

Source: Global Use of Medicines in 2020. Report by the IQVIA Institute for Human Data Science https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2023

“Introducing generic alternatives is the only intervention that consistently and substantially lowers prescription drug”[1]

- **Specifics of cancer therapy:**
  - Intensive research and development of new drugs
  - Newer active ingredients are still subject to patent protection and are therefore expensive.
- **The more important it is to switch to generics where possible**
  - to support research into new, expensive cancer therapies **by freeing up funds**.
  - to ensure the overall supply of medicines **by avoiding global healthcare systems to collapse**.

  → **Generics play a crucial role in reshaping economic burden!**
- Not all generics are the same especially outside western world - **standards for safety and efficacy must be established for all patients regardless of where they live.**
- We must advocate for **good quality (generic) drugs** produced by reliable pharmaceutical manufacturers and provided through secure distribution chains.
- More needs to be done to **avoid falsified medicines and substandard drugs** entering the medicines supply chain.

[1] Bryan Walsh, Postdoctoral Research Fellow, Brigham and Women’s Hospital, Harvard Medical School.
Source: https://www.commonwealthfund.org/blog/2021/skinny-labeling-pathway-timely-generic-drug-competition - accessed 30.10.2023

Falsified drugs can cause harm to patients and even lead to death a serious danger to individual patients and to public health

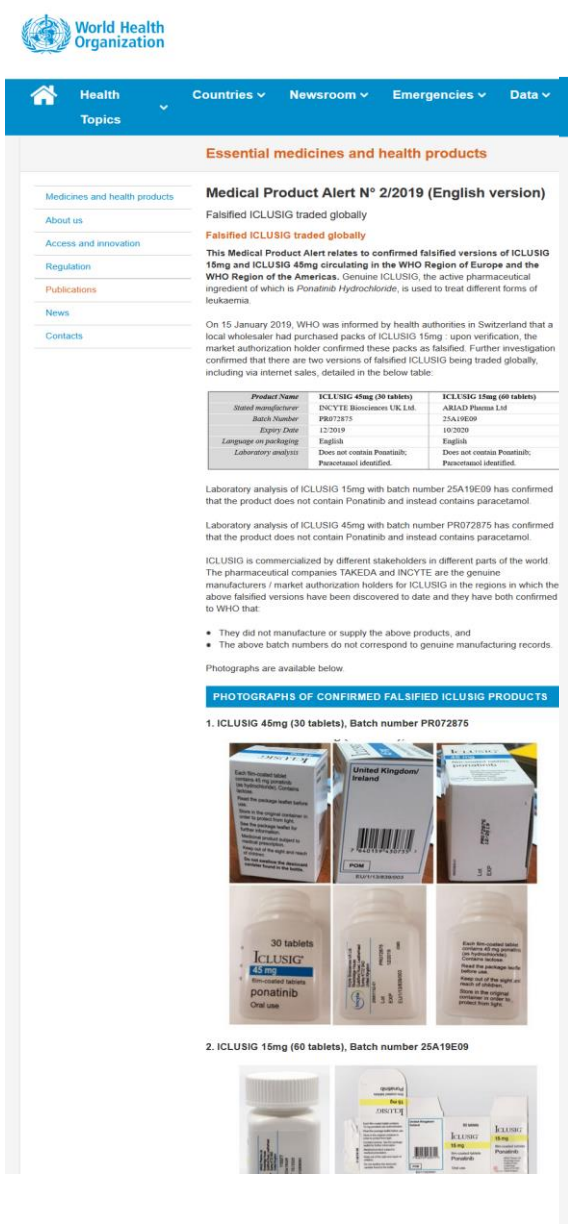
- In 2011 the EU indicated an **alarming increase in falsified medicines**.
- Consumers worldwide are increasingly comfortable **purchasing their medicines online.**
- **Convenience** and **cost** are the main drivers, a trend that has been accelerated by COVID-19.
- Of the roughly 35,000 **online pharmacies worldwide**, **95% operate illegally**,
  - not requiring a valid prescription
  - selling controlled substance such as opioids + non-authorized medicines
  - not holding the required licences to operate a pharmacy.
- The WHO estimates that over **half the medicines sold via the internet are falsified**.
- Coordinated efforts by WHO, Interpol, World Customs organisation, etc. to tackle the threat!

Sources: ASOP Global Foundation, asopfoundation.pharmacy/wp-content/uploads/2021/07/ASOP-Global-Foundation-2021-Consumer-Behavior-Survey-Key-Findings_Final-7.9.2021.pdf - accessed 1.11.2023
EUPATI Toolbox: toolbox.eupati.eu/resources/falsified-medicines - accessed 1.11.2023
nabp.pharmacy/wp-content/uploads/2022/10/Rogue-Rx-Activity-Report-Disrupting-Illegal-Online-Pharmacies-2022.pdf - accessed 1.11.2023
thelancet.com/journals/lancet/article/PIIS0140-6736(15)00394-3/fulltext - accessed 1.11.2023
The Lancet: Rise in online pharmacies sees counterfeit drugs go global, https://doi.org/10.1016/S0140-6736(15)00394-3 - accessed 1.11.2023

The threat is real – also in CML: the example of "Ponatinib" (ICLUSIG®) 2019

- **Four variations of a falsified ponatinib** were traded globally, including via internet sales.
- Tablets contained **paracetamol instead of ponatinib**.
- **Patient community informed the company** before WHO alert went out, based on informal information received from a regulatory staff member.
- Falsified products were discovered in Argentina, Malaysia, Colombia, Switzerland, Turkey, as well as on the internet.
- A **criminal investigation** was initiated.
- **Addressed in CML-CAB with manufacturer of original product. Difficult discussions!**

Source: modified from „Jan Geissler - Impact of falsified medicines on patients and the role which patient organisations should have in addressing counterfeit issues", MPP Annual Conference, October 2020


World Health Organization

Health Topics | Countries | Newsroom | Emergencies | Data

Essential medicines and health products

Medicines and health products
About us
Access and innovation
Regulation
Publications
News
Contacts

Medical Product Alert N° 2/2019 (English version)

Falsified ICLUSIG traded globally

Falsified ICLUSIG traded globally

This Medical Product Alert relates to confirmed falsified versions of ICLUSIG 15mg and ICLUSIG 45mg circulating in the WHO Region of Europe and the WHO Region of the Americas. Genuine ICLUSIG, the active pharmaceutical ingredient of which is *Ponatinib Hydrochloride*, is used to treat different forms of leukaemia.

On 15 January 2019, WHO was informed by health authorities in Switzerland that a local wholesaler had purchased packs of ICLUSIG 15mg . upon verification, the market authorization holder confirmed these packs as falsified. Further investigation confirmed that there are two versions of falsified ICLUSIG being traded globally, including via internet sales, detailed in the below table:

Product Name	ICLUSIG 45mg (30 tablets)	ICLUSIG 15mg (60 tablets)
Stated manufacturer	INCYTE Biosciences UK Ltd.	ARIAD Pharma Ltd
Batch Number	PR072875	25A19E09
Expiry Date	12/2019	10/2020
Language on packaging	English	English
Laboratory analysis	Does not contain Ponatinib; Paracetamol identified.	Does not contain Ponatinib; Paracetamol identified.

Laboratory analysis of ICLUSIG 15mg with batch number 25A19E09 has confirmed that the product does not contain Ponatinib and instead contains paracetamol.

Laboratory analysis of ICLUSIG 45mg with batch number PR072875 has confirmed that the product does not contain Ponatinib and instead contains paracetamol.

ICLUSIG is commercialized by different stakeholders in different parts of the world. The pharmaceutical companies TAKEDA and INCYTE are the genuine manufacturers / market authorization holders for ICLUSIG in the regions in which the above falsified versions have been discovered to date and they have both confirmed to WHO that:

- They did not manufacture or supply the above products, and
- The above batch numbers do not correspond to genuine manufacturing records.

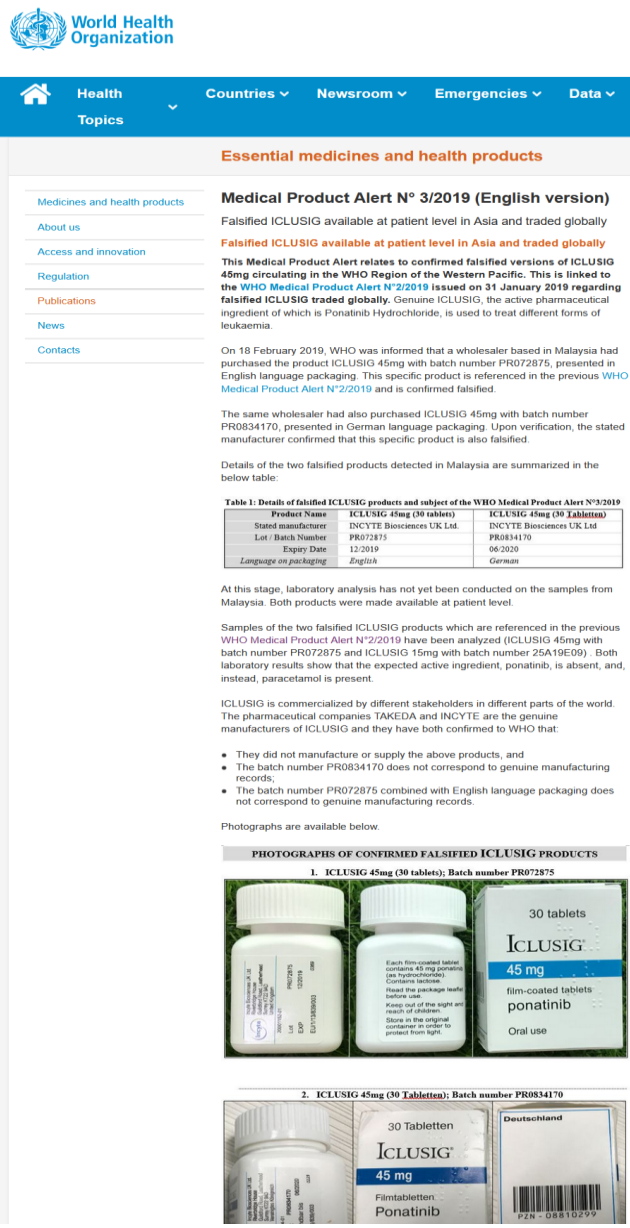
Photographs are available below.

PHOTOGRAPHS OF CONFIRMED FALSIFIED ICLUSIG PRODUCTS

1. ICLUSIG 45mg (30 tablets), Batch number PR072875

2. ICLUSIG 15mg (60 tablets), Batch number 25A19E09

https://www.who.int/news/item/01-02-2019-medical-product-alert-n-2-2019-(english-version)


World Health Organization

Health Topics | Countries | Newsroom | Emergencies | Data

Essential medicines and health products

Medicines and health products
About us
Access and innovation
Regulation
Publications
News
Contacts

Medical Product Alert N° 3/2019 (English version)

Falsified ICLUSIG available at patient level in Asia and traded globally

Falsified ICLUSIG available at patient level in Asia and traded globally

This Medical Product Alert relates to confirmed falsified versions of ICLUSIG 45mg circulating in the WHO Region of the Western Pacific. This is linked to the WHO Medical Product Alert N°2/2019 issued on 31 January 2019 regarding falsified ICLUSIG traded globally. Genuine ICLUSIG, the active pharmaceutical ingredient of which is Ponatinib Hydrochloride, is used to treat different forms of leukaemia.

On 18 February 2019, WHO was informed that a wholesaler based in Malaysia had purchased the product ICLUSIG 45mg with batch number PR072875, presented in English language packaging. This specific product is referenced in the previous WHO Medical Product Alert N°2/2019 and is confirmed falsified.

The same wholesaler had also purchased ICLUSIG 45mg with batch number PR0834170, presented in German language packaging. Upon verification, the stated manufacturer confirmed that this specific product is also falsified.

Details of the two falsified products detected in Malaysia are summarized in the below table:

Table 1: Details of falsified ICLUSIG products and subject of the WHO Medical Product Alert N°3/2019

Product Name	ICLUSIG 45mg (30 tablets)	ICLUSIG 45mg (30 Tabletten)
Stated manufacturer	INCYTE Biosciences UK Ltd.	INCYTE Biosciences UK Ltd
Lot / Batch Number	PR072875	PR0834170
Expiry Date	12/2019	06/2020
Language on packaging	*English*	*German*

At this stage, laboratory analysis has not yet been conducted on the samples from Malaysia. Both products were made available at patient level.

Samples of the two falsified ICLUSIG products which are referenced in the previous WHO Medical Product Alert N°2/2019 have been analyzed (ICLUSIG 45mg with batch number PR072875 and ICLUSIG 15mg with batch number 25A19E09) . Both laboratory results show that the expected active ingredient, ponatinib, is absent, and, instead, paracetamol is present.

ICLUSIG is commercialized by different stakeholders in different parts of the world. The pharmaceutical companies TAKEDA and INCYTE are the genuine manufacturers of ICLUSIG and they have both confirmed to WHO that:

- They did not manufacture or supply the above products, and
- The batch number PR0834170 does not correspond to genuine manufacturing records;
- The batch number PR072875 combined with English language packaging does not correspond to genuine manufacturing records.

Photographs are available below.

PHOTOGRAPHS OF CONFIRMED FALSIFIED ICLUSIG PRODUCTS

1. ICLUSIG 45mg (30 tablets); Batch number PR072875

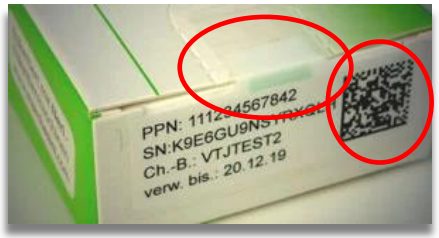
2. ICLUSIG 45mg (30 Tabletten); Batch number PR0834170

https://www.who.int/news/item/21-02-2019-medical-product-alert-n-3-2019-(english-version)

Addressing supply chain risks

- **Falsified Medicines Directive legislations** have come into force in recent years, providing a framework for the distribution of medicines through **licensed pharmacies and approved retailers**, including **approved internet providers**.
- Examples: EU Directive 2011/62/EU (3), UK FMD Directive

Four safety features aiming to prevent falsified drugs:



1. **Two safety features on packaging:**
   a. 2-dimension barcode or unique identifier
   b. an anti-tampering device.
2. **Supply chain and good distribution practice (GDP):** New responsibilities for wholesalers include regulations in quality, personnel training & hygiene, premises & equipment, documentation.
3. **Substances manufactured outside the EU:**
   Written confirmation from regulatory authority of exporting country is requested when active substances are imported into EU. Authorities ensure that Good Manufacturing Practice (GMP) is observed is equivalent to EU GMP regulations.
4. **Internet sales:**
   Obligatory logo that appears on websites of legally operating online pharmacies and approved retailers.

Sources: EUPATI Toolbox: toolbox.eupati.eu/resources/falsified-medicines - accessed 1.11.2023

Summary & conclusion

- Let´s **not mix up concepts** but let´s make sure we know what we are talking about (copy drugs, substandard drugs, falsified drugs vs. quality-controlled generics).
- Let´s not fight generics but let´s advocate for **good quality generic drugs** produced by **reliable pharmaceutical manufacturers** and provided through **secure distribution chains**. → Opportunity for substantial cost savings + access!
- In tightly regulated markets generic drug manufacturers are required to provide evidence that their products are **equivalent to the originator in terms of quality and effectiveness**.
- Bioequivalence studies ensure that the generic drug will have the **same therapeutic effect**.
- Robust **quality assurance** and **post-market surveillance systems** help detect and address quality issues with generic drugs after they have been approved and are in use.
- **No efficacy or safety concerns to date with generic imatinib and dasatinib** as long as purchased through **official distribution chains** and formally **approved by national regulatory bodies**.
- In terms of **tolerability**, in some cases more pronounced side effects have been observed (→ Excipients? Psychological effect?). Cases in which generics were even better tolerated than the reference drug have also been reported.
- Let´s **raise awareness about the risk of falsified medicines and about** purchasing medicine online through ominous internet pharmacies.

Sources & further reading

- FDA GENERIC DRUGS SECTION: www.FDA.gov/GenericDrugs
- EUPATI Toolbox: toolbox.eupati.eu – accessed 1.11.2023
- ema.europa.eu/en/human-regulatory/overview/public-health-threats/falsified-medicines-overview – accessed 29.9.2023
  pfizer.com/news/articles/fake_drugs_101_facts_on_illegal_counterfeit_drugs – accessed 29.10.2023
- toolbox.eupati.eu/resources/falsified-medicines – accessed 1.11.2023
- sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/therapeutic-equivalence – accessed 29.9.2023
- bpac.org.nz/magazine/2009/generics/docs/bpjse_generics_bio_pages_4-8.pdf – accessed 29.09.2023
- https://www.progenerika.de/topics/quality-of-generic-medicines/generic-vs-original-a-comparison/?lang=en – accessed 29.10.2023
- https://gabionline.net/reports/Quality-control-for-generic-drugs – accessed 29.10.2023
- „The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts" (Published in Blood May 2013): ncbi.nlm.nih.gov/pmc/articles/PMC4190613 – accessed 29.10.2023
- „Impfen - Wettlauf mit dem Virus – Leschs Kosmos Spezial", 26 January 2021, in German: https://www.youtube.com/watch?v=UBQeVO6G0gM – accessed 01.11.2023
- https://www.fda.gov/media/111058/download – accessed 29.10.2023
- https://www.fda.gov/media/111058/download – accessed 29.10.2023
- http://gabi-journal.net/overview-of-the-patent-expiry-of-non-tyrosine-kinase-inhibitors-approved-for-clinical-use-in-the-eu-and-usa.html – accessed 30.10.2023
- ErçalışkanA, Seyhan ErdoğanD, Eşkazan AE. Current evidence on the efficacy and safety of generic imatinib in CML and the impact of generics on health care costs. *Blood Adv*. 2021;5(17):3344-3353. doi:10.1182/bloodadvances.2021004194 – accessed 29.10.2023
- Carlo Gambacorti-Passerini, Ph.D. et al, Blood Res 2020; 55(3): 139-145, Published online September 30, 2020, https://doi.org/10.5045/br.2020.2020130, https://www.bloodresearch.or.kr/journal/view.html?uid=2372&vmd=Full& – accessed 29.10.2023
- https://link.springer.com/article/10.1007/s11596-018-1976-0 – accessed 30.10.2023
- https://linkinghub.elsevier.com/retrieve/pii/S2152265022001537 – accessed 30.10.2023

Sources & further reading

- European LeukemiaNet 2020 recommendations for treating CML - Patient-friendly Summary – accessed 30.10.2023
- https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2023 – accessed 30.10.2023
- Lipton, J.H. The expanding CML treatment landscape: an introspective commentary. *Blood Cancer J.* **13**, 145 (2023). https://doi.org/10.1038/s41408-023-00918-3 – accessed 30.10.2023
- https://www.commonwealthfund.org/blog/2021/skinny-labeling-pathway-timely-generic-drug-competition – accessed 30.10.2023ASOP Global Foundation, https://asopfoundation.pharmacy/wp-content/uploads/2021/07/ASOP-Global-Foundation-2021-Consumer-Behavior-Survey-Key-Findings_Final-7.9.2021.pdf – accessed 1.11.2023
- EUPATI Toolbox: https://toolbox.eupati.eu/resources/falsified-medicines/ – accessed 1.11.2023
- https://nabp.pharmacy/wp-content/uploads/2022/10/Rogue-Rx-Activity-Report-Disrupting-Illegal-Online-Pharmacies-2022.pdf – accessed 1.11.2023
- https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00394-3/fulltext – accessed 1.11.2023
- The Lancet: Rise in online pharmacies sees counterfeit drugs go global, https://doi.org/10.1016/S0140-6736(15)00394-3 – accessed 1.11.2023
- https://www.who.int/news/item/01-02-2019-medical-product-alert-n-2-2019-(english-version) – accessed 1.11.2023
- https://www.who.int/news/item/21-02-2019-medical-product-alert-n-3-2019-(english-version) – accessed 1.11.2023
- https://ascopost.com/issues/february-10-2023/influence-of-the-mark-cuban-effect-on-cancer-drug-prices-in-the-united-states-focus-on-cml – accessed 1.11.2023
- https://www.efpia.eu/about-medicines/development-of-medicines/intellectual-property/supplementary-protection-certificates/ – accessed 1.11.2023
- https://www.patientenanwalt.com/download/Expertenletter/Patient/Generika_Baumgaertel_Expertenletter_Patient.pdf – accessed 1.11.2023

BACKUP SLIDES

Looking into generic medicines more deeply

What are generics and how are they regulated?

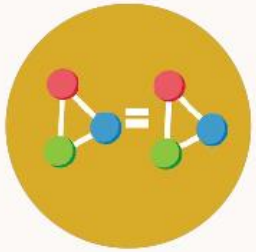
- A generic product has the same **composition** – same active ingredient & same quantity as the reference product (originator).
- It has the same **pharmaceutical form** – e.g. tablet, syrup, inhaler, etc. as the reference product.
- It has proven to **interact with body in a similar manner** to reference product. This is proven by bioequivalence studies.
- Chemically, there is **no difference** between the originator and the generic medicine since only pharmacologically inert agents (excipients) are allowed to change compared to the originator.
- Name, appearance, and packaging vary.
- Generics must comply with appropriate **regulatory approval processes** assessing and ensuring quality, safety, and efficacy.
- Generics are **regulated** in the same way as the original medicines.
- Manufacturing facilities and conditions must be of high standard → regular inspections of facilities e.g. by FDA.
- Following approval of a generic medicine, company producing it must commit to the collection and reporting of additional post-marketing safety data.

Source: https://www.fda.gov/media/111058/download – accessed: 29.10.2023

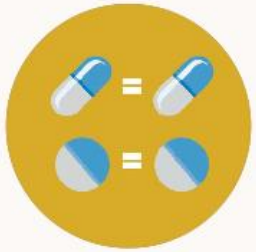
What Makes a Generic the Same as a Brand-Name Drug?

Pharmaceutical Equivalence

Lab test results and other documentation from the generic manufacturer are reviewed by FDA to demonstrate that:



The generic drug has the same active ingredient(s) as the brand-name drug.



The generic drug has the same dosage form as the brand-name drug.

The generic drug has the same strength and route of administration as the brand-name drug.

The generic drug has the same indications as the brand-name drug.

The inactive ingredients of the generic drug are safe and don't change how the drug works.

The generic drug will work as intended for a reasonable amount of time before expiring.

Bioequivalence

Comparisons—often in human volunteers who take both the generic and brand-name drugs—ensure that:

The generic drug performs the same in the human body as the brand-name drug.

The generic drug is as safe and effective as the brand-name drug.

Appropriate Container and Labeling

FDA inspection of the container and labeling demonstrates that:

The generic drug's label is the same as the brand-name drug's label, with some exceptions—such as indications protected by patents or exclusivity.

The generic drug is sold and shipped in an appropriate container.

Appropriate Manufacturing

FDA inspection of facilities demonstrates that:

The generic drug meets the same requirements for identity, strength, purity, and quality as the brand-name drug does.

The manufacturer is capable of making the generic drug correctly and consistently.

Postmarketing Surveillance of Generic Drugs

Once a generic medication is available for prescription or over-the-counter use, FDA continues to monitor its safety, efficacy, and quality.

After FDA approval, generic drug manufacturers must report any problems or serious adverse health effects to FDA for evaluation.

FDA periodically inspects manufacturing plants and continues to monitor drug quality.

Generic drug manufacturers will often propose changes to their products after they are approved; FDA evaluates these changes to ensure the drugs are still safe and effective.

FDA monitors FAERS (the FDA Adverse Event Reporting System) and reviews MedWatch reports to investigate concerns related to generic drug product quality and therapeutic inequivalence.

Visit www.FDA.gov/GenericDrugs to learn more.

U.S. FOOD & DRUG ADMINISTRATION

Source: https://www.fda.gov/media/111058/download – accessed: 29.10.2023

Myths about Generic Drugs

- Generics…are not as safe
- Generics…are not as potent
- Generics…take longer to act in the body
- Generics…are made in sub-standard facilities

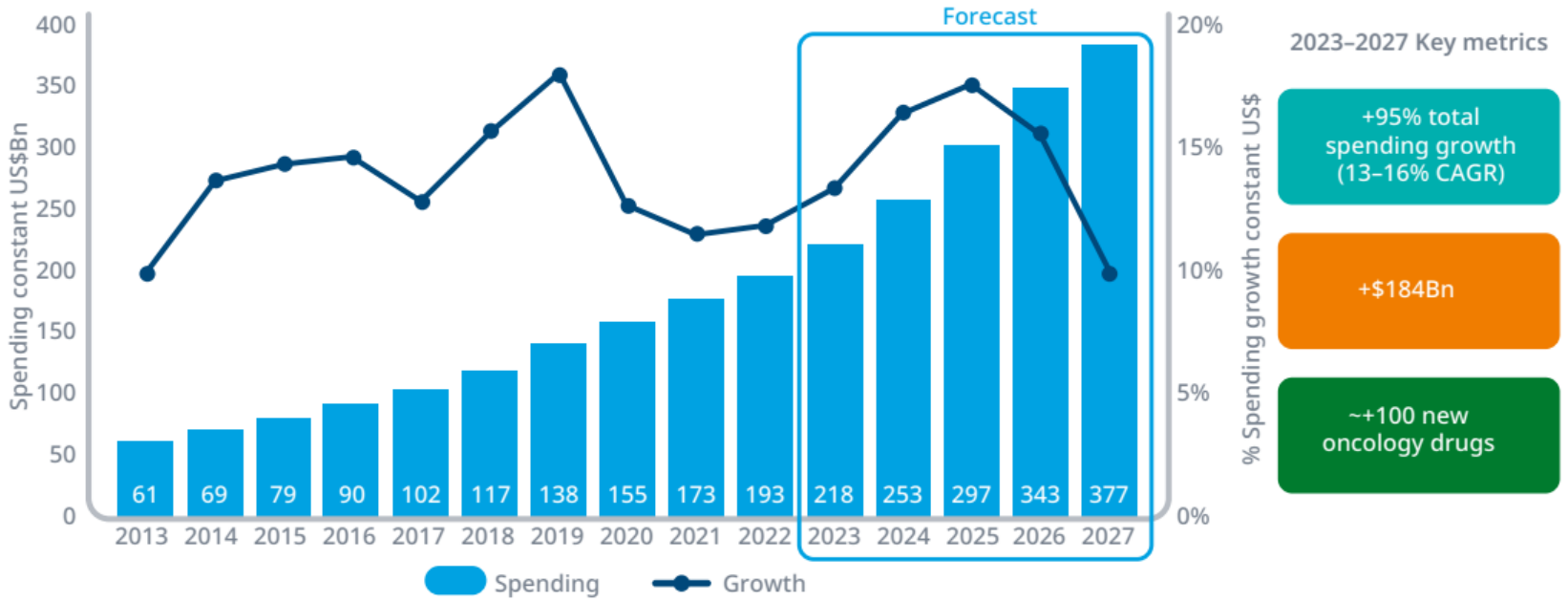
FDA Requirements for Brand-Name and Generic Drugs

	Brand Name Drug	Generic Drug
For reformulations of a brand-name drug or generic versions of a drug, FDA reviews data showing the drug is bioequivalent to the one used in the original safety and efficacy testing.	✓	✓
FDA evaluates the manufacturer's adherence to good manufacturing practices before the drug is marketed.	✓	✓
FDA reviews the active and inactive ingredients used in the formulation before the drug is marketed.	✓	✓
FDA reviews the actual drug product.	✓	✓
FDA reviews the drug's labeling.	✓	✓
Manufacturer must seek FDA approval before making major manufacturing changes or reformulating the drug.	✓	✓
Manufacturer must report adverse reactions and serious adverse health effects to the FDA.	✓	✓
FDA periodically inspects manufacturing plants.	✓	✓
FDA monitors drug quality after approval.	✓	✓

“The elephant in the room – the economic adverse event”[1]

Global oncology spending to reach $370Bn by 2027, with growth accelerating from novel drugs and limited biosimilars

Exhibit 36: Global oncology spending and growth



Source: IQVIA Forecast Link, IQVIA Institute, Nov 2022.

[1] Jeffrey H. Lipton, Leukemia Group, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada. Source: Lipton, J.H. The expanding CML treatment landscape: an introspective commentary. *Blood Cancer J.* **13**, 145 (2023). https://doi.org/10.1038/s41408-023-00918-3 - accessed 30.10.2023

Source: Global Use of Medicines in 2020. Report by the IQVIA Institute for Human Data Science https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2023

“The elephant in the room – the economic adverse event”[1]

Spending in the U.S. is expected to increase by $134Bn through 2027 driven by new and existing brands

Exhibit 18: Spending and growth drivers in US 2017–2027 const US$Bn

Source: IQVIA Market Prognosis, Sep 2022; IQVIA Institute, Nov 2022.

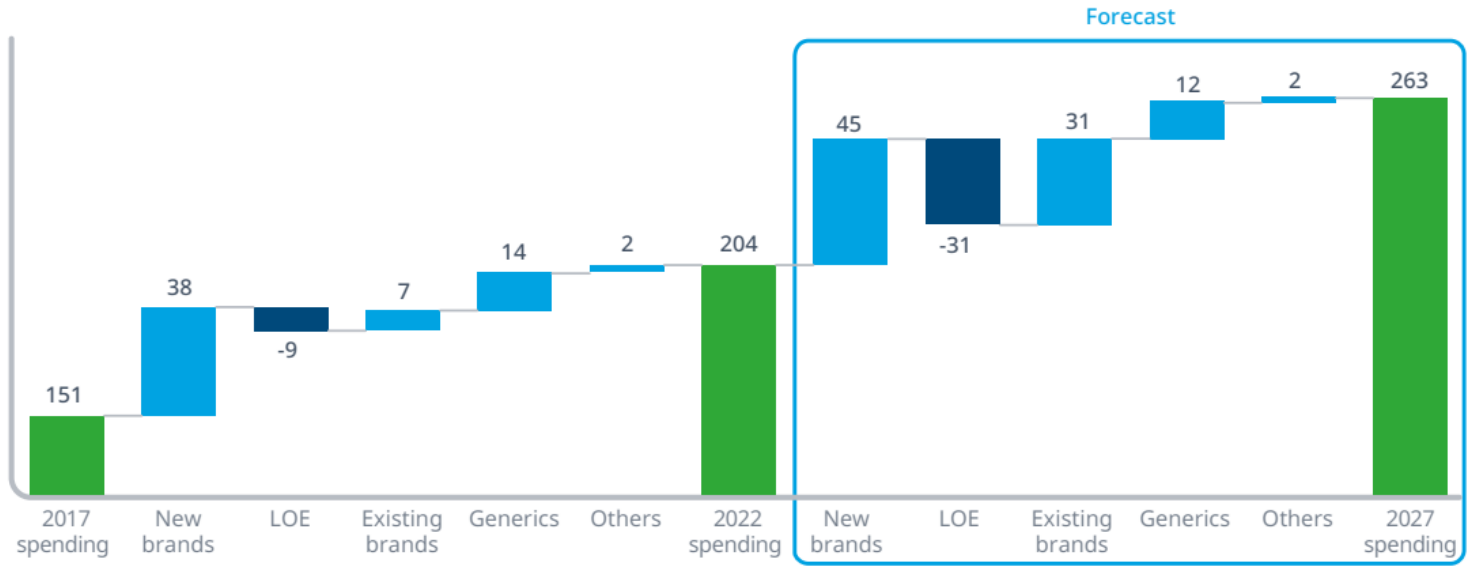
[1] Jeffrey H. Lipton, Leukemia Group, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada. Source: Lipton, J.H. The expanding CML treatment landscape: an introspective commentary. *Blood Cancer J.* **13**, 145 (2023). https://doi.org/10.1038/s41408-023-00918-3 - accessed 30.10.2023

Source: Global Use of Medicines in 2020. Report by the IQVIA Institute for Human Data Science https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2023

“The elephant in the room – the economic adverse event”[1]

Spending in Europe is expected to increase by $59Bn through 2027, driven by new brands

Exhibit 22: Spending and growth drivers in France, Germany, Italy, Spain, and UK 2017–2027 const US$Bn



Source: IQVIA Market Prognosis, Sep 2022; IQVIA Institute, Nov 2022.

[1] Jeffrey H. Lipton, Leukemia Group, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada. Source: Lipton, J.H. The expanding CML treatment landscape: an introspective commentary. *Blood Cancer J.* **13**, 145 (2023). https://doi.org/10.1038/s41408-023-00918-3 - accessed 30.10.2023

Source: Global Use of Medicines in 2020. Report by the IQVIA Institute for Human Data Science https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2023

Average Wholesale Price of CML TKIs in the US in 2022

„costs have exploded from a hundred dollars a month or even less for generic imatinib to tens of thousands of dollars a month for the newest drugs"[1]

TABLE 1: Average Wholesale Price of BCR:ABL1 Tyrosine Kinase Inhibitors in 2022

Tyrosine Kinase Inhibitor	Manufacturer/Distributor	Dose	AWP for 1 Year ($US)
	See Table 2		$5,300–$142,000
Generic Imatinib	Mark Cuban Cost Plus Drug	400 mg/d	$564
Dasatinib		100 mg/d	$228,000
		50 mg/d	$127,000
	Bristol Myers Squibb	20 mg/d	$63,000
Nilotinib		300 mg bid	$240,000
	Novartis	150–200 mg bid	$120,000
Bosutinib	Pfizer	400 mg/d	$250,000
Ponatinib	Takeda Pharmaceutical	15 or 30 or 45 mg/d	$271,000
		40 mg bid	$258,000
Asciminib	Novartis	200 mg bid	$1,289,000

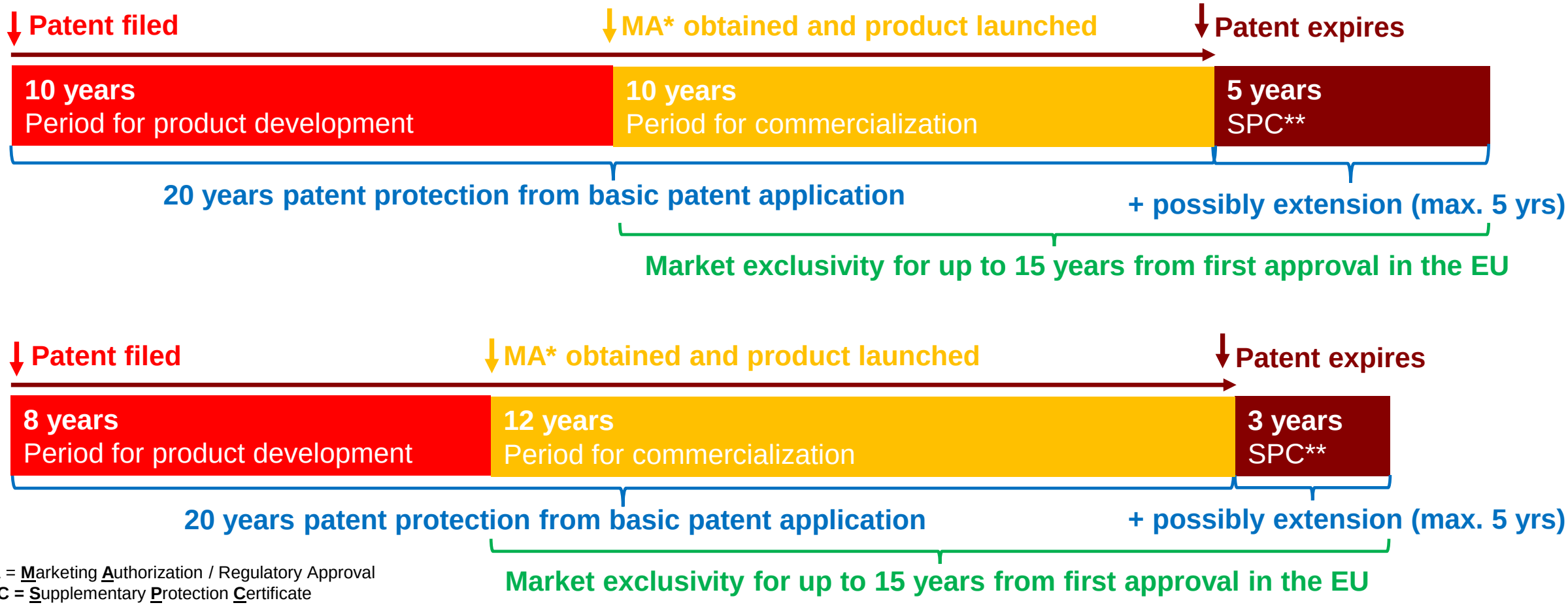
*Adapted from Kantarjian H, et al.[18]
AWP = average wholesale price; bid = two times a day.

Source: Kantarjian H, Welch MA. Influence of the 'Mark Cuban Effect' on cancer drug prices in the United States: focus on CML. The ASCO Post Feb, 2023

[1] Jeffrey H. Lipton, Leukemia Group, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada. Source: Lipton, J.H. The expanding CML treatment landscape: an introspective commentary. *Blood Cancer J.* **13**, 145 (2023). https://doi.org/10.1038/s41408-023-00918-3 - accessed 30.10.2023

Source: Global Use of Medicines in 2020. Report by the IQVIA Institute for Human Data Science https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2023

Patent protection of pharmaceutical products (2 examples)



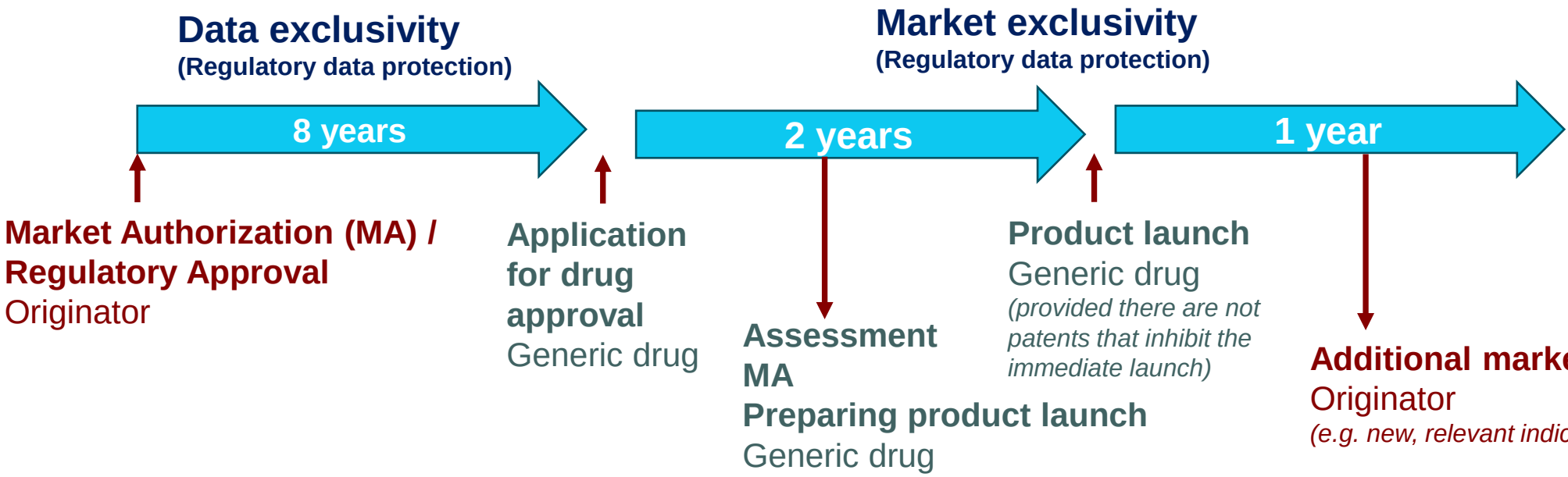
* **MA** = **M**arketing **A**uthorization / Regulatory Approval
** **SPC** = **S**upplementary **P**rotection **C**ertificate

Source: Own representation based on EFPIA (European Federation of Pharmaceutical Industries and Federations): https://www.efpia.eu/about-medicines/development-of-medicines/intellectual-property/supplementary-protection-certificates/ - accessed 1.11.2023

When exactly do generics come into play?

Based on document protection, marketing protection and patent protection periods

The „8 + 2 + 1“ formula:



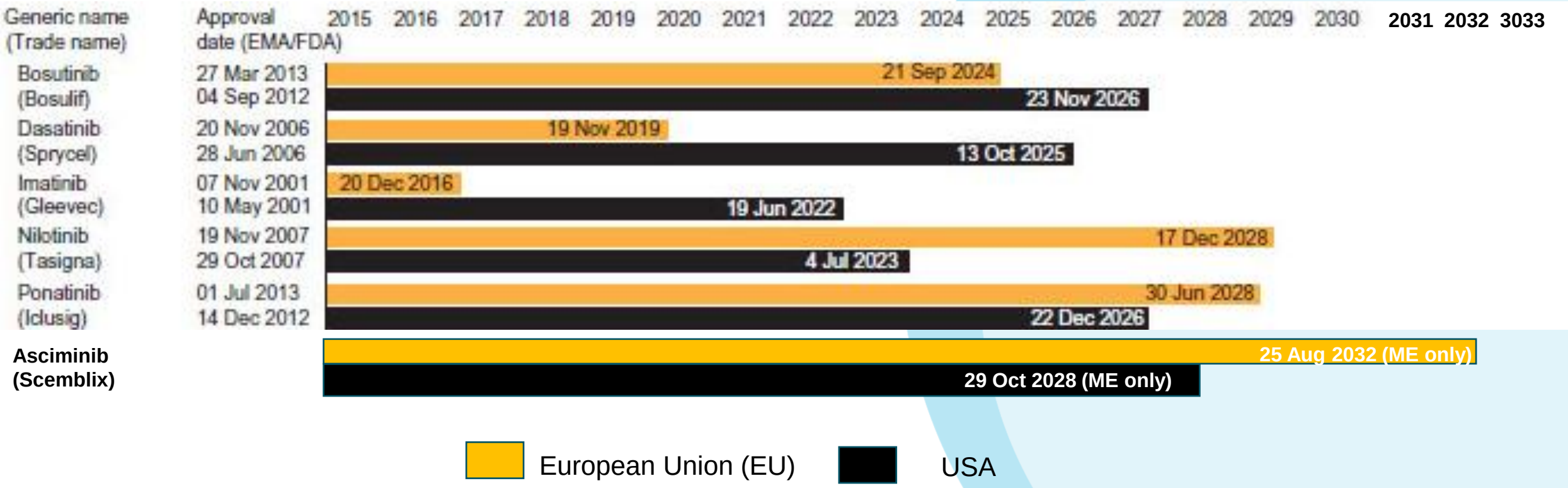
Special cases:

1. Orphan drug status (since 2000): 10 yrs. market exclusivity on products with the same or similar active ingredient;
2. Paediatric exclusivity (since 2007): plus 6 months of additional market exclusivity.

- Generic drug manufacturer must prove that the first approval of the original drug (OP) was at least 8 years ago. → **+ 8**
- As a general rule, the generic drug may only be launched 10 years after the initial approval of the originator in the EU (=regulatory data protection). → **+ 2**
- If the originator receives approval for a new, important indication within the first 8 years, the marketing protection period is extended by a further year. → **+ 1**
- Existing patents may further delay the launch of the generic and extending the originator´s monopoly position.

Source: Own representation based on Dr. Christoph Baumgärtel, Generika, Fragen und Antworten: https://www.patientenanwalt.com/download/Expertenletter/Patient/Generika_Baumgaertel_Expertenletter_Patient.pdf

Overview of patent + market exclusivity (ME) expiration of EMA/FDA approved TKIs for CML treatment



Source: Own representation based on http://gabi-journal.net/overview-of-the-patent-expiry-of-non-tyrosine-kinase-inhibitors-approved-for-clinical-use-in-the-eu-and-usa.html (last updated 2017 / accessed 30.10.2023) and figures kindly provided by Sarunas Narbutas