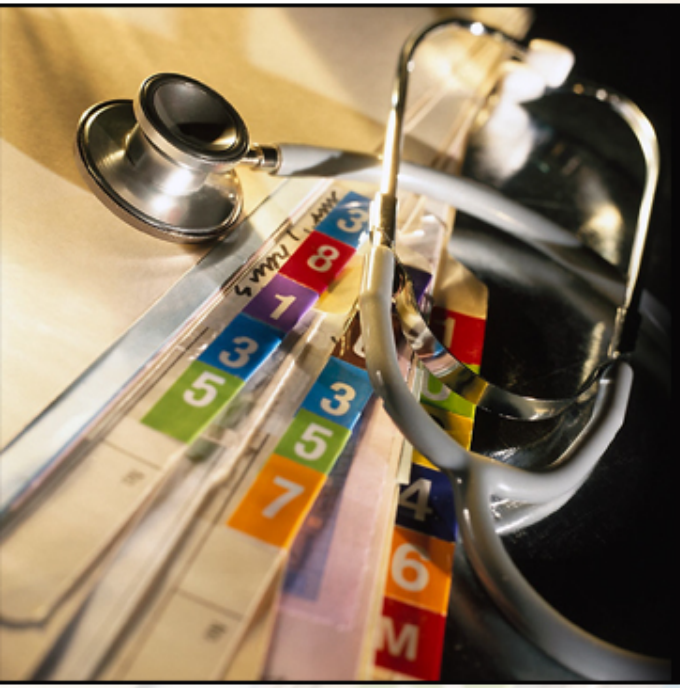

CML generics: Status quo and the CML Declaration

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President, POLA

Frankfurt, 28 May 2017

Lithuanian Cancer Patient Coalition

Outlook: TKI* generics in the EU market

FIRST PATENT EXPIRATION	EXCLUSIVITY EXPIRATION (EMA)	INN NAME	BRAND NAME	THERAPEUTIC AREA
Dec 2016	June 2016	imatinib	Glivec	CML, GIST
Apr 2020	Nov 2016 / 2018	dasatinib	Sprycel	CML
Jul 2023	Nov 2017 / 2019	nilotinib	Tasigna	CML
Mar 2018	March 2023	bosutinib	Bosulif	CML
Dec 2026	July 2023	ponatinib	Iclusig	CML, CLL
Nov 2018	Sep 2015	erlotinib	Tarceva	Carcinoma, Non-Small-Cell Lung, Pancreatic Neoplasms
Jul 2017	June 2018	lapatinib	Tyverb	Breast Neoplasms
Jan 2020	July 2016	sorafenib	Nexavar	Liver cancer, renal cell, carcinoma, DTC
Feb 2021	July 2016	sunitinib	Sutent	GIST, MRCC, PNET
Feb 2025	Nov 2022	crizotinib	Xalkori	Carcinoma, Non-Small Cell Lung

* Tyrosine kinase inhibitors (TKIs) are medicines that block signals that tell a cell to grow and divide. This can slow or stop cancer cells from growing. In some cases it can cause the cells to die.

How to determine quality of medicine?

Registration requirements for generic products	USA	Europe	Developing Countries
Bioavailability and bioequivalence testing with sound scientific methodology and ethical committee surveillance	✓	✓	? Not a common requirement, in some countries not required at all
Evaluation of active ingredient quality including identification and quantification of impurities (e.g. genotoxic impurities)	✓	✓	
Pre and post approval when source of active ingredient changes	✓	✓	
Identification and qualification of **degradation production** in medicines, not just stability testing	✓	✓	✘ Not a requirement in most countries
Strict Good Manufacturing Practice **monitoring** and field inspections of plants	✓	✓	? Few countries require
Actual laboratory testing of finished product, not stamping and paper work	✓	✓	✘ Not a requirement in most countries

How regulators think

Generics save money

Generics are therapeutically equivalent to branded product

↓

It may not be true for poor quality formulations

↓

In such case we will withdraw substandard medicines from market

We should always check if the product documentation proves quality

↓

But we do not normally test if the factual quality of the medicine is the same as documented

↓

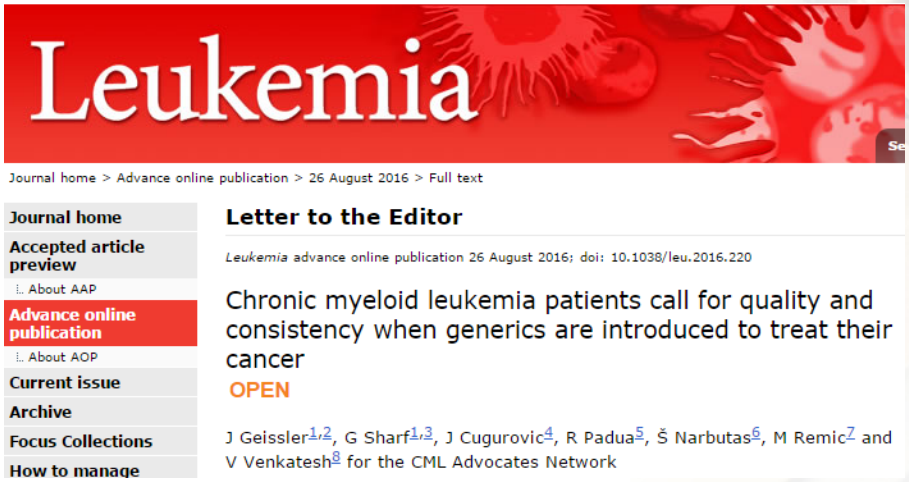
Any problems will be captured via pharmacovigilance process

Generic imatinib: initial assumptions

- Lowering the prices of TKI products should:
  - improve treatment penetration (**true**)
  - increase adherence to therapy (**false**)
  - expand the CML population who live longer and continue using TKI (**answer in 2018?**)
- Generics lead to considerable cost savings, e.g. generic imatinib is 50 times cheaper than original Glivec in India, up to 10 times cheaper in Europe
- Are TKI generics equally EFFICIENT and SAFE? (**preliminary yes, <u>if they are not substandard</u>**)

Patients call for quality and consistency when considering generics

- **Patients** welcome that generics may improve patient access to more affordable therapies in many countries. However, we also raise concerns about impact on the treatment outcomes when switched between different products for non-medical reasons, if equivalence of these products' is still uncertain in terms of quality and efficacy


Leukemia

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Letter to the Editor

Leukemia advance online publication 26 August 2016; doi: 10.1038/leu.2016.220

Chronic myeloid leukemia patients call for quality and consistency when generics are introduced to treat their cancer

OPEN

J Geissler[1,2], G Sharf[1,3], J Cugurovic[4], R Padua[5], Š Narbutas[6], M Remic[7] and V Venkatesh[8] for the CML Advocates Network

- **Patients** ask for:
  - reliable proof of quality and **equivalence** of pharmacokinetics and bioavailability
  - collection of **comparative clinical data** to ensure comparable efficacy
  - no switching for **non-medical reasons** in optimal response and tolerance
  - no switching between products of same compound more frequently than **once a year** to allow consistent follow-up, and in case of loss of response or increased toxicity, switch back or switch treatment
  - more **frequent monitoring** (must: PCR tests, optional: plasma level testing)

Patient led „CML generics resource center“

- www.cmladvocates.net/generics

- **Glossary** of generics, copies, substandard drugs
- Community-run **unofficial TKI register**
- „Community-internal“ **blog**
- List of **scientific publications** on generics and copy drugs use in CML
- **Video streams** of presentations on generics at „CML Horizons“
- **Best practice** of „CML Association of Serbia“ and „CML Society of Canada“

Resource & Knowledge Center on CML generics, copy drugs & substandard drugs

Last Updated: Wednesday, 21 May 2014 12:55 | Print

Welcome to our **"Resource & Knowledge Center" on CML generics, copy drugs and substandard drugs.** The Resource & Knowledge Center intends to pull together all information that is known to us to date. If you have additional information or feedback, please make sure you contact us at info@cmladvocates.net!

Declaration of the CML community

On 2-4 May 2014, patient organisations from 58 countries supporting patients and families affected by Chronic Myeloid Leukemia (CML) met in Serbia to learn from medical experts, share best practice in patient advocacy and grow their organisation's capacity. An important topic of increasing attention discussed between patients and health professionals was the introduction of generics in CML treatment. Patients welcome that generics may improve patient access to more affordable therapies in many countries. However, patients also raise concerns about impact on their cancer when switched between different products for non-medical reasons, if the products' equivalence in terms of of quality and efficacy is uncertain. Read the declaration / press release as of 21 May 2014 here.

CML TKI Register

We have compiled an inofficial directory including all CML tyrosine kinase inhibitors (TKIs) that are - to our knowledge - available to date. Our CML TKI Register provides information on the product name, compound name, registration status of all TKIS available on the international markets, the name of the respective manufacturer and / or Marketing Authorization Holder (MAH) and the specific indication of each drug. If available, it also provides links to publicly available documentation.

Session at CML Horizons 2013:
"Ideal World vs. Reality: New Challenges with Substandard Drugs & Generics"

Please see the videos and PDF files of our session at "CML Horizons 2013" which was addressing the new challenges with substandard drugs, copies and generics in CML. We are also sharing the Excel summary of the data collected in our generics survey in March 2013:

- **Generics, biosimilars, copies, substandard drugs: efficacy, efficiency, sustainable quality? What is the difference?** (Sabine Kopp, Medicines Quality Assurance Programme, WHO)
  PDF - Video Stream
- **Originals, generics, copies: Results of the CML Advocates Network Survey** (Jan Geissler, CML Advocates Network):
  PDF- Video stream - Detailed summary of survey data (Excel) - Survey questions
- **Actions of CML groups: Fighting against Anzovip, a generic drug** (Jelena Cugurovic, Serbia)
  PDF - Video Stream

Session at CML Horizons 2014:
"The new realities: Generics and Copy Drugs in CML"

Please see the videos and PDF files of our session at "CML Horizons 2014":

- **Generics, copies & substandard drugs, How to assess quality of drugs and labs**
  (Prof. Yoseph Caraco, Pharmacologist) - PDF - Video Stream
- **CML generics from a patient perspective**
  (Cheryl-Anne Simoneau, CML Society of Canada) - PDF - Video Stream
- **CML generics from a hematologist perspective**
  (Dr. Andrija Bogdanovic, Serbia) - PDF - Video Stream
- **CML generics from a hematologist perspective**
  (Dr. Qian Jiang, China) - PDF - Video Stream

Perception on Middle East & North Africa Region

- Governments do not follow EU, USA models for creating **robust regulatory systems**
- Lack of international **cooperation** on regulatory matters
- Governments **„favour“** products from local pharmaceutical companies

Latin America region: Lessons to learn from

- Increasing numbers of substandard products
- Lack of quality control from regulatory authorities
- Huge disparities to access, between countries and within countries
- Interruptions in product supply
- Socio-economic barriers
- Lack of physicians
- Lack of information available to patients

Regulators will not help You to answer these questions

IF	• You should take generic or innovator product
WHY	• You should prefer one generic to another
WHEN	• You should take generic

What patient organisations can do (1)

- Encourage patients to obtain their medicines **from reliable sources**
- **Educate patients** what to do when encountering substandard medicines
- **Collect data** on generics that are used locally / internationally
- Encourage politicians and support regulators to **invite all stakeholders** to take part in upgrading regulatory system for approving medicines

What patient organisations can do (2)

- **Promote importance** of good manufacturing / laboratory practices and international standards from development to distribution to ensure quality, safety and efficacy of medicines
- Connect with local and international **experts** for knowledge and guidance on use of generics
- **Collaborate** with international patient advocates / academic networks in case of serious adverse events while taking TKI

Basics:
6 simple rules to follow as a patient

1. Buy medicines from **licensed pharmacies**, not online stores
2. Examine if the **package** is sealed and not damaged
3. **Check the label** for: name, manufacturer, expiry date and instructions of use
4. Do **not buy loose** tablets, capsules or injections
5. **Report any adverse event** to your doctor / pharmacist
6. If you **suspect medicine may be substandard**, report it to pharmacist / doctor / medicine regulatory authority

Advanced: 5 steps to minimise the risk to patient

1. **Record** the date when started taking generic imatinib
2. **Track** and record any changes of quality of life on generic imatinib
3. Tell your physician (hematologist) that you have been **switched** to generic imatinib
4. Be willing to **share** your experience with CML patients community
5. Every time you are renewing your prescription **ask for the same** generic product from the **same** manufacturer. Be ready to show the label / picture of the packaging to the pharmacist

Thank You!

Lithuanian Cancer Patient Coalition

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